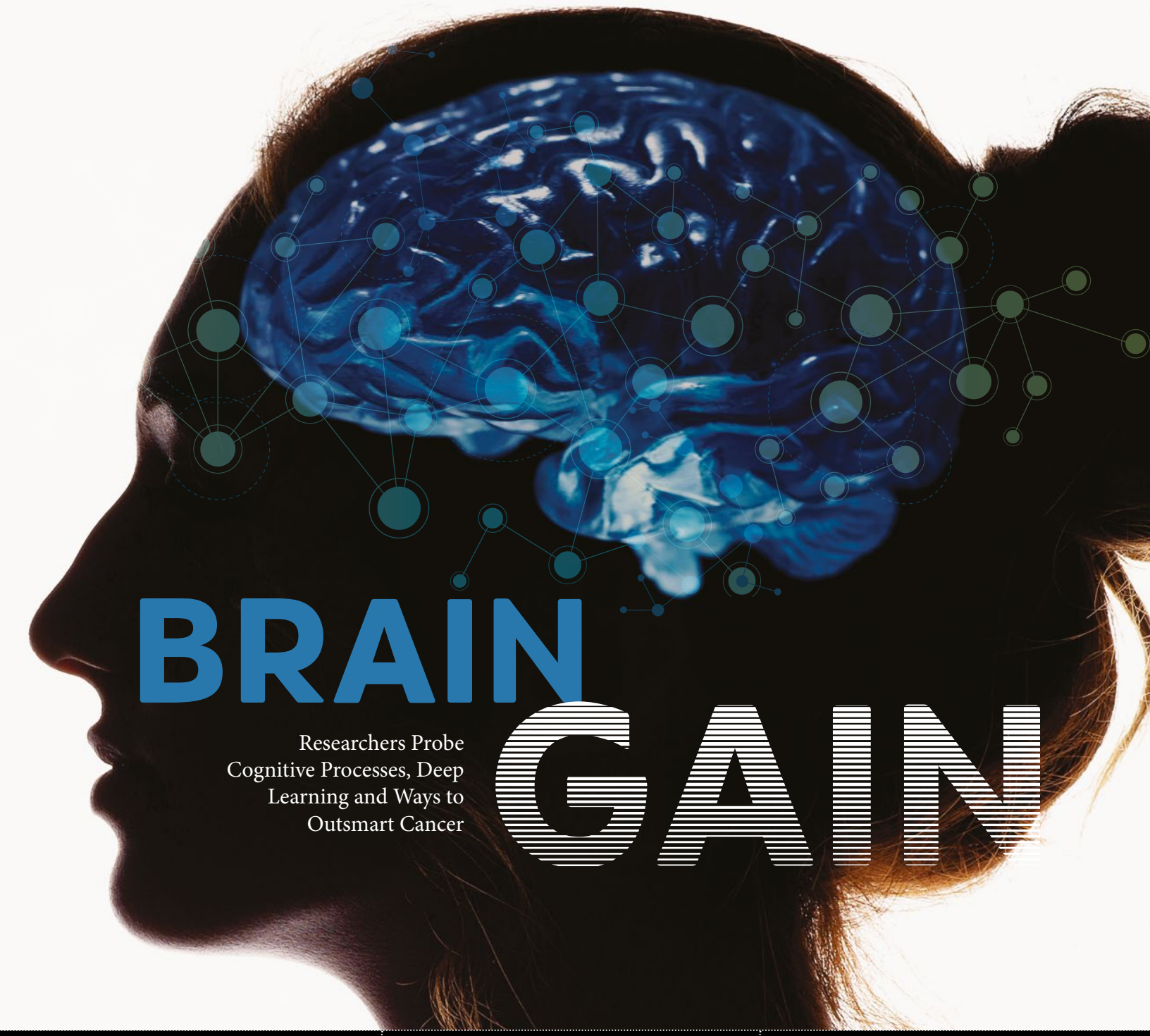
Aperio

SPRING 2023 | ISSUE 04



BRAIN GAIN

Researchers Probe Cognitive Processes, Deep Learning and Ways to Outsmart Cancer

Revolutionary Deep Learning

Putting AI on a data diet to drive advances in imaging

The Secrets of Happiness

Deconstructing the brain's decision-making process

When Immune Cells Fail

Can cutting-edge genomics discover why they shut off?

IN THIS ISSUE

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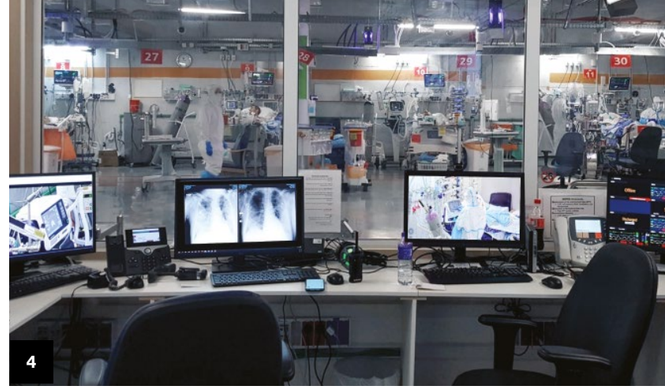
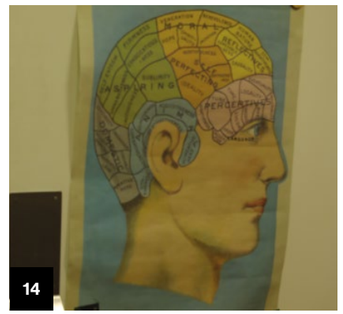
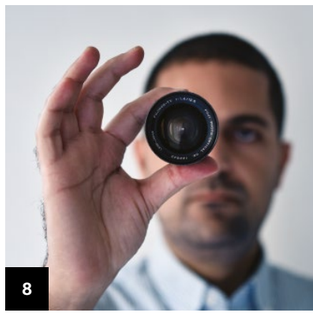
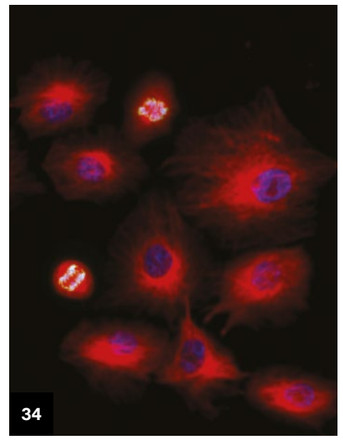
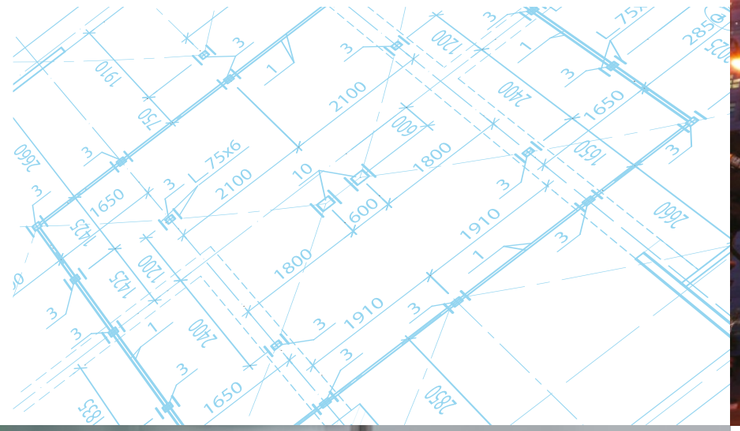
On the cover: Azrieli Fellows conduct research in a wide range of areas related to the brain. In this issue of *Aperio*, articles cover the cognitive processes involved in decision-making, how neural networks can learn with less data and why immune cells switch off upon entering brain tumours.











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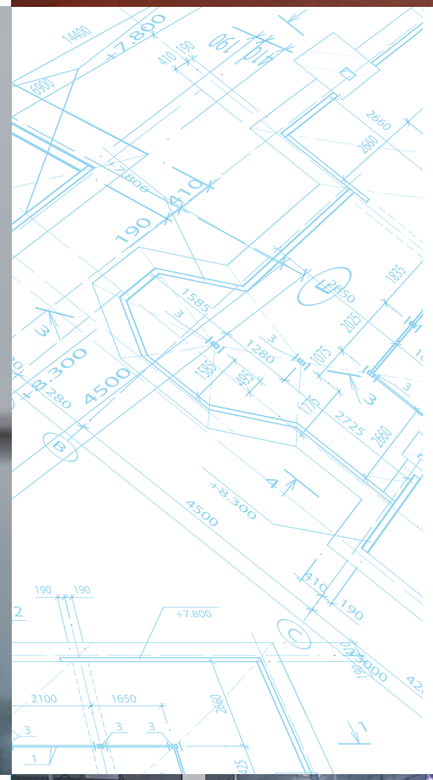
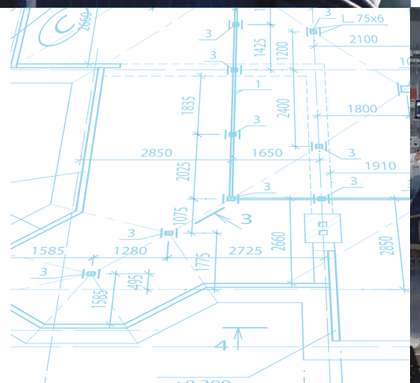
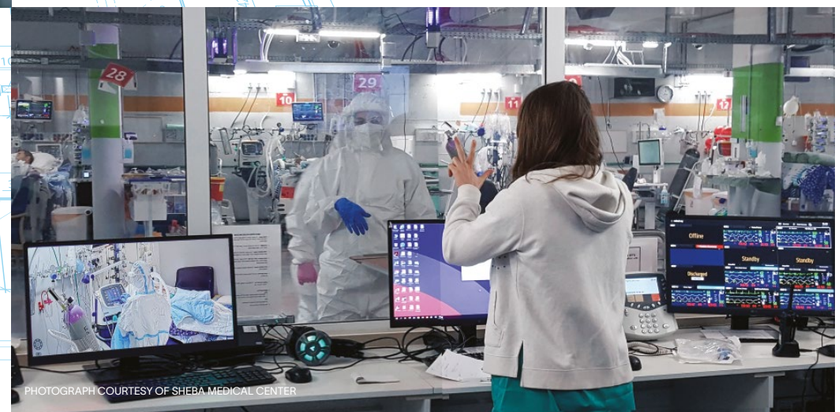






PHOTOGRAPH COURTESY OF SHEBA MEDICAL CENTER

Architect Nirit Pilosof, who was the design project manager for the Tel Aviv Sourasky Medical Center's Sammy Ofer Heart Center (top), had a front-row view of the Sheba Medical Center's rapid transformation and its COVID-19 control room (bottom) when the pandemic began. She is now exploring ways to rethink health care design in the new digital era.

By Alison Motluk

Photographs by Boaz Perlstein

A BLUEPRINT FOR THE HOSPITAL OF THE FUTURE

Revolutionary new directions in remote health care design

In the spring of 2020, to handle a surge of COVID-19 patients, Israel's Sheba Medical Center created 97 new ICU beds in its underground parking lot practically overnight. The space was divided into "clean" and "contaminated" zones. Some staff worked in person in the latter, dressed in full protective gear, while others worked remotely from a control room in the nearby clean zone. Using multiple fixed cameras, interactive audio-video technologies and robots fitted with tablet computers to display their faces, these operators helped tend to the needs of patients and families and managed staff in the contaminated zone.

Confronting an unprecedented pandemic, the hospital was exploring a new way of operating an intensive care unit: remote care for patients who were physically inside its building. The goals were to limit staff exposure to pathogens, to reduce errors caused by working in bulky protective equipment and, perhaps most important, to see how well remote in-patient medicine could work on the ground.

Nirit Pilosof, an architect, researcher and former Azrieli Graduate Studies Fellow who had spent her career designing and studying health care facilities, had just weeks earlier begun postdoctoral research at Cambridge Digital Innovation (CDI), Hughes Hall and Cambridge Judge Business School at the University of Cambridge. She joined an interdisciplinary team at CDI that was investigating the "Smart Hospital of the Future."

Her original plan had been to travel back and forth between the U.K. and Israel to research digital transformation in health care settings. But when lockdowns closed borders, she remained in Israel and took a front-row seat to perhaps the greatest acceleration of digital health care in our time.

Over six months, Pilosof observed Sheba's COVID units and interviewed doctors, nurses, engineers, technology experts and the architectural design team. "They developed a whole new model of care," she says.

It wasn't perfect. The partial views provided by cameras, for instance, were never as good as seeing the whole scene while one was present in the space. No amount of smiling on a camera could replace a human touch. And there was not enough privacy for patients. But the exercise illuminated a future in which, with tweaks, remote care in its various iterations could become a major organizing feature of health care design.

We tend to think of architects designing inert structures, not dynamic systems. But buildings influence their users. Design produces outcomes. And perhaps nowhere is this more evident than in hospitals.

A landmark paper in 1984, written by Roger Ulrich and published in the journal *Science*, found that patients who saw greenery through their hospital windows needed less pain relief and fewer post-operative days in care than patients who could only see a brick wall. That paper helped spawn a field known as "evidence-based design."

Evidence-based design explores, among other things, connections between architecture and health. It recognizes that the built environment has an impact on how a facility performs and how its users fare within it. Everything from ward layout to lighting and acoustics will have consequences related to clinical outcomes, staff performance and the well-being of patients. Some will be life-and-death. And, just as in medicine itself, medical architecture should "do no harm," says Pilosof. In fact, she argues, medical buildings should be designed, as much as possible, to support the healing process.

There are two central lessons from the study of Sheba's COVID units, according to Pilosof. One is that there is great potential for so-called smart hospitals. "The hospital can really change if we start looking at how we can redesign it by using remote technologies," she says. The other is that there are still big ethical questions to be addressed. "How do we redesign health care services," she asks, "without compromising patient privacy and human dignity?"

Although the COVID part of her research is now complete, Pilosof continues to collaborate with Cambridge and Sheba on a project called "Hybrid models of care: Integrating physical care with virtual care." She and her colleagues believe that hospitals will evolve from centralized monoliths that do everything inside their walls into more dispersed health care ecosystems. A transformation that's currently underway at the Sheba Medical Center, led by its ARC (Accelerate, Redesign, Collaborate) Center for Digital Innovation, provides a perfect real-time example to study. The hospital — one of the best in the world — recently launched "Sheba Beyond" to become Israel's first virtual hospital. Through this arm, the facility offers different kinds of care, including ambulatory services, rehabilitation and remote home hospitalization.

"We realize that in the future, physical hospitals will be used only for acute care," says Pilosof, who became head of research in Sheba's Innovation and Transformation Division this past September. "Remote technologies hold the potential to change the layout of medical units completely."

Many in-hospital patient rooms will have to be transformed into intensive care rooms, for instance, which is more complicated than it may sound as they require different types of staffing and infrastructure. At the same time, many other types of patients will be monitored remotely — some within the physical building, but some elsewhere, including in their own homes. According to one vision, patients will be monitored identically, regardless of where they are located, using a tablet to access their medical data. In Sheba's home hospitalization trial, specialists monitor patients at home using virtual technologies. (Only patients who have someone at home to help out are eligible.) If the patient's condition worsens, they can come straight back to the same unit, bypassing the emergency department. "The team already knows them and their medical history," says Pilosof. "The way they look at it is that the unit has both physical beds and virtual beds." Medical professionals are happy to have access to continuous data, rather than relying on self-reports, and patients are often comforted by the fact that they are being monitored closely.

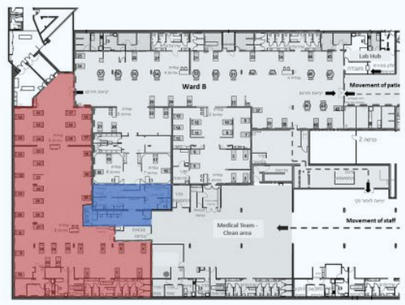
Pilosof is currently assessing how well the project is working by conducting qualitative interviews with all of the relevant stakeholders. She has already found that interactions between medical professionals and patients' families are being altered — in most cases, for the better. In a hospital, during rounds, doctors and their entourage typically move from room to room, and patients' families are often excluded. In Israel, most rooms are semi-private and family members are asked to wait outside to protect the privacy of the other patient. When done remotely, however, families are invited in. "When the patient is at home, they actually ask the family to join the meeting, because they need the family to be involved in the care," says Pilosof. "This has really shifted the relationship between the patient and the family and the medical staff." Families are now part of the team, she says, and almost part of the staff.

The research also indicates a need for control centres, says Pilosof, just like in the COVID units. "We're talking about designing control centres that will manage all the patient data, whether they're at home or in the hospital, with operational and spatial data spread across the health care system." The trick will be integrating the different datasets represented by "digital twins" to optimize operations and support informed clinical decisions.

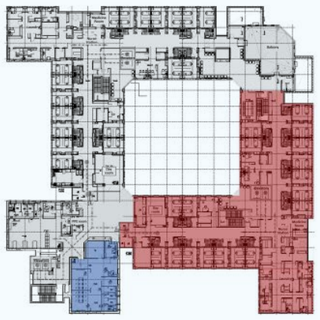
"Multidisciplinarity is absolutely critical in this research," says Michael Barrett, an information systems and innovation studies professor at the Cambridge Judge Business School who is leading the research at Cambridge and has worked closely with Pilosof. "We are bringing together scholars who are experts in digital technologies, digital innovation and service innovation, but then also thinking about the spatial dimension." This type of research has traditionally been weak on thinking spatially, he says, but working with Pilosof has helped to address that gap.

IN-PATIENT TELEMEDICINE IN COVID-19 MEDICAL UNITS AT SHEBA MEDICAL CENTER

Control Room — Clean Zone **Clinical Area — Contaminated Zone**



COVID-19 Intensive Care Unit



COVID-19 Internal Medicine Unit

COVID-19 Mental Health Unit

There are two central lessons from the study of Sheba's COVID units, according to Pilosof. One is that there is great potential for so-called smart hospitals. 'The hospital can really change if we start looking at how we can redesign it by using remote technologies,' she says. The other is that there are still big ethical questions to be addressed.

Pilosof has a special interest in designing for the unknowable future. "We are in an era of transformation," she says. "Everyone is trying to predict what will happen, but we don't really know where it will lead." Unfortunately, medical facilities, she says, are too often tailor-made to fit specific programs and the operational approach of the existing medical director. Sometimes, though, that medical director leaves before construction is even complete. Or, as the pandemic underscored all too clearly, demands can suddenly change. Planning for change, she says, is probably the biggest challenge in health care design today.

"You have to design a building today when you actually don't know what the future needs will be," says Pilosof. Medicine and technology are advancing rapidly, yet it can take seven years — or longer — from a facility's blueprints being completed to the ribbon cutting. "By the time the building is built," she says, "it's already obsolete."

The key is to design with flexibility in mind, says Pilosof — something she knows from experience. From 2005 to 2009, while working at Ranni Ziss Architects, she was the design project manager for the Sammy Ofer Heart Center, a cardiac care facility at the Tel Aviv Sourasky Medical Center (Ichilov). Only three floors were needed for it, but the hospital wanted to make the most of its donation, so it commissioned 11 floors. "We actually built an empty shell," she says. But it was an empty shell with enormous potential: she and her colleagues knew something would fill in the space, even if they didn't yet know what, and they didn't want the design to be a limiting factor. During her PhD studies in the Faculty of Architecture and Town Planning at Technion–Israel Institute of Technology in Haifa, where she was an Azrieli Graduate Studies Fellow from 2016 to 2019, she demonstrated that this was an efficient approach.

Pilosof's interest in planning for change had been sparked earlier, while she was working toward her master's degree at McGill University in Montreal. She had studied the evolution of the McMaster Health Sciences Centre, a utopian building of the 1970s in Hamilton, southwest of Toronto — "an infinitely flexible space," she says, "designed never to be finished." But 30 years on, she discovered in her research, it had not continued growing as predicted, but had instead become a "static monument." The architectural approach was efficient, but management and funding issues overruled the initial vision. This showed that despite the best intentions of architects, Pilosof says, so much remains outside of their control.

Since starting her collaboration with Cambridge, Pilosof has moved further into management studies. Today, in addition to her work at Sheba, she is also a faculty member at Tel Aviv University's Coller School of Management, where she is co-teaching a course on evidence-based design for medical directors in the Health Systems Management MBA program. "Meeting all those future decision makers in high positions and teaching them about health care design — that's really an opportunity to make a change," she says. She hopes to develop a program in which she can bring architecture students into the same room as medical and management students to help them imagine the future together. ▲●■

PICTURE IMPERFECT

How deep learning with less data can drive a huge leap in computer imaging and optical systems

By Zac Unger
Photographs by Boaz Perlstein

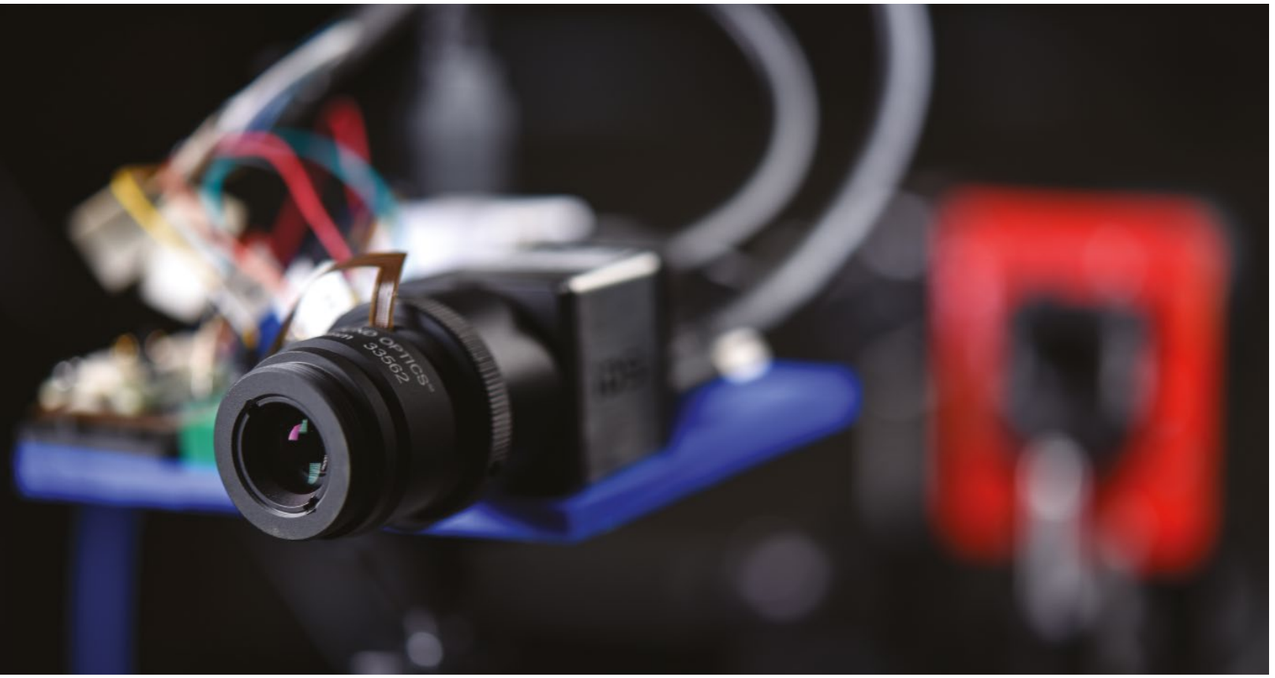
Our world is blanketed by cameras, every square metre recorded and catalogued in pixel upon endless pixel of data. We've got cameras on doorbells, cameras on car-backup screens, security cameras on street corners, GoPros on bike helmets, not to mention cameras on satellites and swallowable pill-cameras that take medical images of our internal organs. Add in screenshots, video calls and smartphones — which record nearly two trillion photos worldwide per year by one estimate — and the volume of recorded images is overwhelming.

And yet, statistically speaking, almost every one of those pictures is garbage. The point of taking all those photos and videos is presumably to use them; however, our cameras, as good as they are, are far from perfect. Low light, bad focus, improper framing and blurring conspire to give us incomplete representations of the world we're trying to accurately capture with our constant clicking and streaming.

This is where Raja Giryes comes into the picture. An electrical engineering professor at Tel Aviv University, Giryes runs the Deep Learning Lab, which combines complex computing and cutting-edge camera design to make sense of all this photographic data. To put it simply — although there isn't much about this field that's simple — "deep learning" is the process by which computers digest and learn from massive amounts of data. On first pass, for example, a computer can't tell you whether it's looking at a picture of an elephant or an orca. But give the computer enough accurately labelled images, and soon it will identify patterns and reliably recognize which animal is which just by looking at a few centimetres of a trunk or a bit of dorsal fin. That same principle can be used to create order and coherence out of the untold billions of photographs taken every day.

"One of the main problems in artificial intelligence is that you need lots of data to train neural networks," says Giryes, who was an Azrieli Graduate Studies Fellow between 2010 and 2013 while working toward his PhD in computer science at Technion–Israel Institute of Technology. Neural networks are the computerized algorithms that mimic how the human brain processes information. "What we're trying to overcome," says Giryes, "is how to learn with less data, how to be efficient, how to adapt your data to apply to new domains and new problems." In essence, Giryes and his team are helping computers get smarter quickly by reducing the amount of data necessary for training.

The human eye and brain are constantly assimilating data, unconsciously learning about the world. Nobody taught you that trees stand still, but by the time you were a toddler you had seen enough to know that you can lean against one and not fall over. For computers, acquiring even this kind of rudimentary knowledge — what is a tree, for instance, and is swaying in the wind the same as moving? — requires massive data. Providing that information for every category and situation means an enormous workload for the humans tasked with uploading and correctly tagging countless images.



Raja Giryes (previous pages) and his lab use deep learning to design optical elements that improve imaging, such as the "phase mask" that allows this camera to reconstruct depth information and change focus while acquiring images, which can be used to remove motion blur from photos.

This camera system uses a beam splitter to capture the same scene with two different sensors. Because the same data can be collected using a high-resolution and low-resolution sensor at the same time, researchers can use this information to learn how to increase the resolution of the latter.

'Our work means that you don't need to train a neural network for each new camera lens from scratch. You only need to model the blurriness of the lens and then modify the already trained neural network inference steps and get great results.'

Giryes's work is broadly applicable to all manner of circumstances where datasets are sketchy or incomplete, solving problems not only for still images but also for video and even medical systems that determine which human cells are cancerous and which are healthy. In one side project, he and his colleagues trained a neural network to accurately assign archaeological artifacts to the correct location and period. Using a publicly available photo database from the Israel Antiquities Authority, the AI was fed a massive amount of information on everything from the Lower Paleolithic period (which started about 1.4 million years ago) to the Late Islamic period (14th century). Using a neural network, the AI extracted features known as "embeddings" from the images of the artifacts. A computer then translated the colours, shapes and other aspects of the artifacts' appearence into a series of numbers that can be compared from artifact to artifact, eliminating the subjectivity that human brains may be prone to when analyzing a piece of pottery.

Archaeology is a particularly difficult field because two temporally or spatially adjacent societies might have tools or weapons that look remarkably similar. In tests, Giryes's algorithm handily beat two trained archaeologists, correctly identifying artifacts with much greater accuracy. This technique is valuable in illuminating new avenues of study for finding meaningful relationships between ancient sites — and much more.

"Getting lots of examples requires lots of effort," says Giryes. "The question for us is do we need to collect all the data every time, or can we develop a technique that would achieve the same result in a faster way?"

Although Giryes's work with large datasets and deep learning has a wide range of applications, his main focus is computational imaging and designing new optical systems using artificial intelligence. The practical outcomes of this work include everything from improving picture quality to image recognition, training a computer to identify real-world images from tiny fragments.

Representation of three-dimensional data presents a particularly thorny problem that his lab is tackling. "You take a photo with your phone," Giryes says, "and you want it to be a 3D photo, but you're only using a single camera. We're figuring out how to design the optics of the camera to get better depth estimation." The easiest way to make a three-dimensional image is by combining regular images from different angles. But computers building models of lifelike objects don't always have the luxury of data inputs from all directions. Instead, Giryes developed an AI technology that teaches a camera (by automatically designing its optical element) how to get 3D information from a single direction. In addition to

EDITING IMPLICIT REPRESENTATIONS

1

Using neural networks, computers transform images made up of 2D pixels into 3D representations composed of "voxels."

2

These representations show what a common object such as a chair looks like not just head-on but from all angles.

3

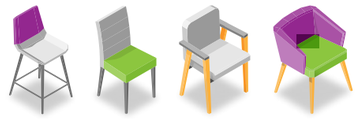
Traditionally, to see how an object responds to digital manipulation, you need to scan the space and check all points.

4

By disentangling component parts into geometric data, you can transform, interpolate and combine shape segments.

5

This process can allow researchers to separate and mix the individual parts of objects and generate new types of shapes.



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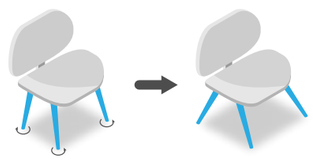
This technique holds promise for designers trying to create new products and test how they might perform under different stressors.



capturing 3D data, Giryes also studies how to better represent it. His team uses "implicit representation" to accurately depict or manipulate objects with realistic depth.

We're all familiar with pixels, the smallest element in a digital display. An alternative approach uses "voxels," the 3D equivalent. Think of a three-dimensional picture of a stack of blocks; each voxel is one block. (Etymology is helpful here: the word pixel derives from "picture" plus "element," whereas voxel comes from "volume" plus "element.") Using neural networks, computers assemble these voxels into images of, say, an airplane and have an understanding not just of what an airplane would look like head-on but from all sides. Although voxels are useful, they are of limited resolution, says Giryes, "but with implicit representation, you can simulate a function with any resolution you want."

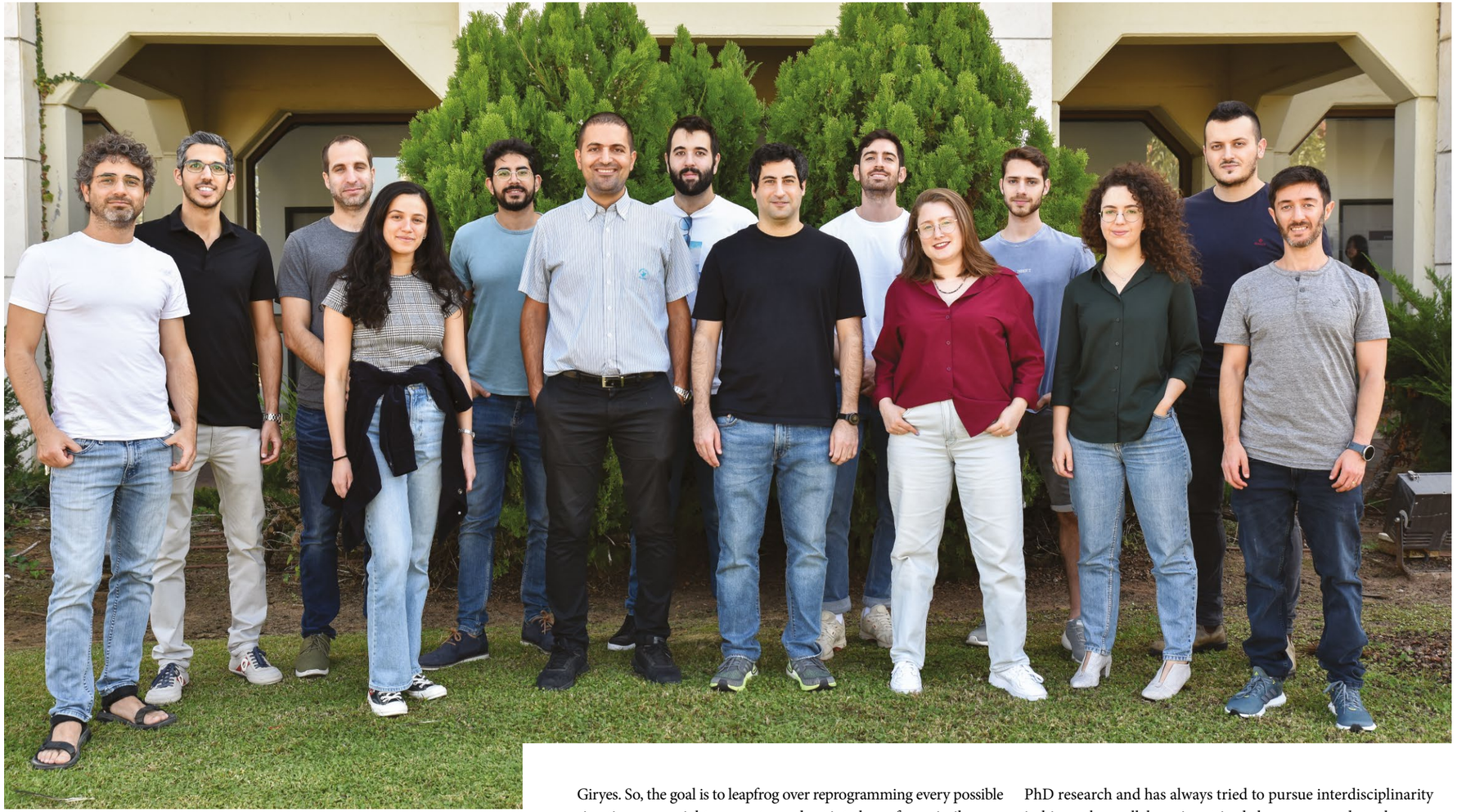
In the paper he wrote with colleagues on the subject, the technique is described as allowing for "manipulation of implicit shapes by means of transforming, interpolating and combining shape segments together without requiring explicit part supervision." In lay terms, "imagine that you have two chairs," says Giryes. "I can take the back of one chair and the legs of another and edit them together, mix up the parts and generate new types of shapes you've never seen before."

The neural network learns to separate out one piece of the model from another, modifying individual parts without disrupting the rest of the image. By taking a three-dimensional representation of a common object and disentangling its component parts into essential geometric data, the model allows users to more easily edit these implicit shapes in high resolution. An image of a chair then ceases to be a chair, but is reduced to its most basic shape segments, which can be reassembled in multiple configurations without requiring direct supervisions of each discrete part. This technique holds promise for designers and engineers trying to imagine new products and test detailed representations of how they might perform under different stressors.

Shady Abu-Hussein, one of Giryes's PhD students, describes how the research team has also worked to combat low resolution in images, a significant factor that reduces the usefulness of many pictures. The goal is to create a "super resolution network" that can decode the fuzz and automatically enhance the quality of what lies beneath. "These networks are usually trained for a specific lens structure," says Abu-Hussein. "Our work means that you don't need to train a neural network for each new camera lens from scratch. You only need to model the blurriness of the lens and then modify the already trained neural network inference steps and get great results."

One of the most exciting real-world applications for Giryes's brand of deep learning is in the field of self-driving cars, which must use computer vision to assess the world around them with critical levels of accuracy. Giryes consults with the Israeli company Innoviz to develop guidance and obstacle-detection systems for autonomous vehicles. Innoviz — which recently signed a $4 billion USD deal with Volkswagen — develops LIDAR (laser imaging, detection and ranging), a technology that employs laser-light rebounds to measure distance and create 3D images of objects ahead. But even the best computerized eyes are only as good as the knowledge base they use to process their inputs.

"It costs enormous amounts of money and time to collect 10,000 hours of driving data and then have a person tell you what's in each frame," says Giryes. So, the goal is to leapfrog over reprogramming every possible situation a car might encounter and get it to learn from similar experiences. For example, a human driver has probably never seen a five-metre cube painted gold with blue polka dots, but we'd still automatically know to swerve if it fell off the truck in front of us. Getting autonomous systems to extrapolate from the data they already have with minimal or no adaptation is the ultimate goal.



Giryes (sixth from left) and his large research team combine complex computing and cutting-edge camera design to make sense of the world's deluge of photographic data.

Giryes's work is broadly applicable to all manner of circumstances where datasets are sketchy or incomplete, solving problems not only for still images but also for video and even medical systems that determine which human cells are cancerous and which are healthy.

"Making decisions using multiple sensors such as both cameras and LIDAR is important as we need to learn how to use data to be adaptive to different environments," Giryes says. "We have a car that works well in the day, but we also need it to drive at night. It has to work as well in the city as it does in the country. It has to drive well in Europe and also drive well in India."

In both academia and industry, Israel has a been a crucial hub in the development of deep learning techniques for processing all manner of inputs. The country is home not only to dozens of successful high-tech start-ups but also Tel Aviv University and Technion's ground-breaking electrical engineering and computer science research groups. Giryes was in one of the latter labs while conducting his PhD research and has always tried to pursue interdisciplinarity in his work, a collaborative attitude he now extends to the many graduate and postdoctoral students he supervises.

"Raja isn't just a great mentor and teacher," says Abu-Hussein, "but he also likes to help out his students with the smallest details, even down to looking at the lines of code, which a lot of professors would just assign another more experienced student to do."

That drive for interdisciplinarity carries over into Giryes's work, as he combines deep learning techniques with advances in optical hardware. "Right now, you have engineers who design optics and engineers who design sensors, and then you have the people who program the post-processing algorithms that give you better results," he says. "But the ultimate goal is to use both deep learning and new optics to design a totally new camera that is innovative and revolutionary."

With so much of our lives recorded on screen, we're going to need exactly that kind of leading-edge thinking to make the images do justice to the magnificent complexity of the real world surrounding us. ▲●■

GOOD VIBRATIONS

By deconstructing the brain's decision-making process, can neuroscientists unravel the secrets of happiness?

By Alex Hutchinson
Photographs by Ziv Koren

Déborah Marciano's path as a cognitive neuroscientist started with a surprise. She was analyzing the data from her very first PhD study, which used electrodes placed on the scalp to explore how regret is encoded in the brain, and saw a pattern emerge in the results. But it was precisely the opposite of what she'd expected.

Research has shown that after choosing between two options, people typically feel worse when they realize that the alternative, unchosen possibility yielded a better result than the one they selected. Think of those TV shows in which a contestant has to decide which door to open to reveal a prize. Getting a thousand dollars feels great, but less so if you learn you could have won a million dollars.

To find the neural correlates of regret, Marciano set up an experiment very similar to these shows: she asked subjects to choose between two boxes displayed on a screen. Each contained either a monetary reward or a loss. After subjects decided, they saw the unchosen outcome and then their own. "We found that people care about the alternative outcome, but not as we predicted," says Marciano. "From looking at their brainwaves, it seemed that for certain outcomes, subjects were *happier* following a good alternative, not less happy. But why?" She reran the analysis and eventually reran the whole experiment, measuring brain activity for hours at a time in 40 volunteers. But the results didn't change.

Untangling how our brains make sense of what-ifs and could-have-beens remains a puzzling challenge for neuroscientists — and an important one: 'I think that understanding what shapes our subjective experiences can help us make objectively better decisions, and also decisions that will make us happier.'

It turned out to be a lucky break. Marciano had stumbled upon what's now known as the alternative omen effect, a striking example of how our subjective experience of a given outcome is shaped by its context. Untangling how our brains make sense of what-ifs and could-have-beens remains a puzzling challenge for neuroscientists — and an important one: "I think that understanding what shapes our subjective experiences can help us make objectively better decisions," she says, "and also decisions that will make us happier."

Marciano was born and raised in Paris and planned to move to Israel after high school, but her parents wouldn't let her go until she'd finished a university degree, so she was left scrambling at the last minute to find a program that would let her in. She'd imagined being a doctor but ended up in a selective and highly unusual double major at the Sorbonne, combining law and economics. Grappling with topics such as utility and satisfaction, and how to incentivize people to do the right thing, she saw a common thread: the question of how people make decisions in the messy real world.

After graduating, she headed to the Hebrew University of Jerusalem, where she studied psychobiology and enrolled in the university's unique interdisciplinary honours program in the humanities. By this point, she'd decided to become a cognitive neuroscientist. Marciano stayed at the Hebrew University for her master's and PhD, supported by an Azrieli Graduate

As a student, grappling with topics such as utility and satisfaction, and how to incentivize people to do the right thing, Déborah Marciano saw a common thread: the question of how people make decisions in the messy real world.

Studies Fellowship from 2015 to 2017, while also completing a program at the Federmann Center for the Study of Rationality, where most of her classmates were philosophers and economists. Despite the seemingly meandering path for a would-be brain scientist, it all led her back to decision-making.

"I think in research it's really an advantage to have all of these backgrounds, because you think of the big questions," she says. "It helps you make connections between all these different fields. You have them in the back of your head, and you just can't help but connect the dots."

The alternative omen effect is a reflection of our angst about the road not taken. Marciano found out in her experiment that when participants were shown the outcome of the unchosen option, they formed biased expectations: "When the box they *didn't* choose turned out to contain a prize, subjects became more pessimistic about the chances that their box would contain a prize. They expected to lose." Even when the experiment was set up to make it clear that there was no correlation between the two options, and that the number of prizes in the game was not limited, the effect persisted. It was as if, she and her colleagues concluded, we intuitively assume that there's a limited amount of luck in the world.

Marciano is still interpreting the implications of a belief in limited luck — whether it's limited in time or space, what it means for how we make decisions, and so on. But the results also carried a broader message: how we perceive a given set of outcomes depends on how they're presented to us. Change the context and you change our response. In this case, some irrelevant information about the other option changed people's expectations and, in turn, their subjective experiences. And that led her to consider another gambling riddle, the near-miss effect, in her postdoctoral research.

In 2019, Marciano moved to the University of California, Berkeley to work with Robert Knight, a world-leading neuroscientist, and Ming Hsu, a neuro-economist based in Berkeley's business school.

Marciano quickly made a positive impression, displaying "that rare combination of theoretical brilliance, empirical skills, productivity and motivation that highlight future scientific leaders," Knight says. She is also committed to building diversity in science, he adds: during the COVID-19 pandemic, she successfully lobbied for enhanced childcare funding for postdoctoral researchers and co-authored a paper on gender bias in academia.

To track how the expectations of people change over time, Marciano uses neuroscience techniques that can capture rapid changes in brain activity, such as electroencephalography (EEG) and intracranial EEG.

'In many real-life situations, expectations are not fixed. They evolve as situations unfold, sometimes within seconds. Consider a football game. You don't sit through the game thinking, "My team has a 30 per cent chance of winning." Your expectations vary as the game evolves and goals are scored.'

The near-miss effect sits comfortably at the intersection of Knight's and Hsu's interests. Consider a slot machine where you have to match two symbols to win. "In theory, there are just two types of feedback: you win or you lose," Marciano explains. "But that's not the way it feels, right?" If the first spin stops at a lemon, and the second spin appears to be slowing to another lemon but then stops one agonizing click short, you'll feel something different compared to a "full miss." Gambling research has found that compared to losing decisively, *almost* winning makes people more unhappy, but also more likely to take another spin — a fact that explains why, in many jurisdictions, casinos are expressly forbidden to program their slot machines to deliver an excessive number of near-misses.

The mechanism behind this curious effect, however, is not clear. "When I first read about the near-miss effect, I immediately wondered whether this was about expectations again," says Marciano. "At a slot machine, the most exciting part of the game is the spinning part. This is what we are attracted to. It's not that we close our eyes and just wait for the game to finish. Something is happening during this spinning, and especially during the deceleration. We're forming expectations, I think, and these expectations change the way we feel about losing."

Gambling researchers have been studying the near-miss effect for decades in the hope of understanding pathological gambling and addictions. But Marciano's interest goes beyond gambling. "I use biases in general, and the near-miss effect in particular, as a window into something bigger and more general," she says. "These experiences help us understand how the brain processes reward. The alternative omen and near-miss effects are very specific situations in which our surprising behaviour gives us a hint about the processes going on in the black box of our mind."

The near-miss effect also made her think about expectations in a new way. Reward expectations play a very important role in cognition, impacting faculties such as memory, learning, motivation and satisfaction, but they have traditionally been studied as static. "In many real-life situations, however, expectations are not fixed," says Marciano. "They evolve as situations unfold, sometimes within seconds. Consider a football game. You don't sit through the game thinking, 'My team has a 30 per cent chance of winning.' Your expectations vary as the game evolves and goals are scored. Same goes for a car accident, or a date. Given the central role of expectations in cognition, we felt it would be important to study the dynamics of expectations. We were wondering how we could capture these dynamic expectations, and if and how they shape our subjective experience."

Slot machines provide Marciano with a real-time way to observe dynamic expectations and develop a deeper understand of how they relate to subjective experience. Plus, because slot machines are used frequently in gambling research, there are already validated research paradigms. To track changes in expectations, Marciano uses neuroscience techniques that can capture rapid changes in brain activity: electroencephalography (EEG) and intracranial EEG.

Knight's research group works with patients who are about to undergo surgery for epilepsy. They've had electrodes implanted in their brains to figure out where the seizures are starting, but often have to wait for a week or so before the surgeons are sure they've identified the right spot. While they wait, many patients agree to take part in neuroscience experiments. The intracranial — inside-the-brain —

After years of studying decision-making from the perspective of economists, philosophers and psychologists as well as brain scientists, Marciano doesn't believe we should aspire to a robotic rationality that makes every decision on the basis of its predicted utility.

electrodes provide high-resolution measurements of brain activity that are impossible with conventional imaging techniques, Knight explains. With a network of collaborating surgeons across the United States and around the world, his research team always has someone ready to hop on a plane whenever one of these patients is available and willing to participate. This tool gives Marciano the ability to observe how subjects' brain activity changes on a moment-by-moment basis.

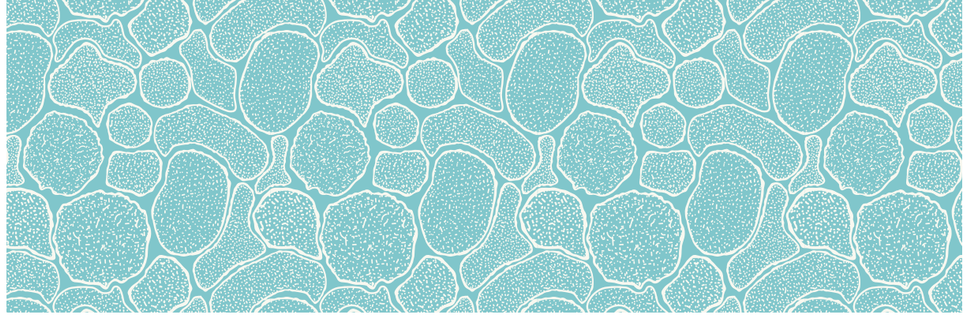
One day last fall, Marciano received data from an epilepsy patient in Oslo who had played a series of virtual slot machine games the previous day. Activity in the patient's orbitofrontal cortex, an area that integrates information about potential rewards from other parts of the brain, "beautifully tracked" their changing expectations as the slot machine spun: a gradually swelling crescendo of hope followed by a sudden crash, in the case of near misses.

The anterior cingulate cortex, meanwhile, keeps track of prediction error: the gap between what you thought was going to happen and what actually happened. The interaction between these two brain regions — between expectation and prediction error — as the wheels spin may be what gives us the mistaken impression that we'll win if we drop just one more quarter into the machine, Marciano suspects. But nailing down the role of other brain regions will take time and luck: the data she gets depends in part on where her volunteers' seizures originate, which determines where the electrodes are placed. In the meantime, a series of EEG and behavioural experiments have confirmed her predictions: our expectations can change within hundreds of milliseconds. This "rollercoaster of expectations," the ups and downs, predicts happiness ratings following gains and losses on the slot machine. Future studies with lesion and Parkinson's patients (who often develop problematic gambling habits once medicated) will help her understand the neurobiological mechanisms at play during expectation formation.

Daniel Kahneman, the Nobel Prize–winning psychologist who helped pioneer the study of cognitive biases, was famously skeptical of our ability to overcome them. Knowing that you're prone to certain patterns of thought doesn't necessarily enable you to avoid them, he argued. Will learning about the near-miss effect help anyone walk away from a slot machine rather than dump more money into it? Or to navigate other situations where near misses influence our responses, from picking stocks to driving in traffic?

To Marciano, this framing of the question is too narrow. To her, there's no doubt that understanding seemingly irrational responses like the alternative omen and near-miss effects can be used to alter behaviour. "I think the casino industry understands this very well," she says, "and they exploit it." But there are also broader benefits to understanding the mechanism behind biases. "The near-miss effect was just the starting point that led us to ask how we form expectations from moment to moment," she says, "and how these expectations relate to outcome evaluation in healthy cognition and in disorders such as depression."

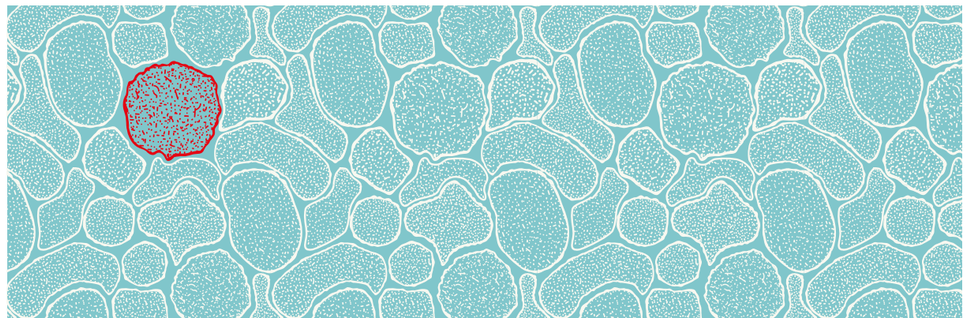
Moreover, after years of studying decision-making from the perspective of economists, philosophers and psychologists as well as brain scientists, Marciano doesn't believe we should aspire to a robotic rationality that makes every decision on the basis of its predicted utility. The changes taking place in our brains as a spinning slot machine wheel slows to a halt reflect a much larger truth about how our subjective experiences depend as much on the journey as the destination. "I think we're now understanding that happiness is not just 'Did I win?' or 'Did I lose?'" she says. "It's also, 'Was I surprised along the way? Did my hopes go up or down?' Just like with a rollercoaster, focusing on the start and the end doesn't tell you much about the experience. Looking at the turns and loops is a whole other story." ▲●■



WHY DON'T IMMUNE CELLS FIGHT CANCER?

Using cutting-edge genomics and creativity to stop immune cells from switching off upon entering tumours

By Dan Rubinstein
Photographs by Hadas Parush



Daniel Kirschenbaum's wide-ranging scientific curiosity found a home in Ido Amit's lab at the Weizmann Institute of Science. The research group is a leader in the development of single-cell genomic analysis — a method for isolating individual cells and quantifying their genetic composition to better understand their condition and properties.

There are two ways to look at brain cancer, suggests Daniel Kirschenbaum, a neuropathologist and immunology researcher at the Weizmann Institute of Science. The disease is traditionally described as the uncontrolled growth of cells, but it can also be seen as the failure of the immune system to identify and attack these cells.

"Our immune system is equipped to fight cancer," says Kirschenbaum, who followed his wide-ranging scientific curiosity from a hospital in Switzerland to a trailblazing immunology lab at Weizmann as an Azrieli International Postdoctoral Fellow. "We have cells that are tailored to do this. But if they fail to do so in the early stages, the cancer just grows."

In fact, in glioblastomas, one of the most common and aggressive types of brain tumour, nearly half of the mass is made up of immune cells. If somebody with cancer gets the flu, immune cells flowing in their blood will usually fight off the virus. "But cells that are supposed to fight the tumour go inside, switch off and essentially become harmful," says Kirschenbaum. "They're supporting a tumour with factors and nutrients.

"If we can stop this, we can help people," he continues. "We can treat their cancer and improve and prolong their lives."

Kirschenbaum was interested in a broad spectrum of science while growing up in Budapest, from chemistry and biology to psychiatry and genetics. But mostly, he was fascinated by the brain. He wondered how physical changes to the "hardware" of an organ you can touch led to cognitive phenomena, such as the changes to personality and perception experienced by stroke patients. He was curious about how people developed free will or the illusion thereof — the capacity to make decisions and perform actions — as their brains developed. Ditto the emergence of language in individuals.

Despite these diverse interests, becoming a doctor felt like a pragmatic choice. After medical school in Hungary, however, he didn't like the clinical aspect of his job at a hospital in Germany. So Kirschenbaum shifted to a neuropathology residency at University Hospital Zurich, where he enjoyed analyzing neurosurgical samples to diagnose tumours and neurodegenerative diseases and completed a PhD. Afterwards, unsure of his next move, he went on holiday in Israel and arranged informal meetings with several research groups.

Immunologist Ido Amit's lab at Weizmann, one of the places where Kirschenbaum gave a talk, is a forerunner in the development of single-cell genomic analysis — a method for isolating individual cells and quantifying their genetic composition to better understand their condition and properties. This technique, which has been revolutionizing immunology for the past decade, can be applied to cells from cancerous tumours and used to create maps of cell states: some healthy, some diseased, some in transition.

Kirschenbaum didn't know much about immunogenetics when he visited Israel, but Amit offered him a postdoctoral position nonetheless. "Many of our group's members don't come from our main areas of research," says Amit, who was struck by Kirschenbaum's passion for technologies that can be used to discover fundamental biology, as well as his intellect, leadership traits and open-mindedness. "As time goes on, people who are in a particular field tend to put themselves in a box, while people who come from the outside bring fresh ideas and perspectives. I like that."

"It was something to switch on my curiosity and excitement," Kirschenbaum says about accepting Amit's offer and moving to Israel in June 2020. "It was a very intuitive decision, and usually these decisions work the best in my life."

Since then, in close collaboration with his lab colleagues, two of whom are also Azrieli Fellows (see "Science as a Team Sport," page 27), Kirschenbaum has been attempting to answer a confounding question: What makes functional immune cells "switch off" when they enter a tumour? What happens after one hour? After two hours? Three? And so on. "To understand this," he explains, "you need to introduce a temporal dimension into studying a dynamic process that changes over time. But when we do single-cell analysis, we just take a snapshot. We don't know what came first and what came second. It's just a mixture."

Kirschenbaum's focus at Weizmann is a method to add "time signatures" to maps of cell states. He calls this technique "zman-seq": "zman" is the Hebrew word for time, while "seq" is short for sequencing. Still a work in progress but already quite promising, it's used to show precisely when cells change states and which genes are responsible for the transition from functional in the blood to dysfunctional in a tumour. Identifying these pathways will allow researchers to develop and test drugs that can alter the trajectory of immune cells, so they do what they are supposed to do upon encountering malignant cells.

"Daniel's technology to move from snapshots to movies allows us to see where the 'bad character' is," says Amit. "Now we can come up with innovative ideas for therapies that prevent that character from changing the immune cell."

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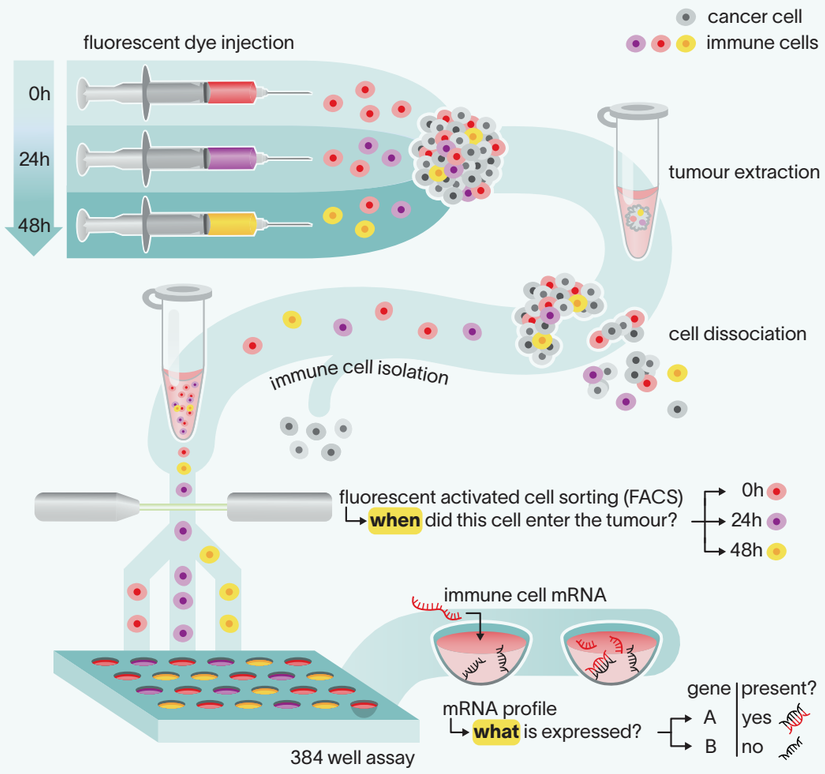
CELLULAR SLEUTHING

After inducing brain tumours in mice, Daniel Kirschenbaum injects fluorescent dyes of different colours into their vascular systems over several days. Immune cells in the blood pick up these colours and enter the tumours. Kirschenbaum then extracts the tumours and dissociates the cells, a three-hour lab protocol that involves centrifuges, filters and digestive enzymes. The cells are then put through a FACS machine, which deposits single cells into 384 individual wells on a plastic plate and records their fluorescence values, allowing him to decode the time signature of each cell. Since each of the wells is pre-coded with genetic barcodes, he can determine which cell each molecule in the experiment is associated with. This genomic data (which can also be described as the mRNA profile of each cell) is clustered and analyzed. Understanding precisely when immune cells change states and which genes are responsible for the transition from functional in the blood to dysfunctional in a tumour will allow researchers to develop and test drugs that help immune cells do what they are supposed to do.

Diagram by
Sarah Nersesian/Designs That Cell



"The problems that really turn on my curiosity are very fundamental, unsolved scientific challenges that require a technical solution," says Kirschenbaum. "I want to help solve big issues. That's what keeps me running. Ido's lab is like this: tackling fundamental problems, resulting in methods that people can start to use around the scientific community."

For more than a year, Kirschenbaum tried various techniques to overlay temporal information atop the molecular data collected from conducting single-cell analysis of immune cells inside tumours. Finally, he zeroed in on an approach that's conceptually fairly simple but technically rather complex.

Working with a cohort of mice, he induces tumours by injecting a few specific cells into their brains. Two weeks later, he injects a coloured fluorescent dye into the vascular systems of the mice. The immune cells in the blood pick up this colour — say, red — and enter the tumour. The next day, he injects a different colour — green — and new immune cells take on *that* colour and enter the tumour, along with some red and red-green cells. On day three, Kirschenbaum introduces a third colour, and the cells that enter the tumour are one of the three colours or some combination thereof. "If you follow these steps, you have cells in the tumour with different colour combinations," he explains, "and by separating the cells by colour, you can understand when they entered the tumour."

To differentiate by colour, Kirschenbaum first extracts the tumour and dissociates the cells, a three-hour lab protocol that involves centrifuges, filters and the application of digestive enzymes to disintegrate the matrix around the cells so individual cells can be isolated. The cells are then put through a FACS (fluorescence-activated cell sorting) machine, which deposits single cells into 384 individual wells on a plastic plate and records their fluorescent values, allowing him to decode the colour or time signature of each cell. Next, using enzymes that can read an RNA sequence, he amplifies the genetic material of each cell to obtain a stronger signal and puts them into a next-generation sequencer. Since each of the 384 wells is pre-coded with genetic barcodes, he can determine which cell each molecule in the experiment is associated with in addition to its time signature. This transcriptomic or genomic data (which can also be described as the mRNA profile of each cell) is clustered and analyzed by computational scientists in Amit's lab, and Kirschenbaum and his colleagues interpret the results together.

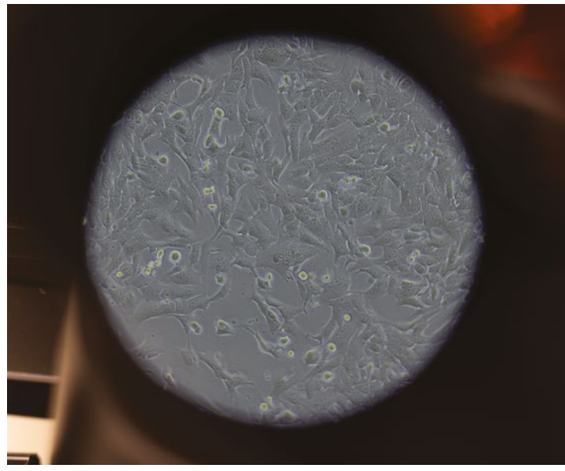
"The fluorescent profile of the cells represents their exposure to the temporally defined injections of fluorescent dyes," he explains. "Using this method, we know the transcriptomic profile and the temporal profile of every single cell we sorted. Based on the temporal signature we can now order the cells in time. This way we see how the transcriptomic profiles of single cells change in sequence across time."

Parallel to this research at Weizmann, two different drugs have shown in tests the potential to modulate how immune cells interact with cancer cells, and one is close to clinical trial. But researchers don't understand exactly how they work, says Kirschenbaum. Using the zman-seq method, "we'll be able to see — beautifully — how certain cells respond to this drug across time," he says. "We'll be able to draw arrows and look at how cells change compared to the non-treated ones. We'll be able to see and understand pathways. This is very concrete." If an immune cell enters a tumour and a certain gene is not expressed, for example, and several hours later that gene is highly expressed, researchers will be able to discern its importance.

"It provides a fresh approach to developing better therapies," Amit says about zman-seq's potential to illuminate the environment in which immune cells become pathological. "Daniel's technology to move from snapshots to movies allows us to see where the 'bad character' is. Now we can come up with innovative ideas for therapies that prevent that character from changing the immune cell."

These days, while writing a paper about his method, Kirschenbaum is also trying to make it more effective. He'd rather use genetic barcodes than colours to time-stamp immune cells, because the range of useable colours is limited, whereas the number of genetic sequences is endless, plus these labels would last longer and provide more precise, higher-resolution pictures.

Zman-seq and any iterations that emerge can be used with all tumours, not just brain cancer, and this research fits with the overarching goal of developing novel immunotherapies in Amit's lab. Yet Kirschenbaum remains somewhat restless. The work satisfies his curiosity. He finds it very stimulating and inspiring. "But at the same time," he says, "it makes me think about next steps and new directions."



Kirschenbaum (top) and his lab mates, including Azrieli Graduate Studies Fellow Yonatan Katzenelenbogen (bottom), are focused on tackling fundamental problems and developing methods that people can start to use around the scientific community.

Kirschenbaum (centre) enjoys brainstorming with Truong San Phan (left), an Azrieli International Postdoctoral Fellow, and Katzenelenbogen (right), a PhD student and Azrieli Graduate Studies Fellow.

Science as a Team Sport

When Daniel Kirschenbaum joined Ido Amit's immunotherapy lab at the Weizmann Institute of Science, he joined a bustling group of nearly three dozen researchers who use single-cell genomic technologies to better understand diseases such as cancer, Alzheimer's and multiple sclerosis. But even though Kirschenbaum had significant lab experience at University Hospital Zurich, where he worked as a neuropathologist before moving to Israel as an Azrieli International Postdoctoral Fellow, he still needed somebody to show him the ropes. Yonatan Katzenelenbogen, a PhD student and Azrieli Graduate Studies Fellow who had been in Amit's lab for two years already, embraced that role.

"This is a big lab, which can be hard to navigate," says Katzenelenbogen, whose research focuses on developing genomic technologies to diagnose and provide precision medicine for cancer patients. "Since we routinely work with a broad range of tools and models, it's necessary to master a large number of techniques, lab-related protocols and devices. As part of his training, I showed Daniel how to use our flow cytometry device, which sorts cells for further processing, and how to use our unique molecular techniques to create a full transcriptomic RNA library from each individual cell."

Not only did Katzenelenbogen support his colleague on the technical side of things, the two creative thinkers also bounced ideas off one another, which helped Kirschenbaum work toward his zman-seq method. "I can come up with ideas very quickly," says Kirschenbaum. "If you give me a problem, a technical issue, they just come. But you have to combine generating ideas with trashing them, because if you try all of your ideas you won't get anywhere. Even if you have very interesting ideas, you have to see the flaws immediately, which happened through my discussions with Yonatan.

"You cannot swim without water," adds Kirschenbaum. "You need a counterforce, someone to give resistance, so it stimulates you to think critically."

About eight months after Kirschenbaum started at Weizmann, Truong San Phan, an Azrieli International Postdoctoral Fellow from Germany, joined the lab. "Daniel was doing large experiments and needed a hand," says Phan, whose research focuses on trying to find out what makes chronic inflammatory diseases chronic. "I helped with any kind of work that had to be done: handling samples, handling tissue, isolating brain cells." The pair talked while they worked, easing the tedium of the manual labour and providing further motivation for both.

"The questions we're asking in this type of research are getting more complicated; the challenges are getting bigger and bigger," says Phan. "Projects cannot be done by one person. It's always a team effort. And the harder the question, the more people we need."

"Science is not an individual sport, like tennis," affirms Amit. "It's more like football, where you can only be great if you learn to work as a team and people are passionate about one another's research. This is the DNA of our lab. We focus not on prizes but on achievements. If you think of big human achievements — like landing on the moon — most are the result of a team effort. If we want to achieve great things, we can only do it as a team."

'I can come up with ideas very quickly. If you give me a problem, a technical issue, they just come. But you have to combine generating ideas with trashing them, because if you try all of your ideas you won't get anywhere.'

The atmosphere in Amit's lab can be credited, in part, to the culture that he nurtures; most of his students and postdocs have two or three or even four projects on the go, so there are what Katzenelenbogen calls "overlapping dependencies," reducing competition. "That's super important in our field," says Katzenelenbogen. "It increases creativity, because we're always brainstorming with each other. This creates more than work-related collaboration. It creates friendships that make it really fun to arrive at work in the morning, which is essential for success."

Moreover, this teamwork is emblematic of the non-hierarchical, merit-based system that's typical of research in Israel. It doesn't matter whether somebody is a PhD student: they can still show a postdoc what to do and get into a deep conversation about science. "Then, after you discuss a big idea, there are no excuses — you just do it," says Kirschenbaum. "If there's a reagent missing, you just go to another lab one floor above and ask if they have it. There's no need to postpone the work while waiting for your supplies to arrive. If you want to do something, you just do it." ▲●■

ISRAEL LEADS THE PACK IN COMPUTER SCIENCE

Researchers in Israel blaze new trails for the machines at the centre of our lives

Between 1996 and 2021, Israeli computer scientists published 54,350 papers, according to data from the Scimago ranking website. On average, each of these papers was cited 20.57 times. **That puts Israel in fourth place in the world** in citations per document among the 50 countries that published the most computer science papers in this span. In some categories, Israel ranks even higher. Here, we explore the strengths of computer science research at higher education institutions in Israel.

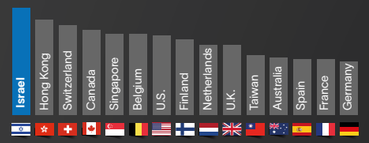
30 AZRIELI FELLOWS

Computer science is well represented within the Azrieli Fellows Program, which has supported more than 30 computer scientists since its inception in 2007.

1ST IN THE WORLD

ARTIFICIAL INTELLIGENCE

The simulation of human intelligence processes by machines



Technion–Israel Institute of Technology

Tel Aviv University

TOP 100

According to CSRankings, which weighs university departments by their presence in the most prestigious publications, in the past decade four Israeli academic institutions ranked among the **top 100 universities worldwide in all areas of computer science.**

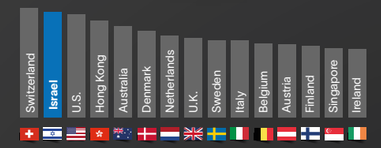
The Hebrew University of Jerusalem

Bar-Ilan University

2ND IN THE WORLD

HARDWARE AND ARCHITECTURE

The design and operational structure of systems



3RD IN THE WORLD

SOFTWARE

The development, design and maintenance of programs and other operating information

9 GÖDEL PRIZES

Over the past decade, nine Israeli-trained scientists have won the Gödel Prize, demonstrating the high quality of Israeli computer science research.

4TH IN THE WORLD

COMPUTER NETWORKS AND COMMUNICATION

Managing interconnected systems of computers

NEW

FRONTIERS FOR TWO-DIMENSIONAL MATERIALS

Unleashing the potential of graphene and other nanomaterials can change the world

By Ty Burke
Photographs by Hadas Parush

Twenty years ago, a pair of researchers at the University of Manchester made a remarkable breakthrough in their lab using an everyday adhesive. While attempting to isolate a layer of carbon that was as thin as possible, they looked through a microscope at the grey, slightly shiny residue from a graphite crystal left behind on a piece of Scotch tape. What they saw was graphene, the first two-dimensional material ever discovered, a eureka moment that eventually led to the Nobel Prize in Physics.

Stronger than steel but lighter than paper, graphene conducts electricity more efficiently than copper wire. Virtually transparent, it also conducts heat better — and is thinner — than any other material. These attributes give graphene almost limitless potential, once we figure out how to use it more effectively.

A form of carbon that's derived from graphite, graphene is the same substance used in a regular pencil. If you lightly trace the tip of a pencil across a sheet of paper, you leave layers of it behind. These one-atom-thick layers can be stacked like Lego to make a nanomaterial that is strong, lightweight and conductive — and that could unlock all kinds of novel applications.

Already a strong candidate for several innovative technologies, graphene could one day be used to make a mobile phone so bendable that you could wrap it around your wrist like a watch, then seamlessly reform it into a rectangle. It could improve the efficiency of solar panels and batteries, enabling electric vehicles to travel tremendous distances on a single charge. It even has the potential to be used in biosensors that could detect cancerous tumours earlier and deliver targeted therapies directly to them before it's too late. But we can't do these things yet. To make the most of graphene, we need a fuller understanding of how it works on a molecular level.

Graphene could one day be used to make a mobile phone so bendable that you could wrap it around your wrist like a watch, then seamlessly reform it into a rectangle. It could improve the efficiency of solar panels and batteries, enabling electric vehicles to travel tremendous distances on a single charge.

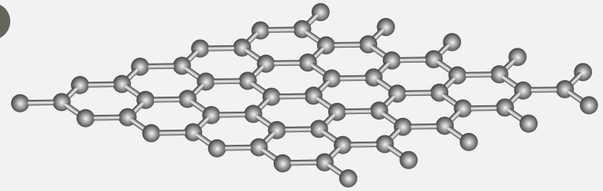
Graphene is just one example of a two-dimensional material. These materials are made of ultra-thin layers just a single atom thick, and they can have all kinds of exciting properties. They have the potential to transform numerous industries, but it is difficult to understand exactly how they work, and even more difficult to harness their potential. Researchers like María Camarasa Gómez are confronting this challenge.

The Spanish physicist, who operates at the confluence of quantum mechanics and theoretical chemistry, joined the quantum theory of materials research group at the Weizmann Institute of Science in August 2021 as an Azrieli International Postdoctoral Fellow. Led by principal investigator Leeor Kronik, the group aims to predict the properties of materials based only on their atomic composition and the laws of quantum mechanics.

GRAPHENE 101

A form of carbon that's derived from graphite, graphene is the same substance used in a regular pencil. If you lightly trace the tip of a pencil across a sheet of paper, you leave layers of it behind. These layers (1) are one atom thick. Electrons move through them as though in a two-dimensional plane. Each carbon atom in these layers is bonded to three other carbon atoms via sigma-type covalent bonds. The atoms share four electrons equally between them, and this creates a hexagonal latticework with the appearance of honeycomb. Because the atoms share electrons with each other, their chemical bonds are especially strong. As a result, graphene is among the strongest materials known to science. Moreover, these layers can be stacked like Lego (2) to make a nanomaterial that is strong, lightweight and conductive. The research that María Camarasa Gómez and her colleagues are doing to better understand the properties of graphene and other two-dimensional materials could unlock all kinds of novel applications.

1



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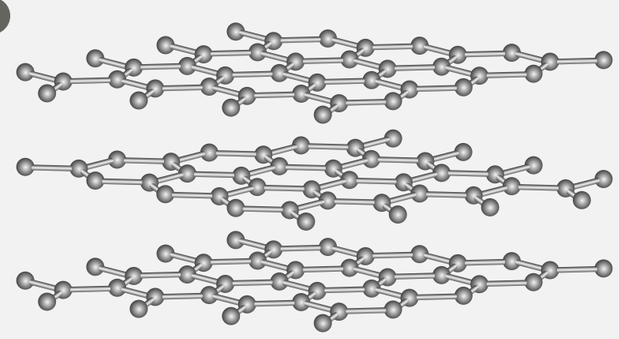


'We are developing new computational methods to study the optical and electronic properties of two-dimensional materials that are both fast and reliable and can be used daily without so much energy consumption. Instead of using 100 computers, you might be able to use just 10.'

To understand the properties of any form of matter, one must first learn how the electrons in that substance interact. Understanding the electronic and optical properties of materials in general, and those of two-dimensional materials in particular, is complex because of the need to describe how the material is perturbed from its lowest energy state. Many-body perturbation theory is one of the main ways to do this. It is highly accurate but can require a great deal of computational power and time — it can take weeks to get results — which forces researchers to consider whether each computation is feasible. Yet Camarasa Gómez is now developing variations on existing computational methods that could allow hypotheses about two-dimensional materials to be probed much more efficiently and quickly.

"We primarily use density functional theory, which is reliable but has logistical constraints," explains Camarasa Gómez, who completed a PhD in computational condensed matter physics at the University of Regensburg in Germany in 2020. "So we are developing new computational methods to study the optical and electronic properties of two-dimensional materials that are both fast and reliable and can be used daily without so much energy consumption. Instead of using 100 computers to complete this task, you might be able to use just 10."

At the quantum level, physics and chemistry intersect. Both seek to understand the properties of individual atoms. Density functional theory (DFT) is used by researchers in both disciplines to build this understanding through mathematical simulations of the quantum mechanics of atomic systems. Camarasa Gómez came across DFT in her PhD studies, then learned about Kronik's work at Weizmann and decided she wanted to collaborate with him.

Normally, a system's energy is calculated using a partial differential equation that can get very complicated when a system has many electrons and nuclei. This is called the many-body problem. DFT works around it by focusing on the density of electrons. This greatly reduces the complexity of the equation and makes simulating an atomic system much less computationally intensive. All of which means that researchers can more readily probe their hypotheses.

The quantum theory of materials research group at Weizmann is both applying DFT and developing approaches that stem from the central equation of DFT. Called the Kohn-Sham equation, it was formulated by Lu Jeu Sham and Walter Kohn in the 1960s. Kohn won the 1998 Nobel Prize in Chemistry for his leading role in DFT's development, but it was largely quantum physicists who used this equation in the decades after it was published. It was not until the 1990s and, more so, the 2000s that DFT became a mainstay of quantum chemistry.

Weizmann's quantum materials research group began to develop DFT-based approaches to compute electronic and optical properties more than a decade ago. First, they focused on very simple molecules, followed by more complex molecular crystals, and then three-dimensional semiconducting solids like silicon.

"Existing techniques were already pretty accurate for predicting, for example, the structural and mechanical properties of a material, but for electrical and optical properties, there was often a systematic failure," says Kronik. "What I mean by this is that calculations were nowhere near what we expected. You could make a prediction, but it would be wrong, so it's not much of a prediction."

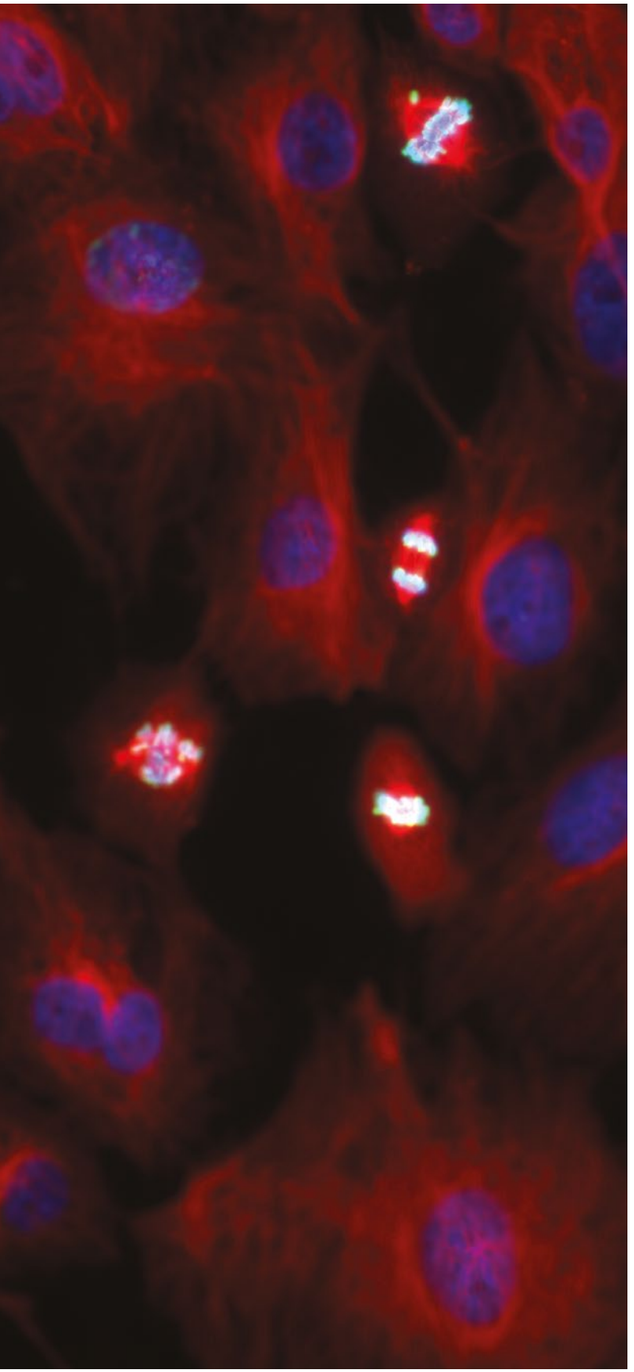
Two-dimensional materials are a new frontier for DFT. Graphene is the best known of these materials, but Camarasa Gómez's work will be used to characterize the properties of around 10 to 15 other substances, representative candidates from various families of materials.

"Almost any property you can think of appears in an exotic way in some 2D material," says Kronik. "Clearly, we want to be able to predict their electrical and optical properties. That is precisely where María's work comes in, and she already has some very nice results. Being able to make predictions about these materials could help us understand experiments that are presently perplexing. It can help us figure out new materials to suggest to experimentalists to synthesize, or to tell them about the predicted properties of an existing material. But we can't do that for electrical and optical properties unless we have relatively inexpensive methods we trust.

"At some level, it is the long-standing dream of chemistry to be able to make predictions based on atomic composition alone," adds Kronik. "At a more practical level, one encounters many phenomena in the study of materials that people measure in experiments but still defy explanation."

"If we can control one layer of a material like graphene, and then put another layer on top, computational methods could help us simulate how they will interact," Camarasa Gómez elaborates. "There could be unexpected electronic or optical properties. The ability to control or 'tune' these properties — for example, enhancing conductivity — is what would enable a wide variety of applications."

Many of these applications are still on the distant horizon, and Camarasa Gómez compares our current state of knowledge to the famous image of an elephant surrounded by blindfolded scientists. Each scientist reaches out to touch the elephant, but no individual can see or feel the entire animal. One touches its leg and says that it is a tree. Another touches its tail and says that it is a snake. "The approximations we are making with density functional theory are a little like this," she says. "We don't know everything and only ever have partial information. We obtain results about certain systems, under certain conditions, but it will take the effort of many people to fully understand what we are looking at." ▲●■



The Great Divide

By Simon Lewsen
Photographs by Boaz Perlstein

Uri Ben-David inspects a bottle containing a culture medium that's used to grow cells in a dish. His research involves studying microscopy images of dividing cells, including the four cells (far left) that were captured while dividing. Two of these four seem to be dividing properly, while the other two present mitotic aberrations (defective cell division) that might result in daughter cells with chromosomal irregularity.

Solving the mysteries of chromosomal abnormalities could hold the key to precision cancer treatments

In the early 1900s, Theodor Boveri, the renowned German zoologist and anatomist, was studying sea urchin eggs under a microscope when he noticed something strange. Boveri — who today is considered the father of modern cytology, or cell biology — was mainly interested in the process by which healthy cells divide. But he noticed that some cells within his sea urchin samples divided abnormally, without the beautiful symmetry he had observed in healthy tissue.

A sea urchin cell has 42 chromosomes, each a thread-like structure containing a single DNA molecule (although Boveri wouldn't have known this at the time). Before cell division, Boveri saw that each cell would create a complete copy of its chromosomal set, doubling the number to 84. When the cell divided, the new 84-piece set would then be shared evenly among the two daughter cells, so that each would have 42 chromosomes, just like the parent. But occasionally, the process got scrambled. A parent might divide into two misaligned daughters, perhaps one with 41 chromosomes and the other with 43. These cells, in turn, would divide unevenly again — and then again and again — giving rise to abnormal progeny. What's more, these abnormal cells, with their uneven assortments of chromosomes, closely resembled cancer tissue.

Boveri didn't have the scientific vocabulary to describe what he was seeing, but he intuited its significance. In his 1914 book, *Concerning the Origin of Malignant Tumours*, he theorized that chromosomal irregularity, a condition that scientists now call

aneuploidy, was an essential characteristic of cancer. The theory held up: today, researchers estimate that in humans 90 per cent of solid cancers and 70 per cent of blood cancers are made up of aneuploid cells. (A healthy — that is, non-aneuploid, or, to use the technical term, euploid — human cell has 46 chromosomes. A human cell with any other number is aneuploid.)

Boveri was far ahead of his time — too far, in fact, to fully explore the implications of his theory. In a world without computer modelling or DNA sequencing, he and his contemporaries had few means with which to study aneuploidy or its effects on cell physiology. (The science of genetics was still in its infancy. Boveri was himself a pioneer in the field.) And so, from a therapeutic standpoint, his observations about cancer and aneuploidy remained more novel than meaningful. They raised tantalizing questions but didn't point the way toward a cancer cure.

Uri Ben-David, a professor in the Department of Human Molecular Genetics and Biochemistry and an Azrieli Early Career Faculty Fellow at Tel Aviv University (TAU), belongs to a new cohort of cancer researchers who are bringing contemporary technology to bear on Boveri's work. His hope is to devise better, more targeted cancer treatments.

A common misconception about cancer cells, Ben-David explains, is that they're difficult to kill. "Cancer cells are easy to kill," he says. "You can do it with bleach." The problem, of course, is that bleach kills everything else, which is why injecting the substance isn't a viable medical intervention. What researchers have sought, instead, are treatments that disproportionately affect cancerous tissue, singling it out for special punishment.

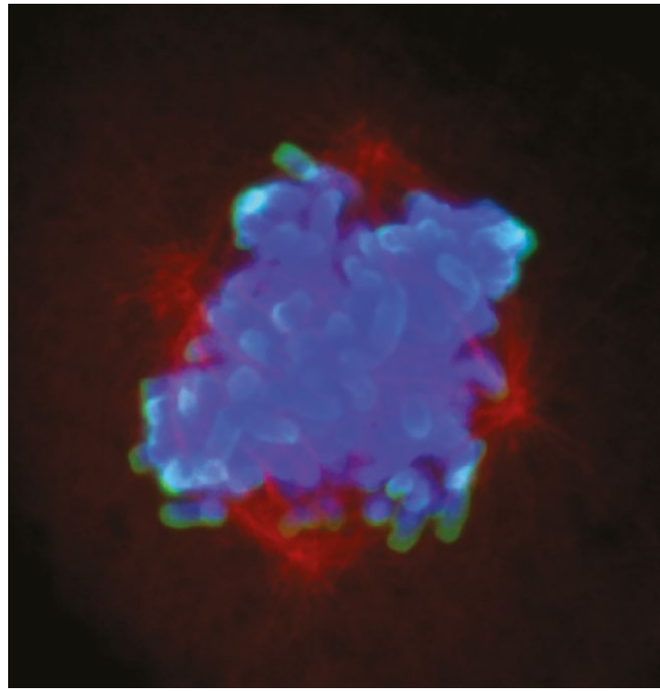
To that end, scientists must ask two key questions: How are cancer cells dissimilar from other kinds of cells? And how might we exploit these dissimilarities to devise more finely targeted therapies? The study of aneuploidy has obvious potential. "It's one of the biggest differences between cancer cells and normal cells," says Ben-David.

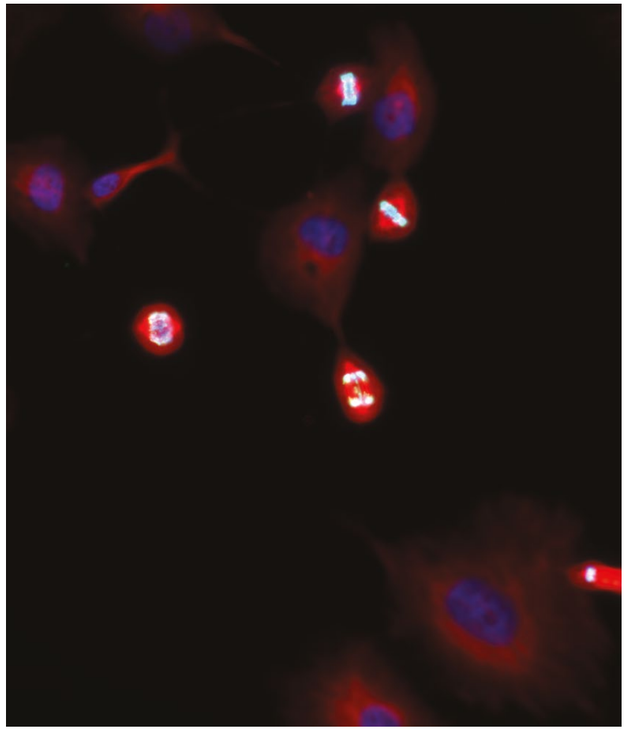
After finishing his PhD in genetics at the Hebrew University of Jerusalem, Ben-David moved to Cambridge, Massachusetts, to pursue a postdoctoral fellowship at the Broad Institute of MIT and Harvard. His initial focus was cancer genomics, and in 2016 he attended a conference on aneuploidy in South Carolina, which cemented his growing interest in the subject.

Technological breakthroughs were enabling new experimental possibilities. The advent of DNA sequencing meant that researchers could quickly assess the level of aneuploidy in a given cell without having to place it under a microscope and then count the number of chromosomes. The arrival of gene editing meant that scientists could engineer aneuploidy cells in a lab and observe how they reproduce. "You could ask questions you wanted to ask 20 years ago," says Ben-David, "but with completely new technologies."

This is what the Ben-David Lab at TAU aims to do. Some of its work is computational. Today, many organizations around the world are producing complex datasets, which document the changing genetic composition of various cancer types as the cells divide and mutate over time. Ben-David and his team can then run computer algorithms to analyze these pre-existing datasets, seeking correlations between aneuploidy and other distinct characteristics of cancer. They might discover, for instance, that when a given cell becomes cancerous and aneuploid, it also expresses a certain gene that it doesn't express in its healthy, euploid state. From there, the team might develop a hypothesis: perhaps the aneuploid cell is depending for its survival on this newly expressed gene?

To test out such a hypothesis in the real world, the team then engineers aneuploid cancer cells — either mouse versions to be observed in live mice or human versions to be observed in lab dishes. Do actual aneuploid cells express the new gene, as the data analysis says they should? And what if you knock the gene out, using gene editing or a chemical intervention? Does the aneuploid cell die? The ultimate goal of this research is to learn as much as possible about cancer aneuploidy in the hopes of finding key vulnerabilities to exploit. "We're





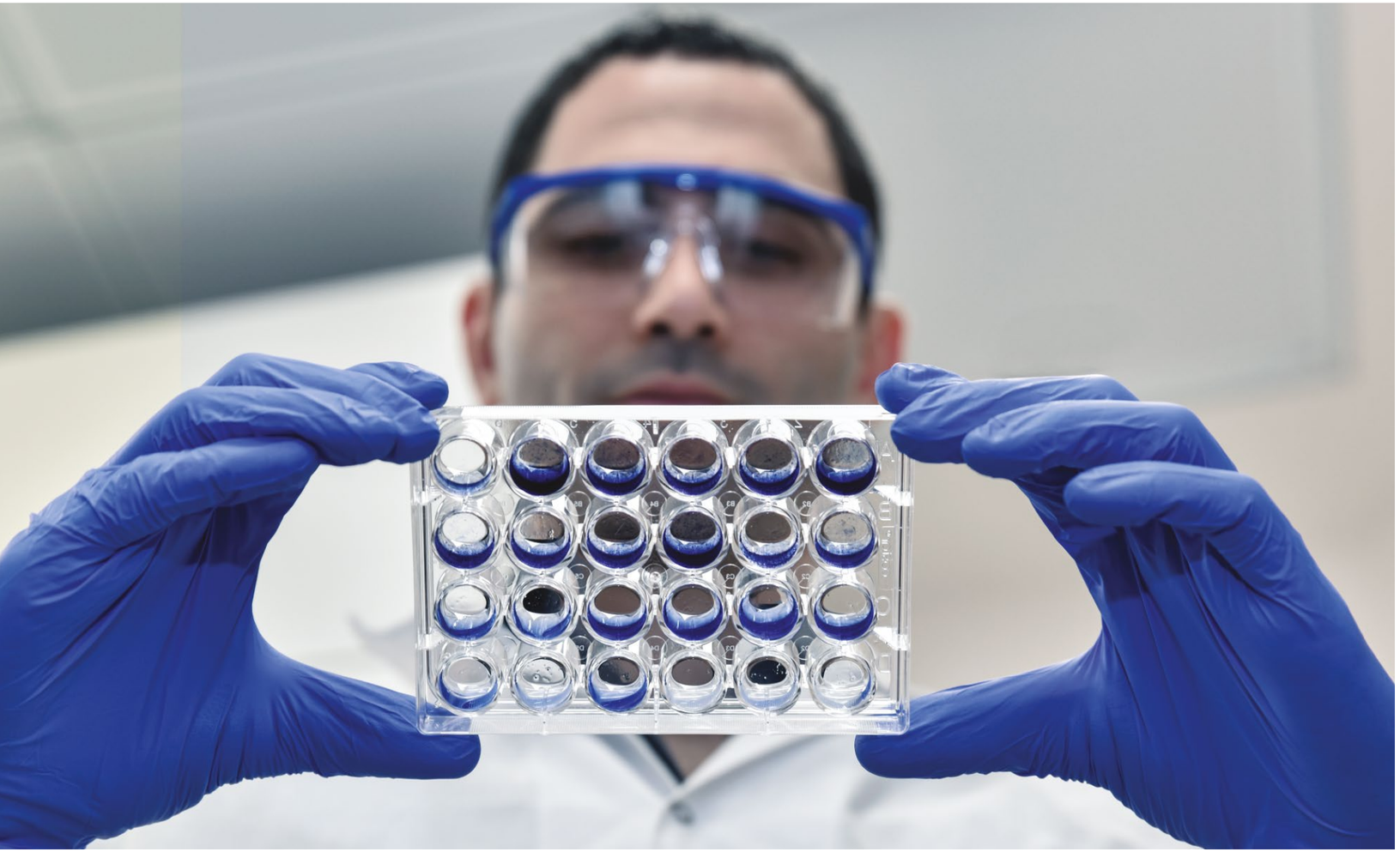
Technological breakthroughs are enabling new experimental possibilities. 'You can ask questions you wanted to ask 20 years ago,' says Ben-David, 'but with completely new technologies.'

Ben-David looks at cells via a light microscope (above left) to follow their proliferation. A cell that divides improperly (above) splits its chromosomes among four daughter cells instead of splitting them between two daughter cells. These microscopy images (left) allow Ben-David to see precisely what happens when cells divide.

interested in the types of cellular stress that aneuploidy can induce," says Ben-David, "because if we can identify these cellular stresses, we might be able to target them as well."

Critically, the lab doesn't do this work single-handedly. "Uri is extremely collaborative," says Floris Foijer, a cancer and aneuploidy researcher at the University of Groningen in the Netherlands. Members of Foijer's and Ben-David's groups meet every month with their colleagues at aneuploidy labs in Porto and Milan to share their work, a ritual Ben-David established early in the COVID-19 pandemic. The four labs now collaborate freely, assigning tasks — such as computational modelling or statistical analysis — to any researcher among them who possesses the relevant know-how. Such an open approach, Foijer argues, is essential to their mutual success. "Science is so technical these days," he says, "you must rely on disparate expertise. If you want to get a paper in a top journal, it's almost impossible to do it alone."

In 2021, Ben-David was the lead principal investigator on a collaborative study published in the journal *Nature*. The impetus for the study was a recent Broad Institute initiative to sequence the



Ben-David studies a plate with both aneuploid and diploid cells, the latter of which contain two complete sets of chromosomes. The blue staining liquid helps him quantify the number of cells and, accordingly, the effect of drugs on the cells (the stronger the colour, the more living cells present in each well).

genomes of 1,000 different cancer cell lines in roughly two dozen cancer types. When the Broad Institute released the project, Ben-David's team — a group that included researchers in his lab and four others — used computer algorithms to comb through the data, assigning a score to each cell line depending on how much aneuploidy exists within it. Did highly aneuploid cancers, they wondered, have anything else in common?

The team's data analyses suggests that the answer is yes: the more aneuploid certain cancers become, the team discovered, the more these cancers depend for their survival on a protein-coding gene called *KIF18A*. (*KIF18A* helps to regulate aneuploidy levels. It intervenes in the process of chromosome segregation, preventing highly aneuploid cells from producing daughter cells that are so aneuploid they can no longer live.) "Normal cells don't really need this gene for survival," says Ben-David, "but the aneuploid cells do."

The team then conducted wet-lab experiments, which bore this hypothesis out. In a lab dish, they engineered human cancer cells that were genetically identical but with different degrees of aneuploidy. They then inhibited the *KIF18A* gene and saw that, when the gene was no longer expressed, the highly aneuploid cancer cells had difficulty surviving. This finding has clear implications: if we can inhibit the *KIF18A* gene in certain human cancers, perhaps we can hasten the demise of the cancer cells.

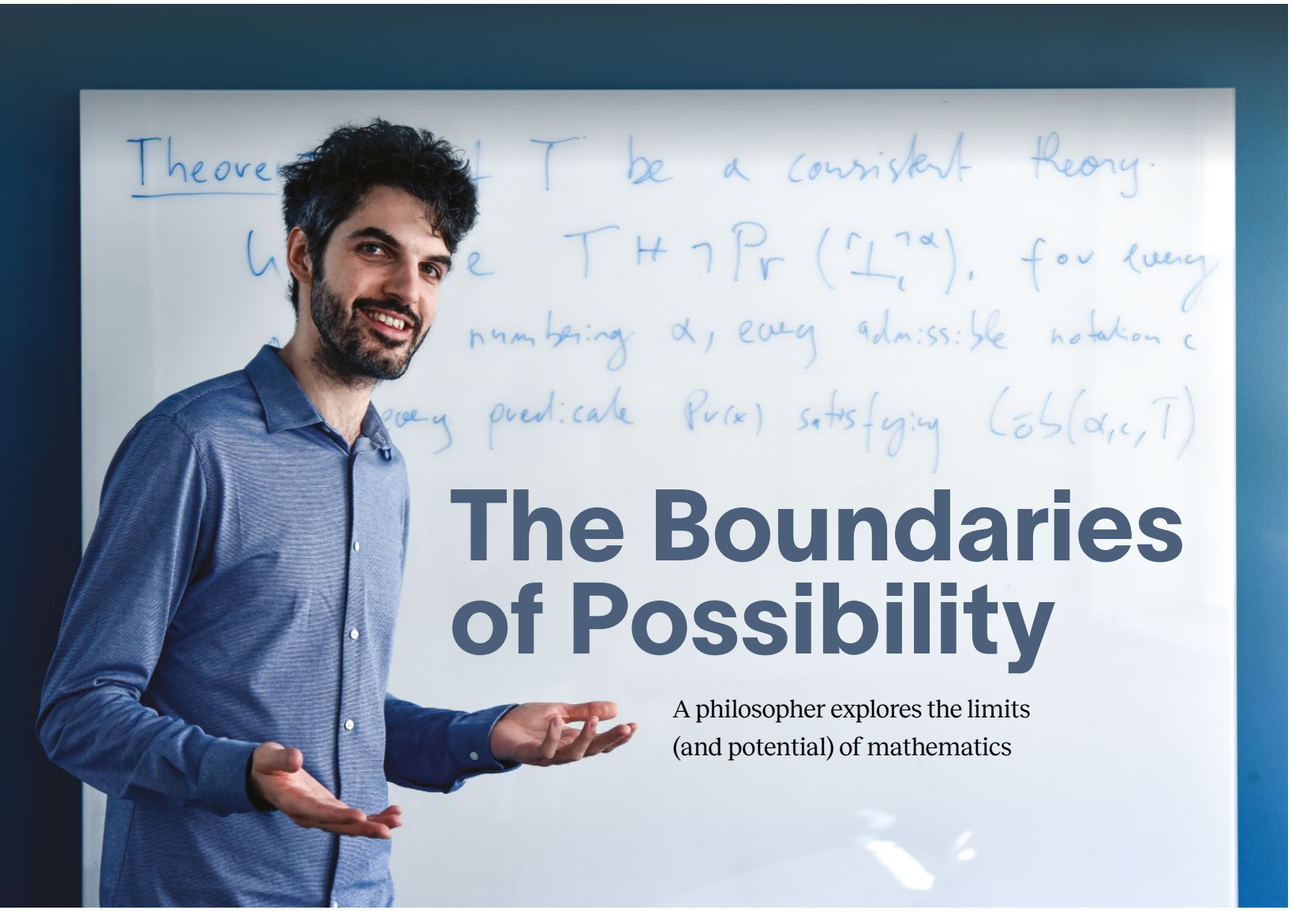
"The protein is druggable," says Ben-David. "You can design small molecules that specifically target it." Thanks in part to Ben-David's research, pharmaceutical companies are now doing just that. If their work succeeds, there will be a new weapon in the war against the most aggressive types of cancer. "The most aneuploid tumours tend to be the ones with the most severe unmet clinical needs," Ben-David says. "Ovarian cancer, pancreatic cancer, triple-negative breast cancer — these are cancers for which the motivation to develop new drugs is the highest to begin with."

The ultimate goal of this research is to learn as much as possible about cancer aneuploidy (chromosomal irregularity) in the hopes of finding key vulnerabilities to exploit. 'We're interested in the types of cellular stress that aneuploidy can induce,' says Ben-David, 'because if we can identify these cellular stresses, we might be able to target them as well.'

With its basis in data, genomics and molecular biology, Ben-David's research may seem fiendishly complicated, but cancer, he points out, is complicated too. Nobody would argue that respiratory or infectious diseases are simple or that the fight against them has been easy, but cancer is a scientific conundrum of a higher order. "When you think about which diseases we've made the least progress in curing," Ben-David says, "it's pretty linear with the complexity of the disease itself."

Ironically, by devising successful treatments for less challenging ailments, we've actually increased the prevalence of cancer in our world. Poor diet and exposure to toxins may partially explain why cancer is so common in developed countries, but the most salient explanation may also be the simplest: we live longer, and the risk of cancer increases with age. "It's estimated that among people currently in their 30s and 40," says Ben-David, "one in two will have cancer at some point in their lives."

That's why devising better, more targeted treatments is an urgent priority. Scientists like Ben-David must build on Boveri's breakthroughs in the late 19th and early 20th centuries to ensure our health and longevity in the 21st. When asked if he has personal reasons for devoting his life to this work, Ben-David mentions an aunt who died of metastatic breast cancer and a mentor who died of ovarian cancer. But he contends that these lived experiences are in no way unique. "When you study cancer, you get almost daily reminders that the work is important," he says. "Cancer is everywhere, and it's personal for everyone." ▲●■



The Boundaries of Possibility

A philosopher explores the limits (and potential) of mathematics

"Why are mathematical truths somehow eternal?" asks Balthasar Grabmayr, who, thanks in part to his Azrieli Fellowship, is starting a new position this spring as a junior professor of philosophy at Germany's University of Tübingen. "Once we prove a theorem, it will hold for eternity. How is that possible? *That* I find super fascinating. It seems like magic."

By Dan Falk

Photograph by Boaz Perlstein

Four centuries ago, Galileo famously described the physical world as a realm that was rooted in mathematics. The universe, he wrote, "cannot be read until we have learnt the language and become familiar with the characters in which it is written. It is written in mathematical language, and the letters are triangles, circles and other geometrical figures, without which means it is humanly impossible to comprehend a single word."

Since Galileo's time, scientists and philosophers have continued to ponder the question of why mathematics is so shockingly effective at describing physical phenomena. No one would deny that this is a deep question, but for philosopher Balthasar Grabmayr, an Azrieli International Postdoctoral Fellow at the University of Haifa, even deeper questions lie beneath it. Why does mathematics work at all? Does mathematics have limits? And if it does, what can we say about those limits?

"I am really fascinated with foundational questions about mathematics," says Grabmayr, who completed master's and undergraduate degrees in math, earned a PhD in philosophy from Humboldt University of Berlin, did postdoctoral research in computer science at Tel Aviv University in 2021, and is now working at the intersection of these three areas. "Philosophical questions such as, 'What is a number? What can mathematics reduce to?' As opposed to many of my peers, who were interested in applications in physics and technology, I was really more interested in this philosophical background."

These questions may sound pie-in-the-sky, which would be par for the course in philosophy. But as elemental as they are, they may also have practical significance, perhaps leading to a better understanding of how computation works and what its limits are. This line of inquiry could also shed light on the nature of language, as well as long-standing puzzles about the functioning of the mind.

Grabmayr found his way to this field from a very different passion: music. Growing up in Vienna, he attended a music conservatory and was set on becoming a classical musician. Eventually, he began to think about what made music work, and then began to think about musical structure. "I started to realize that, actually, what I'm interested in — what I found so attractive in music — is basically mathematics," he recalls. "Mathematics is the science of structure. I was completely captured by that."

He was captivated, too, by the vast sweep of mathematics: once you discover a mathematical truth, it appears to be true everywhere, and for all time. Schoolchildren learn equations like the quadratic formula unquestioningly, but for Grabmayr, such seemingly simple truths contain within them a world of mystery. "Why are mathematical truths somehow eternal?" he muses. "Once we prove a theorem, it will hold for eternity. How is that possible? *That* I find super fascinating. It seems like magic."

One of Grabmayr's main areas of research involves Gödel coding, a technique that, roughly put, allows mathematics to study itself. Gödel coding lets you convert statements about a system of rules or axioms into statements within the original system.

As Grabmayr explains, it's a way to study not the trees of mathematics but the forest. Take mathematical proofs, for example. "Usually, we use proofs in mathematics to establish a result about numbers, or about groups, or about geometric objects," he explains. But to study proofs in their own right, "we have to change the perspective — now the objects of investigations are proofs and our mathematical theories themselves. So suddenly we take a step out of the usual mathematical framework. Now we're looking at mathematical theories and adding mathematical reasoning from outside."

Gödel coding is named for the Austrian logician Kurt Gödel, who in the 1930s developed his famous "incompleteness theorems," which point to the inherent limitations of mathematics. Although expressed as an equation, Gödel's proof was based on the idea that a sentence such as "This statement is unprovable" is both true and unprovable. As Rebecca Goldstein's biography of Gödel declares, he "demonstrated that in every formal system of arithmetic there are true statements that nevertheless cannot be proved. The result was an upheaval that spread far beyond mathematics, challenging conceptions of the nature of the mind."

Grabmayr's work builds on the program that Gödel began nearly a century ago. "What I'm really interested in is what the limitations of mathematics are," he says. "What are the limits of what we can prove? What are the limits of what we can express in formal languages? And what are the limits of what we can calculate using computers?" (That last remark shows that Gödel coding is of interest well beyond the philosophy of mathematics. "We're surrounded by it," says Grabmayr. "I mean, without Gödel coding there wouldn't be any computers.")

Another potential application is in cognitive science and the study of the mind. Psychologists and other scientists have long debated to what extent the mind is, or is not, like a computer. When we "think," are we manipulating symbols the way a computer does? The jury is still out on that question, but Grabmayr believes his work can at least point toward some answers. "Cognitive science is based on the premise that we can use computational models to capture certain phenomena of the brain," he says. "Artificial intelligence, also, is very much concerned with trying to formally capture our reasoning, our thinking processes."

These questions may sound pie-in-the-sky, but as elemental as they are, they may also have practical significance, perhaps leading to a better understanding of how computation works and what its limits are. This line of inquiry could also shed light on the nature of language, as well as long-standing puzzles about the functioning of the mind.

Much of Grabmayr's current research focuses on this question of whether, or to what extent, the mind can be represented through the formal systems used by computer scientists — a line of inquiry that could influence research in AI and the quest to build artificial minds. His work largely entails reading, constructing and rejecting proofs — "my job consists of making one mistake after the other," he says — by writing mathematical formulas on paper, or on blackboards when he is collaborating.

Albert Visser, a philosopher and logician at Utrecht University in the Netherlands and one of Grabmayr's PhD supervisors, sees a number of potential payoffs for this research. "Balthasar's work has some overspill to computer science and linguistics, since it involves a systematic reflection both on coding and on the nature of syntax," he says. "The discussion of ideas from computer science and linguistics in Balthasar's work is also beneficial in the other direction. It informs logicians of the existence and the importance of such ideas."

Grabmayr points out that the path from foundational work to tangible technological benefits can be long and circuitous. "Kurt Gödel and Alan Turing started out discussing or thinking about foundational issues in mathematics, and then, in passing, they invented computers," he says. "That's the whole point of true foundational research: there can be very real-world applications, but they're completely unexpected and cannot be foreseen when the actual work is done."

Meanwhile, he understands that his work is often baffling to non-specialists, a situation he's striving to change. Grabmayr credits the Azrieli Fellowship with allowing him to "focus entirely on my work, and to meet colleagues around the world to discuss new ideas and projects." Recently, he's given presentations to scholars outside his own field. "It's a matter of how to present the material so as not scare them away immediately, to kind of invite them into the conversation," he says. "That's actually a big part of what I'm trying to do now: finding ways to speak about my research in a more accessible way." ▲●■

PHOTOGRAPH BY YURI DOJC

It is not an overstatement to say that our world is in crisis.

Every day we hear about the polarization, catastrophes and struggles facing humanity on a global scale. Every place we look we see big issues that need not only attention but also *intention* — the conscious intention to make change.

While we are certainly not the first generation to face peril, the increasing pace and scale of existing and emerging challenges make it easy to become discouraged. In this unprecedented time, it is important to remember that we can create transformation out of the turmoil.

To bring about this type of change, we need the efforts of people who have exceptional talent, vision and perseverance and think outside the box — people like our Azrieli Fellows. These brilliant scholars are a catalyst for change with their cross-disciplinary, collaborative approach to solving the world's most complex problems.

All of our Fellows, whatever their area of expertise, are engaged in critical research that focuses on improving the condition of humanity. And we, at the Azrieli Foundation, are here to support them at critical stages in their journeys as they rise to the challenges before us all.

I hope you enjoyed reading about how Azrieli Fellows are approaching some of humanity's big questions in this issue of *Aperio*.

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

Aperio

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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.

Uri Ben-David's research (see page 34) uses contemporary technology to explore aneuploidy, or abnormal cell division, with the ultimate goal of helping to devise better, more targeted cancer treatments. This image depicts spectral karyotyping of a human cell — or, in lay terms, the chromosomal composition of a human cell, where each chromosome is labelled with a different colour. In a normal cell, there should be two chromosomes of each colour and a chromosome should always have only one colour. In a cancer cell, like the one in this picture, the number of chromosomes is altered (higher or lower than two) and one chromosome can be labelled with more than one colour (due to the fusion of two or more different chromosomes).

MICROSCOPE SLIDE COURTESY OF URI BEN-DAVID