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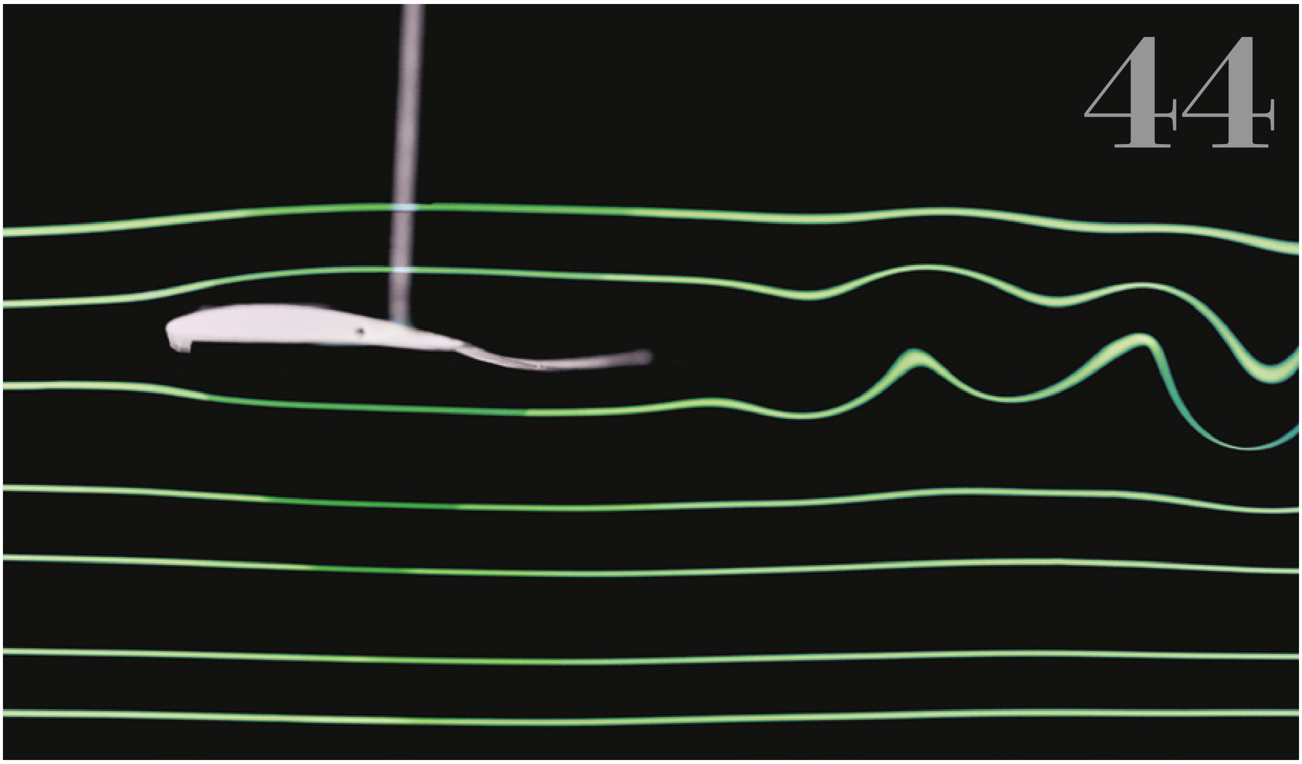

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Brain regions compute mental maps that tell us where we are in relation to our surroundings. New research reveals that these same areas may be involved in knowing our whereabouts in relation to other people and within the rankings of a social hierarchy. **Illustration by Richard Borge.**

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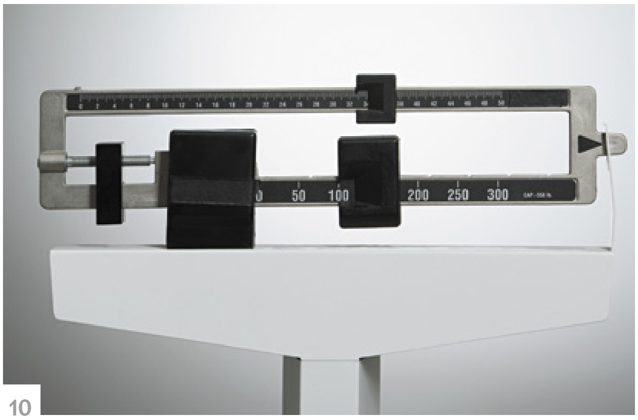
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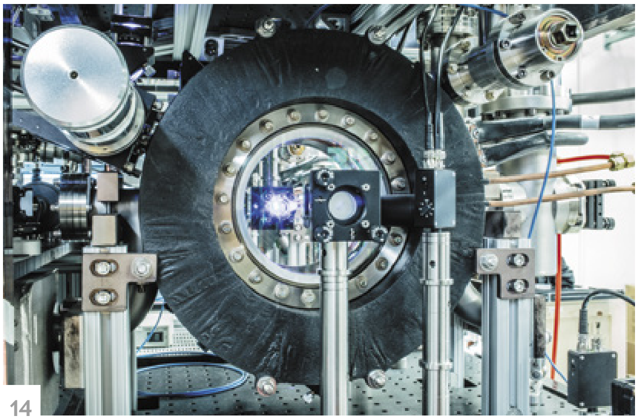
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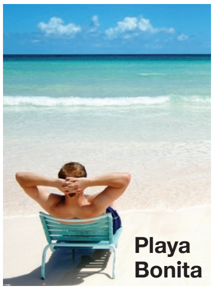
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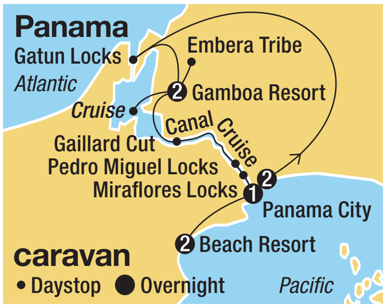

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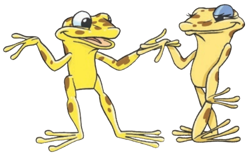
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FROM THE EDITOR

Curtis Brainard is acting editor in chief of *Scientific American.*
Follow him on Twitter @cbrainard

On Navigation

In the age of social media, it's tempting to evaluate our relationships based on whether or not the people we know follow us online and like or share our posts. Yet evidence shows that the brain has a sophisticated social apparatus of its own that relies on maplike coordinates to track our communal connections.

Research on the brain's GPS dates back to the 1970s, but the role of so-called place cells and grid cells has become clearer in recent years. In our January 2016 issue we ran a cover story by Nobel Prize winners May-Britt Moser and Edvard Moser that described how these cells allow us to navigate the world by determining our location and the distance and direction to other locations. The tale continues in this month's lead article, by neuroscientists Matthew Schafer and Daniela Schiller, which reveals how mental maps apply not only to physical space but also to complex social hierarchies and dynamics. Our ability to construct these abstract models may help explain why humans are such adaptive learners, the authors write. Follow your innate cognitive compass to "The Brain's Social Road Maps," on page 30.

Because we've largely figured out how humans decide whether to go this way or that, you may be surprised to learn that we still don't completely understand why airplanes go up and down. As science writer Ed Regis explains on page 44, "there is actually no agreement on what generates the aerodynamic force known as lift." Don't worry, aviation engineers have all the math they need to ensure that we can travel safely aloft from here to there, but we lack a nontechnical, commonsense explanation of the principles of flight. Physics teachers point to Bernoulli's theorem and Newton's third law of motion, yet each fails to give a comprehensive account of the dynamics at play. We still don't have a complete and satisfying answer, Regis notes, but computational fluid dynamics simulations are helping to fill in the blanks in our understanding.

Elsewhere we have a coincidental but illuminating focus on hydrogen. In "First Molecule in the Universe" (*page 58*), chemist Ryan C. Fortenberry tells of scientists at last finding in the depths of space a compound, HeH^+, that they believe begot the chemical world we know today. Without this first bond between helium and hydrogen, H_2^+ and then neutral H_2 would never have formed. And it so happens that H_2 is back in the renewable energy game. Despite disappointing ballyhoo about the hydrogen economy in the early aughts, there is fresh innovation and investment, journalist Peter Fairley writes in the "The H_2 Solution" (*page 36*).

Rounding out the issue, a special report, "AI and Digital Health" (*page S1*), produced independently with support from F. Hoffmann-La Roche Ltd., describes how researchers and doctors are improving health care with advanced algorithms. Alas, finding people with both biomedical and computational know-how is hard.

Finally, as I announced last month, we're celebrating our 175th anniversary year with a series of content spotlights over the course of 2020. We revamped our usual Recommended (*page 67*) to call attention to a lovely new catalog of the works of artist and inventor Rufus Porter, who established *Scientific American* in 1845. If you are in the Northeast, you can view his portraits and illustrations on display at the related exhibition, "Rufus Porter's Curious World: Art and Invention in America, 1815–1860," open until May 31 at the Bowdoin College Museum of Art in Maine. SA

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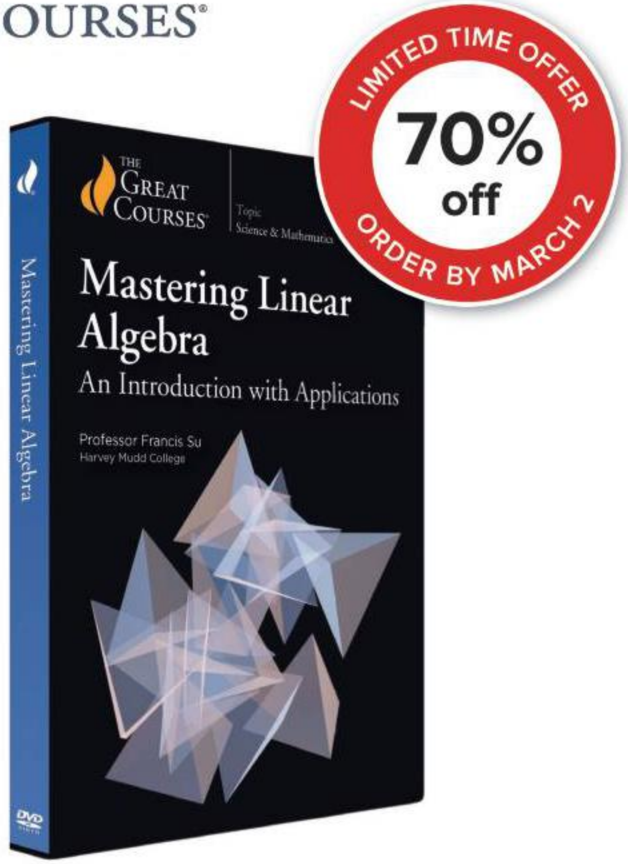

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LETTERS

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October 2019

PTEROSAUR HEAD

"Monsters of the Mesozoic Skies," Michael B. Habib's article on pterosaurs, gives the best discussion of their likely flight mechanisms I have ever read! Some birds with large heads and bills, such as pelicans, fly with their neck retracted over their back so that the weight of the head and bill are close to the shoulders (and thus the center of lift). Would such a posture be a way for pterosaurs to maintain better balance during flight?

Stewart Ware
College of William and Mary

What was the advantage of pterosaurs having such large heads and long necks? Habib describes how flight may have proceeded from a leg vault to a wing catapult to launch. It appears to me that an important additional motion was employed: a sudden upward jerk of the head during launch. This impulse would have utilized the strong neck muscles and long neck to snap the large head upward, providing vertical momentum. Were the utility of this impulse critically important for pterosaurs to launch, it would help explain the evolutionary advantages of some of their ubiquitous morphology.

Gordon Sproul *via e-mail*

As pilots know, an aircraft's vertical stabilizer and its associated rudder are essential for controlled flight. I wonder if the aerodynamic consequences of the large crested heads of these creatures has been investigated.

Wallace Magathan *Miami*

> **"Given science journals' publication bias, is it any wonder that there is a 'replication crisis'?"**
>
> JOSEPH J. LOCASCIO *HARVARD MEDICAL SCHOOL*

HABIB REPLIES: I want to thank readers for their fantastic engagement with a subject that I will continue to probe at the Dinosaur Institute of the Natural History Museum of Los Angeles County. Regarding Ware's thoughts: it turns out that pterosaurs' necks were not very birdlike. Rather than having numerous, small, highly mobile neck vertebrae, they tended to have a handful of large ones with fairly average mobility. In the longest-necked pterosaurs, the neck vertebrae were actually interlocking, making the neck quite stiff. As a result, there was no way for them to arrange it in a classic birdlike S *curve.*

In response to Sproul: The head and neck might have been raised quickly during launch to help give a bit more rise to the center of mass. Pterosaurs could also have moved their head and neck in flight to quickly change the center of mass and thereby improve agility.

To answer Magathan's question: The crests do indeed look like vertical stabilizers or rudders in some species. But flying animals do not use (or need) those mechanisms because they employ a different distribution of lift on their wings as compared with aircraft.

RESULTS THAT BIND

In "A Significant Problem," Lydia Denworth presents some of the major controversies regarding the use and misuse of null hypothesis significance testing (NHST) in published medical and behavioral science studies. She also mentions a special issue of the *American Statistician* concerned with these problems, and I happen to be one of the statisticians who contributed to it. A big part of the problem is science journals' widely cited publication bias, whereby reports showing positive effects in support of hypotheses receive preference. Given this bias, is it any wonder that there is a "replication crisis"?

Publication bias can be largely circumvented by preregistering studies judged methodologically sound with journals before their results are in. Yet an almost equally effective and less cumbersome method that could be more seamlessly adopted would be results-blind manuscript evaluation (RBME), whereby the editor distributes only the introduction and methods sections to reviewers for a first-stage provisional decision on publication acceptance *before the results are seen.* (The Results section would be edited in a second stage if the first-stage provisional decision is for acceptance.) Authors would be made fully aware of the RBME policy to also reduce any incentive to consciously or unconsciously distort results in a more positive direction or to fail to report valid null findings. Such a procedure bases publication solely on the judged importance of the research question addressed by the study and the quality of its methodology, not the results.

Joseph J. Locascio
Harvard Medical School

STEM SUITABILITY

"Closing the Skills Gap," by Rick Lazio and Harold Ford, Jr. [Forum], is an interesting (if incomplete) article arguing for reform in education to better serve a need for workers in STEM that would have been improved if the acronym had been defined in the narrative (it stands for science, technology, engineering and mathematics).

Although I don't disagree that the educational system is failing us (particularly in minority communities), the authors are overlooking another gaping hole: not everyone is destined to (or interested in) becoming a scientist, engineer or mathematician (or even graduating from college). The current system is also sorely lacking in encouragement, opportunity and training for those who would become, for example, plumbers—or enter other fields that are well paid, necessary and unlikely to be replaced by automation in the near future.

Edward Wills *via e-mail*

REVERSING DEATH

After reading Christof Koch's article on reviving the brain after death ["Is Death Reversible?"], I was struck by the similarities to the ideas found in Roald Dahl's short story "William and Mary." It was first published in 1959 and describes a very similar method of keeping the brain alive by connecting the veins and arteries to it and running an artificial bloodlike solution through them. It obviously supports the idea that "death" occurs only when the brain dies and that the soul is contained within the brain. I find it interesting that Dahl had very similar ideas about reversing death 60 years ago and wonder if any of the researchers involved read the story.

ZOE MCNEICE *via e-mail*

Koch appears to imply that Buddhists are reassured by an eternal cycle of reincarnation by citing it among other religious concepts as a "defense mechanism to deal with [the] foreknowledge" of death. But in Buddhism, this cycle, termed "samsara," is laden with suffering and not reassuring at all. In fact, the journey of Buddhists is directed at releasing oneself from it.

LEE TUCKER *Nashville, Tenn.*

Koch repeatedly refers to death and lightly touches on its possible reversibility. Death is primarily defined as the irreversible loss of life, but do we know what life is? It is a property easy to recognize, difficult to describe and impossible to create in the laboratory. We suspect it originated in some earthly pond many millions of years ago, and it is only temporarily housed in all beings. Will science ever be able to restore a property whose nature we are unable to determine or even rationally discuss? And whatever life is, may it also be responsible for the push forward of evolution? This seems to be another intractable mystery.

JOAN GIL *Professor emeritus of pathology, Icahn School of Medicine at Mount Sinai*

ERRATUM

"Is Death Reversible?" by Christof Koch, should have described modern fields such as machine learning as creating an illusion of understanding the "vegetative soul" rather than the "sensitive soul." The vegetative soul defines the body's basic physical functions.

LETTERS TO THE EDITOR

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FOR CHILDREN WITH CONGENITAL HEART DEFECTS, REGENERATIVE MEDICINE HOLDS GREAT PROMISE

A conversation with **CHRISTOPHER BREUER**, MD, director of the Center for Regenerative Medicine at Nationwide Children's Hospital in Columbus, OH

Congenital heart defects are the most common type of birth defect in the United States, affecting around 1 percent of births each year or around 40,000 babies per year — according to the CDC. Nationwide Children's Hospital, in Columbus, OH, is working on improving treatment options for children with congenital heart defects using regenerative medicine. Dr. Breuer and Toshiharu Shinoka, MD (also at Nationwide Children's Hospital) have developed a tissue-engineered vascular graft (TEVG) specially designed for use in children. Dr. Shinoka was the first doctor to implant a TEVG in an infant.

How can regenerative medicine help children with congenital heart defects?

Our focus is on using tissue engineering methods to creating neotissue for use in the reconstruction of complex cardiac anomalies for children that require major congenital cardiac surgery. TEVGs provide a better solution for replacing vessels in children because they use tissues created from the patient's own cells, and can grow with the patient, rather than having to replace artificial vascular grafts as a child grows. Sometimes surgeons can minimize the number of operations by putting in oversized grafts or delaying surgery, but these come with risks and can cause additional strain on the heart.

How do TEVGs work?

To make a TEVG, we harvest an individual's own cells and then we seed those cells onto a device that's called a scaffold, which is a 3-dimensional biodegradable matrix. The scaffold serves to direct the tissue formation. Once implanted in the body, the scaffold begins to dissolve as the new tissue forms. Once the scaffolding is gone, we have a neovessel, which resembles the native blood vessel into which the graft is implanted. The new tissue behaves like a regular blood vessel, including having the ability to grow with the child.

When was the first TEVG implanted in a human?

The first implantation of a TEVG in a human was in Japan in 2001, and the first implantation of a TEVG in the U.S. was in 2011. It was in a three-year-old little girl with a single ventricle cardiac anomaly. She's now eight years out from her procedure, and she's still followed by us. She's doing well. Her graft is growing as she grows.

What challenges remain?

The grafts aren't without their problems. Some of the patients in our first clinical trial developed narrowing or stenosis of the graft and required treatment with angioplasty. Fortunately, all these patients have subsequently done quite well, and the grafts are growing with the patients. One of the unique things about our laboratory is that we not only go from the bench to the clinic but also go from the clinic back to the bench. When we had this high incidence of early stenosis, we went back to the laboratory and were able to better understand how the tissue forms and causes stenosis. We were able to improve the design of the TEVGs based on the new information we had on how the grafts worked.

> **WE NOT ONLY GO FROM THE BENCH TO THE CLINIC BUT ALSO GO FROM THE CLINIC BACK TO THE BENCH.**

What's the outlook for TEVGs?

There's always going to be uncertainty when you're involved in a clinical trial. It's important to remember that these are experimental, and while we have some very promising data, including clinical data, they are still under investigation, so we'll have to wait and see. I have found that, in general, patients are quite interested in participating in the trials. There would be great enthusiasm if the trials are successful and if we are able to confirm the growth capacity of the grafts and show good performance.

What are your future goals in regenerative medicine?

We focused on the TEVG as our first attempt at creating a tissue-engineered construct for use in the clinic, but our preclinical work was done in heart valves. There's a great need for better replacement heart valves for use in congenital heart surgery, so that's a big focus for our laboratory now. The other thing that we've just begun to explore is the application of cardiovascular tissue engineering in the fetal environment. This involves intervening at the fetal stage when the congenital cardiac anomalies are just developing and replacing defective tissues with tissue-engineered constructs. What we've discovered is that you can actually implant these tissue-engineered constructs in the fetal environment and since this environment is very plastic there is the potential to reverse some of the cardiac anomalies.

What's most rewarding about your work?

By far, the greatest joy of research is when you can successfully bring something to the clinic. The patients enrolled in our trial are all incredible children from incredible families, so having the opportunity to work with those families and those patients is extraordinarily rewarding.

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Weight Is Not Enough

Scale-focused health care is failing patients and increasing stigma and bias

By the Editors

At the start of nearly every doctor's visit, chances are you will be asked to step on a scale and get your weight measured for that day's exam record—and you would be hard-pressed to find a person whose physician has not brought up his or her weight at some point. But many conversations around weight have become a hindrance, not a help, in the campaign to make people healthier. Doctors' recommendations to drop pounds are still extremely common, even though using body size as a one-size-fits-all proxy for health can obscure the complexity of an individual's particular physiology.

Higher body masses are associated with increased risk for hypertension, diabetes and coronary disease. Many epidemiological studies of hundreds of thousands (in some cases, millions) of patients have shown that heavier people are at higher risk for these illnesses. But the big picture is not the whole picture. Researchers have identified a subset of obese people considered to be "metabolically healthy"—meaning they do not exhibit elevated blood pressure or the diabetes precursor called insulin resistance, for example. Although the numbers vary greatly depending on the study, the metabolically healthy population could comprise anywhere from 6 to 75 percent of obese individuals.

One intriguing report published in 2016 found that a higher body mass index (or BMI, the ratio of weight to height) "only moderately increased the risks for diabetes among healthy subjects" and that unhealthy thin people were twice as likely to get diabetes as healthy fat people. Clearly, there is more to the equation than weight. Although the association between excess weight and disease is very real, individual experience can vary greatly and hinges on personal physiology and behavior.

Despite such findings, doctors routinely recommend dieting for weight loss as a means to "treat" poor health indicators such as high cholesterol and insomnia in obese patients—an approach with an abysmal success rate. Virtually no diet works in the long term (diet-peddling companies have weak, if any, data to back up their claims of efficacy). The result: 95 to 98 percent of those who attempt to lose weight fail, and up to two thirds end up heavier than when they began. Spending years trapped in a cycle of losing weight, regaining it, then losing it again is associated with poorer cardiovascular health outcomes and contributes to hypertension, insulin resistance and high cholesterol. It is time that doctors ditch the scale-centric health care practice and focus on behaviors that have proven positive outcomes for health. Lifestyle changes, such as enhancing one's nutrition by eating fruits, vegetables and whole grains, along with increased physical activity and smoking cessation, can improve blood pressure, blood lipid levels and insulin sensitivity—often independently of changes in body weight.

Among the more insidious by-products of weight-centric health care are the increased stigma and shame experienced by the overweight. The well-reported anecdotal experience of innumerable fat people is that doctors often prescribe weight loss without examining them, running tests or performing other normal procedures for conditions that thin people would be screened for automatically. Research over the past two decades has shown that health professionals have negative attitudes toward obese people, as the authors of a large review paper wrote in 2013 in *Current Obesity Reports*. Not only that but doctors' appointments with fat patients are shorter on average, and physicians routinely use negative words in their medical histories of such people.

Some refuse to see these patients at all, as the *South Florida Sun Sentinel* reported in 2011. Such biased practices keep people from regular annual exams and prevent the detection of serious underlying conditions. And research suggests that the chronic stress of living with the shame of being a heavy person may underlie metabolic changes that increase the storage of fat, elevate blood pressure and drive up blood lipid levels.

To practice evidence-based medicine untainted by stigma, doctors should stop relying on weight alone as an indicator of health and slavishly prescribing weight loss to treat health ailments. Instead practitioners should focus on behavioral changes to improve health outcomes. People of all sizes are entitled to evidence-based protocols that empower them and keep them healthy. SA

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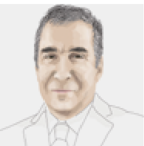

Andrew Rosenberg is director of the Center for Science and Democracy at the Union of Concerned Scientists.

The EPA Hits a New Low

A proposed rule would threaten, not protect, public health

By Andrew Rosenberg

The U.S. Environmental Protection Agency has one job: to protect public health and safety and the environment we live in, with the best available science. It is a mission that saves lives. But that mission could end if EPA administrator Andrew Wheeler succeeds in restricting the science that the agency can use.

Wheeler is pushing a new proposed rule—cloaked in the rhetoric of "transparency"—that in most cases would effectively bar the EPA from using a study in its policy making if all of that study's data, computer code and models have not been made public. In practice, this eliminates all studies that protect the confidential medical information of participants, even though such research is vital for understanding the public health impacts of pollution. The rule would make laws such as the Clean Air Act harder to fully implement. It sounds like a small change, but it has the potential to do enormous damage.

An attempt to add this rule in 2018 was met with widespread condemnation from public health experts and the science community. A supplemental proposal is a new effort by Wheeler to abandon science-based protections that have worked effectively for decades to deliver cleaner air, cleaner water and healthier communities. So what does the rule do in its "clarified" form?

It applies to all the science used by the agency. Initially the new rule applied to "dose-response" studies used to quantify the effects of a pollutant or chemical on human health. But now the EPA says that all science used by the agency would fall under the same constraint, whether it is a survey, an environmental assessment, a modeling study or anything else that could help inform policy.

The use of gold-standard studies of health impacts based on personal medical data that participants and researchers agreed, legally, to keep private would be restricted. And even without such restrictions, companies could pick and choose what research they show the agency. This could be applied retroactively to studies published years ago, meaning that as regulations are reconsidered and updated, some of the original scientific basis for existing protections may be excluded, inevitably resulting in weaker rules.

It requires endless, pointless reanalysis. EPA scientists already critically review the quality and strength of scientific research, going above and beyond the rounds of peer review that are standard in science. But the proposed rule calls for the agency to engage in reanalysis, effectively forcing it to check the math of every study to make sure it gets the same answer. It also requires an overly broad set of sensitivity studies on all parameters. That work is quite time-consuming and impractical.

It upends the value placed on studies. There are established ways to evaluate scientific research: Is it well designed? Are its assumptions reasonable? Are sample sizes big enough? Are the methods solid? Is the evidence strong enough to point to a conclusion, and if so, how does it compare with findings from other studies in the field? The supplemental proposal imposes an arbitrary bureaucratic standard unrelated to robustness or merit. The weight the evidence received would be based primarily on the public availability of raw data.

It is a political change made to achieve political goals. Far from a move toward transparency, this rule was designed by political staff on the basis of proposals long pushed by lobbyists for the tobacco industry and fossil-fuel extractors. The EPA's own scientific experts were secondary to the process, and its Science Advisory Board was given very little opportunity to review it. Worse, the EPA administrator can pick and choose when the rule does and does not apply—the exact opposite of a transparent or science-based process. The EPA got nearly 600,000 critical comments on the original proposal, including opposition from major scientific societies, public health groups and universities. It largely ignored them.

This proposal puts a set of handcuffs on the agency, with industry-linked political appointees holding the key. It will make it harder for the EPA to protect communities or to hold polluters accountable. It is a declaration by Wheeler and his deputies that they don't care about public health. SA

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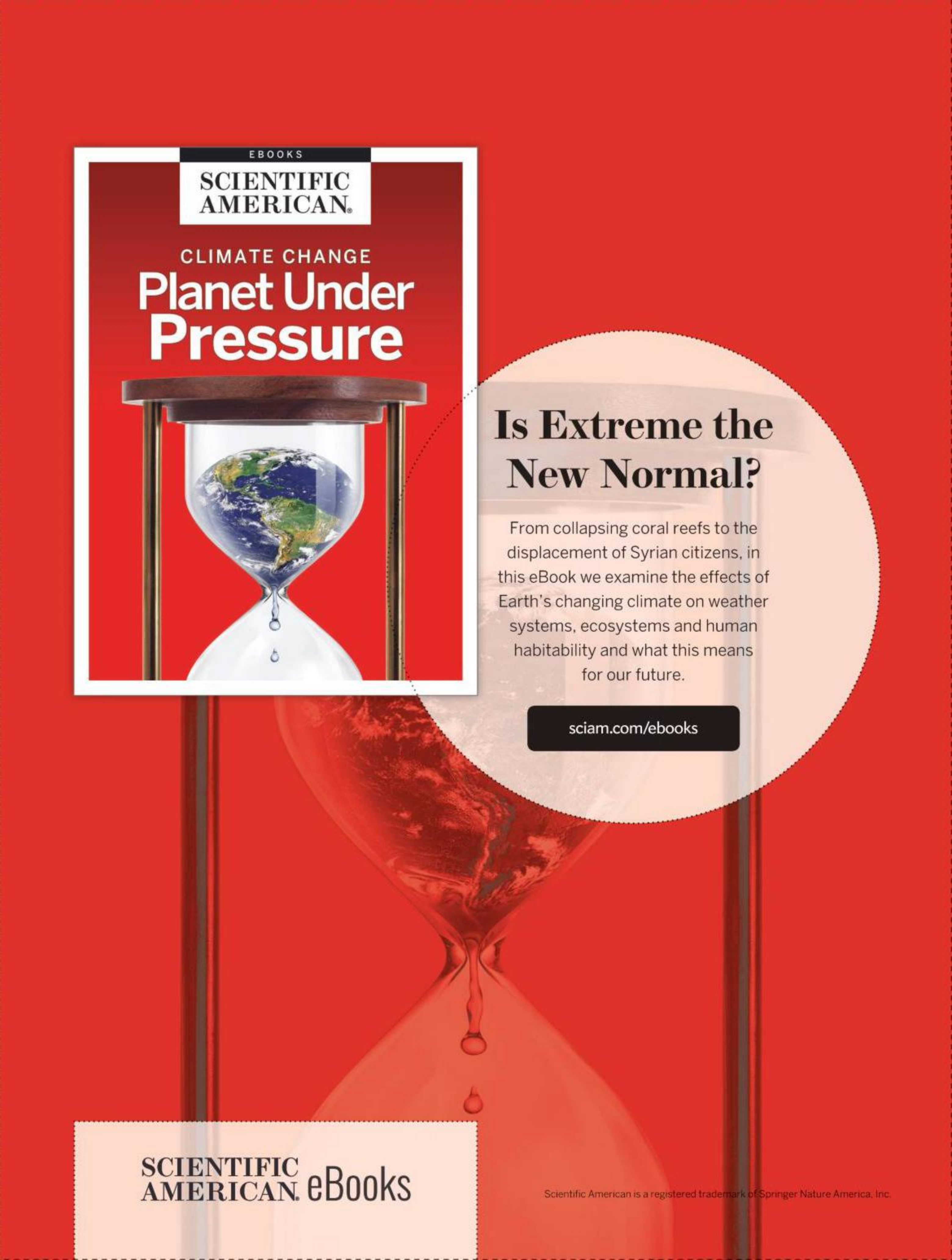
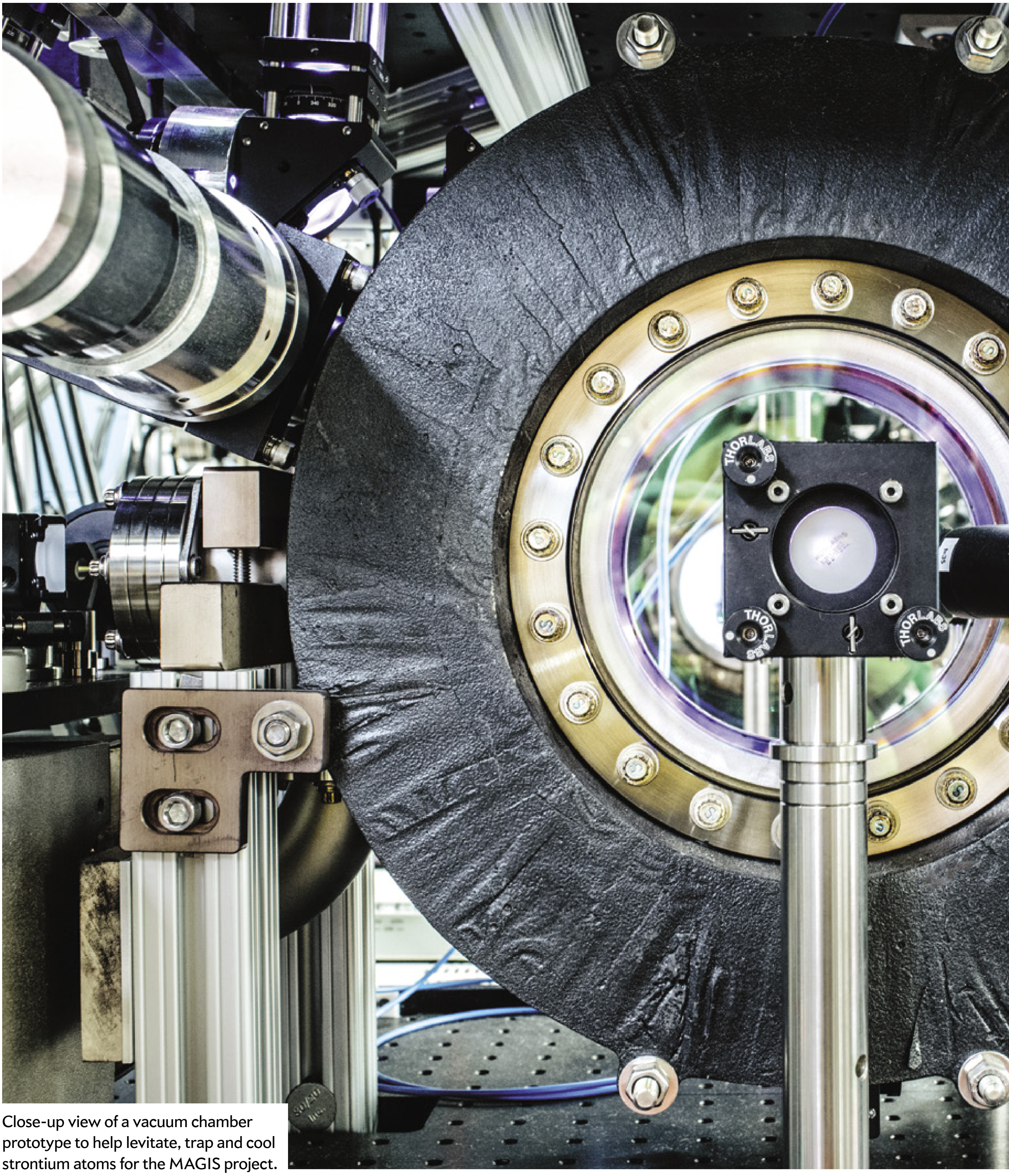
Illustration by Thomas Fuchs

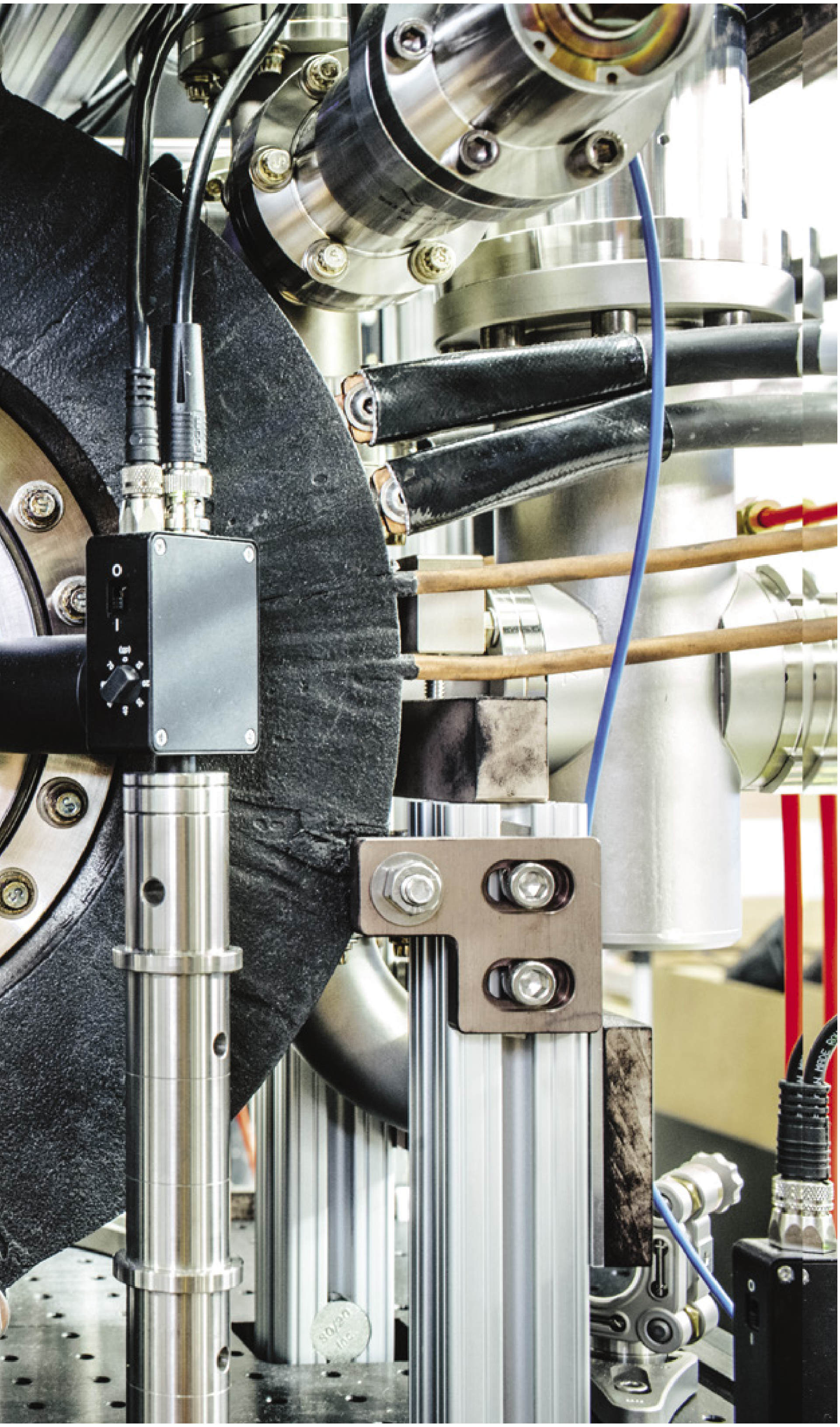


ADVANCES



Close-up view of a vacuum chamber prototype to help levitate, trap and cool strontium atoms for the MAGIS project.

Photograph by Timothy Archibald



PHYSICS

Giant Atoms

Room-sized "atom waves" could help probe the quantum realm

Researchers are preparing to scrutinize nature at tiny scales by stretching supercooled atoms into room-length waves as they drop them down a 100-meter vacuum tube. By exploiting the atoms' wavelike properties, the experiment will look for ripples in the bizarre quantum realm: potential fingerprints of missing dark matter and, in future iterations, new frequencies of gravitational waves.

Collaborators from eight institutions have come together to turn an Illinois mine shaft into the world's largest atom interferometer—the Matter-wave Atomic Gradiometer Interferometric Sensor, or MAGIS-100. After finalizing the design, the researchers plan to assemble the instrument in 2021 and start harnessing lasers to expand submicroscopic strontium atoms into macroscale "atom waves" soon after. "The summer of 2021 is when things start to get completely mind-boggling," says Rob Plunkett, principal investigator at Fermilab, where MAGIS-100 will reside.

With public and private funding totaling $12.3 million, the project joins a trend of precision research bridging the gap between single-university "tabletop" experiments and billion-dollar, multidecadal undertakings such as the Large Hadron Collider and the Laser Interferometer Gravitational-wave Observatory (LIGO).

To search the vast array of masses and qualities dark matter could have, "you [also] need to do small scale—you cannot put all your eggs in one basket," says Asimina Arvanitaki, a researcher at the Perimeter Institute for Theoretical Physics in Ontario, who is not involved in MAGIS.

MAGIS-100 will measure atoms in free fall as they are manipulated by lasers. A laser pulse can tickle a single atom in such a way that, because of its quantum properties, it both absorbs and does not absorb the laser's energy—much as Schrödinger's hypothetical cat persists in a mixed state of life and death. Quantum-mechanically, everything from a photon to a baseball has wavelike qualities, although they are usually imperceptible for larger objects. When an atom is properly excited by the MAGIS laser, its wavelike nature lets it stretch out in space, with the laser-absorbing portion racing ahead.

A 10-meter-tall MAGIS prototype at Stanford University, currently one of the world's largest such instruments, has already created record-setting atom waves more than half a meter long; the Fermilab facility should produce waves of dozens of feet or more. As the atom waves travel down the shaft, a second laser pulse will reunite the excited portion of each wave with its slower counterpart, and researchers will precisely determine the acceleration of the falling atom by measuring interference between the two parts of the wave. Because the atoms will be in free fall throughout the process, tremors from earthquakes or passing trucks should have little effect on the measurements.

MAGIS-100 will simultaneously drop a million such atom waves along the upper and lower sections of the shaft. By checking even more interference patterns—those between the top and bottom clouds of atoms—the apparatus will be able to detect minuscule contradictions to the known laws of physics down the entire football-field distance. Any tiny differences in the way the atom waves fall, for instance, will reveal the influence of a third party—such as undiscovered particles present in the space they traveled through. "The longer you watch [the atoms] fall, the more accurately you can measure them," says Stanford physicist Jason Hogan, who helped to develop the prototype.

Dark matter, which scientists suspect makes up about 80 percent of the matter in the universe but which cannot be detected by conventional means, could cause noticeable effects in this experiment. Most hunts have searched for predicted heavy objects called weakly interacting massive particles (WIMPs), but as these relative giants fail to materialize, new search parties are mobilizing.

Amid the crowded field of dark matter models, possible ultralight particles—which Plunkett calls "a whole unexplored continent"—are gaining prominence. These phantasms could influence familiar particles in several ways, according to Johns Hopkins University theorist and MAGIS collaborator Surjeet Rajendran. The MAGIS-100 apparatus should be able to spot two resulting behaviors—variations in fundamental constants and nudges from an undiscovered fifth force of nature—originating from particles perhaps a billion trillion times lighter than the electron. The setup will be hundreds to thousands of times more sensitive to these changes than existing instruments.

Whereas some researchers prefer seeking particles with specific properties predicted by theory, others want to cast as wide a net as technology permits. High-energy particle colliders have already been used to conduct a thorough search of the realm of heavy, strongly interacting particles, yet the Standard Model of physics still seems to be missing some crucial pieces. "There is a feeling that discoveries in the lower masses are lower-hanging fruit," says Gray Rybka, a physicist at the University of Washington, who is not involved

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TECH

Triage Takes Flight

Machine learning can help drones distinguish the living from the dead

In the aftermath of disasters, drones have already been used to map the destruction and help rescuers find possible survivors. Now a new system could take this to the next level, automatically analyzing drone footage to determine whether the people spotted are still alive.

"We're using computer vision, and what we're looking for are very small changes that are associated with movement—that rhythmic movement of breathing," says Javaan Chahl, a sensor systems researcher at the University of South Australia and senior author of a study describing the process, published last October in *Remote Sensing.*

The system uses machine learning to analyze a 30-second video clip of a human body, measuring changes in light reflected from the part of the chest region where motion would be most apparent. Then it determines whether shifts in intensity are consistent with a live, breathing person. The researchers tested the system on footage of nine subjects: eight living humans and one mannequin with a wig and makeup.

Test subjects were unobscured, but Chahl says the system could also work on people partially covered by rubble—as long as their torsos are visible. Past attempts at identifying vital signs using drones measured subtle changes in skin color, which can indicate blood flow. But those systems have to view exposed skin over pulse points, meaning the drones must hover much closer.

Drone footage reveals which figures are breathing.

UNIVERSITY OF SOUTH AUSTRALIA

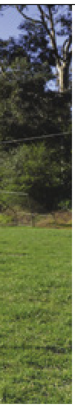
The researchers have yet to test their system in the field. "This experiment seems to work in very controlled conditions, where bodies are lying in static poses on the ground and drones four to eight meters up in the air are performing these visible-light video captures," says Lisa Parks, a media with MAGIS. Those who agree, he adds, form "a community that I've seen grow severalfold in size over the last decade."

Even without knowing exactly what it is looking for, MAGIS will be "expanding the reach of current experiments by a lot," Arvanitaki says.

And even if dark matter operates through channels invisible to MAGIS-100, the apparatus doubles as a pathfinding gravitational-wave detector. Although MAGIS-100 will not be able to detect gravitational waves itself, it will test and develop technology for a future upgrade—one keen enough to pick up smaller spatial disturbances by dropping clouds of atom waves one kilometer apart. This setup could sense spacetime ripples with frequencies too low for LIGO and too high for the future space-based detector LISA (Laser Interferometer Space Antenna), such as gravitational waves emanating from black holes and neutron stars before collisions; a "MAGIS-1000" could offer telescopes advanced warnings of upcoming mergers.

For now, the researchers look forward to cutting a new path into the world of ultralight dark matter with the MAGIS-100. "We've got to do the best we can," says Tim Kovachy, a physicist working on the laser system at Northwestern University. "There's a lot of motivation to leave no stone unturned."

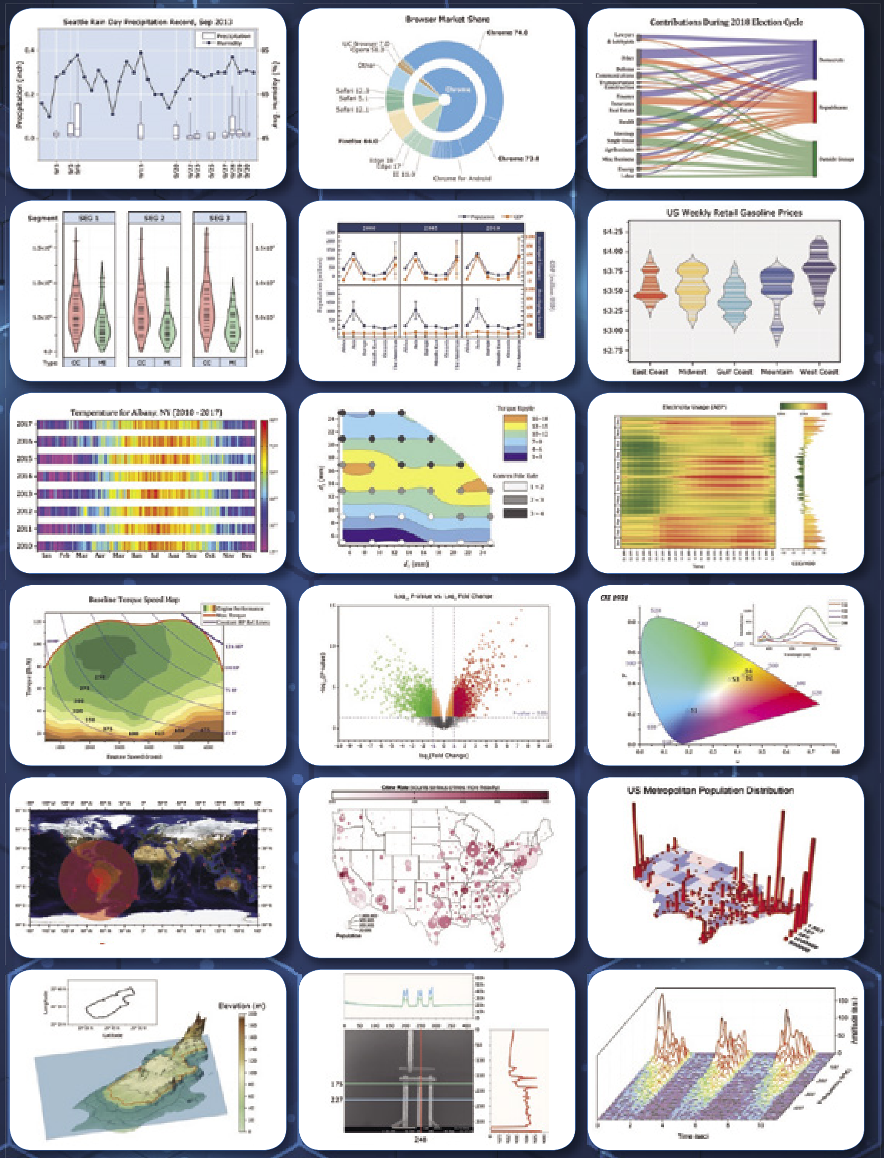
—Charlie Wood



researcher at the Massachusetts Institute of Technology, who studies drones and surveillance but was not involved in the new study. In real disaster-recovery situations, Parks notes, conditions such as wind, rain, temperature fluctuations and running water could interfere with reflected light. Without a more realistic test scenario, she says, "I wonder how feasible this really would be if rolled out into an actual post-disaster context."

Chahl agrees that the system's current version has limits. "At the moment, the drone is … looking for people on the ground, and then it looks to see whether they're alive," he says. "That's not quite the *Star Trek* life-sign scanners that I've always wondered about." But now that the basic concept has been proved, Chahl hopes to develop it further. "What we'd like to do is actually use the life signs to detect the people," he says, "so you can make a map of where there's likely to be people and not."

—Sophie Bushwick



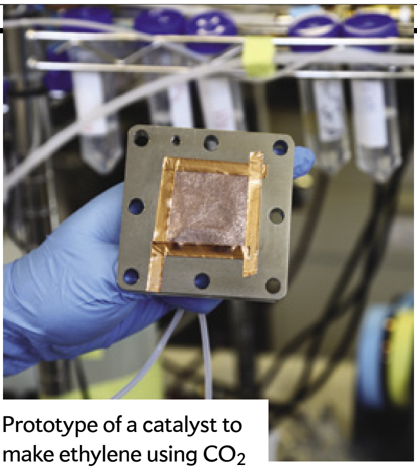
CHEMISTRY

New Path to Plastics

A crucial component could come from existing carbon sources

Ethylene is the world's most popular industrial chemical. Consumers and industry demand 150 million tons every year, and most of it goes into countless plastic products, from electronics to textiles. To get ethylene, energy companies crack hydrocarbons from natural gas in a process that requires a lot of heat and energy, contributing to climate change–causing emissions.

Scientists recently made ethylene by combining carbon dioxide gas, water and organic molecules on the surface of a copper catalyst inside an electrolyzer—a device that uses electricity to drive a chemical reaction. The process, described last November online in *Nature,* could point the way toward using carbon dioxide as feedstock for chemicals and potentially fuels, helping to reduce reliance on fossil fuels and to put a dent in industrial carbon emissions.



Prototype of a catalyst to make ethylene using CO_2

TYLER IRVING *University of Toronto Engineering*

The discovery grows out of work published last year by University of Toronto engineer Ted Sargent, describing a similar process that used more electricity and was less efficient overall. So Sargent says he sought out researchers at the California Institute of Technology who are "black belts in molecular design and synthesis."

Caltech chemists Jonas Peters and Theodor Agapie and their colleagues experimented with organic molecules to add to the copper catalyst. An arylpyridinum salt turned out to be the Goldilocks molecule, Sargent says: it formed a water-insoluble film on the copper that positioned the carbon dioxide so its molecules reacted most efficiently with one another, without slowing down the reaction. The result was more ethylene, with fewer by-products such as methane and hydrogen.

Still, the process must become even more efficient before it can be commercially scalable and use carbon scrubbed or captured from facilities such as coal- or gas-burning power plants. Lower energy costs, already occurring with renewable energy sources such as wind, could also help make it more feasible.

"This is a significant breakthrough," says Randy Cortright, a senior research adviser at the National Renewable Energy Laboratory in Golden, Colo., who was not involved in the study. This result, he says, is "something that a lot of people are going to pay attention to, and they're going to be able to build on." —*Susan Cosier*

PSYCHOLOGY

Trusting Bots

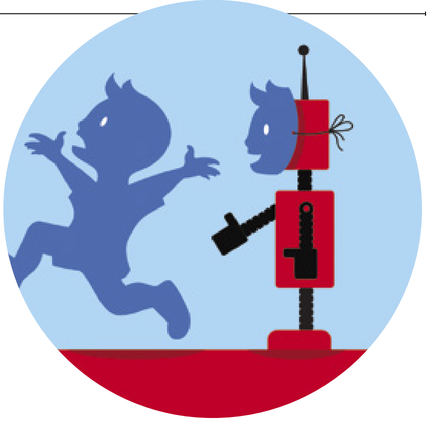
AI elicits better cooperation through deception

As artificial-intelligence products steadily improve at pretending to be human—an AI-generated voice that books restaurant reservations by phone, for example, or a chat bot that answers consumers' questions online—people will increasingly be put in the unsettling situation of not knowing whether they are talking to a machine. But the truth may make such products less effective: recent research finds a trade-off between transparency and cooperation in human-computer interactions.

The study used a simple but nuanced game in which paired players make a series of simultaneous decisions to cooperate with or betray their partner. In the long run, it pays for both to keep cooperating—but there is always the temptation to defect and earn extra points short term, at the partner's expense. The researchers used an AI algorithm that, when posing as a person, implemented a strategy that was better than people are at getting human partners to cooperate. But previous work suggested people tend to distrust machines, so the scientists wondered what would happen if the bot revealed itself as such.

The team hoped people playing with a known bot would recognize its ability to cooperate (without being a pushover) and would eventually get past their distrust. "Sadly, we failed at this goal," says Talal Rahwan, a computer scientist at New York University in Abu Dhabi and a senior author on the paper, published last November in *Nature Machine Intelligence.* "No matter what the algorithm did, people just stuck to their prejudice." A bot playing openly as a bot was less likely to elicit cooperation than another human, even though its strategy was clearly more beneficial to both players. (In each mode, the bot played 50 rounds against at least 150 individuals.)

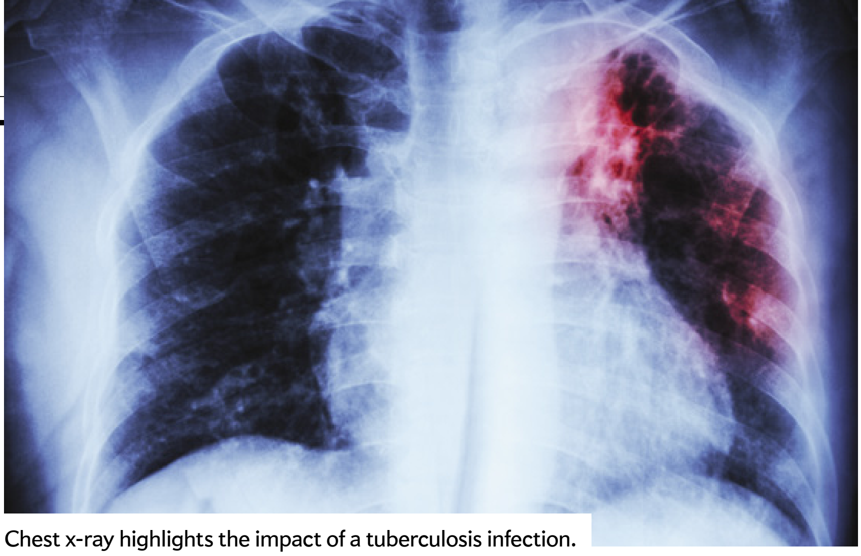
In an additional experiment, players were told, "Data suggest that people are better off if they treat the bot as if it were a human." It had no effect.



Virginia Dignum, who leads the Social and Ethical Artificial Intelligence group at Umeå University in Sweden and was not involved in the study, commends the researchers for exploring the transparency-efficacy trade-off, but she would like to see it tested beyond the paper's particular setup.

The authors say that in the public sphere, people should be asked for consent to be deceived about a bot's identity. It cannot be on an interaction-by-interaction basis, or else the "deception" obviously will not work. But blanket permission for occasional deception, even if it can be obtained, still raises ethical quandaries. Dignum says humans should have the option to know after they have interacted with a bot—but if she is calling customer service with a simple question, she adds, "I just want to get my answer." —*Matthew Hutson*

Illustration by Thomas Fuchs



Chest x-ray highlights the impact of a tuberculosis infection.

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EPIDEMIOLOGY

A Disease's Journey

Mutation-tracking tools that traced a drug-resistant TB strain could help squash epidemics

In 2005 and 2006, 53 patients who checked into a rural South Africa hospital turned out to be infected with extensively drug-resistant tuberculosis (XDR TB). The bacterium proved impervious to antibiotics, ultimately killing 52 of the patients.

This outbreak in Tugela Ferry, KwaZulu-Natal province, was the largest ever reported for XDR TB—and the primary strain involved currently accounts for nearly 80 percent of such infections in the province. New research finally tells the full story of the deadly strain's origin. As reported last October in the *Proceedings of the National Academy of Sciences USA,* it in fact emerged 250 miles away, more than a decade before the first recorded case. The researchers behind the paper say the multidisciplinary tool set they used to find its origin could help identify other drug-resistant pathogens early, as they emerge, and stop them from spreading.

"The bottom line is that this strain, like many other pathogens, took time to build," says Barun Mathema, an epidemiologist at Columbia University and the paper's senior author. "But if you have your eye on the ball, you can pick up on these mutations and take action."

Mathema and his colleagues sequenced more than 300 TB genomes from patients infected in KwaZulu-Natal, mostly from 2011 to 2014, and found 78 percent of the samples were genetically related to the Tugela Ferry strain. Phylogenetic reconstruction (a statistical method used to infer evolutionary history) revealed when the strain's mutations appeared and expanded, and the scientists built 3-D models of the bacterium's protein structures to find how each mutation helped the pathogen build resistance and adapt. They learned the strain had acquired three important and unusual mutations, the first in the early 1980s and the last around 1993. In the mid-1990s South Africa's HIV epidemic—which created a population with compromised immune systems—helped the strain to spread. The researchers looked at the samples' geographical distribution from associated GPS data and used population genetics and geospatial modeling to determine how genetic changes propagated from place to place. They found that the strain originated far from Tugela Ferry and migrated via popular travel routes. "All these factors came together to make this an explosive outbreak," Mathema says.

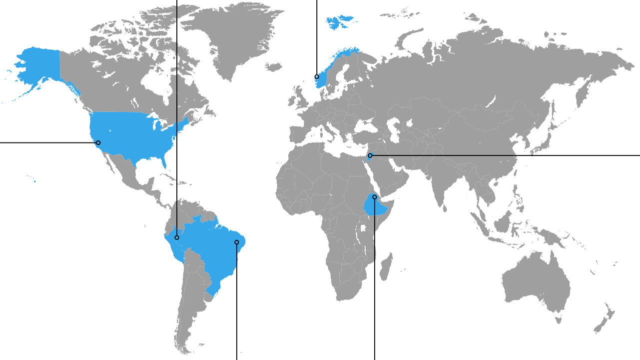
Drug resistance is a growing problem worldwide. Mathema adds that applying whole-genome sequencing in real time to samples taken from patients, combined with a multipronged analytical approach akin to the one applied here, could help researchers detect worrying mutations before they become emergencies. Public health agencies in London, New York City, and elsewhere already do whole-genome sequencing on a small scale—but a lack of funding, expertise and capacity presents obstacles for expanding this vision.

"A lot of people in the field agree that this is where things should go," says Maha Farhat, a biomedical informatics researcher at Harvard Medical School and pulmonary and critical care physician, who was not involved in the research. "But that would involve public health agencies investing in these tools." —*Rachel Nuwer*

IN THE NEWS

Quick Hits

By Sarah Lewin Frasier



PERU
Researchers analyzing satellite and imaging data have found 143 new Nazca lines—large line drawings of humans, animals and symbols etched into the Peruvian landscape millennia ago. They include a humanoid figure 16 feet across, spotted by IBM's Watson AI system.

NORWAY
Archaeologists' ground-piercing radar found a Viking-era ship, surrounded by a filled ditch, lurking below the soil of a western Norway farm. It was once within a burial mound.

U.S.
Off the California coast, scientists measured a blue whale's heart rate for the first time, using a device attached to the animal's skin by suction cup. The heart, likely weighing hundreds of pounds, beats from two to 37 times per minute, varying dramatically between diving, feeding and surfacing.

JORDAN
Researchers uncovered a two-horned figure in early Islamic ruins that may be the earliest chess piece ever found. The roughly 1,300-year-old object matches a "rook" found in an Iranian chess set from about 400 years later.

BRAZIL
Despite the long dry spells in Brazil's Caatinga region, scientists found the tree *Hymenaea cangaceira* drizzles copious nectar from flowers to attract pollinating bats; a full-size tree can release 240 gallons of the stuff, with 38 distinct scent compounds, over a single dry season.

ETHIOPIA
Microbes thrive in many of Earth's harshest environments, but researchers found no life at all in briny, scorching, acidic pools near Ethiopia's Dallol volcano. Knowing boundaries for life's adaptation helps to narrow the search for Earth-like life on other planets.

For more details, visit www.ScientificAmerican.com/feb2020/advances

CONSERVATION

Beating Back Extinction

Indigenous-managed lands may provide a model for maintaining biodiversity

Writing-on-Stone/Áísínai'pi in Canada

RONNIE CHUA *Getty Images*

Scientists, conservation organizations and governments trying to stem the tide of extinction often focus efforts on protected areas such as national parks and wildlife preserves. But with as many as a million species at risk, this strategy may not be enough to conserve wildlife, especially in a world increasingly disrupted by climate change.

Slowing the mass extinction that now appears to be underway will require more creative means of coexisting alongside wild plants and animals. A new study underscores the effectiveness of some such approaches by examining indigenous-managed lands.

"We show really strongly that, from a biodiversity standpoint in terms of species richness, indigenous-managed lands are at least comparable to protected areas," says biologist Richard Schuster of Carleton University. And in some places, they far surpass parks and preserves—even though indigenous communities may utilize their lands' resources by hunting or foraging for food.

Schuster and his team analyzed more than 15,000 areas in Australia, Brazil and Canada. They found that the total diversity of birds, mammals, amphibians and reptiles was highest on lands either managed or co-managed by indigenous groups, whereas randomly selected locations with no formal protection were the least biodiverse. For threatened species in particular, indigenous lands scored slightly higher than protected lands on overall species richness in Brazil and Canada, as well as higher for threatened amphibians and reptiles in Australia, mammals in Brazil, and birds and reptiles in Canada. The results were published last November in *Environmental Science and Policy.*

Each country has a different geography, climate and colonization history. Yet remarkably, Schuster says, the best indicator for species diversity is whether a given area was managed by an indigenous community. He points out that practices such as sustainable hunting, fishing and foraging, as well as prescribed burning, are more likely to occur in such areas. Don Hankins, an ecologist at California State University, Chico, who is a member of the Plains Miwok indigenous nation and was not involved in the study, agrees. "There's probably going to be more of a connection to the land," he says, "and a use of the land for the things that are there, compared to a national park."

"It's really important to listen to the people who live on the land and have them drive the stewardship efforts going forward," Schuster says, adding that partnering with indigenous communities may enable the world's countries to better meet a wide range of conservation goals: "We really need all the help we can get as a global community to avert the extinction crisis that we're facing right now."

—Jason G. Goldman

Jackdaw flock

GETTY IMAGES

ANIMAL BEHAVIOR

Flocking Phase Change

New study shows how jackdaw flocks vary between chaos and order

Jackdaws switch between two sets of flocking rules with differing results, a new research has found. Flocks flying to winter roosts are orderly no matter how many birds they contain; those rallying to ward off predators are initially disorganized when their numbers are small and then suddenly flip to order once enough birds join in.

Swimming bacteria, marching locusts, schooling fish and flocking birds all function as cohesive units. This phenomenon can emerge when individual agents following identical rules come together, says Alex Thornton, who studies cognitive evolution at the University of Exeter in England. “We got used to thinking of collective behavior as this almost physical phenomenon,” he says. “So the idea that animals might actually change the rules that they use when their environment and what they’re trying to achieve are different is quite novel and exciting.” Thornton is co-author on the new work, detailed last November in *Nature Communications.*

The researchers filmed flocking wild jackdaws in Cornwall, England, with four synchronized high-speed cameras, charting individuals’ positions and trajectories.

Of the 16 flocks recorded, six were “transit flocks”—jackdaws returning to their roosts on winter evenings. In these groups, regardless of size, each jackdaw adjusted its trajectory based on a fixed number of neighbors and always maintained order.

To initiate “mobbing flocks,” the researchers presented to groups of jackdaws a taxidermy fox holding a fake, flapping bird and played alarm calls that the birds commonly use to recruit allies against predators. In this context, jackdaws instead navigated by tracking all birds that were within a fixed distance. “With these [predator-mobbing] rules, you have emergence of order from chaos,” Thornton says. “Small flocks are disorganized. When the density of the flock reaches a threshold level, suddenly there is order—much like how a gas transitions into a liquid.” These transitions have never been observed in birds before, he adds.

“The novelty comes in comparing the same species in different ecological contexts, which [the researchers] implemented via a clever technique,” says Shashi Thutupalli, who studies living systems’ self-organization at India’s National Center for Biological Sciences and who was not involved in the research. He wonders whether “influencers” in a flock might lead these adjustments and whether other species make similar behavioral switches.

“What our work shows is that you cannot ignore the external environment in trying to model collective behavior in biological systems,” says Nicholas Ouellette, a physicist at Stanford University and co-author on the study. Drawing inspiration from jackdaws, he says, engineers could someday use context-dependent responses to build fleets of drones that work together for firefighting, surveying and search-and-rescue missions: “It allows you to think about designing systems that are more flexible, that can change the rules to make the behavior more robust.” —*Harini Barath*

PHARMACOLOGY

Fungus Secret

Next-generation opioids may spring from a tiny fungal protein


Illustration of *Penicillium* fungi

DR MICROBE *Getty Images*

Opioids relieve pain very effectively by activating particular receptors—proteins that are found on cells and respond to specific substances. But these drugs also cause serious side effects, including respiratory depression, which can be lethal. New research could inspire next-generation opioids that provide pain relief with fewer such risks.

Scientists in Australia have discovered peptides, tiny strands of amino acids, that act like opioids in some ways and come from an unlikely source: a *Penicillium* fungus. “This beast was found in a very pristine estuary at the end of the world, in Tasmania,” says Macdonald Christie, a neuropharmacologist at the University of Sydney and senior author on the new study, detailed last October in the *Proceedings of the National Academy of Sciences USA*. Peptides that can activate opioid receptors to modify pain levels are rarely found outside the vertebrate nervous system, he says.

Opioid receptors belong to a family that controls countless brain functions. These receptors send signals within associated cells using molecules called G-proteins. For a long time, researchers thought drugs interacting with an opioid receptor would simply instigate G-protein signaling or block it, Christie says. But scientists have since learned that opioid receptors associate with many other proteins, too, influencing multiple signaling pathways within cells.

“Most drug discovery has been based on efforts to turn on or off that G-protein interaction,” says Laura Bohn, a neuroscientist now at the Scripps Research Institute in Florida, who was not involved in the work. But “instead of continuing to just flip the switch, we can look for ways to dial in what we want—and what we want is pain relief. What we don’t want is respiratory depres-

BIOLOGY

Cryptic Predators

Beetles have an outsize impact on their vertebrate prey


Diving beetle

GEORGE GRALL *National Geographic Image Collection*

When ecologist Jose Valdez and his team released 10,000 tadpoles to populate a new conservation site in Newcastle, Australia, they surrounded the area with a mesh fence to keep out hungry snakes, birds and mammals. But they hadn’t considered much smaller predators: diving beetles. The researchers soon began to witness the insects’ violent attacks, and three years later only a handful of frogs remained. In two recent papers, Valdez, a researcher at Denmark’s Aarhus University, and his colleagues documented the beetles’ devastating predation tactics and possible implications for conservation efforts.

Predators are usually larger than their prey, with vertebrates such as amphibians typically doing the eating when it comes to insects. Although role reversal has been reported—such as praying mantises consuming lizards—scientists consider this rare. Valdez suspects insects’ predatory behavior has been underestimated, however. “Our two studies show that perhaps they may have a big effect,” he says, “especially for endangered species with small populations.”

It is unusual to see insects hunting in packs. But while monitoring one pond at night, Valdez saw about 12 adult diving beetles surround a tadpole and quickly pull it apart. “I was shocked at how viciously and quickly these beetles took down a much larger tadpole,” he says.

The researchers also noticed that certain diving beetles laid their eggs inside frog egg clutches, seemingly timed to hatch so the insect larvae could hunt down newborn tadpoles. The beetle larvae killed up to three tadpoles an hour, often discarding a half-eaten one if another was close by. “None of these behaviors were documented before,” Valdez says. His team detailed its work last December in *Entomological Science* and online last August in the *Australian Journal of Zoology*.

Because insects are small, their predasion to [the point of] overdose, and we don't want addiction." Bohn's research connected the pain-relief effects of the common opioid morphine to activation of G-proteins, and it linked morphine's respiratory depression to activating a regulatory protein called beta-arrestin.

Most opioids (and all known naturally occurring ones, Christie says) activate beta-arrestin as well as G-protein signals. But bilorphin—a compound the researchers in the new study created based on the fungal peptides—focused on just the G-proteins, Christie says. "That was something big to us," he adds, "because we knew that everyone in pharma was working on developing [opioid compounds] that don't signal to arrestin." (Bohn and Christie agree, however, that finding drugs free of side effects will be more nuanced than simply avoiding beta-arrestin signaling.)

The researchers tested bilorphin in mice, but it blunted pain signals only when injected directly into the spinal cord, which means that it could not cross the blood-brain barrier. The challenge will be to design bilorphin-inspired compounds that can get inside the brain and retain their unique signaling capabilities—ideally stopping pain without stopping breathing.

—Stephani Sutherland

tory behavior is easy to miss—and they often attack in difficult-to-observe settings, such as at night or underwater. But such assaults are emerging from the shadows: recent studies have documented praying mantises regularly eating small birds, as well as giant water bugs consuming vertebrates such as turtles, frogs and snakes in Japanese rice fields.

Insect predation could play a hidden role in declining amphibian populations. The International Union for Conservation of Nature estimates that at least 40 percent of amphibian species are threatened with extinction; Eric Nordberg, an ecologist at James Cook University in Australia, says attempts to protect them typically focus on environmental factors such as habitat loss and invasive species, whereas the impact of invertebrate predation is understudied.

Next, Valdez plans to quantify diving beetle predation on various amphibians. He will analyze insect gut contents and use cameras to capture more of the behavior. "We may finally begin to recognize their role in shaping vertebrate communities," he says.

—Sandrine Ceurstemont

BIG QUESTIONS FROM...
CARLA SHATZ

Carla Shatz has revolutionized our understanding of the human brain not once, but several times. Here, she explains how making and breaking neural connections help us learn, and how we could sharpen our cognitive skills, treat memory loss, and even reveal the roots of consciousness itself.

Paradigm-shifting discoveries are few and far between. But neuroscientist Carla Shatz has made several. Shatz, a professor of biology and neurobiology at Stanford University, has spent her career exploring how the brain develops and learns. Her journey began with vision. In adults, precisely arranged columns of neurons convey visual information from the eyes to the brain. These visual circuits take shape from the jumble of cells in the early fetal brain some time before a baby is born.

Biologists had believed that only hard-wired genetic programming could sculpt such precise circuitry before birth. Shatz instead found that the fetal eye sends test patterns to the brain that tune up the visual circuits before vision is even possible.

The finding was so surprising that many biologists didn't believe it. Since then, scientists have found that this sort of circuit testing is not limited to the vision system, but also happens throughout the brain very early in development. These findings revealed how the brain lays the foundation for a lifetime of learning.

As Shatz investigated these early test patterns, she revealed key molecules that sculpt neural circuits. This won over skeptics, and also proved something that scientists had long suspected: that activity strengthens the connections between neurons. Meanwhile, inactive connections are removed by a process called synaptic pruning. These observations shaped today's understanding of neuroplasticity, changes in brain structure and organization that occur as we learn, adapt and think. They also led Shatz to coin the phrase, "Cells that fire together, wire together"—a maxim that guides modern neuroscience.

In 2016, Shatz and Professors Eve Marder at Brandeis University, and Michael Merzenich at University of California, San Francisco, were awarded the Kavli Prize in Neuroscience for uncovering how experience and neural activity reshape brain circuits. Now, Shatz outlines the next big questions about neuroplasticity, and how solving them could help treat Alzheimer's disease, make the adult brain more youthful, and uncover how brain cells and circuits create consciousness.

Can we restore our childhood capacity for learning?

It's difficult to learn how to speak French without an accent as an adult, but we can learn many different languages and speak them perfectly if we learn them during childhood. Why is that? We discovered molecules that are turned on in adulthood that apply the brakes to learning. One of these molecules regulates the ability of the brain to remove synaptic connections between nerve cells, which are absolutely critical for learning and memory. If we give adult mice a pill that blocks this molecular brake on learning, we restore juvenile-like neuroplasticity. The treated mice have more synaptic connections, and they are better at navigating a complicated maze. The results suggest that being able to retain more connections in our brain makes us better able to learn new things.

Can we visualize the circuitry of a working human brain?
The brain has trillions of synaptic connections, yet neuroscientists have no way of looking at all of them in a noninvasive way in humans. Techniques like magnetic resonance imaging allow us to observe brain function, but, sadly, they provide only a coarse image. It's like looking at Earth from the Moon. You can see New York City lit up at night, but what you really want is a resolution that would allow you to see the details—each of the lights in all of the homes at once. That's going to take every tool in our toolkit—and new methods for monitoring all those neurons, collecting all the data, and working out the spatial and temporal organization of the computations as they happen. But it's what we will need to really understand both how the human brain computes at the level of circuits and synapses, and what goes wrong with brain wiring in neurological diseases.

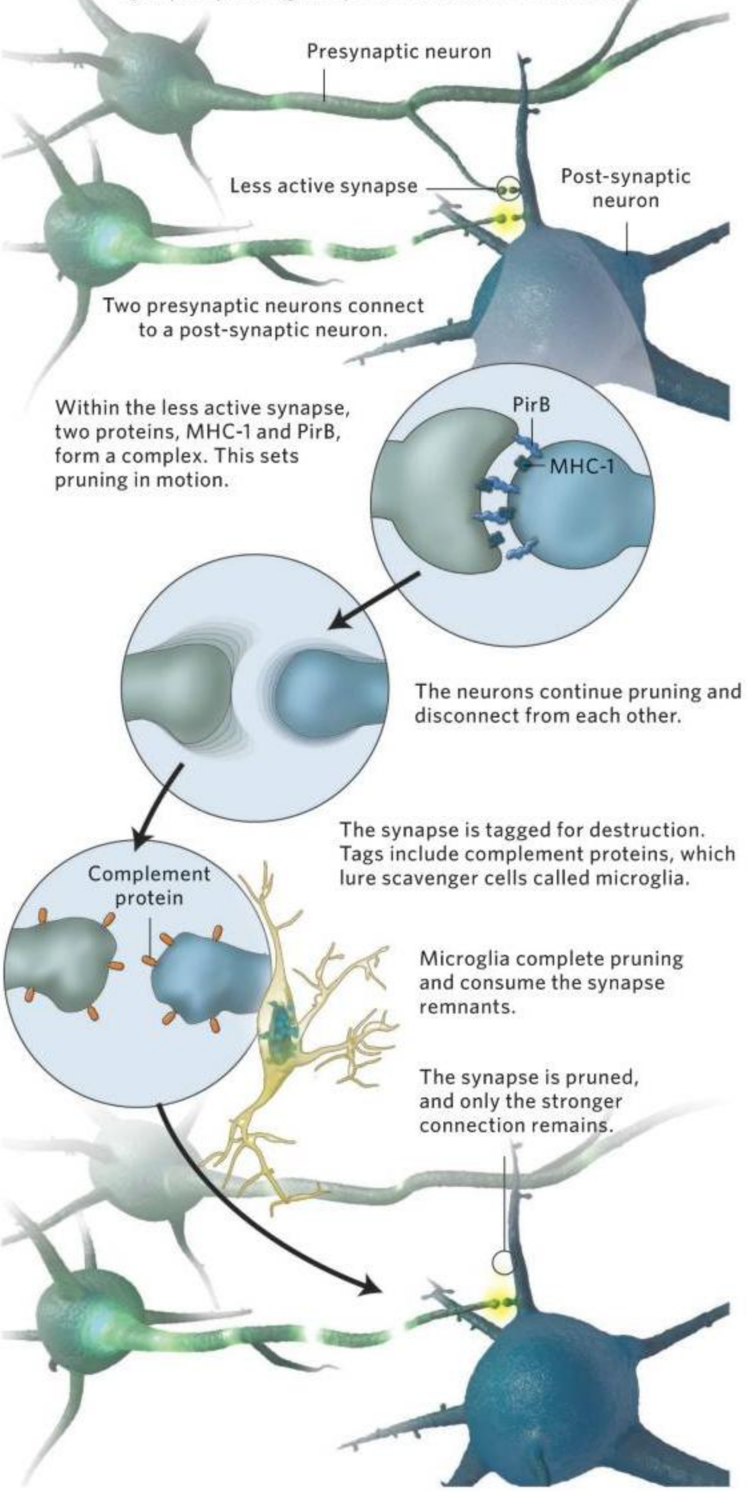
Can we help Alzheimer's patients recover lost memories?
In Alzheimer's disease, it's clear that the memory loss is due to the pruning or loss of synaptic connections. It gets to be pretty grim if you're losing the connections where your memories are stored—in a way, you're losing your personality and yourself. There is a family of molecules that are important for synaptic pruning. Maybe if we block their functions, we could prevent the loss of these connections in Alzheimer's disease and treat the disease and treat memory loss. That would be incredibly exciting.

How does brain biology generate the mind?
This is a huge challenge and a very exciting area of research. How do you bridge the gap between molecules, cells and circuits, and how we think and feel, and even the unanswered question of consciousness? We've been so reductionist in our approach to understanding the biology of the brain. What's exciting now is that other areas of science and technology are being brought to bear to bridge this gap, including engineering, computer science, artificial intelligence, and even deep learning techniques. We pioneered this kind of collaboration at Stanford in the Bio-X program, which I direct. These kinds of novel, interdisciplinary collaborations have been incredibly transformative. It's one thing to sit around and talk about this really cool idea for a collaboration with a colleague in a different field, and another thing to actually be able to launch it.

To learn more, listen to a podcast with Carla Shatz on ScientificAmerican.com. Also, stay tuned for the announcement of the next Kavli Prize laureates on May 27, 2020.

SYNAPTIC PRUNING

As the brain develops, it strengthens active synapses, or connections, between neurons, and it weakens and then prunes away inactive synapses. This same process, called synaptic pruning, helps us learn and remember.



Two presynaptic neurons connect to a post-synaptic neuron.

Within the less active synapse, two proteins, MHC-1 and PirB, form a complex. This sets pruning in motion.

The neurons continue pruning and disconnect from each other.

The synapse is tagged for destruction. Tags include complement proteins, which lure scavenger cells called microglia.

Microglia complete pruning and consume the synapse remnants.

The synapse is pruned, and only the stronger connection remains.

THE KAVLI PRIZE

METER

Edited by Dava Sobel

Jennifer Gresham is a Ph.D. scientist, a U.S. Air Force veteran and founder of Work for Humanity. She lives in Seattle.

Mathematical Glossolalia

As though time could have a hobby
we speak in eigenvalues, the harmonious
oscillations in the green flash before sunset.

We interpret *raised to the power* to mean
you were taken in by numbers
as a young babe & your childhood

can be classified irrational. Euclid,
Euler, the empty set's a nest atop a piling.
If two words diverge on the open seas &

the dot product is without derivative, the intercept
can be found only by Venn diagrams on the tongue.
Swallowed by wave functions, turning back, theorems

to explain the circumference of illusion, good heavens,
the sailboat's isosceles never goes slack.

Illustration by Cornelia Li

Claudia Wallis is an award-winning science journalist whose work has appeared in the *New York Times, Time, Fortune* and the *New Republic.* She was science editor at *Time* and managing editor of *Scientific American Mind.*

The Case for Less Heart Surgery

For some of the most common cardiac conditions, medication is a solid alternative

By Claudia Wallis

Modern heart surgery is miraculous. To think a failing aortic valve can be replaced via catheter without even cutting open the chest is to appreciate one of the wonders of 21st-century medicine. But as two recent landmark studies suggest, we may be a bit too avid for cardiac procedures. When it comes to treating some common heart conditions, medication can often get the job done.

That was the lesson of the much anticipated ISCHEMIA trial, the results of which were revealed at last November's meeting of the American Heart Association. The study involved 5,179 people with moderate to severe ischemia—insufficient blood flow to the heart—caused by narrowing of the coronary arteries. All participants in ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) got medication optimized for their needs: statins and sometimes additional cholesterol-reducing drugs; aspirin or other blood thinners; plus drugs to lower their blood pressure and heart rate where helpful. Subjects were educated on diet, exercise and relaxation techniques. But half the participants were randomly selected to also be treated with either stents—devices that prop open narrowed vessels—or, if stenting was not possible, with bypass surgery.

Although both procedures are routinely used to treat blocked vessels, researchers found that over a three-year period they offered no advantage over drug therapy alone in reducing the rate of heart attacks, hospitalization for heart failure or chest pain, or cardiac death. Past studies had come to similar conclusions, but this trial was larger and better designed, involving patients with more severe cardiovascular disease—the very patients thought to benefit from an invasive approach. Still, it makes sense that medication works so well: "When you have coronary narrowing, it's not just where you see it; it's all throughout the arteries," explains study chair Judith Hochman, senior associate dean of clinical sciences at NYU Langone Health. "Medical therapy addresses all of them where stenting addresses only the focal ones."

Where the procedures did outshine drugs was in reducing chest pain, or angina. One out of five patients who had daily or weekly chest pain became angina-free within one year with drug therapy, but that rose to one out of two with the invasive strategy. That finding suggests that people prone to angina might want to opt for a procedure. It's important to note that stents and bypass remain vital therapies for people suffering from heart attacks or unstable angina and those with narrowing of the left main coronary artery—all higher-risk groups not included in this trial.

Another study comparing heart medication with a more invasive treatment yielded similar results. Published last March, the CABANA trial looked at two approaches to atrial fibrillation—bouts of rapid, irregular heartbeats that afflict about 2 percent of adults younger than 65 and 9 percent of seniors in the U.S. The 2,204 patients in the study were randomly assigned to be treated with just medication or with catheter ablation, a procedure in which heat or cold was used to isolate or destroy heart tissue causing the abnormal rhythm. In this study, too, there was no difference between the two groups in mortality or in rates of disabling stroke, serious bleeding or cardiac arrest. Again, there was a difference in terms of symptoms: ablation patients were less likely to have recurrent attacks of A-fib and reported a better quality of life. By some measures ablation also outperformed drugs for patients younger than 65, minorities, and people with heart failure, says cardiologist Douglas Packer of the Mayo Clinic, who led the trial.

The studies should help put more decision-making power into the hands of patients. Rather than being rushed to the "cath lab" for a procedure on pain of death, people can take time to weigh their options. "I think the two studies are, in some senses, are twins," says Stephen Wiviott, a cardiovascular medicine specialist at Brigham and Women's Hospital, who was not involved in either trial. "They are fairly patient-empowering."

The studies' impact will be fascinating to see. At least 500,000 cardiac stent procedures are done annually in the U.S., many on an emergency basis. If doctors simply stopped doing them electively in the least symptomatic patients—those without angina—the U.S. could eliminate about 22,800 procedures a year, saving about $570 million, Hochman says. Ablations may also decline for people with few A-fib symptoms, but Packer says the quality-of-life argument for many patients is strong: "CABANA can't support the notion that people will live longer because of an ablation. It supports the notion that they will live better."

Illustration by Fatinha Ramos

Wade Roush is the host and producer of Soonish, a podcast about technology, culture, curiosity and the future. He is a co-founder of the podcast collective Hub & Spoke and a freelance reporter for print, online and radio outlets, such as *MIT Technology Review,* Xconomy, WBUR and WHYY.

Augmenting Reality, for Real

The gap between the real and digital worlds is narrowing

By Wade Roush

The names we give our technologies are often ... aspirational. *Automobiles* can move on their own—meaning without horses—but they still can't steer themselves reliably. Visiting via *telepresence* is nothing like being there. *Smartphones* have very low IQs. *Augmented reality* (AR) has been in this same hopeful category since the term was coined in the early 1990s. It was meant to describe screen-mediated experiences that add information to one's surroundings rather than replacing those surroundings, as *virtual reality* does. The problem turns out to be very hard to solve.

For one thing, AR objects need to look real, to stick solidly in place, and to stay there in shared environments (the "localization" problem). Creators need tools to build them, and users need ways to find and interact with them. And all of it needs to happen without blocking out the actual world; otherwise AR feels more like degraded reality. One by one, however, innovators have been removing those roadblocks. An era when we can all use AR for work, learning and entertainment is coming into view:

- In 2016 Microsoft introduced HoloLens, a self-contained AR headset, and last November it started selling an improved version to business users for $3,500 per unit. Consumers can now buy a similar headset for $2,300 from the lavishly funded and much hyped start-up Magic Leap. Both devices use see-through lenses called waveguides to create a 3-D effect.

I tried the Magic Leap One glasses recently. Used indoors, they generate remarkably bright, solid-looking objects, such as animated animals or robots, that register perfectly with their surroundings. For the moment, though, both headsets suffer from a limited field of view: about 50 degrees diagonally. That's less than half the arc visible to the human eye, meaning that not much of your surrounding reality gets augmented.

- Last November, San Francisco–based start-up Ubiquity6 released Display.land, an app that lets users capture, annotate, decorate and share photorealistic 3-D models of real-world places using the cameras on their smartphones. Phone-sensor data and computer-vision techniques allow Ubiquity6 to pin these models to the real world with an accuracy of centimeters.

Anjney Midha, co-founder and CEO of Ubiquity6, says he thinks of Display.land as the grown-up version of Minecraft, Roblox, Fortnite Creative and other virtual worlds that allow kids to author and share their own creations. "The worlds they're building have Lego-like aesthetics, but once you bring in photorealism, you 'age up,'" Midha says. "Adults also have a desire to express themselves and be creative in immersive ways. They just haven't had an easy-enough tool to do it."

- Also in November, a start-up called Sturfee in Milpitas, Calif., emerged from stealth mode with a technique that helps to solve the localization problem outdoors. It uses satellite imagery and computer vision to figure out what a smartphone camera is pointing at and to retrieve the right underlying 3-D mesh to anchor shared, persistent AR objects. But even before this was available, producers were going beyond games to create compelling outdoor AR projects. One example is the interactive Museum of the Hidden City, a tour from Walking Cinema that shows visitors to San Francisco powerful visual evidence of the way racist "slum clearance" projects transformed a minority neighborhood.
- Tech Web sites are abuzz with rumors that Apple will place 3-D distance sensors alongside the back-facing cameras of new iPhones in 2020, allowing developers to build more powerful AR apps. The company is also thought to be designing its own AR glasses, with a release date as soon as this year or as late as 2023.

AR has already reached consumers through smartphone-based games such as Pokémon Go and Harry Potter: Wizards Unite, both from Niantic. Such experiences will gain fidelity and become more collaborative—but they will run mostly on phones because AR headsets are still bulky and expensive. "If I want to allow real-time collaboration for people in my warehouse, I'm happy to pay for $2,000-plus hardware," Midha says. "But consumers are going to be on smartphones for a while." Which leaves us plenty to aspire to. SA

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Identifying the mechanisms of cancer initiation and its origins/early stages has important implications for improving early detection, cancer prevention and treatment. This conference aims to examine mechanisms at the cellular level, as well as system-wide influences. It will include cutting-edge research on what 'steps' a normal cell must go through to become cancerous, and what the cell of origin for a cancer is.

SPEAKERS:

Anton Berns (Netherlands Cancer Institute, Netherlands)
Chris Counter (Duke, USA)
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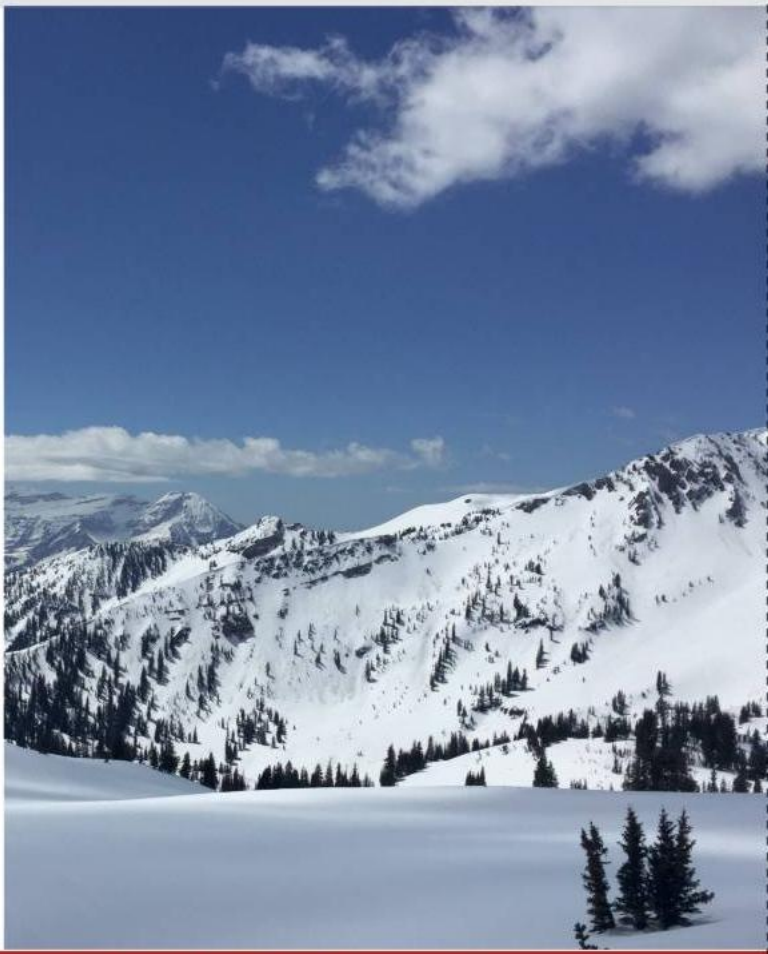
Michael Karin (UC San Diego, USA)
Allison Kurian (Stanford, USA)
Sancy Leachman (Oregon Health & Science University, USA)
Serena Nik-Zainal (Wellcome Sanger Institute, UK)
Olufunmilayo Olopade (University of Chicago, USA)
Electra Paskett (Ohio State University, USA)
Chirag Patel (Harvard Medical School, USA)
Timothy Rebbeck (Dana Farber Cancer Institute, USA)
June Round (Huntsman Cancer Institute, USA)
Jared Rutter (Huntsman Cancer Institute, USA)
Pepper Schedin (Oregon Health and Sciences University, USA)
Avrum Spira (Boston University, USA)
Sean Tavtigian (Huntsman Cancer Institute, USA)
Neli Ulrich (Huntsman Cancer Institute, USA)
Eduardo Vilar Sanchez (MD Anderson, USA)
Jane Visvader (Walter Eliza Hall Institute, AUS)
David Wetter (Huntsman Cancer Institute, USA)

*Lineup is subject to change



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NEUROSCIENCE

THE BRAIN'S SOCIAL ROAD MAPS

Neural circuits that track our whereabouts in space and time may also play vital roles in determining how we relate to other people

By Matthew Schafer and Daniela Schiller

Illustration by Richard Borge

WE ARE OFTEN TOLD THAT THERE ARE NO SHORTCUTS IN LIFE. BUT the brain—even the brain of a rat—is wired in a way that completely ignores this kind of advice. The organ, in fact, epitomizes a shortcut-finding machine.

The first indication that the brain has a knack for finding alternative routes was described in 1948 by Edward Tolman of the University of California, Berkeley. Tolman performed a curious experiment in which a hungry rat ran across an unpainted circular table into a dark, narrow

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corridor. The rat turned left, then right, and then took another right and scurried to the far end of a well-lit narrow strip, where, finally, a cup of food awaited. There were no choices to be made. The rat had to follow the one available winding path, and so it did, time and time again, for four days.

On the fifth day, as the rat once again ran straight across the table into the corridor, it hit a wall—the path was blocked. The animal went back to the table and started looking for alternatives. Overnight, the circular table had turned into a sunburst arena. Instead of one track, there were now 18 radial paths to explore, all branching off from the sides of the table. After venturing out a few inches on a few different paths, the rat finally chose to run all the way down path number six, the one leading directly to the food.

Taking the path straight to the food cup without prior experience may seem trivial, but from the perspective of behavioral psychologists at the time, the rat's navigational accomplishment was a remarkable feat. The main school of animal learning in that era believed that maze behavior in a rat is a matter of simple stimulus-response associations. When stimuli in the environment reliably produce a successful response, neural connections that represent this association get strengthened.

In this view, the brain operates like a telephone switchboard that maintains only reliable connections between incoming calls from our sense organs and outgoing messages to the muscles. But the behavioral switchboard was unable to explain the ability to correctly choose a shortcut right off the bat without having first experienced that specific path. Shortcuts and many other intriguing observations along these lines lent support to a rival school of thought promulgated by theorists who believe that in the course of learning, a map gets established in a rat's brain. Tolman—a proponent of that school—coined the term: the cognitive map.

According to Tolman, the brain does more than just learn the direct associations among stimuli. Indeed, such associations are often brittle, rendered outdated by changes in the environment. As psychologists have learned in the decades since Tolman's work, the brain also builds, stores and uses mental maps. These models of the world enable us to navigate our surroundings, despite complex, changing environments—affording the flexibility to use shortcuts or detours as needed. The hungry rat in Tolman's experiment must have remembered the location of the food, inferred the angle to it and chosen the route most likely to bring it to its goal. Quite simply, it must have built a model of the environment.

Such model building or mapmaking extends to more than physical space. Mental maps may exist at the core of many of our most "human" capacities, including memory, imagination, inferences, abstract reasoning and even the dynamics of social interactions. Researchers have begun to explore whether mental maps document how close or distant one individual is to another and where that individual resides in a group's social hierarchy. How does the brain, in fact, create the maps that allow us to make our way about the world?

A SPATIAL MAP

THE FIRST HINTS of a neural basis for mental maps came in the 1970s. While studying a brain region called the hippocampus in rodents, John O'Keefe of University College London, along with his student Jonathan Dostrovsky, discovered a particular class of neurons that becomes active when mice occupy specific locations in their environment. Some of these neurons fired when the animal was in one location, and others switched on when it moved to the next spot on the path along which it traveled, as if the cells were specialized to track *where* the animal was in space. By linking sequences of these "place cells" together, researchers were able to reconstruct an animal's navigational trajectory. Work over the intervening decades confirmed the existence of place cells in other animals, including humans, and clarified many of their properties. Along the way, a host of cell types surfaced, each uniquely contributing to the brain's encoding of spatial representations.

In the nearby entorhinal cortex, a region connected to the hippocampus, a research team led by Edvard Moser and May-Britt Moser, former postdoctoral visiting fellows in O'Keefe's laboratory, discovered neurons highly similar to place cells. These cells also fired when an animal was in specific locations. But unlike place cells, each of these newly discovered cells spiked in multiple, regular locations. When mapped onto the animal's position, the activity patterns of these "grid cells" resembled highly regular, equilateral triangles. Like a spatial metric, these cells fired when an animal passed over the vertices of the triangles. The discovery of these cell types sparked excitement because of the emerging picture of how the brain controls navigation. Place cells and grid cells could provide a means to locate oneself in space and determine distance and direction. These navigational tools are crucial for building mental maps. (O'Keefe and the Mosers received the 2014 Nobel Prize in Medicine or Physiology for their work on place and grid cells.)

A wide variety of information is useful for creating such a map,

IN BRIEF

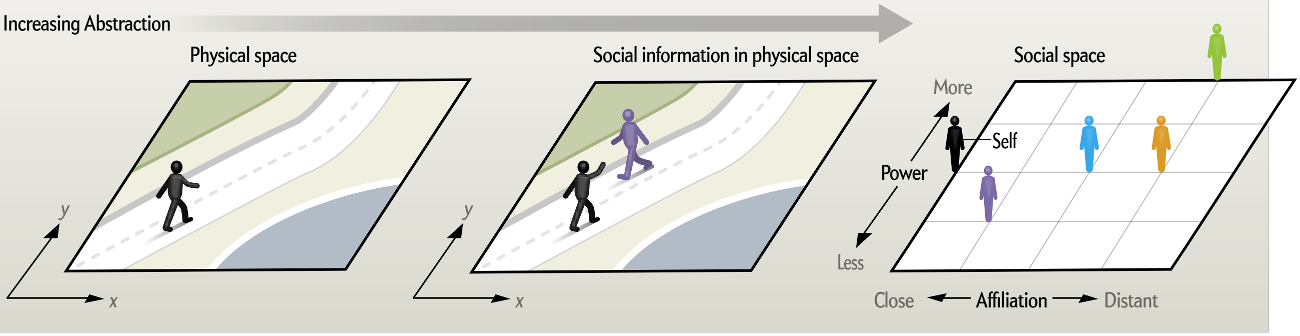
How do animals, from rats to humans, intuit shortcuts when moving from one place to another? Scientists have discovered mental maps in the brain that help animals picture the best routes from an internalized model of their environments.

Physical space is not all that is tracked by the brain's mapmaking capacities. Cognitive models of the environment may be vital to mental processes, including memory, imagination, making inferences and engaging in abstract reasoning.

Most intriguing is the emerging evidence that maps may be involved in tracking the dynamics of social relationships: how distant or close individuals are to one another and where they reside within group hierarchies.

Giving Way to the Abstract

Maps simplify the world by reducing an overwhelming amount of sensory and cognitive data into a format that can be used for navigating physical space, pointing to shortcuts and detours to reach a destination faster. The organization of such maps—built on the activity of cells dedicated to tracking both space and time—scales in the abstraction of what they represent: from the recognition of another individual along the way to even a complex space that denotes social power and closeness to others.



SOURCE: "NAVIGATING SOCIAL SPACE," BY MATTHEW SCHAFER AND DANIELA SCHILLER, IN *NEURON*, VOL. 100; OCTOBER 24, 2018

and the hippocampus-entorhinal system encodes much of it. Discovering the location of a physical goal is one example: as an animal navigates toward an objective, some hippocampal neurons fire depending on the direction and distance to reach it. The cells increase their firing rate as the animal approaches the goal.

Other cells also enter the picture. A dedicated population of "reward" cells encodes reward locations across different environments, providing a signal to guide an animal's navigation (think of an "X" marking the spot of treasure on a pirate's map). Other cells track speed and direction and in doing so act like internal speedometers and compasses that compute an animal's progress as it travels through the environment. Specific cells that signal the locations of landmarks in the surroundings serve as references to correct errors in the animal's trajectory. A map must also have edges: cells that fire more as the animal approaches the map's perimeter.

For humans, the importance of such an abundance of cell types seems obvious: the brain is responsible for knowing the location of home and work, walls and dead ends, a favorite shop or the corner store. It is still a mystery as to how all of this information is drawn together into a coherent map, but these cells appear to provide the parts list for the elements of neural mapmaking.

This hippocampal-entorhinal system is more than a mapmaker, though, and the maps are more than a way to locate oneself in space. Active planning occurs by using these maps. When a rat comes to a junction in a familiar maze, it will pause while place cell firing sequences that relate to the different options are activated, as if the animal is contemplating the choices.

Humans engage similar processes. Research in participants navigating virtual environments while their brains were scanned with functional magnetic resonance imaging shows that the hippocampus becomes active in ways consistent with spatial planning, such as considering and planning routes.

Shaping plans also occurs during sleep. Sequences of place cell activity can reactivate during sleep to replay the past or simulate the future. Without the ability to simulate new behaviors, we would have to explore a multitude of real-world options before deciding on what action to take. We would be constant empiricists, only able to act on direct observations. Instead offline simulations give us the ability to envision possibilities without directly experiencing them.

MENTAL TIME TRAVEL

TIME AND SPACE are inextricably linked. It is difficult to talk about time without borrowing a spatial metaphor: time "passes" as we "move" through it. We look "forward" to the future and "back" on our past. The same hippocampal-entorhinal system tracks movement through time. Work done largely in the lab of the late Howard Eichenbaum of Boston University revealed neurons in the hippocampal-entorhinal system that encode the time course of an animal's experience. Time cells fire at successive moments but do not track time in a simple clocklike fashion. Instead they mark temporal context—stretching or shrinking their firing durations if the length of a task changes, for example. Some time cells encode space as well. In the brain, in fact, physical and temporal space may be bound together.

The discovery of the crucial importance of these brain areas in space and time was not totally surprising. Psychologists had long suspected it to be the case. In 1953 Henry Molaison underwent bilateral hippocampal resection surgery to reduce extreme, life-disrupting epileptic seizures. The surgery was successful at quelling the seizures. But Molaison—known for decades only as H.M.—became one of the most renowned cases in the history of the brain sciences.

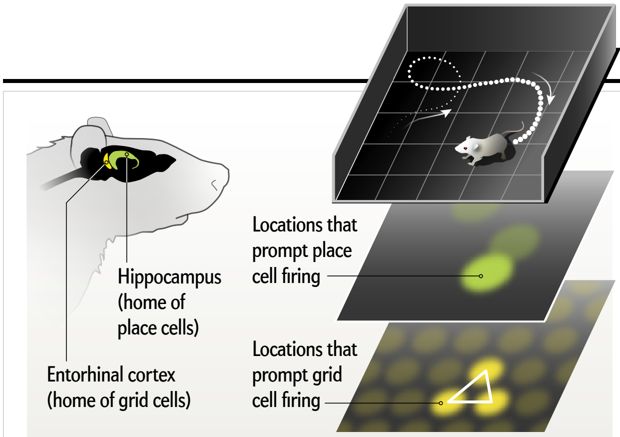
Molaison could remember most experiences from before his surgery—people he knew and recollections from culture and politics. But his ability to form such explicit memories postsurgery was practically nonexistent. Even so, certain types of learning and memory remained untouched: he could still learn some new skills with enough practice. But his recollections of new people, facts and events were immediately lost.

From observing Molaison, neuroscientists discerned that the hippocampus was essential in forming the episodic memories that record facts and events. Research on the role of the hippocampus in episodic memory exploded, largely in parallel to studies on its maplike functions.

Illustrations by Jen Christiansen

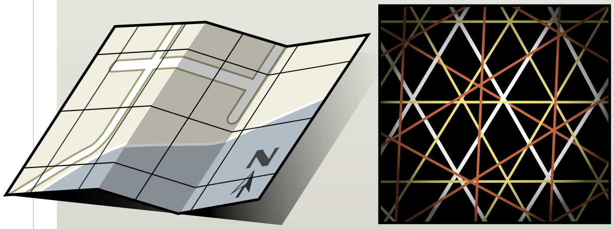
Cognitive Cartography Is Physical *and* Social

The brain forms the idea of friend or foe by stitching together diverse social characteristics from memories that track one's whereabouts. The recollections, research suggests, can then be used to place an individual within a social hierarchy that elucidates, say, where one stands in relation to others.



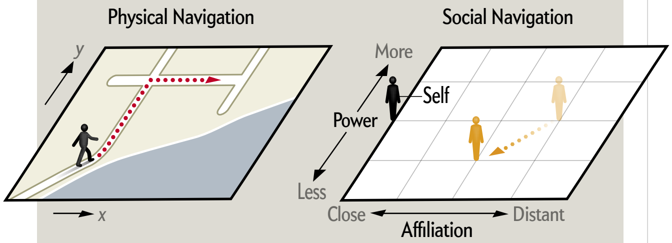
PLACE AND GRID CELLS

Place cells pinpoint the animal's whereabouts, each cell firing when a particular spot on a mental map is reached. A grid cell activates when an animal passes over the vertices of triangles superimposed on a mental map. The triangles' pattern of activation helps the animal compute the direction and distance traveled along a route.



MAKING THE LEAP TO SOCIAL MAPS

Go right at the corner and continue to your destination. Building a map of physical surroundings is the work of place and grid cells. But the brain may also use these cells for constructing maps for social milieus: locating an acquaintance who grows closer but loses power in a relationship.



SOURCES: "SCIENTIFIC BACKGROUND: THE BRAIN'S NAVIGATIONAL PLACE AND GRID CELL SYSTEM," BY OLE KIEHN AND HANS FORSSBERG, WITH ILLUSTRATIONS BY MATTIAS KARLEN. NOBELPRIZE.ORG; "NAVIGATING SOCIAL SPACE," BY MATTHEW SCHAFER AND DANIELA SCHILLER, IN *NEURON*, VOL. 100; OCTOBER 24, 2018

The discoveries about the roles of the hippocampus and entorhinal cortex in spatial navigation and episodic memory were significant for at least a couple of reasons. The work in spatial navigation in rodents marked the first time that a higher-order cognitive function—something beyond basic sensory processes—mapped onto clear neural correlates. H.M. showed us that there were multiple types of memory supported by at least partially different neural systems, with the hippocampus playing a central role in the formation and storage of new episodic memories. These discoveries hinted that mechanisms of spatial and temporal navigation might underlie episodic memory. This synthesis is perhaps best explained by the theoretical construct proposed decades earlier by Tolman; both episodic memory and spatial navigation might reflect the brain's formation and use of cognitive maps.

Maps are not accurate portraits of the world in all of its complexity. Rather they are representations of relations—distances and directions between locations and what exists where. Maps reduce a dizzying amount of real-world information into a simple, easily readable format that is useful for effective, flexible navigation. The cell types mentioned earlier (place cells, grid cells and border cells, among others) may piece together such related elements into a mental map, which other brain regions can then read out to guide "navigation," amounting to adaptive decision-making. Mapping allows relations to be inferred, even when they have not been experienced. It also allows for mental shortcuts that go beyond the purview of the spatial and temporal domains. In fact, reasoning using abstract concepts may depend on some of these same neural foundations.

In one example of this new line of work, researchers Alexandra Constantinescu, Jill O'Reilly and Timothy Behrens, all then at the University of Oxford, asked participants to learn associations of different symbols with images of "stick" birds with various neck and leg lengths. A bird with a long neck but short legs, for example, might be linked with the image of a bell, whereas a bird with a short neck and long legs might be connected to a teddy bear. These linkages created a two-dimensional association space. Despite neuroimaging being too crude to detect actual grid cells in the human brain, imaging conducted during the learned-association testing nonetheless revealed a gridlike pattern of activation within the entorhinal cortex.

This finding builds on earlier work by Christian Doeller of the Max Planck Institute for Human Cognitive and Brain Science in Leipzig, Germany, and Neil Burgess of University College London that first showed an entorhinal gridlike representation in humans navigating a virtual maze. For both physical and abstract relations, the gridlike organization is highly efficient. It makes the linkages of places or concepts more predictable, enhancing how quickly inferences can be made about these relations. As in physical space, this organization of information allows for inferring shortcuts—relations between ideas or perhaps analogies, stereotypes and even some aspects of creativity itself could depend on such inferences.

PEOPLE MAPS

THE PROGRESSION from the physical to the abstract carries over into the way the brain represents social relationships. Various bits of knowledge about another person are distilled into the concept of that individual. When we see a photograph of someone or hear or see that person's name, the same hippocampal cells will fire, regardless of the sensory details of the stimulus (for example, the famous "Jennifer Aniston neuron" described by Itzhak Fried of the University of California, Los Angeles, and his colleagues). These hippocampal cells are responsible for representing concepts of specific individuals.

Other hippocampal cells track the physical locations of others and are called social place cells. In an experiment by David Omer of the Hebrew University of Jerusalem, Nachum Ulanovsky of the Weizmann Institute of Science in Rehovot, Israel, and their colleagues, bats observed other bats navigating a simple maze to reach a reward. The task of an observer bat was to simply watch and learn from a navigating bat, enabling it to subsequently navigate the same route to get the same reward. When the observer bat watched, hippocampal cells fired corresponding to the location of the other bat.

Neural circuitry within specific hippocampal subregions (in particular, areas called CA1 and CA2) contribute to such social memories. Artificial stimulation or inactivation of these hippocampal areas enhances or diminishes an animal's ability to recognize other animals. In humans, hippocampal injury often spares memory for specific, individual faces, but the relation between this cardinal identifier of another person and that individual's behavior may be lost. That observation suggests that the hippocampus does not simply record a face or some other personal detail but rather ties together diverse social characteristics.

Hippocampal activity also tracks social hierarchies: the demands of a boss and a co-worker, for instance, may be valued differently and confer different social standings. Common metaphors illustrate the spatial dimensions of a hierarchy: a person may try to gain status to "climb the social ladder" or "look down" at someone below them. Other factors are also critical. Biological relatedness, common group goals, the remembered history of favors and slights—all determine social proximity or distance. Human relationships can be conceived of as geometric coordinates in social space that are defined by the dimensions of hierarchy and affiliation.

Work in our lab has explored these ideas in recent years. Our results suggest that, as with other spaces, the hippocampus organizes social information into a maplike format. To test this hypothesis, we put individuals in a role-playing game in which they interacted with cartoon characters and made decisions while their brains were scanned.

In the game, players had just moved to a new town and needed to interact with the fictional characters to secure a job and a place to stay. Participants made decisions on how to deal with a given character. Players could request that others perform favors to demonstrate their power, or they could submit to demands made on them. In a subsequent interaction, they could decide whether or not to make a gesture of attachment—giving a hug or remaining at a distance.

Using these decisions, we plotted each character at certain coordinates on a map representing their movement along the dimensions of power and affiliation. In each interaction, we drew a line or vector from the participant to the character. In this way, we charted the evolving relations as trajectories through social space and computed information about the angles and lengths of the social vectors.

We searched for neural signals that tracked this information by correlating a participant's brain activity with the angle and length of the vectors for each decision. Activity in the hippocampus tracked the angle of the characters to the participant. The degree to which hippocampal activity captured these social coordinates also reflected the participants' self-reported social skills. These findings suggest that the hippocampus monitors social dynamics as it does physical locations by encoding relations between points in multidimensional space. Indeed, it may be that along any arbitrary dimension in which we can order information, whether physical or abstract, the hippocampus-entorhinal system plays a part.

Many questions about the brain's social maps still remain unanswered. How does this system interact with other brain regions? For example, in our role-playing study, we found that the posterior cingulate cortex, a region also involved in representing spatial information, tracked the length of social vectors—functioning in effect as a measuring stick of "social distance." Further, a gridlike signal was found in brain regions that are interconnected with and tend to co-activate with the hippocampal-entorhinal system, suggesting they form a network of brain regions with common functional properties.

As research accumulates, questions of clinical importance arise as well. Can flawed mapping processes explain psychiatric dysfunction? Another possibility is that insights garnered from this brain architecture could inform artificial-intelligence development. Well-organized internal models of the world might be key to building more intelligent machines.

That the same mapping system may underlie navigation through space and time, reasoning, memory and imagination, and even social dynamics suggests that our ability to construct models of the world might be what makes us such adaptive learners. The world is full of both physical and abstract relations. Road maps of city streets and mental maps of interrelated concepts help us make sense of the world by extracting, organizing and storing related information. A new coffee shop on a familiar street can be easily placed within an existing spatial map. Fresh concepts can be related to older ideas. And a new acquaintance can reshape our social space.

Maps let us simulate possibilities and make predictions, all within the safety of our own heads. The mental shortcuts we can so readily conjure up might have their basis in the same system that allows us to figure out a detour around a traffic jam. We have just begun to discover the varied properties and capacities of this system. Mental maps do more than help us find shortcuts through physical space—they enable us to navigate life itself. SA

MORE TO EXPLORE

Social Place-Cells in the Bat Hippocampus. David B. Omer et al. in *Science,* Vol. 359, pages 218–224; January 12, 2018.

Navigating Social Space. Matthew Schafer and Daniela Schiller in *Neuron,* Vol. 100, No. 2, pages 476–489; October 24, 2018.

What Is a Cognitive Map? Organizing Knowledge for Flexible Behavior. Timothy E. J. Behrens et al. in *Neuron,* Vol. 100, No. 2, pages 490–509; October 24, 2018.

Navigating Cognition: Spatial Codes for Human Thinking. Jacob L. S. Bellmund et al. in *Science,* Vol. 362, Article No. eaat6766; November 9, 2018.

FROM OUR ARCHIVES

Where Am I? Where Am I Going? May-Britt Moser and Edvard I. Moser; January 2016.

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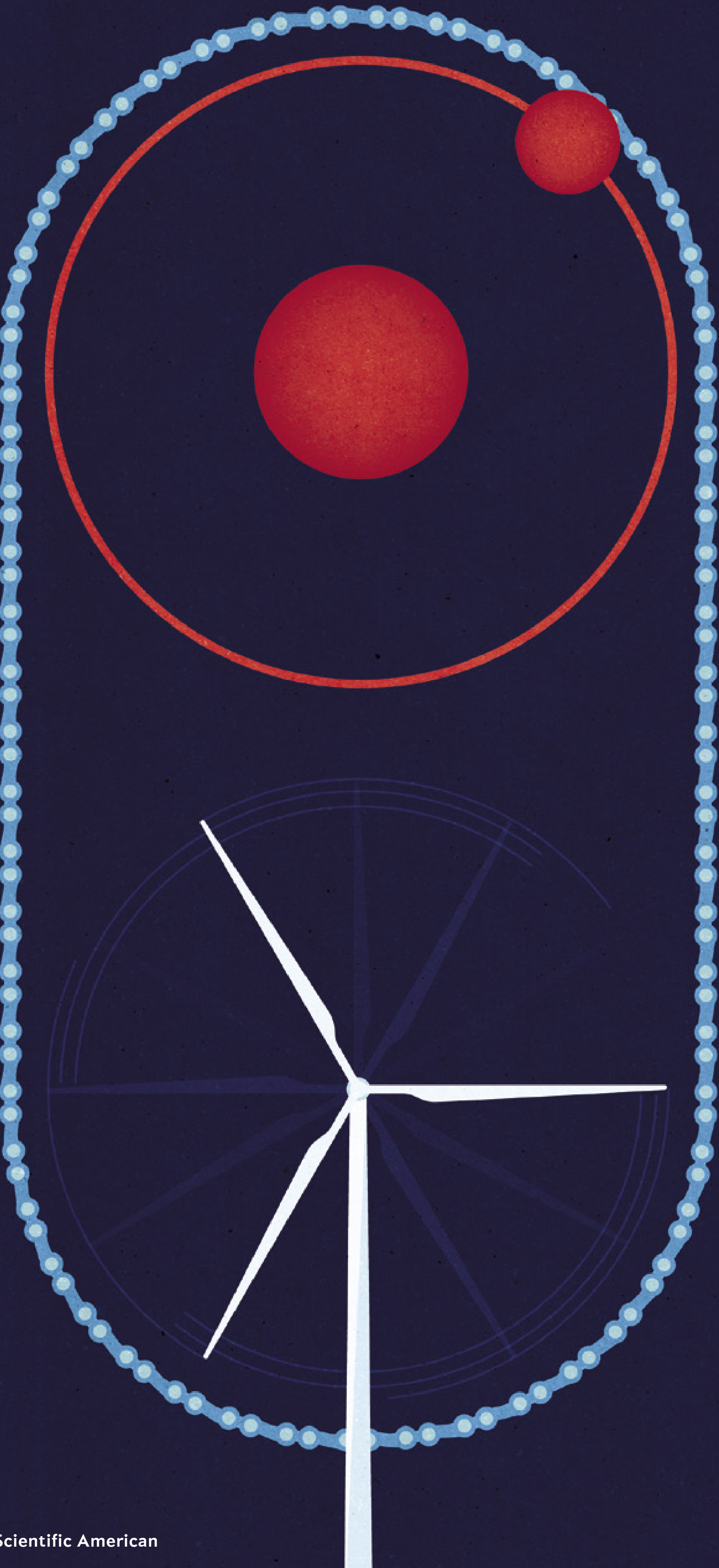


ENERGY

THE H_2 SOLUTION

Hydrogen energy could make a comeback as an important piece of the all-renewable energy puzzle

By Peter Fairley

Illustration by Kotryna Zukauskaite

Peter Fairley writes about energy and the environment from Victoria, B.C., and San Francisco. He wrote our 2018 article "Building a Weather-Smart Grid."

HYDROGEN IS FLOWING IN PIPES UNDER THE STREETS in Cappelle-la-Grande, helping to energize 100 homes in this northern France village. On a short side road adjacent to the town center, a new electrolyzer machine inside a small metal shed zaps water with electricity from wind and solar farms to create "renewable" hydrogen that is fed into the natural gas stream already flowing in the pipes. By displacing some of that fossil fuel, the hydrogen trims carbon emissions from the community's furnaces, hot-water heaters and stove tops by up to 7 percent.

Cappelle-la-Grande's system is a living laboratory created by Paris-based energy firm Engie. The company foresees a big scale-up of hydrogen energy as the cost of electrolyzers, as well as of renewable electricity, continues to fall. If Engie is right, blending hydrogen into local gas grids could accelerate a transition from fossil to clean energy.

The company is not alone. Renewable hydrogen is central to the European Commission's vision for achieving net-zero carbon emissions by 2050. It is also a growing focus for the continent's industrial giants. As of next year, all new turbines for power plants made in the European Union are supposed to ship ready to burn a hydrogen–natural gas blend, and the E.U.'s manufacturers claim the turbines will be certified for 100 percent hydrogen by 2030. European steelmakers, meanwhile, are experimenting with renewable hydrogen as a substitute fuel for coal in their furnaces.

If powering economies with renewable hydrogen sounds familiar, it is. Nearly a century ago celebrated British geneticist and mathematician J.B.S. Haldane predicted a post-fossil-fuel era driven by "great power stations" pumping out hydrogen. The vision became a fascination at the dawn of this century. In 2002 futurist Jeremy Rifkin's book *The Hydrogen Economy* prophesied that the gas would catalyze a new industrial revolution. Solar and wind energy would split a limitless resource—water—to create hydrogen for electricity, heating and industrial power, with benign oxygen as the by-product.

President George W. Bush, in his 2003 State of the Union address, launched a $1.2-billion research juggernaut to make fuel-cell vehicles running on hydrogen commonplace within a generation. Fuel cells in garages could be used as backup sources to power homes, too. A few months later *Wired* magazine published an article entitled "How Hydrogen Can Save America" by breaking dependence on dirty imported petroleum.

Immediate progress did not live up to the hype. Less expensive and rapidly improving battery-powered vehicles stole the "green car" spotlight. In 2009 the Obama administration put hydrogen work on the back burner. Obama's first secretary of energy, physicist and Nobel laureate Steven Chu, explained that hydrogen technology simply was not ready, and fuel cells and electrolyzers might never be cost-effective.

Research did not stop, however, and even Chu now acknowledges that some hurdles are gradually being cleared. The Cappelle-la-Grande demonstration is one small project, but dozens of increasingly large, ambitious installations are getting started worldwide, especially in Europe. As the International Energy Agency noted in a recent report, "hydrogen is currently enjoying unprecedented political and business momentum, with the number of policies and projects around the world expanding rapidly."

This time around it is the push to decarbonize the electric grid and heavy industry—not transportation—that is driving interest in hydrogen. "Everyone in the energy-modeling community is thinking very seriously about deep decarbonization," says Tom Brown, who leads an energy-system modeling group at Germany's Karlsruhe Institute of Technology. Cities, states and nations are charting paths to reach nearly net-zero carbon emissions by 2050 or sooner, in large part by adopting low-carbon wind and solar electricity.

But there are two, often unspoken problems with that strategy. First, existing electric grids do not have enough capacity to handle the large amounts of renewable energy needed to put fossil-fueled power plants out of business. Second, backup power plants would still be needed for long stretches of dark or windless weather. Today that backup comes from nat-

IN BRIEF

Plans to fully power nations with renewable electricity will not succeed unless countries reconfigure all their energy systems, including fuels.

Excess solar and wind energy can run electrolyzers that convert water into hydrogen, which is distributed in pipelines and converted back into electricity when needed.

Hydrogen can be stored in tanks and underground caverns, forming a network that can energize industry and back up electric grids.

ELECTRODES inside an electrolyzer split water molecules into oxygen (*left*) and hydrogen (*right*). The electrodes are one centimeter high.

DURK GARDENIER *Alamy*

ural gas, coal and nuclear power plants that grid operators can readily turn up and down to balance sagging and surging renewable supply.

Hydrogen can play the same role, its promoters say. When wind and solar are abundant, electrolyzers can use some of that energy to create hydrogen, which is stored for the literal rainy day. Fuel cells or turbines would then convert the stored hydrogen back into electricity to shore up the grid.

Cutting carbon deeply also means finding replacement fuels for segments of the economy that cannot simply plug into a big electrical outlet, such as heavy transport, as well as replacement feedstocks for chemicals and materials that are now based on petroleum, coal and natural gas. "Far too many people have been misled into believing that electrification is the entire [carbon] solution" that is needed, says Jack Brouwer, an energy expert at the University of California, Irvine, who has been engineering solutions to his region's dirty air for more than two decades. "And many of our state agencies and legislators have bought in," without considering how to solve energy storage or to fuel industry, he says.

Can renewable hydrogen make a clean-energy grid workable? And could it be a viable option for industry? Some interesting bets are being made, even without knowing whether hydrogen can scale up quickly and affordably.

DARK DOLDRUMS

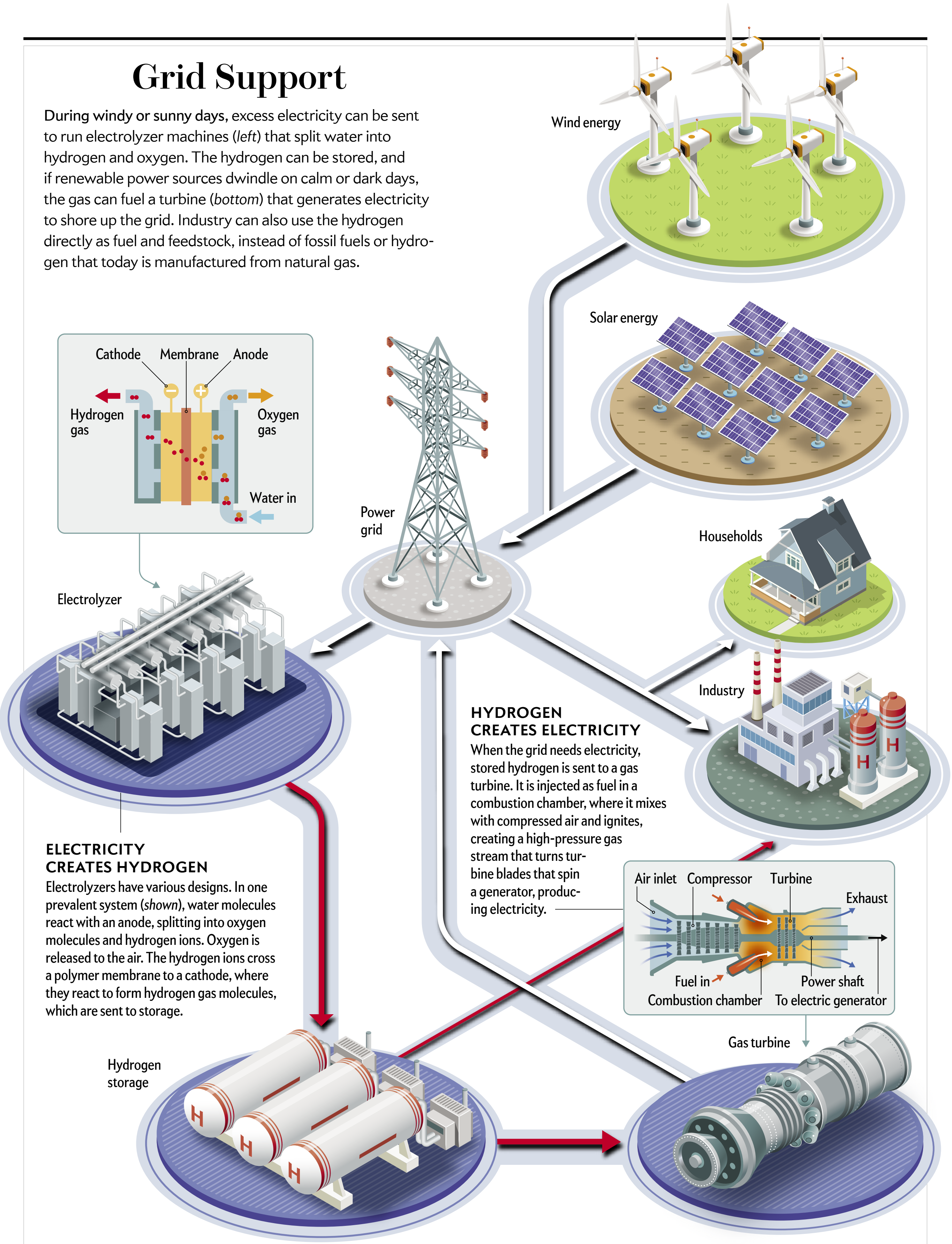
THE FEW NATIONS that have bet big on replacing coal and natural gas with solar and wind are already showing signs of strain. Renewable energy provided about 40 percent of Germany's electricity in 2018, though with huge fluctuation. During certain days, wind and solar generated more than 75 percent of the country's power; on other days, the share dropped to 15 percent. Grid operators manage such peaks and valleys by adjusting the output from fossil-fuel and nuclear power plants, hydropower reservoirs and big batteries. Wind and solar also increasingly surge beyond what Germany's congested transmission lines can take, forcing grid operators to turn off some renewable generators, losing out on 1.4 billion euros ($1.5 billion) of energy in 2017 alone.

The bigger issue going forward is how nations will cope after the planned phaseout of fossil-fueled power plants (and, in Germany, also their nuclear plants). How will grid operators keep the lights on during dark and windless periods? Energy modelers in Germany invented a term for such renewable energy droughts: *dunkelflauten,* or "dark doldrums." Weather studies indicate that power grids in the U.S. and Germany would have to compensate for *dunkelflauten* lasting as long as two weeks.

Beefier transmission grids could help combat *dun-*

Grid Support

During windy or sunny days, excess electricity can be sent to run electrolyzer machines (*left*) that split water into hydrogen and oxygen. The hydrogen can be stored, and if renewable power sources dwindle on calm or dark days, the gas can fuel a turbine (*bottom*) that generates electricity to shore up the grid. Industry can also use the hydrogen directly as fuel and feedstock, instead of fossil fuels or hydrogen that today is manufactured from natural gas.



ELECTRICITY CREATES HYDROGEN

Electrolyzers have various designs. In one prevalent system (*shown*), water molecules react with an anode, splitting into oxygen molecules and hydrogen ions. Oxygen is released to the air. The hydrogen ions cross a polymer membrane to a cathode, where they react to form hydrogen gas molecules, which are sent to storage.

HYDROGEN CREATES ELECTRICITY

When the grid needs electricity, stored hydrogen is sent to a gas turbine. It is injected as fuel in a combustion chamber, where it mixes with compressed air and ignites, creating a high-pressure gas stream that turns turbine blades that spin a generator, producing electricity.

Illustration by 5W Infographics

kelflauten by moving electricity across large regions or even continents, sending gobs of power from areas with high winds or bright sun on a given day to distant places that are calm or cloudy. But grid expansion is a slog. Across Germany, adding power lines is years behind schedule, beset by community protests. In the U.S., similar opposition prevents new lines from gaining approval.

To some experts, therefore, *dunkelflauten* make wind and solar energy look risky. For example, grid simulations done in 2018 by energy modelers at the Massachusetts Institute of Technology project an exponential rise in costs as grids move toward 100 percent renewable energy. That is because they assumed big, expensive batteries would have to be installed and kept charged at all times, even though they might be used only for a few scarce days or even hours a year.

A California-based team of academics reached a similar conclusion in 2018, finding that even with big transmission lines and batteries, solar and wind power could feasibly supply only about 80 percent of U.S. electricity needs. Other power sources will definitely be needed, said team member Ken Caldeira, a climate scientist at the Carnegie Institution for Science, when the study was released.

Certain European experts say the M.I.T. and California studies are too myopic. For several decades European researchers have been zooming out from the power grid to a larger view, considering the full spectrum of energy used in modern society. Pioneered by Roskilde University physicist Bent Sørensen and several Danish protégés, such "integrated energy systems" studies combine simulations for electric grids, natural gas and hydrogen distribution networks, transportation systems, heavy industries and central heating supply.

The models show that coupling those sectors provides operational flexibility, and hydrogen is a powerful way to do that. In this view, a 100 percent renewable electric grid could succeed if hydrogen is used to store energy to cover the *dunkelflauten* and without the price jump seen in M.I.T.'s projections.

Some U.S. grid studies ruled out hydrogen energy storage because it is costly today. But other modelers say that thinking is flawed. For example, many grid studies being published about a decade ago downplayed solar energy because it was expensive at the time—this was a mistaken assumption, given solar's dramatic cost decreases ever since. European simulations such as Brown's take into account anticipated cost reductions when they compute the cheapest ways to eliminate carbon emissions. What emerges is a buildout of electrolyzers that cuts the cost of renewable hydrogen.

In the models, electrolyzers scale up first to replace hydrogen that is manufactured from natural gas, used by chemical plants and oil refineries in various processing steps. Manufacturing "gray" hydrogen (as energy experts call it) releases more than 800 million metric tons of carbon dioxide a year worldwide—as much as the U.K. and Indonesia's total emissions combined, according to the International Energy Agency. Replacing gray hydrogen with renewable hydrogen shrinks the carbon footprint of hydrogen used by industry. Some hydrogen could also replace natural gas and diesel fuel consumed by heavy trucks, buses and trains. Although fuel cells struggle to compete with batteries for cars, they may be more practical for heavier vehicles; truck developer Nikola Motor Company says the tractor-trailer rigs it is commercializing will travel about 800 to 1,200 kilometers (500 to 750 miles) on a full fuel cell, depending on the various equipment and hauling factors.

The cost of electrolyzers may be the biggest challenge facing the renewable hydrogen future. To make inroads in industry, producing the gas needs to drop from about $4 or more per kilogram today to $2 or less.

If industry and heavy transport embrace renewable hydrogen, regional hydrogen networks could emerge to distribute it, and they could also supply the carbon-free gas to power plants that back up electricity grids. That is what happens in integrated energy simulations: as more renewable hydrogen is created and consumed, mass-distribution networks develop that store months' worth of the gas in large tanks or underground caverns, much as natural gas is stored today, at a cost that is cheaper than storing electricity in batteries. "Once you acknowledge that hydrogen is important for the other sectors, you get the long-term storage for the power sector as a sort of by-product," Brown says.

That perspective comes alive in simulations by Christian Breyer of Finland's LUT University. In his team's latest 100 percent renewable energy scenarios, published in 2019 with the Energy Watch Group, an international group of scientists and parliamentarians, power plants burning stored hydrogen fire up to fill the grid's void during the deepest *dunkelflauten*. "They are a final resort," Breyer says. "Without these large turbines, we would not have a stable energy system during certain hours of the year."

In Breyer's model, less than half of the wind and solar energy required to make and store hydrogen

ENGINEER checks pipes that distribute hydrogen made with renewable energy in Hamburg, Germany.

JOERG BOETHLING *Alamy*

gets converted back into electricity, a big loss, and the hydrogen turbine generators sit idle for all but a few weeks every year. But the poor efficiency of the hydrogen-to-electricity conversion does not break the bank, because this pathway is used infrequently. Breyer says the scheme is the most economical solution for the energy system writ large, and it is not that different from how many grids use natural gas–fired plants today. “For decades there have been power plants that are switched on only once every few years,” he says.

REPURPOSED PIPELINES

EVEN THOUGH TODAY’S renewable hydrogen generation is meager, Europe is counting on hydrogen to decarbonize its energy systems. The European Commission anticipates renewable energy rising to greater than 80 percent of Europe’s power supply in 2050, supported by more than 50 gigawatts of electrolyzers—the capacity of approximately 50 nuclear power plants. Member states are setting their own goals, too. France is calling for its hydrogen-consuming industries to switch to 10 percent renewable hydrogen by 2022 and 20 to 40 percent by 2027.

These goals will be difficult to reach without policies that encourage entrepreneurial firms to jump-start mass production of electrolyzers. Blending hydrogen into natural gas pipelines is a place to start because it uses existing infrastructure. Engineers had long assumed that molecular hydrogen—the smallest molecule and highly reactive—would degrade or escape from existing natural gas pipes. But recent research shows that blending of up to 20 to 25 percent hydrogen can be done without seeping from or hurting such pipes. European countries permit blending, and firms in Italy, Germany, the U.K., and elsewhere are injecting hydrogen at dozens of sites to help fuel customers’ heaters, cookstoves and other appliances, which do not need alterations as long as the hydrogen content stays below about 25 percent.

Engie has been blending at Cappelle-la-Grande for more than a year without incident or opposition, according to project manager Hélène Pierre. She says that public acceptance is helped by extensive monitoring that shows that homes using the blend have cleaner air; adding hydrogen improves gas combustion in appliances, she notes, trimming levels of pollutants such as carbon monoxide that are created when natural gas burns incompletely.

Europe’s next wave of renewable hydrogen projects could push production to a larger scale. Industrial consortia in France and Germany are seeking financing and authorization for 100-megawatt electrolyzers, 10 times larger than the biggest in operation. Two huge electrolyzer projects are vying for government support to boost a regional hydrogen economy around Lingen, a city in northwestern Germany that is home to a pair of oil refineries. One project that involves a large utility called Enertrag and several of Germany’s biggest energy and engineering firms could provide a blueprint for a nationwide hydrogen network. The project takes advantage of existing gas infrastructure but not via blending. Instead the idea is to repurpose spare gas pipelines to deliver renewable hydrogen to the local refineries, as well as a power plant and even a planned filling station for fuel-cell vehicles. “Our idea is to build up a 100 percent hydrogen gas grid,” says Frank Heunemann, who is managing director at Nowega, one of the partners on the project and the region’s gas-network operator.

Nowega can reuse some empty pipes because the region has two natural gas networks. One carries standard natural gas that is nearly all methane. The other was originally built to deliver local natural gas that was high in hydrogen sulfide, and hydrogen can make some steel pipes brittle. Nowega is phasing out the local gas, leaving empty steel pipes that Heunemann says should be able to endure any reactivity with pure hydrogen. European energy supplier RWE will build the consortium’s main electrolyzer and plans to burn some of the hydrogen output at its Lingen power station. Engineering giant Siemens intends to optimize one of the station’s four gas turbines to handle pure hydrogen.

The consortium is thinking about expansion as well. Lingen is about 48 kilometers from underground salt caverns created to store natural gas. Stocking some of Lingen’s hydrogen, more than 1,000 meters deep in one of the caverns, could be a logical next step, Heunemann says. (Hydrogen is already stored en masse in caverns in Texas and the U.K.)

Nowega also envisions a 3,200-kilometer pipeline network that could reach most of Germany's steel plants, refineries and chemical producers. The plan centers on repurposing natural gas pipes that were originally built to carry hydrogen-rich "town gas" produced from coal, which was common in Europe until the 1960s. Pipelines that historically coped with 50 percent hydrogen should also be fine "to use for 100 percent hydrogen," Heunemann says.

THE FUTURE IS TENTATIVE

EUROPE'S GROWING INTEREST in renewable hydrogen is not unique. Japan is planning a multidecadal shift to a "hydrogen society" that has been baked into official energy policy since 2014. Meeting one of Japan's first goals—demonstrating technology to efficiently import hydrogen—is set to begin in 2020 with tanker shipments of gray hydrogen from Brunei, a tiny gas-rich nation nestled in Borneo. Australia's rival political parties are developing competing plans to export hydrogen to Japan. In December 2019 energy ministers across Australia's states and territories adopted a national hydrogen strategy, and the national government announced a $370-million (Australian; $252 million U.S.) hydrogen-stimulus package.

Even in the U.S., there are signs of renewed interest. The federal government is once again setting goals for hydrogen technologies, some energy firms are investing and a few states are offering support. Los Angeles may be a leader. "L.A.'s Green New Deal," unveiled by Mayor Eric Garcetti in April 2019, commits the city to reach 80 percent renewable electricity by 2030 and 100 percent by 2050. The mayor is advancing plans to build solar farms and is also constructing a new natural gas–fired power plant to ensure the city has a backup electricity source. That plant could be converted to burn renewable hydrogen; about 125 kilometers of pipelines already push gray hydrogen to the area's refineries. And fuel cells are vying with batteries in plans to repower the roughly 16,000 trucks that haul freight at the region's ports. Fueling those trucks with hydrogen instead of diesel could significantly improve L.A.'s hazy skies.

Brouwer says the entire state needs to think more deeply about energy as it seeks to eliminate carbon emissions. The state may be wasting more than eight terawatt-hours of renewable energy potential every year by 2025, according to projections by Lawrence Berkeley National Laboratory—energy that Brouwer says California should instead be socking away as hydrogen to clean up its refineries and to meet soaring electricity demand during summer heat waves.

Other experts agree that hydrogen can connect those dots. A recent study by the Energy Futures Initiative, a think tank led by former M.I.T. nuclear physicist Ernest Moniz, who was Obama's second energy secretary, calls on California to tap the "enormous value" offered by renewable hydrogen and other low-carbon fuels. The study concludes that California's carbon-cutting goals may be impossible to meet without them.

A host of potential problems could still stall or prevent the scale-up of hydrogen infrastructure in California, Europe, and elsewhere. A persistent issue is public anxiety. Hydrogen is extremely flammable, and accidents happen. Last summer a faulty valve caused a hydrogen explosion at a Norwegian filling station for fuel-cell cars. Concrete blast walls minimized injuries, but media reports immediately questioned whether hydrogen energy would survive the incident. In November 2019 California governor Gavin Newsom asked the state's public utility commission to expedite closure of an underground gas-storage facility, where a four-month leak of natural gas four years earlier had prompted the evacuation of thousands of families.

All energy options have their risks, and community opposition complicates many paths to carbon-free energy. In many places, the public is not enamored with nuclear energy, transmission lines or wind turbines. The cost of electrolyzers may be the biggest challenge facing the renewable hydrogen future, however. To begin replacing gray hydrogen in industry, the cost of producing renewable hydrogen needs to drop from about $4 or more per kilogram today to $2 or less. Several studies indicate that could happen by 2030 if electrolyzer costs continue to fall as they have in the past few years.

The studies also suggest that pattern may not emerge without government incentives. In a recent report, the International Energy Agency notes that hydrogen needs the same kind of government support that fostered early deployments of solar and wind power—industries that now attract more than $100 billion in annual investment worldwide. Those examples, the agency writes, show that "policy and technology innovation have the power to build global clean energy industries."

Improved technology may be arriving. A new class of electrolyzers is entering the market—solid oxide electrolyzers that produce almost 30 percent more hydrogen than the industry-leading proton-exchange membrane electrolyzers, which Engie is using. Former energy secretary and doubter Chu, now a professor at Stanford University, is working on a novel electrolyzer that relies on tighter spacing of components and other tricks to produce hydrogen faster with less energy. According to Chu, the changes could make "a huge difference in operating cost." It's just one more reason, Chu says, why he is warming up to hydrogen. SA

MORE TO EXPLORE

Hydrogen Roadmap Europe. Fuel Cells and Hydrogen Joint Undertaking, February 2019.

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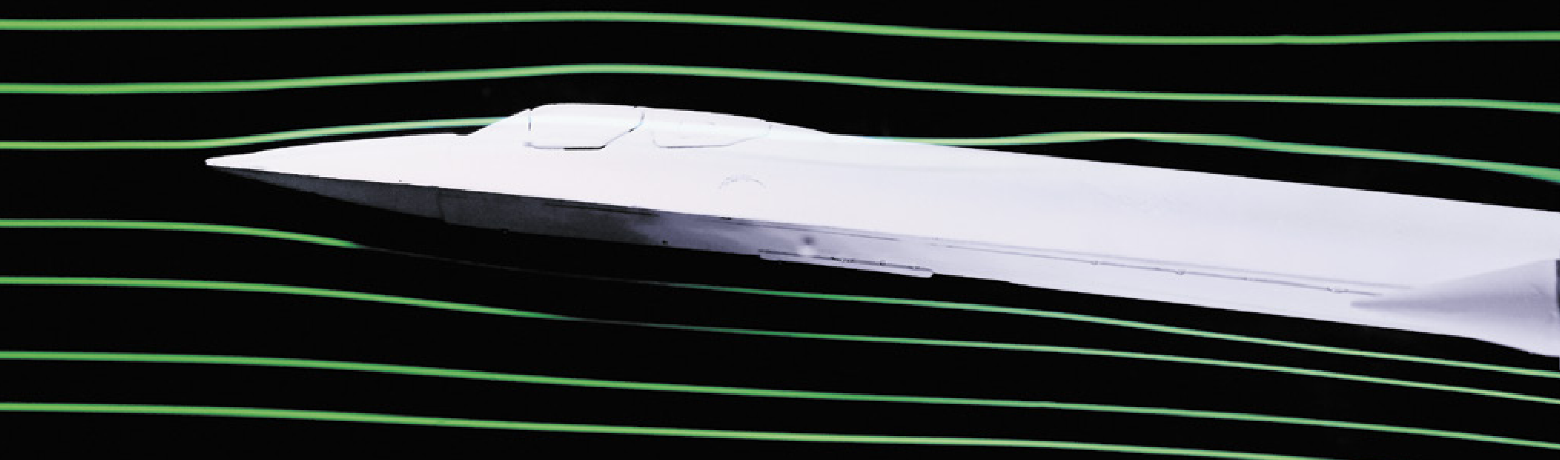
the enigma



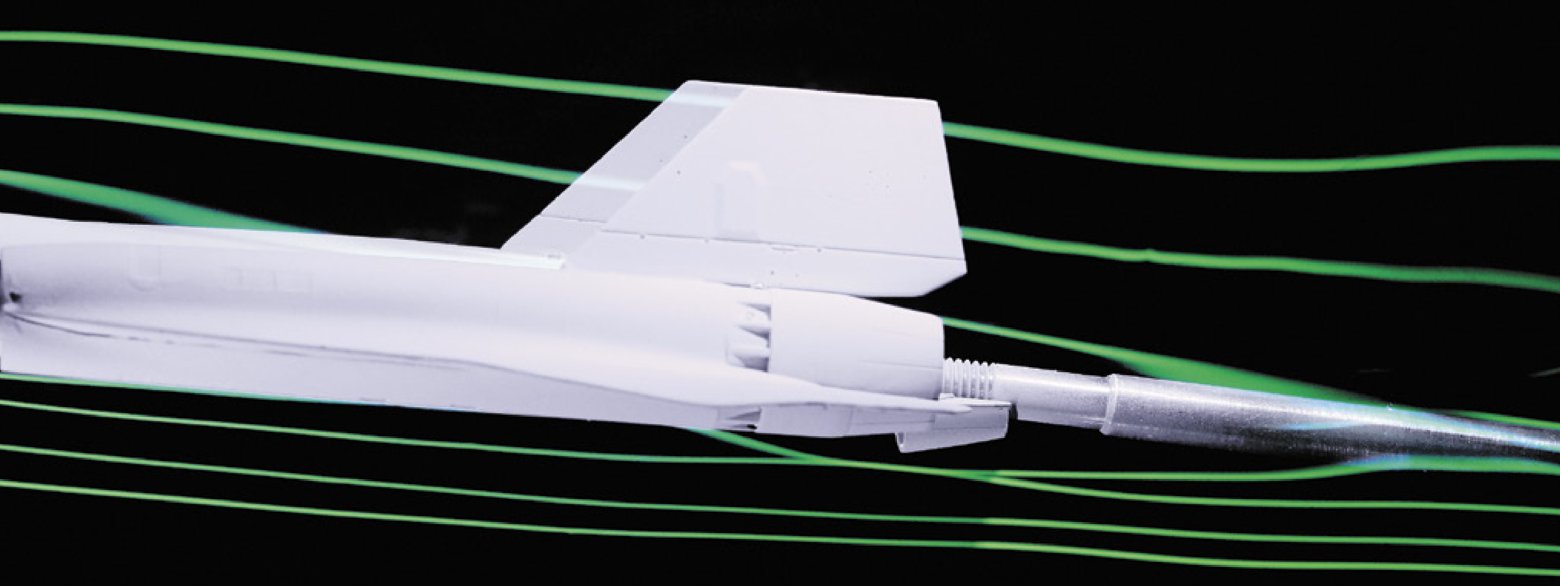
# of aero

PHYSICS

No one can completely explain why planes stay in the air

By Ed Regis

Photographs by Ian Allen



AT NASA AMES Fluid Mechanics Laboratory, streamlines of dye in a water channel interact with a model airplane.

dynamic lift

IN DECEMBER 2003, TO COMMEMORATE THE 100TH ANNIVERSARY OF THE FIRST flight of the Wright brothers, the *New York Times* ran a story entitled "Staying Aloft; What Does Keep Them Up There?" The point of the piece was a simple question: What keeps planes in the air? To answer it, the *Times* turned to John D. Anderson, Jr., curator of aerodynamics at the National Air and Space Museum and author of several textbooks in the field.

Ed Regis has written 10 science books, including *Monsters: The Hindenburg Disaster and the Birth of Pathological Technology* (Basic Books, 2015). He has also logged 1,000 hours flying time as a private pilot.

What Anderson said, however, is that there is actually no agreement on what generates the aerodynamic force known as lift. "There is no simple one-liner answer to this," he told the *Times*. People give different answers to the question, some with "religious fervor." More than 15 years after that pronouncement, there are still different accounts of what generates lift, each with its own substantial rank of zealous defenders. At this point in the history of flight, this situation is slightly puzzling. After all, the natural processes of evolution, working mindlessly, at random and without any understanding of physics, solved the mechanical problem of aerodynamic lift for soaring birds eons ago. Why should it be so hard for scientists to explain what keeps birds, and airliners, up in the air?

Adding to the confusion is the fact that accounts of lift exist on two separate levels of abstraction: the technical and the nontechnical. They are complementary rather than contradictory, but they differ in their aims. One exists as a strictly mathematical theory, a realm in which the analysis medium consists of equations, symbols, computer simulations and numbers. There is little, if any, serious disagreement as to what the appropriate equations or their solutions are. The objective of technical mathematical theory is to make accurate predictions and to project results that are useful to aeronautical engineers engaged in the complex business of designing aircraft.

But by themselves, equations are not explanations, and neither are their solutions. There is a second, nontechnical level of analysis that is intended to provide us with a physical, commonsense explanation of lift. The objective of the nontechnical approach is to give us an intuitive understanding of the actual forces and factors that are at work in holding an airplane aloft. This approach exists not on the level of numbers and equations but rather on the level of concepts and principles that are familiar and intelligible to nonspecialists.

It is on this second, nontechnical level where the controversies lie. Two different theories are commonly proposed to explain lift, and advocates on both sides argue their viewpoints in articles, in books and online. The problem is that each of these two nontechnical theories is correct in itself. But neither produces a complete explanation of lift, one that provides a full accounting of all the basic forces, factors and physical conditions governing aerodynamic lift, with no issues left dangling, unexplained or unknown. Does such a theory even exist?

TWO COMPETING THEORIES

BY FAR THE MOST POPULAR explanation of lift is Bernoulli's theorem, a principle identified by Swiss mathematician Daniel Bernoulli in his 1738 treatise, *Hydrodynamica*. Bernoulli came from a family of mathematicians. His father, Johann, made contributions to the calculus, and his Uncle Jakob coined the term "integral." Many of Daniel Bernoulli's contributions had to do with fluid flow: Air is a fluid, and the theorem associated with his name is commonly expressed in terms of fluid dynamics. Stated simply, Bernoulli's law says that the pressure of a fluid decreases as its velocity increases, and vice versa.

Bernoulli's theorem attempts to explain lift as a consequence of the curved upper surface of an airfoil, the technical name for an airplane wing. Because of this curvature, the idea goes, air traveling across the top of the wing moves faster than the air moving along the wing's bottom surface, which is flat. Bernoulli's theorem says that the increased speed atop the wing is associated with a region of lower pressure there, which is lift.

IN BRIEF

On a strictly mathematical level, engineers know how to design planes that will stay aloft. But equations don't explain why aerodynamic lift occurs.

There are two competing theories that illuminate the forces and factors of lift. Both are incomplete explanations.

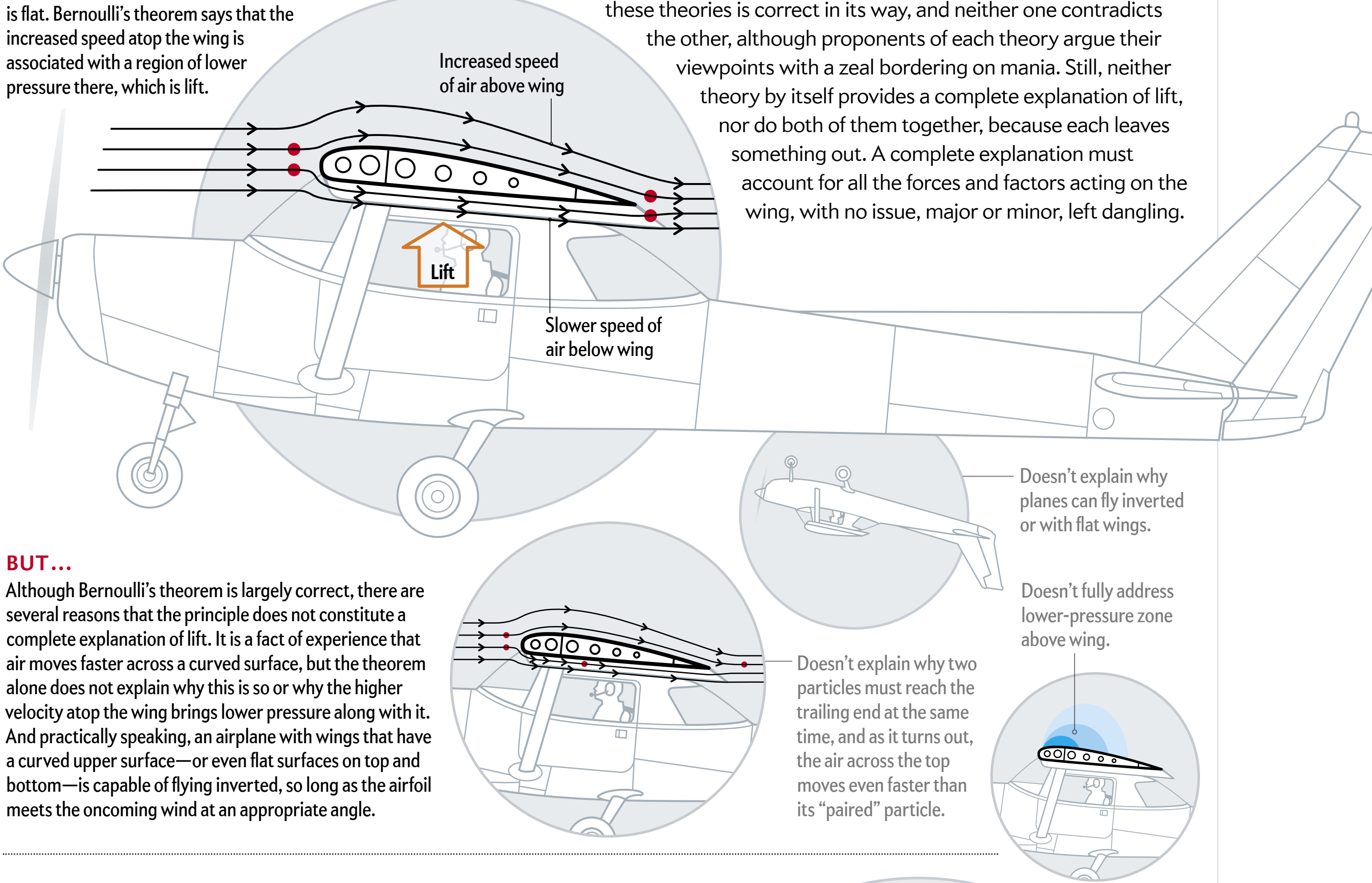
Aerodynamicists have recently tried to close the gaps in understanding. Still, no consensus exists.

The Flawed Classics

On a commonsense, everyday basis, two theories have been advanced to explain what keeps an airplane aloft. One is Bernoulli's theorem, which associates lift with the area of higher speed and lower pressure atop the wing. The other is the Newtonian principle of action and reaction, which explains lift as an upward push on the wing from the moving air below. Each of these theories is correct in its way, and neither one contradicts the other, although proponents of each theory argue their viewpoints with a zeal bordering on mania. Still, neither theory by itself provides a complete explanation of lift, nor do both of them together, because each leaves something out. A complete explanation must account for all the forces and factors acting on the wing, with no issue, major or minor, left dangling.

BERNOULLI'S THEOREM

As applied to an airplane wing—technically called an airfoil—Bernoulli's theorem attempts to explain lift as a consequence of the wing's curved upper surface. The idea is that because of this curvature, the air traveling across the top of the wing moves faster than the air moving along the wing's bottom surface, which is flat. Bernoulli's theorem says that the increased speed atop the wing is associated with a region of lower pressure there, which is lift.



BUT…

Although Bernoulli's theorem is largely correct, there are several reasons that the principle does not constitute a complete explanation of lift. It is a fact of experience that air moves faster across a curved surface, but the theorem alone does not explain why this is so or why the higher velocity atop the wing brings lower pressure along with it. And practically speaking, an airplane with wings that have a curved upper surface—or even flat surfaces on top and bottom—is capable of flying inverted, so long as the airfoil meets the oncoming wind at an appropriate angle.

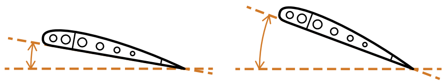
Doesn't explain why planes can fly inverted or with flat wings.

Doesn't explain why two particles must reach the trailing end at the same time, and as it turns out, the air across the top moves even faster than its "paired" particle.

Doesn't fully address lower-pressure zone above wing.

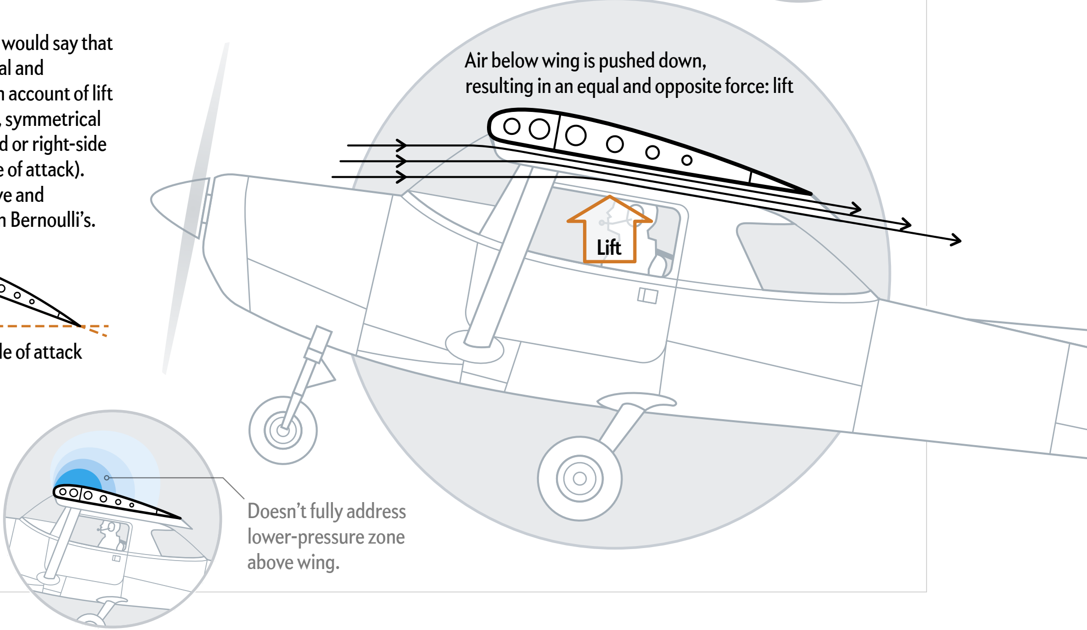
NEWTON'S THIRD LAW

Air has mass. Therefore, Newton's third law would say that the wing's downward push results in an equal and opposite push back upward. This Newtonian account of lift applies to wings of any shape, curved or flat, symmetrical or not, and it holds for aircraft flying inverted or right-side up (the critical feature being a suitable angle of attack). For these reasons, it is a more comprehensive and universally applicable explanation of lift than Bernoulli's.



BUT…

Taken by itself, the principle of action and reaction still fails to explain the lower pressure atop the wing, which exists in that region irrespective of whether the airfoil is cambered or not.



Doesn't fully address lower-pressure zone above wing.

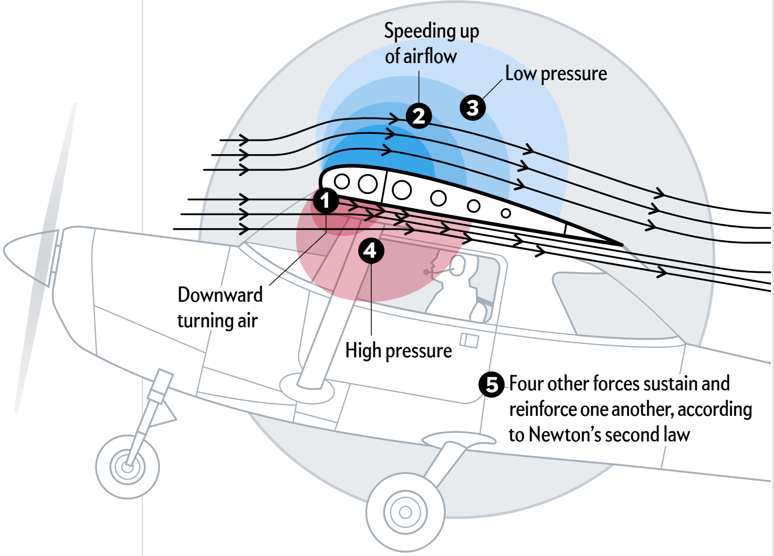
Illustrations by L-Dopa

New Ideas of Lift

Today's scientific approaches to aircraft design are determined by computational fluid dynamics (CFD) simulations, as well as equations that take full account of the actual viscosity of real air. Although we still do not have a singular and satisfying physical, qualitative explanation of lift, some recent attempts may have gotten us a bit closer.

CO-DEPENDENCY OF LIFT'S FOUR ELEMENTS

The four critical components (*shown*) in aerodynamicist Doug McLean's explanation of lift support one another in a reciprocal cause-and-effect relation. This interrelation constitutes the novel fifth element of McLean's explanation, which is rooted in Newton's second law of motion: force equals mass times acceleration. The acceleration of a body—or in this case, a parcel of fluid—is proportional to the force exerted on it. Each parcel affecting the others brings the elements into existence, sustaining flight.

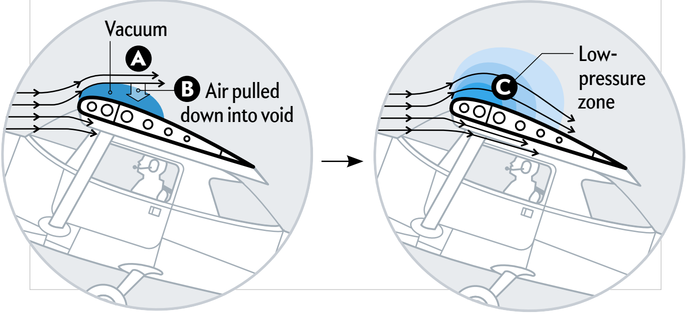


BUT…

Although McLean says the reduced pressure above and increased pressure below result from the airfoil being "completely surrounded by flowing air," this doesn't explain how the reduced pressure up top got there initially.

HOW LOW PRESSURE FORMS ABOVE THE WING

Mark Drela, an expert on fluid dynamics, has attemped to address what evaded Newton and Bernoulli: how the low-pressure zone, or partial vacuum, above the wing comes into existence. The air above the wing momentarily flows straight back Ⓐ, forming a void or vacuum. This vacuum will then strongly pull the air back down Ⓑ, filling in and thus eliminating most—but not all—of the vacuum. Just enough vacuum remains to pull the air into the curved path that follows the wing Ⓒ.



Mountains of empirical data from streamlines (lines of smoke particles) in wind-tunnel tests, laboratory experiments on nozzles and Venturi tubes, and so on provide overwhelming evidence that as stated, Bernoulli's principle is correct and true. Nevertheless, there are several reasons that Bernoulli's theorem does not by itself constitute a *complete* explanation of lift. Although it is a fact of experience that air moves faster across a curved surface, Bernoulli's theorem alone does not explain why this is so. In other words, the theorem does not say how the higher velocity above the wing came about to begin with.

There are plenty of bad explanations for the higher velocity. According to the most common one—the "equal transit time" theory—parcels of air that separate at the wing's leading edge must rejoin simultaneously at the trailing edge. Because the top parcel travels farther than the lower parcel in a given amount of time, it must go faster. The fallacy here is that there is no physical reason that the two parcels must reach the trailing edge simultaneously. And indeed, they do not: the empirical fact is that the air atop moves much faster than the equal transit time theory could account for.

There is also a notorious "demonstration" of Bernoulli's principle, one that is repeated in many popular accounts, YouTube videos and even some textbooks. It involves holding a sheet of paper horizontally at your mouth and blowing across the curved top of it. The page rises, supposedly illustrating the Bernoulli effect. The opposite result ought to occur when you blow across the bottom of the sheet: the velocity of the moving air below it should pull the page downward. Instead, paradoxically, the page rises.

The lifting of the curved paper when flow is applied to one side "is not because air is moving at different speeds on the two sides," says Holger Babinsky, a professor of aerodynamics at the University of Cambridge, in his article "How Do Wings Work?" To demonstrate this, blow across a straight piece of paper—for example, one held so that it hangs down vertically—and witness that the paper does not move one way or the other, because "the pressure on both sides of the paper is the same, despite the obvious difference in velocity."

The second shortcoming of Bernoulli's theorem is that it does not say how or why the higher velocity atop the wing brings lower pressure, rather than higher pressure, along with it. It might be natural to think that when a wing's curvature displaces air upward, that air is compressed, resulting in increased pressure atop the wing. This kind of "bottleneck" typically slows things down in ordinary life rather than speeding them up. On a highway, when two or more lanes of traffic merge into one, the cars involved do not go faster; there is instead a mass slowdown and possibly even a traffic jam. Air molecules flowing atop a wing do not behave like that, but Bernoulli's theorem does not say why not.

The third problem provides the most decisive argument against regarding Bernoulli's theorem as a complete account of lift: An airplane with a curved upper surface is capable of flying inverted. In inverted flight, the curved wing surface becomes the bottom surface, and according to Bernoulli's theorem, it then generates reduced pressure *below* the wing. That lower pressure, added to the force of gravity, should have the overall effect of pulling the plane downward rather than holding it up. Moreover, aircraft with symmetrical airfoils, with equal curvature on the top and bottom—or even with flat top and bottom surfaces—are also capable of flying inverted, so long as the airfoil meets the oncoming wind at an appropriate angle of attack. This means that Bernoulli's theorem alone is insufficient to explain these facts.

The other theory of lift is based on Newton's third law of motion, the principle of action and reaction. The theory states that a wing keeps an airplane up by pushing the air down. Air has mass, and from Newton's third law it follows that the wing's downward push results in an equal and opposite push back upward, which is lift. The Newtonian account applies to wings of any shape, curved or flat, symmetrical or not. It holds for aircraft flying inverted or right-side up. The forces at work are also familiar from ordinary experience—for example, when you stick your hand out of a moving car and tilt it upward, the air is deflected downward, and your hand rises. For these reasons, Newton's third law is a more universal and comprehensive explanation of lift than Bernoulli's theorem.

But taken by itself, the principle of action and reaction also fails to explain the lower pressure atop the wing, which exists in that region irrespective of whether the airfoil is cambered. It is only when an airplane lands and comes to a halt that the region of lower pressure atop the wing disappears, returns to ambient pressure, and becomes the same at both top and bottom. But as long as a plane is flying, that region of lower pressure is an inescapable element of aerodynamic lift, and it must be explained.

It is as if these four components of lift collectively bring themselves into existence, and sustain themselves, by simultaneous acts of mutual creation and causation. There seems to be a hint of magic in this synergy.

HISTORICAL UNDERSTANDING

NEITHER BERNOULLI NOR NEWTON was consciously trying to explain what holds aircraft up, of course, because they lived long before the actual development of mechanical flight. Their respective laws and theories were merely repurposed once the Wright brothers flew, making it a serious and pressing business for scientists to understand aerodynamic lift.

Most of these theoretical accounts came from Europe. In the early years of the 20th century, several British scientists advanced technical, mathematical accounts of lift that treated air as a perfect fluid, meaning that it was incompressible and had zero viscosity. These were unrealistic assumptions but perhaps understandable ones for scientists faced with the new phenomenon of controlled, powered mechanical flight. These assumptions also made the underlying mathematics simpler and more straightforward than they otherwise would have been, but that simplicity came at a price: however successful the accounts of airfoils moving in ideal gases might be mathematically, they remained defective empirically.

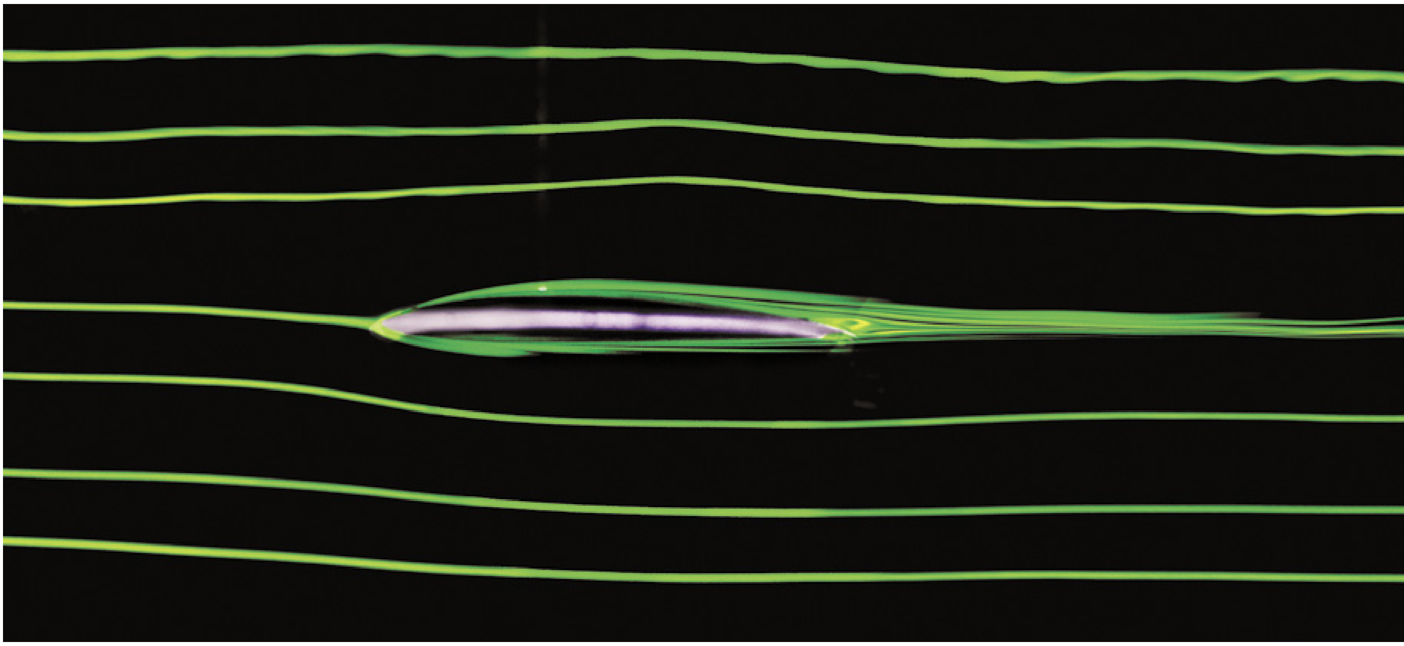
In Germany, one of the scientists who applied themselves to the problem of lift was none other than Albert Einstein. In 1916 Einstein published a short piece in the journal *Die Naturwissenschaften* entitled "Elementary Theory of Water Waves and of Flight," which sought to explain what accounted for the carrying capacity of the wings of flying machines and soaring birds. "There is a lot of obscurity surrounding these questions," Einstein wrote. "Indeed, I must confess that I have never encountered a simple answer to them even in the specialist literature."

Einstein then proceeded to give an explanation that assumed an incompressible, frictionless fluid—that is, an ideal fluid. Without mentioning Bernoulli by name, he gave an account that is consistent with Bernoulli's principle by saying that fluid pressure is greater where its velocity is slower, and vice versa. To take advantage of these pressure differences, Einstein proposed an airfoil with a bulge on top such that the shape would increase airflow velocity above the bulge and thus decrease pressure there as well.

Einstein probably thought that his ideal-fluid analysis would apply equally well to real-world fluid flows. In 1917, on the basis of his theory, Einstein designed an airfoil that later came to be known as a cat's-back wing because of its resemblance to the humped back of a stretching cat. He brought the design to aircraft manufacturer LVG (Luftverkehrsgesellschaft) in Berlin, which built a new flying machine around it. A test pilot reported that the craft waddled around in the air like "a pregnant duck." Much later, in 1954, Einstein himself called his excursion into aeronautics a "youthful folly." The individual who gave us radically new theories that penetrated both the smallest and the largest components of the universe nonetheless failed to make a positive contribution to the understanding of lift or to come up with a practical airfoil design.

TOWARD A COMPLETE THEORY OF LIFT

CONTEMPORARY SCIENTIFIC APPROACHES to aircraft design are the province of computational fluid dynamics (CFD)



WATER-channel test at NASA Ames Fluid Mechanics Lab uses fluorescent dye to visualize the flow field over an airplane wing. The streamlines, moving from left to right and curving as they encounter the wing, help to illustrate the physics of lift.

simulations and the so-called Navier-Stokes equations, which take full account of the actual viscosity of real air. The solutions of those equations and the output of the CFD simulations yield pressure-distribution predictions, airflow patterns and quantitative results that are the basis for today's highly advanced aircraft designs. Still, they do not by themselves give a physical, qualitative explanation of lift.

In recent years, however, leading aerodynamicist Doug McLean has attempted to go beyond sheer mathematical formalism and come to grips with the physical cause-and-effect relations that account for lift in all of its real-life manifestations. McLean, who spent most of his professional career as an engineer at Boeing Commercial Airplanes, where he specialized in CFD code development, published his new ideas in the 2012 text *Understanding Aerodynamics: Arguing from the Real Physics*.

Considering that the book runs to more than 500 pages of fairly dense technical analysis, it is surprising to see that it includes a section (7.3.3) entitled "A Basic Explanation of Lift on an Airfoil, Accessible to a Nontechnical Audience." Producing these 16 pages was not easy for McLean, a master of the subject; indeed, it was "probably the hardest part of the book to write," the author says. "It saw more revisions than I can count. I was never entirely happy with it."

McLean's complex explanation of lift starts with the basic assumption of all ordinary aerodynamics: the air around a wing acts as "a continuous material that deforms to follow the contours of the airfoil." That deformation exists in the form of a deep swath of fluid flow both above and below the wing. "The airfoil affects the pressure over a wide area in what is called a *pressure field,*" McLean writes. "When lift is produced, a diffuse cloud of low pressure always forms above the airfoil, and a diffuse cloud of high pressure usually forms below. Where these clouds touch the airfoil they constitute the pressure difference that exerts lift on the airfoil."

The wing pushes the air down, resulting in a downward turn of the airflow. The air above the wing is sped up in accordance with Bernoulli's principle. In addition, there is an area of high pressure below the wing and a region of low pressure above. This means that there are four necessary components in McLean's explanation of lift: a downward turning of the airflow, an increase in the airflow's speed, an area of low pressure and an area of high pressure.

But it is the interrelation among these four elements that is the most novel and distinctive aspect of McLean's account. "They support each other in a reciprocal cause-and-effect relationship, and none would exist without the others," he writes. "The pressure differences exert the lift force on the airfoil, while the downward turning of the flow and the changes in flow speed sustain the pressure differences." It is this interrelation that constitutes a fifth element of McLean's explanation: the reciprocity among the other four. It is as if those four components collectively bring themselves into existence, and sustain themselves, by simultaneous acts of mutual creation and causation.

There seems to be a hint of magic in this synergy. The process that McLean describes seems akin to four active agents pulling up on one another's bootstraps to keep themselves in the air collectively. Or, as he acknowledges, it is a case of "circular cause-and-effect." How is it possible for each element of the interaction to sustain and reinforce all of the others? And what causes this mutual, reciprocal, dynamic interaction?

McLean's answer: Newton's second law of motion.

Newton's second law states that the acceleration of a body, or a parcel of fluid, is proportional to the force exerted on it. "Newton's second law tells us that when a pressure difference imposes a net force on a fluid parcel, it must cause a change in the speed or direction (or both) of the parcel's motion," McLean explains. But reciprocally, the pressure difference depends on and exists because of the parcel's acceleration.

Aren't we getting something for nothing here? McLean says no: If the wing were at rest, no part of this cluster of mutually reinforcing activity would exist. But the fact that the wing is moving through the air, with each parcel affecting all of the others, brings these co-dependent elements into existence and sustains them throughout the flight.

TURNING ON THE RECIPROCITY OF LIFT

SOON AFTER THE PUBLICATION of *Understanding Aerodynamics,* McLean realized that he had not fully accounted for all the elements of aerodynamic lift, because he did not explain convincingly what causes the pressures on the wing to change from ambient. So, in November 2018, McLean published a two-part article in *The Physics Teacher* in which he proposed "a comprehensive physical explanation" of aerodynamic lift.

Although the article largely restates McLean's earlier line of argument, it also attempts to add a better explanation of what causes the pressure field to be nonuniform and to assume the physical shape that it does. In particular, his new argument introduces a mutual interaction at the flow field level so that the nonuniform pressure field is a result of an applied force, the downward force exerted on the air by the airfoil.

Whether McLean's section 7.3.3 and his follow-up article are successful in providing a complete and correct account of lift is open to interpretation and debate. There are reasons that it is difficult to produce a clear, simple and satisfactory account of aerodynamic lift. For one thing, fluid flows are more complex and harder to understand than the motions of solid objects, especially fluid flows that separate at the wing's leading edge and are subject to different physical forces along the top and bottom. Some of the disputes regarding lift involve not the facts themselves but rather how those facts are to be interpreted, which may involve issues that are impossible to decide by experiment.

Nevertheless, there are at this point only a few outstanding matters that require explanation. Lift, as you will recall, is the result of the pressure differences between the top and bottom parts of an airfoil. We already have an acceptable explanation for what happens at the bottom part of an airfoil: the oncoming air pushes on the wing both vertically (producing lift) and horizontally (producing drag). The upward push exists in the form of higher pressure below the wing, and this higher pressure is a result of simple Newtonian action and reaction.

Things are quite different at the top of the wing, however. A region of lower pressure exists there that is also part of the aerodynamic lifting force. But if neither Bernoulli's principle nor Newton's third law explains it, what does? We know from streamlines that the air above the wing adheres closely to the downward curvature of the airfoil. But why must the parcels of air moving across the wing's top surface follow its downward curvature? Why can't they separate from it and fly straight back?

Mark Drela, a professor of fluid dynamics at the Massachusetts Institute of Technology and author of *Flight Vehicle Aerodynamics,* offers an answer: "If the parcels momentarily flew off tangent to the airfoil top surface, there would literally be a vacuum created below them," he explains. "This vacuum would then suck down the parcels until they mostly fill in the vacuum, i.e., until they move tangent to the airfoil again. This is the physical mechanism which forces the parcels to move along the airfoil shape. A slight partial vacuum remains to maintain the parcels in a curved path."

This drawing away or pulling down of those air parcels from their neighboring parcels above is what creates the area of lower pressure atop the wing. But another effect also accompanies this action: the higher airflow speed atop the wing. "The reduced pressure over a lifting wing also 'pulls horizontally' on air parcels as they approach from upstream, so they have a higher speed by the time they arrive above the wing," Drela says. "So the increased speed above the lifting wing can be viewed as a side effect of the reduced pressure there."

But as always, when it comes to explaining lift on a nontechnical level, another expert will have another answer. Cambridge aerodynamicist Babinsky says, "I hate to disagree with my esteemed colleague Mark Drela, but if the creation of a vacuum were the explanation, then it is hard to explain why sometimes the flow does nonetheless separate from the surface. But he is correct in everything else. The problem is that there is no quick and easy explanation."

Drela himself concedes that his explanation is unsatisfactory in some ways. "One apparent problem is that there is no explanation that will be universally accepted," he says. So where does that leave us? In effect, right where we started: with John D. Anderson, who stated, "There is no simple one-liner answer to this."

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AUTONO

TECHNOLOGY

Ensuring meaningful human control over killer machines is vital to global security

By Noel Sharkey

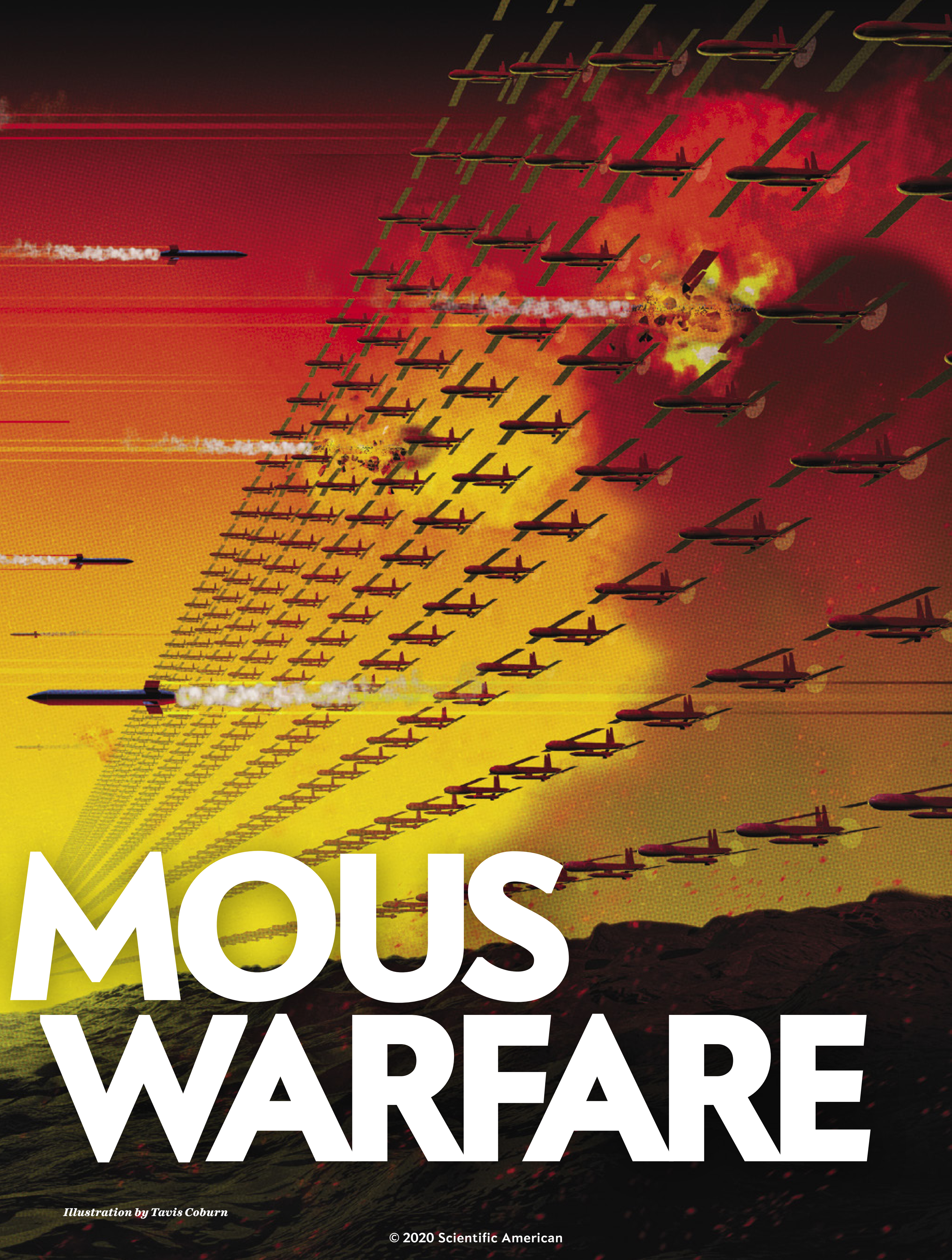

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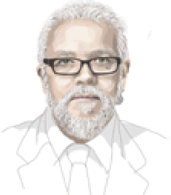
Illustration by Tavis Coburn



Noel Sharkey is professor emeritus of artificial intelligence and robotics at the University of Sheffield in England. He is a founder and chair of the International Committee for Robot Arms Control.

In September 2019 a swarm of 18 bomb-laden drones and seven cruise missiles overwhelmed Saudi Arabia's advanced air defenses to crash into the Abqaiq and Khurais oil fields and their processing facilities. The surprisingly sophisticated attack, which Yemen's Houthi rebels claimed responsibility for, halved the nation's output of crude oil and natural gas and forced an increase in global oil prices. The drones were likely not fully autonomous, however: they did not communicate with one another to pick their own targets, such as specific storage tanks or refinery buildings. Instead each drone appears to have been preprogrammed with precise coordinates to which it navigated over hundreds of kilometers by means of a satellite positioning system.

IN BRIEF

Partially autonomous weapons are already being used to defend territories and installations against nonhuman attackers.

Several nations are racing to develop fully autonomous weapons systems, which select and attack targets—including people—without human supervision.

Autonomous drone swarms could soon be deployed in war theaters. But outsourcing the decision to kill to computers poses unique dangers to humankind.

A binding international treaty to ensure meaningful human control over weapons systems becomes more essential every day.

Fully autonomous weapons systems (AWSs) may be operating in war theaters even as you read this article, however. Turkey has announced plans to deploy a fleet of autonomous Kargu quadcopters against Syrian forces in early 2020, and Russia is also developing aerial swarms for that region. Once launched, an AWS finds, tracks, selects and attacks targets with violent force, all without human supervision.

Autonomous weapons are not self-aware, humanoid "Terminator" robots conspiring to take over; they are computer-controlled tanks, planes, ships and submarines. Even so, they represent a radical change in the nature of warfare. Humans are outsourcing the decision to kill to a machine—with no one watching to ascertain the legitimacy of an attack before it is carried out. Since the mid-2000s, when the U.S. Department of Defense triggered a global artificial-intelligence arms race by signaling its intent to develop autonomous weapons for all branches of the armed forces, every major power and several lesser ones have been striving to acquire these systems. According to U.S. Secretary of Defense Mark Esper, China is already exporting AWSs to the Middle East.

The military attractions of autonomous weapons are manifold. For example, the U.S. Navy's X-47B, an unmanned fighter jet that can land and take off from aircraft carriers even in windy conditions and refuel in the air, will have 10 times the reach of piloted fighter jets. The U.S. has also developed an unmanned transoceanic warship called *Sea Hunter,* to be accompanied by a flotilla of DASH (Distributed Agile Submarine Hunting) submarines. In January 2019 the *Sea Hunter* traveled from San Diego to Hawaii and back, demonstrating its suitability for use in the Pacific. Russia is automating its state-of-the-art T-14 Armata tank, presumably for deployment at the European border; meanwhile weapons manufacturer Kalashnikov has demonstrated a fully automated combat module to be mounted on existing weapons systems (such as artillery guns and tanks) to enable them to sense, choose and attack targets. Not to be outdone, China is working on AI-powered tanks and warships, as well as a supersonic autonomous air-to-air combat aircraft called Anjian, or Dark Sword, that can twist and turn so sharply and quickly that the g-force generated would kill a human pilot.

Given such fierce competition, the focus is inexorably shifting to ever faster machines and autonomous drone swarms, which can overwhelm enemy defenses with a massive, multipronged and coordinated attack. Much of the push toward such weapons comes from defense contractors eyeing the possibility of large profits, but high-ranking military commanders nervous about falling behind in the artificial-intelligence arms race also play a significant role. Some nations, in particular the U.S. and Russia, are looking only at the potential military advantages of autonomous systems—a blinkered view that prevents them from considering the disturbing scenarios that can unfold when rivals catch up.

As a roboticist, I recognized the necessity of meaningful human control over weapons systems when I first learned of the plans to build AWSs. We are facing a new era in warfare, much like the dawn of the atomic age. It does not take a historian to realize that once a new class of weapon is in the arsenals of military powers, its use will incrementally expand, placing humankind at risk of conflicts that can barely be imagined today. In 2009 I and three other academics set up the International Committee for Robot Arms Control, which later teamed up with other nongovernmental organizations (NGOs) to form the Campaign to Stop Killer Robots. Now a coalition of 130 NGOs from 60 countries, the campaign seeks to persuade the United Nations to negotiate a legally binding treaty that would prohibit the development, testing and production of weapons that select targets and attack them with violent force without meaningful human control.

TIME TO THINK

THE ULTIMATE DANGER of systems for warfare that take humans out of the decision-making loop is illustrated by the true story of "the man who saved the world." In 1983 Lieutenant Colonel Stanislav Petrov was on duty at a Russian nuclear early-warning center when his computer sounded a loud alarm and the word "LAUNCH" appeared in bold red letters on his screen—indications that a U.S. nuclear missile was fast approaching. Petrov held his nerve and waited. A second launch warning rang out, then a third and a fourth. With the fifth, the red "LAUNCH" on his screen changed to "MISSILE STRIKE." Time was ticking away for the U.S.S.R. to retaliate, but Petrov continued his deliberation. "Then I made my decision," Petrov said in a BBC interview in 2013. "I would not trust the computer." He reported the nuclear attack as a false alarm—even though he could not be certain. As it turned out, the onboard computing system on the Soviet satellites had misclassified sunlight reflecting off clouds as the engines of intercontinental ballistic missiles.

1

2

U.S. ARSENAL of fully autonomous weapons could include Gremlin drones (1) and the *Sea Hunter* warship (2), to be accompanied by DASH submarines.

DARPA (1, 2)

This tale illustrates the vital role of deliberative human decision-making in war: given those inputs, an autonomous system would have decided to fire. But making the right call takes time. A hundred years' worth of psychological research tells us that if we do not take at least a minute to think things over, we will overlook contradictory information, neglect ambiguity, suppress doubt, ignore the absence of confirmatory evidence, invent causes and intentions, and conform with expectations. Alarmingly, an oft-cited rationale for AWSs is that conflicts are unfolding too quickly for humans to be making the decisions.

"It's a lot faster than me," Bruce Jette, a U.S. Army acquisitions officer, said last October to *Defense News,* referring to a targeting system for tanks. "I can't see and think through some of the things it can calculate nearly as fast as it can." In fact, speed is a key reason that partially autonomous weapons are already in use for some defensive operations, which require that the detection of, evaluation of and response to a threat be completed within seconds. These systems—variously known as SARMO (Sense and React to Military Objects), automated and automatic weapons systems—include Israel's Iron Dome for protecting the country from rockets and missiles; the U.S. Phalanx cannon, mounted on warships to guard against attacks from antiship missiles or helicopters; and the German NBS Mantis gun, used to shoot down smaller munitions such as mortar shells. They are localized, are defensive, do not target humans and are switched on by humans in an emergency—which is why they are not considered fully autonomous.

The distinction is admittedly fine, and weapons on the cusp of SARMO and AWS technology are already in use. Israel's Harpy and Harop aerial drones, for instance, are explosive-laden rockets launched prior to an air attack to clear the area of antiaircraft installations. They cruise around hunting for radar signals, determine whether the signals come from friend or foe and, if the latter, dive-bomb on the assumption that the radar is connected to an antiaircraft installation. In May 2019 secretive Israeli drones—according to one report, Harops—blew up Russian-made air-defense systems in Syria.

These drones are "loitering munitions" and speed up only when attacking, but several fully autonomous systems will range in speed from fast subsonic to supersonic to hypersonic. For example, the U.S.'s Defense Advanced Research Projects Agency (DARPA) has tested the Falcon unmanned hypersonic aircraft at speeds around 20 times the speed of sound—approximately 21,000 kilometers per hour.

In addition to speed, militaries are pursuing "force multiplication"—increases in the destructive capacity of a weapons system—by means of autonomous drones that cooperate like wolves in a pack, communicating with one another to choose and hunt individual targets. A single human can launch a swarm of hundreds (or even thousands) of armed drones into the air, on the land or water, or under the sea. Once the AWS has been deployed, the operator becomes at best an observer who could abort the attack—if communication links have not been broken.

What happens when enemy autonomous weapons systems, all controlled by top-secret algorithms, confront one another? The worrisome answer is that no one knows or can know.

To this end, the U.S. is developing swarms of fixed-wing drones such as Perdix and Gremlin, which can travel long distances with missiles. DARPA has field-tested the coordination of swarms of aerial quadcopters (known for their high maneuverability) with ground vehicles, and the Office of Naval Research has demonstrated a fleet of 13 boats that can "overwhelm an adversary." The China Electronics Technology Group, in a move that reveals the country's intentions, has (separately) tested a group of 200 fixed-wing drones, as well as 56 small drone ships for attacking enemy warships. In contrast, Russia seems to be mainly interested in tank swarms that can be used for coordinated attacks or be laid out to defend national borders.

GAMING THE ENEMY

THE PETROV STORY also shows that although computers may be fast, they are often wrong. Even now, with the incredible power and speed of modern computing and sensor processing, AI systems can err in many unpredictable ways. In 2012 the Department of Defense acknowledged the potential for such computer issues with autonomous weapons and asserted the need to minimize human errors, failures in human-machine interactions, malfunctions, degradation of communications and coding glitches in software. Apart from these self-evident safeguards, autonomous systems would also have to be protected from subversion by adversaries via cyberattacks, infiltration of the industrial supply chain, jamming of signals, spoofing (misleading of positioning systems) and deployment of decoys.

In reality, protecting against disruptions by the enemy will be extremely difficult, and the consequences of these assaults could be dire. Jamming would block communications so that an operator would not be able to abort attacks or redirect weapons. It could disrupt coordination between robotic weapons in a swarm and make them run out of control. Spoofing, which sends a strong false GPS signal, can cause devices to lose their way or be guided to crash into buildings.

Decoys are real or virtual entities that deceive sensors and targeting systems. Even the most sophisticated artificial-intelligence systems can easily be gamed. Researchers have found that a few dots or lines cleverly added to a sign, in such a way as to be unnoticeable to humans, can mislead a self-driving car so that it swerves into another lane against oncoming traffic or ignores a stop sign. Imagine the kinds of problems such tricks could create for autonomous weapons. Onboard computer controllers could, for example, be fooled into mistaking a hot dog stand for a tank.

Most baffling, however, is the last directive on the Defense Department's list: minimizing "other enemy countermeasures or actions, or unanticipated situations on the battlefield." It is impossible to minimize unanticipated situations on the battlefield because you cannot minimize what you cannot anticipate. A conflict zone will feature a potentially infinite number of unforeseeable circumstances; the very essence of conflict is to surprise the enemy. When it comes to AWSs, there are many ways to trick sensor processing or disrupt computer-controlled machinery.

One overwhelming computer problem the Department of Defense's directive misses, rather astonishingly, is the unpredictability of machine-machine interactions. What happens when enemy autonomous weapons confront one another? The worrisome answer is that no one knows or can know. Every AWS will have to be controlled by a top-secret computer algorithm. Its combat strategy will have to be unknown to others to prevent successful enemy countermeasures. The secrecy makes sense from a security perspective—but it dramatically reduces the predictability of the weapons' behavior.

A clear example of algorithmic confrontation run amok was provided by two booksellers, bordeebook and profnath, on the Amazon Web site in April 2011. Usually the out-of-print 1992 book *The Making of a Fly* sold for around $50 plus $3.99 shipping. But every time bordeebook increased its price, so did profnath; that, in turn, increased bordeebook's price, and so on. Within a week bordeebook was selling the book for $23,698,655.93 plus $3.99 shipping before anyone noticed. Two simple and highly predictable computer algorithms went out of control because their clashing strategies were unknown to competing sellers.

Although this mispricing was harmless, imagine what could happen if the complex combat algorithms of two swarms of autonomous weapons interacted at high speed. Apart from the uncertainties introduced by gaming with adversarial images, jamming, spoofing, decoys and cyberattacks, one must contend with the impossibility of predicting the outcome when computer algorithms battle it out. It should be clear that these weapons represent a very dangerous alteration in the nature of warfare. Accidental conflicts could break out so fast that commanders have no time to understand or respond to what their weapons are doing—leaving devastation in their wake.

ON THE RUSSIAN BORDER

IMAGINE THE FOLLOWING SCENARIO, one among many nightmarish confrontations that could accidentally transpire—unless the race toward AWSs can be stopped. It is 2040, and thousands of autonomous supertanks glisten with frost along Russia's border with Europe. Packs of autonomous supersonic robot jets fly overhead, scouring for enemy activity. Suddenly a tank fires a missile over the horizon, and a civilian airliner goes down in flames. It is an accident—a sensor glitch triggered a confrontation mode—but the tanks do not know that. They rumble forward en masse toward the border. The fighter planes shift into battle formation and send alerts to fleets of robot ships and shoals of autonomous submarines in the Black, Barents and White Seas.

After less than 10 seconds, NATO's autonomous counterweapons swoop in from the air, and attack formations begin to develop on the ground and in the sea. Each side's combat algorithms are unknown to its enemy, so no one can predict how the opposing forces will interact. The fighter jets avoid one another by swooping, diving and twisting with centrifugal forces that would kill any human, and they communicate among themselves at machine speeds. Each side has many tricks up its sleeve for gaming the other. These include disrupting each other's signals and spoofing with fake GPS coordinates to upset coordination and control.

Within three minutes hundreds of jets are fighting in the skies over Russian and European cities at near-hypersonic speed. The tanks have burst across the border and are firing on communications infrastructure, as well as at all moving vehicles at railway stations and on roads. Large guns on autonomous ships are pounding the land. Autonomous naval battles have broken out on and under the seas. Military leaders on both sides are trying to make sense of the devastation that is happening around them. But what can they do? All communications with the weapons have been jammed, and there is a complete breakdown of command-and-control structures. Only 22 minutes have passed since the accidental shooting-down of the airliner, and swarms of tanks are fast approaching Helsinki, Tallinn, Riga, Vilnius, Kyiv and Tbilisi.

Russian and Western leaders begin urgent discussions, but no one can work out how this started or why. Fingers are itching on nuclear buttons as near-futile efforts are underway to evacuate the major cities. There is no precedent for this chaos, and the militaries are befuddled. Their planning has fallen apart, and the death toll is ramping up by the millisecond. Navigation systems have been widely spoofed, so some of the weapons are breaking from the swarms and crashing into buildings. Others have been hacked and are going on killing sprees. False electronic signals are making weapons fire at random. The countryside is littered with the bodies of animals and humans; cities lie in ruins.

THE IMPORTANCE OF HUMANS

A BINDING INTERNATIONAL TREATY to prohibit the development, production and use of AWSs and to ensure meaningful human control over weapons systems becomes more urgent every day. A human expert, with full awareness of the situation and context and with sufficient time to deliberate on the nature, significance and legitimacy of the targets, the necessity and appropriateness of an attack and the likely outcomes, should determine whether or not the attack will commence. For the past six years the Campaign to Stop Killer Robots has been trying to persuade the member states of the U.N. to agree on a treaty. We work at the U.N. Convention on Certain Conventional Weapons (CCW), a forum of 125 nations for negotiating bans on weapons that cause undue suffering. Thousands of scientists and leaders in the fields of computing and machine learning have joined this call, and so have many companies, such as Google's DeepMind. At last count, 30 nations had demanded an outright ban of fully autonomous weapons, but most others want regulations to ensure that humans are responsible for making the decision to attack (or not). Progress is being blocked, however, by a small handful of nations led by the U.S., Russia, Israel and Australia.

At the CCW, Russia and the U.S. have made it clear that they are opposed to the term "human control." The U.S. is striving to replace it with "appropriate levels of human judgment"—which could mean no human control at all, if that were deemed appropriate. Fortunately, some hope still exists. U.N. Secretary-General António Guterres informed the group of governmental experts at the CCW that "machines with the power and discretion to take lives without human involvement are politically unacceptable, are morally repugnant and should be prohibited by international law." Common sense and humanity must prevail—before it is too late. SA

MORE TO EXPLORE

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FROM OUR ARCHIVES

Broken Shield. Laura Grego and David Wright; June 2019.

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ASTROCHEMISTRY

first molecule in the universe

Scientists have identified mystery molecules in space and the compound thought to have started chemistry in the cosmos

By Ryan C. Fortenberry

Illustration by Mondolithic Studios

Ryan C. Fortenberry is an assistant professor of physical chemistry at the University of Mississippi and a former NASA scientist. His research uses quantum-chemical computer models to predict how molecules absorb light, enabling their potential detection in space.

IN BRIEF

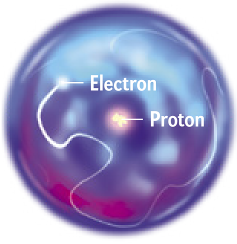
Astrochemists study the molecules found in space, where temperatures and pressures are wildly different than on Earth. Consequently, many of the chemicals there are different from those we are familiar with, and some are even unknown.

Several recent breakthroughs in this field are changing how we understand chemistry in space. Scientists finally spied a long-predicted molecule called helium hydride, or HeH^+, believed to be the first compound ever formed in the universe.

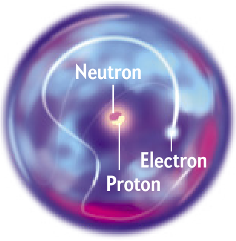
Researchers have also started identifying some of the molecules responsible for diffuse interstellar bands, mystery chemical signatures seen for decades in interstellar space.

THE FIRST "ATOMS" IN THE UNIVERSE WERE NOT ATOMS at all—they were just nuclei that had not found electrons yet. The simplest nucleus, that of common hydrogen, is a bare proton with no frills. When the universe banged into existence, energy was rampant. Everything was smashing into everything else. Protons and neutrons often collided, and some formed larger nuclei, such as that of deuterium (containing a proton and a neutron), as well as helium nuclei with two protons and two neutrons. Various other arrangements of protons and neutrons also formed, but because the identity of an atom is determined by its number of protons, all these other conglomerations were basically just different versions of hydrogen, helium and traces of lithium.

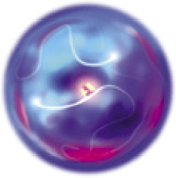
Of these three, helium was the first to begin forming "real" atoms. An atom is more than a nucleus—it must also possess electrons. Helium nuclei were the first to gather a full purse of electrons en masse. Why not hydrogen or lithium? Well, helium is the first "noble gas" on the periodic table—the first atom with enough electrons to completely fill the available slots in its electron shell. Thus, if electrons are the currency of chemistry, helium is the master pilferer of the periodic table. In a modern laboratory, it takes more energy to steal an electron from helium than from any other element. And the energy required to remove a second electron is more than twice what it takes for the first. In the early universe, once helium nuclei began to find electrons, they filled the coffers of their electron clouds well before the hydrogen nuclei could begin to catch up and before enough lithium nuclei were even



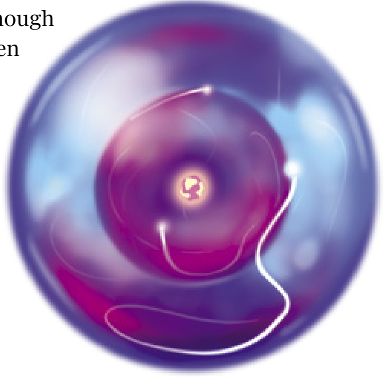
Hydrogen
Nucleus: one proton



Deuterium
Nucleus: one proton and one neutron



Helium
Nucleus: two protons and two neutrons



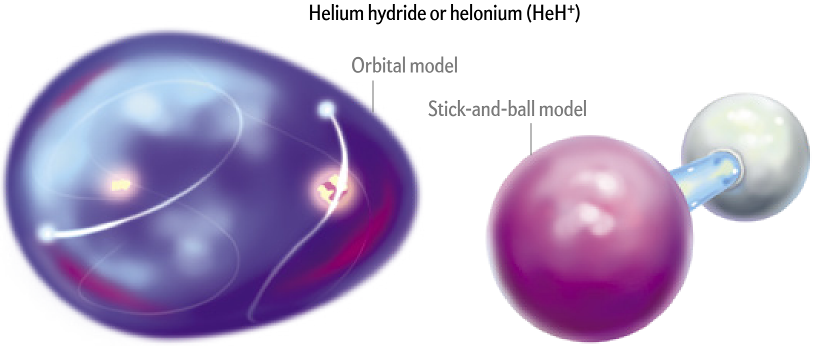
Lithium
Nucleus: three protons and four neutrons

Atoms are shown here in orbital models, which reveal their subatomic constituents. On the following pages we portray molecules—bonds of two or more atoms—using traditional models where balls represent atoms and sticks represent the electrons they share.

Illustrations by Elena Hartley

present to collect all three of their desired electrons.

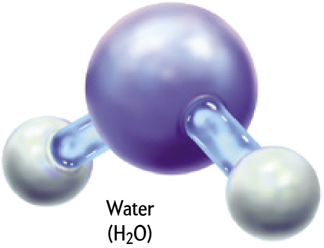
The rest of the matter in the universe at that time was still largely composed of lone protons, which were starting to feel the effects of being bereft of an electron. They began slowing down and looking for oppositely charged partners to make them electrically neutral. But catching free electrons for themselves was difficult, so the protons turned to helium, which already had some. Although helium is loath to share, it kept running into persistent hydrogen nuclei all the time. The collisional pressure eventually led a few helium atoms to share their electrons with protons. Thus, the first chemical bonds were formed. The new compound of helium and hydrogen was called helium hydride or helonium (HeH^+), the very first molecule (of any sustained abundance) in the universe.

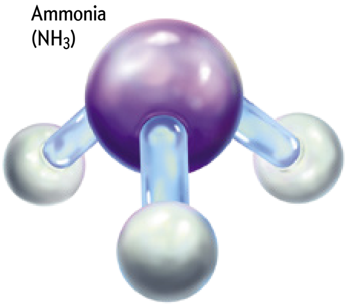


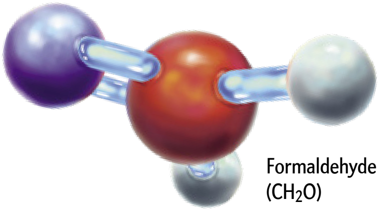
That helium was the first element to bond is surprising because in our current age, we think of helium as the least likely element to link up with others—the satisfied noble gas with just the right number of electrons. But in the early universe, helium was the only game in town—the only bank with electrons to lend.

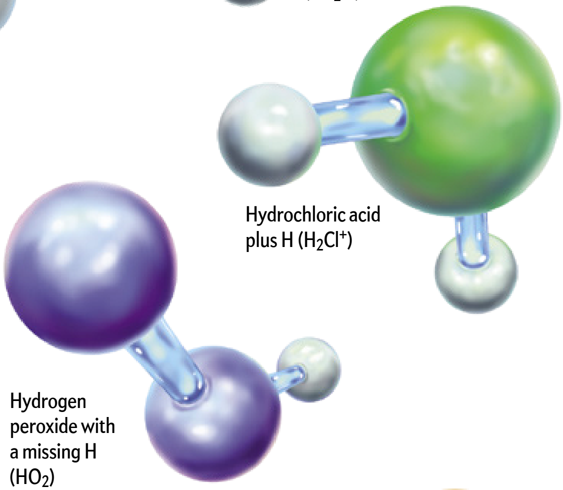
This story has stood on solid theoretical ground for decades, but it has long lacked observational corroboration. HeH^+ cannot form on Earth, except in labs, and for decades it went undetected in space. Last year, however, astronomers announced that they had observed this molecule for the first time, lurking in the funeral pyre of a dying star. A 40-year search had paid off, and a new and vital piece was added to our picture of how the early universe took shape.

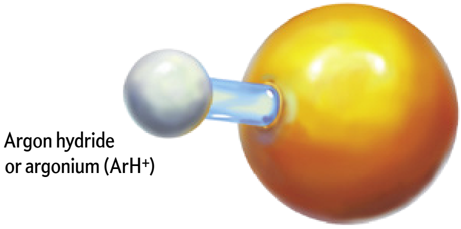
HeH^+ now joins the ranks of extraterrestrial molecules; so far scientists have detected more than 200 molecular species in space. This study of chemistry beyond Earth—astrochemistry, as we practitioners like to call it—is aimed at clarifying what molecules are present in space, how they form, and what their evolution means for observational and theoretical astrophysics. Many of the known astromolecules, including water, ammonia and formaldehyde, are common here on Earth. Others are terrestrially bizarre, such as hydrochloric acid with an extra proton and hydrogen peroxide with one of its hydrogen atoms amputated. Charged molecules, systems with unpaired electrons and strange arrangements of atoms in otherwise common molecules have also been observed. We have even seen molecules containing the so-called inert noble gases, such as ArH^+ (a combo of argon and hydrogen) and the newly documented HeH^+.











Most disciplines of chemistry are focused on making the world safer, more efficient or more enjoyable for humans. Astrochemistry, however, looks at the most fundamental properties of molecules. It helps to define what bonding really is, how long molecules can remain intact and why certain chemical species are more common than others. By studying chemistry in environments so very alien compared with Earth—with temperatures, pressures and available ingredients quite different from what we are used to—we can find molecules that challenge our usual notions of how atoms interact and that bring us to a deeper chemical understanding. Ultimately we hope to learn how chemistry led to the ingredients that ended up in the planets in our solar system and eventually enabled life.

WHERE WAS HeH$^+$?

IN A UNIVERSITY OF CALIFORNIA, Berkeley, lab in 1925, T. R. Hogness (who later worked on the Manhattan Project) and teaching fellow E. G. Lunn found that mixing helium and hydrogen gas in the presence of an electric arc within a vacuum chamber could create different ions with different masses. Measuring the mass-to-charge ratio of molecules is the forte of the chemical discipline called mass spectrometry; the early implementation of this now common chemical technique showed that this mixture produced a transient mass-to-charge ratio of 5. That could only be HeH$^+$. But keeping this noble gas molecule around long enough to study it proved exceptionally difficult, even in Hogness and Lunn's controlled lab.

In the early universe, it would have been even more unstable because HeH$^+$ is likely to let go of its proton on even the slightest contact with another atom. In this relationship, helium gives two electrons, whereas hydrogen gives none. Such uneven bonding (called dative bonding) is weaker than traditional covalent bonds, in which both atoms contribute more evenly.

In 1978 John H. Black, then at the University of Minnesota, was the first to argue that HeH$^+$ could still be present in space. Black suggested that a good place to look was planetary nebulae, the puffed-out and highly energized matter created in a star's death throes. In these clouds, a thin layer of ionized helium atoms is typically found in the presence of neutral hydrogen atoms; helium's strong need for electrons could drive it to borrow one from hydrogen, creating a bond. Consequently, since the late 1970s astronomers and their chemist collaborators have been looking for HeH$^+$ in myriad places, from the edge of the universe to supermassive stars. Yet for decades these searches found nothing, leading some to doubt the validity of HeH$^+$'s role in jump-starting chemistry. Did helium really bond with H$^+$? It seemed like it must have; there was nothing else to bond with back then. But if that were the case, then where was HeH$^+$?

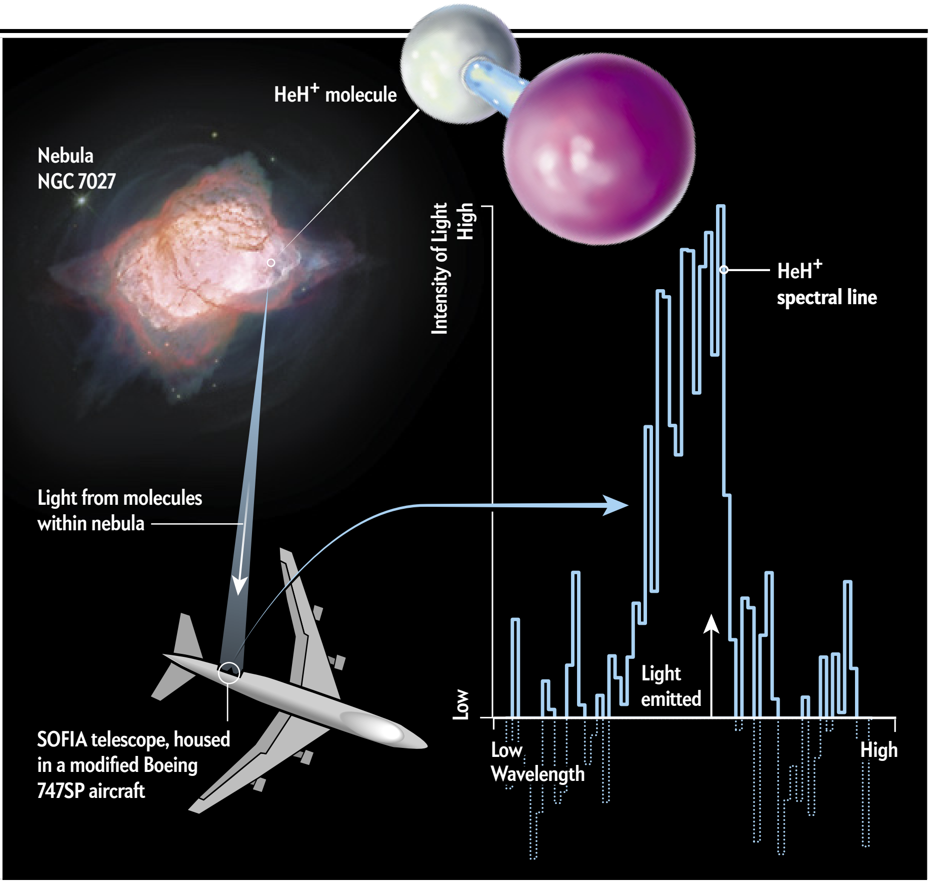
MOLECULAR FINGERPRINTS

WHILE ASTROCHEMISTS WERE LOOKING for HeH$^+$ and coming up empty, researchers found many other molecules they were not expecting. They could not even identify some of them.

It began in 1919, when Mary Lea Heger was using the Lick Observatory on top of Mount Hamilton in Santa Clara County, California, to observe the behavior of a pair of orbiting binary stars, a twin system akin

Spectral Signals

Astronomers identify molecules in space by observing their spectral features—the particular wavelengths of light they absorb and emit. Each molecule has a unique spectral signature based on its particular chemistry. Scientists first saw the signature of helium hydride (HeH$^+$) when they created this compound in Earth-based labs, and they predicted that it would have formed in the early universe. A long search for it in space finally paid off in 2016, when scientists spied this line in light coming from the nebula NGC 7027, using the Stratospheric Observatory for Infrared Astronomy (SOFIA), an infrared telescope mounted in a repurposed jumbo jet.



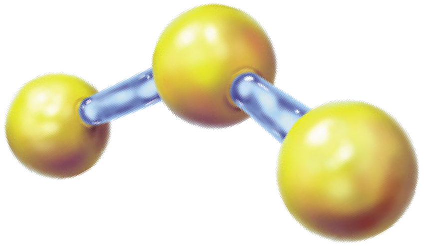
HUBBLE, NASA, ESA, PROCESSING BY JUDY SCHMIDT (*nebula*); SOURCE: "ASTROPHYSICAL DETECTION OF THE HELIUM HYDRIDE ION HEH$^+$," BY ROLF GÜSTEN ET AL., IN *NATURE*, VOL. 568; APRIL 2019 (*spectrum*)

Illustrations by Elena Harltey (molecules) and Amanda Montañez (schematic) to the suns of Tatooine. What she saw was surprising.

Each molecule has its own arrangement of atoms and electrons and therefore absorbs light in a unique way. These "absorption features" give every molecule its own set of fingerprints, seen when astronomers separate incoming light into its constituent wavelengths—a process called spectroscopy. As Heger's binary stars orbited their central point of gravity, the spectral features in each star's atmosphere also shifted in wavelength (the Doppler effect).

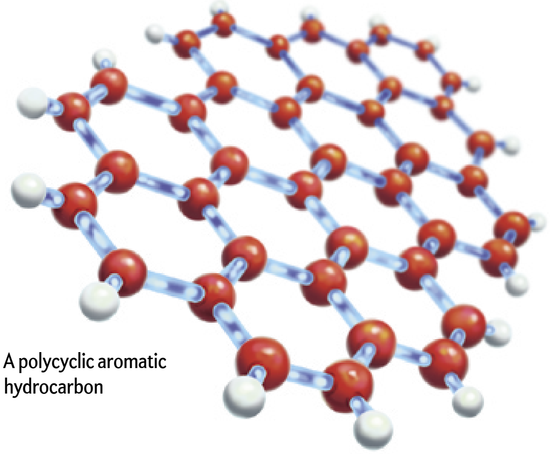
But Heger also found some spectral fingerprints that were standing still as the stars moved around. She then looked at another binary star system and saw the same pattern. Follow-up work showed that these nonmoving features also showed up when telescopes were aimed toward single stars. The imprints must have been coming from molecules not around stars but in the vast, cold regions between them. The craziest part was that basically the same fingerprints were present for all observed stars and even for other galaxies. The signatures, dubbed diffuse interstellar bands (DIBs), were everywhere. Scientists scoured the documented spectral features of molecules on Earth, newly synthesized ones from labs and those observed in space through radio-telescopic fingerprinting. Nothing matched the DIBs—they were something novel.

The late Harvard University professor William Klemperer, one of the foremost pioneers of astrochemistry, once suggested that the DIB signatures might belong to the trisulfur anion, S_3^-. When this proved untrue, he was so dejected that he wrote, "There is no better way to lose a scientific reputation than to speculate on the carrier[s] of the diffuse [interstellar] bands." Hypotheses as to the provenance of the DIBs circulated through the decades, but none stuck—it was known as the longest-standing problem in spectroscopy.



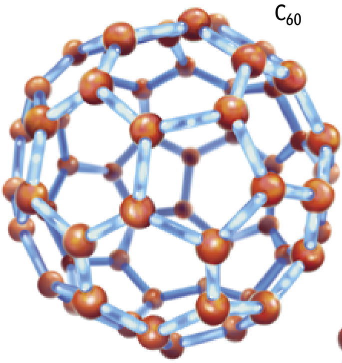
Trisulfur anion, S_3^-

One of the most intriguing hypotheses proposed polycyclic aromatic hydrocarbons (PAHs) as a DIB suspect. PAHs—hexagons of carbon atoms laid out in sheets—are the major component of soot, asphalt and graphite. They are unlikely to react with other molecules but do tend to stick to them. For astrochemists, the problem with PAHs is that their many varieties are so similar to one another that their spectroscopic fingerprints, or spectra, run together. It is like trying to spot the individual brushstrokes of Vincent van Gogh's *Starry Night* instead of seeing the full painting—the many parts are subsumed by the whole. But the DIBs seemed to behave in a similar fashion. Could PAHs explain the DIBs?

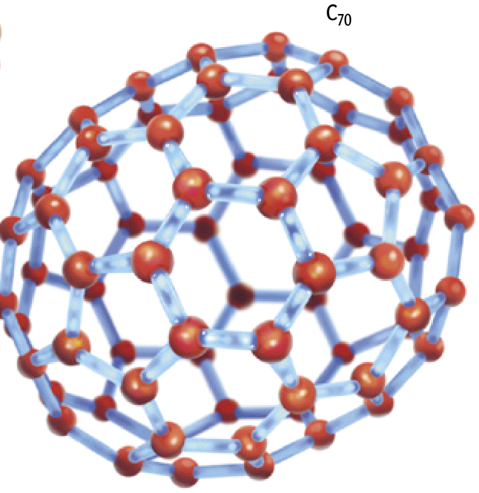


A polycyclic aromatic hydrocarbon

Such ideas have bounced around in astrochemistry circles since the 1970s, but one experiment forever changed how we think about carbon. Harry Kroto, who died in 2016, was at the University of Sussex in England in the 1980s and worked on a team to detect new molecules in space. He heard about an experiment by Robert F. Curl and Richard E. Smalley, both chemists at Rice University at the time, in which they had ablated an aluminum surface and found all kinds of new aluminum molecular clusters. When they substituted graphite (a so-called grand-PAH) for aluminum, a most bizarre molecule appeared: C_{60}, 60 carbon atoms arranged like a soccer ball. In 1996 Kroto, Curl and Smalley were awarded the Nobel Prize in Chemistry for their roles in discovering the molecule, called buckminsterfullerene, or just fullerene (also known as a buckyball). Kroto was convinced that buckyballs were present in space and were likely to be the source of some DIB fingerprints. Only a few people believed him, though, and he and his colleagues moved on. Yet in 2010, a quarter of a century after their initial discovery in the laboratory, C_{60} and its cousin C_{70} were observed in the infrared in planetary nebula Tc1 in the constellation Cygnus. Whether these



C_{60}

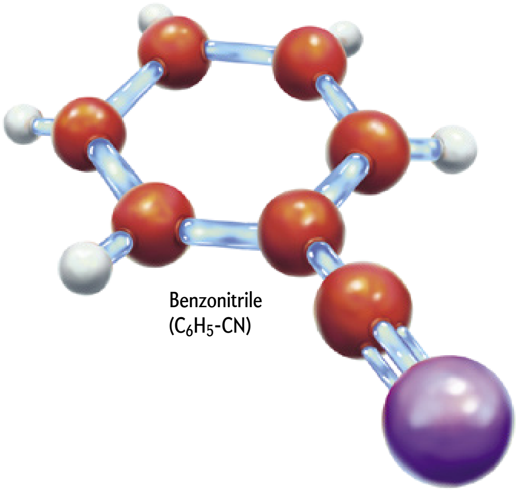


C_{70}

molecules were, in fact, related to the visible-wavelength DIBs was still undecided. Theoretical work suggested so, but scientists lacked confirming experimental data.

In 2015 the cation form of fullerene, C_{60}^+, was finally trapped in the lab, and scientists were able to conclusively measure its near-infrared spectrum. One, then two lines from this molecule matched known DIB wavelengths. Later, researchers showed that these fingerprints matched four or five DIBs. Then, in 2019, an international team led by Martin A. Cordiner of NASA's Goddard Space Flight Center used the Hubble Space Telescope to examine the DIB wavelengths seen in the direction of 11 mostly red (older, bigger) stars and found that they matched the experimental data for C_{60}^+, confirming at last that this molecule's fingerprints are responsible for some of the DIBs.

This discovery indicates that at least one type of molecule conclusively leaves its fingerprints all over interstellar space. Buckyballs are believed to evolve from PAHs, and their presence in space implies that their parent molecules must also be out there. Yet it was not until 2018 that researchers observed the fingerprints of a PAH-family molecule in space. The compound they saw, benzonitrile (C_6H_5-CN), is a rare aromatic hydrocarbon that is more easily detected than its relatives. And even more recently, scientists observed double-ring cyanonaphthalene molecules, revealing that larger PAHs are present as well.


Benzonitrile (C_6H_5-CN)

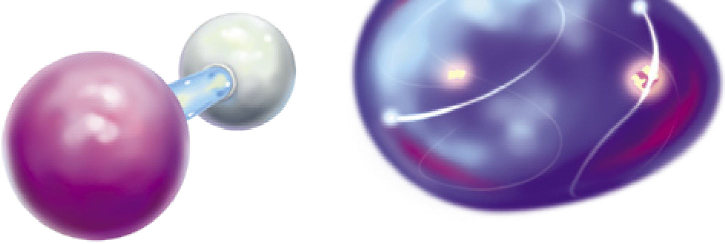
DISCOVERY

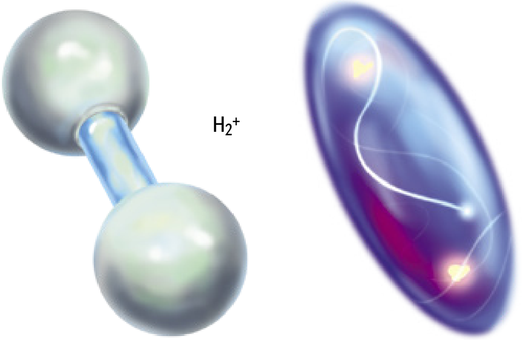
DESPITE THESE BREAKTHROUGHS, for a long time HeH^+ remained elusive.

The first molecules would have dissipated fairly quickly after the earliest epochs. As the universe matured, expanded and cooled, the leftover hydrogen nuclei began to gather electrons of their own. At that point these now neutral hydrogen atoms presumably felt the positive charge on the HeH^+ molecules. When the atoms and molecules collided, the relatively weak He-H dative bond broke, and a much stronger covalent bond between two hydrogens formed to create H_2^+. After that, the helium atoms were largely left alone.

It might seem, then, that the brief existence of HeH^+ was inconsequential, but that is far from the case. Models of potential chemical reactions in this period indicate that without HeH^+ formation, H_2^+, and then neutral H_2, would have come together much more slowly. Once H_2 had been made, though, the entire tree of chemistry unfolded. Next came H_3^+, which begot CH^+, which begot CH_2^+ and a cascade of other molecules. Eventually this chain led to water, ethanol and larger species. These processes are all the product of the unbalanced bonding in HeH^+; without this initial relation, the universe would be a different place.

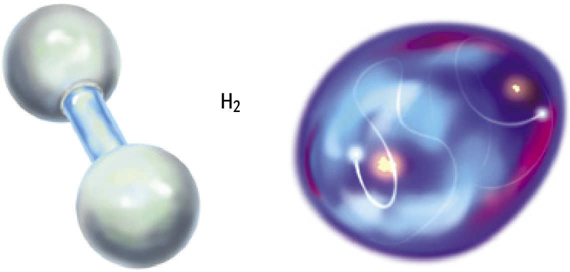
Helium hydride or helonium (HeH^+)

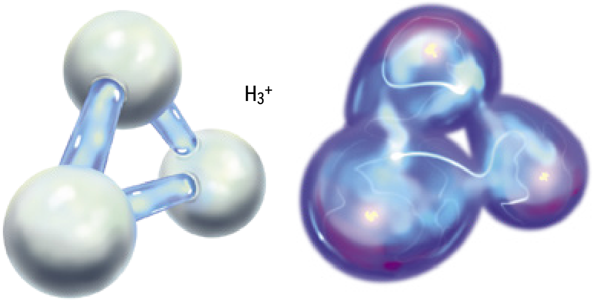


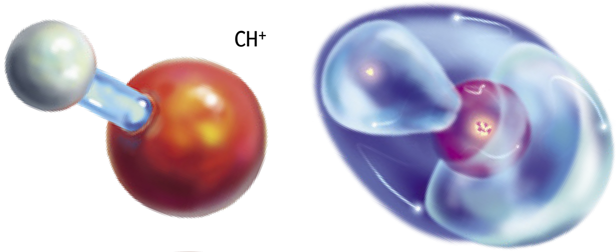

H_2^+

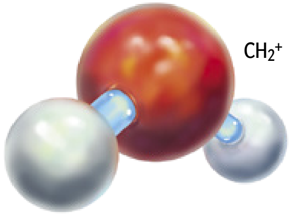
Still, by 2013 astrochemists were getting frustrated that HeH^+ was nowhere to be found. But that year a hopeful sign came when researchers discovered the related noble gas molecule ArH^+ in the Crab Nebula supernova remnant. Scientists focused the search for HeH^+ in similar, superenergized environments. The larger problem, though, was that the spectra of HeH^+ fell in the same region as fingerprints of the very first molecule ever observed in space, the CH radical. No telescopes had the power to separate these signatures.

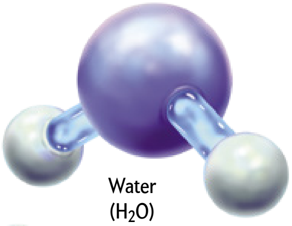
Then along came the Stratospheric Observatory for Infrared Astronomy (SOFIA), a repurposed 747 jumbo jet with a hole cut in its side so an infrared telescope can look out. In May 2016 an international team used SOFIA, a joint project of NASA and the German Aerospace Center, for three nights of observations. The SOFIA scope has the resolution necessary to discern HeH^+'s unique rotational-frequency fingerprint at

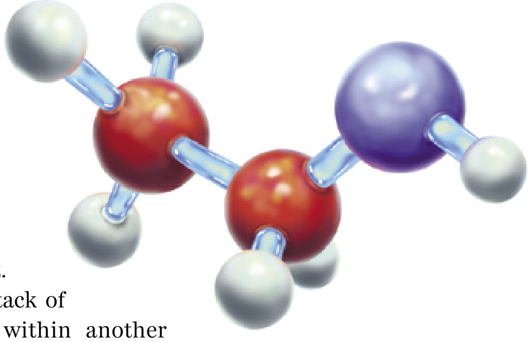

H_2


H_3^+


CH^+


CH_2^+


Water (H_2O)


Ethanol (C_2H_5OH)

2,010.184 gigahertz. There, in the haystack of far-infrared data within another burned-out cinder of an exploded star in the planetary nebula NGC 7027, part of the constellation Cygnus, was the fingerprint that had gone missing for so long. This hellish place, with its high temperatures and energies, was not unlike the early universe. On April 17, 2019, a team led by Rolf Güsten of the Max Planck Institute for Radio Astronomy in Bonn, Germany, published a report in *Nature* heralding the discovery of HeH^+.

Granted, this sighting is not of primordial HeH^+. We believe that the molecules Güsten and his colleagues observed were created much more recently. Nevertheless, the finding helps to constrain our knowledge of this compound. Scientists can now design better models of the universe as it existed when HeH^+ was the only molecule in town. The discovery might also give us clues about where else this chemical may be lurking in space today, directing us toward other planetary nebulae or even other regions of space that are so far away they correspond to earlier epochs of time, going back to the edge of the universe.

Ultimately we hope to learn how chemistry led to the ingredients that ended up in the planets in our solar system and eventually enabled life.

HARDER QUESTIONS

THIS IS AN EXCITING TIME in astrochemistry. Three grand questions have been conclusively answered in quick succession. Scientists have observed the first molecule to form in the cosmos and identified the first fingerprints belonging to the mysterious DIBs, and they are finally elucidating PAHs from the blackness of space.

Additionally, lab simulations of interstellar conditions are showing how amino acids and nucleobases might have formed. Space telescopes such as SOFIA and Hubble, as well as the upcoming James Webb Space Telescope, promise to provide unprecedented spectral characterization of stellar objects where new, less common molecular fingerprints may be seen.

Now that we are finding answers to these known problems, other quandaries are popping up. Eventually astrochemists hope to tackle harder questions, such as "What are the rest of the DIBs?," "What are the molecular origins of life?" and "What chemical mix is necessary for the formation of rocky planets rather than gas giants?" It was the sharing of electrons that created observable matter in the cosmos. When we have a deeper comprehension of these chemical processes, we can gain a finer-grain understanding of astrophysics and the overall history of our universe. SA

MORE TO EXPLORE

The Cosmic-Chemical Bond: Chemistry from the Big Bang to Planet Formation. David A. Williams and Thomas W. Hartquist. Royal Society of Chemistry, 2013.

Astrophysical Detection of the Helium Hydride Ion HeH^+. Rolf Güsten et al. in *Nature,* Vol. 568, pages 357–359; April 18, 2019.

The Astrochymist: Resources for Astrochemists & Interested Bystanders: **www.astrochymist.org**

FROM OUR ARCHIVES

Fullerenes. Richard E. Smalley and Robert F. Curl; October 1991.

scientificamerican.com/magazine/sa

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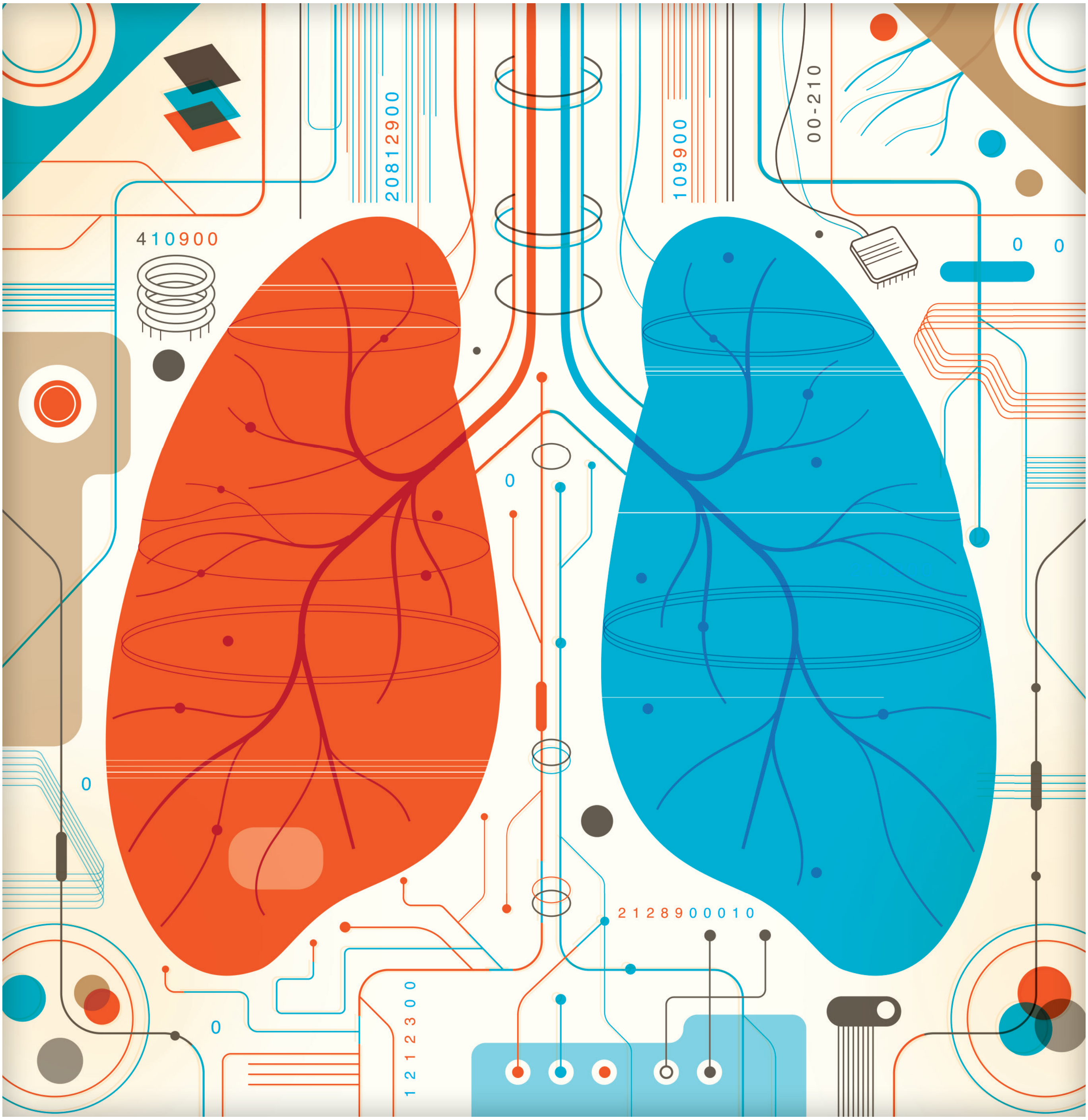

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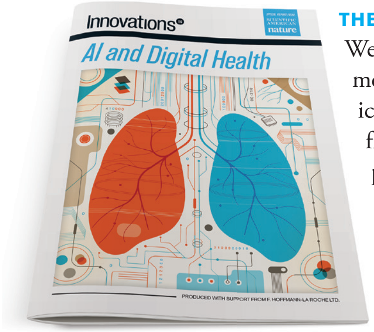
How Artificial Intelligence Will Change Medicine



THE BIOMEDICAL WORLD IS AWASH IN DATA. We have terabytes of genomic information from mouse to human, troves of health metrics from clinical trials, and reams of so-called real-world data from insurance companies and pharmacies. Using powerful computers, scientists have scrutinized this bounty with some fine results, but it has become clear that we can learn much more with an assist from artificial intelligence. Over the next decade deep-learning neural networks will likely transform how we look for patterns in data and how research is conducted and applied to human health. This special report explores the promise of this nascent revolution.

Right now the biggest bets are being placed in the realm of drug discovery (*page S3*). And for good reason. The average cost of bringing a new drug to market nearly doubled between 2003 and 2013 to $2.6 billion, and because nine out of 10 fail in the final two phases of clinical trials, most of the money goes to waste. Every large pharma company is working with at least one AI-focused start-up to see if it can raise the return on investment. Machine-learning algorithms can sift through millions of compounds, narrowing the options for a particular drug target. Perhaps more exciting, AI systems—unconstrained by prevailing theories and biases—can identify entirely new targets by spotting subtle differences at the level of tissues, cells, genes or proteins between, say, a healthy brain and one marked by Parkinson's—differences that might elude or even mystify a human scientist.

That same sharp-eyed ability is also being deployed to interpret medical scans (*page S8*). Some systems can already detect early signs of cancer that might be missed by a radiologist or see things that are simply beyond human capacity—such as assessing cardiovascular risk from a retinal scan. The Food and Drug Administration is approving imaging algorithms at a rapid clip. Other AI applications lie a bit further down the road. Will the inefficiencies of today's electronic health records (EHRs) be addressed by smart systems that prevent prescribing errors and provide early warnings of disease? Some of the world's biggest tech giants are working on it (*page S13*).

Despite fears that machines will displace humans, most experts believe artificial and human intelligence will work synergistically. The bigger concern is a shortage of people with both biomedical knowledge and algorithm-building proficiency (*page S16*). If this human problem can be resolved, the key to creating successful AI applications may depend on the quality and quantity of what we feed their hungry maw. "We rely on three things," says the CEO of one deep-learning start-up. "Data, data and more data."

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Claudia Wallis, Contributing Editor

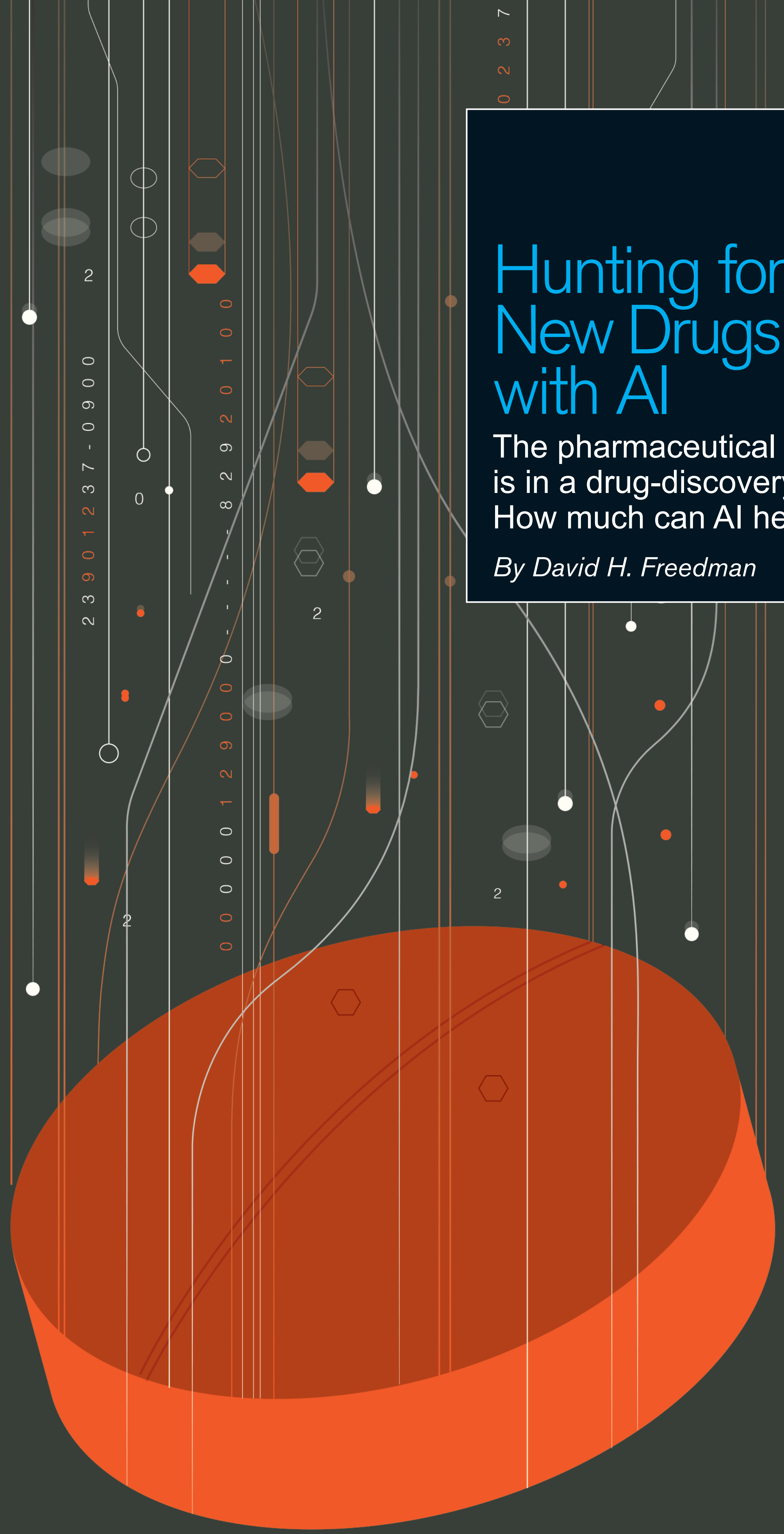
INSIDE

Cover and main illustrations by Harry Campbell

Hunting for New Drugs with AI

The pharmaceutical industry is in a drug-discovery slump. How much can AI help?

By David H. Freedman



THERE ARE MANY REASONS that promising drugs wash out during pharmaceutical development, and one of them is cytochrome P450. A set of enzymes mostly produced in the liver, CYP450, as it is commonly called, is involved in breaking down chemicals and preventing them from building up to dangerous levels in the bloodstream. Many experimental drugs, it turns out, inhibit the production of CYP450—a vexing side effect that can render such a drug toxic in humans.

Drug companies have long relied on conventional tools to try to predict whether a drug candidate will inhibit CYP450 in patients, such as by conducting chemical analyses in test tubes, looking at CYP450 interactions with better-understood drugs that have chemical similarities, and running tests on mice. But their predictions are wrong about a third of the time. In those cases, CYP450-related toxicity may come to light only during human trials, resulting in millions of dollars and years of effort going to waste. This costly inaccuracy can, at times, feel like "the bane of our existence," says Saurabh Saha, senior vice president of research and development and translational medicine at Bristol-Myers Squibb.

Inefficiencies such as this one contribute to a larger problem: the $1-trillion global pharmaceutical industry has been in a drug development and productivity slide for at least two decades. Pharmaceutical companies are spending more and more—the 10 largest ones now pay nearly $80 billion a year—to come up with fewer and fewer successful drugs. Ten years ago every dollar invested in research and development saw a return of 10 cents; today it yields less than two cents. In part, that is because the drugs that are easiest to find and that safely and effectively treat common disorders have all been found; what is left is hunting for drugs that address problems with complex and elusive solutions and that would treat disorders affecting only tiny portions of the population—and thus could return far less in revenue.

Because finding new, successful drugs has become so much harder, the average cost of bringing one to market nearly doubled between 2003 and 2013 to $2.6 billion, according to the Tufts Center for the Study of Drug Development. These same challenges have increased the lab-to-market time line to 12 years, with 90 percent of drugs washing out in one of the phases of human trials.

It's no wonder, then, that the industry is enthusiastic about artificial-intelligence tools for drug development. These tools do not work by having expert-developed analytical techniques programmed into them; rather users feed them sample problems (a molecule) and solutions (how the molecule ultimately behaves as a drug) so that the software can develop its own computational approaches for producing those same solutions.

Most AI-based drug-discovery applications take the form of a technique called machine learning, including a subset of the approach called deep learning. Most machine-learning programs can work with small data sets that are organized and labeled, whereas deep-learning programs can work with raw, unstructured data and require much larger volumes. Thus, a machine-learning program might learn to recognize the different features of a cell after being shown tens of thousands of examples of photographs of cells in which the parts are already labeled. A deep-learning version can figure out those parts on its own from unlabeled cell images, but it might need to look at a million of them to do it.

Many scientists in the field think that AI will ultimately improve drug development in several ways: by identifying more promising drug candidates; by raising the "hit rate," or the percentage of candidates that make it through clinical trials and gain regulatory approval; and by speeding up the overall process. A machine-learning program recently deployed by Bristol-Myers Squibb, for instance, was trained to find patterns in data that correlate with CYP450 inhibition. Saha says the program boosted the accuracy of its CYP450 predictions to 95 percent—a sixfold reduction in the failure rate compared with conventional methods. These results help researchers quickly screen out potentially toxic drugs and focus instead on candidates that have a stronger shot at making it all the way through multiple human trials to U.S. Food and Drug Administration approval. "Where AI can make a huge difference is having drugs that fail early on, before we make all that investment in them," says Vipin Gopal, chief data and analytics officer at Eli Lilly.

Resources are now piling into the field. AI-based drug-discovery start-ups raised more than $1 billion in funding in 2018, and as of last September, they were on track to raise $1.5 billion in 2019. Every one of the major pharmaceutical companies has announced a partnership with at least one such firm. Only a few AI-discovered drugs are actually in the human-testing pipeline, however, and none has begun phase 3 human trials, the gold-standard test for experimental drugs. Saha concedes that it will be several years before he can say for sure whether the company's hit rates will go up as a result of the AI prediction rate of CYP450 inhibition. For all the hype in the industry, it is far from certain that early results will translate to more and better drugs.

SIFTING THROUGH MILLIONS OF MOLECULES

EMERGING AI PROGRAMS are not exactly a revolutionary update in the drug industry, which has for some time been building sophisticated analytical solutions that aid with drug development. The rise of powerful statistical and biophysical modeling programs well over a decade ago as part of the growth of the field of bioinformatics—the quest to use computational tools to derive biological insights from large amounts of data—led to tools that can predict the properties of molecules. But these programs have been limited by scientists' incomplete understanding of how molecules interact: they cannot tell conventional software how to find insights in data when they do not know what elements of the data are most important and how they relate to one another. Imbued with the ability to derive their own insights into which data elements matter, newer AI programs can extract better predictions for a wider range of variables.

AI tools tackle different aspects of drug discovery in several ways. Some AI companies, for example, are focusing on the problem of designing a drug that can safely and effectively work on a known target—usually a specific, well-studied protein that is associated with a disease. The goal is typically to come up with a molecule that can chemically bind to the target protein and modify it so that it no longer contributes to the disease or its symptoms. Cyclica, a Canadian firm, puts its software to work on matching the biophysical structures and biochemical properties of millions of molecules to the structures and properties of some 150,000 proteins to uncover molecules likely to bind to target proteins, as well as those to avoid.

But molecules that are good candidates as drugs still have to jump through other hoops. Those include making it through the gut into the bloodstream without being immediately broken down by the liver or metabolic processes; working in a particular organ such as the kidney without disrupting other organs; avoiding binding to and incapacitating any of the thousands of other proteins in the human body that are important to health; and breaking down and leaving the body before drug levels become potentially dangerous. Cyclica's AI software takes all those requirements into consideration. "A molecule that can interact with a protein target can usually interact with upward of 300 proteins," Cyclica's CEO Naheed Kurji says. "If you're designing a molecule, it behooves you to consider the other 299 interactions that could have disastrous effects in humans."

There is growing recognition among biomedical researchers that complex diseases such as cancer and Alzheimer's involve hundreds of proteins, and hitting just one of them is not likely to be disruptive enough. Cyclica is attempting to find individual compounds that can interact with dozens of target proteins yet avoid interacting with hundreds of other proteins, Kurji explains. Currently under development, he adds, is the incorporation of a wealth of anonymized global genetic data about variations in proteins, so that the software can specify which patients the candidate drugs would work best on. Kurji claims that together these features will eventually be able to shave five years off the typical seven-year-long time frame for bringing a candidate drug from initial identification to human trials.

Merck and Bayer are among the big pharma companies that have announced partnerships with Cyclica. As is the case with most AI-pharma partnerships, the companies are not releasing much insight into exactly what AI-generated drug candidates may be coming out of the collaborations. But Cyclica has shared some details of its successes in identifying a key target protein linked to already FDA-approved drugs for systemic scleroderma, an autoimmune disease of the skin and other organs, as well as one linked to the Ebola virus. Each drug is already FDA-approved for the treatment of other disorders—HIV and depression, respectively—which means they both could be quickly "repurposed" for the new applications if the research continues to pan out.

Sometimes researchers identify a target protein that might play a critical role in disease but find that—as is true of about 90 percent of the proteins in the human body—not much is known about its structure and properties. With little data to go on, most machine- and deep-learning programs will not be able to figure out how to "drug" the protein—that is, come up with compounds that will bind to it and meet the other criteria for safety and efficacy. A handful of AI companies are focusing on these kinds of "small data" problems, including Exscientia, which uses its software to hunt down molecules that might work with a target protein. It can produce useful insights with as few as 10 pieces of data about a protein, says the company's CEO, Andrew Hopkins, a professor of medicinal informatics at the University of Dundee in Scotland.

Resources are now piling into the field. Only a few AI-discovered drugs are actually in the human-testing pipeline, however, and none has begun phase 3 human trials, the gold-standard test for experimental drugs.

Exscientia's algorithms compare the limited information available about a target protein against a database of about a billion protein interactions. This step narrows down the list of possible compounds that might work and specifies what additional data would help further refine the focus. Such data might come from looking at tissue samples to learn more about how the protein behaves in the body, for example. The resulting new data are then fed into the software, which pares the list again and suggests another round of needed data. This process is repeated until the software is ready to generate a manageable list of compounds that are favorable drug candidates for the target.

Hopkins claims that Exscientia's process can cut the time spent in discovery from 4.5 years to as little as one year, reduces discovery costs by 80 percent and results in one-fifth the number of synthesized compounds as is normally needed to produce a single winning drug. Exscientia is partnering with biotech giant Celgene in an effort to find new potential drugs for three targets.

Meanwhile an Exscientia partnership with GlaxoSmithKline has led to what the companies say is a promising molecule targeting a novel pathway to treat chronic obstructive pulmonary disease. But as with any AI company addressing drug development, Exscientia simply has not been in the game long enough to have generated enough new candidates that could have made it through to late-stage trials—a process that typically takes five to eight years. Hopkins claims one of the candidates Exscientia has identified may reach human trials as early as this year. "At the end of the day we'll be judged on the drugs we deliver," he says.

THE NEED FOR NEW TARGETS

FINDING A MOLECULE to hit a new target is not the only major challenge in drug discovery. There is also the need to identify targets in the first place. To spot proteins that might have roles in diseases, biopharma company Berg applies AI to sift through information derived from human tissue samples. This approach aims to solve two problems that hang over most research into drug targets, according to Berg's CEO Niven R. Narain: the efforts tend to be based on a researcher's theory or hunch, which can bias the results and overly restrict the pool of candidates, and they often turn up targets that are correlated to the disease but do not ultimately prove causative, which means drugging them will not help.

Berg's approach involves plugging in every piece of data that can be wrung out of a patient's tissue samples, organ fluids and bloodwork. These extracted data include genomics, proteomics, metabolomics, lipidomics, and more—an unusually broad range to consider in a hunt for targets. Samples are taken from people with and without a particular disease and at different stages of disease progression. Living cells from the samples are exposed in the laboratory to various compounds and conditions, such as low levels of oxygen or high levels of glucose. This method produces data on corresponding changes ranging from a cell's ability to produce energy to the rigidity of its membrane.

All the data are then run through a set of deep-learning programs that search for any differences between nondisease and disease states, with an eye to eventually focusing on proteins whose presence seem to have an impact on the disease. In some cases, those proteins become candidates as targets, at which point Berg's software can start searching for compounds to drug those targets. What is more, because the software can discern when the target seems to cause disease in only a subset of patients, it can look for distinguishing characteristics of those patients, such as certain genes.That paves the way for a precision-medicine approach, meaning patients can be tested before they take the drug to determine whether it is likely to be effective for them.

90

Percentage of drug candidates that wash out of development during human trials, which take place after years of investment have already been made. AI could make the process more efficient.

The most exciting drug to come out of Berg's work—and perhaps the most exciting to emerge from any drug-discovery-related AI effort to date—is a cancer drug called BPM31510. It recently completed a phase 2 trial for patients with advanced pancreatic cancer, which is extremely aggressive and difficult to treat. Phase 1 trials often do not indicate much about a drug's potential except whether it is dangerously toxic at a given dose, but BPM31510's phase 1 trial against other cancers provided some verification of the ability of Berg's software to predict the roughly 20 percent of patients who were likely to respond to it, as well as those who were more likely to experience adverse reactions.

Additionally, tissue-sample analysis from the trial led Berg's software to predict, counterintuitively, that the drug would work best against more aggressive cancers because it attacks mechanisms that play a larger role in those cancers. Should the drug gain approval, Berg might do a postmarket analysis of perhaps one out of 100 patients taking it, "so that we can keep improving how it's used," Narain says.

Berg is partnering with pharma giant AstraZeneca to seek targets for Parkinson's and other neurological diseases and with Sanofi Pasteur to pursue improved flu vaccines. It is also working with the U.S. Department of Veterans Affairs and the Cleveland Clinic on targets for prostate cancer. The software has already identified mechanisms for diagnostic tests that could differentiate prostate cancer from benignly enlarged prostates, which currently is often difficult to do without surgery.

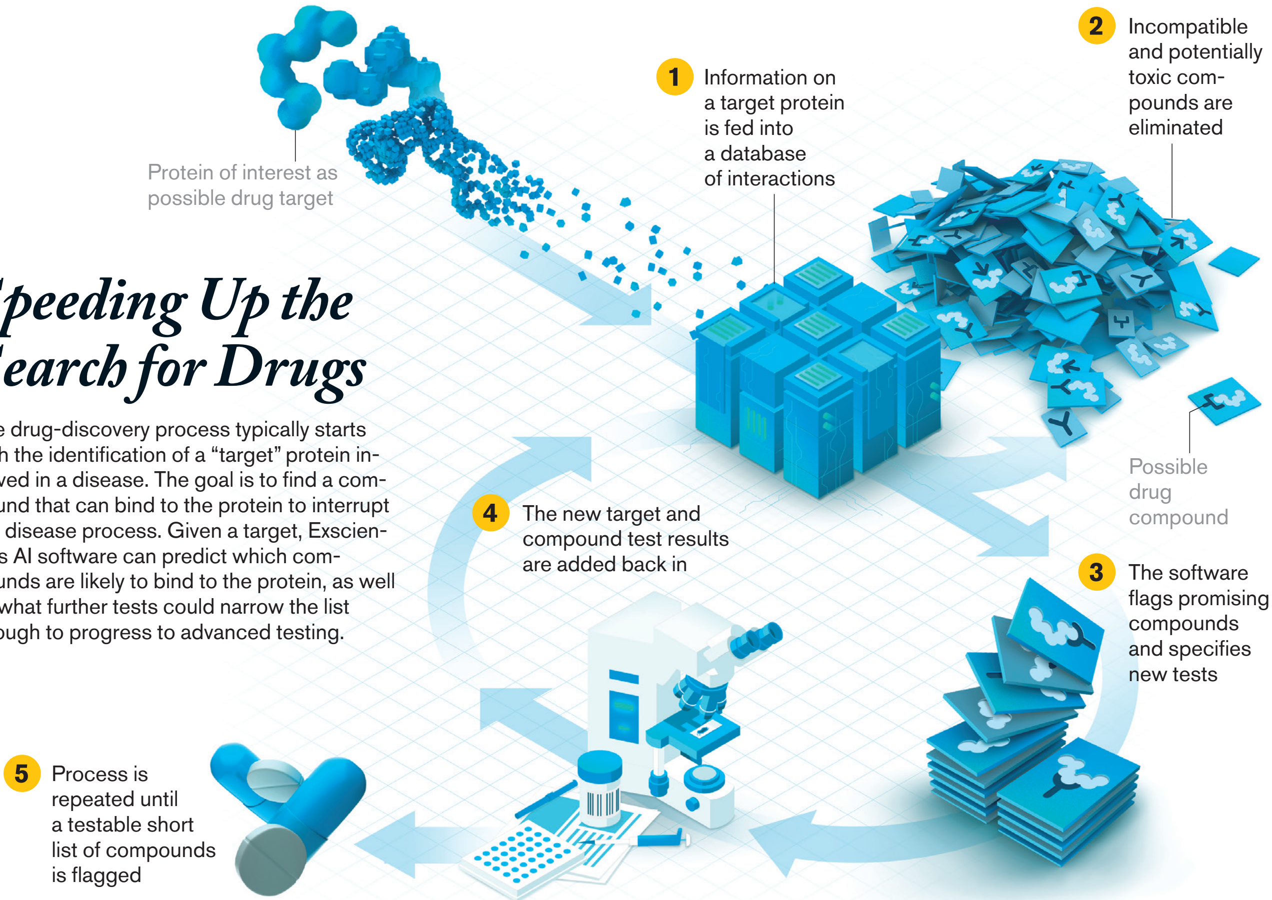
GETTING BEYOND THE HYPE

BIG PHARMA'S INTEREST in injecting these kinds of AI efforts into drug discovery can be gauged by the fact that at least 20 separate partnerships have been reported between the major companies and AI-drug-discovery tech companies. Pfizer, GlaxoSmithKline and Novartis are among the pharma companies said to have also built substantial AI expertise in-house, and it is likely that others are in the process of doing the same.

Although research executives at these companies have expressed enthusiasm for some of the early results, they are quick to admit that AI is no sure thing for the bottom line given how few new AI-aided candidates have made it to the animal-testing stage of drug development, let alone to human trials. The jury is out on whether AI will successfully make drug discovery more efficient, says Sara Kenkare-Mitra, senior vice president of development sciences at Roche subsidiary Genentech, and even if it does, "we can't yet say whether it will be an incremental improvement or an exponential leap." If many of the drugs that result from AI efforts make it well into human testing, this question will

Speeding Up the Search for Drugs

The drug-discovery process typically starts with the identification of a “target” protein involved in a disease. The goal is to find a compound that can bind to the protein to interrupt the disease process. Given a target, Exscientia’s AI software can predict which compounds are likely to bind to the protein, as well as what further tests could narrow the list enough to progress to advanced testing.



still not be answered fully unless the drugs progress all the way through to FDA approval.

Bristol-Myers Squibb’s Saha suggests that AI-aided drugs’ rate of entry into the market is likely to remain low for some time. That rate could pick up dramatically, however, if the processes for testing and approval were streamlined to take into account the ability of machine- and deep-learning systems to more accurately predict which drugs are highly likely to be safe and effective and which patients they are best suited for. “When regulatory agencies see the same value we see in AI, the floodgates could open,” he says. “In some cases, we might be allowed to pass over animal models and go straight to human testing once we show these drugs can hit their targets with no toxicity.” But those changes are probably many years away, he admits. He adds that it is wrong to imply that AI replaces scientists and conventional research—whereas AI supports and amplifies human efforts, it still depends on humans to generate novel biological insights, set research directions and priorities, guide and validate results, and produce needed data.

The breathless hype around AI-based drug discovery might actually be damaging, Berg’s Narain says, because overpromising could lead to disappointment and backlash. “These are early days, and we need to be sober about the fact that these are tools that can help—they’re not solutions yet,” he says. Cyclica’s Kurji points the finger at AI companies that make what he says are exaggerated marketing claims, such as having reduced the many years and billions of dollars it takes to develop a drug to a few weeks and a few hundred thousand dollars. “It’s simply not true,” he says. “And it’s irresponsible and destructive to say so.”

But if hype hurts, Kurji insists he also knows what will give the AI-drug-discovery industry a big boost: more high-quality information to feed the various programs. “We rely on three things: data, data and more data,” he says. That sentiment is echoed by Enoch Huang, vice president of medicinal sciences at Pfizer, who says that having the right algorithm isn’t the most important factor.

The need to feed AI software with large volumes of relevant data is actually starting to change science, as researchers run more experiments specifically with the production of AI-relevant data in mind. Genentech’s Kenkare-Mitra notes that this has already happened in immunotherapy drug research. “There aren’t always enough data from the clinic to use with machine learning,” she says. “But we can [often] generate that data in vitro and feed them to the system.”

That kind of approach could lead to a virtuous cycle in drug discovery in which AI helps elucidate areas where researchers need to look for targets and drugs. Moreover, the resulting research provides larger, more relevant data sets that allow the software to point to even more fertile research avenues. “It’s not so much AI we believe in,” Kenkare-Mitra says, “as a human-AI partnership.”

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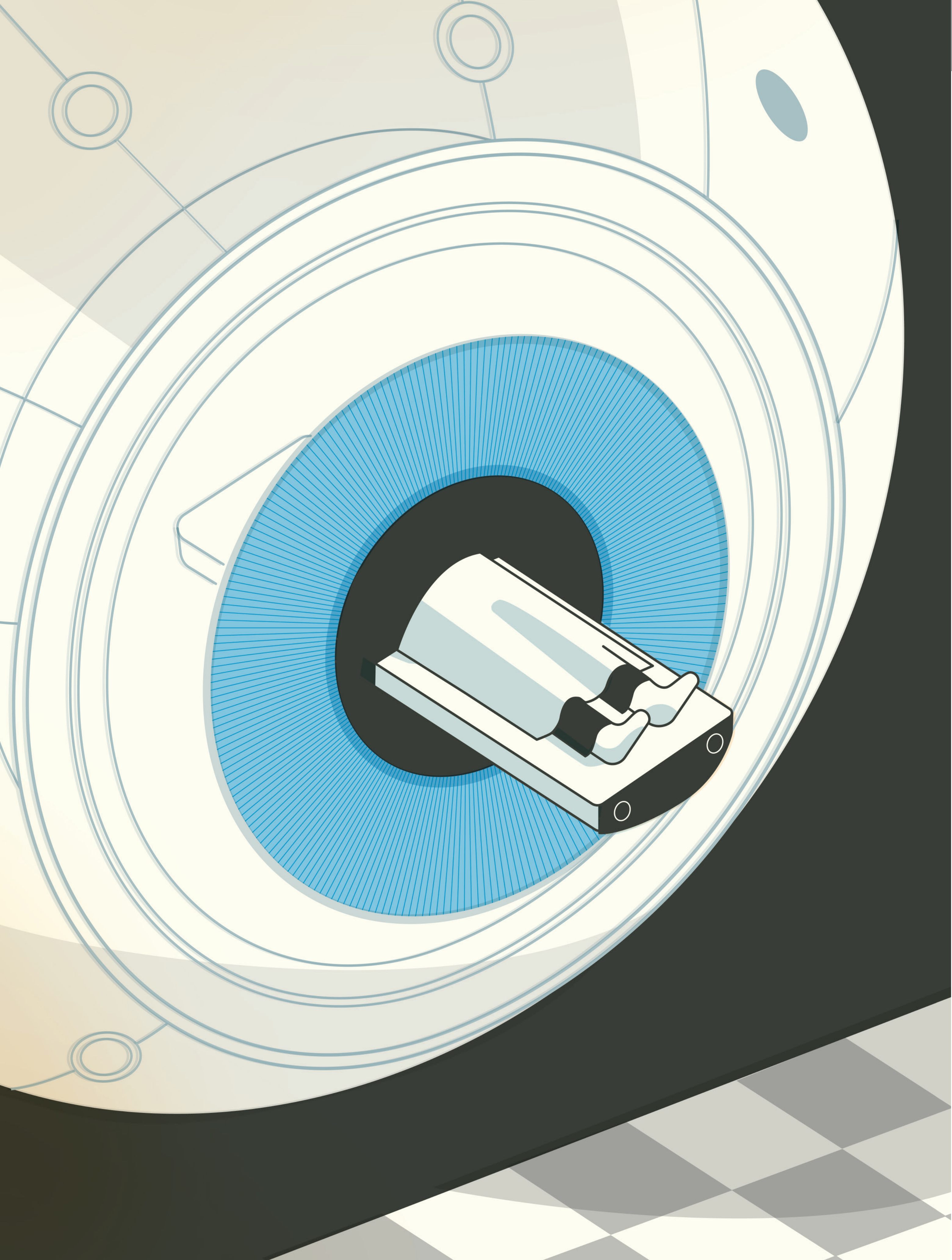
Illustration by Campbell Medical Illustration



Rise of Robot Radiologists

Deep-learning algorithms are peering into MRIs and x-rays with unmatched vision, but who is to blame when they make a mistake?

By Sara Reardon

WHEN REGINA BARZILAY had a routine mammogram in her early 40s, the image showed a complex array of white splotches in her breast tissue. The marks could be normal, or they could be cancerous—even the best radiologists often struggle to tell the difference. Her doctors decided the spots were not immediately worrisome. In hindsight, she says, "I already had cancer, and they didn't see it."

Over the next two years Barzilay underwent a second mammogram, a breast MRI and a biopsy, all of which continued to yield ambiguous or conflicting findings. Ultimately she was diagnosed with breast cancer in 2014, but the path to that diagnosis had been unbelievably frustrating. "How do you do three tests and get three different results?" she wondered.

Barzilay was treated and made a good recovery. But she remained horrified that the uncertainties of reading a mammogram could delay treatment. "I realized to what extent we are unprotected with current approaches," she says, so she made a career-altering decision: "I absolutely have to change it."

A computer scientist at Massachusetts Institute of Technology, Barzilay had never studied health before. Her research used machine-learning techniques—a form of artificial intelligence—for natural-language processing. But she had been looking for a new line of research and decided to team up with radiologists to develop machine-learning algorithms that use computers' superior visual analysis to spot subtle patterns in mammograms that the human eye might miss.

Over the next four years the team taught a computer program to analyze mammograms from about 32,000 women of different ages and races and told it which women had been diagnosed with cancer within five years of the scan. They then tested the computer's matching abilities in 3,800 more patients. Their resulting algorithm, published last May in *Radiology,* was significantly more accurate at predicting cancer—or the absence of cancer—than practices generally used in clinics. When Barzilay's team ran the program on her own mammograms from 2012—ones her doctor had cleared—the algorithm correctly predicted she was at a higher risk of developing breast cancer within five years than 98 percent of patients.

AI algorithms not only spot details too subtle for the human eye to see. They can also develop entirely new ways of interpreting medical images, sometimes in ways humans do not understand. The numerous researchers, start-up companies and scanner manufacturers designing AI programs hope they can improve the accuracy and timeliness of diagnoses, provide better treatment in developing countries and remote regions that lack radiologists, reveal new links between biology and disease, and even help to predict how soon a person will die.

AI applications are entering clinics at a rapid rate, and physicians have met the technology with equal parts excitement about its potential to reduce their workload and fear about losing their jobs to machines. Algorithms also raise unprecedented questions about how to regulate a machine that is constantly learning and changing and who is to blame if an algorithm gets a diagnosis wrong. Still, many physicians are excited about the promise of AI programs. "If these models can be sufficiently vetted and we can raise our level of understanding of how they work, this can help raise the level of health care for everybody," says Matthew Lungren, a radiologist at Stanford University.

"A VERY, VERY HOT TOPIC"

THE IDEA OF using computers to read radiological scans is not new. In the 1990s radiologists started using a program called computer-assisted diagnosis (CAD) to detect breast cancer in mammograms. The technology was hailed as revolutionary, and clinics adopted it rapidly. But CAD proved to be more time-consuming and difficult to use than existing methods, and according to some studies, clinics that used it made more errors than those that did not. The failure made many physicians dubious of computer-aided diagnostics, says Vijay Rao, a radiologist at Jefferson University in Philadelphia.

In the past decade, however, computer vision has improved by leaps and bounds—in everyday applications such as face recognition and in medicine. The advance has been largely driven by the development of deep-learning methods, in which a computer is given a set of images and then left to draw its own connections between them, ultimately developing a network of associations. In medical imaging, this might, for example, involve telling the computer which images contain cancer and setting it free to find features common to those images but absent in cancer-free images.

Development and adoption of AI technologies in radiology has spread rapidly. "Last year, at every large meeting I went to, the main theme was AI and imaging," says Rao, past president of the Radiological Society of North America. "Clearly, this is a very, very hot topic."

The U.S. Food and Drug Administration says that it does not keep a list of AI products that it has approved. But Eric Topol, a digital medicine researcher at the Scripps Research Institute in La Jolla, Calif., estimates that the agency is approving more than one medical imaging algorithm per month. A 2018 survey by marketing-intelligence firm Reaction Data found that 84 percent of U.S. radiology clinics had adopted or planned to adopt AI programs. The field is growing especially quickly in China, where more than 100 companies are designing AI applications for health care.

"It's a fascinating time to be in this market," says Elad Walach, CEO of the Tel Aviv–based start-up Aidoc. The company develops algorithms to analyze CT scans for abnormalities and move those patients to the top of a doctor's priority list. Aidoc also tracks how often doctors use the program and how long they spend second-guessing its conclusions. "Initially they're skeptical, but after two months they get used to it and are very trusting," Walach says.

Saving time can be crucial to saving a patient. One recent study of chest x-rays for collapsed lungs found that radiologists flag more than 60 percent of the scans they order as high priority, which suggests that they might spend hours wading through nonserious cases before getting to those that are actually urgent. "Every doctor I talk to has a story where they lost a patient because of a collapsed lung," says Karley Yoder, vice president and general manager of AI at Boston-based GE Healthcare, one of the leading manufacturers of medical imaging equipment. Last September the FDA approved a set of AI tools that will now come embedded in GE scanners, automatically flagging the most urgent cases.

Because they can process massive amounts of data, computers can perform analytical tasks that are beyond human capability. Google, for instance, is using its computing power to develop AI algorithms that construct two-dimensional CT images of lungs into a three-dimensional lung and look at the entire structure to determine whether cancer is present. Radiologists, in contrast, have to look at these images individually and attempt to reconstruct them in their heads. Another Google algorithm can do something radiologists cannot do at all: determine patients' risk of cardiovascular disease by looking at a scan of their retinas, picking up on subtle changes related to blood pressure, cholesterol, smoking history and aging. "There's potential signal there beyond what was known before," says Google product manager Daniel Tse.

84

Percentage of U.S. radiology clinics that have adopted or plan to adopt AI programs, according to a 2018 survey.

THE BLACK BOX PROBLEM

AI PROGRAMS COULD END UP revealing entirely new links between biological features and patient outcomes. A 2019 paper in *JAMA Network Open* described a deep-learning algorithm trained on more than 85,000 chest x-rays from people enrolled in two large clinical trials that had tracked them for more than 12 years. The algorithm scored each patient's risk of dying during this period. The researchers found that 53 percent of the people the AI put into a high-risk category died within 12 years, as opposed to 4 percent in the low-risk category. The algorithm did not have information on who died or on the cause of death. The lead investigator, radiologist Michael Lu of Massachusetts General Hospital, says that the algorithm could be a helpful tool for assessing patient health if combined with a physician's assessment and other data such as genetics.

To understand how the algorithm worked, the researchers identified the parts of images that it used to make its calculations. Some, such as waist circumference and the structure of women's breasts, made sense because these areas can hint at known risk factors for certain diseases. But the algorithm also looked at the region under patients' shoulder blades, which has no known medical significance. Lu guesses that flexibility might be one predictor of a shorter life span. Taking a chest x-ray often requires patients to hug the machine, and less healthy people who cannot put their arms all the way around it might position their shoulders in a different way. "They're not things I would have thought of de novo and might not understand," Lu says.

The disconnect between the way computers and humans think is known as the black box problem: the idea that a computer brain operates in an obscured space that is inaccessible to humans. Experts differ on whether this presents a problem in medical imaging. On the one hand, if an algorithm consistently improves doctors' performance and patients' health, doctors do not need to know how it works. After all, researchers still do not fully understand the mechanisms of many drugs such as lithium, which has been used to treat depression since the 1950s. "Maybe we shouldn't be so fixated, because the way humans work in medicine is about as black box as you can get," Topol says. "Do we hold machines to a higher standard?"

“AI won’t replace radiologists, but radiologists who use AI will replace radiologists who don’t.”
—*Curtis Langlotz, Stanford University*

Still, there is no denying that the black box presents ample opportunity for human-AI misunderstanding. For instance, researchers at the Icahn School of Medicine at Mount Sinai were deeply puzzled by a discrepancy in the performance of a deep-learning algorithm they had developed to identify pneumonia in lung x-rays. It performed with greater than 90 percent accuracy on x-rays produced at Mount Sinai but was far less accurate with scans from other institutions. They eventually figured out that instead of just analyzing the images, the algorithm was also factoring in the odds of a positive finding based on how common pneumonia was at each institution—not something they expected or wanted the program to do.

Confounding factors like these worry Samuel Finlayson, who studies biomedical applications of machine learning at Harvard Medical School. He notes that data sets on which AI is trained can be biased in ways that developers fail to consider. An image taken in an emergency room or one taken in the middle of the night may be more likely to show a sick person than one taken during a routine examination, for instance. An algorithm could also learn to look at scars or medical device implants that indicate a previous health problem and decide that people without these marks did not have the condition. Even the way that institutions label their images can confuse an AI algorithm and prevent the model from functioning well in another institution with a different labeling system. “If you naively train [an algorithm] at a hospital from one location, one time, and one population group, you’re unaware of all the thousands of little factors that models are taking into account. If any of those change, you can be in for a world of hurt,” Finlayson warns.

The solution, Finlayson says, is to train an algorithm with data from many locations and in diverse patient populations, then test it prospectively—without any modifications—in a new patient population. But very few algorithms have been tested this way. According to Topol’s recent *Nature Medicine* review, among dozens of studies claiming an AI performs better than radiologists, only a handful were tested in populations that were different from the population where they were developed. “Algorithms are very, very delicate,” says Cynthia Rudin, a computer scientist at Duke University. “If you try to use one outside the training set [of images], it doesn’t always work.”

As researchers become aware of this problem, more prospective studies in novel settings could be on the horizon. Barzilay’s team recently finished testing its mammogram AI on 10,000 scans from the Karolinska Institute in Sweden and found that it performed just as well there as it did in Massachusetts. The group is now working with hospitals in Taiwan and Detroit to test it in more diverse patient groups. The team found that current standards for assessing breast cancer risk are much less accurate in African-American women, Barzilay says, because those standards were developed mostly using scans from white women: “I think we really are in a position to revamp this sad state of affairs.”

LEGAL TERRA INCOGNITA

EVEN IF THE AI’S conclusions are medically relevant, the black box still presents a number of concerns from a legal perspective. If an AI gets a diagnosis wrong, it can be hard to determine whether the doctor or the program is at fault. “Lots of bad things happen in health care, and you don’t necessarily know why the bad things happened,” says Nicholson Price, a health law expert at the University of Michigan. If an AI system leads a physician to make an incorrect diagnosis, the physician may not be able to explain why and the company’s data on the test’s methodology are likely to be a closely guarded trade secret.

Medical AI systems are still too new to have been challenged in medical malpractice lawsuits, so it is unclear how courts will determine responsibility and what kind of transparency should be required.

The tendency to build black box algorithms frustrates Rudin. The problem comes from the fact that most medical algorithms are built by adapting deep-learning tools developed for other types of image analysis. “There’s no reason you can’t build a robot that can explain itself,” she insists. But it is exponentially harder to build a transparent algorithm from scratch than to repurpose an existing black box algorithm to look at medical data. That is why Rudin suspects most researchers let an algorithm run and then try to understand later how it came to its conclusion.

Rudin is developing transparent AI algorithms that analyze mammograms for suspected tumors and constantly inform researchers what they are doing. But her research has been stymied by the lack of available images on which to train the algorithm. The images that are publicly available tend to be poorly labeled or taken with old machines that are no longer in use, Rudin says, and without enormous, diverse data sets, algorithms tend to pick up confounding factors.

Black boxes, along with an AI algorithm’s ability to learn from experience, also present challenges to regulators. Unlike a drug, which will always work in the same way, machine-learning algorithms change and improve over time as they gain access to more patient data. Because the algorithm draws meaning from so many kinds of input, seemingly innocuous changes such as a new IT system at a hospital could suddenly ruin the AI program. “Machines can get sick just like humans get sick, and they can be in-

> **"You can't trust an algorithm when someone's life is on the line." —*Eric Topol, Scripps Research***

fected with malware," Topol says. "You can't trust an algorithm when you have someone's life on the line."

Last April the FDA proposed a set of guidelines to manage algorithms that evolve over time. Among them is an expectation that producers keep an eye on how their algorithms are changing to ensure they continue to work as designed and asking them to notify the agency if they see unexpected changes that might prompt reevaluation. The agency is also developing best manufacturing practices and may require companies to spell out their expectations for how algorithms might change and a protocol for how to manage those changes. "We need to understand that not one size fits all," says Bakul Patel, director of digital health at the FDA.

WILL MACHINES REPLACE DOCTORS?

THE LIMITATIONS OF AI should reassure radiologists who worry about machines taking their jobs. In 2012 technology venture capitalist and Sun Microsystems co-founder Vinod Khosla horrified a medical audience by predicting that algorithms would replace 80 percent of doctors, and more recently he claimed that radiologists still practicing in 10 years will be "killing patients." Such remarks caused panic and backlash in the radiology field, Rao says. "I think the hype is creating a lot of expectations."

But that concern has also had real impacts. In 2015 only 86 percent of radiology resident positions in the U.S. were filled, compared with 94 percent the previous year, although those numbers have improved over the past several years. And according to a 2018 survey of 322 Canadian medical students, 68 percent believed AI would reduce the demand for radiologists.

Still, most experts and AI manufacturers doubt AI will be replacing doctors any time soon. "AI solutions are becoming very good at doing one thing very well," Walach says. But because human biology is complex, he says, "you typically have to have humans who do more than one thing really well." In other words, even if an algorithm is better at diagnosing a particular problem, combining it with a physician's experience and knowledge of the patient's individual story will lead to a better outcome.

An AI that can do a single task well could free radiologists from drudgework, allowing them more time to interact with patients. "They could come out of the basement, which is where they live in the dark," Topol says. "What we need in medicine is more interhuman contact and bonding."

Still, Rao and others believe that the tools and training that radiologists receive, including their day-to-day work, will change drastically over the coming years as a result of artificial-intelligence algorithms. "AI won't replace radiologists, but radiologists who use AI will replace radiologists who don't," says Curtis Langlotz, a radiologist at Stanford.

There are some exceptions, however. In 2018 the FDA approved the first algorithm that can make a medical decision without the need for a physician to look at the image. The program, developed by IDx Technology in Coralville, Iowa, looks at retinal images to detect diabetic retinopathy and is 87 percent accurate, according to the company's data. IDx chief executive officer Michael Abramoff says that because no doctor is involved, the company has assumed legal liability for any medical errors.

In the short term, AI algorithms are more likely to assist doctors than replace them. For instance, physicians working in developing countries might not have access to the same kinds of scanners as a major medical institution in the U.S. or Europe or trained radiologists who can interpret scans. As medicine becomes more specialized and dependent on image analysis, the gap between the standard of care provided in wealthier and poorer areas is growing, Lungren says. Running an algorithm can be a cheap way to close that gap and may even be done on a mobile phone.

Lungren's group is developing a tool that allows doctors to take cell-phone pictures of an x-ray film—not the digital scans that are standard in wealthy nations—and run an algorithm on the photographs that detects problems such as tuberculosis. "It's not replacing anybody," he says—many developing countries have no radiologists in the first place. "We're augmenting nonradiologists to bring expertise to their fingertips."

Another short-term goal of AI could be to examine medical records to determine whether a patient needs a scan in the first place, Rao says. Many medical economists believe that imaging is overused—more than 80 million CT scans are performed every year in the U.S. alone. Although this abundance of data is helpful to researchers using it to train algorithms, scans are extraordinarily costly and can expose patients to unnecessary amounts of radiation. Similarly, Langlotz adds that algorithms could one day analyze images while a patient is still in the scanner and predict the final outcome, thus reducing the amount of time and radiation exposure required to get a good image.

Ultimately, Barzilay says, AI will be most useful when it serves as a sharp-eyed partner in tackling problems that doctors cannot detect and solve alone. "If there were a convenient and describable pattern," she notes, "humans would already be able to do it." She knows firsthand that, too often, this is not the case.

Sara Reardon is a freelance journalist based in Bozeman, Mont. She is a former staff reporter at *Nature*, *New Scientist* and *Science* and has a master's degree in molecular biology.

Can AI Fix Medical Records?

Digitized patient charts were supposed to revolutionize medical practice. Artificial intelligence could help unlock their potential

By Cassandra Willyard

A YOUNG MAN, let's call him Roger, arrives at the emergency department complaining of belly pain and nausea. A physical exam reveals that the pain is focused in the lower right portion of his abdomen. The doctor worries that it could be appendicitis. But by the time the imaging results come back, Roger is feeling better, and the scan shows that his appendix appears normal. The doctor turns to the computer to prescribe two medications, one for nausea and Tylenol for pain, before discharging him.

This is one of the fictitious scenarios presented to 55 physicians around the country as part of a study to look at the usability of electronic health records (EHRs). To prescribe medications, a doctor has to locate them in the EHR system. At one hospital a simple search for Tylenol brings up a list of more than 80 options. Roger is a 26-year-old man, but the list includes Tylenol for children and infants, as well as Tylenol for menstrual cramps. The doctor tries to winnow the list by typing the desired dose—500 milligrams—into the search window, but now she gets zero hits. So she returns to the main list and finally selects the 68th option—Tylenol Extra Strength (500 mg), the most commonly prescribed dose of Tylenol. What should have been a simple task has taken precious minutes and far more brainpower than it deserved. This is just one example of the countless agonizing frustrations that physicians deal with every day when they use EHRs.

These EHRs—digital versions of the paper charts in which doctors used to record patients' visits, laboratory results and other important medical information—were supposed to transform the practice of medicine. The Health Information Technology for Economic and Clinical Health (HITECH) Act, passed in 2009, has provided $36 billion in financial incentives to drive hospitals and clinics to transition from paper charts to EHRs. Then president Barack Obama said the shift would "cut waste, eliminate red tape and reduce the need to repeat expensive medical tests." He added that it would "save lives by reducing the deadly but preventable medical errors that pervade our health care system."

When HITECH was adopted, 48 percent of physicians used EHRs. By 2017 that number had climbed to 85 percent, but the transformative power of EHRs has yet to be realized. Physicians complain about clunky interfaces and time-consuming data entry. Polls suggest that they spend more time interacting with a patient's file than with the actual patient. As a result, burnout is on the rise. Even Obama observed that the rollout did not go as planned. "It's proven to be harder than we expected," he told Vox in 2017.

Yet EHRs do have the potential to deliver insights and efficiencies, according to physicians and data scientists. Artificial intelligence in the form of machine learning—which allows computers to identify patterns in data and draw conclusions on their own—might be able to help overcome the obstacles encountered with EHRs and unlock their potential for making predictions and improving patient care.

DIGITAL DEBACLE

IN 2016 the American Medical Association teamed up with MedStar Health, a health care organization that operates 10 hospitals in the Baltimore-Washington area, to examine the usability of two of the largest EHR systems, developed by Cerner, based in North Kansas City, Mo., and Epic, based in Verona, Wis., respectively. Together these two companies account for 54 percent of the acute care hospital market. The team recruited emergency physicians at four hospitals and gave them fictitious patient data and six scenarios, including the one about Roger, who presented with what seemed like appendicitis. These scenarios asked the physicians to perform common duties such as prescribing medications and ordering tests. The researchers assessed how long it took the physicians to complete each task, how many clicks were required and how accurately they performed.

What they found was disheartening. The time and the number of clicks required varied widely from site to site and even between sites using the same system. And some tasks, such as tapering the dose of a steroid, proved exceptionally tricky across the board. Physicians had to manually calculate the taper doses, which took anywhere from two to three minutes and required 20 to 42 clicks. These design flaws were not benign. The physicians often made dosage mistakes. At one site the error rate reached 50 percent. "We've seen patients being harmed and even patients dying because of errors or issues that arise from usability of the system," says Raj Ratwani, director of MedStar Health's National Center for Human Factors in Healthcare.

But clunky interfaces are just part of the problem with EHRs. Another stumbling block is that information still does not flow easily between providers. The system lacks "the ability to seamlessly and automatically deliver data when and where it is needed under a trusted network without political, technical, or financial blocking," according to a 2018 report from the National Academy of Medicine. If a patient changes doctors, visits urgent care or moves across the country, her records might or might not follow. "Connected care is the goal; disconnected care is the reality," the authors wrote.

In March 2018 the Harris Poll conducted an online survey on behalf of Stanford Medicine that examined physicians' attitudes about EHRs. The results were sobering. Doctors reported spending, on average, about half an hour on each patient. More than 60 percent of that time was spent interacting with the patient's EHR. Half of office-based primary care physicians think using an EHR actually diminishes their clinical effectiveness. Isaac Kohane, a computer scientist and chair of the department of biomedical informatics at Harvard Medical School, puts it bluntly: "Medical records suck."

Yet despite the considerable drawbacks of existing EHR systems, most physicians agree that electronic records are a vast improvement over paper charts. Getting patients' data digitized means that they are now accessible for analysis using the power of AI. "There's huge potential to use artificial intelligence and machine learning to develop predictive models and better understand health outcomes," Ratwani says. "I think that's absolutely the future."

It is already happening to some extent. In 2015 Epic began offering its clients machine-learning models. To develop these models, computer scientists start with algorithms and train them using real-world examples with known outcomes. For example, if the goal is to predict which

“Health data is like crude oil. It is useless unless it is refined.” *—Leo Anthony Celi, M.I.T. Laboratory for Computational Physiology*

patients are at greatest risk of developing the life-threatening blood condition known as sepsis, which is caused by infection, the algorithm might incorporate data routinely collected in the intensive care unit, such as blood pressure, pulse and temperature. The better the data, the better the model will perform.

Epic now has a library of models that its customers can purchase. “We have over 300 organizations either running or implementing models from the library today,” says Seth Hain, director of analytics and machine learning at Epic. The company’s sepsis-prediction model, which scans patients’ information every 15 minutes and monitors more than 80 variables, is one of its most popular. The North Oaks Health System in Hammond, La., implemented the model in 2017. If a patient’s score reaches a certain threshold, the physicians receive a warning, which signals them to monitor the patient more closely and provide antibiotics if needed. Since the health system implemented the model, mortality caused by sepsis has fallen by 18 percent.

But building and implementing these kinds of models is trickier than it might first appear. Most rely solely on an EHR’s structured data—data that are collected and formatted in the same way. Those data might consist of a blood-pressure reading, lab results, a diagnosis or a drug allergy. But EHRs include a wide variety of unstructured data, too, such as a clinician’s notes about a visit, e-mails and x-ray images. “There is information there, but it’s really hard for a computer to extract it,” says Finale Doshi-Velez, a computer scientist at Harvard University. Ignoring this free text means losing valuable information, such as whether the patient has improved. “There isn’t really a code for doing better,” she says. Moreover, Ratwani points out that because of poor usability, data often end up in the wrong spot. For example, a strawberry allergy might end up documented in the clinical notes rather than being listed in the allergies box. In such cases, a model that looks for allergies only in the allergy section of the EHR “is built off of inaccurate data,” he adds. “That is probably one of the biggest challenges we’re facing right now.”

Leo Anthony Celi, an intensive care specialist and clinical research director at the Massachusetts Institute of Technology’s Laboratory for Computational Physiology, agrees. Most of the data found in EHRs are not ready to be fed into an algorithm. A massive amount of curation has to occur first. For example, say you want to design an algorithm to help patients in the intensive care unit avoid low blood glucose, a common problem. That sounds straightforward, Celi says. But it turns out that blood sugar is measured in different ways, with blood drawn from either a finger prick or a vein. Insulin is administered in different ways, too. When Celi and his colleagues examined all the data on insulin and blood sugar from patients at one hospital, “there were literally thousands of different ways they were entered in the EHR.” These data have to be manually sorted and clustered by type before one can even design an algorithm. “Health data is like crude oil,” Celi says. “It is useless unless it is refined.”

AN INTELLIGENT FIX

THE CURRENT PITFALLS of EHRs hamper efforts to use artificial intelligence to glean important insights, but AI might itself provide a possible solution. One of the main drawbacks of the existing EHR systems, doctors say, is the time it takes to document a visit—everything from the patient’s complaint to the physician’s analysis and recommendation. Many physicians believe that much of the therapeutic value of a doctor visit is in the interactions, Kohane says. But EHRs have “literally taken the doctor from facing the patient to facing the computer.” Doctors have to type up their narrative of the visit, but they also enter much of the same information when they order lab tests, prescribe medications and enter billing codes, says Paul Brient, chief product officer at athenahealth, another EHR vendor. This kind of duplicate work contributes to physician frustration and burnout.

As a stopgap measure, some hospitals now have scribes sit in on appointments to document the visit while the physician interacts with the patient. But several companies are working on digital scribes, machine-learning algorithms that can take a conversation between a doctor and a patient, parse the text and use it to fill in the relevant information in the patient’s EHR.

Indeed, some such systems are already available. In 2017 Saykara, a Seattle-based start-up, launched a virtual assistant named Kara. The iOS app uses machine learning, voice recognition and language processing to capture conversations between patients and physicians and turn them into notes, diagnoses and orders in the EHR. Previous versions of the app required prompts from the physician—much like Apple’s Siri—but the current version can be put in “ambient mode,” in which it simply listens to the entire conservation and then selects the relevant information. EHRs turned physicians into data-entry clerks, Kohane says. But apps like Kara could serve as intelligent, knowledgeable co-workers. And Saykara is just one of a host of start-ups developing such tools. Athenahealth’s latest mobile app allows physicians to dictate their documentation. The app then translates that text into the appropriate billing and diagnostic codes. But “it’s not perfect by any stretch of the imagination,” Brient says. The physician still has to check for errors. The app does reduce the workload, however. The systems that Robert Wachter, chair of the department of medicine at the University of California, San Francisco, has seen are “probably not quite ready for prime time,” he says, but they should be in a couple of years.

Artificial intelligence might also help clinicians make better, more sophisticated decisions. “We think of the decision support in a computer system as an alert,” says Jacob Reider, a physician and CEO at Alliance for Better Health, a New York–based health care system that works to improve the health of communities. That alert might be a box that pops up to warn of a drug allergy. But a more sophisticated system might list the likelihood of a side effect with drug option A versus drug option B and provide a cost comparison. From a technological standpoint, developing such a feature is “no different from Amazon putting an advertisement or making you aware of a purchasing opportunity,” he says.

Wachter sees at least one encouraging sign that progress is coming. In the past few years the behemoths of the tech world—Google, Amazon, Microsoft—have developed a strong interest in health care. Google, for example, partnered with researchers from U.C.S.F., Stanford University and the University of Chicago to develop models aimed at predicting events relevant to hospitalized patients, such as mortality and unexpected readmission.

To deal with the messy data problem, the researchers first translated data from two EHR systems into a standardized format called Fast Healthcare Interoperability Resources, or FHIR (pronounced "fire"). Then, rather than hand-selecting a set of variables such as blood pressure and heart rate, they had the model read patients' entire charts as they unfolded over time up until the point of hospitalization. The data unspooled into a total of 46,864,534,945 data points, including clinical notes. "What's interesting about that approach is every single prediction uses the exact same data to make the prediction," says Alvin Rajkomar, a physician and AI researcher at Google who led the effort. That element both simplifies data entry and enhances performance.

But the involvement of massive corporations also raises serious privacy concerns. In mid-November 2019 the *Wall Street Journal* reported that Google, through a partnership with Ascension, the country's second-largest health care system, had gained access to the records of tens of millions of people without their knowledge or consent. The company planned to use the data to develop machine-learning tools to make it easier for doctors to access patient data.

This type of data sharing is not unprecedented or illegal. Tariq Shaukat, Google Cloud's president of industry products and solutions, wrote that the data "cannot be used for any other purpose than for providing these services we're offering under the agreement, and patient data cannot and will not be combined with any Google consumer data." But those assurances did not stop the Department of Health and Human Services from opening an inquiry to determine whether Google/Ascension complied with Health Insurance Portability and Accountability Act regulations. As of press time, the inquiry was ongoing.

But privacy concerns should not halt the quest for better, smarter, more responsive electronic health records, according to Reider. There are ways to develop these systems that maintain privacy and security, he says.

Ultimately real transformation of medical practice may require an entirely new kind of EHR, one that is not simply a digital file folder. All the major EHRs are built on top of database-type architecture that is 20 to 30 years old, Reider observes. "It's rows and columns of information." He likens these systems to the software used to record inventory at a brick-and-mortar bookstore: "It would know which books it bought, and it would know which books it sold." Now envision how Amazon uses algorithms to predict what a customer might buy tomorrow and to anticipate demand. "They've engineered their systems so that they can learn in this way, and then they can autonomously take action," Reider says. Health care needs the same kind of transformative leap.

Cassandra Willyard is a science writer based in Madison, Wis.

Wiring Minds

Successfully applying AI to biomedicine requires innovators trained in contrasting cultures

By Amit Kaushal and Russ B. Altman

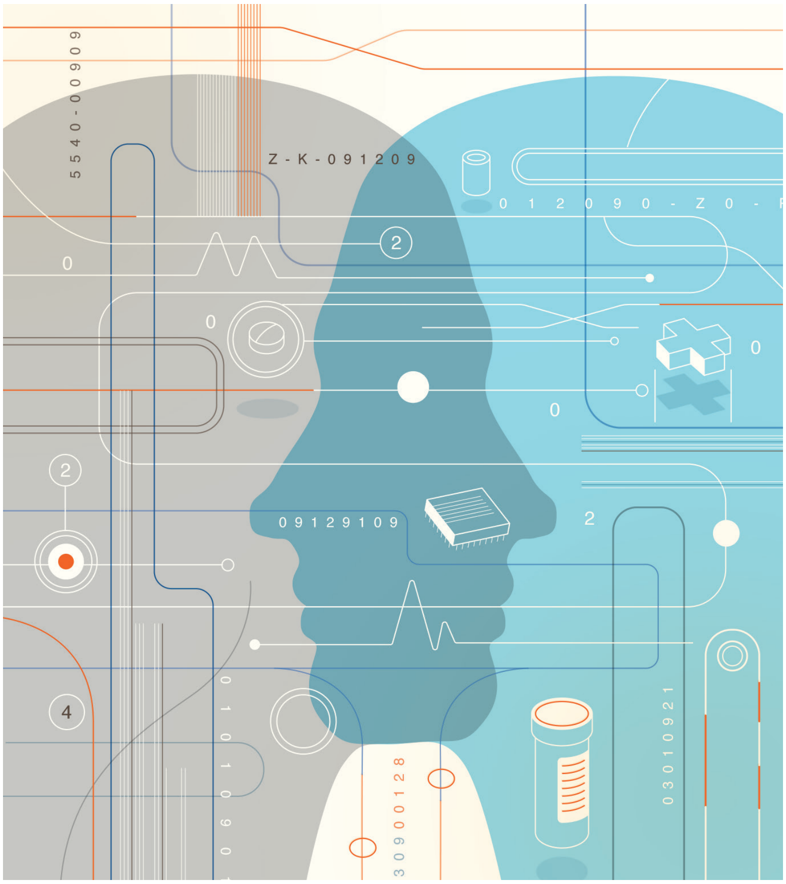
From the popular press to the largest health care conferences, promises of artificial intelligence revolutionizing biomedicine are ubiquitous. It often seems as if we are on the cusp of AI systems that can remotely identify a person about to get sick, make a diagnosis (no doctor needed!), select a custom AI-designed pharmaceutical and deliver it to the patient just in time—in an AI-powered self-driving car, of course.

If indeed this is the future, we are far from reaching it. To be sure, the pace of change has been rapid. Deep learning—the fast-growing subfield of AI that enables machines to diagnose pneumonia from chest x-rays or predict health deterioration from medical records—was unfamiliar even to most computer scientists a decade ago. And we do not know what evolutionary or revolutionary advances will drive AI in the coming decades. What we do know is that the success of biomedical AI depends not just on developing the technology but also on developing the people behind it.

Translating algorithmic advances to biomedical breakthroughs requires critically considering both realms of knowledge and endeavor on many levels. What, for example, are the true capabilities of a new technology, and what is simply hype? What problems in biomedicine are most likely to benefit from emerging computational capabilities? And how do we go from an interesting biomedical application of a new technology to the implementation of systems that actually improve human health? These challenging, multifaceted questions will need to be answered by interdisciplinary teams. The teams will require experts in AI, experts in biology and medicine, and, most important, leaders who can motivate and guide individuals with such diverse talents.

Unlike some domains in which AI has been applied, in biomedicine the consequences of failure are weighty. For a social media company, an AI model that is ineffective at increasing ad clicks can be detected and rolled back the same day. When it comes to medicine, however, human lives are at stake. Inadequately informed uses of AI can lead to obvious harm, such as inaccurate diagnostic or therapeutic recommendations, but also to more insidious failures, such as an algorithm that gives racially biased recommendations because it was trained with subtly biased data. Given the complexities of biomedicine and the inscrutable nature of many AI algorithms, it might be years before such a flaw is uncovered. Group leaders—whether in academia, pharmaceutical laboratories or start-ups—must not only understand the technical and scientific issues but also anticipate and articulate the potential risks, benefits and implications of the projects they undertake.

We need men and women who can build AI systems in med-



icine that improve care. It is relatively easy to generate excitement by solving the technical aspects of a problem, but making those advances useful often involves wrestling with the complex interplay of regulatory, economic and workflow issues in health care systems. Successful leaders benefit from deep knowledge and intuition in both the AI and the biomedical domains. But we face a critical shortage of such versatile individuals.

Tackling this gap is crucial to ensuring the long-term success of biomedical AI. A primary challenge is the length of study required in these disciplines, but a greater one is training students in two realms that could hardly be more different in their approaches to problem-solving. Computer science involves the quantitative rigor of mathematics, statistics and engineering, whereas biology is underpinned by the haphazard products of evolution. Properties of living things are, literally and figuratively, organic. We seek students with the intellectual flexibility and passion to undergo lengthy training in both these contrasting cultures. Are we asking for the impossible?

These individuals do exist, and their numbers are growing. The first approach to their training is to identify individuals who already have a deep background in either biomedical or computational science and then help them become skilled in the other area. Graduate programs (M.S., Ph.D. and M.D./Ph.D.) in biomedical informatics have filled this role since the early 1980s. These programs attract diverse students and have grown to include disciplines that go by various names: computational biology, bioinformatics, clinical informatics, biomedical data science, and so on. All are concerned with different applications of computer science to biomedicine.

But what about training students at the intersection of these disciplines even earlier in their careers—while their intellectual intuitions are still forming? The difference would be like that between learning a second language as an adult and growing up in a bilingual household: fluency is second nature for early starters.

In 2001 we launched an engineering major at Stanford University to enable undergraduates to learn computer science and statistics in the context of biology and medicine. The program creates graduates with a bachelor of science degree who have already wrestled intensively with the challenges of applying computational tools to hard problems in biomedicine. Our students take biology with premedical students and computer science with classmates who will work in Silicon Valley, and each completes a two- or three-quarter-long research project during his or her time at Stanford. They acquire knowledge with breadth across the biomedical and technical fields and depth in a narrower application area. At least one course on the societal and ethical implications of technology is also required.

After almost two decades of training biomedical-computation undergraduates, we can say that the model works. Many of our graduates have gone on to careers in academia, clinical medicine, start-up companies (both in and outside of the biology field), large companies, law firms, venture capital, and elsewhere. And the major has consistently drawn a 50–50 balance of men and women—true for only a minority of quantitatively intensive engineering majors.

For most, the major has shaped their professional identity: they are not “AI people doing bio” or “Bio people doing AI.” Instead both of these intellectual traditions reside comfortably within their minds, each informing their understanding of the other. Whereas it is impossible to learn the entirety of biomedicine and computer science in just four years (or even in 40), these people move freely between the cultures of biology and computer science and have already learned to apply deep technical skills to the hardest societal challenges in biology and human health.

In addition to graduate programs, the development of a robust set of undergraduate programs at the interface of biomedicine and computation could give students who are in a formative period of their education the ability to move fluidly between these very different disciplines. Such programs would accelerate the emergence of the workforce required for appropriate use of AI to advance biology and health care.

Amit Kaushal is a clinical assistant professor of medicine and an adjunct professor of bioengineering at Stanford University.

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SPECIAL REPORT FROM

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By Andrea Gawrylewski

Rufus Porter's Curious World: Art and Invention in America, 1815–1860

Edited by Laura Fecych Sprague and Justin Wolff. Pennsylvania State University Press, 2019 ($39.95). Exhibit: 12/12/19 to 5/31/20, Bowdoin College Museum of Art

In his obituary in this magazine, published on September 6, 1884, Rufus Porter is described as a "remarkable natural genius" who had a peculiar tendency to move quickly from one occupation and place to another. "Although he might be doing well at the business which for the time engaged his attention, he would sell out and abandon it the moment a new idea came into his mind," the writer remarked. "His brain was an overflowing fountain of new ideas and active projects."

Porter was a prolific inventor and is credited with dozens of inventions, including a flying ship, a portable camera obscura, a rotary plow, and more. He left many of his projects unfinished—this happened with a revolving almanac he was perfecting in 1823, when he quickly changed gears to work on a new kind of boat intended to traverse the Connecticut River. He made his primary living as an artist, painting portraits, landscapes and architecture.

In 1845 he published the first issue of *Scientific American,* which he ran for less than a year before moving on to his next occupation. Thankfully, this endeavor endured well beyond his lifetime. The image of our first issue is in this new collection of Porter's works and part of an exhibition alongside many of his portraits and illustrations of his inventions, housed at the Bowdoin College Museum of Art in Brunswick, Maine.

1. Plumb and level indicator, circa 1846, New York, N.Y.; hand-colored engraving, metal pointer, wood frame. By Rufus Porter, 1792–1884, designer; and unidentified engraver.
2. Rufus Porter, circa 1872; photographic print by an unidentified photographer.
3. Revolving almanack, circa 1841; framed engraving by Samuel Maverick (1789–1845), engraver, after Rufus Porter.
4. The first and other early issues of *Scientific American,* established in 1845.

PHOTOGRAPHY BY LUC DEMERS, BOWDOIN COLLEGE MUSEUM OF ART, BRUNSWICK, MAINE (1); COURTESY HOWARD W. AND JEAN LIPMAN PAPERS, ARCHIVES OF AMERICAN ART, SMITHSONIAN INSTITUTION (2); COURTESY AMERICAN ANTIQUARIAN SOCIETY (3); *SCIENTIFIC AMERICAN* (4)

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Macquarie University

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Professor of Medicine University of California Medical Center

Millie Hughes-Fulford was selected as a Scientist-Astronaut on the first Spacelab mission dedicated to biomedical studies in 1991 and has since continued her research into the mechanisms of cell growth and activation in spaceflight, winning an award from NASA in 2012 for discovering why the immune system is weakened in zero gravity.

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Emeritus Chair for SETI Research, SETI Institute

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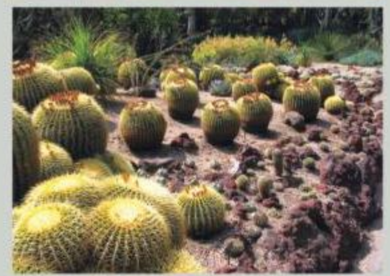

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OBSERVATORY
KEEPING AN EYE ON SCIENCE

Naomi Oreskes is a professor of the history of science at Harvard University. She is author of *Why Trust Science?* (Princeton University Press, 2019) and co-author of *Discerning Experts* (University of Chicago, 2019).

Let Them Eat Meat?

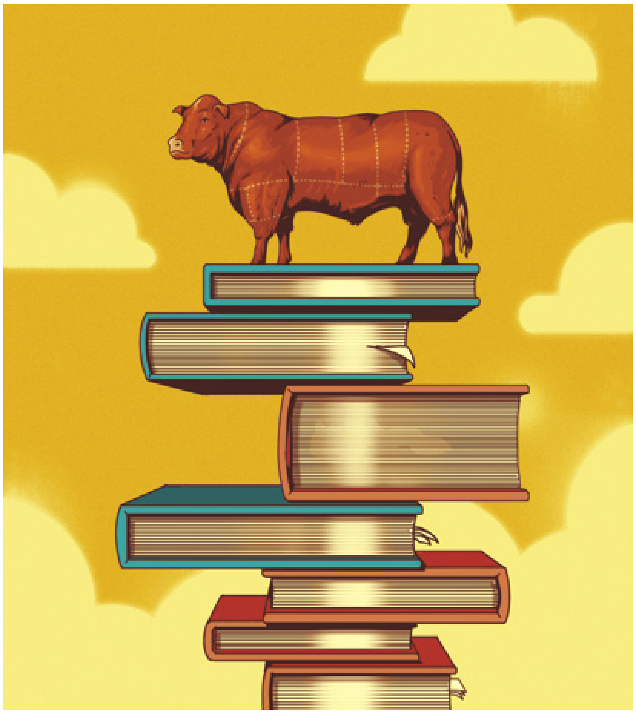
When journals behave irresponsibly, it can cause real harm

By Naomi Oreskes

Last October the Physicians Committee for Responsible Medicine, a nonprofit with 12,000 doctor members, asked Philadelphia's Office of the District Attorney to launch a reckless-endangerment investigation. The trigger for this extraordinary request was not a new attempt by the tobacco industry to sell cigarettes to children or by the petroleum industry to reintroduce lead into gasoline. It was a set of papers and proposed dietary guidelines, published in the *Annals of Internal Medicine,* suggesting it's fine for Americans to continue eating a diet rich in red and processed meats.

The guidelines set off a media frenzy, with dramatic headlines suggesting that conventional nutritional wisdom had been overturned. This response produced a counterreaction, with various experts and public health organizations slamming the guidelines. Walter Willett, a Harvard professor of epidemiology and nutrition, called them "the most egregious abuse of data I've ever seen."

Critics pointed out numerous flaws with the *Annals* publications. Most conspicuously, the authors had used a review methodology that valorizes randomized clinical trials (RCTs). But it is famously difficult to do RCTs for nutrition, so by choosing this particular assessment tool, the investigators excluded most of the benchmark studies on red meat and health. And we soon learned that some of them had undisclosed ties to the food industry. In particular, the lead author was senior author on a similar study in 2016 that challenged the advice to eat less sugar. That paper, which also appeared in the *Annals of Internal Medicine,* was paid for by the International Life Sciences Institute, an industry group founded by a Coca-Cola executive and notorious for its repeated attempts to challenge international health guidelines.



More to the point, the "red meat is fine" message flies in the face of a large and well-established body of evidence from epidemiological cohort studies, randomized trials with established risk factors as outcomes and animal studies. People (and lab animals) whose diets are high in red and processed meats are more likely to suffer and die from type 2 diabetes, cardiovascular disease, respiratory ailments, neurodegenerative diseases and cancer than those whose diets are less meat-laden. One study of tens of thousands of men and women followed for an average of 26 years showed that every extra daily serving of red meat was associated with a 13 percent higher risk of death from all causes. Eating processed red meat increased that number to 20 percent. Given what the literature has shown about meat, more than a dozen experts asked the *Annals* to retract the papers. Some suggested they should never have been published in the first place.

If science is to be open to new evidence and ideas, sometimes bad or even reckless studies will be published. But the *Annals* did two troubling things. First, it did not just publish a set of research papers on nutrition; it published a set of *guidelines*. Moreover, the authors said, "We suggest continuing current unprocessed red meat consumption (weak recommendation, low-certainty evidence).... [And] we suggest continuing current processed meat consumption (weak recommendation, low-certainty evidence)."

This is astonishing: a group of scientists, critiquing existing nutritional studies for their (alleged) lack of methodological rigor, offered radically contrary and potentially dangerous guidance based on low-certainty evidence! Further, the *Annals* did not simply *publish* the guidelines. It *promoted* them with an accompanying editorial and a press package that began with an unqualified headline—"No need to reduce red or processed meat consumption for good health"—and ended with a statement that, within 24 hours, had been credibly challenged: "Those that seek to dispute the ... findings will be hard-pressed finding appropriate evidence with which to build an argument."

We live in a world where industries exaggerate scientific uncertainty and promote outlier views as a means to defend dangerous products and activities. In this context, it behooves journals to exercise caution when publishing controversial findings and not to take sides. There is enough sound and fury in the popular press to confuse us all. The last thing we need is for scientific journals to contribute to the cacophony.

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Illustration by Glenn Harvey

Steve Mirsky has been writing the Anti Gravity column since a typical tectonic plate was about 36 inches from its current location. He also hosts the *Scientific American* podcast Science Talk.

Light Blight

Too much illumination is killing vital insects

By Steve Mirsky

For many years we've been hearing about a so-called War on Christmas. And for centuries we've heard that the meek shall inherit the earth. But what we haven't heard a lot about is that for decades Christmas has been waging a war on the meek. I'm talking, of course, about decorative lights and insects.

Outdoor lighting in general poses a deadly threat to insects. That's according to a study published online in November 2019 in the journal *Biological Conservation,* entitled "Light Pollution Is a Driver of Insect Declines."

The article notes that steep drops in insect numbers around the world have happened over the past couple of decades in what amounts to an "insect apocalypse." The blame is usually assigned to "habitat loss, chemical pollution (especially pesticide use), invasive species, and climate change." But the authors contend that the forces of lightness have not gotten their due. And they cite what they call "diurnal bias."

The allegorically intoxicated man famously searches for his lost wallet under the streetlight where he can see better. Conversely, so may exist "a preference among ecologists for studying daytime phenomena"—diurnal bias. When would you rather count bugs, after a nice breakfast or four hours before breakfast when you can barely see your hand in front of your bleary eyes?

The research team thus asserts that a preference for sleeping at night "has led insect conservationists to overlook another widespread habitat disturbance, pollutant, and method of insect control: artificial light at night (ALAN)."

ALAN's iniquitous influence occurs "through its interference with the development, movement, foraging, and reproductive success of diverse insect species." Another factor is light's "positive effect on insectivore predation." That is, birds, bats, amphibians and arachnids aren't stupid—if a lot of insects start swirling around lights in the night, predators will also show up. The result is a big buggy banquet of hefty hexapodal helpings that precipitates a plummeting in part of the Pancrustacea population.

Sadly, ALAN spikes sharply after Thanksgiving, as many people add festive illumination to the exterior of their houses to celebrate the approach of Christmas. As you read these words in early 2020, stubbornly bedecked houses may still be sucking electricity out of the grid at unusually high rates.

Many neighborhoods, mine included, have a particular house that embraces the spirit of the season in such an outsized way as to produce a radiant haze perhaps visible to exoplanet hunters in other star systems. (For an example, search online using the term "Griswold electricity meters.") The massive carnage to insects is accompanied by lines of slow-moving cars belching noxious gases in front of the home, just to catch a glimpse of the outward manifestation of the family's deep-rooted obsession.

The task then must be to lessen "the ecological consequences of ALAN on insects while still maintaining sufficient levels of nighttime illumination for human safety and enjoyment," the researchers write. Fortunately, their study offers some solutions to this existential pestilential crisis.

The first is of the category in which one both possesses a pastry and partakes of it as well: "Monochromatic LEDs can be engineered to produce light of any desired spectral composition," the investigators write. "Therefore, once we know the specific wavelength affinities of insects, we can in theory design lights with minimal output in the wavelengths that most affect insect fitness."

The second is astonishingly ingenious: turn some of the lights off. (One must wonder if a paradoxical and figurative lightbulb came on above the scientists' heads when they came up with the idea of turning the lights off.) "In many cases," they write, "it is far easier, quicker, and cheaper to shield, dim, or turn off a light source than it is to find the particular bulb type or narrow bandpass filter that makes its emissions visible to humans alone." Help end the war on insects. It is better to blow out one candle than to curse the planet. SA

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Illustration by Matt Collins

50, 100 & 150 YEARS AGO

INNOVATION AND DISCOVERY AS CHRONICLED IN *SCIENTIFIC AMERICAN*

Compiled by Daniel C. Schlenoff

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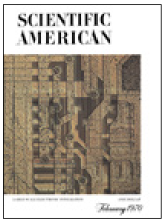
FEBRUARY

1970 Era of Microelectronics

"Since the introduction of the transistor in 1948—which in its day seemed a marvel of compactness compared with the glass vacuum tube—the size of electronic devices has been reduced by a factor of 10 roughly every five years. A great part of the stimulus for miniaturizing electronic circuits came from ballistic-missile programs. As the microtechnology was developed, however, it was speedily applied to commercial computers. It now seems inevitable that microelectronic circuits will soon find their way into a variety of new applications whose impact on everyday life—in the home, in the office, in the school and on the highway—will be profound."

1920 First Rocket Man

"Dr. Robert H. Goddard of Clark University, in an account of apparatus invented by him for the purpose of exploring the extreme upper strata of the atmosphere, mentioned casually the possibility of giving this apparatus sufficient driving power to carry it to the distance of the moon. In conformance with the purposes which impelled him to make this investigation, Dr. Goddard, the first time he sends this little messenger aloft, will recover data of much meteorological value. But he will not shoot at the moon—somebody else will have to do that for now."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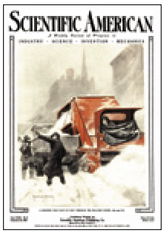
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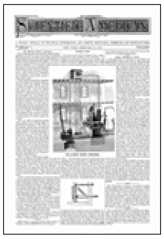

1870

1


1920: Harvesting natural river ice with a gasoline-powered saw.

Ice for Cooling

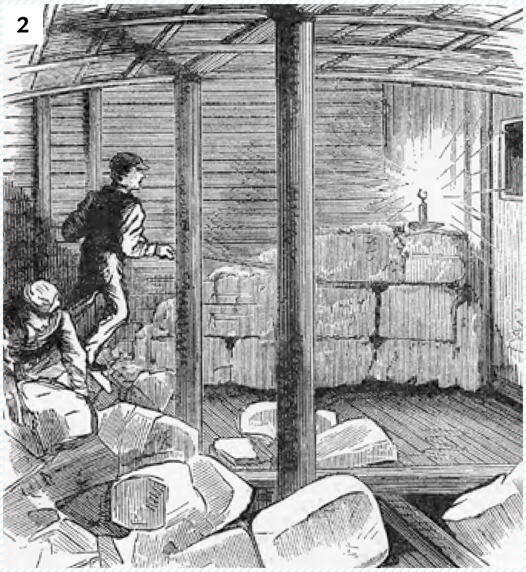
"In order to expedite the harvesting of natural ice, there has been introduced a gasoline-driven saw of the type shown. This saw consists of an automobile-type power plant and a circular saw. The saw is pushed along, the operator behind furnishing the motive power. The portable saw cuts the ice into 20-foot squares. These squares are guided through the water to a gang of four circular saws, which cuts them into the regulation sized cakes."

1870 Diving Engineers

"No operation in submarine engineering is more important or attended with greater personal risk than diving. This art has, however, been so far advanced, and apparatus for diving has been so far perfected, that divers now descend to depths of over one hundred feet. There are about thirty professional divers in the United States, and the annual mortality has been on the average about four of this number."

EPIC TALES

2



CELEBRATING 175 YEARS

Comfortably Cold

A comment from an 1848 issue still holds true: "Down to the present era … mankind has been incessantly in quest of refrigeratives." In the 19th century ice harvested during winter months kept food fresher at home and during shipping. Artificial cold, first demonstrated in 1756, remained complex and sometimes dangerous and was limited until the 20th century. By 1909 the average diet of "rural and urban, rich and poor, has undergone a great change in consequence of the practical application of cold." After 1928 the wonder chemical freon (not so wonderful: banned and replaced in 1987) allowed workable home refrigerators to displace the "icebox." Cold also helped manufacturing efficiency and human comfort. In a 1933 article Willis Carrier (you're probably familiar with his company) lauded "our new command of the conditions of the air which surrounds us." Cooling (or, in February, heating!) the air around us requires energy and increases carbon emissions. But improved technology will help decrease energy use and reduce the amount of food grown and thrown away worldwide.

Stacked blocks of ice onboard a steamship cool a cargo of fresh meat from New York to Liverpool, 1877.

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Digital health: Smartphone-based monitoring of multiple sclerosis using Floodlight

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In order to improve care for people with multiple sclerosis (MS), we need to understand more about their disease. The way we measure the impact of MS on daily life has remained relatively unchanged for decades and is heavily reliant on clinic visits that may only occur once or twice each year. Unfortunately, this paradigm fails to capture the subtle mental and physical changes, possibly reflecting MS disease worsening, that can occur between visits. With the emergence of digital health there is the potential for daily monitoring of disease activity and progression in MS using tools such as Floodlight, a smartphone-based digital assessment developed by Roche and Genentech. Floodlight could help people with MS and healthcare professionals to have a greater understanding of the disease, ultimately leading to improved patient care. Approaches such as Floodlight may kick-start the use of novel measures to help detect whether symptoms of a disease are worsening. Floodlight and other digital tools aim to support Roche's ability to develop medicines with smaller, more efficient, and more patient-centric trials.

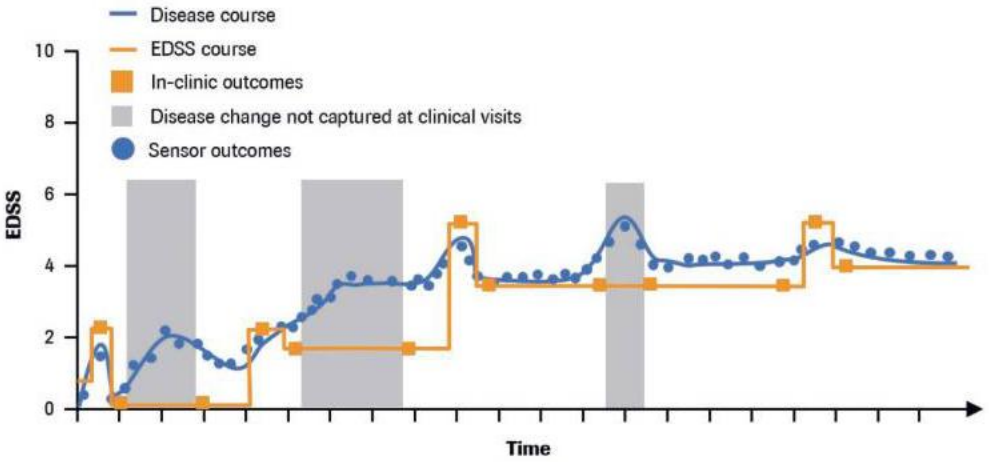

Figure 1. The disease course of multiple sclerosis (MS) is insidious and unpredictable. In-clinic assessments can detect some of the changes in MS, such as the Expanded Disability Status Scale (EDSS) score, which quantifies a person's disability level. However, some of these measures do not capture subtle changes in the MS disease course, and the infrequency of clinic visits means that many changes are missed. Digital sensor outcomes, such as smartphone-based applications, allow continuous real-time monitoring of MS to capture all of these changes, allowing the disease course to be monitored more accurately.

THE UNPREDICTABILITY OF LIVING WITH MS

MS is an incurable chronic disease in which the body's own immune system destroys tissue in the brain and spinal cord[1]. It affects 2.3 million people worldwide and is the leading cause of non-traumatic disability in young adults[2]. Symptoms may include visual disturbances, fatigue, pain, mobility problems and mental decline, although the specific disease course of MS is unpredictable and highly variable across individuals[3] (**Fig. 1**). Many people with MS experience permanent disability.

The negative consequences of MS can be life-changing. Notably, MS is primarily diagnosed in active young adults in their twenties and thirties[3], two-thirds of whom are women[4]. Put another way, MS has a substantial impact on people who have their whole lives ahead of them, who may be early on in their careers and making decisions about starting and raising families[1].

> SOMETIMES MY BODY AND ENERGY LEVELS FEEL LIKE AN OLD CELL PHONE BATTERY. I CAN CHARGE IT ALL NIGHT BUT RUN OUT OF ENERGY AND SHUT DOWN COMPLETELY AND UNEXPECTEDLY.
> FIRST-PERSON ACCOUNT OF A PERSON LIVING WITH MS

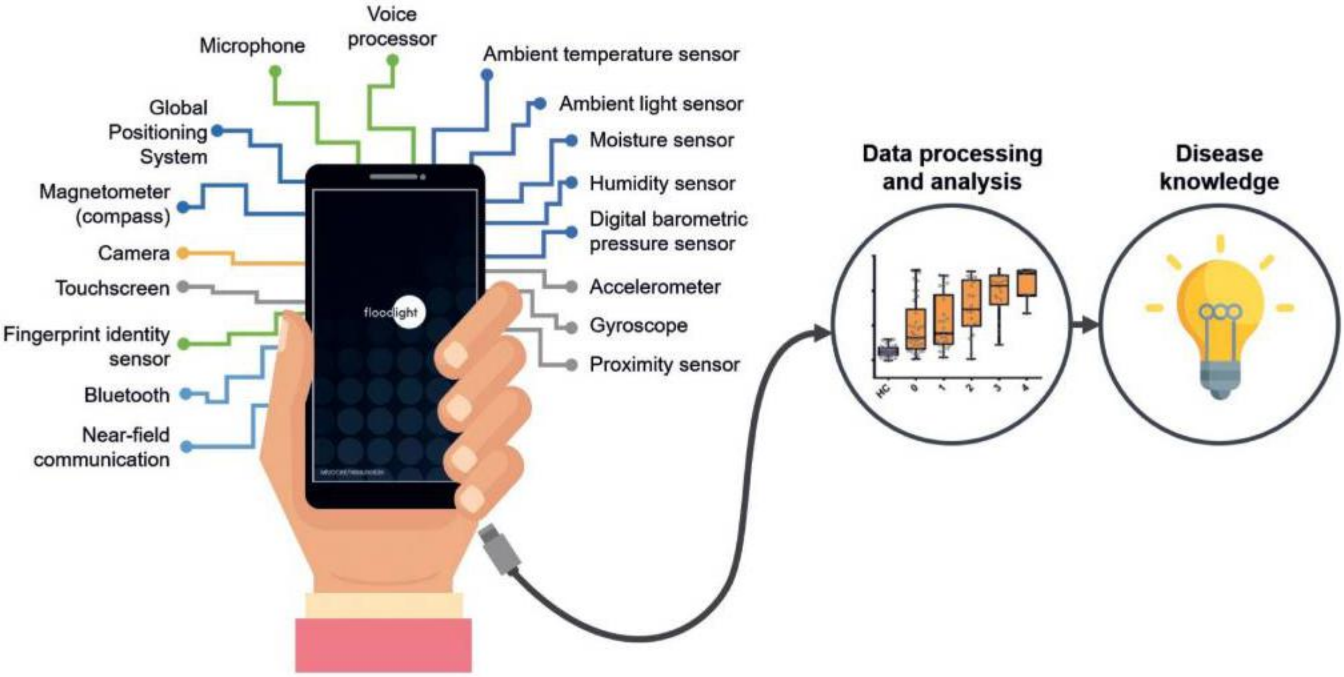

Figure 2. The potential of digital health is expanding because there have been many advances in smartphone technology combined with the ubiquity of personal devices. There is hope that one day a person's disease progression may be continuously monitored remotely[7].

> THE DIFFERENCE BETWEEN AN AMAZING VISIT AND A WASTED CO-PAY CAN BE AS SIMPLE AS MY PROVIDER CLARIFYING WHAT I JUST SAID: 'SO, LET'S GET THIS STRAIGHT, YOU'RE HAVING AN ISSUE WITH...'
> FIRST-PERSON ACCOUNT OF A PERSON LIVING WITH MS

CHALLENGES FACING THE CURRENT STANDARDS OF CARE IN MS

The main goal of a healthcare provider involved in treating a person with MS is to manage disease activity and reduce the risk of disability worsening in a way that is meaningful to that individual. A critical factor for achieving this goal is the ability to monitor MS symptoms and disability progression, which is difficult with the current standards of care: clinic visits may be infrequent, appointment times tend to be short, and examinations can vary between clinicians. Consequently, the more subtle changes in disease progression that may occur between visits are missed (**Fig. 1**). Moreover, the tools typically used to assess symptoms are often irrelevant to an individual's everyday life or impractical for routine assessment. For example, the Expanded Disability Status Scale (EDSS), which is a globally recognized assessment of disability in people with MS both in trials and clinical practice, is heavily focused on ambulation[5] and may not adequately capture many other important symptoms for patients, such as upper limb function and cognition. Another commonly used measure, the nine-hole peg test, assesses hand function by measuring how quickly a person can place into and then remove nine pegs from nine holes, one at a time[6]. Measures such as these do not directly assess tasks that might be considered important to people with MS, such as writing or ability to work, making it difficult to translate findings into meaningful care.

The consequence of these challenges is delayed recognition of disease activity by the healthcare professional; a delay can subsequently impact timely treatment decisions and, ultimately, lead to irreversible disability. Real-time digital monitoring of MS outside of the clinic has the potential to overcome such challenges. Efforts are already ongoing to develop tools for enhanced monitoring of MS, and with the evolution of both mobile technology[7] and wearable biosensors[8], digital health tools promise change.

THE RISE OF NEW TECHNOLOGY

The rise of smartphones has given us the ability to connect with our family, friends and doctors, and to continuously monitor our health no matter where we are, every day.

Smartphones combine multiple, high-quality sensors into one indispensable device

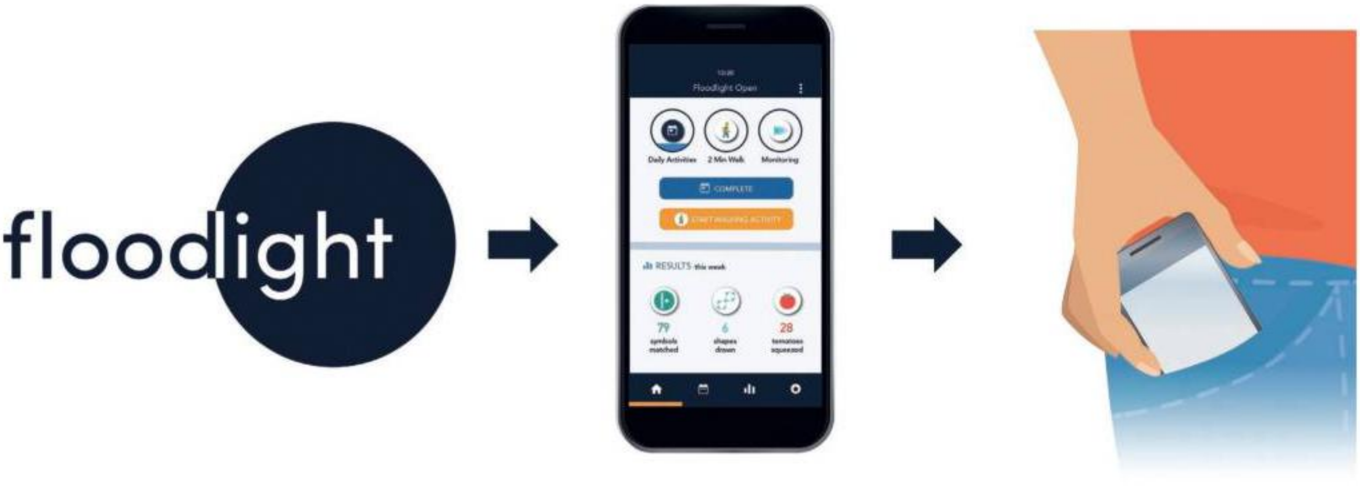

Figure 3. Floodlight is a smartphone-based digital assessment that allows passive and active monitoring of multiple sclerosis disease activity. The app prompts the user to perform various assessments, referred to as 'active tests'.

(**Fig. 2**). These sensors allow us to take basic measurements such as acceleration, and calculate parameters that describe how a person walks or the number of steps that they take during a day. Most smartphones can also sense geographic position, ambient light, voice and touchscreen pressure, and some even monitor atmospheric pressure. Utilizing sensors can turn a smartphone into a useful tool for monitoring heart rates or detecting falls[7].

SMARTPHONE-BASED SELF-MONITORING OF MULTIPLE SCLEROSIS USING FLOODLIGHT

Floodlight is an app developed by Roche that contains a range of active and passive remote monitoring tests that measure a person's ability to perform simple tasks on their smartphone (**Fig. 3**). The aim of Floodlight is to gain an understanding of the effects of MS on the brain, hands and body, and allow the symptoms of MS to be continuously monitored every day.

REDISCOVERING MS WITH FLOODLIGHT

The Floodlight app consists of several tasks that measure cognition, hand motor function and mobility in order to collect precise, real-time data and that one day may track subtle changes in symptoms between doctor visits. Simple tasks were designed by physicians to help people with MS understand their personal journey. The tests are intended to enhance the findings from several gold standard in-clinic tests, accurately tracking disease activity and progression while at the same time providing a clearer and more continuous picture of the reality experienced by people living with MS (**Fig. 4**).

Consider hand motor function, which, as previously described, is typically measured by the nine-hole peg test. In the Floodlight app, one of the tests used to assess hand motor function is a test called draw a shape, in which users hold the smartphone in one hand and draw six different shapes of increasing difficulty on the touchscreen with the finger of the opposite hand[9]. The complete interaction with the touchscreen is recorded, performance features such as accuracy and speed are measured, and changes are tracked over time. The hope is that the draw a shape test is faster and more accurate, can be carried out every day, and reflects a person's ability to write, a task that is particularly meaningful to people with MS.

EMPOWERING PEOPLE LIVING WITH MS

Giving people living with MS the opportunity to actively engage in understanding and managing their disease can be empowering. This is becoming increasingly important because therapeutic decisions are mostly made in partnership between the doctor and the patient, and there is evidence to suggest that involvement of people with MS in shared decision-making is central to improving their treatment satisfaction and adherence[10,11]. The hope is that one day, tools such as the Floodlight app will allow people with MS to do this by tracking their own disease journey on their smartphone, enabling them to accurately identify changes in their symptoms and to engage in informed patient-led discussions. Digital monitoring is not about replacing a healthcare professional. Rather, it has the potential to bring people together, make healthcare more personalized and improve the patient-clinician relationship[12]. In a recent exploratory study, we found that people living with MS who completed the Floodlight tests regularly over a six-month period were highly engaged and satisfied with the app, supporting the feasibility of using smartphone-based monitoring of MS in a person's daily life.

MAKING DIGITAL HEALTHCARE A REALITY

Roche's commitment to neuroscience extends beyond the development of new medicines. In the age of the digital healthcare revolution, tools like Floodlight represent a promising avenue to enable minimally intrusive, precise and continuous

Brain: To assess a person's mood and cognitive functioning

Daily Mood Question
Quick daily questions about how the person feels to help understand well-being and mood

Matching Symbols
Matching symbols to digits measures how quickly information is processed

Hand: Hand motor function tasks designed to measure manual dexterity, strength and precision over time

Squeeze a Tomato
Designed to measure changes in hand–eye coordination and fine motor skills

Draw a Shape
Measures the speed and accuracy of hand and finger movements

Mobility: Walking and posture tasks measure changes in a person's mobility, stability, speed and balance

Two-Minute Walk
Walking quickly for two minutes measures stamina and mobility

Balance
Standing still for 30 seconds measures posture and stability

U-Turn
Task measures how the person walks and their ability to change direction

Passive Monitoring:

Passive Monitoring
Measures incremental changes in the way people move throughout the day
Gathering information through the smartphone sensor on step counts/duration and asymmetry

Figure 4. The Floodlight app contains a range of tests that measure brain function, hand function and mobility. In addition, passive monitoring is carried out throughout the day[9].

> THE FINE MOTOR COORDINATION IN MY LEFT HAND WAS AFFECTED, AT TIMES MY SPEECH WAS SLURRED, AND THE STIFFNESS IN MY LEGS MADE WALKING EXTREMELY TIRING AND DIFFICULT...I HAD GONE FROM A VERY HEALTHY AND PHYSICALLY ACTIVE PERSON TO A VERY HANDICAPPED ONE. MY WHOLE LIFE HAD CHANGED[1].
> FIRST-PERSON ACCOUNT OF A PERSON LIVING WITH MS

assessment of MS disease activity integrated into people's daily routines. Implementing digital monitoring could identify disease progression earlier, leading to more rapid and appropriate treatment decisions, and therefore has the potential to improve long-term health in people with MS. With the advent of the digital healthcare revolution and the rapid advances in technology, it may be possible that one day, a patient's disease can be passively monitored 365 days a year, using the technology that exists around us. To make the idea of digital healthcare a reality and ensure that we measure what matters to patients, collaborations are required between digital experts, healthcare providers, people with MS and the wider community of MS researchers. The digital assessments and tests need to be designed alongside people with MS, and the results need to be reported in a way that facilitates smooth integration into research and healthcare workflows. A cross-industry and ultimately even cross-healthcare system approach is required to define the standards of digital monitoring, with the ultimate goal of improving the lives of people living with MS.

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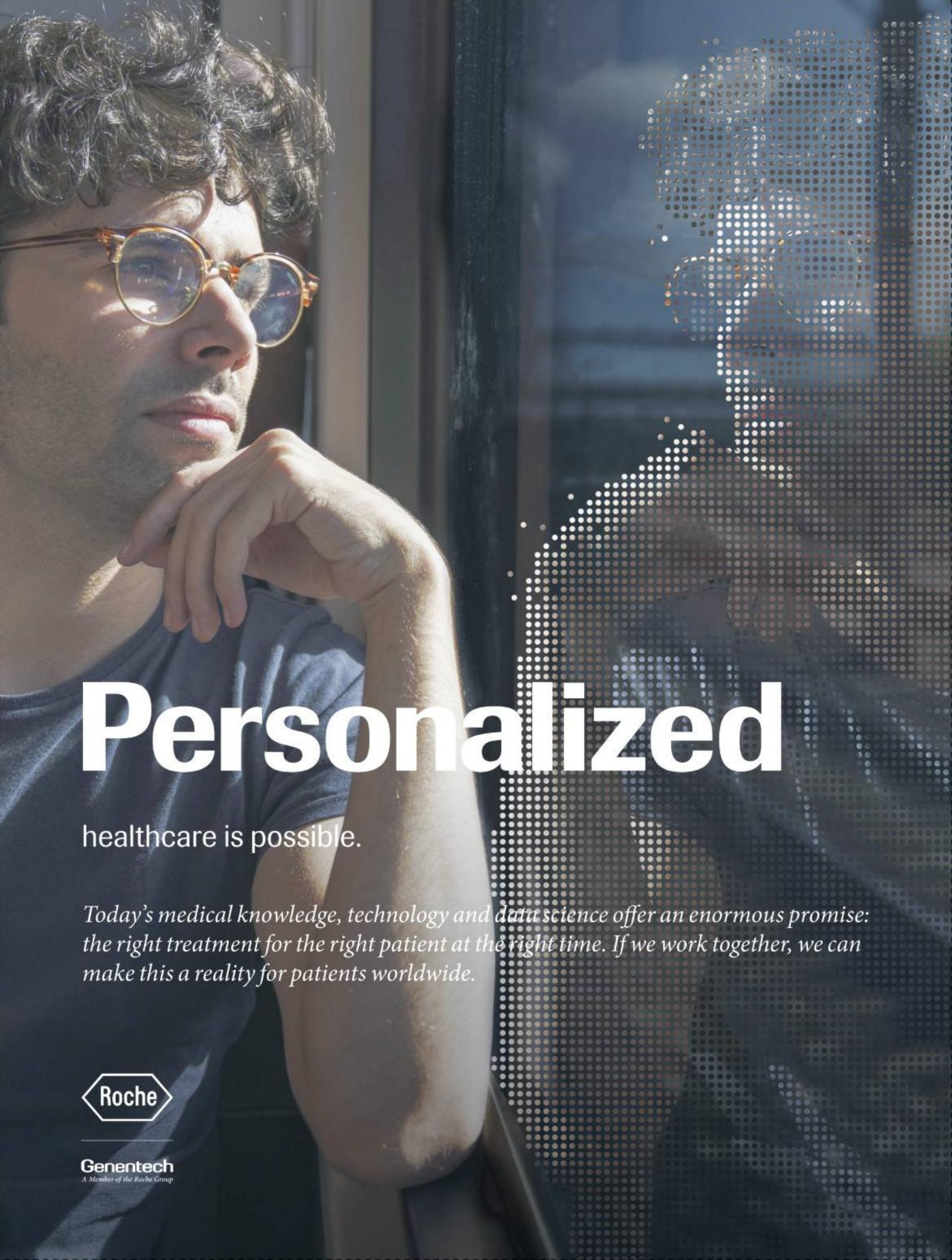

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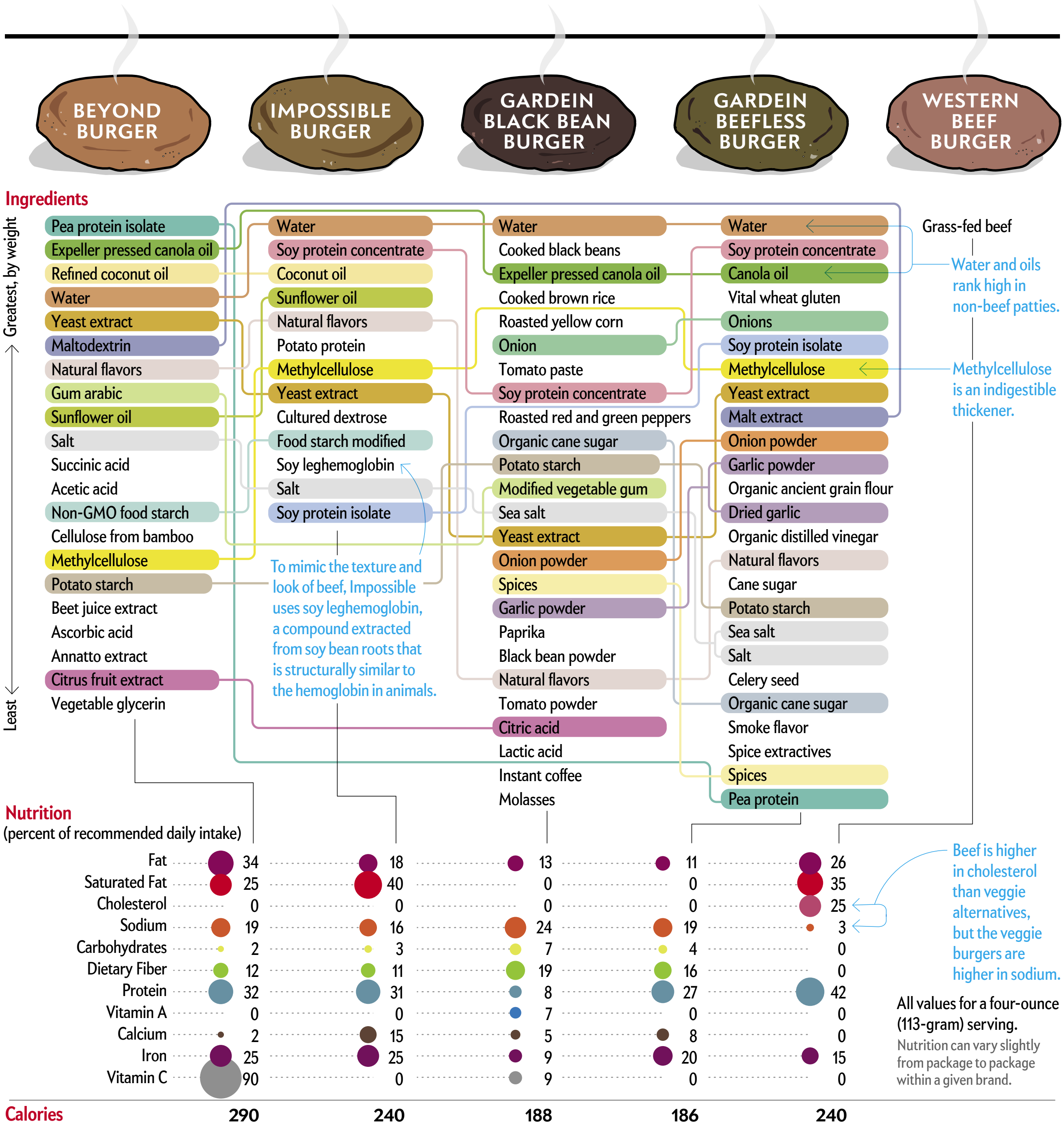

Ingredients

Greatest, by weight → Least

BEYOND BURGER	IMPOSSIBLE BURGER	GARDEIN BLACK BEAN BURGER	GARDEIN BEEFLESS BURGER	WESTERN BEEF BURGER
Pea protein isolate	Water	Water	Water	Grass-fed beef
Expeller pressed canola oil	Soy protein concentrate	Cooked black beans	Soy protein concentrate	
Refined coconut oil	Coconut oil	Expeller pressed canola oil	Canola oil	
Water	Sunflower oil	Cooked brown rice	Vital wheat gluten	
Yeast extract	Natural flavors	Roasted yellow corn	Onions	
Maltodextrin	Potato protein	Onion	Soy protein isolate	
Natural flavors	Methylcellulose	Tomato paste	Methylcellulose	
Gum arabic	Yeast extract	Soy protein concentrate	Yeast extract	
Sunflower oil	Cultured dextrose	Roasted red and green peppers	Malt extract	
Salt	Food starch modified	Organic cane sugar	Onion powder	
Succinic acid	Soy leghemoglobin	Potato starch	Garlic powder	
Acetic acid	Salt	Modified vegetable gum	Organic ancient grain flour	
Non-GMO food starch	Soy protein isolate	Sea salt	Dried garlic	
Cellulose from bamboo		Yeast extract	Organic distilled vinegar	
Methylcellulose		Onion powder	Natural flavors	
Potato starch		Spices	Cane sugar	
Beet juice extract		Garlic powder	Potato starch	
Ascorbic acid		Paprika	Sea salt	
Annatto extract		Black bean powder	Salt	
Citrus fruit extract		Natural flavors	Celery seed	
Vegetable glycerin		Tomato powder	Organic cane sugar	
		Citric acid	Smoke flavor	
		Lactic acid	Spice extractives	
		Instant coffee	Spices	
		Molasses	Pea protein	

Water and oils rank high in non-beef patties.

Methylcellulose is an indigestible thickener.

To mimic the texture and look of beef, Impossible uses soy leghemoglobin, a compound extracted from soy bean roots that is structurally similar to the hemoglobin in animals.

Nutrition (percent of recommended daily intake)

	Beyond Burger	Impossible Burger	Gardein Black Bean Burger	Gardein Beefless Burger	Western Beef Burger
Fat	34	18	13	11	26
Saturated Fat	25	40	0	0	35
Cholesterol	0	0	0	0	25
Sodium	19	16	24	19	3
Carbohydrates	2	3	7	4	0
Dietary Fiber	12	11	19	16	0
Protein	32	31	8	27	42
Vitamin A	0	0	7	0	0
Calcium	2	15	5	8	0
Iron	25	25	9	20	15
Vitamin C	90	0	9	0	0
Calories	290	240	188	186	240

Beef is higher in cholesterol than veggie alternatives, but the veggie burgers are higher in sodium.

All values for a four-ounce (113-gram) serving.

Nutrition can vary slightly from package to package within a given brand.

Meat the Imitators

What's in that burger you're eating?

Meatless patties such as the Impossible Burger and Beyond Burger are catching on quickly. But what are they made of? And how do they compare nutritionally with actual meat and the classic veggie and black bean alternatives? We compare the information on five product labels here. Beyond Burger's protein comes from ground peas, Impossible's from soy and potato; fats are from various oils. How producers create a savory "umami" taste is a kitchen secret. Some consumers choose meatless offerings to reduce their beef intake for personal or environmental reasons, and some people simply prefer the vegan varieties. But whether any choice is "healthier" is debatable; see the facts.


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UNHEALTHY PRACTICES
SPEAKING IN WHISTLES
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