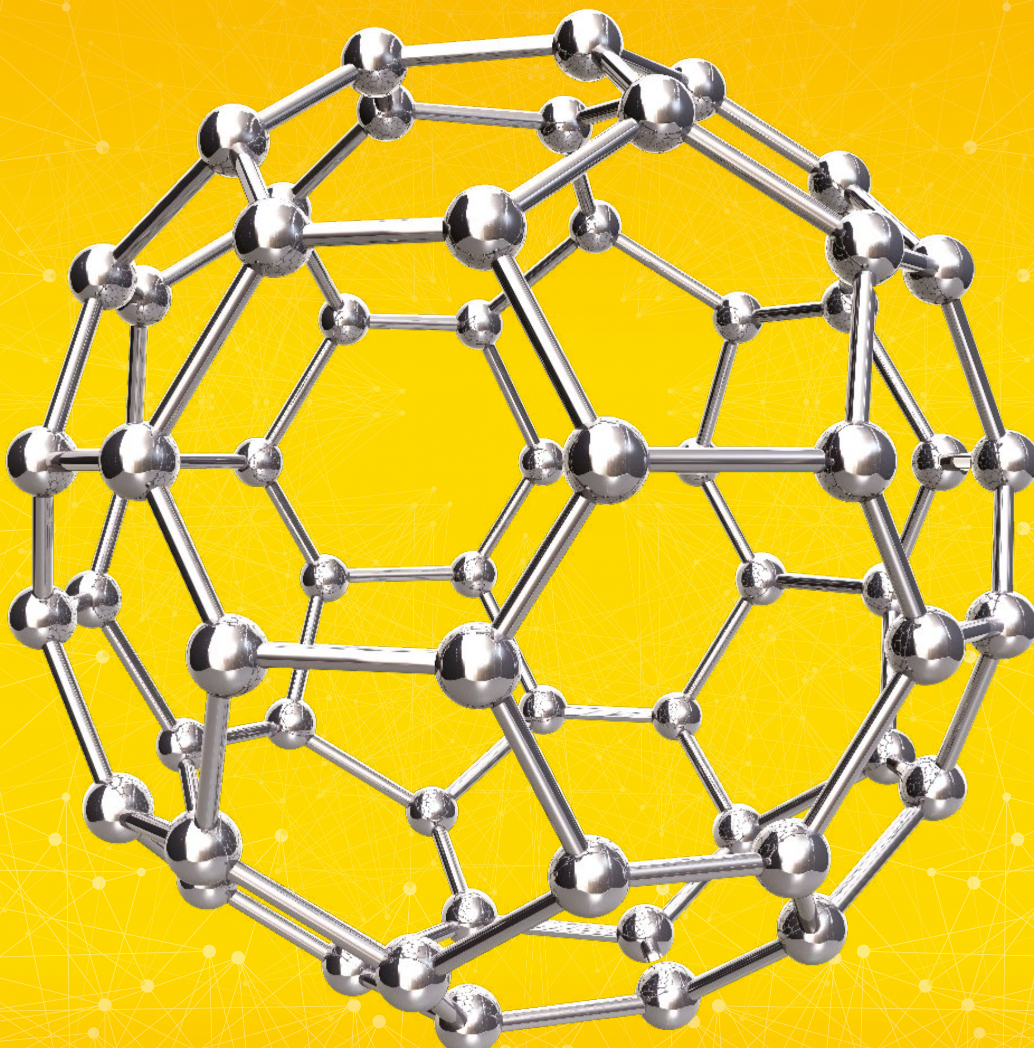
# Aperio

FALL 2023 | ISSUE 05



# SMALL WONDERS

**HOW NANOPARTICLES, MARGINALIA AND OTHER TINY THINGS CAN LEAD TO BIG ADVANCES**

## Rethinking the Cognitive Revolution
The history of math reveals that what we believe might not add up

## Micro Marvels, Mighty Impact
Unleashing the power of nanofiltration to quench the world's thirst

## Orchestrating a Breakthrough
Can nanoparticles and music deliver personalized medicine to the brain?

# IN THIS ISSUE

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SCAN ME

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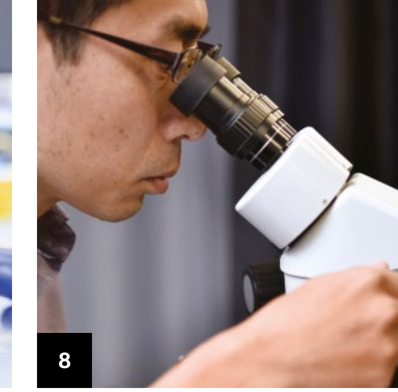
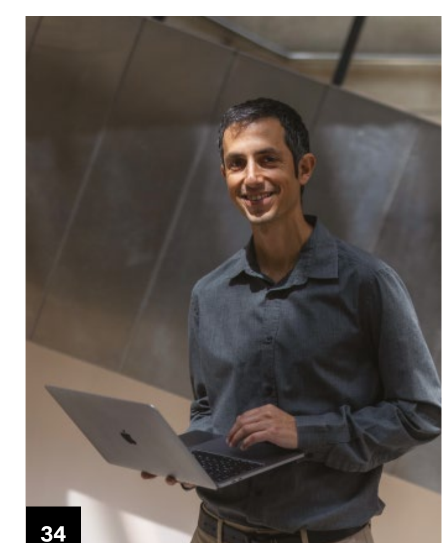
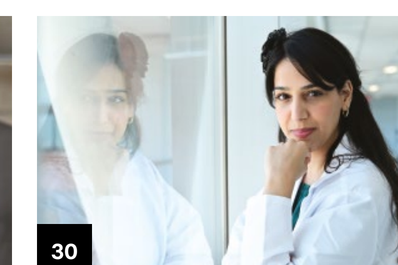
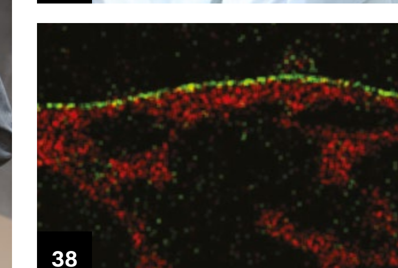
**On the cover:** Fullerene is a form of carbon, and is one of the nanomaterials that is sometimes used in water filtration systems. Nanofiltration technologies force water through tiny microscopic pores to filter out contaminants at a molecular level.



By Diana Kwon
Photographs by Hadas Parush

# Orchestrating a Cure

## How nanoparticles and music harmonize to get medicine through the blood-brain barrier

**The blood-brain barrier is an important part of human physiology, yet it also presents a medical challenge.** First observed in the late 1800s, it's a protective layer that surrounds the vasculature of the brain, preventing pathogens from invading the body's most crucial organ. While this network of closely spaced blood vessels and tissue plays a vital role in keeping harmful microorganisms at bay, it also restricts the passage of medicines into the central nervous system, hindering the treatment of neurological diseases.

Patricia Mora-Raimundo hopes to solve this problem with an unconventional approach: using music to guide drug-carrying nanoparticles to the brain.

Nanoparticles are ultra-small materials that are under 100 nanometres in size (for comparison, a human hair is about 100,000 nanometres in thickness). For decades, scientists have been studying the use of nanoparticles for the delivery of therapeutics — in addition to their size, the ability to tweak these minuscule materials to enhance their ability to reach a specific target makes them an ideal vehicle for this task.

Today, nanoparticles are used in a variety of medicines. Several COVID-19 vaccines, for example, contain nanoparticles in their formulations. These include the widely used messenger RNA (mRNA) vaccines, which use nanoparticles to deliver their cargo: genetic material known as mRNA that contains the blueprint for producing a piece of the SARS-CoV-2 virus's protein that generates an immune response within our bodies.

"Nanoparticles caught my attention from the beginning," says Mora-Raimundo, an Azrieli International Postdoctoral Fellow in the Wolfson Department of Chemical Engineering at Technion–Israel Institute of Technology. "I was fascinated by how such a teeny, tiny thing can have these huge possibilities. You can modify them on the outside or on the inside, and transport different types of therapeutics just by modifying the nanoparticles properties."

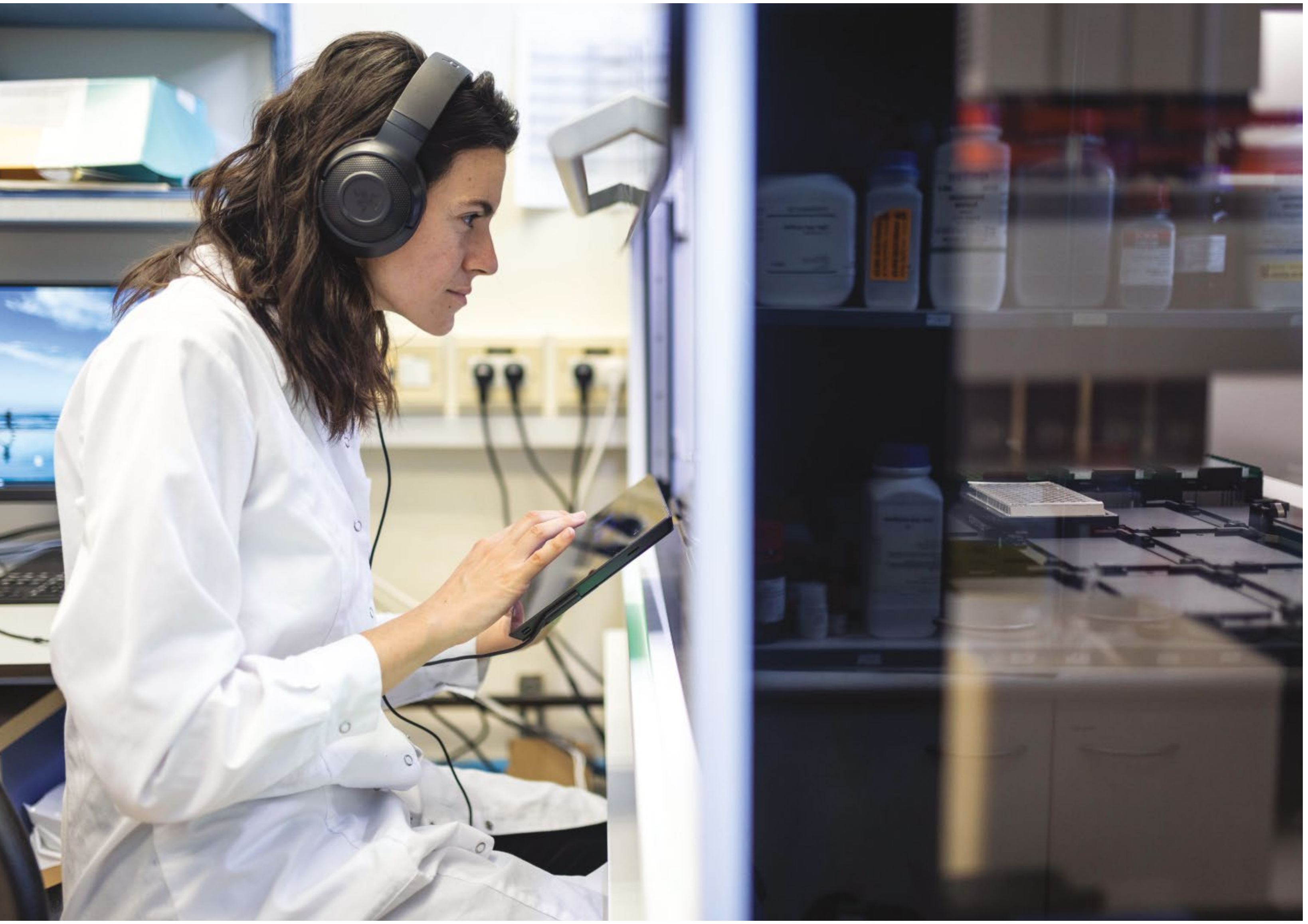
Mora-Raimundo was first introduced to nanoparticles as an undergraduate student at the Universidad Complutense de Madrid in Spain. She majored in pharmacy, a field she was attracted to because it combined many different disciplines: chemistry, biology, botany, pathology and immunology, among others. During her second year, one of her professors, Miguel Manzano-Garcia, invited her to apply for an open position in the lab of María Vallet-Regí, where he worked. Vallet-Regí's group, which focuses on developing biomaterials for the treatment of bone pathologies, had a wide range of ongoing projects. But there was one in particular that caught Mora-Raimundo's eye: a study aimed at using nanoparticles to help treat bone cancer.

After completing her bachelor's degree, Mora-Raimundo remained in Vallet-Regí's lab as a doctoral student and continued her work with nanoparticles. Her PhD project was focused on using nanoparticles to treat osteoporosis, a common disease that leads to a reduction in the mass of bones, causing them to become weaker and more vulnerable to fracture. Drawing on her knowledge of biology and biochemistry, she designed a nanoparticle to simultaneously carry two drugs that promote bone formation.

To evaluate the effect of these nanoparticles in osteoporotic mice, Mora-Raimundo examined how they affected the expression of different genes and what that meant for the underlying architecture of the animals' bones. In osteoporotic mice, this combination of drugs led to greater bone regeneration than the currently available gold standard treatment for the disease. "The new bone formed was similar to healthy [non-osteoporotic] bone," says Manzano-Garcia, who was Mora-Raimundo's PhD thesis supervisor. "We were able to revert the osteoporotic process in animals."

In 2020, during the last year of her PhD, Mora-Raimundo went to Israel to spend a few months working on nanoparticles with professor Avi Schroeder, the head of the targeted drug delivery and personalized medicine

Azrieli International Postdoctoral Fellow Patricia Mora-Raimundo is attempting to improve the delivery of nanoparticles to the brain with music. First, she modifies nanoparticles with glucose, the main fuel for brain activity. Then these particles are administered to patients while they listen to music, which also boosts brain activity. In effect, glucose acts as a kind of disguise for the nanoparticles; because the brain needs this molecule as fuel, covering the surface of a nanoparticle with glucose helps it pass through the blood-brain barrier.



"I was fascinated by how such a teeny, tiny thing can have these huge possibilities," Mora-Raimundo says about nanoparticles. "You can modify them on the outside or on the inside, and you can transport whatever you can imagine just by modifying their properties."

group at Technion. A three-month stint turned into six months after the COVID-19 pandemic forced countries to shut their borders and she decided to remain in Israel to continue her research. By the end of this unexpectedly extended stay, Mora-Raimundo decided to return as a postdoc in Schroeder's lab.

At Technion, Mora-Raimundo made the pivot from bones to the brain, adding neuroscience to her growing interdisciplinary repertoire. "I've always considered myself a curious person," she says. "Integrating such different fields into my research offers me the opportunity to be in a constant process of learning."

Her current project, which aims to improve the delivery of nanoparticles to the brain with music, was born serendipitously. After spending weeks coming up with almost a dozen ideas for a project, Mora-Raimundo was on the phone with her mother, talking about her grandfather, who had Alzheimer's disease. Even after losing most of his memories, he continued to react to music for years. But her mother had called to share the news that the disease had progressed to the point where even music failed to elicit a reaction.

Thinking about her grandfather's ability to react to music even when his other cognitive capacities had disappeared made Mora-Raimundo wonder: was there something unique about what music was doing to the brain?

After probing the scientific literature, she learned that listening to music boosted brain activity and led to the formation of new neuronal connections. This gave her an idea: brain activity requires energy, and the main fuel of the brain is glucose. If she modified nanoparticles with glucose and administered these to patients while they listened to music, could this increase the uptake of the nanoparticles into the brain? Glucose acts as a kind of disguise for the nanoparticles — because the brain needs this molecule as fuel, covering the surface of a nanoparticle with glucose enables it to pass through the blood-brain barrier. Researchers have used this method to overcome the blood-brain barrier in the past, but the problem, according to Mora-Raimundo, was that the number of glucose-modified nanoparticles that got past the brain's protective layer was still relatively small.

Mora-Raimundo is now hard at work testing her hypothesis. She has two main aims. The first is finding the best way to arrange glucose on the surface of the nanoparticles to optimize their uptake. The second involves using neuroimaging techniques such as functional magnetic resonance imaging to detail how music changes brain activity and assessing whether different types of music — classical compositions by Mozart compared to the psychedelic soundscapes of Pink Floyd, for instance — awaken different parts of the brain. She will also use a technique known as positron emission tomography-computed tomography (PET-CT) to measure how music affects glucose uptake into the brain.

**'There is no cure for Alzheimer's or Parkinson's — we can only treat the symptoms. But if you try something radically new, such as using nanoparticles to send drugs to the brain, there may be a potential solution.'**

Once Mora-Raimundo determines the optimal musical conditions for the maximum glucose uptake in mice, she plans to inject glucose-modified nanoparticles into the animals and track how many of those nanoparticles end up in the brain. If this proves to be fruitful in animals, the next step will be to test this technique with people. In humans, Mora-Raimundo sees further parameters to explore, such as whether a person's emotional connection to a song further boosts brain activity or leads to a unique pattern of activation.

While her present focus is to increase nanoparticle uptake to the brain, Mora-Raimundo's eventual goal is to examine whether it might be possible to direct particles to specific brain regions. In the future, she envisions combining this technique with artificial intelligence-based algorithms that can detect which pieces of music best boost brain activity, adding computer science to her diverse portfolio of tools. "The final aim of this research is personalized medicine," she says. "The patient will have specific conditions that bring the particles to the target in the most effective manner."

Although Mora-Raimundo was inspired to carry out this study by her grandfather's illness, she sees potential applications of this technique for a wide range of brain diseases. Manzano-Garcia agrees. "There is no cure for Alzheimer's or Parkinson's — we can only treat the symptoms," he says. Doing the same thing researchers have been attempting for the last 50 years will make it difficult to find a solution, he adds. "But if you try something radically new — such as using nanoparticles to send drugs to the brain — there may be a potential solution."

For Mora-Raimundo, this project is also providing the opportunity to blend two of her passions: art and science. "I've always felt that if you choose the path of science, you're turning your back to the path of art," she says. "This project proves to me that there is the possibility of combining art and science to improve human lives." ▲●■

While her present focus is to increase nanoparticle uptake to the brain, Mora-Raimundo's eventual goal is to examine whether it might be possible to direct nanoparticles to specific brain regions.

# COULD THE BRAIN OF A TINY FISH HELP SPARK A BIG ADVANCE?

By Ty Burke
Photographs by Boaz Perlstein

NOVEL NEUROSCIENCE RESEARCH EXPLORES THE POTENTIAL OF PSILOCYBIN FOR TREATING DEPRESSION

**For somebody with depression, everyday life can be a struggle. It is among the most common mental health disorders worldwide, affecting more than 280 million people. Depression can negatively impact personal relationships and work performance. In severe cases, it can be debilitating and contribute to suicide.**

Depression is commonly treated with a class of antidepressants called selective serotonin reuptake inhibitors (SSRIs). These drugs have been in use since the 1980s and have helped countless patients cope, but their side effects can make them intolerable. And even though SSRIs have been around for decades, we still don't know much about how they actually work.

Weizmann Institute of Science neuroscientist Takashi Kawashima, who is based in the institute's Department of Brain Sciences and was an Azrieli Early Career Faculty Fellow until 2022, is exploring whether an entirely different kind of drug could yield similar benefits, without the unintended consequences of SSRIs. His research is probing the potential of a psychoactive chemical called psilocybin, which is better known for inducing hallucinations (see "A Brief History of Psilocybin," page 11). Kawashima is investigating whether psilocybin can mimic serotonin's effects in the brain and, if so, which mechanisms it uses. In the long run, this could help lead to the development of depression treatments that are more effective and faster acting than the drugs that doctors rely on now.

Serotonin is a chemical that functions as a neurotransmitter, a kind of messenger that transmits signals. A deficit of serotonin in the brain is thought to be a major underlying factor in depression. This is called the serotonin theory of depression, and it is widely accepted, although we don't know *how* serotonin deficiency actually leads to depressive symptoms.

Commonly prescribed SSRIs such as Prozac and Zoloft work by increasing the amount of serotonin in the brain. But these drugs have distinct drawbacks. In addition to mood regulation, serotonin is also involved in digestion, sleep, learning and sexual drive. When serotonin levels are increased, any of these functions can be affected. For some people, nausea and diarrhea make SSRIs intolerable.

Beyond that, SSRIs can take several weeks to have an impact. They work by blocking the brain's reabsorption of serotonin, which increases the amount of serotonin that's available. But this change takes time, so patients don't immediately know whether a prescription is working, and identifying the right regimen is a trial-and-error process. It often takes months for people to find a tolerable balance between recovery from depressive mood and the side effects of SSRIs. Some never do.

Zebrafish have few obvious similarities with humans, but their serotonergic system is one of them. All mammals are descended from fish, and this is one of the features we retained. And because zebrafish are transparent, this makes zebrafish an ideal research model for the *in vivo* imaging that Takashi Kawashima does to better understand brain activity in living animals.

Kawashima, a former Azrieli Early Career Faculty Fellow at the Weizmann Institute of Science, is analyzing a rich trove of data detailing the effects of psilocybin on zebrafish.

Psilocybin is different. It doesn't increase the amount of serotonin but appears to act as a serotonin mimic. Because psilocybin causes changes in the brain's function, treatments derived from it could work more quickly than SSRIs with fewer side effects. We don't know how psilocybin produces these effects either, but that's one of the things Kawashima is working on. And he is using an innovative new model to understand psilocybin: the tiny zebrafish (*Danio rerio*).

Kawashima's research sits at the intersection of neuroscience and computer science, and it builds on knowledge that he began developing while studying to become a medical doctor at the University of Tokyo. In Japan, his programming skills weren't useful at medical school, and although he enjoyed learning about psychiatry and neurosurgery, he was much less enthused about the prospect of working in a hierarchical hospital environment.

Instead, Kawashima pursued a PhD in neuroscience, and during his studies he began learning about *in vivo* imaging — using technology to study brain activity in living animals. He didn't start with psilocybin or zebrafish, though. Kawashima initially explored the neocortical (or outer brain layer) mechanisms of learning in rodents. Seeing limitations in rodents, he changed his model animal to zebrafish, focusing on the role of serotonin in learning. He established his laboratory at Weizmann to continue basic research on serotonin, and it seemed as if this work would never cross paths with his medical past — until psilocybin began to re-emerge as a promising antidepressant.

Zebrafish have a highly unusual trait: they are transparent. And even though they have few obvious similarities with humans, our brains have a few things in common. The serotonergic system is one of them. All terrestrial vertebrates — including mammals — descended from fish. Over hundreds of millions of years of evolution, mammalian brains grew larger and more complex, but they retained some aspects of their distant ancestors' brains. One of these is the subcortical area — part of the central nervous system that encloses the brainstem and cerebellum, below the cerebral cortex — where serotonin is produced. Because of this, findings about how psilocybin affects fish can help us understand how it works in humans.

"The subcortical part of the brain is hidden beneath the neocortical area. That's where serotonin molecules controlled mood in our ancestors and still should in us," says Kawashima. "This is a primitive and reactive area of the brain, but it is almost impossible to study it in mammals. That's why I chose to work with zebrafish. Because they are transparent, we can see the entire brain at once, including its serotonin system."

**'In neuroscience, there are scientists who look at the molecular level, and there are scientists who think of the brain as a system with computational principles. Historically, there has not been very much research that bridges them, but Takashi does this. He makes observations about the molecular machinery and uses them to look at the whole network as a complete system, and then uses computational techniques to understand what's happening.'**

Neuroscience research often uses rodent models because mammal brains have anatomical similarities to humans. But in this case, that's exactly what gets in the way. Like human brains, mouse brains have outer layers — the neocortex — that are relatively easy to access with imaging technology. The majority of neuroscience research is focused on this area; it's where many of the human brain's high-level functions are performed, including language learning, sensory perception and cognition. Other important functions happen deeper in the brain, and they are much less studied.

To see what happens when zebrafish are given psilocybin, Kawashima puts them in a small water chamber and adds a pure form of psilocybin to the water. The fish ingest the psilocybin as they breathe; water is taken in through their mouths, and it passes it through their gills. And then they are put in a test arena under a camera.

This is not your average camera. Zebrafish swim fast; their acceleration rivals a Formula 1 racing car if scaled to that size. Interpreting every single aspect of their motions is necessary to decipher their emotional states. So even though Kawashima's experiments look simple, with tiny fish swimming around a palm-sized dish, his camera captures millions of pixels at the

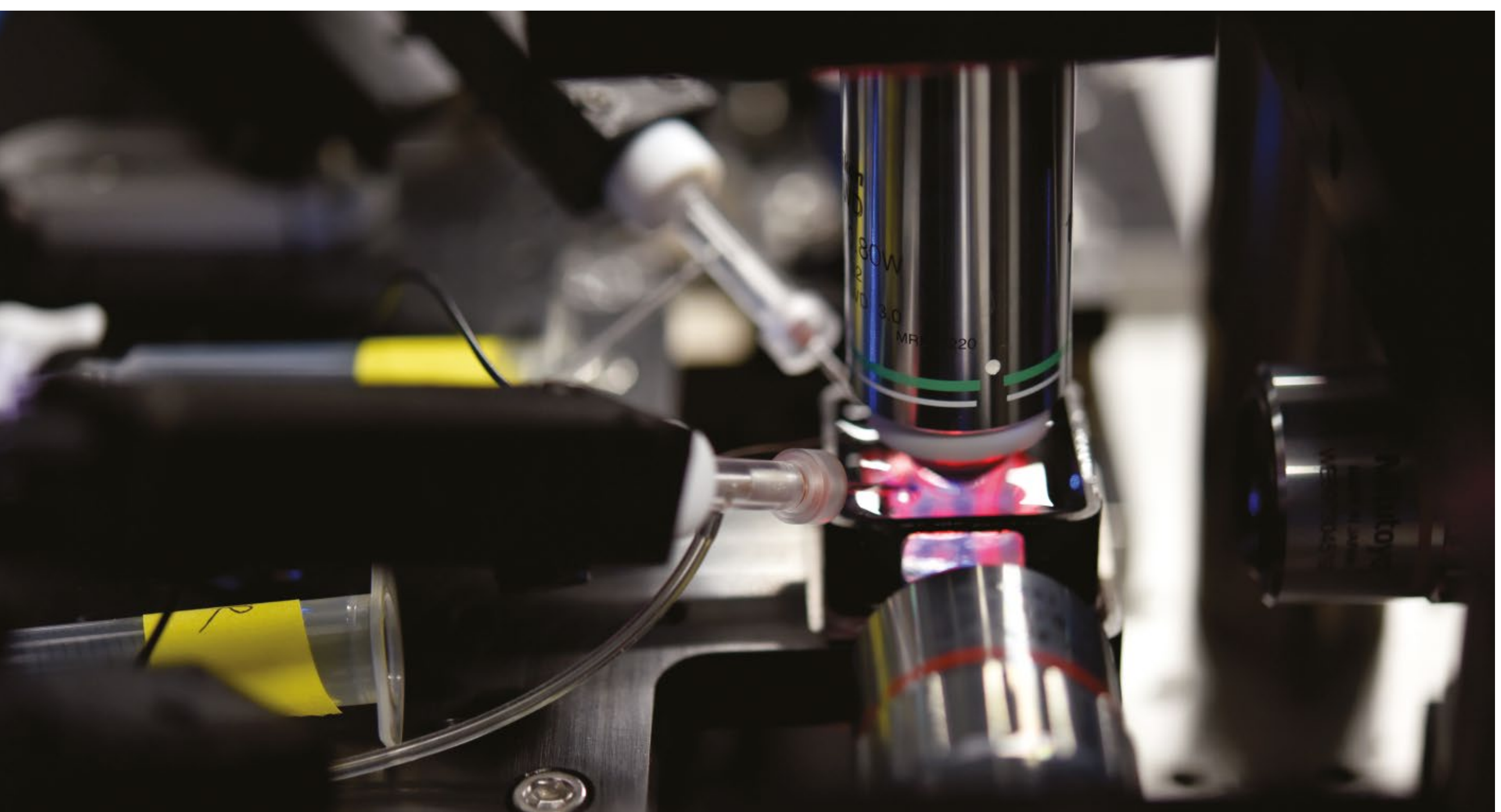
## A BRIEF HISTORY OF PSILOCYBIN

Psilocybin occurs naturally in more than 200 species of mushrooms. Their capacity to produce visual and auditory hallucination led to recreational use beginning in the 1950s. But they've been known for much longer. Indigenous peoples have used psilocybin-containing mushrooms for ceremonial and healing purposes for centuries.

These unusual fungi first piqued popular curiosity in 1957, when an American banker and amateur mycologist named Robert Gordon Wasson travelled to Mexico and consumed psilocybin mushrooms as part of a traditional Mazatec ceremony. They were not criminalized at the time, and the story about Wasson's experience made the cover of *Life* magazine, then one of the most widely read publications in the United States. *Life*'s banner headline read "Seeking the Magic Mushroom," and the name stuck. Today, many know psilocybin mushrooms by this moniker.

Psilocybin mushrooms went on to become part of the cultural zeitgeist of the psychedelic 1960s, with some scientists recognizing that their ability to shift perception could have therapeutic uses. But academic research was stunted in 1971 when the United Nations Convention on Psychotropic Substances was signed. Magic mushrooms were criminalized, and research paused for decades.

Today, psilocybin mushrooms are making a comeback. Academic research has resumed in several countries, and the rules are beginning to change. Recent studies have already yielded promising findings about psilocybin's ability to treat depression and alcohol addiction. It has also been used to reduce anxiety about death in the terminally ill. ▲●■



**Kawashima is investigating whether psilocybin can mimic serotonin's effects in the brain and, if so, which mechanisms it uses. In the long run, this could help lead to the development of depression treatments that are more effective and faster acting than the drugs that doctors rely on now.**

The zebrafish larvae that Kawashima inspects under a microscope (above left) are roughly four millimetres long. Before Kawashima positions fish under his microscope (above), he attaches a pair of electrodes to the tail of each zebrafish to record its swim signals; these signals are used to infer zebrafish behaviour during brain scans. Kawashima uses a bespoke light-sheet microscope (left) to observe the activity of individual neurons across the brain in live zebrafish.

speed of several hundred frames per second, which amounts to a terabyte of data in half an hour. Kawashima analyzes these data with an artificial intelligence module that he programmed. And he has seen that the psilocybin appears to be increasing brain activity.

"When a fish is given psilocybin, it has a stimulatory effect, and its swimming patterns change," explains Kawashima, whose AI algorithm identifies these changes. This appears to align with the stimulatory effect that psilocybin has in humans, but he doesn't know yet exactly what is happening when this occurs.

Kawashima made another observation, one that aligns with serotonin's affects in humans. Psilocybin seems to reduce zebrafish anxiety. "It is possible to induce anxiety in zebrafish by dropping the temperature of the water around them," he says. "When this happens, the stressed fish typically begin swimming in a zigzag pattern. But fish that are given psilocybin are not affected by the stressors. This indicates that the psilocybin is potentially working in the fish's brain in a way that is similar to its effect on the human brain."

To further this research, Kawashima's lab has developed a technology called whole brain neural activity imaging, or PyZebrascope. This is an open-source platform that can record the neural activity from every single neuron in a zebrafish's brain. For this experiment, he uses fish that have been genetically modified so that they produce a protein when their neurons fire that allows for fluorescent capture. Kawashima uses the technology to determine the effects of psilocybin, but the approach could be used to image other aspects of subcortical function, such as locomotion and movement.

Kawashima's work also helps bridge areas of neuroscience research that often functioned separately. "In neuroscience, there are scientists who look at the molecular level, and there are scientists who think of the brain as a system with computational principles," says Rony Paz, one of Kawashima's neuroscience colleagues at Weizmann. "Historically, there has not been very much research that bridges them, but Takashi's research does this. He makes observations about the molecular machinery and uses them to look at the whole network as a complete system, and then uses computational techniques to understand what's happening.

"Until recently, we didn't have an animal model that allows these observations, but the fish model does. Moreover, the more models we have, the better. It is the only way to do neuroscience. You need to find the right model for the questions you have."

But even though the zebrafish model reveals much more about the inner workings of the brain, it will take time to understand the results. Brain function is complex, and Kawashima has begun collaborating with researchers who use rodent models to build an understanding of how his findings connect with the data they have collected about the neocortex.

"We need to figure out the underlying neural mechanism, and that could take years," he says. "Think of the brain's serotonin system like a giant tree with many branches. There are so many possible pathways, and it's very difficult to know which are most important. The brain is combinatorial, and the serotonin system doesn't work alone. Finding the parts of the brain it works with is not a trivial task because there are thousands of possible combinations. But because we have the ability to scan the entire brain, maybe we can reveal the right ones." ▲●■

By Simon Lewsen
Photographs by Boaz Perlstein

A typical 16th-century accounting book from Italy held together by a tacket hand-sewn binding. Sources like this from the special collections of Tel Aviv University's Central library and numerous other research libraries around the world convey important clues about the social, cultural, cognitive and intellectual lives of early-modern merchants

# THINK AGAIN

An examination of the evolution of mathematical practices reveals that accepted accounts of the great cognitive shift might not add up

**There's a familiar story about the history of modernity and mathematics — a story that Ray Schrire, a historian and Azrieli Early Career Faculty Fellow at Tel Aviv University, believes is mostly wrong.** It goes like this: in premodern Europe, people practised premodern math. Merchants and shopkeepers managed their books with Roman numerals, but these weren't numbers, at least as we understand them. They were more like codes or coordinates — a set of instructions that would tell you how to move beads around on an abacus or slide a token around a table.

For the average bookkeeper, mathematics was less a system of abstract thought than a set of practices. If you kept diligent records and used your abacus well, you could perform basic calculations and get the results you were seeking. But people had limited insights into what they were doing: *performing* calculations is different from *understanding* them. And medieval practitioners couldn't get their heads around exponents, infinite series or negative numbers. Tellingly, there is no Roman numeral for zero. Why would there be? You can't move zero beads from one abacus rung to another.

In the early-modern era (the period beginning in the late 15th century and ending with the dawn of the 18th century), everything changed, or so the story goes. Europeans abandoned Roman numerals for the Hindu-Arabic notational system we still use today, and they adopted written arithmetic, a practice imported from the Middle East. Some of the smartest thinkers in the West — Isaac Newton, Blaise Pascal, Gottfried Leibniz — began pushing mathematics into abstract territory, inventing entire disciplines that hadn't existed before. And thanks to the advent of global capitalism, members of the European professional classes suddenly found themselves calculating dividends, compound interest rates and insurance premiums. These new ideas quickly proliferated, making ordinary working people more sophisticated, more capable of abstract thought — in a word, more modern — than their medieval forebears had been. A commercial and industrial revolution gave rise to a cognitive one.

Or did it? Schrire isn't convinced. He has studied the documents left behind by early-modern professionals — poring over account books and bills of sale from merchants, shopkeepers, land surveyors and notaries — and been surprised by what he found. Or rather, what he *didn't* find.

If the advent of capitalism and industrial modernity really led to the advent of modern mathematics, not just among Europe's brightest minds but among its rank-and-file practitioners too, you'd expect written proof. You'd expect, for instance, to see evidence that everyday professionals were practising double-entry bookkeeping, a modern system of accounting where transactions are entered twice, once as a debit and once as a credit, to safeguard against arithmetic error. You'd expect to see records kept in Hindu-Arabic numerals rather than their Roman predecessors. And you'd expect to find seemingly endless piles of scrap paper on which bookkeepers, having abandoned the abacus, had written out their calculations in longhand.

**Schrire is not yet sure what to make of his finding. But it may have profound implications for how we understand European history — and even how we understand ourselves in the present day.**

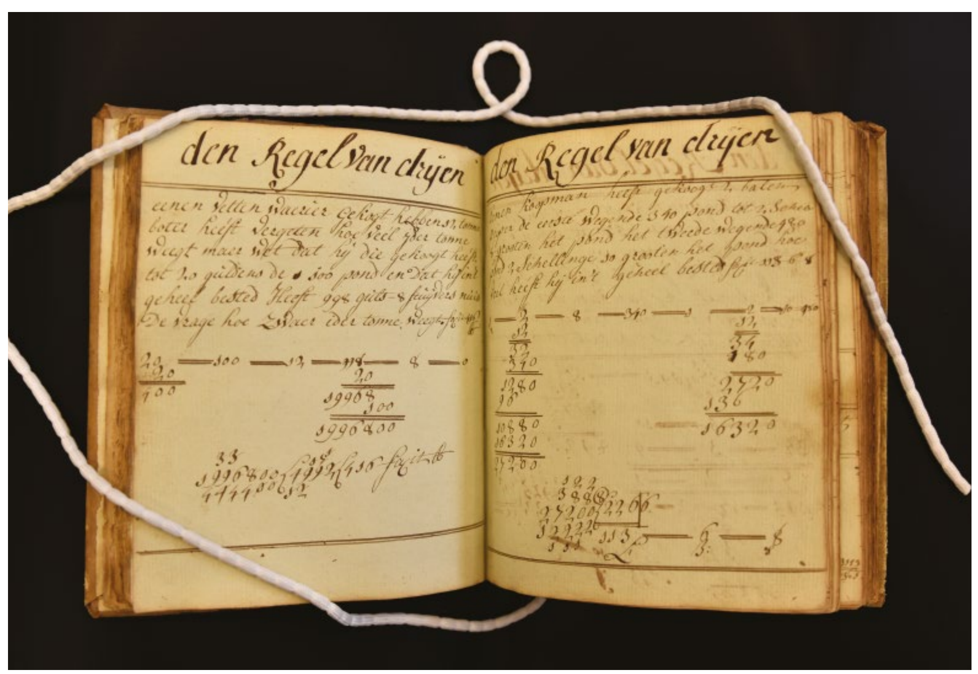
But Schrire hasn't seen any of this, at least not in sufficient quantities. "When we think about capitalism, we think about people doing stuff with numbers," he says. "A precondition for capitalism is that individuals are rational and can calculate the best ways of increasing their utility. But my research suggests that people simply weren't doing the things that historians say they should have done." He's not yet sure what to make of this finding. But it may have profound implications for how we understand European history — and even how we understand ourselves in the present day.

Schrire discovered his scholarly interests mostly by accident. As a master's student at the Hebrew University of Jerusalem, he attended a talk by Ayelet Even-Ezra, a professor in the history department who had reviewed late-medieval manuscripts and noticed the proliferation of horizontal tree diagrams: flow charts that map out a set of ideas via a series of forking paths.

Even-Ezra believed that these drawings, which hadn't appeared before the 12th century, could give us a glimpse into the late-medieval mind at work. Novel visualization techniques had surely given rise to novel modes of thought. Thanks to the advent of tree diagrams, she argued, ancient scholars had practised new forms of counter-factual reasoning, which they applied to theology, law and natural sciences. Schrire was fascinated by Even-Ezra's talk. She was doing the same basic task that all historians did — looking closely at archival documents — but she was asking questions that belonged more to cognitive science than to history: how do people think? How do their modes of cognition determine their understandings of the world? "I went to her office," Schrire recalls, "and basically said, 'I want to do whatever you're doing.'"

He decided to devote his graduate research to book history and human thought, although he didn't have much of a game plan. During the last year of his MA and the first two years of his PhD, he split his time between Israel and California's Bay Area, with his partner (now wife) Ella Elbaz, then a PhD student in the Department of Comparative Literature at Stanford University. In the United States, he frequented the rare books collections at the University of California, Berkeley. "I had no idea what I was doing," he says. "I would page up old books at random, hoping for insights into cognition."

Tel Aviv University historian and Azrieli Early Career Faculty Fellow Ray Schrire carefully scrutinizes an early-modern accounting book for traces of arithmetical practice exposed through the types of numerals used and kinds of calculation errors made.





A 17th-century student's notebook from the Netherlands (above right) attests to the types of training received in early-modern business schools, as well as to the performative aspect of bookkeeping. A reckoning token minted in 16th-century Nuremberg (above left) that was used for performing actual calculations across Europe. The image on the token shows an early-modern merchant engrossed in such arithmetical activity. These and other sources (top) suggest to Schrire "that people simply weren't doing the things that historians of mathematics say they should have done."

Soon, he found an intriguing specimen: a classic Latin grammar textbook that had been used in Britain from the Middle Ages to the early 19th century. The owner of this particular copy, a 17th-century pupil, had filled the pages with marginalia. Schrire didn't know Latin, but he nevertheless grasped the significance of what he was holding. "I wasn't interested in content," he says. "I wanted to understand *how* this student was thinking, not *what* they were thinking about." The annotations were more compelling to him than the text itself.

This discovery set him on a new scholarly quest, which formed the basis for both his MA and doctoral research. Schrire learned Latin and tracked down as many copies of the grammar book as he could: over 200, of which roughly 80 per cent had annotations. He also studied the diaries of schoolchildren and teachers, pedagogical guides and classroom floorplans. Collectively, these texts pointed to a profound shift in culture and cognition, beginning in the 16th century. These social changes were the subject of several of Schrire's published research papers, and will be the focus of his first scholarly monograph.

The cultural shift he writes about coincides roughly with the end of the Middle Ages. Medieval pedagogy, Schrire theorized, was based in rote memorization, with teachers reading aloud to bookless students who were likely standing in rows. But with the advent of the Renaissance, schoolroom practices changed. "Books went from the hands of the teachers to the knees of the students," Schrire explains. Not only did students have their own texts, they also now sat at desks

**'The thing with PhDs,' Schrire says, 'is that we always look at the world through a tiny peephole.' He wanted to expand this aperture by seeking out texts that had little to do with his immediate interests.**

and annotated the pages with conjugation tables, translations and relevant lines from Cicero and Virgil. While medieval students had memorized Latin, their Renaissance successors had internalized both its structure and its literary history. "Renaissance humanism reshaped pedagogy," says Schrire. "Comprehension became the new gold standard of learning."

In some respects, Schrire's findings were counterintuitive. They implied that, in the medieval era, schoolchildren had somehow kept Latin alive without actually comprehending the language: they often spoke without even knowing what they were saying. His work also broadened our understanding of Renaissance humanism. The shift to a humanistic worldview, Schrire suggested, was as much about cognition as it was about morals.

Schrire's recent findings on numeracy are more contentious, though. They suggest that a cognitive revolution in Europe — the advent and proliferation of modern mathematics — didn't really happen, at least not when we thought it did. As with his previous project, he came across these findings mostly at random. While researching Latin pedagogy, Schrire continued to visit rare books rooms and to arbitrarily call up books. "The thing with PhDs," he says, "is that we always look at the world through a tiny peephole." He wanted to expand this aperture by seeking out texts that had little to do with his immediate interests. Financial documents, he quickly discovered, offer insights into a cohort of people whom historians usually neglect: Europe's ascendent entrepreneurial classes, who were not in the right social class to study Latin in grammar school.

For Reviel Netz, a classics professor at Stanford, it is Schrire's willingness to go beyond his intellectual comfort zone that sets him apart from his peers. "People who study book history usually pick their subject area because they don't like numbers," says Netz. "Ray is travelling into uncharted territory, and he's going to make a wonderful contribution. We need more humanists who aren't scared of mathematics."

Schrire doesn't yet have a thesis for his new project. He wants to visit many more libraries and peruse many more archival books before drawing substantive conclusions. What he does have is a set of tantalizing questions and provisional answers. If, during early modernity, ordinary professionals weren't doing modern math, what were they doing? How did they conceptualize numbers? And how did early capitalism, with its banks, brokerages and trading floors, survive?

One answer to the latter question — which Schrire considers far-fetched but perhaps not so outlandish that it can be ruled out immediately — is that the professional classes were more sophisticated than the historical record would make them out to have been. Perhaps they were doing advanced arithmetic in their heads. A less ennobling but more credible answer is that the early-capitalist period was chaotic, an era in which price signals regularly misfired, suppliers constantly over- or under-produced, lenders sooner or later went bankrupt, and investors and insurers frequently got stiffed.

"Perhaps people simply weren't that rational," says Schrire. "Perhaps they were trying their best and hoping things would work out." Early capitalism, by this account, was a chaotic system sustained by subpar math.

A third answer is that the system functioned passably well because it was somehow better than the sum of its parts. If people were faking knowledge of modern mathematics, perhaps faking was good enough: the mere façade of rationality can be as compelling as the thing itself. This argument at first seems implausible until one applies it to the present day. True, in certain respects, the present really is different from the past. Today, we *actually* practise modern mathematics — primary school students use Hindu-Arabic numerals and high school students write algebraic equations in longhand — although Schrire suspects that these trends took hold later than one might suppose, perhaps in the 19th century. But even if the math of today is more sophisticated than the math of the past, is it really as sophisticated as the commercial and financial systems in which we operate? Or are we fumbling through life, just as our early-modern forebears likely did?

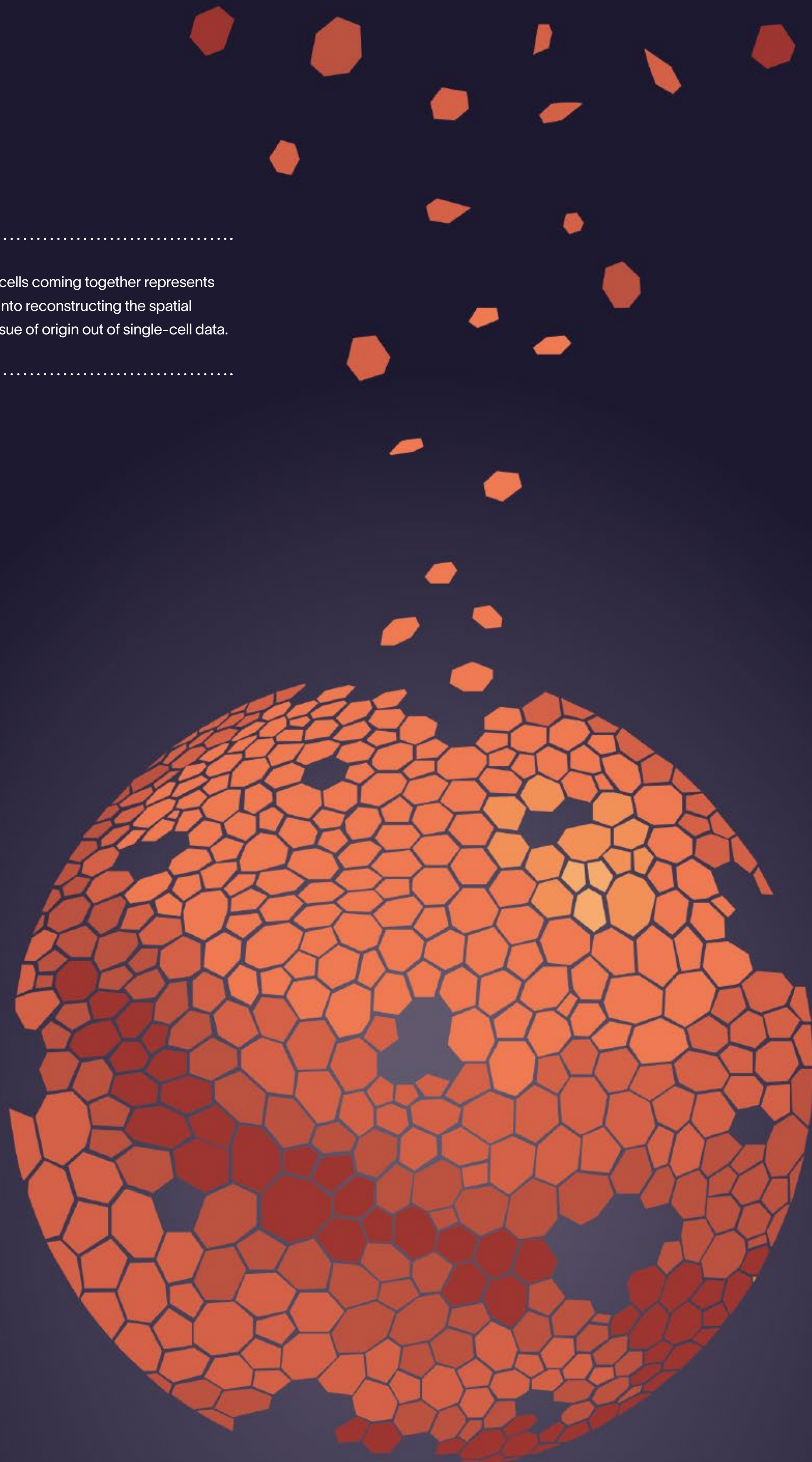
**'People who study book history usually pick their subject area because they don't like numbers. Ray is travelling into uncharted territory, and he's going to make a wonderful contribution. We need more humanists who aren't scared of mathematics.'**

Over the past decade, for instance, many ordinary people across North America and Europe have made good money in the housing market. But when a person buys a house, do they consider every possible variable to ensure they're getting the right price? Or do they act on instinct and hope for the best? And how many people deeply understand the insurance policies they hold and can say with certainty that they're getting a fair deal? Schrire acknowledges that, like most insurance buyers, he basically does what his advisor tells him to do. "There aren't a lot of rational thoughts going through my mind," he says. "If there were, I would probably cut my insurance in half."

Schrire's work hasn't led him to definitive conclusions, but his initial suppositions are humbling. His research suggests that in early modernity — and maybe in our time, too — rationality is and was a delusion, sustained only by our collective willingness to believe in it.

"Why do people buy and sell?" he asks. "We would like to find a model that accounts for this behaviour. Contrary to conventional wisdom, I'm pretty certain that such a model can't explain capitalism in the past. I'm not even sure it can explain capitalism today." ▲●■

Studying the afterlives of early-modern merchants requires dealing with the material objects they left behind. Bookkeepers used objects like this reckoning token to perform calculations, but these tokens are not well-suited to complex mathematical concepts, and those who used them might not have had a deep understanding of the math they were performing.



A globe composed of cells coming together represents Mor Nitzan's research into reconstructing the spatial configuration of the tissue of origin out of single-cell data.

ILLUSTRATION BY REO F.

By Dan Rubinstein
Photographs by Boaz Perlstein

# LOOKING FOR LOST LAYERS OF INFORMATION

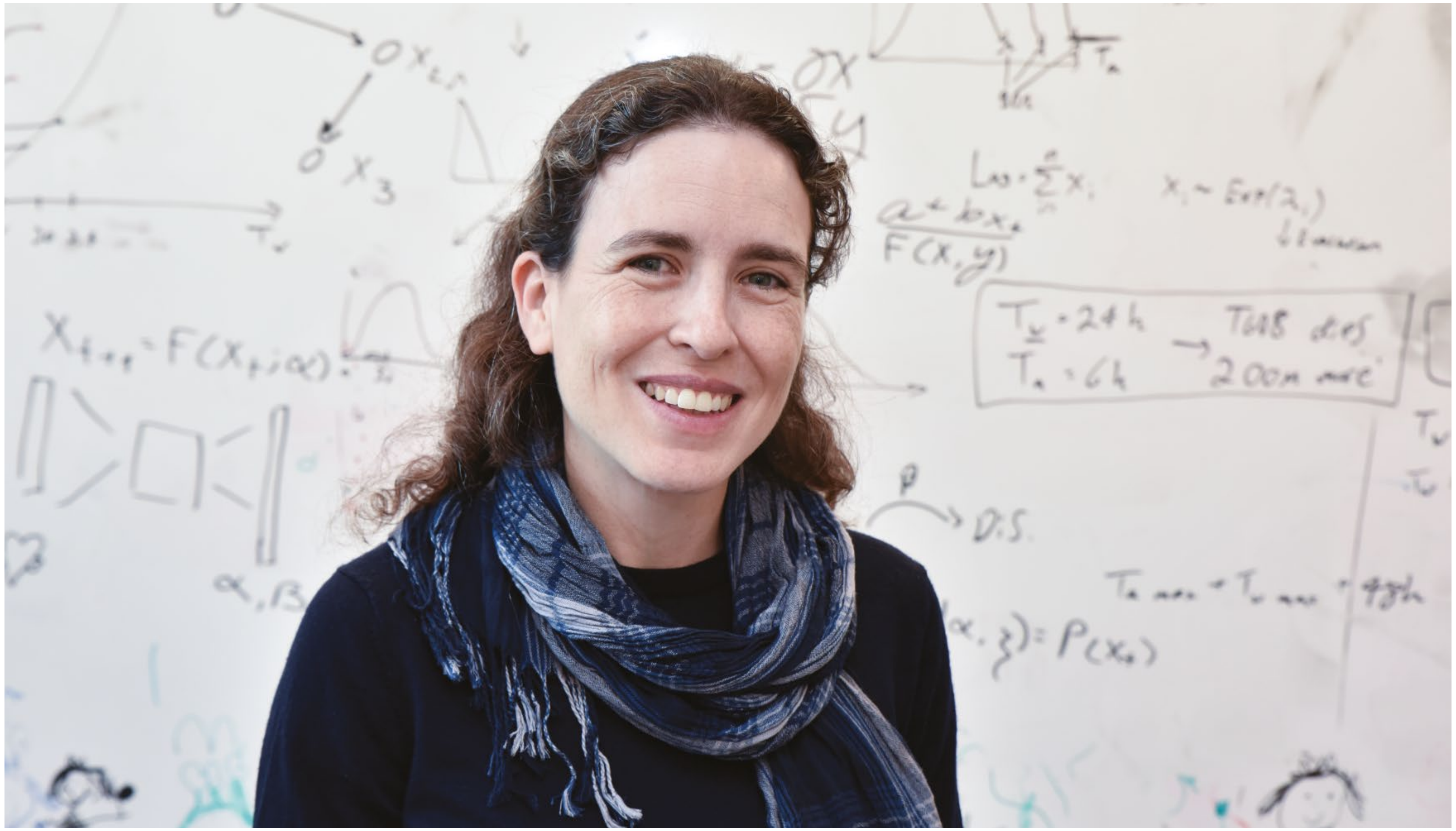
Can we computationally recover spatial and temporal data about cellular behaviour to better understand complex biological systems?

**Revolutionary advances in experimental biology over the past decade have given researchers the ability to take an in-depth look at individual cells. In many ways, this represents a huge scientific leap forward.**

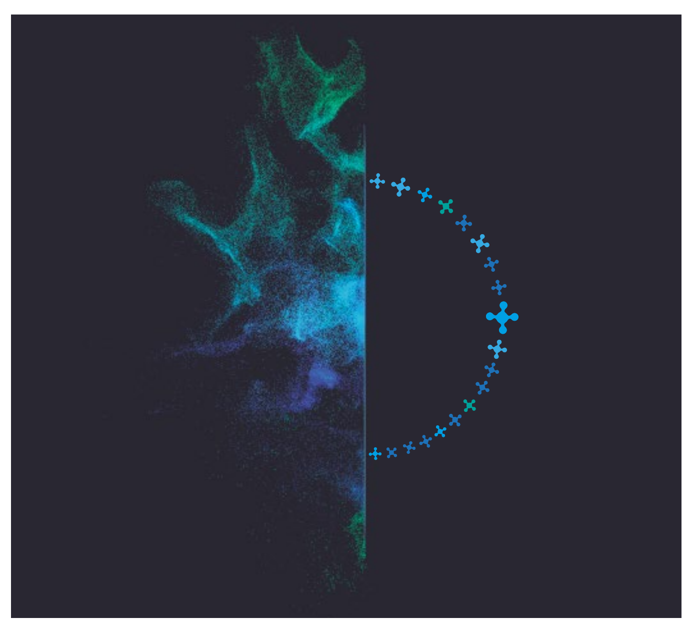
Consider the role of ribonucleic acid, or RNA, a molecule that's central to the process of converting the genetic information stored in our DNA into proteins, which are the building blocks of our cells and help carry out various functions. When a gene is active, it is transcribed into RNA; because biologists now have the ability to measure the amount and type of RNA molecules present inside a cell, they can determine which genes are active. This is giving research groups around the world access to a rapidly expanding collection of datasets through which they can study the behaviour of individual cells in diverse tissues, organisms and biological contexts, such as health and disease.

To conduct single-cell RNA-sequencing experiments, however, one must first dissociate cells from their tissues of origin. This means you can only measure cells once and can't follow their dynamics.

"You lose any spatial or temporal context you originally had," says Mor Nitzan, a researcher in the School of Computer Science and Engineering, Racah Institute of Physics and Faculty of Medicine at the Hebrew University of Jerusalem (HUJI). "You lose all of the information you could have had about how the tissue was organized, which cells were next to one another, how they communicated, even things like what the 'body plan' was for an animal in the early stages of development.spatially.



**‘There are a lot of very fundamental questions in biology that require access to these layers of information.** In fact, many of the most interesting questions in biology and science in general have to do with spatial and temporal context.’



DESIGNED BY PEARLCOM

An Azrieli Early Career Faculty Fellow at the Hebrew University of Jerusalem, Nitzan (above) manipulates biological signals derived from single-cell data based on “topological priors,” transforming the cloud of data on the left-hand side of this representation (left) into an easier-to-decipher configuration of cells.

“There are a lot of very fundamental questions in biology that require access to these layers of information,” she continues. “In fact, many of the most interesting questions in biology and science in general have to do with spatial and temporal context.”

In other words, while understanding the intimate genomic details of individual biological building blocks is a cornerstone of contemporary research, deciphering the organization and dynamics of cell *populations* could hold a key to fundamental knowledge and, ultimately, critical medical applications.

Nitzan, an Azrieli Early Career Faculty Fellow, is learning how to computationally recover the layers of data that are lost in experiments. Operating at the interface of computer science, physics and biology, with an injection of abstract mathematics, she uses computational tools, informed by dynamical systems theory and machine learning, to map the arrangement and trajectories of cells. She looks at their interaction patterns and at the division of labour within tissues, as well as the way in which cells encode information and self-organize into complex three-dimensional structures. “My group is tackling some of the core computational challenges in single-cell research,” she says. “We are using this exponentially growing, complex data to ask and answer questions about the collective behaviour of biological systems.”

Before beginning her undergraduate studies, Nitzan struggled to decide between pursuing physics or medicine. She chose the former — with minors in mathematics and cognitive science, at HUJI — because she was interested in basic questions about how the world works. But even though she stuck with physics, Nitzan knew she wanted to eventually use this background to address more applied questions. So she broadened her lens during her MSc and doctorate, which she completed at HUJI as well, incorporating computational biology and zeroing in on the interplay between structure and dynamics in multifaceted biological networks. That research, the latter supported by an Azrieli Graduate Studies Fellowship, was the groundwork for the work she’s doing today.

“During my master’s work, I started asking questions about collective phenomena,” says Nitzan, “about how many small, dynamic systems come together and interact with each other, in a networked way, and display complex behaviours that aren’t possible for individual systems.” She realized, after moving on to her PhD with professors Hanah Margalit and Ofer Biham, that it would be powerful to not only model and test these questions in a “bottom-up, physics-based” way, but also to apply computer science techniques and use available data to inform her models — to combine methodologies and start looking at the bigger picture. Nitzan further developed this amalgamated approach during a postdoctoral fellowship at HUJI and the Broad Institute of MIT and Harvard in 2017 with professors Nir Friedman and Aviv Regev, and a year later as a John Harvard Distinguished Science Fellow and James S. McDonnell Fellow at Harvard. When she returned to HUJI in 2020 as a faculty member, it formed the backbone of her research.

Today, leading a group of about 10 researchers, from undergraduates to postdocs, and equipped with a European Research Council grant worth nearly 1.5 million Euros, Nitzan remains focused on developing computational methods to infer the underlying structure and function of biological systems and formulate mathematical models drawn out from countless biological details. Although they are abstract representations of physiological systems, these models aim to simplify and help researchers make sense of elaborate phenomena. For instance, how do cells discriminate between different environments and prepare for future challenges they may face? How do they process complex information? And how do cells divide labour to perform collective tasks?

“They’re not individual units,” says Nitzan. “They have to work together, transfer information and self-organize into multicellular 3D structures with different functions. We want to find out how cells make these processes robust and efficient.”

Nitzan and her students are working on a spectrum of projects, ranging from theoretical research to collaborations with experimental biologists. But most of their work falls somewhere in the middle and starts with a sprawling array of data. And computationally recovering the spatial configuration of cells within their tissue of origin is only step one.

The greater task, Nitzan explains, is disentangling layers of spatial and temporal information from each other, *manipulating* layers (enhancing one, filtering out another) and virtually shifting cell states across space and time. This method — in effect, conducting virtual experiments, using mathematical models — allows her, for example, to predict cellular response to the perturbations of drugs. Moreover, even if a cell has only been exposed to one drug, the same approach can be used to infer how that cell will respond to a different drug, or the same drug administered at a different time of day.

"We can computationally or virtually shift cells across time, across space, across perturbations, to get predictions on how they'd behave and what the response would be," she says. "And we can do so in a much more scalable way than what would be possible in biological experiments, which have a lot more limitations in terms of time and budget, beyond the fact that some experiments are simply not feasible."

**'I started asking questions about collective phenomena, about how many small, dynamic systems come together and interact with each other, in a networked way, and display complex behaviours that aren't possible for individual systems.'**

One of the holy grails of this type of research involves cellular populations that are not healthy, as is the case with cancer. Pharmaceutical researchers want to discover which drugs to introduce to make these cells or tissues healthy. A better understanding of the common cellular mechanisms that drive the progression of cancer and other diseases, and the ability to accurately predict which mechanisms might be more vulnerable to interventions, says Nitzan, "will allow you to design effective treatments for different types of diseases and even to tailor them to individuals, thinking about this ambitiously, for particular conditions.

"I'm very excited about the ability to do something that I can connect back to the real world. I love the abstract, mathematical aspects of the research, but it is also very important for me to think and contribute to an understanding of natural systems, specifically in a biological or medical context."

Nitzan thinks "deeply and carefully about the questions before her and always manages to put her finger on the crux of the problem," says collaborator Klaas Mulder, a researcher at Radboud University in the Netherlands whose lab investigates the mechanisms underlying human epidermal stem cell renewal. "The work she and her co-workers are doing can certainly have an impact on health applications and interventions. Yet I think what will actually make a difference for the future is the fact that the approaches her lab develops empower other researchers to address their challenges in new and unexpected ways. That, I believe, is the real influence Mor has, not only on the single-cell genomics field, but far beyond that through the uptake of single-cell approaches and the computational tools by much wider scientific communities."

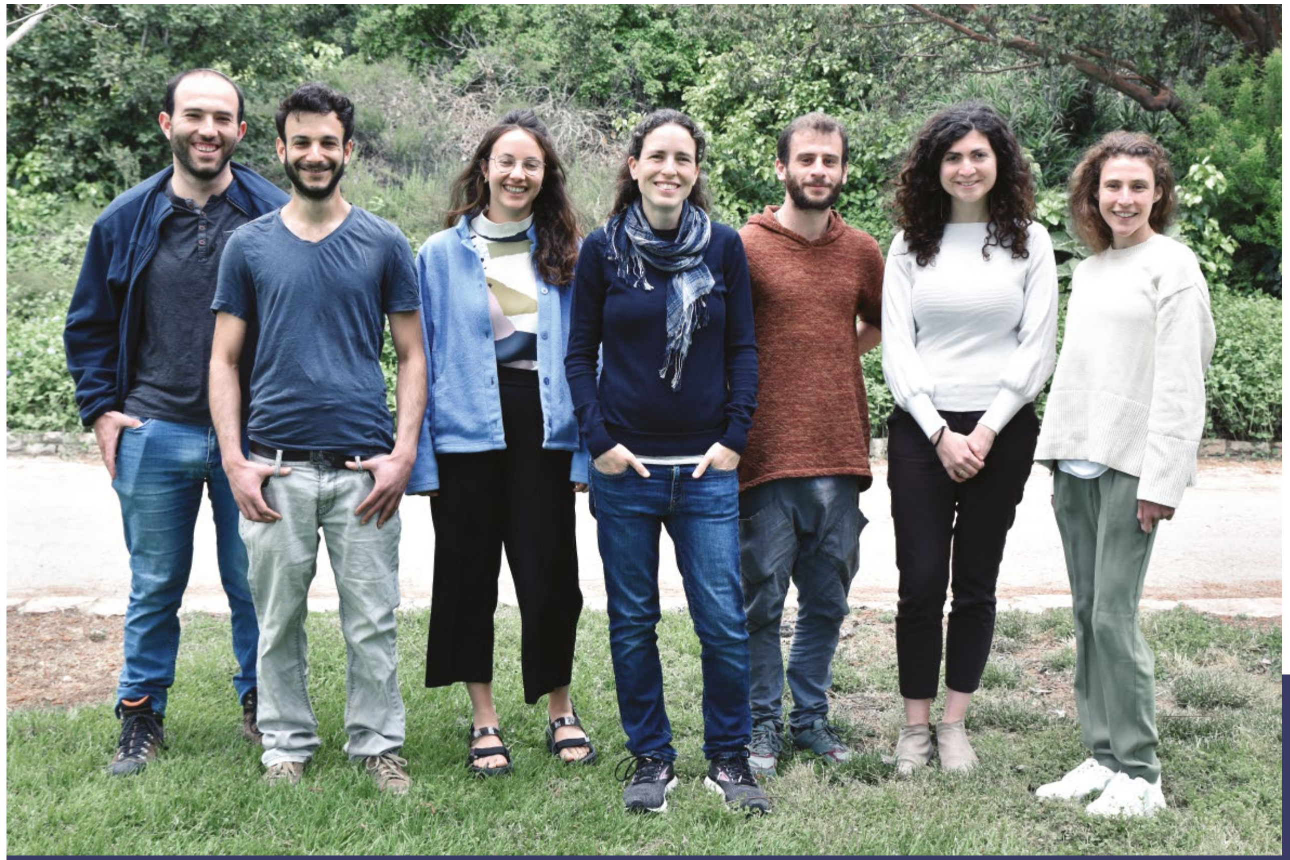
The abundance of single-cell data that Nitzan has at her disposal represents both an opportunity and a challenge. It keeps flowing from research projects around the world, and much of it can be downloaded with the push of a button. But it's "noisy" and confusing, she says, and it can be challenging to transform it or use it to answer the questions she's really interested in.

This is by no means a problem that's unique to her field. Human beings have to constantly disentangle layers of information to make decisions, and we are increasingly tapping into modelling and machine learning to push through that data bottleneck. "The questions I'm asking are basic, and there are interesting analogies to how our minds work and how we can process huge amounts of information," says Nitzan. "It's the same for biological data and what's meaningful to know about cellular populations. It's fine that you can measure the expression of every gene in a cell for hundreds of thousands of cells experiencing hundreds of different conditions, but to answer fundamental questions and make predictions that are relevant for medical applications, you don't need all these individual bits of information — you need to be able to *integrate* all that complex information into meaningful nuggets."

Thinking about this puzzle and trying to come up with the right mathematical language to describe and simplify complex systems is the most engaging aspect of this work for Nitzan. She loves the creativity. ("Although most of the technicalities of the math involved go beyond my level of comprehension," says Mulder, "Mor always ensures that we understand what we need to be able to assess the results.") But now that she's a principal investigator, Nitzan has another dynamic system to navigate — the community of students and postdocs in her lab. She is busy providing mentorship and guidance, not to mention teaching, writing papers and grant proposals, and trying to maintain some work-life balance.

"I'm never up to speed with everything I want to do," she says. "It's always overflowing. But I'm dedicated not only to the research itself, but also to steering the group toward creative, effective and successful directions and making sure that everybody is supported in a way that's tailored toward helping them find and pursue their scientific passion."

In her lab and in her research, Nitzan pays attention to individual people and individual cells, but she knows the real breakthroughs will come from the community as a whole. ▲●■



Members of Nitzan's research group include (left to right) undergraduate researcher Yehuda Mescheloff, MSc student Rotem Tal, MSc student Michal Erez, Nitzan, and PhD students Hagai Rappeport, Sima Dubnov and Zoe Piran.

## IGNITING THE VOLUNTEERISM GENE

**When Mor Nitzan was a PhD student in physics and computational biology at the Hebrew University of Jerusalem (HUJI), she was an Azrieli Graduate Studies Fellow.** The fellowship opened several different doors for her. Beyond the generous funding, it provided a community of support. It gave her a group of young academics to talk to and bounce ideas off, conversations that helped shape the direction of Nitzan's research journey. The fellowship also had a volunteer component, which prompted her to co-start a program, A Taste of Science, that introduces high school students in Israel to role models in different fields and encourages them to consider university studies and careers in science.

Nitzan handed that program over to HUJI when she left for a postdoc in the United States, but it has remained active over the past half-dozen years, showing thousands of high school students the opportunities they might have. And despite her own demanding career, Nitzan hasn't lost her zeal for educational outreach and volunteer work that the Azrieli Fellows Program awoke. She organizes and is involved with a range of activities focused on women in science, including events designed to prepare female PhDs for postdoctoral positions, and serves as the gender equity coordinator in HUJI's School of Computer Science and Engineering as well as a member of the university's overarching gender equity committee.

"There's an underrepresentation of women in science, which is especially apparent in fields such as physics and computer science," says Nitzan. "One of the most problematic aspects of this is that the percentage of women decreases as you get to advanced stages of an academic career, to PhDs and postdocs and faculty positions."

Increasing the diversity of role models is one way to help close this gap. Making women and other underrepresented groups aware of their opportunities — and providing or pointing the way to specific supports — is another. So is changing the system itself, to level the playing field. And it's not just about equity for the sake of equity. Diversity in science is important because successful research needs access to the vast array of brain power out there in the world.

"Any improvement makes the university better and the research community stronger," says Nitzan. "It's true for my scientific community and the scientific community at large. And it's not just about women — it's a general statement about diversity and the ability to draw from the entire population and not only subsets of it." ▲●■

# NEUROSCIENCE EXCELLENCE IN ISRAEL

## Breakthroughs from an international neuroscience research powerhouse

**The study of the nervous system, primarily the brain, has long captivated the scientific community.** Israel has established itself as a leader in this realm, making substantial advancements in research and innovation and attracting global scientific recognition in terms of funding and citations. From 2007 to 2022, for example, the European Research Council supported 599 neuroscience projects, 58 of which were Israeli, putting the country in fifth place despite its small size. Israel also achieved a 10th-place global ranking in neuroscience citations per document from 1996 to 2021, averaging 39.09 citations, as per Scimago (considering only nations with over 1,000 published papers). Here is a summary of significant contributions made by several Israeli neuroscientists spanning diverse areas: pharmacological breakthroughs, theoretical insights into brain function and therapeutic innovations.

## PARKINSON'S TREATMENT REVOLUTION

Both the monoamine oxidase B inhibitors l-deprenyl (selegiline) and rasagiline (Azilect) were discovered by Prof. **Moussa Youdim** from Technion–Israel Institute of Technology. These two anti-Parkinsonian drugs are widely used worldwide and help millions of patients daily. Another treatment for Parkinson's disease was initially studied in the U.S. by Prof. **Hagai Bergman** from the Hebrew University of Jerusalem and the city's Hadassah Medical Center during his postdoctoral training. Bergman pioneered this deep brain stimulation (DBS) approach via surgically implanted permanent electrodes in Israel. DBS releases adjustable electrical pulses that block tremors, dramatically improving the lives of numerous Parkinson's patients.

## STRESS NEUROSCIENCE

The research of Prof. **Hermona Soreq**'s group from the Hebrew University of Jerusalem has made groundbreaking contributions to the understanding of the molecular mechanisms underlying neurological disorders, particularly those involving acetylcholine signalling and stress reactions. Additionally, the president of the Weizmann Institute, Prof. **Alon Chen**, has significantly improved the understanding of stress mechanisms. His group's studies at Weizmann and Munich's Max Planck Institute focus on elucidating the molecular and neural mechanisms that regulate the stress response. They have significantly advanced our comprehension of stress-related disorders and hold promise for developing novel therapeutic interventions.

## THEORETICAL INSIGHTS INTO NEURAL SYSTEMS

Prof. **Haim Sompolinsky** from the Hebrew University of Jerusalem pioneered computational neuroscience theories, advancing our understanding of cortical dynamics, sensory processing, motor control and memory. His group's main contributions have been in human visual neuroscience and the neuronal underpinning of spontaneous behaviour. Prof. **Rafael Malach** from the Weizmann Institute of Science has made major insights into the neural basis of how humans create visual images, spontaneous thoughts and memories. His discoveries uncovered the organization of human visual areas in general and recognition processes in particular, and pioneered the use of fMRI to clarify how human brain regions contribute to perceptual and cognitive functions.

## SLOWING THE PROGRESS OF ALZHEIMER'S DISEASE

Alzheimer's disease initially involves the loss of the neurotransmitter acetylcholine, which produces neurons in deep brain nuclei. Prof. **Marta Weinstock-Rosin** from the Hebrew University of Jerusalem is the inventor of rivastigmine (Exelon), a palliative medication for Alzheimer's. It temporarily limits memory loss by inhibiting acetylcholinesterase, an enzyme that breaks acetylcholine down. Recently, Prof. **Michal Schwartz** from the Weizmann Institute of Science discovered the key role played by the immune system in repair processes within the brain, as well as its importance to brain functioning in health and the link between the decline in immune system function and dementia.

## THE NEUROBIOLOGY OF HUMAN ATTACHMENT

Prof. **Ruth Feldman** at Reichman University has made significant contributions to understanding the social brain. She discovered the neural basis of social interaction between parents and infants, for example, and found hormonal evidence for the importance of touch to infant development. She has also demonstrated that interventions aimed at improving parenting behaviours can have a powerful impact on childhood development, including in high-risk populations. Prof. **Mario Mikulincer**, also at Reichman, demonstrated the correlation between secure attachment in infancy and better social relationships later in life, such as romantic relationships, and its positive impact on stress coping, cognition, health outcomes and emotional regulation.

# PIECING TOGETHER THE PTSD PUZZLE

How deconstructing trauma could help doctors come up with more targeted treatments

**There is a lot we don't understand about trauma. Two people work side by side to pull bodies out from piles of concrete, steel and dust. One can head home, hug their loved ones and go back to their routine. The other will find themselves, months later, shaking and crying as their mind keeps replaying the horrific images.**

We don't have a clear roadmap for treating post-traumatic stress disorder (PTSD), either. Exposure therapy, in which people recount traumatic events in a calm state of mind, might work. But it might not. The same holds for cognitive behavioural therapy, meditation and other interventions.

Then there's the trauma of childhood abuse, which people may not even realize they're carrying until decades later. How can you treat something that you can't even identify?

Shilat Haim-Nachum, a postdoctoral fellow in Columbia University's Department of Psychiatry, knows the mysterious, frustrating impacts of trauma first-hand. When her mother died of cancer when she was 16 years old, Haim-Nachum and her four siblings experienced "five different trajectories of trauma," she says. Since then, she's been driven to help people figure out the unique ways in which trauma affects their lives and how they can heal.

"PTSD is like this big puzzle that I keep trying to add pieces to," says Haim-Nachum, who is currently helping lead three studies to fill in this picture at Columbia's PTSD Research and Treatment Program. Her work builds on research she did as an Azrieli Graduate Studies Fellow, from 2018 to 2022, during her doctorate at Bar-Ilan University in Ramat Gan, Israel.

In her PhD studies, supervised by Einat Levy-Gigi, Haim-Nachum explored how "cognitive flexibility" could partly explain why some people develop PTSD and others don't. She ran studies involving firefighters and trauma-exposed students, in which participants played video games. In one game, they would open a box with an image of a car on it and discover a bomb. Later, they would see the same box, but with an image of a hat on it. Some people reacted differently to the box based on the new illustration; those who were able to adjust their thinking about the outcome of the box based on this change were defined as more cognitively flexible.

By Wendy Glauser
Photographs by Chris Taggart

Shilat Haim-Nachum, a postdoctoral fellow in Columbia University's Department of Psychiatry and a former Azrieli Graduate Studies Fellow at Bar-Ilan University, is doing research to help develop novel treatment options for PTSD and other forms of trauma. Looking at the brain scans (opposite page) of patients could one day help determine the degree of trauma people are experiencing and help improve treatments.

Overall, in her experiments, people who had symptoms of PTSD were much less cognitively flexible than those who didn't have symptoms. "People experiencing PTSD were less likely to open the box that was originally associated with a negative outcome," she says, "even if it was different from the original box."

The importance of cognitive flexibility hit home for Haim-Nachum when she spent time with firefighters in Israel as part of a volunteer activity. On the job, they would talk about sports and make jokes immediately after rescuing people, sometimes from gruesome scenes.

"Distraction was the best and most efficient way for them to cope at the time," she says. "But if they were distracting themselves to avoid connecting emotionally with their families, that wouldn't be adaptive. Flexibility is about the ability to change your behaviour according to that specific situation."

Yuval Neria, a clinical medical psychology professor at Columbia and Haim-Nachum's mentor, says that her combination of "motivation and talent" is rare and that her ability to measure cognitive flexibility in people exposed to trauma could guide novel treatment options.

"The idea that cognitive capacities in the brain can be amenable to intervention is compelling," says Neria. "We typically employ our interventions toward emotional capacities." In other words, part of effective PTSD treatments might lie in changing how people think, not just how they feel.

Still, cognitive flexibility is just one aspect of PTSD, says Neria, and while it may play a large role in some cases, it could have a smaller bearing on others. "There are numerous ways in which one meets criteria for PTSD, which makes the patient population very heterogeneous," he says. As Neria explains, research being done by Haim-Nachum and others he's mentoring could move the field closer toward identifying different types of PTSD and tailoring treatments to them.

Although there are myriad causes of PTSD, childhood abuse is quite a common cause, according to Haim-Nachum. Many people who carry trauma from childhood don't seek treatment until years later. Some don't seek treatment at all. Guilt and shame, at least partly, explain why.

"There's so much shame when it comes to being hurt by the people who are supposed to take care of and protect you," says Haim-Nachum, "and it kind of twists the way they perceive themselves and others and the world."

This explanation is affirmed by the Toronto-based Centre for Addiction and Mental Health, which says, "Many people don't know that abuse can affect their lives many years later, and do not connect the common effects of trauma to experiences of childhood abuse." The U.S. federal government's Center for Substance Abuse Treatment, meanwhile, notes that people "often don't recognize the significant effects of trauma in their lives; either they don't draw connections between their trauma histories and their presenting problems, or they avoid the topic altogether."

To encourage people to recognize how childhood trauma is affecting their lives and help them feel safe enough to seek help, Haim-Nachum is leading a study with Neria and Doron Amsalem, another Columbia psychiatrist, using a brief video intervention aiming at reducing the stigma around childhood trauma. The video features an actor who describes how childhood abuse affected her. "It took me a while to understand what I went through was truly wrong," says the actor, sitting on a staircase and looking at the camera. "There were even times where I felt, 'There must have been something wrong with me.'" She explains why she sought help and how insights from therapy helped her build the life she has today, with a fully supportive partner and the awareness that she's part of a "community of people" who have overcome similar adversity. (For study participants who identify as male, another version of the video features a male actor.)

Participants — all of whom self-identify as having experienced childhood trauma — will be randomly assigned into two groups to determine whether the video has an effect on their self-stigma levels. One group will watch the intervention video; the control group will watch a "day in my life" video in which the same actor describes their life in general, without talking about overcoming trauma. Haim-Nachum is using questionnaires and scales, filled out by each participant, to measure the levels of guilt, judgment and shame people feel about their personal traumas before and after watching the video, as well as 30 days later. She'll also be asking participants about their willingness to seek treatment — and providing referrals for those who request help — to determine whether the video has a positive impact. (An informed consent process explains that the video may involve an actor talking about how trauma has affected them. All participants are given phone numbers they can call if they experience emotional distress.)

While other research found that videos can reduce stigma among people with various conditions, such as depression, this is the first study Haim-Nachum is aware of that applies the technique to self-stigma stemming from childhood trauma. Given that so many children around the world experience abuse, Haim-Nachum's study could have a significant impact. If the intervention proves successful, short videos to reduce internalized stigma could be introduced in doctors' offices, campus orientations and other settings.

Determined to look at as many different approaches to treatment as possible, Haim-Nachum is collaborating with Tel Aviv University psychology professor Amit Lazarov and Neria on another study that, as she puts it, "has a long and fancy name — gaze-contingent music reward therapy — but it's really about helping people with PTSD shift their attention from negative cues to neutral ones."

Participants with PTSD will look at 16 faces, half with threatened expressions and half with neutral expressions. For one of the intervention groups, music that the participants have identified as pleasurable will stop playing when the eye-tracking technology detects they are fixating on the threatened expressions. For the other intervention group, music will play when the study participants fixate on the threatened faces. The idea here is that pairing music with positive and negative stimuli can somehow change how the brain responds to the latter.

**'The idea that cognitive capacities in the brain can be amenable to intervention is compelling. We typically employ our interventions toward emotional capacities.' In other words, part of effective PTSD treatments might lie in changing how people think, not just how they feel.**

"We know that people with PTSD have this overgeneralization of fear and negative emotions and thoughts, so they tend to focus on negative cues," Haim-Nachum explains. While the project is "a bit ambitious," she says, it's aiming to examine whether training the brain to focus away from negative stimuli could be linked with reduced PTSD symptoms.

These projects allow Haim-Nachum to take a clinical look at the consequences of trauma. But she also interviews people with PTSD as part of her research at Columbia, and their stories are intense. The veterans, first responders and survivors of childhood abuse require exhaustive treatment, with varying degrees of effectiveness.

Yet Haim-Nachum remains hopeful. "In my intake interviews, I'm sometimes meeting with people in their 70s and they share with us that they've been through so many different treatments, and it sucks, right? Because clearly, something isn't working for so many people," she says. "But it's also hopeful to see that, even after so many years, people don't give up on themselves. They keep that desire to not only survive, but to have a meaningful, hopeful life. Humans are really resilient." ▲●■

## CAN BRAIN SCANS REVEAL PTSD PATTERNS?

**One way that Shilat Haim-Nachum is working to better understand different presentations of PTSD is through brain scans.** She and neurobiology researcher Xi Zhu at Columbia are analyzing the MRIs of people who have been exposed to various types of trauma — by force of nature, by accident, or by the hands of others, and at different ages, from childhood to later in life. She will look at patterns in connections between the amygdala (the fear centre of the brain), the hippocampus (a vital brain region for learning and memory) and the medial prefrontal cortex, which is involved in processing threats in a more cognitive or high-level way than the amygdala. (More activity in the medial prefrontal cortex has been associated in research with fewer PTSD symptoms.) She will also test brain networks related to reward processing, especially the nucleus accumbens, because people with PTSD are generally less reactive to positive rewards, possibly due to so-called "numbing" defence mechanisms.

This type of research could one day help doctors use brain scans to determine the degree of trauma people experience, which is helpful given that survivors of traumatizing events, especially children, may not have the language to identify and seek help for PTSD symptoms. Brain scans could also help practitioners improve treatments, says Yuval Neria, because they'll be able to see how the brain patterns of patients change, or don't change, after various treatments. ▲●■

In a neural network, data points are represented by abstract mathematical quantities known as “vectors,” and “the whole process happens in some high-dimensional vector space, which is very hard for people to interpret,” says Azrieli Early Career Faculty Fellow Yonatan Belinkov. “It’s not a two-dimensional or even three-dimensional space that we can understand. It’s maybe 1,000 dimensions. We don’t really know what’s going on there . . . it’s really a black box.”

# Chatbots Say the Darndest Things

By Dan Falk
Photographs by Boaz Perlstein

Neural networks are becoming more human-like and powerful, but we still don’t really understand how they work.

**What’s it like to specialize in a branch of science that’s in the news almost every day? That’s the unusual position in which Yonatan Belinkov finds himself.**

He’s an expert on artificial intelligence (AI) and natural language processing, which includes the study of large language models (LLMs) such as ChatGPT. Released last November by OpenAI, ChatGPT is a sophisticated chatbot that can generate text in response to just about any prompt a user gives it. The text it produces can seem very human.

But the technology has also proven controversial. On one hand, ChatGPT appears to be bolstering productivity in fields such as marketing, grant writing and data analysis. At the same time, there are concerns about its effects in schools and universities — it can produce passable undergraduate-level essays in the blink of an eye — and worries that it threatens journalism and even democracy, with its potential to flood the world with fake news.

That’s because sentences produced by ChatGPT aren’t necessarily true. Belinkov, a professor of computer science and Azrieli Early Career Faculty Fellow at Technion–Israel Institute of Technology, put the software to the test recently by asking it who won the Nobel Peace Prize in 1948.

“It told me that the United Nation Committee on Civil Rights won the Nobel Prize,” he says, “and it told me why it won the Nobel Prize. It gave a very convincing answer — except that it’s false. The prize wasn’t awarded that year. Gandhi was nominated, but he was murdered just a few days before the decision, so it wasn’t awarded. But ChatGPT was very convinced.” (Cases where chatbots seem to go off the rails in this manner have been dubbed “hallucinations” and are thought to be triggered when the system strays too far from its training data.)

Falsehood is only one problem. AI language systems have also been known to perpetuate biases. For example, studies have shown that when prompted with statements such as “the nurse said that . . .” the system is more likely to complete the sentence on the assumption that the nurse is a woman rather than a man. And it found the reverse bias when prompted with the word “doctor.”

These are big changes from a decade ago, when chatbots could barely string together a coherent sentence. “In 2012, when I started my PhD, I couldn’t imagine anything like what we have today,” says Belinkov. “It’s a little challenging to be in a field that is very, very hot, because progress is so fast. Every day, there’s a new research article that I need to read. Staying up to date can be tricky.”

The key development enabling this leap forward is the rise of “deep learning” architectures known as artificial neural networks. These networks use a series of “layers” of mathematical processing to assess the information they’re fed. The connections between the layers are assigned weights that reflect the importance of each connection relative to the others, and those weights are adjusted as the network is exposed to more and more input data. Finally, the last layer produces an output. In recent years, neural networks have become proficient at recognizing faces, translating languages and, with programs such as ChatGPT, creating human-like text. (A few months ago, an even newer version, called GPT-4, was released; it can create websites in minutes, explain jokes and suggest recipes based on a photo of what’s in your fridge.)

Although programs like ChatGPT are certainly impressive, shortcomings such as bias and hallucinations demand our attention, Belinkov says. But exactly why a neural network gives one particular output rather than another has always been rather opaque. While the overall architecture of such networks is well understood, the actual cause-and-effect links from input to output can seem deeply mysterious. In a neural net, data points are represented by abstract mathematical quantities known as “vectors,” and “the whole process happens in some high-dimensional vector space, which is very hard for people to interpret,” Belinkov says. “It’s not a two-dimensional or even three-dimensional space that we can understand. It’s maybe 1,000 dimensions.” As a result, he adds, “we don’t really know what’s going on there. In this sense, it’s really a black box.”

With no way to track in detail what that vast array of vectors is actually doing, how can one tackle problems like bias in chatbots and similar AI systems? Belinkov’s strategy is to probe the network’s internal structure, examining which parts of a network are active at each stage of the process. He describes the process as an “intervention” in which one runs the program multiple times, each time tweaking one, or a few, components. “And every once in a while, you find there’s a neuron” — he uses the same term used to refer to cells in the brain — “where, when you switch it off, the machine gets lost. And that tells you, OK, maybe that’s where things are happening.”

Belinkov draws a comparison to an old-time arcade game in which a ball is inserted at the top of a wide, flat box with an array of pegs in it that allow the ball to move along some paths but not others. The user can remove or insert various pegs in order to try to steer the ball one way or another. Often, he says, many of the pegs — or in the case of a chatbot, network connections — don’t actually affect the end result.

“We have to understand where, in the system, there’s a switch — maybe one or more switches — that determines what it will say,” explains Belinkov. Only a few of these switches would actually determine what text the system produces in response to a particular input. “So, this question of ‘why’ is, I think, very much related to the question of ‘where,’” he says. “If we can pinpoint one switch, or multiple switches, that are responsible for producing a particular output, then we have an answer of why.”

The fact that some parts of the network seem to be much more important than others comes as a surprise, Belinkov says, given how interconnected the whole setup is. “If everything is connected to everything, then computation should be distributed and information should be likewise distributed. But it turns out that it’s not. For certain inputs, certain neurons activate much more than everything else.”

Another potential strategy is to feed the system new inputs, but that’s not as easy as it sounds, cautions Belinkov. For example, if an LLM was trained two years ago, some of its outputs will be out of date — but retraining it on the entire internet could cost millions of dollars. So, a more efficient strategy is to just tweak the specific parts of the system that have been implicated in producing problematic outputs, Belinkov explains. To combat a problem like gender bias, then, a better approach, he says, is “to look at the internal structure, identify the roles of different components, and then change them or edit them in a way that we think is desirable.”

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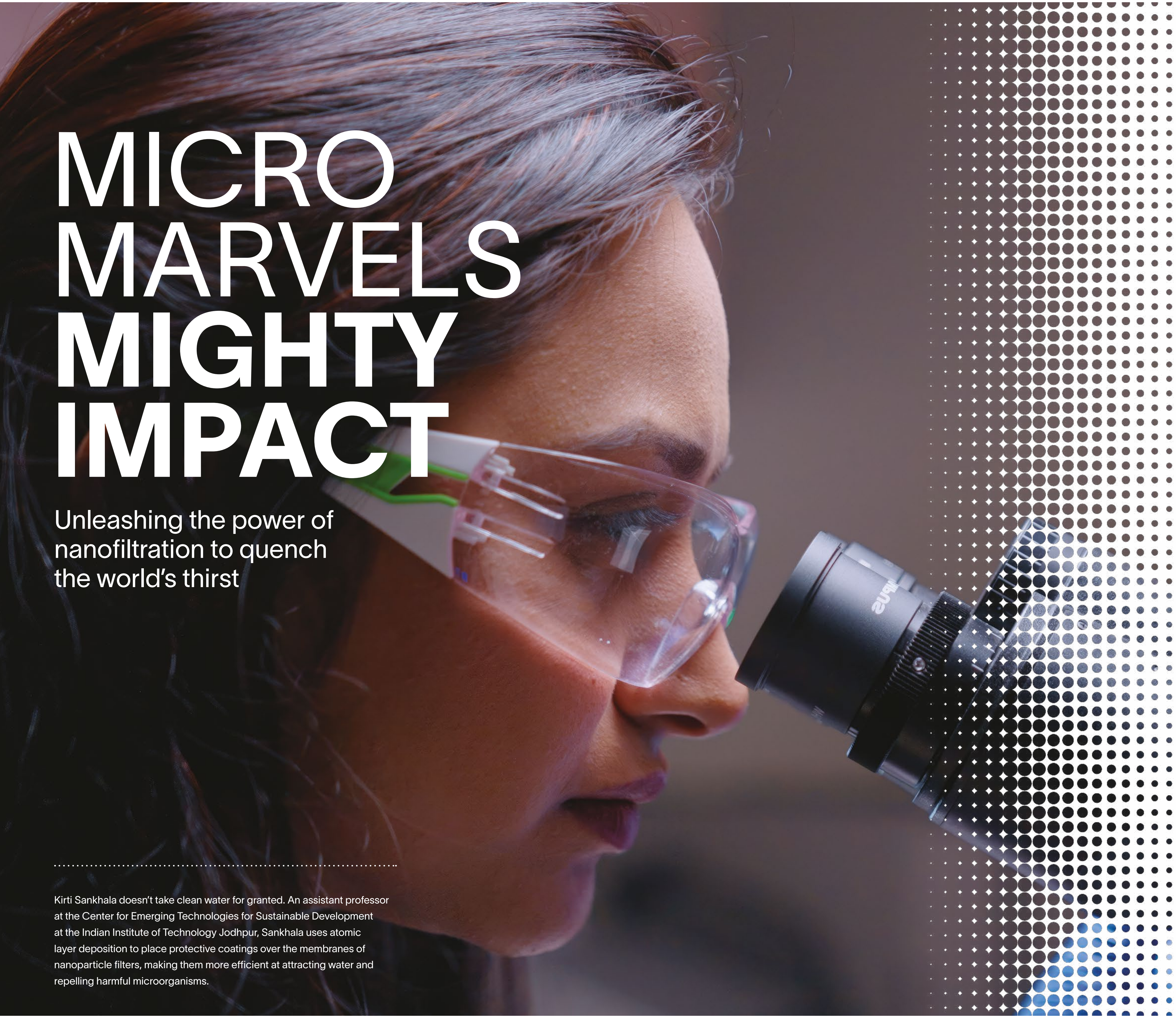
David Bau, a computer scientist at Northeastern University in Boston who has collaborated with Belinkov, notes that the remarkable capabilities of large language models “have been a genuine surprise, even among the experts of the field.” Belinkov’s research is important, he says, because the opacity of LLMs makes traditional debugging techniques ineffective. “Yonatan’s research about these models’ internal mechanisms will be critical in closing our gaps in understanding. Already, his work is laying the groundwork to help identify and solve potential problems of bias, robustness, misinformation and privacy that can emerge in large models.”

Studying the internal architecture of AI systems may sound like an esoteric pursuit, but with AI systems playing an ever-increasing role in society, the stakes are high. When computers were first invented some 75 years ago, the assumption was that they would help us. And in many ways they have. But to continue to aid humankind, the objectives of AI systems have to be aligned with our own. Indeed, Australian philosopher Toby Ord has estimated there’s a one-in-ten chance that “non-aligned” AI will trigger a catastrophe during the next century.

Belinkov admits that for much of his career he considered the “alignment” problem to be a low priority, something to worry about in the far future. The threat “seemed so far-fetched and so remote,” he says. “But I have to say that, recently, I’ve started thinking that, yes, maybe it is time for both scientists and legislators to start thinking about the alignment problem more seriously. We need to make sure that AI systems are not biased and perform what we want them to perform. But at the same time, we should think about longer-term risks.” ▲●■

Studying the internal architecture of AI systems may sound like an esoteric pursuit, but with these systems playing an ever-increasing role in society, the stakes are very high. “We need to make sure that AI systems are not biased and perform what we want them to perform,” says Belinkov. “At the same time, we should think about longer-term risks.”



# MICRO MARVELS **MIGHTY IMPACT**

## Unleashing the power of nanofiltration to quench the world's thirst

Kirti Sankhala doesn't take clean water for granted. An assistant professor at the Center for Emerging Technologies for Sustainable Development at the Indian Institute of Technology Jodhpur, Sankhala uses atomic layer deposition to place protective coatings over the membranes of nanoparticle filters, making them more efficient at attracting water and repelling harmful microorganisms.

By Zac Unger
Photographs by Blue Monkeys Productions

**It's easy to take water for granted. Throughout much of the world, a twist of the tap yields the instant reward of clean, abundant water, usually at minimal cost. But the process of getting that water from source to glass is staggeringly complex, involving hundreds of engineering solutions along the way.**

In some places, concerns about cleanliness must be addressed because water travels through agricultural fields, small settlements or ancient pipes, picking up contaminants on its journey. In addition to disease-generating bacteria, water is often polluted with pesticides, pharmaceuticals and dyes from textile processing. The United Nations estimates that two billion people around the globe do not have access to safe drinking water and that at least half of the planet's population experiences water scarcity at least once a year. Around 17 million women give birth annually in health care facilities with inadequate water, and 206 million people spend more than half an hour per trip collecting water.

"Where I grew up, there is no 24-hour-per-day water supply," Kirti Sankhala says about her hometown, Jodhpur, in India's arid northern state of Rajasthan, where she works as an assistant professor at the Center for Emerging Technologies for Sustainable Development at the Indian Institute of Technology Jodhpur (IIT Jodhpur). "Sometimes we only get water once every two days. But water culture is different here. Everyone has a storage tank, so when water is supplied, people store it.

"We all want a safe glass of water," continues Sankhala, who was an Azrieli International Postdoctoral Fellow in the Department of Chemical Engineering at Technion–Israel Institute of Technology in 2021 and 2022. "We want high purity — the rejection of contaminants that are a health threat — and at the same time we also want high productivity, which means generating more clean water using less energy and time."

At IIT Jodhpur, her new research group is contributing toward objective number six on the United Nations' list of sustainable development goals: ensure availability and sustainable management of water and sanitation for all. For Sankhala, that means providing sustainable water treatment solutions using local natural resources, such as sand, clay and plants, as well as applying emerging membrane technology for water treatment.

Her research focuses on nanofiltration, in which water is forced through microscopic pores to filter out contaminants at a molecular level. The pores in these membranes are between one and 10 nanometres in size. (For comparison, a human hair is 100,000 nanometres across, and a bacterium is 2,000 times larger than the smallest pores in Sankhala's membranes.) Cleaning water with a membrane, then, is like making coffee in the morning, she says: "You pour everything into the filter on top and then only your coffee will come out, but all the particles will stay on top of the sieve."

Unfortunately, it's not quite that easy, otherwise contamination and water-borne diseases would be a thing of the past. The same way you can't use a single coffee filter repeatedly, these membranes can get clogged. But while a coffee filter is cheap and easily replaced, membranes must be able to last a long time in order to reliably provide safe water on a regular basis.

Nanoparticle filtration is highly affected by electrostatic charges because of how the membranes and molecules interact. A negative charge helps the surface attract unwanted pollutants, but it also makes the membrane less hydrophilic, or less able to move water freely through its pores. A more hydrophilic — or "water loving" membrane — "will suck the water easily and repel the proteins and viruses," Sankhala explains. "But when everything accumulates on the surface, the membranes become fouled and they get less efficient, and we can't get much water through."

The challenge then becomes how to make the membrane more efficient and less prone to clogging. A problem at a nano scale requires a solution that's just as small, making this a much more complicated engineering puzzle than simply brushing coffee grounds into the garbage can and shaking out the filter. Sankhala and her colleagues are using a technique known as atomic layer deposition to place a protective coating over the membrane, making it more efficient at attracting water and repelling harmful microorganisms.

"It's literally atoms upon atoms, sitting on top of the membrane," she says. Using compounds such as aluminum oxide, "we can get the thickness we need with sub-nanometre precision. This allows us to have a layer that loves water and rejects the salts."

One of Sankhala's projects at Technion was using atomic layer deposition to deposit molecules of aluminum oxide on top of the polymer membrane. The polymer itself is a macro-molecule, made up of repeated units of smaller molecules, linked together almost like blocks of Lego. "As part of her work, she investigated what happens to the performance of these membranes once we grow aluminum oxide on them," says Tamar Segal-Peretz, Sankhala's supervisor at the time and group leader in the university's Functional Nanostructures and Advanced Imaging Lab (and an Azrieli Early Career Faculty Fellow from 2016 to 2020). "Along the way she discovered a very interesting thing."

The team's original hypothesis was that the aluminum oxide would grow on top of the polymers and modify the membrane on a surface level. "But in fact, what we saw," Segal-Peretz continues, "was that some of the molecules penetrated into the separating layer of these membranes," because of the way they diffuse and react inside the polymer.

Building on this finding, Sankhala is exploring the potential of atomic layer deposition for other applications. She worked on a separate project to grow inorganic material not just on top of membranes, but to make the technology work in three dimensions inside polymer foams, including those used as absorbents and insulation. (Because they have a highly porous bicontinuous structure, these foams provide a large surface area that's well suited for hosting reactions, such as the degradation of pollutants through catalytic activity.)

Foams present a complex, multi-parameter problem, however, since a combination of substances with different chemical properties is required to polymerize the foam while simultaneously maintaining a high surface area. Initially, Sankhala had hypothesized that the process would create extremely small clusters of zinc-oxide molecules, growing atop each other a single layer at a time. Instead, she found that even with a single treatment, it wasn't clusters that formed but nanorods, a more organized structure for collections of extremely small particles. Using a process called sequential infiltration synthesis — similar to atomic layer deposition except that it relies on chemical reactions that occur within the pores of a material rather than on the surface — the team was able to distribute zinc oxide very uniformly throughout the foam in a controlled way. Thanks to the catalytic activity this supports within the foam, the material is a candidate for the efficient treatment of wastewater from textile production because of the way zinc oxide nanoparticles react with dye molecules.

"This was a very impressive result," Sankhala recalls, because it allowed the team to essentially create a hyper-efficient water-treatment sponge. "Now if I have a one-centimetre cube I can treat almost one litre of wastewater from a textile plant."

**'We all want a safe glass of water. We want high purity — the rejection of contaminants that are a health threat — and at the same time we also want high productivity, which means generating more clean water using less energy and time.'**

In the process of improving membranes and filtering technology, some of the most elegant work that Sankhala did was in using transmission electron microscopy to better understand the filtration process at a basic level, exploring the composition of the membranes on a nanoscale. Incorporating aluminum oxides into the polymers provided a high contrast for the electron beam, allowing her to clearly image exactly how and where the polymers were mixing with the membranes. Seeing how each experimental modification affects the membrane at an atomic resolution enhances the ability to minimize production and maintenance costs of a filter while also maintaining high performance.

The ultimate goal is to provide higher quality water treatment in the cheapest, greenest and most space-efficient manner possible. Currently, much of the world uses reverse osmosis (RO) rather than nanofiltration to treat its water. This is in part because RO, which removes contaminants by using pressure to force water molecules through a semipermeable membrane, can filter out much smaller particles than nanofiltration. It's particularly effective for purifying seawater, as is common in Israel, where more than 70 per cent of the country's freshwater comes originally from the ocean (and where 80 per cent of wastewater is treated and returned to agriculture). But the ability to hyper-filter has its downsides, as RO removes many minerals that compounds like calcium and magnesium need to be added back in for human health. More important, RO requires much higher energy input because pressure is applied to the water in order to accomplish treatment. While RO requires about 25 bars of pressure — or 25 times atmospheric weight at sea level — nanofiltration works at only four or five bars.

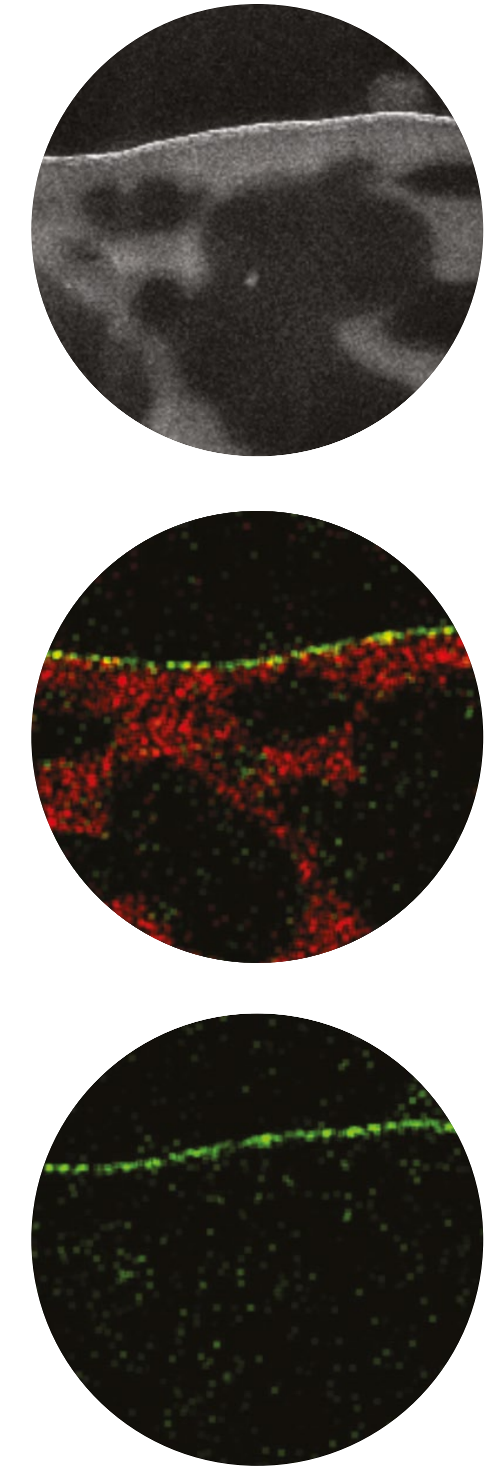
"Increasing the pressure increases the energy input required," says Sankhala. When it comes to wastewater, traditional treatment facilities are huge, energy-intensive spaces. "But if you are working with efficient membranes, you can stack them vertically and do the work of an entire plant in a single room."

Conducting research in Israel was something of a revelation for Sankhala, as she noticed that "the young generation there has crossed those thoughts of scarcity out of their mind because water is so dependable and clean." Working with the Azrieli Fellows Program was another highlight of her time at Technion. "The efforts they put in for us are so impressive," she says. "It's not only about the funding — the bond between Azrieli members is so strong, and you know that everyone is really there to support you."

Growing up in a parched region of India, Sankhala encountered water issues at an early age and was confronted constantly with concerns about both purity and scarcity. "She has both lived experience and many skills in the lab, and that combination will be incredibly valuable for her career," says Segal-Peretz. "The chance to bring life-improving reliability back to her hometown is a force that continues to motivate every aspect of her work."

While nanofiltration is already highly efficient, Sankhala is working to continue advances in this field, pushing for higher purity and lower energy costs while reducing harmful chemical by-products. Back home in India, she is supplementing her high-tech lab work with a project to help rural residents filter water through ceramic filters in earthen pots.

"The drive to have good water is a human survival instinct," says Sankhala. "It's also a human right and we have to protect the value of each drop." ▲●■



Microscopy images from Sankhala's lab work provide a close-up view of the six-nanometre-thick layer of tin oxide deposited on the surface of a nanofiltration membrane. Her team originally hypothesized that adding oxides would modify the membrane on a surface level, but in fact some of the oxide molecules penetrated into the separating layer of these membranes, providing opportunities for additional approaches to filtration.

PHOTOGRAPH BY YURI DOJC

## SMALL BUT MIGHTY

Have you heard of the butterfly effect?

Put simply, it's the theory that a butterfly flapping its wings on one side of the planet can have a great consequence (such as a tornado) on the other side.

This notion — that a small act can create profound change — has relevance in our everyday lives. Our simple, small-scale actions can grow and accumulate to have great societal impact.

Perhaps your small gesture of kindness starts a ripple effect that encourages others to perpetuate the thoughtfulness. Maybe your donation to a local organization, when coupled with others, helps it to grow and make real change in a community.

In this issue of *Aperio*, this theory is put into practice in a variety of ways. We see that studying and using tiny things — nanoparticles, zebrafish or cellular behaviour — can be a significant step toward understanding, and then addressing, large-scale challenges.

The Azrieli Fellows Program is another example. It started in 2007 with 11 researchers and an idea to create a network of scholars that would forge strong academic links between Israel and the rest of the world. Today, with more than 400 alumni, the program is the most generous and wide-ranging of its kind in Israel and attracts talented researchers from around the world.

Our first steps in Canada and Israel in 2007 have supported and empowered a vibrant global research community for almost 17 years.

I hope this issue has you thinking about change — and about the next small but mighty step you will take.

**Naomi Azrieli, OC, D.Phil**
Chair and CEO
The Azrieli Foundation

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**Aperio: Latin for *uncover*, *reveal* or *make clear*; the source of the English word "appear."**

*Aperio* is a magazine of the Azrieli Fellows Program, which empowers promising academics worldwide through opportunities to conduct cutting-edge research at elite institutions of higher education in Israel, a country long recognized for outstanding achievements in research. The program is operated by the Azrieli Foundation, which aims to improve the lives of present and future generations through philanthropic initiatives in education, research, health care and the arts in Canada and Israel.




PHOTOGRAPH BY HADAS PARUSH

Reckoning tokens, or jetons, were medieval calculation devices used in Europe until well into modern times. These tokens were minted in Nuremberg in the 16th century (left) and 18th century (right). The one on the left depicts an early modern merchant using such tokens to perform his arithmetical activities. A constellation of small clues like these have led Tel Aviv University historian Ray Schrire to the counterintuitive suggestion that in early modernity—and maybe in our time too—rationality is and was a delusion, sustained only by our collective willingness to believe in it.

PHOTOGRAPH BY BOAZ PERLSTEIN