• Spring 2011 Issue 20

berkeley science review

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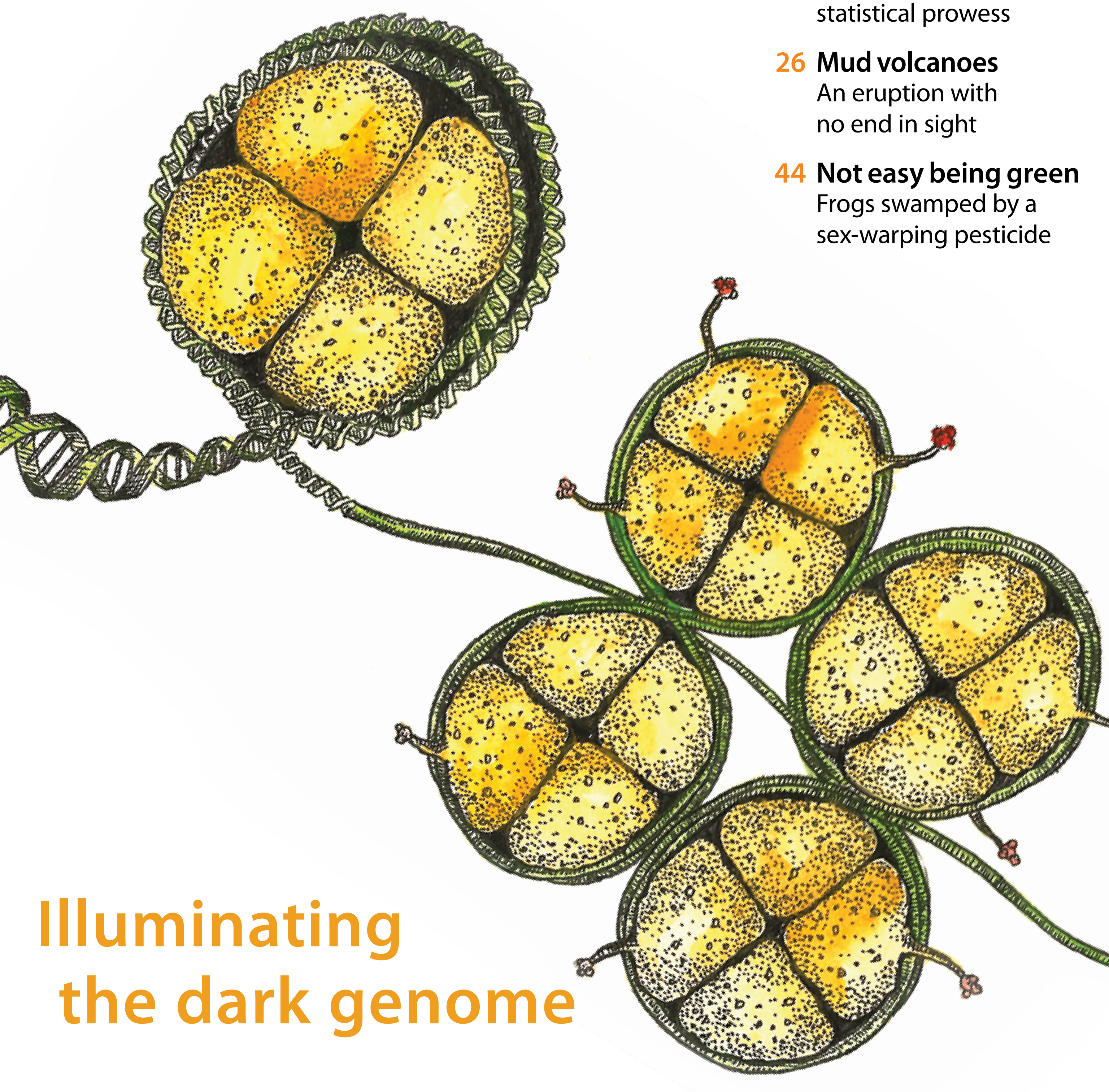

Illuminating the dark genome

berkeley science review

from the editor

Dear readers,

Welcome to the 20th issue of the *Berkeley Science Review* and our tenth anniversary. To celebrate, I decided to rummage back through our archives and spend some time with Issue 1. It was remarkable to see how little has changed, including, coincidentally, an enduring fascination with volcanoes (Issue 1 p. 7, Issue 20 p. 26), hormonal regulation of sexual behavior (Issue 1 p. 5, Issue 20 p. 9), and solar storms (Issue 1 p. 4, Issue 20 p. 6), phenomena which will continue to fill Berkeley labs and our pages for many years to come. Nevertheless, I am very proud to say that we have come a long way from the black, white, and blue of the first edition. I would like to dedicate this issue to the memory of Eran Karmon, our founding Editor in Chief, who, by starting a science magazine that anyone on campus could pick up and enjoy, planted a seed which has since flowered into an expanding voice for research with a reach far beyond Bancroft and Hearst.

As science writers, we aspire to communicate complex ideas effectively, hoping to increase the impact of science in society. Less often considered are influences going in the other direction, yet the interplay between personalities, politics, economics, and research takes center stage this issue. On page 44, Sisi Chen and Mark DeWitt chronicle the decade-long struggle over the effects of a pesticide between a controversial professor, Tyrone Hayes, and the chemical company Syngenta, waged through experiments, regulatory agencies, and personal vitriol. Keith Cheveralls documents the damning scientific evidence that an oil company caused the continuing eruption of the devastating Lusi mud volcano in Indonesia (p. 26) Finally, on page 60 Jacques Bothma makes the case for why Professor Michael Eisen's dream of a scientific literature free for everyone to access should, and is, becoming a reality.

The *BSR* is run by students who also happen to be scientists, and thus it is no surprise that we continually tinker with (and sometimes dramatically alter) the form and content of our magazine. While we always have an opinion of what works best, I am pleased to announce a new way for you, our readers, to have a say: the Reader's Choice Award, to be given each issue. Go online (http://sciencereview.berkeley.edu) to vote for your favorite feature or brief; the author(s) of the winning article receives a $150 cash prize and a profile on the BSR blog, which is already chock-full of wonderful pieces to keep you informed between print issues. In addition to highlighting particularly strong writers, prize-winning articles will inspire future stories relevant and interesting to you.

As I hang up my editor's hat, I would like to thank all of the writers, editors, and layout staff for making the past year such a wonderful experience and for two issues that highly paid professionals (by journalist standards, at least) would be hard-pressed to beat. It has been an honor.

Enjoy the issue,

Greg Alushin
Editor in Chief

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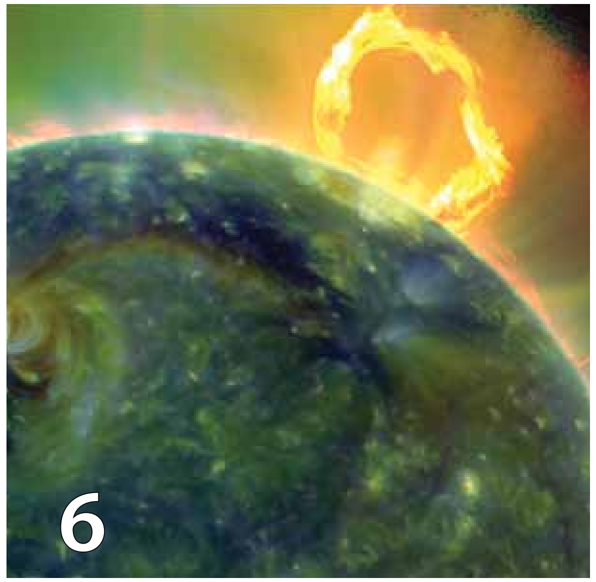
features



departments

CLOCKWISE FROM TOP-RIGHT: NASA; PAUL SAPIANO; STEVE AXFORD; MAREK JAKUBOWSKI; JOE KLOC; MAREK JAKUBOWSKI

current briefs

COVER: Histone proteins (yellow), the spools around which DNA (green) is wrapped, are critical for turning genes on and off. The modENCODE project is generating genome-wide maps of dynamic chemical marks (red) on the histones to uncover the rules that allow an animal to develop from a single cell.

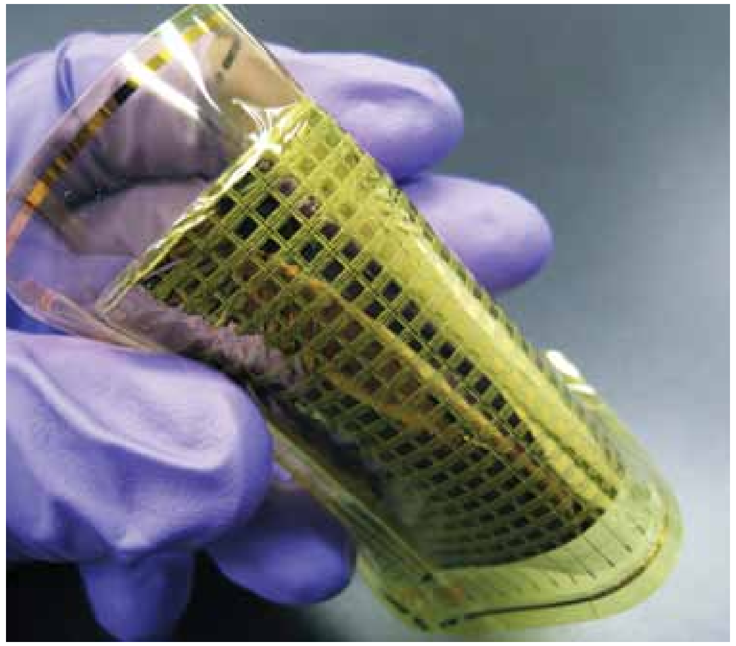
 Financial assistance for the 2010-2011 academic year was generously provided by the Office of the Vice Chancellor of Research, the UC Berkeley Graduate Assembly (GA), the Associated Students of the University of California (ASUC), and the Eran Karmon Memorial Fund. *Berkeley Science Review* is not an official publication of the University of California, Berkeley, the ASUC, the GA, or Lawrence Berkeley National Laboratory. The views expressed herein are the views of the writers and not necessarily the views of the aforementioned organizations. All events sponsored by the BSR are wheelchair accessible. **For more information** email sciencereview@gmail.com. **Letters to the editor** and **story proposals** are encouraged and should be emailed to sciencereview@gmail.com or posted to the Berkeley Science Review, 10 Eshleman Hall #4500, Berkeley, CA 94720. **Advertisers:** contact sciencereview@gmail.com or visit sciencereview.berkeley.edu.

labscopes

Touchy feely

Every day we use our sense of touch to guide our way through life without giving it a second thought. Engineers have long sought to replicate the complex sense of touch in electronic components to give robots and, eventually, prosthetic limbs the same ability to interact with the surrounding world. A group of electrical engineers at UC Berkeley have made a significant breakthrough in the pursuit of producing a sensor similar to human skin in its ability to detect pressure. Professor Ali Javey and his team fabricated a seven square centimeter sensor array using inorganic semiconductors called nanowires mounted onto flexible, pressure-sensitive rubber. Previous electronic skins used flexible organic components that were 50 times smaller in area and required a large battery to provide the voltage needed to operate them. Javey's group instead opted to use nanowires that require smaller voltages. "Previous research using nanowires was limited to using single nanowire transistors on a very small scale," says Dr. Kuniharu Takei, a postdoctoral scholar in Javey's group and lead author of the paper. The sensor makes use of an innovative contact printing technique pioneered by the team to mount hundreds of nanowires onto the sensor. The electronic skin is durable, making it ideal for future applications, which Javey explains can range, "from robotics, to giving gas pipelines the ability to self diagnose the formation of cracks, and one day even interfacing with prosthetic limbs."

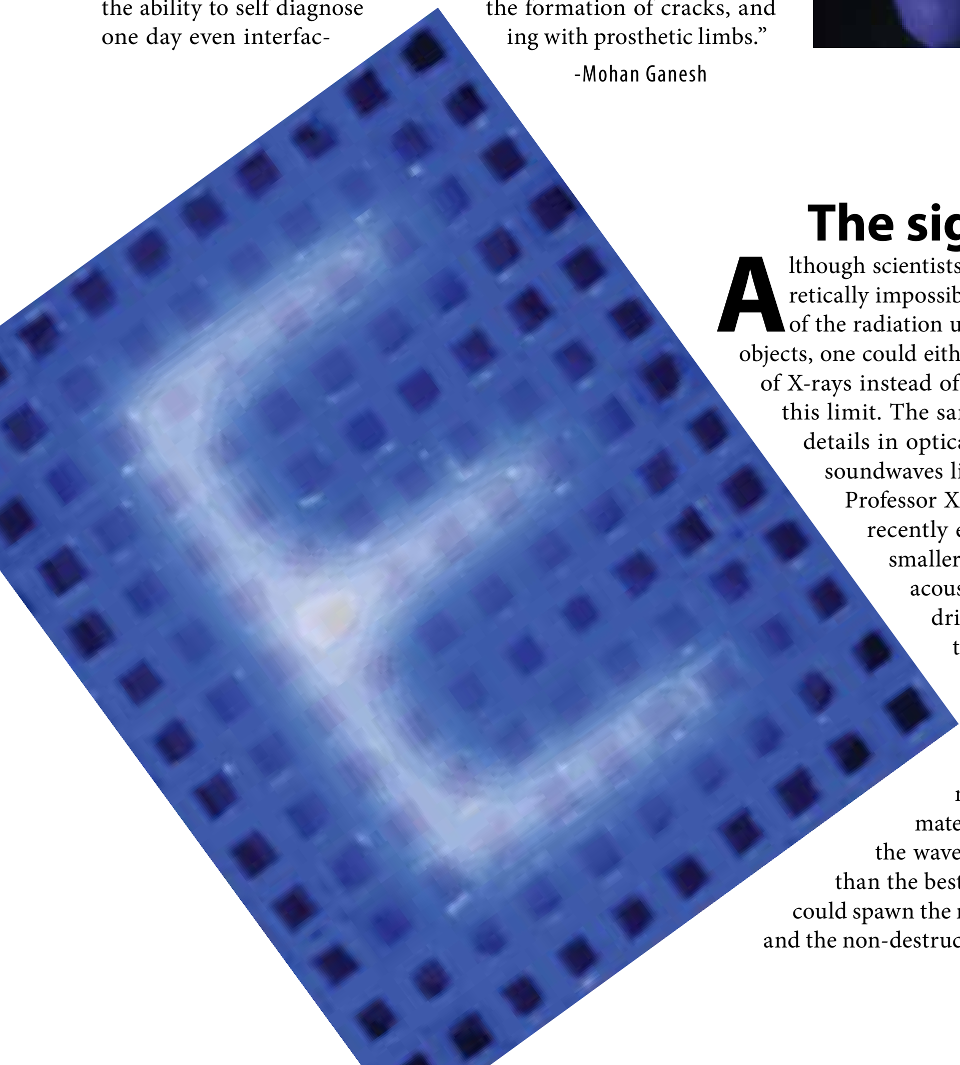
-Mohan Ganesh



Wireless water

In many developing countries like India, running water is scarce and only intermittently available. To tackle this challenge, UC Berkeley graduate students Thejo Kote, Emily Kumpel, and Ari Olmos, launched a social enterprise called NextDrop in the fall of 2009, with advice from Assistant Professor Tapan Parikh of the School of Information. NextDrop aims to address the problem of unreliable piped water in India by exploiting the ubiquity of cell phones in the country. "Mobile phones are everywhere," explains Kumpel. "They're a very easy way to get information to people." Local families participate by sending a text message to NextDrop as soon as water becomes available. As an incentive, the first set of callers receives a micropayment. NextDrop then verifies the accuracy of the water delivery update and immediately sends a text to all its subscribers in the same neighborhood. Since its modest beginnings as a class project, NextDrop has gone on to win UC Berkeley's 2010 Big Ideas competition and grants from the Gates Foundation and the Clinton Global Initiative. In July 2010 they began their first pilot program in the southern Indian town of Hubli, with 200 families as well as the local water utility board participating. In the future, NextDrop hopes to use delivery data accumulated over time to predict when water will arrive in a particular locality, thereby empowering consumers to actively participate in improving a vital utility.

-Sharmistha Majumdar



The sight of sound

Although scientists often want to look at very tiny things, it is theoretically impossible to see something smaller than the wavelength of the radiation used to image it. In order to observe even smaller objects, one could either use a shorter wavelength, for instance a beam of X-rays instead of light, or play a number of tricks to get around this limit. The same principles that restrict the ability to resolve details in optical imaging also hold true for methods that use soundwaves like ultrasound. Jie Zhu, a postdoctoral fellow in Professor Xiang Zhang's lab at UC Berkeley, and colleagues recently engineered a device capable of imaging objects smaller than the wavelength of sound used to create the acoustic image. The device has very small, square holes drilled through a block that act as perfect lenses for transmitting sound waves. When waves with the proper wavelength hit an object on one side of the block, information contained in standing waves that only exist very close to the object is faithfully transferred through the device. A microphone placed close to the output of the "holey" material can detect features up to 50 times smaller than the wavelength emitted by the source, seven times better than the best resolution previously available. This technology could spawn the next generation of probes for medical sonography and the non-destructive evaluation of materials.

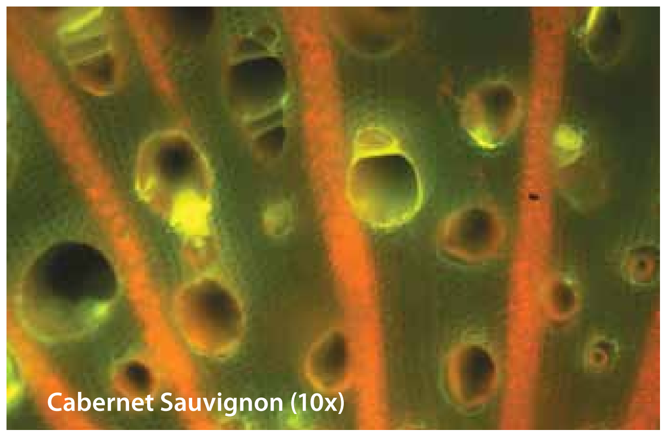
-Monica Smith

CLOCKWISE FROM TOP-LEFT: ALI JAVEY AND KUNIHARU TAKEI; NEXTDROP TEAM; CLELIA BACCARI; JIE ZHU AND JOHAN CHRISTENSEN

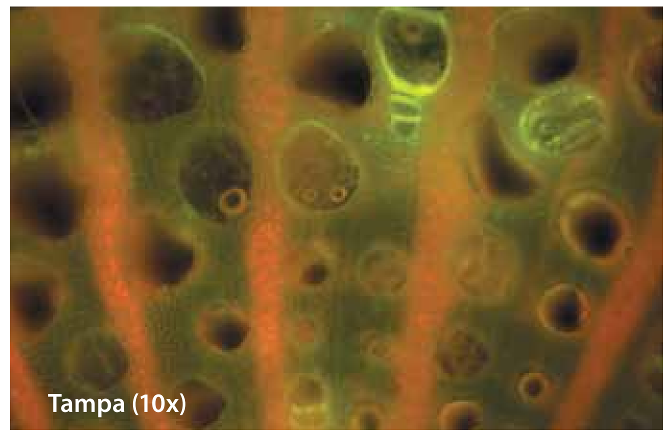
Winey pests

When you think of the Napa and Sonoma Valleys, you probably imagine rolling hills adorned with row upon row of succulent grapes vine-ripening in the sun. However, beneath this idyllic exterior the bacterium *Xylella fastidiosa* is wreaking havoc on California's wine grapes. By cutting off water transport through the plants, *Xylella* causes leaves to wither and fall off, ultimately killing entire vines. In an effort to better understand the mechanism of this disease, Associate Specialist Clelia Baccari and Professor Steven Lindow of the Department of Plant and Microbial Biology are studying the movement of the bacteria through the tissues of resistant and susceptible grape varieties. They use a strain that expresses green fluorescent protein, making the bacterial cells easy to visualize under a microscope. The plant's ray cells appear red, and between them are xylem vessels—water-transporting vascular tissue. The bright yellow-green areas on the walls of the xylem are full of bacteria. Dr. Baccari found that susceptible varieties, such as Cabernet Sauvignon on the left, had about five times as many infected xylem vessels as the Tampa grape, on the right, which is relatively resistant to the disease. Current hypotheses as to why some grape varieties are more resistant include differences in sap composition and the production of tyloses—outgrowths of cells surrounding xylem vessels, which may block bacterial movement through the plant.

-Molly Sharlach



Cabernet Sauvignon (10x)



Tampa (10x)

current briefs

Sun storms

Modeling solar phenomena

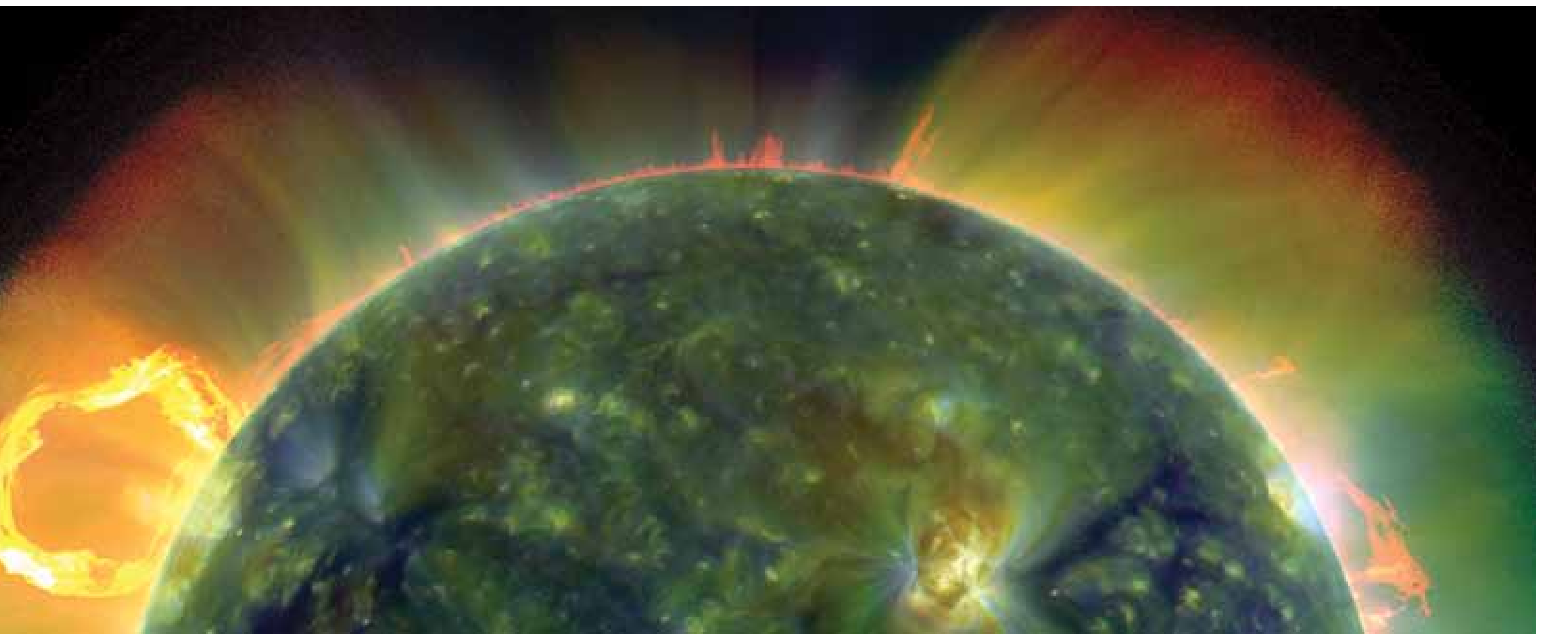
Every second, five million tons of matter are converted into energy deep within the Sun. Nuclear reactions in the core provide the source of the Sun's energy, which then radiates through the dense interior and exits through the Sun's surface and atmosphere into space. Along with this radiation, the Sun emits a variable stream of charged particles referred to as the solar wind. With a speed of up to 2.5 million miles per hour, the solar wind blows past Earth and eventually escapes our solar system. During active periods, however, large magnetic eruptions called flares or coronal mass ejections (CMEs) can drastically alter the solar wind in ways that can greatly affect the Earth's geomagnetic environment.

The enormous electromagnetic eruption of a CME can interfere with our communications and electric power infrastructures. A better understanding of how CMEs affect us on Earth is necessary to ensure their integrity. Our planet has its own magnetic field that acts as a giant protective bubble, shielding us against the incoming solar wind, but it is not always an impenetrable barrier against a CME. An enhancement in the northern lights is among the visual effects of such a disturbance, but charged particles associated with CMEs can have other, potentially destructive consequences. They can interfere with the normal operation of radio and satellite communications and electric power grids, as well as disrupt global positioning networks. Magnetic disturbances associated with CMEs have occurred throughout history, with the strongest geomagnetic storm in recent memory occurring in March 1989.

Over the past decade, a team at UC Berkeley, NASA, and other concerned industry partners, have been working toward reliable models of CMEs that could eventually serve as forecasting tools. The collaborative Solar Multidisciplinary University Research Initiative (MURI) was formed in 2001, led by principal investigator George Fisher, a solar physicist at the Space Sciences Laboratory, and several of his colleagues also at UC Berkeley. From 2001 to 2006, Fisher's group played the lead role in a coordinated effort by nine research institutions across the US to investigate the mechanisms of magnetic eruptions on the Sun and their effects on our solar system at large.

To understand the research at MURI, we must first understand a bit about the structure of our Sun. Imagine traveling from the Sun's core all the way to the outermost layer of the Sun, the solar corona. To do so, you would need to pass through three distinct regions. You would start in the deep interior surrounding the core, where the energy generated by nuclear reactions is transported by little packets of light called photons. Next you would reach the solar convection zone, a turbulent layer that spans the outer 30 percent or so of the Sun, where energy is transported through rolling convective motions, much like in a boiling pot of water. Finally, you would travel out through the surface of the Sun at the top of the convection zone, where the density of the plasma is low enough for photons to escape past the corona and into space.

While the core is extremely hot at 27 million degrees Fahrenheit, the temperatures gradually cool as you travel outward. At the surface of the Sun, the temperature is a relatively cool 9980 degrees. However, as you move beyond the surface and into the solar atmosphere, something strange happens—the temperature suddenly rises millions of degrees. Physicists generally attribute this dramatic temperature increase to the dynamic magnetic field that threads its way through the convective interior and fills the corona.

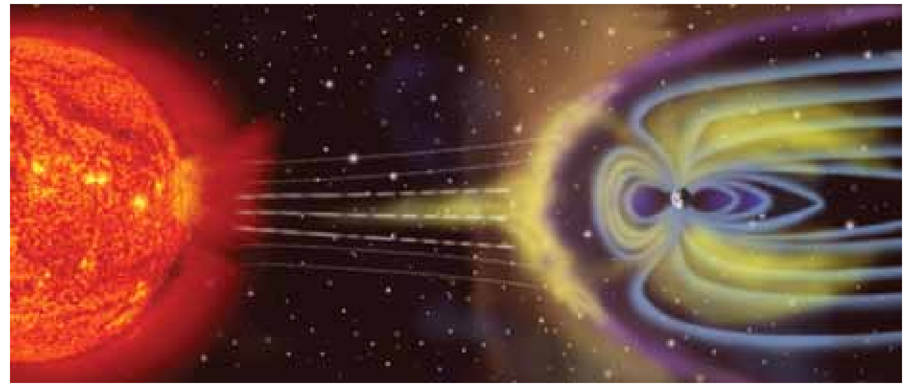


NASA

The UC Berkeley team's primary goal has been to develop and use advanced numerical models to understand the physics behind this dramatic temperature change and the trigger mechanism for eruptive events like flares and CMEs. These numerical tools will hopefully be used to understand and predict the potentially destructive geomagnetic storms that result from solar eruptions, providing a means to forecast space weather. Unfortunately, the large variations in physical conditions between the solar interior and its outer atmosphere make such models incredibly difficult to develop. The plasma of the solar convection zone (between the core and the surface) is dense, opaque, and turbulent, whereas the solar corona is rarified and transparent, with its structure and evolution dominated by its magnetic field. Although each domain may be separately understood quite well, "a quantitative understanding of the global magnetic behavior of the Sun poses a formidable challenge," says William Abbett, a MURI researcher at UC Berkeley's Space Sciences Lab.

To efficiently model and predict the behavior of dynamic and electrically charged fluids, physicists often use a set of conservation equations called Magneto-Hydro-Dynamic equations, or MHD. Abbett developed a specialized code called RADMHD (RADiative MHD) that is designed to simultaneously simulate the transition region between the cool dense sub-surface layers and the hot rarified corona—the very region that may hold the key to a better understanding of coronal heating and magnetic eruptions.

"RADMHD has enough physics incorporated into the code to be able to simulate the granular convective pattern observed at the Sun's photosphere," says Abbett. A key strength of the RADMHD model is its ability to incorporate magnetograms—maps of the surface magnetic field observed by NASA satellites—directly into a computational model that includes the coronal magnetic field. This enables a new paradigm in solar physics: much like simulations used for terrestrial weather forecasting, it is now feasible to use previous observations of the evolving magnetic field at the surface to predict its future state.



While the Earth's magnetosphere protects it from most forms of solar wind, large magnetic surges in the outer layer of the Sun, called "coronal mass ejections" or CMEs, can occasionally penetrate the Earth's defenses .

The UC Berkeley-led MURI effort has deepened and extended computational capabilities and allowed realistic modeling of how solar magnetic fields emerge and evolve. Modeling how CMEs and other eruptions are launched, however, remains an ongoing challenge. "The mechanisms that trigger and drive these eruptions are the least understood aspects of space weather," says Fisher. "As yet, no one has demonstrated the ability to use a physics-based solar model that incorporates observed data to make a deterministic prediction of a CME." To date, all CME forecasts rely upon statistical associations between how properties of the solar surface have related to the occurrence of CMEs in past data. All that can be said today is that if the Sun's surface looks a certain way, we can guess that it might produce a CME soon, with the operative words being "might" and "soon."

The UC Berkeley group is conducting ongoing studies of pre-CME coronal evolution. One of the current objectives of their research is a better understanding of how magnetic flux systems emerge across the solar surface, a process that some researchers contend is primarily responsible for CME initiation.

The Great Magnetic Storm in September 1859, known as the Carrington event, is still the strongest magnetic storm on record. For several days, it produced spectacular auroral displays that were seen at latitudes as low as Hawaii, and it severely disrupted telegraph communications in Europe and North America. Today, the effects would be far more devestating, affecting space-based communication, reconnaissance, GPS, and millions of users dependent on the power grid. Is a similar magnetic storm in our future? The MURI team can't say for sure, even using their sophisticated RADMHD code. In the early months of 2011, the Sun unexpectedly kicked up a series of unusually intense X-ray flashes. Despite continuing progress in solar physics, we still have a lot to learn about our central star.

Alireza Moharrer *is an employee of the solar power company Flagsol in Oakland, CA.*

What's the antimatter?

Probing the origins of the universe with antihydrogen

Antiprotons were first discovered at Lawrence Berkeley National Laboratory's Bevatron.

LBL

For many, the word "antimatter" elicits images of the Starship Enterprise ripping through space faster than the speed of light, or canisters of tiny glowing balls threatening to obliterate Vatican City. Scientific inaccuracies in popular culture aside, the prospect of isolating antimatter, which annihilates in a burst of light upon contact with matter, has eluded physicists for decades. And yet, this is just what a group of scientists working at CERN, the European Organization for Nuclear Research, recently succeeded in doing. Several months ago, the international ALPHA (Antihydrogen Laser PHysics Apparatus) collaboration, which includes many researchers from UC Berkeley and Lawrence Berkeley National Laboratory, managed to create and, more importantly, capture 38 antihydrogen atoms for about one sixth of a second—an eternity in the world of subatomic particles. This exciting breakthrough will allow physicists to study matter's counterpart in detail and will ultimately deepen, and possibly fundamentally change, our understanding of the origins of the universe. The first question at hand: why is our universe made almost entirely of matter and not antimatter?

A particle of matter and its antimatter complement have the same mass but opposite charges. While hydrogen is composed of a proton and an electron, an antihydrogen atom consists of an antiproton, the proton's negatively charged counterpart, and a positron, the positively charged analog of the electron. Though scientists at CERN have been creating antihydrogen atoms from positrons and antiprotons for several years now, they have not been able to contain them for a significant period of time. The net neutral charge makes the anti-atom impossible to confine with an electric field, and its kinetic energy makes it challenging to control with a magnetic field.

Joel Fajans, UC Berkeley physics professor and one of the lead scientists of the ALPHA collaboration, explains the experiment starting with the process of creating antihydrogen atoms: "It's not actually that hard—you essentially just need to throw together a lot of positrons and low-energy antiprotons, and eventually you get antihydrogen atoms." Just like UC Berkeley's own Bevatron, where antiprotons were first discovered in the 1950s, the CERN laboratory creates antiprotons for a variety of scientific experiments. Unlike the Bevatron, CERN is unique in its capability not only to produce these particles, which are byproducts of high-energy particle interactions, but also to slow them down. Once cooled to low energies, the plasma of antiprotons is introduced to a cloud of positrons, letting pairs of particles combine to form bound systems—antihydrogen atoms.

The real difficulty lies in trapping the antihydrogen atom, which Fajans' group can do with remarkable finesse. The ALPHA trap consists of a complex system of repulsive magnets that takes advantage of antihydrogen's magnetic moment to suspend the atom in space. However, despite state-of-the-art technology, this is a very weak magnetic trap. Even the smallest residual energy above a certain threshold allows the atom to escape. Fajans likens the magnetic trap to a "tiny little dimple on a sheet of paper" and the antihydrogen atom to a "ball rolling around inside the dimple. Because the dimple is very shallow, the ball will only stick in it if it's rolling very, very slowly." Despite the challenges, the team was able to coax many atoms of antihydrogen to stay put in that "dimple." As of last November's publication in *Nature*, the ALPHA team had managed to isolate 38 particles of antihydrogen for just enough time to be sure of the new anti-atoms' identities. They subsequently turned off the trap to release the antihydrogen and observe the resulting annihilation event. Since then, the number of trapped antihydrogen atoms has increased significantly, as has the time spent in the trap—up to about 30 minutes! More time in the trap means more time to study the properties of the antihydrogen atom.

Ultimately, the success of the antihydrogen-trapping experiment could play a crucial role in filling a gap in the fields of particle physics and cosmology. Currently preferred theories state that equal amounts of matter and antimatter should have been created in the conditions that were present in the infancy of our universe. However, the amount of matter overwhelmingly outweighs the amount of antimatter we observe in our universe. "Conceivably, there could be a galaxy out there made entirely of antimatter," says theoretical cosmologist Chung-Pei Ma, professor of astronomy at UC Berkeley. However, signs supporting the existence of such an "anti-galaxy" have never been observed.

Experimental study of antihydrogen might take us a step towards understanding what happened to all the antimatter during the birth of our universe. Do antihydrogen atoms interact with gravity differently than hydrogen atoms? Do they have different atomic signatures? "If not, this is just a 'gee-whiz' experiment," Fajans remarks. However, if there is indeed a difference in the properties and behavior of matter and antimatter, both Ma and Fajans agree that this would have revolutionary implications for how physicists think about the beginnings of our universe. The general consensus among scientists is that finding these differences seems highly unlikely, though the mere possibility of such a profound discovery is very exciting. We may never be able to power spaceships with antimatter, but the search for answers to the mysteries of the universe will never run out of fuel.

Denia Djokic *is a graduate student in nuclear engineering.*

Hormonal hassle

How stress can hurt your sex drive

We've all been there. You come home after a stressful day at work and find yourself barely motivated enough to eat dinner. Despite your partner's advances, being intimate is the last thing on your mind. This problem is not unique to humans; the opposing action of stress and sex is an issue faced by all species on our planet. It is a basic fact of life that energy spent on reproduction must be balanced against self-survival, but only in the last ten years have researchers pinpointed one of the hormones capable of turning off sex drive in response to external stressors.

The discovery of a molecular link between stress and sex came from research studying the effects of stress on bird and rat behavior. George Bentley, Associate Professor of Integrative Biology at UC Berkeley, showed that stressed animals have elevated levels of gonadotropin-inhibitory hormone (GnIH). GnIH prevents proper sperm and egg development by blocking the action of gonadotropins, a well-studied class of hormones secreted from the pituitary gland that stimulate sperm and egg maturation. The connection between GnIH and stress revealed the first known mechanism of how environmental stress (e.g. predators, storms, etc.) suppresses the reproductive systems of animals.

Researchers discovered GnIH ten years ago while searching for new hormonal regulators of animal behavior, finding that it was capable of inhibiting the release of reproductive hormones in quails. Their study motivated Bentley to test the function of GnIH in sparrows, a species that has long served as a model for reproduction research due to its complex mating behavior. "A link between quails and sparrows would verify the evolutionary importance of GnIH while also allowing us to investigate its effect on mating behavior," says Bentley. By administering GnIH directly to the brains of female sparrows, Bentley found an immediate decrease in levels of luteinizing hormone—the hormone responsible for ovulation. Remarkably, he also saw a change in behavior. Female sparrows normally find the song of male sparrows irresistible, but direct administration of GnIH decreased the frequency with which female sparrows solicited copulation. This marked the first discovery of a hormone capable of negatively regulating sex hormones and behavior.

Given its ability to turn off sexual behavior in animals, GnIH may be the long-sought link between stress and sexual reproduction. Bentley's work with wild birds supports this hypothesis. "We stress birds when we catch

LUIS SILVA

Research led by Professor George Bentley is uncovering the molecular links between stress and libido by observing mating habits and biological changes in stressed-out sparrows. Mapping out these biological links is the first step to understanding the effects of stress on the human libido.

them in cloth bags," explains Bentley, "and once they are captured their GnIH levels increase dramatically." These findings describe the first connection between stress and sex drive: the release of stress hormones activates neurons in the brain that secrete GnIH, leading to widespread decreases in reproductive potential and behavior. This makes intuitive sense, says Bentley, because "if there is a major storm, it would be a bad idea for to you lay eggs; they would probably not survive."

After his latest observations in birds, Bentley began looking for a connection between GnIH and stress in mammals. In collaboration with Daniela Kaufer, Assistant Professor of Integrative Biology, Bentley's lab acutely stressed rats with three hour immobilizations. Initial experiments showed an increase in GnIH levels accompanied by a decrease in luteinizing hormone and, therefore, in ovulation. Furthermore, rats that experienced chronic stress, brought on by immobilization for three hours a day over 14 days, had significantly higher levels of GnIH and lower levels of luteinizing hormone than rats that experienced acute stress. The ability for chronic stress to elicit higher levels of GnIH raises the interesting possibility that GnIH release may limit or turn off reproductive drive completely, depending on the extent of environmental stress.

Bentley has also been looking for GnIH in other species. Comparison of GnIH DNA sequences allowed him to discover GnIH-related hormones in a multitude of species such as hamsters, sheep, and even humans. "One of the first things I did when I started my lab at UC Berkeley was to begin looking for the presence of GnIH in human brains," says Bentley. His preliminary work has shown that GnIH is indeed present. Even though a functional link still needs to be established, many evolutionarily conserved genes between birds, rodents, and humans tend to retain the same function, so it is likely that GnIH plays a role in negatively regulating human sexual behavior.

Michael Cianfrocco *is a graduate student in biophysics.*

It's a bird...it's a plane...it's a robot!

Machines that fly themselves

The big one has hit. After an earthquake, remains of buildings lie in haphazard heaps of debris, forming elusive recesses inaccessible to even the most experienced rescue team. A small group of flapping-winged robots swoops in to locate otherwise hidden victims trapped beneath the wreckage. Capable of autonomous scouting, these mini-bots would be equipped with surveillance, heat sensors, and GPS, all elements that would help identify the location of victims or structural hazards in the event of an emergency like the recent earthquake in Japan. While such technology is still a distant prospect, according to Stan Baek, a graduate student in Professor Ron Fearing's Biomimetics Millisystems lab at UC Berkeley, it does motivate the lab's research in the development of flapping-winged robots.

A logical starting point for designing a flying robot might be to adapt the design of an airplane and miniaturize it. The working components of conventional airplanes consist of a turbine engine and an assortment of rudders, stabilizers, and wings. This type of rigid-winged flight provides stability (minimal turbulence) and ease of manufacturing, features which have made such systems excellent for commercial applications. However, this kind of flight is limited in its range of motion and has not been proven to work in very small-scale, insect-sized systems. For an autonomous, highly maneuverable scouting device to be feasible, a different kind of flight mechanism is required.

Taking their inspiration from nature, Fearing's lab has chosen to develop a flapping-wing design for their mini-bot. Unlike propeller-driven and rigid-winged flight, flapping flight provides an incredible range of aerial control. Brief observation of a bird in flight or a darting dragonfly highlights its quick, agile movements, hovering capability, and maneuverability. Winged flight in nature is resilient in all kinds of environments and is known to work for creatures as massive as a golden eagle and as small as a gnat. If researchers better understood this type of flight, they could use this knowledge to engineer small systems that mimic its efficient and dynamic motion.

Over the past few years, the Biomimetics lab has been developing an autonomous bird-like robot, known as iBird. As a test model, Baek and fellow graduate student Fernando Bermudez have taken the body of a store-bought, radio-controlled glider (which they've dubbed the ornithopter) and modified it. The brain of the robot, an onboard microcontroller, is equipped with an antenna for receiving signals and various motion sensors to monitor the ornithopter's movement. In order to make iBird fully autonomous, it must be a self-contained entity capable of interacting with its surroundings without communicating with a human controller, by no means an easy task.

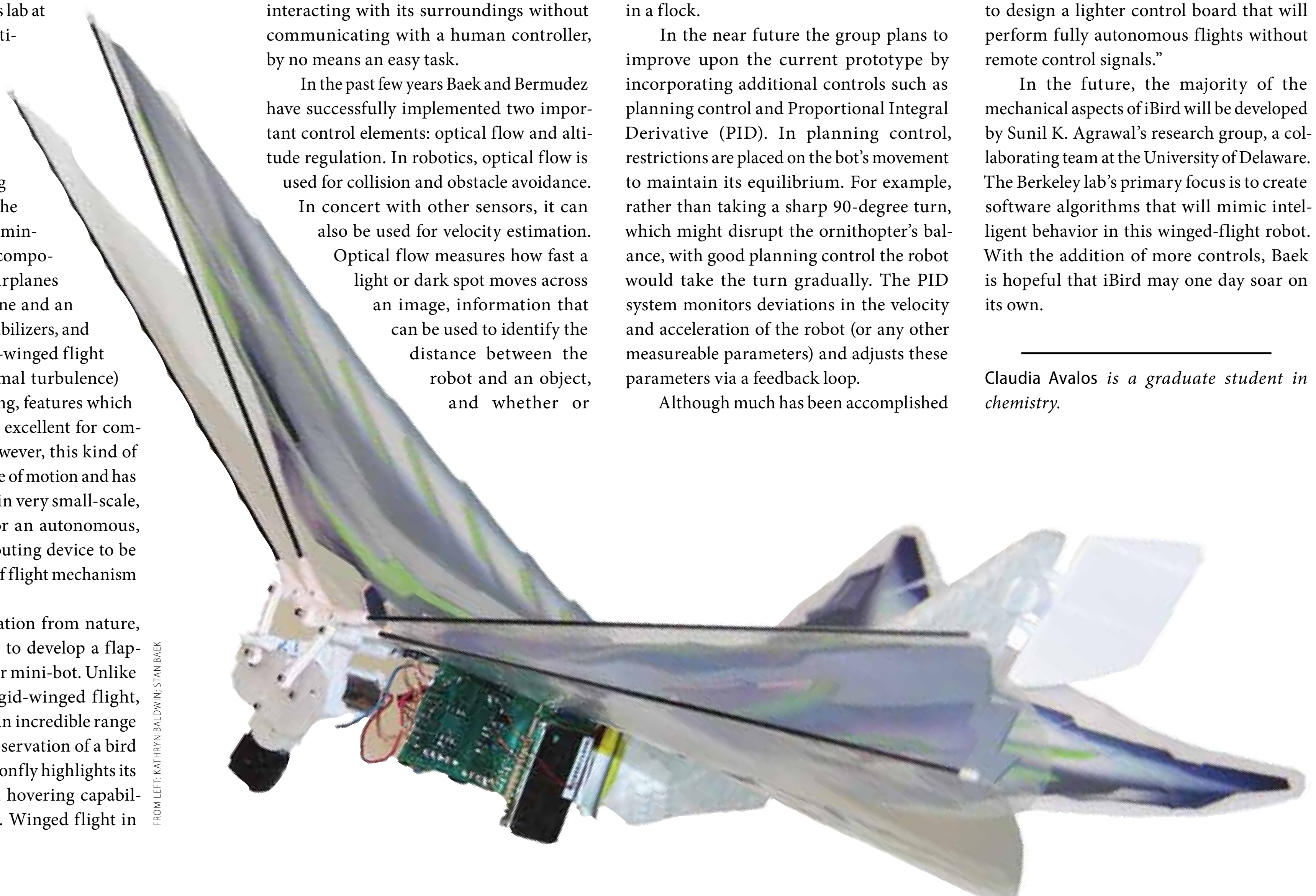
In the past few years Baek and Bermudez have successfully implemented two important control elements: optical flow and altitude regulation. In robotics, optical flow is used for collision and obstacle avoidance. In concert with other sensors, it can also be used for velocity estimation. Optical flow measures how fast a light or dark spot moves across an image, information that can be used to identify the distance between the robot and an object, and whether or not the object is in the robot's path. To add optical flow to their device, the team used a high-resolution cell-phone camera in tandem with a commercially available visual processing chip. For altitude control, Baek used an infrared sensor from the Nintendo® Wii mounted on iBird and a panel of angled light emitting diodes (LEDs) for monitoring and controlling the relative altitude of the bird bot. The LED display rests several feet away from the bot on a shelf or table. The light from the LEDs reaches the Wii sensor from several directions and thus, within a certain field of view, iBird's height relative to the panel can be determined. The bot also rises or falls depending on the light input it observes. Baek and Bermudez hope to extend this control and have the bot follow a moving target, and perhaps have a set of bots interact and follow one another just like birds flying in a flock.

In the near future the group plans to improve upon the current prototype by incorporating additional controls such as planning control and Proportional Integral Derivative (PID). In planning control, restrictions are placed on the bot's movement to maintain its equilibrium. For example, rather than taking a sharp 90-degree turn, which might disrupt the ornithopter's balance, with good planning control the robot would take the turn gradually. The PID system monitors deviations in the velocity and acceleration of the robot (or any other measureable parameters) and adjusts these parameters via a feedback loop.

Although much has been accomplished since the project started about four years ago, the team still faces many challenges. Winged flight is itself a poorly studied system; computer simulations take days to run and flight dynamics become very complicated because material flexibility, weight, wing size and many other parameters must be taken into account. The team has used experimental data from test runs to circumvent this last problem.

Once the software components for an autonomous robot have been developed and thoroughly tested, the next step will be to miniaturize the system. "From observing nature, we know for certain that flapping-winged flight can be miniaturized," Baek says. "The next step for smaller-scale flapping-winged robots will be to find a small battery source that can supply enough power to drive the system, along with a way to design a lighter control board that will perform fully autonomous flights without remote control signals."

In the future, the majority of the mechanical aspects of iBird will be developed by Sunil K. Agrawal's research group, a collaborating team at the University of Delaware. The Berkeley lab's primary focus is to create software algorithms that will mimic intelligent behavior in this winged-flight robot. With the addition of more controls, Baek is hopeful that iBird may one day soar on its own.



FROM LEFT: KATHRYN BALDWIN; STAN BAEK

Claudia Avalos *is a graduate student in chemistry.*

BRIEFS Memristors

Smart circuits

Making electronics that remember

Electrical engineering is on the cusp of a breakthrough—one that will allow engineers to create circuits that drastically increase the speed of processing, use far less power than modern computers, and even mimic the kind of computations carried out by the human brain. This shift comes in the form of the "memristor," a long-theorized but only recently constructed electrical component that stores information about its past activity and uses this information to influence its behavior. First theorized nearly 40 years ago, and finally built by Hewlett-Packard Labs in 2008, it promises to redefine the abilities and applications of computers of the future.

While memristors have only recently been constructed, they have existed in theoretical electronics for many years. Leon Chua, a longstanding member of the Department of Electrical Engineering and Computer Sciences at UC Berkeley, laid out the original theory in 1971. In his paper, Chua addressed a hole that existed in our knowledge of electrical engineering.

The world of electronics is largely built around devices that carry out interactions between the basic variables in any circuit: charge, resistance, voltage, and flux. For example, a capacitor creates a voltage by maintaining an imbalance of electrons (or charge) on either side of a gap. At the time of the theory's publication, there was a clear explanation for how a real-world device could connect each combination of these elements but one: charge and flux.

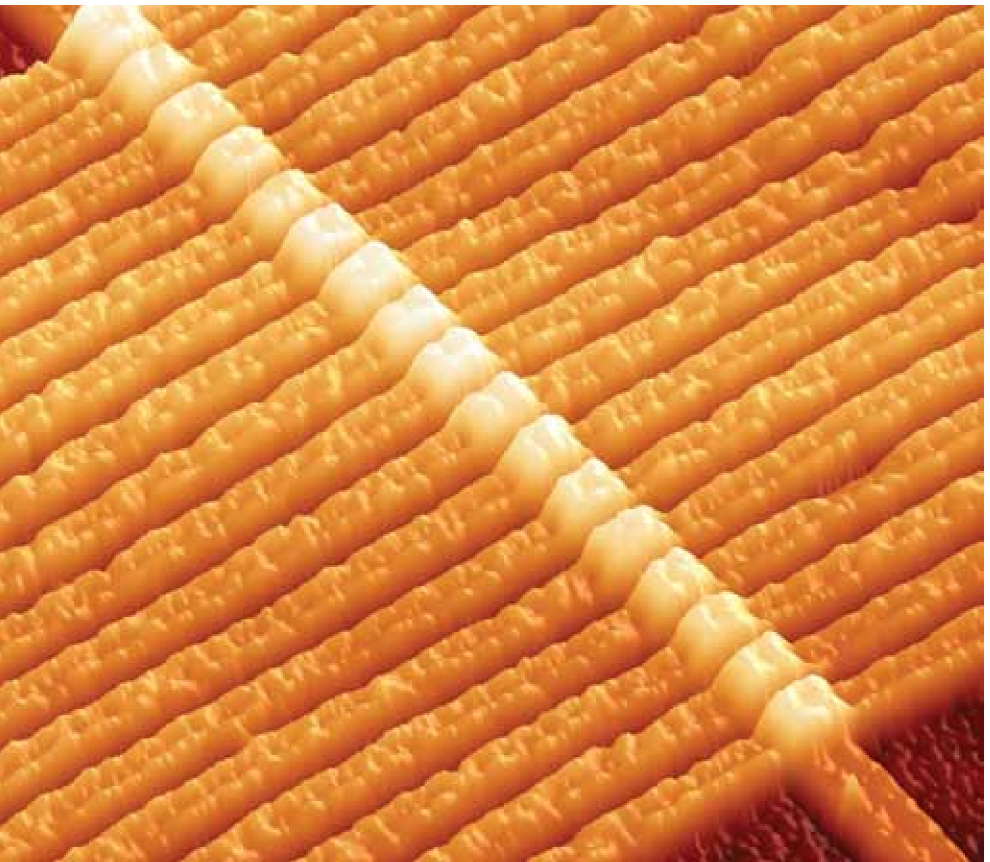
Chua theorized a new circuit element to carry out the missing interaction. This element would behave very similarly to a resistor, but with one key difference: the amount that it impeded the flow of electricity would depend on the current that had already passed through. In essence, this electrical element would have a memory, combining information about the past with its input in the present. For this reason, Chua dubbed this new element the "memristor."

Though it made a splash in theoretical electronics, it would be nearly 40 years until the memristor would be realized in the laboratory. Up to that point, Chua's depiction of the properties of memristors had been likened to the elusive "Higgs boson" of theoretical physics: a particle that exists in theory but has not yet been observed. Then, in 2008, HP Labs announced that they had created a nano-scale circuit that showed exactly the same properties that Chua had theorized. Memristors were real.

Although memristors have yet to be successfully integrated into standard electronics, the ability to engineer circuits with memristors is improving rapidly, and hybrid memristor/traditional computers are expected to make their first appearance in consumer technology in the next few years. Your next computer could have memristors that allow for faster booting and processing. These early successes bode well for a paradigm shift in the future of electronics. While most modern computers perform calculations using dynamic random access memory (DRAM) that must be wiped clean every time a computer loses power, a new memristor-equipped computer could "remember" the state from when it was last turned off and boot up nearly instantaneously.

Memristors could also decrease computers' power consumption, which has increased exponentially as demands on processors continue to rise. Currently, this power consumption poses a significant challenge to increasing the complexity and power of processing chips. Memristors, however, consume relatively little power because storing memory within small units, rather than in a separate system, allows designers to use fewer and shorter wires, and thus less power. "Memristor systems bring data close to computation, much as biological systems do," explains Massimiliano Versace, a researcher at Boston University who is using memristors to study, and possibly create, models that are inspired by human cognition.

The potential to create highly interconnected systems that are eerily similar to the way our own brains are structured is one of the most exciting potential applications for memristors. For many years, scientists have tried to model human cognition, but have often fallen short due to the limitations of our current hardware. Such systems are built with specific locations for computations (central processing units, or CPUs), short-term memory (dynamic random-access memory, or DRAM), and long-term memory (the hard drive). It is an inherently inefficient process, requiring lots of cross-talk and bottlenecks between these discrete areas.



An image of an array of memristors formed at the intersection of crossed microscopic wires. Each is approximately 150 atoms wide.

HP LABS

Unfortunately for cognitive scientists (but fortunately for the rest of us), brains don't work this way at all. And so our efforts to simulate brains have hit this fundamental roadblock: it is exceedingly difficult to create machines that act like brains without being built like them. Although artificial models of neural systems have grown remarkably in complexity and scope, artificial intelligence is still a far cry from resembling actual human brain function.

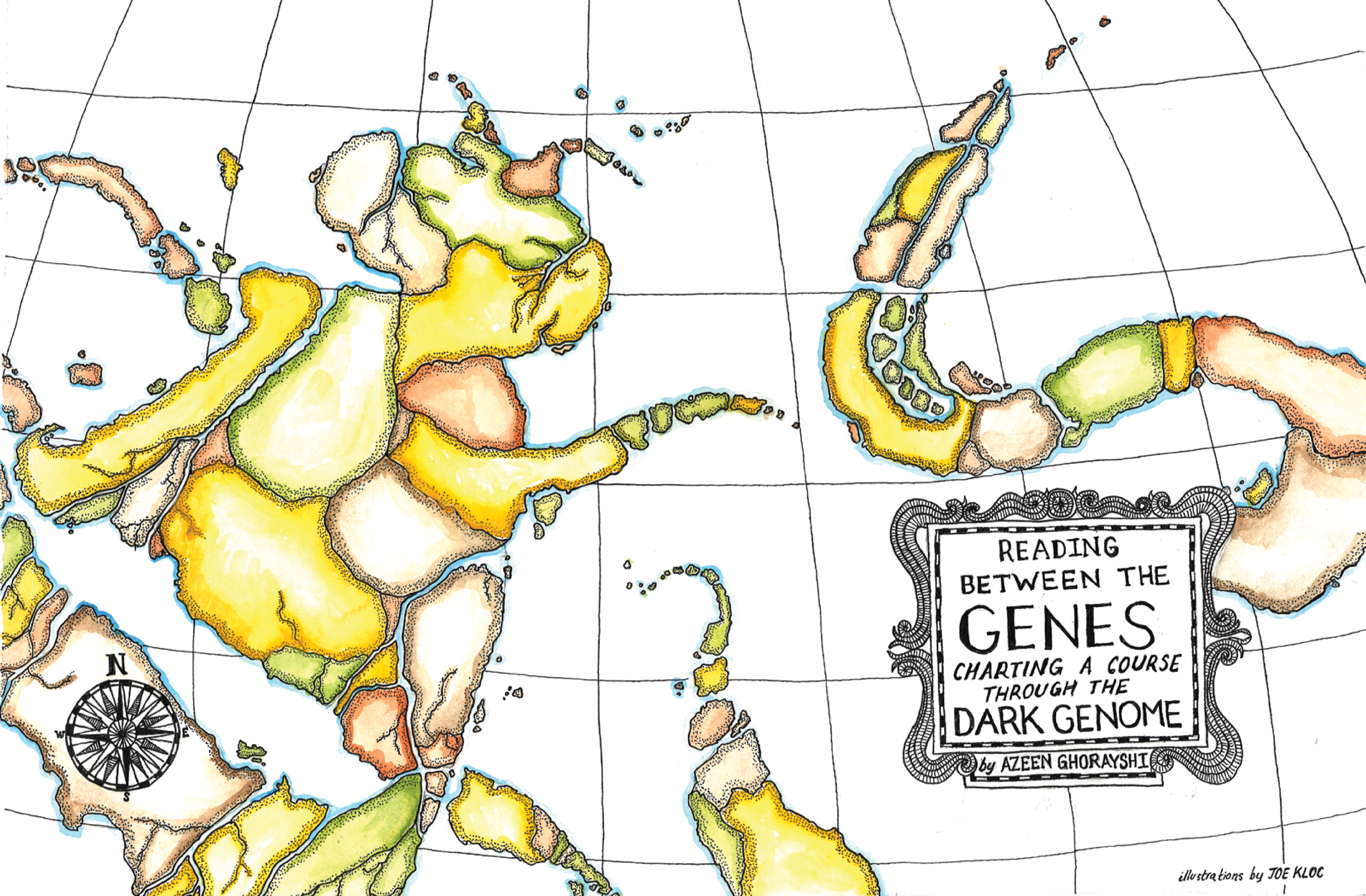
By allowing memory to be embedded directly within artificial networks, memristors are bringing cognitive science one critical step closer to mimicking the way that biological neural networks compute and store information. The CPU, DRAM, and hard drive of current computer systems can now be replaced with a constantly changing, interconnected system of simple memristor units, blurring the line between "computation" and "memory" and allowing engineers to produce more effective artificial intelligence models that truly mimic brain function.

At the forefront of this new approach to artificial cognition is the very man who first brought memristors into the public lexicon, Leon Chua. "Synapses are in fact memristors, axons are made of memristors, and thus, brains are made of memristors," Chua suggests. At the foundation of his vision of a memristor brain is associative memory—in a nutshell, the ability to recognize an entire picture or idea when presented with only a small fraction of it. It is a process theorized to be a fundamental function of biological brains, and it requires retaining information about the past. In artificial circuits, a memristor does this well, essentially "storing" information about its previous activity, even when the circuit isn't active, supporting Chua's analogy.

Chua isn't the only one interested in integrating memristors into brain-inspired circuits. Researchers at HP Labs and Boston University are already working toward a brain-like microprocessor based on memristor technology. "It will perceive its surroundings, decide which information is useful, integrate that information into the emerging structure of its reality, and in some applications, formulate plans that will ensure its survival," write BU researchers Versace and Ben Chandler.

It has been only three years—an extremely short time in the world of technology—since the first memristors were created. What the future brings is anyone's guess; memristors may eventually be used in ways that are unimaginable today. However, if Chua's vision is realized, then they will certainly play a role in creating computers that are more powerful, more efficient, and maybe even more "human" than we can yet imagine.

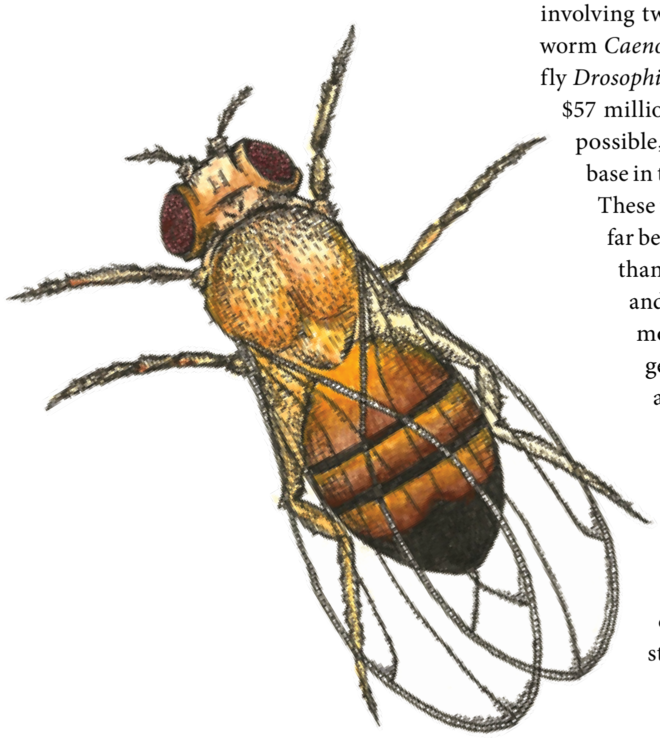
Chris Holdgraf *is a researcher in computational cognitive neuroscience.*



illustrations by JOE KLOC

In 1972, geneticist Susumu Ohno coined the term "junk DNA" to describe every component of the human genome that was not a gene. Suspicious of the assumption that all three billion base pairs of human DNA were functionally important, Ohno wrote, "Triumphs as well as failures of nature's past experiments appear to be contained in our genome." Nearly a decade later, Francis Crick and Leslie Orgel published a review in *Nature* entitled "Selfish DNA: the ultimate parasite," arguing that most DNA in higher organisms was, similarly, "little better than junk."

For many years, the idea that the genome was divided cleanly into two categories—short stretches of genes interspersed among long spans of junk—was a widely accepted view. But by the early 1990s, the concept had begun to grow stale. Geneticists were gradually uncovering more and more functionally significant roles within the "junk" regions, and the very definition of a gene itself was beginning to change. Nevertheless, when the full sequence of the human genome was finally published in 2004, many people were shocked to discover just how few genes our DNA actually contains. Representing only two percent of the entire genome, genes were vastly outnumbered by mysterious non-coding regions. But if this "dark genome" really wasn't junk, what could it all be doing?



"When you first think about genetics 15-20 years ago, the goal was simply to understand the code—the code as it related to genes, gene expression, and the production of proteins," says Gary Karpen, a senior staff scientist in the Life Sciences Division of Lawrence Berkeley National Laboratory (LBL). "But then it became clear that the code was simply not enough." Karpen and a team of over 150 other scientists have just completed an ambitious project whose aims were, according to Karpen, "the next level up" from straight code—at the level of mapping function in the dark genome. What is emerging is a far better idea of the importance of this largely unexplored genetic landscape, a picture of DNA as a dynamic template for life.

The birth of modENCODE

The project, called the model organism Encyclopedia of DNA Elements (modENCODE), was born out of a sister initiative launched in 2003 called ENCODE, which aimed to catalog the complete "parts list" of the entire human genome. The pilot phase of ENCODE centered on annotating only one percent of human DNA, but the complexity of the human genome and the limits of technology at the time necessitated a slight shift in focus.

Thus, in 2007 the National Human Genome Research Institute (NHGRI) launched modENCODE as a parallel effort involving two simpler subjects: the roundworm *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster*. The four-year, $57 million project hoped to identify, if possible, the functional role of every base in the worm and fruit fly genomes. These two model organisms represent far better understood genetic systems than the human genome and, at 100 and 180 million base pairs each, far more feasible approaches to the genome-wide analysis NHGRI aimed to achieve. The hope was that ultimately modENCODE could serve as an extended pilot for the entire human ENCODE project, helping us better understand how it is that complex, three-dimensional organisms arise out of linear strands of DNA.

A manifold blueprint

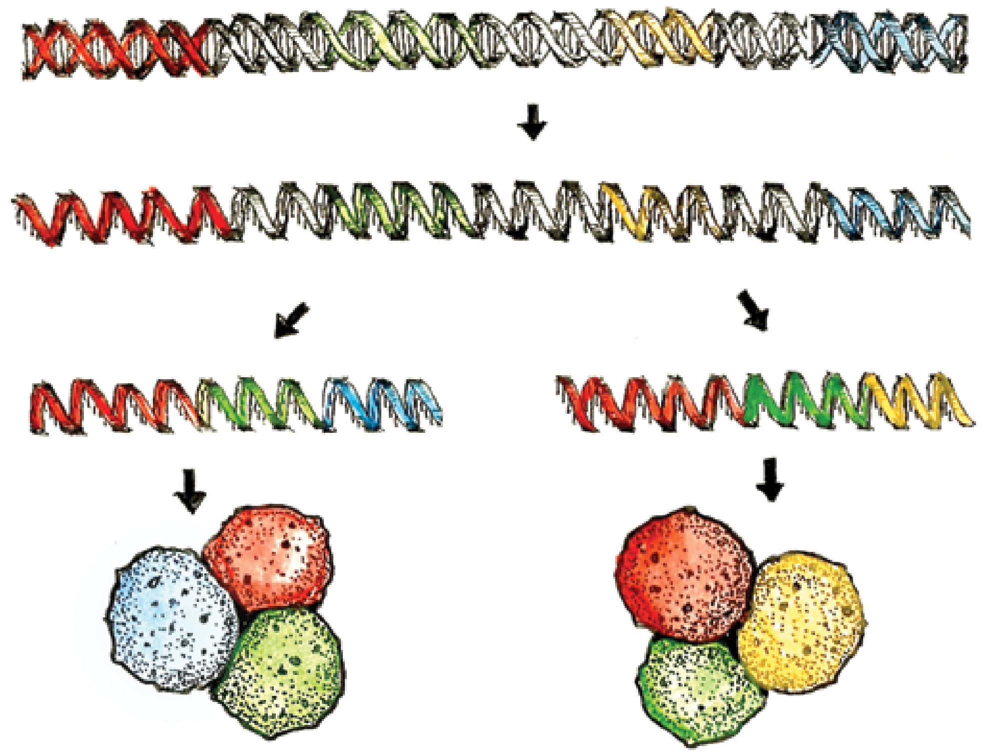
DNA is made up of four different molecules called nucleotides, paired and bound together to form the two anti-parallel twisting threads of the double helix. Some segments of DNA are known as genes, meaning that their nucleotides will be transcribed into a slightly different chemical form called RNA. A specific type of this RNA—called messenger RNA, or mRNA—will then leave the nucleus to serve as a template for synthesis of the protein building blocks that carry out our cellular processes. Proteins not only make up the structural framework of our cells, they also catalyze most of the chemical reactions that make cells work.

Yet all cells, from kidney cells to neurons to muscle cells, possess exactly the same copy of DNA. In its entirety, DNA exists only as a template from which an immense number of readouts can occur; not all genes are expressed at all times in all cells, and it is precisely this capacity for different combinations of expression that allows for the astonishing diversity of our cellular processes. Geneticists are still unclear exactly how these highly ordered patterns of gene expression are achieved. The answer may lie in the dark genome.

From base to function

The architects of the modENCODE project sought to chip away at this question by first assembling a map. By annotating the function of every base of DNA in the two model organisms, they hoped to gain some insight into how transcription is regulated across cell types and throughout development.

They analyzed function along two broad sets of factors. The first set, referred to as "functional elements," include small proteins that regulate transcription, as well as non-coding RNAs (ncRNAs) that help to regulate gene expression after transcription but before protein synthesis. The second set, known as epigenetic elements, are not contained in the sequence of DNA itself, but include chemical marks on the surface of DNA that physically influence what regions of the genome are silent or active. Over 50 participating labs around the world analyzed specific types of functional or epigenetic elements in one of the two model organisms to assemble a topographical map of function along the linear DNA sequence.



In alternative splicing, a single gene can be read in multiple ways to produce different proteins. After transcription occurs (step 1), distinct segments of the RNA called introns (gray) are removed by cuts made on both sides at locations called splice junctions. The remaining RNA (colored) can then be reconnected to form different strands of mRNA (step 2). The different mRNAs will then serve as templates for the synthesis of different proteins (step 3).

The transcriptome

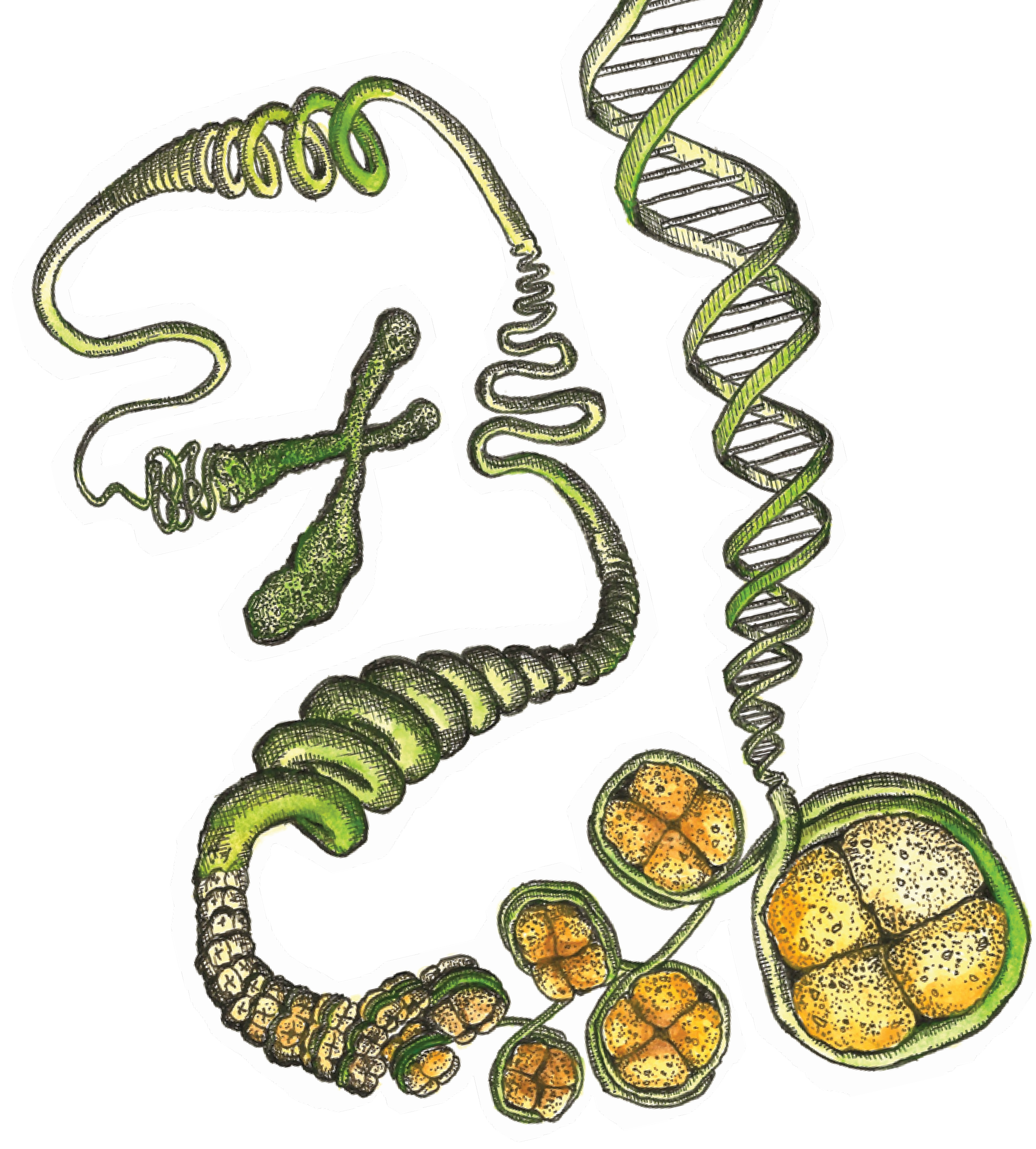
"We wanted to crack the code to discover the rules required to read a genome—any genome," says Susan Celniker, head of the Department of Genome Dynamics at LBL who, along with Karpen, was one of the senior principal investigators for modENCODE. Her lab was on the *Drosophila* team and was responsible for mapping out the entire transcriptome—all of the sequences of DNA that are transcribed into RNA.

Counting both coding and non-coding RNAs, the transcriptome comprises about 60 percent of the fly genome. In order to screen such vast amounts of RNA with single-base resolution, Celniker's group used a high-throughput technique known as RNA-seq. Investigators isolate the more than 25 million scattered fragments of RNA that have been transcribed from DNA. After making some chemical modifications that allow sequencing to occur, they convert the RNA back to DNA through a process called reverse transcription, giving them the coding DNA, or cDNA, for the original set of RNA fragments. They then sequence the cDNA and align it with the original genome sequence to map the transcriptome.

Celniker's group generated almost six thousand-fold coverage of the previously annotated fly transcriptome. Combing through their RNA-seq data, they identified nearly two thousand new transcribed regions that had been missed in previous annotations. These new regions include sequences that encode small proteins, as well as small non-coding RNAs that participate in the regulatory machinery that help control gene expression and protein production. In perhaps their highest-impact finding, Celniker's group identified over 22,000 new splice junctions—areas where, after transcription, distinct chunks of transcripts can be cut out, allowing for different combinations of mRNA. Alternative splicing thus allows a single gene to code for several different proteins, based on the different possible patterns of cutting and pasting.

The discovery of the vast number of previously unidentified splice junctions and new transcripts gives us a far better idea of the sheer quantity of potential protein products in each cell. Insight into an additional layer function, however, is provided by the identification of the new non-coding RNAs, many of which are involved in splicing events, promoting or repressing transcription, or silencing mRNAs to finely control levels of protein synthesis. The overlapping output of these two mechanisms—variety of combinations within transcripts and an intricate regulatory machinery—is crucial to understanding our genome's differential workings from cell to cell.

Illustrating this, Celniker's group then carried out comparisons across 27 distinct developmental stages as well as between the sexes. Interestingly, they found that the



To fit inside each individual cell, DNA must be condensed and packaged into fibers called chromatin. The double-stranded helical DNA first wraps around clusters of proteins called histones. The histones are arranged along the DNA like beads on a string, allowing the histone-DNA spools to coil, fold, and loop around themselves. The final product is the tightly packed fiber of chromatin, organized into distinct sets of chromosomes.

number of expressed genes increases from around 7,000 in embryonic flies to around 12,000 in adults. They also analyzed changes in expression patterns of specific genes across development, finding genes that are highly upregulated in the larval developmental stages and then essentially shut off as the fly matures. Between the sexes, they noted

> "We can only assume that the rules are there and keep looking. But the reproducibility of biology tells us that these rules must exist."
>
> *-Manolis Kellis, modENCODE computational biologist*

that adult males express around 3,000 more genes than their female counterparts. The functions of all of these genes are not yet known, but they are all clearly implicated in development—both across time and between sexes. Celniker hopes that her group's identification of the genes will spark more targeted research in the *Drosophila* community.

"For me," says Celniker, "the project will not be over until I know exactly how a single cell with its single copy of DNA turns into a complex organism like the fly. We're not there yet, but we're certainly assembling the building blocks."

The chromatin landscape

With 100 and 180 million base pairs even in organisms as "simple" as the worm and the fruit fly, each copy of DNA is simply too long to exist as a linear molecule in a tiny cell. Instead, it is condensed and packaged into chromosome pairs—the worm has six and the fruit fly has four, while humans have 23. Chromosomes are made up of chromatin, which consists of DNA wrapped around clusters of tiny proteins called histones, arranged along the DNA like beads on a string. These histone-DNA spools then supercoil around themselves in meandering loops and folds, finally forming the tightly-packed structure of chromatin.

Karpen and his lab at LBL study what is called the "chromatin landscape" of the fruit fly—the hundreds of chemical tags that can be added to histones to ultimately affect levels of transcription. The modifications are then recognized by the cellular machinery that respond to these chemical signals, resulting in silencing or activation of the DNA in the tagged region of chromatin.

Histone modifications are one of several types of epigenetic mechanisms that influence gene expression. They are not encoded within the genome; rather, they impact the readout of DNA through changes to the protein components of chromatin. These epigenetic changes are also heritable, meaning the modifications are passed along through cell divisions and can lead to unique signatures amongst different cell types.

"Most of the time, people have studied these histone modifications in isolation," says Karpen. "But what we were interested in is how they work in combination." Using a method called chromatin immunoprecipitation (ChIP) and high-throughput sequencing, Karpen and his group were able to identify chromatin marks associated with various regions of the fly genome. By looking at different combinations of 18 specific chromatin marks, they delineated about 30 distinct chromatin states correlated with the position of genes and their levels of expression. These states included highly predictable associations with transcription start sites, gene length, silent or active regions, and even gene function. "There's an issue here with cause and effect," Karpen says. "It's not just the type of modification that's important, but where the modification is, which histone, which amino acid in that histone, what recognizes that modification, what other proteins are brought in—there's a lot of complexity."

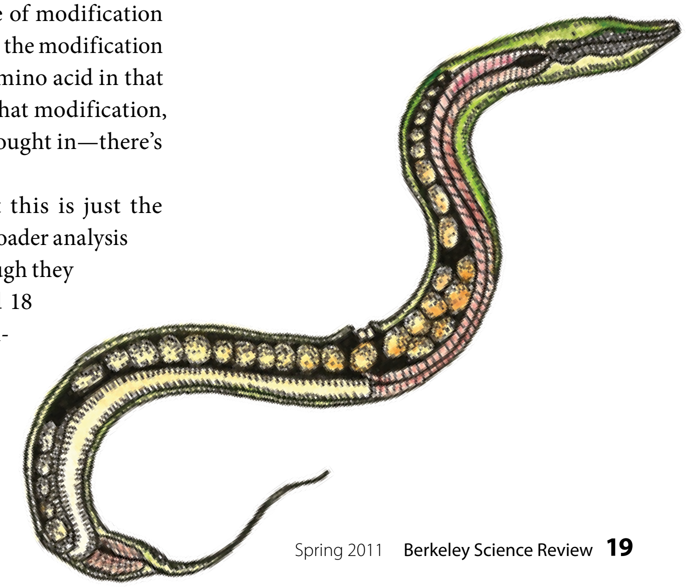
Karpen stresses that this is just the beginning of this type of broader analysis of chromatin marks; although they thoroughly characterized 18 histone modifications, hundreds remain. Regardless, Karpen's work adds another topographical layer to the genomic landscape. While functional elements control gene expression at the level of DNA and RNA, transcription and protein synthesis, epigenetic elements allow for yet another route of cell divergence—one that occurs above the level of DNA sequence. "This is really the level of dynamic genomics," Karpen says. "I have to say, I just find the fact that we know so little incredibly exciting."

From map to model

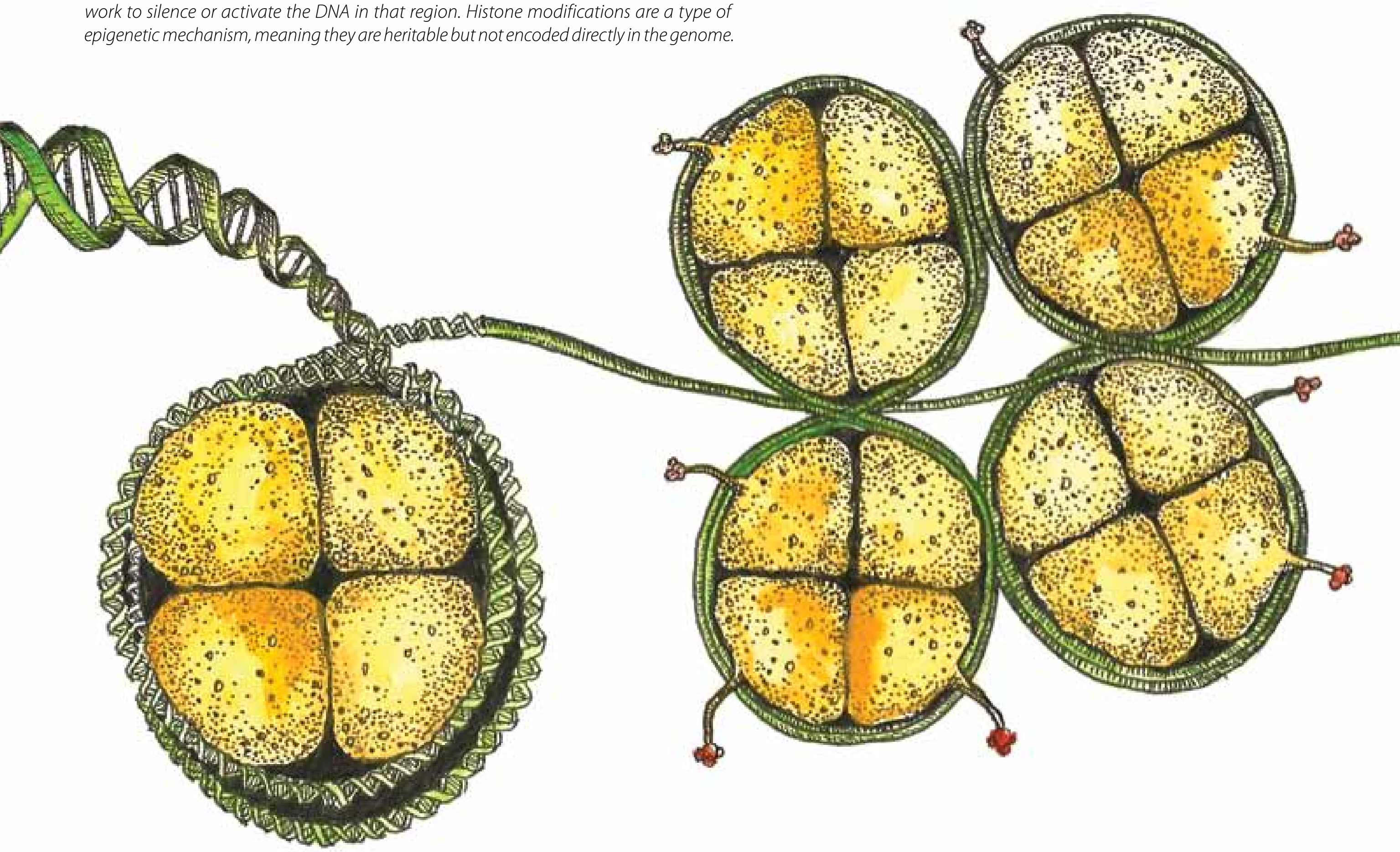
Once the individual research groups had all assembled their final data, *Drosophila* modENCODE had over 700 datasets profiling transcripts, histone modifications, and replication programs. Karpen, Celniker, and the rest of the *Drosophila* team then submitted their finished datasets to Manolis Kellis, head of the Computational Biology Group at Massachusetts Institute of Technology. Kellis headed the modENCODE Data Analysis Center, which took all of the finished data and integrated it into a coherent story, creating the predictive and comparative genomics models that the consortium hopes will eventually help shed light on parallels in the human genome.

"The biggest question we asked ourselves was, how do we go beyond simple annotation? How do we compare all these datasets together to reveal new insights?" says Kellis. To do so, Kellis and his group at MIT attempted to reconstruct the full regulatory network of the fly from the pooled datasets.

To assess the completeness of their reconstructed model, Kellis's Data Analysis Center attempted to predict gene expression



Histone modifications are one of many cellular mechanisms that work to control gene expression. Possessing long amino acid tails (yellow), histones can be "tagged" with chemical modifications (red). These tags are then recognized by other cellular machinery that can work to silence or activate the DNA in that region. Histone modifications are a type of epigenetic mechanism, meaning they are heritable but not encoded directly in the genome.



levels based solely on the expression levels of their regulators. Looking across numerous developmental stages and cell lines, Kellis's group was able to successfully predict over 60 percent of gene expression patterns in about a quarter of the cell lines studied.

These are only very preliminary models, Kellis says, and predicting the expression patterns of an entire genome remains an enormously complex problem. For modENCODE's first round of predictive modeling, for example, the group was only able to incorporate a certain subset of pre-transcriptional functional elements whose targets are already well-established. As more and more of the targets of the newly mapped regions are characterized, Kellis and others in the computational field will be able to cast a wider net to tease out the underlying logic of genomics. "We can only assume that the rules are there and keep looking," says Kellis. "But the reproducibility of biology tells us that these rules must exist."

The future of ENCODE

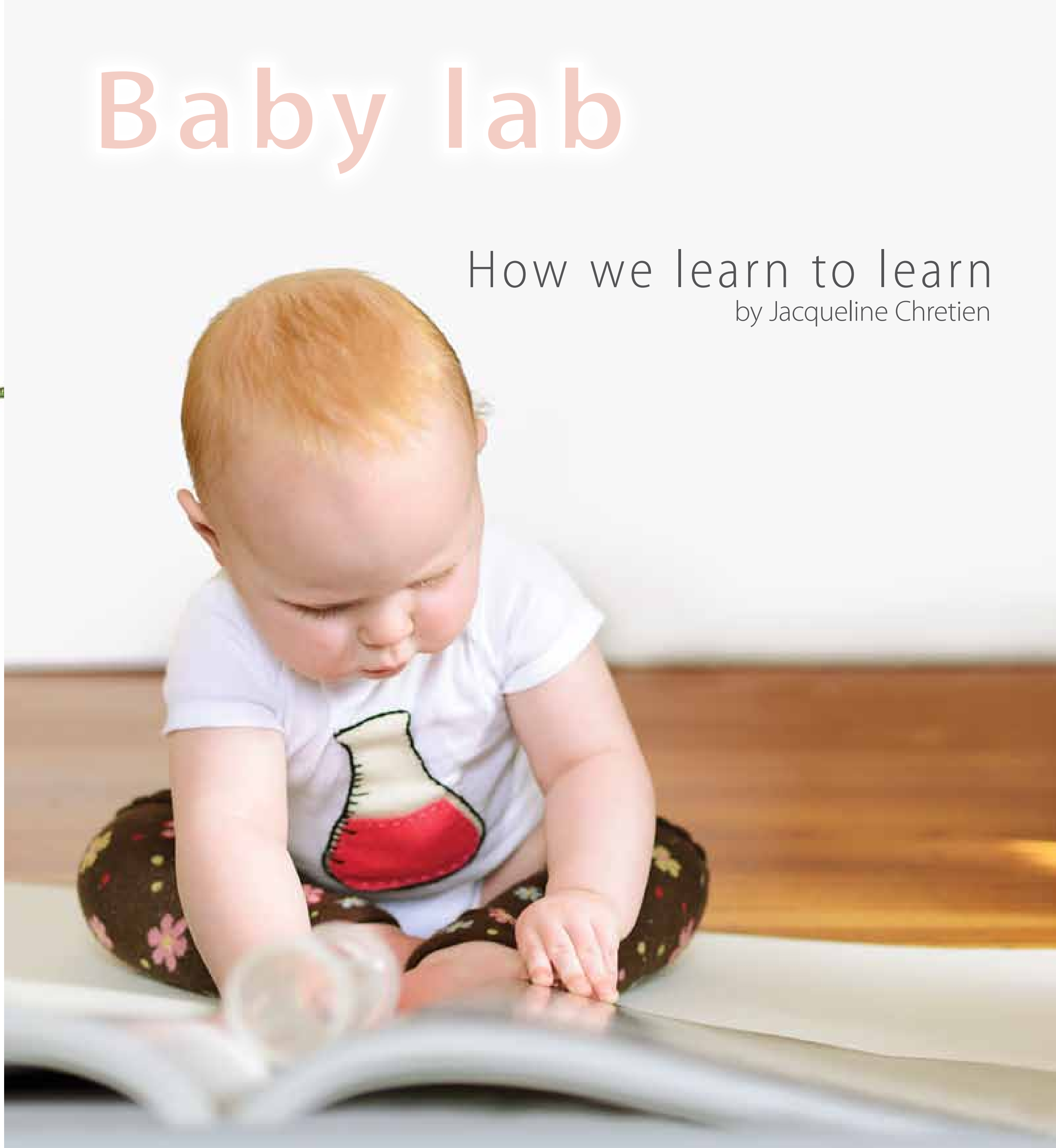
The original draft of the human ENCODE stated that the project would proceed in three stages: a pilot phase, a technology development phase, and a production phase. Now that modENCODE is complete and the methodologies are finally tested and refined, all that remains for ENCODE is the massive production phase. "There's been a lot of thinking about how to go about systematically understanding the human genome, and it's out of those conversations that modENCODE emerged," says Kellis. The task is no less gargantuan, but with the technology and framework finally in place, a completed human ENCODE may only be a few years away.

With the modENCODE papers now published, more than 80 percent of the fruit fly genome is annotated and fully available to the public—up from about 25 percent before the project began. Yet though the consortium has assembled an impressively huge dataset, we are still unable to trace exactly how a single cell with a single copy of DNA becomes a complex living and breathing organism. The *Drosophila* and *C. elegans* genomes have been "mapped," but it's really only the faint outlines of function that have emerged—we do not yet know the intricate mechanisms by which each of the elements work, let alone their very specific targets. "The modENCODE project was really just interested in providing a starting map—the equivalent of the first explorers coming to the New World," says Karpen. "We need large-scale projects like this to provide the kind of foundational knowledge that allows the more intricate mechanisms to be worked out from there." A complete understanding of life's genetic computations may be far off, but we now have the first maps to guide us. The dark genome is getting lighter and lighter.

Azeen Ghorayshi *is a research technician in molecular and cellular biology.*

OPPOSITE: MAREK JAKUBOWSKI

Baby lab

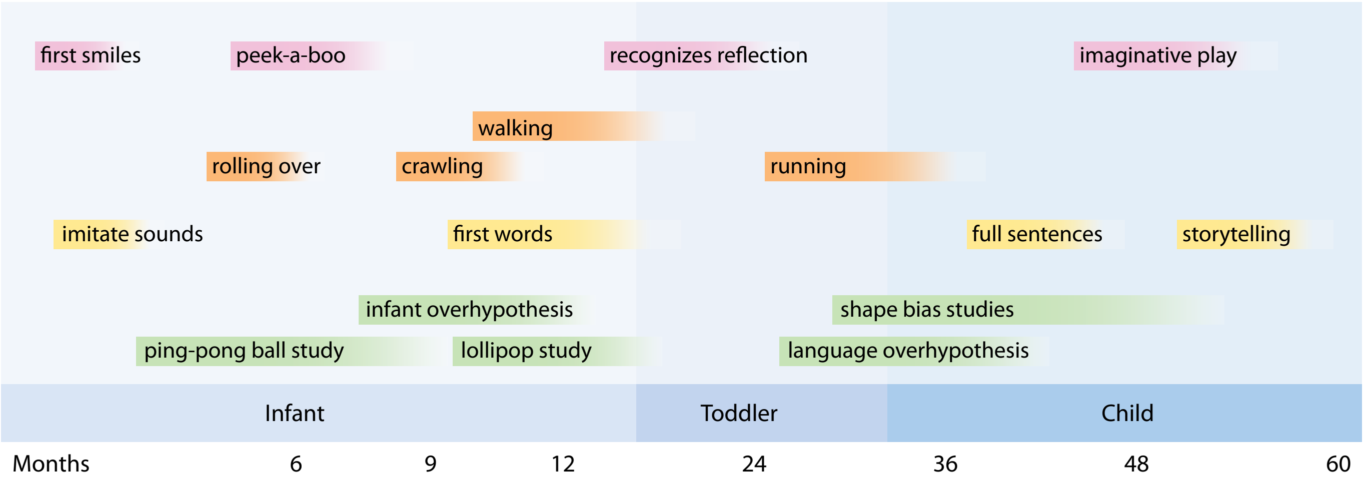


How we learn to learn

by Jacqueline Chretien

My nine-month-old daughter, Ellie, is a statistics genius. This may sound like typical new mom bragging, but it's not; it's scientific fact. According to research from Professor Fei Xu's Infant Cognition and Language Lab in the Department of Psychology at UC Berkeley, the average six-month-old is pretty good at making basic estimates of probability, and by the time they learn to walk—around a year old—most babies are experts. Children are also masters of language acquisition, pattern recognition, and inductive reasoning. In fact, in almost every arena that's been investigated, babies and children are remarkably adept at learning. But while they may be excellent at figuring out the world around them, it's still unclear exactly how much they know, and when, and what mechanisms are in place to allow this rapid learning.

Armed with colored ping pong balls, light-up lollipops, stuffed animals, and invented words, researchers in the Xu lab are making strides toward answering these questions. The answers they find may have applications in fields from parenting to computer programming.



What's in a name?

It's the oldest debate in developmental research: do we learn to learn, or are we simply biologically programmed to soak up information from our surroundings and experiences? The obvious answer, of course, is that it's probably a little bit of both, but the precise location of the boundary between nature and nurture is a matter of intense debate.

Postdoctoral researcher Sylvia Yuan is investigating this boundary by studying word learning in toddlers. Previous research has suggested that by the age of two or so, children have a number of cognitive biases that help them solve the nearly impossible logic problem of what words mean. "Even if we explicitly label something, like, 'this is a Lego'," Yuan says, holding up a yellow block, "there are lots of logical possibilities as to what the word could be referring to. It could be referring to the color yellow, it could be referring to something hard, it could be referring to something on my hand."

But kids don't run through all of these possibilities every time they learn a new word. Instead, they have a number of biases that help them narrow in on the right definition fairly quickly. For example, children tend to assume that a word refers to an entire object, rather than just part of it—"car" describes the whole vehicle, not just its hood. Similarly, they assume that labels apply to the shape of the object, rather than another characteristic, like color or texture. This is a useful assumption, because objects are likely to have a stereotypical shape (a "ball" is usually ball-shaped, a "cup" is usually cup-shaped) but may not always come in the same color or size.

These biases have long been thought to be innate, since they arise so early in development and are so universal. Intriguingly, though, children seem to weigh information differently depending on the type of object that's being defined (color, for example, is more important when learning the names of foods, while texture becomes important when learning the names of animals), suggesting that experience might play a role in bias formation.

This process of bias-building is referred to as overhypothesis formation. "As they're learning about each word," Yuan explains, "they might be testing in their head: is it the texture, is it the color, is it the shape? And when they see another example, they might be thinking, 'okay, it doesn't seem like it's the texture, it seems like it's more the shape.'" As children form a hypothesis about what each object is called, they're also forming a more abstract rule, or overhypothesis, that defines how object names are assigned in general.

Yuan and others in the lab are trying to determine what factors affect overhypothesis formation when children are acquiring new vocabulary. Instead of examining established biases, like shape, the lab introduces artificial categories so they can study the overhypothesis formation process as it happens. In one typical experiment, preschoolers must figure out that markings on the tail and left foot of otherwise identical stuffed animals determine their identity—for example, ones with a question mark on the tail and an exclamation point on the left foot might be "daxes," while animals with a different set of marks on these two appendages might be "blickets." Here, the usual biases aren't helpful, so children have to learn not only what each animal is called (the hypothesis), but at the same time figure out a weird new rule that governs how these animals are named (the overhypothesis).

By manipulating this basic experimental setup, researchers can ask what variables affect how children form overhypotheses. One key finding has been that the number of categories presented seems to be more important than the number of examples per category. Preschoolers shown eight animals are more easily able to classify them if there are four categories with two animals each (two daxes, two blickets, two faps, two zoogs) than if there are two categories with four animals each (four daxes and four blickets). This suggests that each new category a child sees either strengthens or changes her overhypothesis about how categories are defined in general, indicating that it's a dynamic process.

Yuan plans to use these initial studies as a launching point to investigate how other factors, like adding noise by varying the sizes or shapes of the items, or introducing exceptions to the rules, affect overhypothesis formation. Increasing the number of non-informative marks, for example, could go either way—it might help children focus in on the actually useful information more quickly, or it might just confuse them. "We're trying to figure out what the environmental inputs are that make it easier or harder for them to achieve an overhypothesis," Yuan says.

MAREK JAKUBOWSKI

Behind door number three...

This sort of "smart" mechanism that allows children to draw up broad, organizing principles based on a small number of examples is crucial for learning. Without an efficient way to generalize the knowledge gained from one experience and apply it to another, it would simply take too long for kids to figure out how the world works. (And as anyone who has ever watched a child repeatedly test gravity with the food items on her high chair tray will tell you, it takes long enough as it is.) But until recently, it hasn't been clear whether overhypothesis formation is limited to word learning, or when this skill first arises.

"Our working hypothesis is that there is a set of learning mechanisms in children that support rapid learning," says principal investigator Fei Xu. She and others have predicted that even babies less than one year old might be able to form overhypotheses, but probing infant psychology can be difficult. Simply working with babies can be a challenge in and of itself. After all, there aren't many fields in which papers routinely include lines like, "An additional four subjects were tested but excluded due to fussiness." Entertainingly, researchers report that fussiness isn't as much of a problem as bodily functions. Stephanie Denison, a graduate student in the lab, puts it delicately: "Occasionally they get distracted by... digestion during the trial." Yuan elaborates, "We would have observers write down, for example, 'face is all red and squinty'... the kids sort of stop looking at what's going on on the stage and in the trial." Distractability can also be problematic. "One little one just pulled off her socks in the middle of it. There's a foot flying over there, a foot flying over here," lab manager Christie Reed recounts. And the occasional baby will fall asleep during a study, too.

It's also tough to find experimental methodologies that can truly illuminate infant cognition. "Smart as infants are, it is hard to work with them, since they do not yet talk or follow instructions," Xu says. Researchers can't just ask very young babies what they're thinking—they have to figure it out in some other way. "We often capitalize on the fact that infants, just like older children and adults, are very curious," says Xu. "They pay more attention to things that are new, interesting, and unexpected." This is used to researchers' advantage in the classic "looking time/violation of expectation" measure, a well-established test for determining what babies are able to predict. Because babies spend a longer time looking at things that are novel or surprising, an infant's looking behavior can be measured to provide a metric of whether he finds an event expected or unexpected.

Another day at the Infant Cognition and Language Lab...

We get the best one-liners from preschoolers. I had this preschooler today, actually. I said...

So, why do you think that that's how this works?

Oh. I know *LOTS* of things.

Oh, you do?

I do. I really know a lot of things.

She's barely four...

-Stephanie Denison, PhD Student

Measuring looking time was crucial for the Xu lab's studies of overhypothesis formation in infants (as opposed to the toddlers in the object naming study). In these experiments, nine-month-olds watched while a researcher removed objects from various boxes. The first few boxes contained objects of the same shape, but of different colors and sizes. Then, surprise! The final box contained, say, a star and a circle. If the babies had formed an overhypothesis based on their previous experience—"boxes contain items with the same shape"—they should have looked longer at this unexpected event. And, indeed, this was the case. Importantly, babies formed overhypotheses equally well when the items in each box were all of the same color but different shapes, showing that this learning mechanism is general and not, say, the manifestation of an innate shape bias.

These experiments make it clear that infants can recognize patterns very quickly and use them to make generalizations at a very early age. According to Xu, that suggests the presence of a powerful learning mechanism that might underlie many different biases that were previously thought to be innate. Of course, it remains to be seen whether this mechanism is itself learned—are there over-overhypotheses to be discovered? In the future, comparisons between overhypothesis formation in infants and toddlers may also help illuminate how this process changes with age. If pattern recognition is something that improves with practice, it's possible that young babies will have a harder time with confusing cases than more experienced toddlers and children; on the other hand, it's also possible that the younger subjects may actually have an easier time because

JACQUELINE CHRETIEN

Researchers can measure babies' looking behavior to determine whether they find a particular event (here, a sample of colored ping pong balls from a larger box with a different color distribution) to be expected or unexpected.

> Kids will let you know that they think your game is a little boring. They'll sigh, they'll say...
> *Are we almost done? This game's too easy for me.*
> And they're totally bombing, but they say...
> *I'm WAY too smart for this, just so you know.*
> -Stephanie Denison, PhD Student

Graduate student researcher Stephanie Denison (left) tries to get the attention of a subject with a glowing pink lollipop while mom looks on.

MAREK JAKUBOWSKI

they haven't yet learned to privilege certain kinds of information over others.

Masters of probability

Early in January, I had a firsthand look at studies investigating whether infants are able to use statistical reasoning to predict the likelihood of an event when my six-month-old daughter, Ellie, participated in an experiment in the Xu lab. After getting a basic rundown of the protocol from lab manager and researcher Christie Reed and signing some consent forms, we strapped Ellie into a high chair facing what looked like a puppet show stage in the experiment room. I was allowed to stay, but had to turn my back to the experimental setup. Babies pay close attention to cues from their parents, so any subtle shift in my behavior could have skewed Ellie's responses and invalidated the results. On the other hand, babies are prone to meltdowns when left alone in a strange place. So: parents stay, but face away from the stage.

While Ellie watched from her high chair, Reed showed her a box containing a 4:1 ratio of pink to yellow ping pong balls. (Other versions of this study have used red, white or green balls—colors selected "entirely based on ping pong ball availability," says Denison, one of the lead researchers on this project). After this demonstration, Reed took out different samples of ping pong balls, and filmed Ellie's reaction when each sample was revealed. Was she surprised when the sample contained four yellow balls and one pink ball, instead of the opposite?

We weren't told her looking time results (although, like most overbearing and/or intellectually curious parents, I did ask), but according to Reed, odds are pretty good that she was surprised and her reaction reflected it. "The four-month-olds aren't doing all that well," she says, "but so far the six-month-olds do have a grasp on it."

Amazingly, older infants can even adjust their expectations based on other sources of information, from both the social and physical realms. For example, if, prior to the trial, the experimenter demonstrates a preference for white balls, 11-month-old babies will usually look longer at a sample that doesn't match the researcher's preference, even when it matches the contents of the box. More impressively, if the researcher is blindfolded the 11-month olds know to disregard the researcher's preference and expect a representative sample. "This tells us that they understand something about some of the sampling processes, like visual access being important, random sampling versus non-random sampling, those kinds of things," Denison says. Eight-month-olds, however, don't adjust their expectations when the experimenter shows that they prefer a particular color. This suggests either that infants start to figure out other minds at some point between eight and 11 months of age, or that it takes a little while for them to apply that filter to the probabilitic intuitions they have already mastered.

Another permutation of this experiment—in which Ellie also participated this February—looks at how babies are able to "recalculate" expected probabilities. Babies were shown boxes containing three colors of ping pong balls, one of which was immobilized with Velcro. "We teach them that the ones with the Velcro don't move, we obviously don't think they know anything about Velcro," explains Denison. The 11-month-olds were able to integrate the new information, and expected to see a sample that reflected only the remaining, mobile balls, showing again that babies' probability estimates can be adjusted based on their knowledge about the physical world.

Now, Denison and others in the lab are investigating how babies deal with a slightly more sophisticated scheme, where some, but not all, balls of a particular color are immobilized. This effectively requires the babies to multiply two probabilities together, which should make it harder for them to predict what a representative sample would look like.

Determining how well babies can estimate expected probabilities under many kinds of conditions allows the researchers to probe more deeply into how infants arrive at these estimates. Humans are notorious for failing to evaluate probabilities accurately, depending on a variety of external factors (the 10 percent of American homeowners who are underwater on their mortgages can tell you about the perils of optimism bias), but not much is known about why we make the mistakes we do. Studying whether babies are susceptible to the same kinds of errors as adults may help us solve this cognitive puzzle.

Come on over, baby

While looking time is a well-respected and frequently used experimental measure, it can be tricky in practice. Looking behavior can be affected by many different factors, all of which need to be controlled. Even then, the difference between the reactions to an expected and unexpected condition may only be a few seconds. And of course, no matter how good the assay, it's always nice to have a complementary experiment, particularly one that's very different in approach.

With this in mind, the Xu lab has developed a novel, active, and frankly just darn cool measure of babies' thought processes: crawling toward a hidden lollipop. For this assay, babies are first offered a black lollipop and a pink lollipop; whichever one they reach for or crawl to is established as the preferred color. Once a preference is determined, the babies are shown two boxes containing opposite ratios of pink to black, and the researcher removes one lollipop from each container in such a way that the baby can only see the stick. If this were a looking time experiment, the lollipop's color would be revealed and the baby's reaction would be monitored. In this new measure, however, the baby is allowed to crawl or walk to either cup to show that she knows which one is more likely to contain the preferred color. Eleven-month-olds pick the right cup about 70 to 80 percent of the time, showing that they have a reasonably firm grasp of single-event probability.

As with any research with babies, however, the crawling measure has its fair share of difficulties. First, it's difficult to be sure that the baby has a true preference for one color. After all, babies can be fickle. The initial experimental design called for four preference trials, but the babies lost interest by the time the test trials rolled around, making the results difficult to interpret. "It's always funny when as a researcher you think you're doing this really intelligent, wonderful task, and the baby should be so engaged, and they're like, 'hmm, I think I'm just going to go see what's over there on the door,'" Denison says. Short attention spans have also complicated the experiment in cuter ways. Some babies, when asked to select a lollipop, choose to hug the experimenter instead.

So, the experimenters try to make the single preference trial really count. After the selection is made, the researchers add some positive reinforcement, clapping and generally encouraging the baby to feel that she's made a truly excellent choice. (This technique will also be familiar to anyone who has ever tried to convince a skeptical baby that she likes the new vegetable she just tried.) And at the end of the experiment, babies shown jars containing all pink or all black lollipops usually head for the preferred color, suggesting that the preference is consistent throughout the experiment.

The researchers also aren't above using some tricks in an effort to achieve uniform color preference. "The pink one lights up now, which has made it much, much, much easier to get basically all the babies to prefer pink," Denison says.

So far, this new method has been used to show that babies not only understand which bin is more likely to yield a pink pop, but that they can apply this understanding to guide their physical actions. Now, variations on this setup can be used to pick apart any number of cognitive processes, including overhypothesis formation. It's also much easier to apply an active measure like this to non-human animals (in fact, Denison and Xu originally came up with the idea as something that could be used with rhesus macaques), and future comparative experiments are planned in monkeys and even squirrels. These comparisons may help us understand what makes human cognition so unique.

Lab to life

The Xu lab's insights into baby cognition are fascinating in their own right, but there are also practical applications for this research. Increasingly, computer scientists are collaborating with developmental psychologists to create models of reasoning, learning, and language acquisition that inform artificial intelligence and natural language processing. There are also applications in clinical psychology. Infants' performance in basic cognitive tasks like these is increasingly understood to be correlated with their abilities later in life, so more detailed knowledge of typical development may make it easier to identify atypical development at very early stages, when interventions would be the most effective.

Normally developing children can benefit from new insights, too. Knowing when specific cognitive skills are emerging can help parents and educators engage with these processes and give children richer learning environments. "I feel that if you're aware of this sort of thing, that could make you interact with the baby differently, or maybe provide different kinds of stimulation," Yuan says. Personal experience bears this out—now when I'm browsing at the toy store, I'm on the lookout for games that will challenge Ellie's probabilistic reasoning skills. And when she approaches the age at which language acquisition explodes on the scene, I'll be sure to rein in my use of expletives at just the right time.

> **Another day at the ICL Lab...**
> The cutest thing is seeing their little faces when they kind of squint, or they'll be perplexed. You can see they're thinking, they're looking.... you can just tell that in their little minds, the gears are going.
> - Christie Reed, Lab manager

Though major questions still remain, and the nature versus nurture debate is increasingly thought of as something of a straw man, work from the Xu lab and others in the field has certainly shown that babies are—as Denison puts it—"really, really smart." As a doting mom, this just confirms what I already believed, but as a scientist? It's nice to have some peer-reviewed citations to back me up.

Jacqueline Chretien *is a graduate student in molecular and cell biology.*

Drowning in mud

Scientists confront an ongoing eruption

The Lusi mud volcano *devastates the landscape in Sidoarjo, Indonesia. In the distance, steam rises from the volcano's vent.*

Photograph by Craig Cooper

At 5:00am on May 29, 2006, residents of the Indonesian city of Sidoarjo awoke to explosive eruptions of gas, water, and so much mud that within days the entire village was buried up to its rooftops. Although devastating, the eruption would have been manageable—were it not for the fact that it has never stopped. Nearly five years later, the eruption has a name, Lusi, and has set a record as the largest mud volcano in the world. Since that May morning in 2006, Lusi has ejected an average of 50,000 cubic meters of mud—enough to flood a football field to a depth of ten meters—every day.

by Keith Cheveralls

with photo essay by Steve Axford

After flowing for nearly five years, the mud now covers over six square kilometers and has buried a dozen villages. Tens of thousands of Indonesians, most of whom were already poor, have seen their homes and land destroyed, and thousands more are threatened by the flow of mud, which, while currently contained by a series of levees, shows no sign of stopping.

Two competing explanations for Lusi's sudden eruption have emerged. Measurements indicate that the mud is coming from a vast, pressurized reservoir about one and a half kilometers below the surface. Geologists posit that a series of pressure spikes in an exploratory natural gas well 140 meters away from the volcano perturbed the reservoir and triggered the eruption. Another theory, championed by the drilling company that owns the well, focuses on an earthquake that occurred two days prior to the eruption and 150 miles away from it. This theory suggests that the earthquake reactivated a dormant fault beneath the reservoir, destabilizing it and triggering the eruption.

The severity of the eruption itself, combined with the dramatic debate between geologists, who mostly favor the drilling hypothesis, and the drilling company, with its obvious interest in blaming the eruption on a natural cause, has led to extensive media coverage. Meanwhile, the eruption continues, the mud advances, and other questions haunt geologists and displaced residents alike. Why is Lusi ejecting so much more mud for so much longer than any other mud volcano? Will the surface near the volcano eventually collapse under its own weight, forming a crater-like depression that could destroy even more of the surrounding communities? And—perhaps the most urgent question of all—when will the eruption stop?

The Berkeley connection

Michael Manga speaks with a striking precision and calm for someone who studies some of the most brutal and elemental forces on earth. He began his career by modeling how bubbles in magma can drive volcanic eruptions and now, ten years after coming to UC Berkeley's earth and planetary science department, studies fluid processes in many geological systems—everything from how planets evolve over millions of years, to how volcanoes work, to how water flows through porous rocks. In 2006, he published a paper on hydrological responses to earthquakes—including mud volcano eruptions.

EUROPEAN PRESSPHOTO AGENCY

Steam rises from Lusi's eruption site, surrounded by sandbags and earth-moving equipment. Unlike a magma volcano, Lusi does not have a prominent, mountain-like cone. Instead, Lusi consists of a vent surrounded by a vast plain of mud, formerly farmland.

Before (top) and after (bottom) images from NASA's Terra satellite show the size of Lusi's eruption. In these false-color images, red indicates areas of dense vegetation. Before Lusi erupted, in August 2004, the area is occupied by villages and farmland. In November 2008, approximately six square kilometers of mud and levees mar the landscape. The white spot in the center of the mud is steam rising from the volcano's vent.

NASA

Then, a few months later, Lusi erupted. Manga was drawn into the debate about the cause of the eruption when engineers at the drilling company cited his study to support their theory that the distant earthquake triggered the eruption. Manga disagreed with their interpretation of his results, and felt obligated to formally respond. "Because of the consequences and the relevance to who's responsible," he explains, "and because we thought there were certain things being misrepresented, we had a moral obligation to respond in writing."

Four years later, Manga's group has not only issued two written responses rebutting the drilling company's theory, with which he disagrees, but has run experiments on mud from Lusi, studied mud volcanoes in California, and developed a physical model of Lusi's eruption—the results of which provide the first concrete predictions of the eruption's duration.

Mud volcanoes around the globe

Mud volcanoes are not rare; thousands of them dot geologically active areas around the world. The archetypical mud volcano is simply a vent from which varying quantities of mud and gas bubble to the surface. Indeed, mud volcanoes look much like their better-known cousins, magmatic volcanoes, except that they erupt mud instead of magma. This resemblance holds beneath the surface, too; both mud and magmatic volcanoes typically discharge fluid (be it mud or magma) through channels and fractures that are connected to pressurized reservoirs deep underground.

The mechanism that drives eruptions is also, on a basic level, the same. Because mud and magma are both very dense, pressure in an underground reservoir alone cannot drive the fluid to the surface. Instead, the fluid rises when dissolved gases form bubbles that

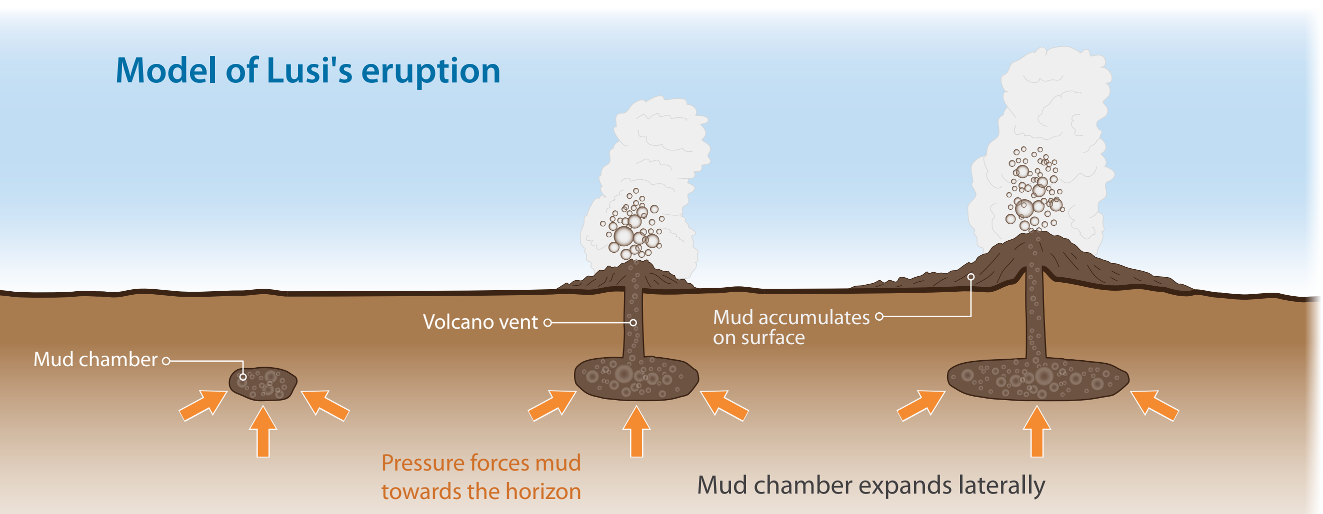
FEATURES Mud volcanoes

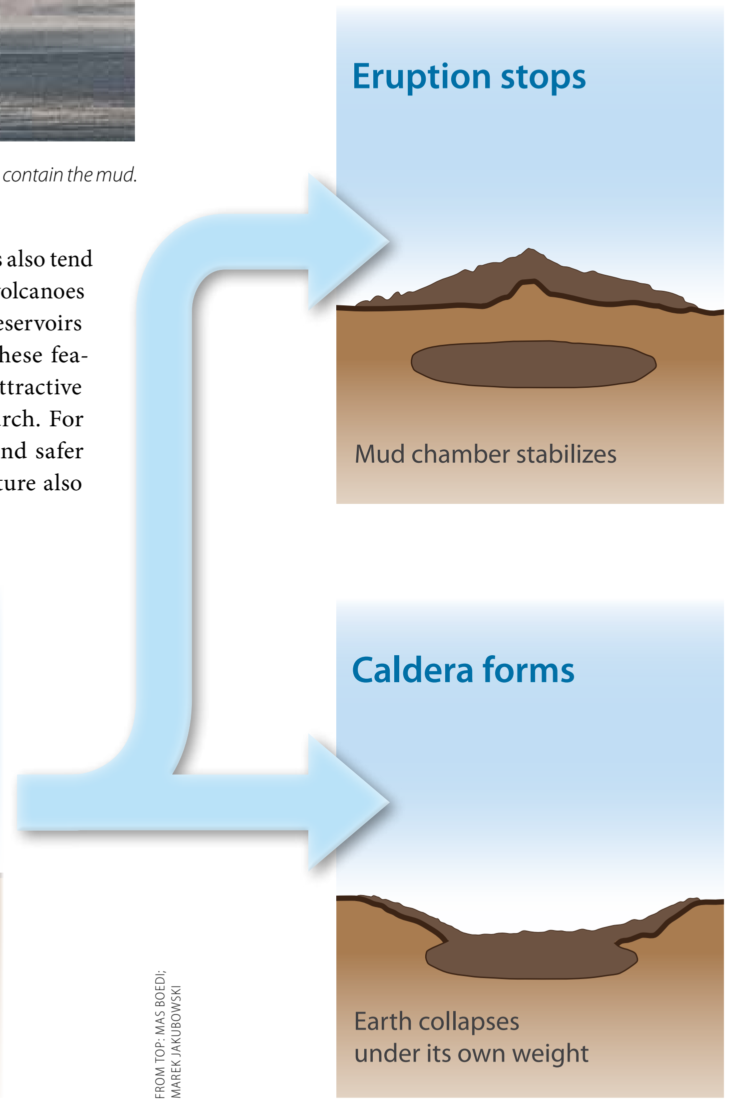
Lusi's enormous size dwarfs excavation equipment. Rising steam hovers over the volcano's vent, obscuring piles of dirt that are part of the levee system built to contain the mud.

become immobilized by the fluid's viscosity. These trapped bubbles decrease the effective density of the fluid, creating a buoyant force that carries it to the surface. Important details, however, remain unknown—including how the fluid begins moving, and how this basic mechanism can produce eruptions of diverse intensities and durations.

The principal difference between mud and magmatic volcanoes is that the magmatic ones, trafficking as they do in molten rock, are very hot—so hot that the transfer of heat significantly influences the eruption dynamics. Mud volcanoes, by comparison, are relatively cool, which is why they tend to erupt nonviolently and are only rarely as dangerous or destructive. Mud volcanoes also tend to be smaller than magmatic volcanoes because their underground reservoirs tend to be much smaller. These features make mud volcanoes attractive subjects for geological research. For one, they are much easier and safer to study. Their cool temperature also means that the complicating effects of heat are absent. "The most compelling reason to study them is that they're low temperature versions of magmatic volcanoes," says Manga.

Although Lusi is no ordinary mud volcano—the eruption began violently, and has been longer, and bigger, than that of any other documented mud volcano—Lusi is scientifically promising, Manga says, because the proximity of the gas well provides unprecedented information about what the earth looked like at the eruption site before the eruption. "At best, an eruption happens, and then you can drill into it," Manga explains. "But you never know what things were like before the eruption. And we'll never have that information again, I suspect."





FROM TOP: MAS BOEDI; MAREK JAKUBOWSKI

By exploiting this information to construct a model of Lusi, Manga has made predictions about the future of the eruption and has also learned something about how volcanoes erupt generally. But first, back in 2006, Manga felt obligated to help settle the debate about the triggering mechanism: was it the drilling, or was it an earthquake?

> "If I'm wrong about this, then I don't deserve to keep my job."
> -Professor Michael Manga

The earthquake hypothesis

When an earthquake occurs, it disturbs the earth in two ways. The movement of tectonic plates during an earthquake permanently redistributes stresses on the Earth's crust, while the propagation of seismic waves causes transient fluctuations in stress. It is well known that these transient fluctuations, which can travel hundreds of miles from an earthquake's epicenter, could alter fluid flows deep underground, resulting in a variety of phenomena at the surface, including geyser activity, changes in water well levels, and mud volcano eruptions.

In his 2006 paper, Manga and his colleague Emily Brodsky at UC Santa Cruz collected data on earthquakes that triggered a hydrological response. They then plotted the distance between each earthquake and the event it triggered against the magnitude of the earthquake, creating a scatter plot that revealed a roughly linear correlation between earthquake magnitude and distance to the triggered event. When Manga added the Indonesian earthquake, it landed well outside of the scattered points—indicating that the earthquake was much weaker and farther away from Lusi than any earthquake known to have triggered hydrological activity.

This analysis alone, Manga argued in a one-page paper he published in 2007, was strong evidence against the earthquake-triggering hypothesis. His paper contradicted, rather than supported, the drilling company's theory. But the results were statistical in nature, and it was possible that Lusi was an extreme outlier. To test the hypothesis further, Manga and graduate student Max Rudolph analyzed samples of erupted mud from Lusi. Their results provided direct experimental evidence against the earthquake-triggering hypothesis.

Let it flow

Rudolph and Manga's analysis rested on the complex fluid behavior of mud. Some fluids, like water, have the important property that their viscosity is a constant; they will always flow at a rate proportional to the force acting on them. Most fluids, however, exhibit a more complex response to force. Toothpaste is one example. "You could leave the cap off your toothpaste tube and put it upside down, and the toothpaste would stay in the tube," Rudolph explains, "but when you squeeze the tube it flows out."

In other words, toothpaste has a yield strength; it won't flow at all until a force above a certain threshold acts on it. Mud also has a yield strength, but with a twist: that strength will decrease if it is subjected to oscillating shear stress—that is, it will flow more easily when shaken.

Rudolph and Manga set out to test whether shaking from the earthquake's seismic waves reduced the strength of the mud in the underground reservoir, freeing it to flow to the surface. They obtained samples of erupted mud from the volcano and measured how it responds to shear forces of varying frequencies. They compared these

text continued on page 40

Before the eruption begins (far left), the pressurized mud chamber is dormant. Then, a conduit to the surface forms, pressure drives mud to the surface, and the mud chamber expands laterally as more of the surrounding material is drawn into the chamber. Given this eruption course, two outcomes are possible. Eventually, the eruption may cease (top right), or the chamber may collapse under the weight of erupted mud, forming a depression called a caldera (bottom right).

Impacts

Photographs by Steve Axford

The unrelenting flow of mud from Lusi has come at enormous cost to those who live and work near the volcano. The mud has destroyed factories, farmland, and at least a dozen whole villages, permanently displacing tens of thousands of Indonesians. The eruption occurred in an impoverished area where residents lack the resources to rebuild, and, to make matters worse, the government has been slow to manage the disaster and ensure that victims receive compensation.

In 2006, the government ordered Lapindo Brantas, the company responsible for the drilling that probably triggered Lusi, to pay $400 million to displaced Indonesians. Five years later, only 20 percent of the promised sum has reached residents. The company says it will distribute the full amount by 2012—six years after the eruption began. Meanwhile, the Indonesian House of Representatives voted last year to declare the eruption a natural disaster and to discourage holding Lapindo Brantas responsible for further costs. Lawsuits from environmental groups against Lapindo Brantas are stalled in the Indonesian legal system.

Many believe the government's response is compromised by the complex relationship between the drilling company and government officials. The billionaire Aburizal Bakrie indirectly controls Lapindo Brantas. At the time of the eruption, he was also the minister of social welfare in the Indonesian cabinet. Currently, Bakrie remains one of Indonesia's wealthiest men, is the chairman of one of Indonesia's most powerful political parties, and is a major financial supporter of Indonesian President Susilo Yudhoyono. Bakrie denies accusations that his control of the drilling company constitutes a conflict of interest between his political and business activities.

The mud continues to flow; occasionally, it overtops the levees the government built to contain it, flooding adjacent communities. Whether those residents will ever be compensated for damage caused by ongoing flooding is uncertain.

In California, mud volcanoes are several meters in height. Top: Fresh mud flows from a mud volcano near the Salton Sea in southern California. A yellow research book shows the size of the volcano. Bottom: Graduate student Max Rudolph stands next to the mud volcanoes he studies.

FROM TOP: MAX RUDOLPH; MAX RUDOLPH; MAREK JAKUBOWSKI

measurements to the magnitude of the shear forces induced by the earthquake in 2006, and found that those forces were one hundred times smaller than the smallest forces that caused Lusi's mud to lose yield strength in the lab.

This result allowed Rudolph and Manga to conclude that the mud would not have lost yield strength during the earthquake, adding to the evidence against an earthquake-triggered eruption of Lusi. But this result revealed little about the mechanisms by which earthquakes might trigger other volcanic eruptions—a subject Rudolph and Manga decided to pursue last spring by studying smaller and more accessible mud volcanoes. Careful experiments on these mud volcanoes, they hoped, would extend their general understanding of the responses volcanoes exhibit to the ground motions that occur during earthquakes.

Mud volcanoes closer to home

Rudolph and Manga chose to study a collection of small, harmless, and easily observed mud volcanoes located near the Salton Sea in southern California. They began making detailed observations of the volcanoes—recording their temperature, estimating how much mud and gas they ejected, and analyzing samples of the mud—in order to correlate these measurements with the area's frequent minor seismic activity. Instead, a few months into the study, a remarkable thing happened: a major earthquake occurred just 60 miles south of the volcanoes. Instruments nearby revealed that the seismic waves at the site induced shear forces strong enough to alter the mud's properties, and, tellingly, they observed fresh mud flows and a 70 percent increase in the flow of gas two days after the earthquake. How likely was such a large earthquake to occur during their observations? "We got very lucky," says Rudolph.

It was a rare chance to test two competing theories that they had developed to explain how an earthquake could trigger a volcanic eruption. One model hypothesized that an earthquake, by reducing the mud's yield strength, could allow bubbles of gas immobilized in the mud to begin rising to the surface. Under the right conditions, the rising bubbles could entrain the mud and bring it to the surface, much as the gas bubbles released by opening a can of shaken soda carry along with them much of the soda.

To test this model, Rudolph and Manga used fluid dynamics to calculate how quickly the bubbles rose through the mud from measurements of their size at the surface. They found that the time required for the bubbles to rise to the surface was much greater than the time that elapsed between the earthquake and the appearance of new mud flows. This result indicated that bubbles mobilized by the earthquake's shaking couldn't have dragged mud or gas to the surface fast enough to explain the observed increase in volcanic activity.

They turned to a second model, in which seismic waves transiently increase the permeability of the earth, allowing more gas and mud to escape. Rudolph and Manga aren't exactly sure how this might happen; one idea is that an earthquake could unblock the many small cracks and channels through which mud and gas can travel deep underground, leading to an increase in flow until the channels became blocked again. By a series of estimations, they demonstrated the plausibility of this mechanism and now believe it is the correct model for the California mud volcanoes.

Back to Lusi

Could this mechanism explain the eruption of Lusi? No, asserts Rudolph, because their estimates indicate that it requires that the mud volcano be very close to the earthquake. Indeed, all the evidence—the historical data,

Non-Newtonian fluids

To quantify the differences between a fluid like water and a more complicated fluid like mud, scientists use theories from a branch of physics called fluid mechanics. "Newtonian" fluids, like water and oil, are a class of fluids that have a linear relationship between how much they flow and how much force is applied to them: the harder they're pushed on, the faster they flow. The ratio between the intensity of the applied force and the flow rate defines the fluid's viscosity. A Newtonian fluid always flows in response to a force, no matter how small, and always with the same viscosity (provided that thermal fluctuations and quantum effects are negligible).

The vast majority of fluids we encounter are non-Newtonian. The reason is that the Newtonian model of fluids only works when the fluid's constituent particles are identical, weakly interacting, and very small. Because most fluids are a mixture of interacting molecules and larger particles, the Newtonian model often fails. What makes fluid mechanics so complicated is that there are many ways the model can fail—that is, there are many different kinds of non-Newtonian fluids. Some, like molasses, paint, and blood, simply have a nonlinear force-flow relationship, which means that their viscosity depends upon the applied force. Push harder and harder on molasses, for example, and its apparent viscosity will decrease. Other fluids have a time-dependent viscosity: the longer a force is applied, the faster (or slower) they flow.

Some fluids, like toothpaste and mud, have a non-linear force-flow relationship that fails below a certain threshold force; that is, they do not flow in response to an applied force unless it is sufficiently strong. The threshold force at which these fluids begin to flow is called the yield strength. In something like mud, the yield strength is a consequence of interactions between small (micron-sized) particles of soil and silt. Mud, at its most basic, is nothing but a dense suspension of such particles in water. When unperturbed, these particles tend to pack together such that the application of a small force is not sufficient to dislodge them. Larger forces, however, easily disrupt the packing and allow the mud to flow.

Theory vs Theory

The drilling theory: Most geologists believe that drilling activity at the natural gas well triggered the eruption of Lusi when pressurized water and mud from deep underground flowed into the well, creating fractures that allowed the mud to reach the surface. The drilling company claims that pressurized fluids never flowed into the well.

The earthquake theory: The chief proponent of this theory is the drilling company that owns the natural gas well near Lusi. It claims that an earthquake triggered the eruption by shaking the mud and enabling it to flow more easily, but geologists counter that the earthquake was too far away to affect the mud's properties.

their measurements of the mud's properties, and their results in California—argue against the triggering of Lusi's eruption by an earthquake.

Consequently, Manga is confident that an earthquake did not trigger Lusi's eruption. "If I'm wrong about this," he says, "then I don't deserve to keep my job. That's how comfortable I should feel. Because we apply all the best science we've done, we calculate things, and there's absolutely no reason to think that it could have been caused by the earthquake." Over the years, most geologists familiar with the eruption have come to agree. And, while establishing that drilling operations at the natural gas well did cause the eruption is more difficult, the present consensus is that they probably did.

The volcano has a 1 in 3 chance of erupting for at least **80 more years**.

According to Manga, the eruption was probably caused by mistakes made by engineers working on the gas well. Exactly how these mistakes led to the eruption will probably never be known. But what is clear is that engineers did not install steel casing inside the well, allowing fluid to flow into and out of the well at varying depths. This flow likely unleashed such high pressures that new fractures appeared in rock near the well—a process called hydrofracturing—which eventually formed a conduit from the mud reservoir to the surface.

With the debate surrounding the cause of the eruption of Lusi largely settled—an important development, because it helps determine who will bear the cost of compensating those displaced by the mud—Manga and his students have started looking to the future. They began thinking about how to predict when the eruption would end. "I think that's a more forward looking perspective, instead of just dwelling on the eruption that happened in 2006," Rudolph says.

Predictions, predictions

Many parameters determine how long a volcano eruption will last. The properties of the erupting fluid, the quantity of fluid that lies beneath the ground, and the nature of the conduit between the reservoir and the surface all influence eruption dynamics. Generally, however, there are only two ways an eruption can end: either the fluid simply stops flowing or the weight of the erupted fluid—essentially, the weight of the volcano's cone—causes the volcano to collapse on itself and into the emptying reservoir, forming a depression on the surface called a caldera. The formation of calderas by both mud and magmatic volcanoes is well documented, and the formation of one by Lusi could devastate the area surrounding the eruption.

But how is it possible to predict which of these outcomes will occur, or when, given the complexity of an erupting volcano? Such predictions are normally very difficult to make, because so many properties of volcanoes are simply unmeasurable. Manga, with Rudolph and graduate student Leif Karlstrom, overcame this difficulty by exploiting data collected from the natural gas well to constrain many unknown parameters, like the depth of the reservoir and the forces driving the mud to the surface. This allowed them to build a simple model of Lusi in which a pressurized reservoir of mud drives the eruption.

Crucially, their model included the counter-intuitive fact that the effective size of the mud reservoir increases as the eruption progresses. As mud erupts and more fluid flows into the reservoir, the solid mud at the boundary of the reservoir undergoes a transition from a solid-like to a fluid-like state. As the amount of fluid mud increases, the reservoir, in effect, grows larger. This, Manga thinks, explains why the eruption rate has been constant for the last five years—the pressure in the reservoir is buffered by the addition of more mud.

With their model constructed, and many of its parameters constrained by the drilling data, they used a clever trick to generate predictions despite uncertainty in some remaining parameters. They used their model to perform computer simulations of the eruption for many plausible values of these parameters, generating a distribution of different eruption types and durations. Using this distribution, they calculated the probability of each outcome. The results which emerged are, consequently, probabilistic, but place important and surprising constraints on the future of the eruption.

Their most important result is that the volcano has about a 1 in 3 chance of erupting for at least 80 more years. This result is, obviously, bad news for those affected by the volcano, but should inform the Indonesian government's long-term response to the disaster. A second result tempers the bad news: the longer the volcano erupts, the less likely it is to collapse and form a caldera—which would likely impact an even greater area near the eruption. In another twist, however, the probable size of a caldera, if one forms, increases the longer the eruption continues.

These results present a complex picture of Lusi's future and pose difficult questions for officials overseeing the response to the disaster. They clearly establish, however, that the eruption will likely continue impacting its local environment for many years. And while there remains significant uncertainty in their predictions, Manga's model establishes which of the unknown parameters are most likely to influence eruption dynamics, and which are unimportant. "I think the prediction is the most important thing we've done," Manga says. "Hopefully it will inspire people to either send us information that's relevant or collect information, and then we can update and revise the model."

Geologists' understanding of Lusi has grown enormously since its violent birth in 2006. While Manga and his students' model of the eruption advances that understanding even further, much remains to be discovered, including the detailed structure of the mud reservoir and how the future of the eruption depends upon the properties of the earth surrounding the eruption site.

The elucidation of these details will inevitably require the work of many geologists. For his part, Manga intends to continue his work on Lusi. With the model that he and his students developed, Manga now has a solid basis on which to build more detailed theories of how Lusi works. "A model," he concludes, "is just a starting point."

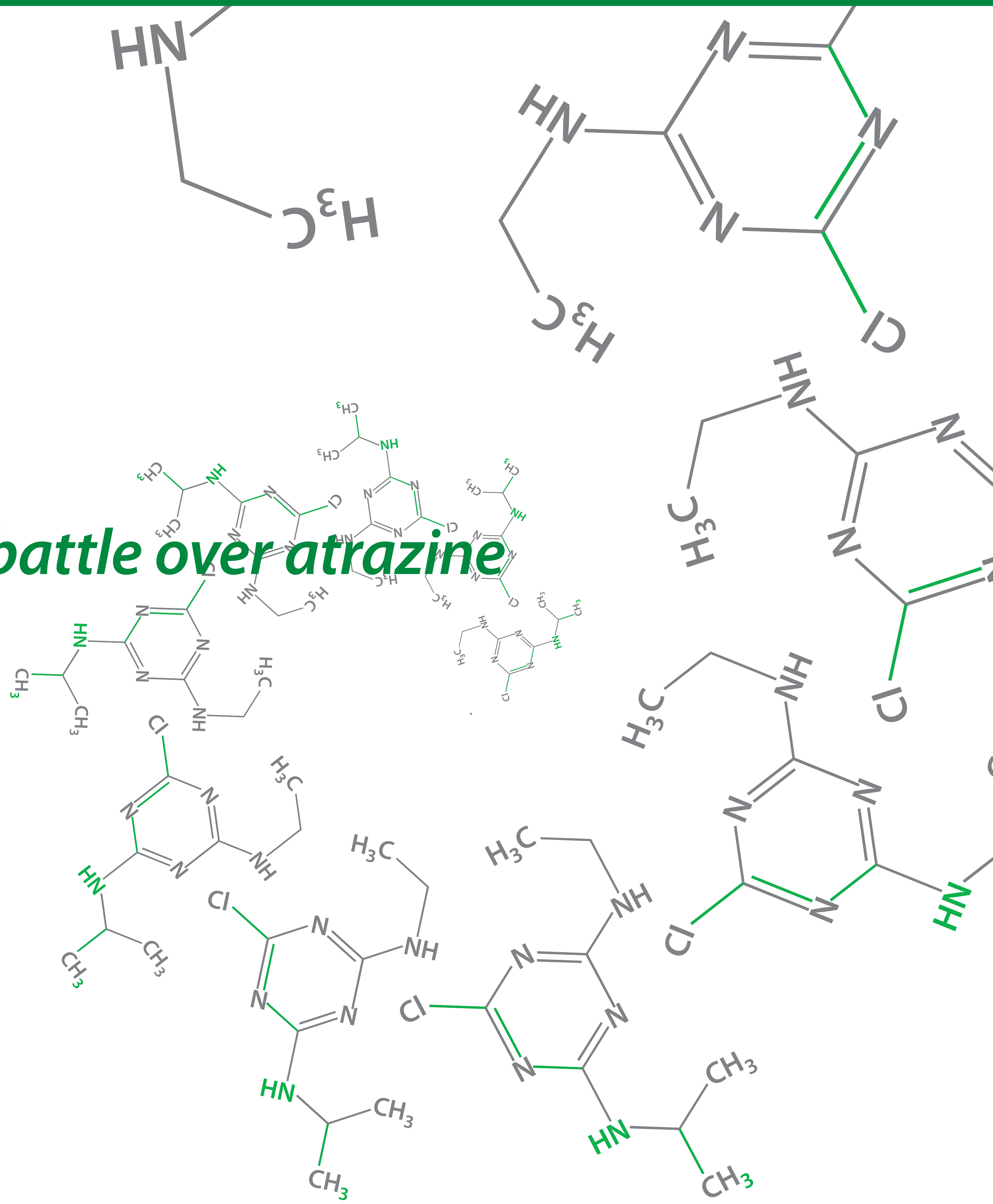
Keith Cheveralls *is a graduate student in biophysics.*

JON SHEER

An enormous plume of steam rises from Lusi. The small shape below the steam cloud is an excavator.

Murky waters

Science, money, and the battle over atrazine



by Sisi Chen and Mark DeWitt

"You won't have to worry about funding any more."

For any scientist, these are magical words. Independent researchers rarely receive such grand offers of unsolicited funding. Tyrone Hayes is one of the lucky few.

At the time, Hayes was already a noted amphibian developmental biologist in UC Berkeley's integrative biology department. His patent for using frogs to screen potential environmental toxins caught the attention of EcoRisk Inc., who contracted him to sit on a panel of scientists in 1997.

The funding came from the agrochemical giant Syngenta, then Novartis. Atrazine, one of their most profitable products, had

KATIE BERRY

Professor Tyrone Hayes holding an African clawed frog (*Xenopus laevis*), the model organism used for his atrazine studies.

recently come up for reregistration with the Environmental Protection Agency (EPA). A small company of three or four employees, EcoRisk was essentially a financial conduit between Syngenta and independent researchers who could conduct the studies necessary for atrazine's re-approval.

Initially, Hayes was tasked with reviewing studies showing that atrazine did not have adverse effects in frogs. The paucity of data in the open literature made it an easy job. While sipping expensive whiskey at beachfront resorts, Hayes whipped up reports and wrote review papers with other members of the panel. His keen recommendations on an experimental proposal so impressed Syngenta that they asked him to perform the studies instead.

In those early days, Hayes was unconcerned with any potential conflicts of interest; the relationship was purely transactional. "I'll do the experiment however you want. I'll give you the results you want, and you go away. That was how I approached it," says Hayes. "Until I did the experiment and got the results."

Not expecting to find any effect, Hayes was surprised to discover quite the opposite: he saw a striking decrease in the size of the laryngeal muscles in male frogs raised in atrazine-containing water. The larynx, also known as the voice box, is crucial for reproduction. Smaller larynxes result in elevated pitch, and female frogs don't like male sopranos. Most surprisingly, the effect was significant even at extremely low concentrations, down to one part per billion (ppb), one third of the EPA limit for atrazine in drinking water and roughly equivalent to half a teaspoon in an Olympic size swimming pool.

If correct, the results were exciting news. Hayes sent them along to EcoRisk, expecting to be praised for his good work. "Naively, I thought that would be what they wanted," says Hayes. Instead, he got a chilly reception, marked by, "a series of efforts to get [him] to change the results." A Syngenta scientist contacted him directly, suggesting that he normalize laryngeal size by the size of individual animals to make the effect go away. The company continued to ask for more and more experiments. Money slowed to a trickle.

When Hayes began to suspect that both EcoRisk and Syngenta were intentionally stalling publication of the results, he resigned from the panel so that he could continue the work. Hayes was contractually bound to ask EcoRisk for approval when publishing any research that had been funded by the company. Thus, he needed to reproduce the results to publish them independently. By that time, atrazine had already taken center stage in his lab. Without Syngenta funding, he had to scrape together money from disparate sources to pay for supplies. Dedicated undergraduates volunteered their time to perform the lab work.

As Hayes was cutting the strings of financial dependency, Syngenta and EcoRisk repeatedly offered to fly him out to their headquarters for negotiations. According to Hayes, the chairman of the panel wanted him to change dates on lab notebooks to allow EcoRisk to take retroactive control of his new data, presumably to indefinitely delay its publication. In return, Syngenta would shower Hayes with funding. Though he had only been paid about $250,000 for his two-and-a-half year stint with the company, they were hinting at figures around two million dollars to continue his research under their wing. Ron Kendall, the chairman of EcoRisk at the time, has not responded to requests for comment.

For any scientist, it would be a very tempting offer. Hayes's refusal was the first shot in what would be become a nearly decade-long battle with Syngenta.

Metamorphosis

Growing up poor in rural South Carolina, Hayes didn't always have many educational resources at his disposal. Yet he seemed to possess a natural inquisitiveness about animals and an uncommon scientific talent. At an early age, he ran controlled experiments on color-changing lizards called anoles, built a concrete turtle pond in the backyard with his father, and observed tadpoles as they went through the stages of metamorphosis.

His precocity attracted the attention of Harvard University, which recruited him heavily. As an undergraduate, he had the opportunity to work with Bruce Waldman, a celebrated amphibian biologist. While working in Waldman's lab, Hayes's childhood love of frogs and his preference for self-driven education converged in his independent project, a study on the sexual differentiation of wood frogs in response to temperature fluctuations. This research led directly to a very successful graduate career at UC Berkeley. In less than four years, Hayes produced half a dozen publications and received multiple job offers upon the completion of his PhD.

Despite this success, his career was not without its share of challenges and conflicts. As an undergraduate, he was so discouraged by the rigidity of Harvard's educational ethos and the elitist social atmosphere that he nearly dropped out. Only the strong encouragement of Waldman and Hayes's future wife kept him going. Later, as the only African-American professor in UC Berkeley's integrative biology department, he was perpetually assigned to the diversity committee while other faculty members sat on the committees that made crucial decisions on hiring, fees, and lab space assignments. He claims that within ten years, these decisions resulted in a pricing structure that overcharged him significantly for his animal facilities. When he found out and demanded to be placed on a different committee, he was rebuffed by the administration. According to Hayes, one dean even told him, "Well, you're disagreeable, so they don't want you on the committee."

Hayes has since been appointed to other committees that make decisions directly impacting his work. "I've never been asked until this year to evaluate one of my colleagues," he says, "but they're all evaluating me."

Atrazine's origins

First registered in 1958 by a predecessor of Syngenta, atrazine is now blanketing America's croplands and golf courses at a staggering rate of 80 million pounds per year, surpassed in quantity only by Monsanto's Roundup. The favored herbicide of corn farmers across the Midwest, atrazine chokes the growth of broadleaf weeds by blocking photosynthesis. Certain plants like corn, sorghum, and grasses have natural pathways to break down the compound before it can wreak metabolic havoc. The selective toxicity of atrazine to weeds is crucial to its success.

At the time atrazine was developed, American attitudes and government involvement in environmental issues were at an inflection point. The publication of Rachel Carson's *Silent Spring* in 1962 launched a nationwide panic about the health risks of the widely used insecticide DDT. These changing perspectives led to the federal government taking over the reins of environmental stewardship from the states, culminating in the establishment of the EPA in 1970.

Atrazine snuck onto the scene just before these events transpired. The Department of Agriculture, which was then tasked with registering pesticides, only required that they be as effective as advertised. The use of atrazine was authorized without fanfare and avoided regulatory scrutiny until 1996, when an amendment to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) was passed, addressing concerns that previous government standards were not stringent enough. It stipulated that all pesticides registered before 1985 be reregistered, including atrazine.

A few bad eggs

Even as Syngenta was attempting to buy him out, Hayes was expanding his research beyond laryngeal shrinkage. Smaller voice boxes seemed to be the least of the problems facing male frogs exposed to atrazine. At concentrations as low as 0.1 ppb, the frogs began sprouting eggs in their testes. In some cases, they became fully hermaphroditic, with multiple testes and ovaries strung together in series. Having dissected over 100,000 frogs, Hayes had never seen these types of gonadal structures before.

When he looked in the field, Hayes and his group found that the frequency of gonadal abnormalities correlated with atrazine levels in the wild. In areas with atrazine concentrations as low as 0.2 ppb, up to 80 percent of the native leopard frogs tested had gonadal abnormalities.

The presence of these abnormalities could alter the sex ratio in wild frog populations, significantly reducing their reproduction rate. Hayes believes that environmental toxins like atrazine may be responsible for a well-established nationwide decrease in amphibian populations.

The work of a handful of other independent researchers was also coming to light, confirming atrazine's deleterious effects and

> "I'll give you the results you want, and you go away. That's how I approached it."
> -Professor Tyrone Hayes

FROM TOP: PEG SKORPINSKI; DAVID KAY

offering up a possible mechanism. One paper detailed gonadal abnormalities in response to atrazine (albeit at a single, much higher dose) in the same species of frog studied by Hayes's research group, *Xenopus laevis*. A native of Africa, *Xenopus* is a widely used model organism due to simple requirements for growth in captivity and because the frog's response to cancer-causing agents is similar to that of mammals. Of importance to regulatory agencies, native North American frog species showed a similar response outside the lab. In cricket frogs, researchers found intersexed frogs in areas contaminated with atrazine.

Results from the laboratory of Martin van den Berg at the University of Utrecht hinted at a possible mechanism for the gender-bending effects of atrazine. Using cultured mammalian cells, he showed that atrazine induced the expression of aromatase, the enzyme responsible for converting testosterone into estradiol. Induction of this enzyme in frogs was hypothesized to be responsible for increased estradiol production, leading to the feminization that Hayes observed. Since estradiol is well known to cause feminization in frogs when they are exposed to it at early developmental stages, the hypothesis was plausible. However, it remains unproven in frogs.

These studies establish a general consensus that atrazine can affect vertebrate sexual development, but the magnitude of these effects and the concentration at which they occur varies substantially. To date, no other research group has reported reproducing Hayes's results at the extraordinarily low atrazine concentrations he used, although few have tried.

As these results were emerging, the Syngenta-sponsored EcoRisk panel published paper after paper claiming to demonstrate that atrazine had no effect. According to Hayes, the EPA, and other scientists, much of this work was crippled by poor technique. In a field study, no systematic procedures were in place to control for how the animals were treated while en route from the field to the laboratory for testing. Over half of the animals died before maturation during one set of experiments. In one study purporting to measure aromatase activity, the positive controls failed. The text of another claimed no effect of atrazine on gonadal development, while the corresponding figure and statistics showed the opposite.

Data flooding

The simmering conflict between Hayes and EcoRisk in the scientific literature came to a head in the first of two meetings of the EPA's Scientific Advisory Panel (SAP) in June 2003. In light of Hayes's research, the Natural Resources Defense Council (NRDC) forced the EPA to evaluate the effect of atrazine on amphibians, using settlement terms from a lawsuit it had previously won against the agency.

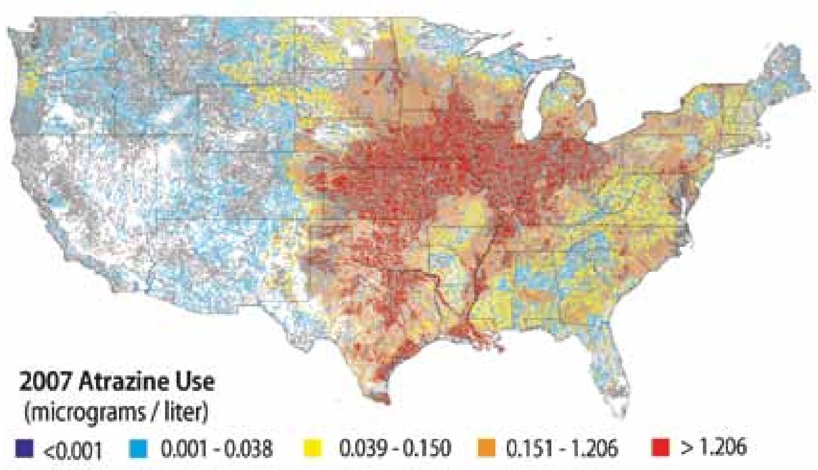
The panel, a collection of prominent independent scientists, was tasked with advising the EPA on how to interpret the science on atrazine. They found Hayes's results on hermaphroditism cause for alarm. "I've cut up…more [frogs] than my children would ever want me to. And I've never seen eggs in the testes," says Professor Darcy Kelley, the lead discussant of the 2003 SAP and a renowned expert on frog sexual differentiation at Columbia University.

Additionally, they were skeptical of the results from the EcoRisk scientists and questioned them at length about their methodologies. "It was very disturbing that the people Syngenta hired to look into this couldn't replicate some of the most basic things that people in amphibian biology know," says Kelley.

The EcoRisk scientists were the only other scientists who repeated Hayes's experiments directly. In spite of their public stance on atrazine, they wrote in private emails to Tyrone that they agreed with his conclusions about atrazine's ability to disrupt gonadal formation in frogs. "Atrazine is bad news," wrote one member. "There is no denying" the effect, wrote another.

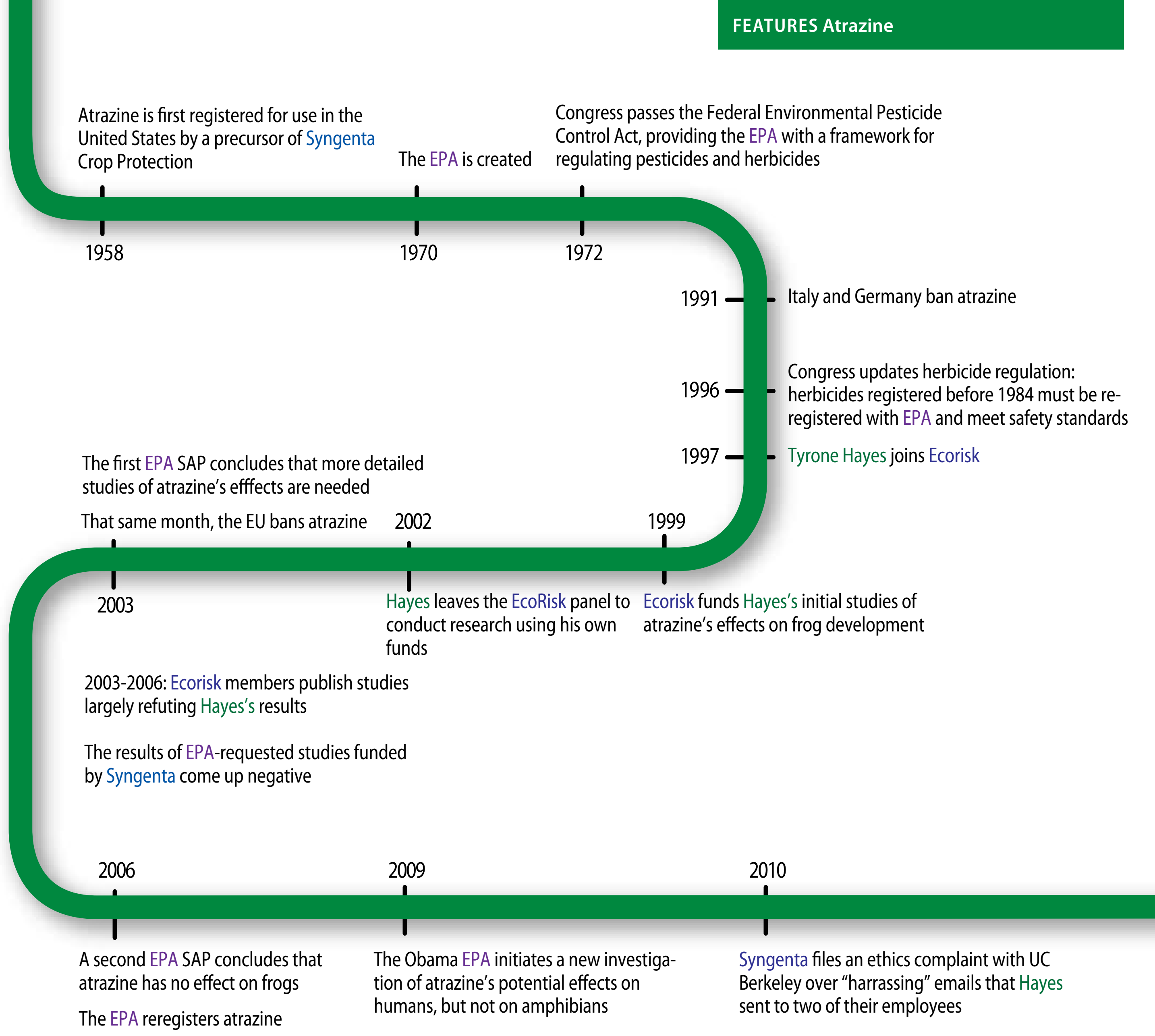
Still, they published numerous papers asserting the opposite, giving the impression that Hayes's results were anomalous, even though no fully financially independent investigator had corroborated the EcoRisk results. Of the 17 studies submitted for review by the SAP, 11 were funded by Syngenta.

The discrepancies in the open literature meant that the 2003 panel could not conclude that atrazine had an effect on amphibians at ecologically relevant levels. Instead, they offered a set of recommendations for further studies, specifying the appropriate ranges of atrazine doses, the inclusion of native species, the elucidation of a mechanism, and the use of flow-through water tanks to ensure water quality. In response to these recommendations, the EPA called in a study to address the lingering issues about atrazine's effects on frogs. The requested study was required to adhere to the "good laboratory practices" (GLPs), a set of agency-wide quality control standards that ensure the reproducibility and reliability of research data. For the proposed amphibian studies, the specific GLP standards were tailored to the experimental recommendations of the SAP for atrazine.



Atrazine use in the United States is concentrated in heavy agricultural areas, mainly in the Midwest.

USGS



KATIE BERRY, MAREK JAKUBOWSKI

Not only are flow-through tanks prohibitively expensive for independent researchers, the GLP also required a large number of replicates and dose levels. The only party with the means to conduct the study was the registrant, Syngenta, which stood to lose millions of dollars as a result of regulatory action. They commissioned two large studies at separate contract labs, which were collectively known as the data call-in (DCI) studies. The results came back negative.

When the EPA's second scientific advisory panel met in 2007 to discuss the results of the Syngenta-funded studies, the fix was in. Tom Steeger, the EPA scientist in representing the agency before the panel, steered the proceedings carefully. When panel members suggested that the DCI results were insufficient, Steeger pushed back, often restating their comments in such a way as to diminish any need for further investigation. He dismissed all the published results from both Hayes and EcoRisk, saying that the open scientific literature "cannot hope to compete" with the Syngenta-sponsored DCI study. The panel did explicitly recommend some further investigation: a study on native frog species, and a re-examination of the microscope slides from the first study by different pathologists. Neither of these studies was conducted.

Instead, the EPA let the issue go. As of April 2010, the EPA still considers the amphibian issue closed. In the end, the EPA decided that there was no cause for concern based solely upon the results of a single industry-sponsored study.

The case isn't closed

But, according to many scientists, the case is still open. Robert Denver, a prominent endocrinologist at the University of Michigan and a member of both panels, said at the 2007 meeting that the DCI study did not "fully test" Hayes's hypotheses. According to Denver, the flow-through tanks used in the DCI studies do not "mimic the characteristics of exposure that are encountered in nature." Although the 2003 SAP recommended it for water quality issues, its applicability was controversial because developing frogs are known to avoid running streams. The EPA also overlooked the fact that no native species were tested.

FEATURES Atrazine

Most strikingly, the crucial positive control, estradiol, failed. The scientists performing the DCI study could not get 100 percent feminization with estradiol, maxing out at 70 percent. "Anyone can come to my lab and we could get 100 percent females right now—to get incomplete feminization is a red flag," says Kelley. A few members of the panel were concerned that the strain of *Xenopus* used was naturally resistant to hormone disruption.

The DCI study was only designed to address the narrow hypothesis that atrazine can cause malformed gonads in frogs. The panel was not asked to address whether atrazine is an endocrine disruptor, a legally defined class of chemicals believed to interfere with the human endocrine system. This category includes two heavy hitters of environmental toxicology: DDT and the PCBs (polychlorinated biphenyls), which are a class of highly toxic industrial chemicals. Because these toxins are associated with a wide variety of developmental defects and cancers, the classification of atrazine as an endocrine disruptor would present a major obstacle to reregistration.

"The question of whether or not atrazine affects this strain or that strain of frogs actually isn't all that important," says Hayes. The main questions are broader, he argues: "Is atrazine an endocrine disruptor? Do we see consistent effects of atrazine across vertebrate classes? And the answer is yes."

The NRDC, whose lawsuit brought about the 2003 and 2007 SAPs, also strenuously objects to the EPA's narrow line of inquiry. "The question we wanted looked at," said an NRDC representative at the 2007 panel "is atrazine's potential effects on endocrine disruption." To Hayes, the NRDC, and others, it appeared that the EPA had skirted the real issue.

It's not just about the science

There are millions of chemicals on the market, and each can potentially affect human health and the environment in numerous ways. How to decide which of these chemicals are safe and which may cause lasting damage requires exceptional triage. This is the job we entrust to the EPA.

"Necessarily, not all chemicals can be investigated as thoroughly as many scientists would like," says Dr. Kelley. More studies can always be done, but the line must be drawn somewhere. As a government agency, the EPA's decisions on where to draw those regulatory lines are influenced by the prevailing political atmosphere. Atrazine's reregistration began during the George W. Bush administration, which had all but declared war on regulation in general and the EPA in particular. Budgets were being cut, and the already attenuated requests for regulatory action were met with blanket rejections by political appointees. EPA officials may have decided that the Bush administration would never regulate atrazine based on amphibian evidence alone.

Under Lisa Jackson, the Obama-appointed EPA Administrator, the atrazine case has resurfaced. The reevaluation was called largely in response to atrazine's association with cancer in humans, neglecting recent progress on the amphibian front.

> "Is atrazine an endocrine disruptor?
> Do we see consistent effects across vertebrate classes?
> The answer is yes."
>
> *-Professor Tyrone Hayes*

Very recent work by Hayes has shown that with enough atrazine, some male frogs become completely female. In behavioral studies, these feminized genetic males mated successfully with real males to produce viable offspring. These results indicate that atrazine's ecological impact may be larger than previously thought, but have not yet been officially evaluated by the EPA. Conflicting statements on separate sections of the EPA website leave it unclear whether these recent studies will ever be considered in future reregistration decisions.

Is atrazine worth it?

Certainly in the case of atrazine, the EPA's stance seems to be that a positive burden of proof is required before regulatory action can be taken. To be pulled off the shelves, atrazine must be proven to have acutely adverse effects on human health and the environment.

Contrast that with the approach of European regulatory agencies, which do not necessarily require that pesticides be shown to have toxic effects. Atrazine has been banned throughout Europe for more than five years, solely because its half-life in water systems is extremely long, between 10 and 200 days, making it impossible to keep pesticide levels below 0.1 ppb in ground and drinking water, the European limit across the board.

Even in the United States, Syngenta has been fighting a long, hard battle on numerous fronts for atrazine, which comes as no surprise given the profits it generates. Yet, Syngenta is not atrazine's only defender; farmers have long been voting for it with their wallets, and with good reason. According to analyses from different sources, a ban on atrazine would cost the corn industry anywhere from $350 million to $1.6 billion yearly, a two to six percent loss per bushel. Farm lobbyists flock to every EPA meeting to defend atrazine, claiming that alternative weed-killers could plausibly have even worse effects. Although Europe's ban on atrazine has resulted in no losses in crop yields, farmers there have shifted to a cocktail of other herbicides whose ecological effects are largely unknown. Who knows if there even exists a good alternative that's both effective and environmentally friendly?

Apparently Syngenta does. Ten years ago, they requested EPA registration for an herbicide called mesotrione (tradename Callisto). Recent studies have shown that mesotrione is just as effective on broadleaf weeds as atrazine, if not more so. Moreover, mesotrione has low toxicity and is rapidly degraded in soil and water by microorganisms. The only downside is that it is more expensive, but according to an analysis by Dr. Frank Ackerman, an economist at Tufts University, the additional cost constitutes less than one percent of the market value of corn. Individual corn farmers are unlikely to make this switch without regulatory pressure; for the average 1,000-acre farm, a switch would cost between $3,000 and $7,000 per year.

Why Syngenta is still fighting the battle for atrazine is less clear. When asked about the relative benefits of both herbicides, the company simply maintains that "when used according to the labels, both products are friendly to the environment."

He just keeps coming back

Hayes reached a dead end with the EPA. Compared to most scientists, the EPA held a drastically different philosophy on what constituted adequate scientific evidence. Reproducibility was key, and no one but Hayes found a positive effect at such low atrazine levels in frogs. Thus, the EPA overlooked Hayes's singular positive results in favor of the DCI study's "no effect" finding, which better satisfied their particular data standards.

Convinced of the EPA's "hidden agenda" favoring Syngenta, Hayes took his show on the road. He gave presentations on his work highlighting how atrazine feminizes amphibians at public health, endocrinology, and toxicology conferences, as well as legislative hearings and other public venues.

Then, things started to take a turn for the bizarre. Two Syngenta employees, a scientist named Timothy Pastoor and a public relations representative named Sherry Duvall Ford, began following him to these events. According to Hayes, they had a predilection for mischief. "At the American Public Health Association, they handed out fliers…and

Hayes has shown that a genetic male frog exposed to atrazine (below) can develop egg-filled ovaries and mate with an unexposed male (above) to produce viable offspring.

IMAGE ADAPTED FROM TYRONE HAYES; PROC. NAT. ACAD. SCI., 2010, 107, 4612-7; COPYRIGHT 2010 NATIONAL ACADEMY OF SCIENCES

From the Inbox

During the course of an intensely personal conflict with Syngenta employees, Tyrone Hayes sent hundreds of emails, which range from the provocative to the philosophical. Although the responses of the Syngenta employees have not been made public, the company has released a hundred pages of Hayes's emails, excerpted below:

from "I OWN THIS: A MADMAN'S MANIFESTO"

From: <Tyrone Hayes>
To: <[redacted]>
Date: January 21, 2008

…Imagine… a five year old… holding his finger just millimeters away from an older sibling's face, "I'm not touching you, I'm not touching you."… On the most base level, that's the game we play. "I'm not touching you.."….over and over again…until you give…

Regardless of the content of your email, just by responding, YOU lose…

I don't HAVE to do anything… If you quit, however, you will leave the world to face the truth. You can't quit! How much money do you spend campaigning against me, driving bogus science to buck me… how many conference calls, emails, meetings, how many? Because you have to…me…because I choose to…because I own this.

From: <Tyrone Hayes>
To:<[redacted]>
Date: December 20, 2005

… They told you to shut up, not me. were you there for the second talk when your little cranially deficient friend tried to work the crowd? … "smacked in the sack by the man in black"
tyrone hayes is hard as hell
battle anybody, i don't care who you tell!
you object you will fail!
mercy for the weak is not for sale!…

From: <Tyrone Hayes>
To:<[redacted]>
Date: February 23, 2010

…i'm sittin here rappin 'bout
how you should be tappin' out
cuz i dropped that ILL-I-NOIS(E)
yeah the man in black
just keeps coming back,
you don't want to step to me, boys!…

actually disrupted one of my talks," he says. "They called a fire emergency when I was lecturing in Sydney, Australia."

At the Illinois State House, during preliminary hearings into whether the state should pursue legal action over atrazine use, Pastoor allegedly physically threatened Hayes. "Next time you give a talk, I'm going to have some of my boys [come after you]," Pastoor said, according to Hayes. He says he has informed the FBI about these threats. To this day, his number is unlisted and his lab is always locked, as if on high alert. Ford and Pastoor have not responded to requests for comment.

In response to goading emails from Pastoor and Ford, Hayes responded in kind, with much creative flourish. His responses are filled with speculations on the nature of life, science, and truth, as well as quotes, poems, and often-explicit rap lyrics.

The conflict had moved beyond the scientific arena. "High-minded scientific discourse was still going on," says Hayes. "But if you come to intimidate me and make comments about my wife for example… that's a different kind of conversation." He apologizes for, "offending some people that I care about, but I said what I meant."

Syngenta, however, filed an ethics complaint several months ago with UC Berkeley against Hayes over emails they claimed to be, "not only aggressive, unprofessional and insulting, but also salacious and lewd." With Pastoor's and Ford's names blacked out, the one-sided transcript of the emails was released by the company as ammunition in its attacks on Hayes's work. These emails are available for download at the company website. Hayes claims that the emails from the Syngenta employees were equally offensive, but declined to release them, citing legal concerns.

Hayes made no serious threats and it is hard to see what he wrote as anything worse than unprofessional. Although the racy emails may have damaged his credibility in some circles, they mostly just kicked up a storm of public attention about atrazine. In the past year, many articles have been appearing in outlets ranging from *Gawker* to the *New York Times*.

Hayes's level of involvement in the atrazine case far exceeds what most scientists could ever imagine committing to the societal implications of their work. In the midst of heavy teaching and research loads, who has the time to fly around the world to deliver politicized invectives against a company and compose elaborate emails and poems for a pair of its hired guns?

He could have let the matter go at any time. Why didn't he just pull out?

The easy answer is that he is a selfless advocate, devoted to getting the truth out about a dire environmental hazard. His presentations and writings highlight a desire to speak out for the underdog, be it powerless frogs or the largely Hispanic agricultural laborers who bear the brunt of atrazine exposure in the fields. While these reasons do contribute to Hayes's outrage, it is also fueled by something deeper.

When asked why he continued to study atrazine after EcoRisk withdrew its funding, Hayes says it is a question he has been rethinking lately. While he says he, "cares about public health and environmental health and all that stuff," he also realizes that Syngenta's offer angered and offended him. "You can't buy me," he says. "You can't pay me enough money to be dishonest."

Sisi Chen *is a graduate student in bioengineering;* Mark DeWitt *is a graduate student in biophysics.*

AWARD PHOTO: MAREK JAKUBOWSKI; OPPOSITE: SOFFIE HICKS; BENEDICT CAMPBELL. DESIGN: NICOLE BENNETT

Perchance to dream

Uncovering the role of the unconscious mind

by Naomi Ondrasek

Running as fast as you can, you quickly turn for a fleeting glimpse of an unknown pursuant. Your heart and legs pump furiously, but you can't run fast enough—your limbs feel heavy and move infuriatingly slowly, as if you're slogging through water. As the entity behind you (is it a person? an animal?) continues to gain ground, you see a wall looming ahead and realize that you're going to be caught. With nowhere further to run, you wait as the mysterious creature approaches. But just before the frightening hands (or claws?) draw you close, your eyes flare open, and you discover that it was all just a dream.

For the vast majority of human beings—and at least a few nonhuman species, too—the slumber hours are enlivened by a unique internal experience known as dreaming. Written records, oral traditions, and even ancient petroglyphs reveal that dreams have fascinated people at least since the appearance of the earliest historical records, yet humankind continues to know little about them. Recently, researchers from a variety of backgrounds, including theology, psychology, and neuroscience, have stepped forward to shed light on what exactly our brains are doing—and why—during the dark hours of the night.

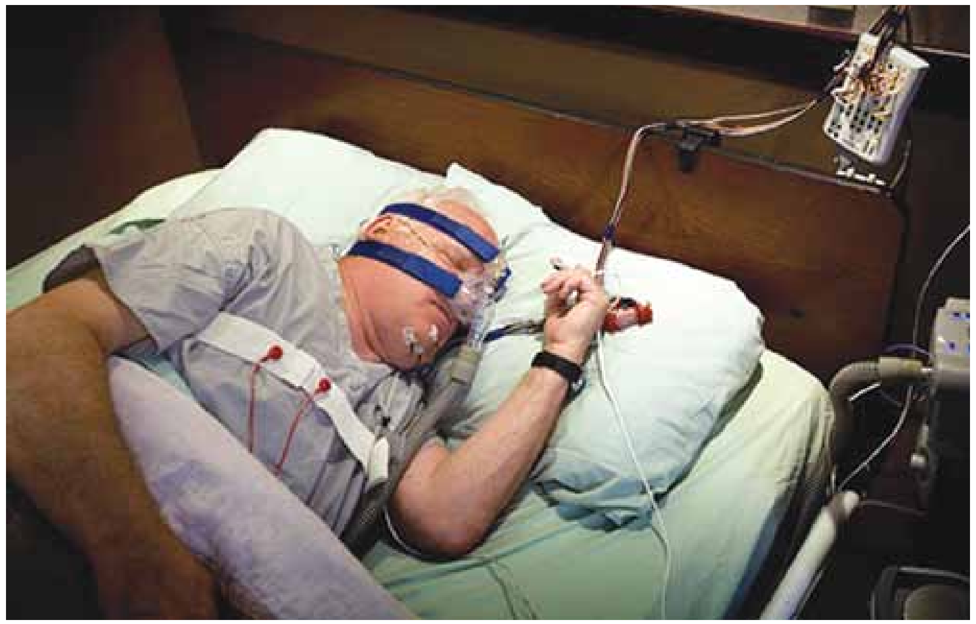
FEATURES Dreaming

Sleep to forget, sleep to remember

When you awaken after a night's rest, the preceding hours may seem to have passed uneventfully, but in reality your brain cells were busily firing away, engaging in tasks that scientists are only beginning to understand. In the mid-20th century, researchers discovered that sleep, neurologically speaking, is not a homogenous state—rather than remaining static throughout the night, the brain cycles through two major phases of activity known as Rapid Eye Movement (REM) and non-REM sleep. Sleep scientists can distinguish between the four substages of non-REM sleep and REM sleep by examining electroencephalograms (EEG) and electromyograms (EMG), which depict the electrical activity patterns, or waves, within the brain and muscles, respectively.

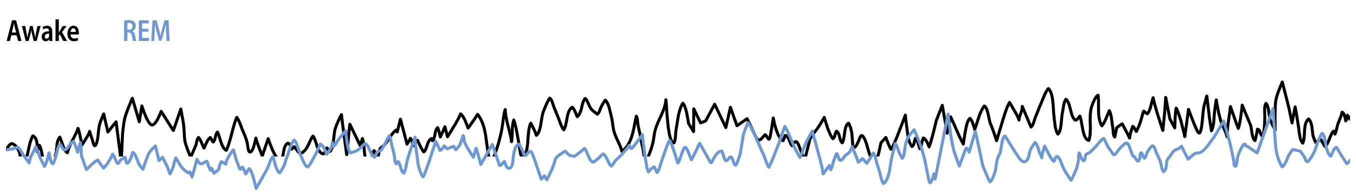
Much about the functional significance of the various sleep stages remains a mystery, but scientists are steadily chipping away at the unknowns. REM sleep is particularly fascinating because its electrical and neurochemical characteristics are quite different from those of non-REM sleep. Unlike the other stages, REM sleep produces an EEG dominated by high frequency, short amplitude waves—a pattern that shows striking resemblance to the EEG produced during waking. Similarities in brain waves aside, the neural processes of REM sleep and wakefulness are distinct. "REM sleep is different from non-REM sleep and it's different from waking," says Els van der Helm, a psychology graduate student in Associate Professor Matthew Walker's lab. "If you just look at the EEG, it looks exactly like waking, except that your EMGs show that your muscular tone is completely damped, to the point that you're basically paralyzed." She also points out that during REM sleep, unique patterns of neural activation arise. While the emotional, visual, and memory areas become highly active, the prefrontal cortex, which provides inhibition to other regions of the brain and helps you assess the realism of your experiences, lies quiet. "What you're left with is a really visual and highly emotional brain during REM sleep," van der Helm says.

> "Psychology is becoming more and more divorced from the way that people's minds function in daily life."
>
> -*Professor Eleanor Rosch*



Left: A sleep study, also known as polysomnography (PSG), is conducted to determine various physiological changes that occur during sleep. Researches employ an assortment of instruments to measure these changes, including electroencephalograms (EEG), which record electrical activity patterns in the brain.

Below: Amongst the sleep stages, REM sleep is unique in terms of its neurochemical and electrophysiological characteristics; muscle tone is extremely low (in fact, you're effectively paralyzed during REM sleep) and, as shown below, the brain waves of REM sleep more closely resemble those of waking than those of non-REM sleep. In particular, REM sleep brain waves are dramatically different from the delta waves of slow wave sleep (shown on the right).



TIMOTHY SNYDER

Van der Helm aims to illuminate our understanding of the brain's special functions during REM sleep by focusing on the processing of emotional memories. Earlier findings that implicated REM sleep as a major player in the processing of emotions led van der Helm and Walker to develop the "sleep to forget and sleep to remember" hypothesis, which proposes that the neural activities occurring during REM sleep modify our emotional memories by stripping them down to their bare essentials. "When you think back on something emotional, you may be good at remembering the details and how you felt and what happened, but you're not re-experiencing the emotionality of it," says van der Helm. "You don't get sweaty hands again when you think about that presentation you gave, and your heart doesn't start racing again. So it seems as if the memory is contained really well, but the tone has been stripped away."

Given the unique neurochemical milieu present in the brain during REM sleep, van der Helm and Walker proposed that the modification of emotions may occur during this stage. The tendency of emotional memories to persist more strongly than neutral memories appears to depend upon activation of the adrenergic system, which relies on cell-to-cell communication mediated in part by epinephrine (also known as adrenaline; this same system gives us that extra boost during the so-called fight-or-flight response). In other words, emotional memories stick around better than their neutral competitors because of an extra kick provided by the adrenergic system at the time of memory formation. But during REM sleep, when these memories are brought forth for processing, the adrenergic system is suppressed. Van der Helm and Walker proposed that this period of suppression allows the brain to shave away components that are unnecessary to remember, leaving behind only the most essential elements of the memory.

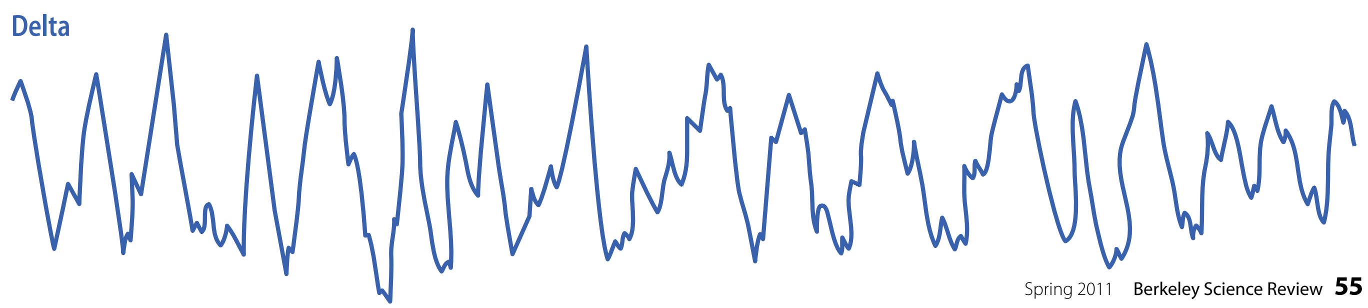
Who needs sleep anyway?

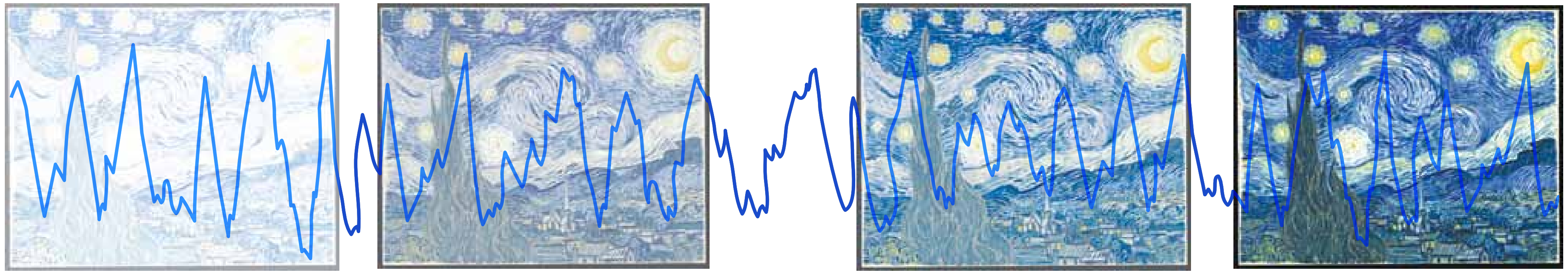
In today's fast-paced, busy-body world, speed is the secret to success. Do you want to scramble up the corporate ladder like a mountain goat? Make your kids shine on their college applications? Impress your academic advisor and future employers? The winning approach can be summed up in four words: do more, finish faster. But with a measly 24 hours in a single day, how do we accomplish this? The simplest solution: sleep less.

While cutting back on sleep in the short term may get that paper finished on time, in the long term, it may actually cause harm. Catching a 15 minute nap can't replace a full night's rest, since sleep is a dynamic process consisting of various stages, each of which correlates with characteristic brain waves and certain physiological changes. In stage 1 of non-REM sleep, the brain transitions out of wakefulness; during stages 2-4 of non-REM sleep, many physiological factors, including muscle tension and the rate of respiration, gradually decrease; and in stage 4, large amplitude, slow waves appear, marking the synchronized firing of cortical neurons (which carry out higher level information processing). A full cycle typically lasts for about 90 minutes, reaching completion when the brain transitions from stage 4 back to stage 2 or 3 and then moves into REM sleep. During an average night, humans progress through five or six sleep cycles, and these cycles evolve as the hours pass—initially, we predominately engage in slow wave sleep, but as the night wears on, we begin to devote increasing amounts of time to stage 2 and REM sleep.

Given its involvement in the processing of memories and emotions, REM sleep may seem like the golden child of the sleep stages, but recent work in Professor Matthew Walker's lab suggests that non-REM sleep also affects our waking lives in important ways. In a study published in the March issue of *Current Biology*, the Walker lab discusses a link between learning ability and non-REM brain wave oscillations. Specifically, they found a significant correlation between sleep spindles—short, rapid bursts of electrical activity in the brain that occur during stage 2—and learning ability in participants who were tested after a 90 minute nap. Sleep spindles are associated with activity in the hippocampus, a key memory-processing area in the brain, and may help clear space for new memories by facilitating the transfer of older memories from the hippocampus to the prefrontal cortex. Cutting back on sleep may hinder this process, since spindles occur most commonly during the latter half of the night, when stage 2 non-REM sleep becomes more prevalent.

Want to ace that test? Make sure you get your daily dose of spindles.





Currently, van der Helm is testing this hypothesis by placing study participants into an fMRI (or functional magnetic resonance imaging) machine and exposing them to photographs with varying valence (positive, negative, or neutral) and arousal (or intensity) values. "These pictures come from a big database used by researchers all over the world and are standardized, so they have specific scores on arousal and valence," she explains. As participants assign scores to the pictures, the fMRI apparatus measures changes in blood flow, which indicates locations of neural activity in the brain. To assess the impact that sleep has on the intensity of emotional memories, van der Helm allows one group of subjects to get a full night's rest in the lab after their first scoring session, and then asks them to score the same set of photographs again the following morning. To account for the effects of second exposure (and to determine if the modification of emotions requires an intervening period of sleep), a second group undergoes both sessions on the same day—first in the morning and the second 12 hours later.

Van der Helm expected that sleep would decrease the intensity of an emotional memory, which is exactly what her initial results suggest. First, fMRI scans reveal that as subjects view increasingly emotional pictures, the amygdala (a region of the brain that plays a key role in the processing of emotions) also increases in activity; interestingly, this effect appears dampened in the sleep group and augmented in the awake group. Second, a night of sleep modifies the scores that participants assign to photographs of high-level, but not mid-level, intensity. "It seems as if sleep decreases emotional reactivity for the most extreme pictures, but not for the pictures that were mediocre in their emotional intensity," says van der Helm.

The well of creativity

Studies like van der Helm's strongly refute old perceptions of the sleeping brain as a dormant mass of resting neurons. Today, we have an image of a brain that busily shuffles through a variety of nightly tasks, many of which may significantly affect the way we function while we're awake. While van der Helm's research suggests a role for sleep (and more specifically, REM sleep) in the processing of emotional memories, work by psychology graduate student Jared Saletin, also in the Walker lab, provides evidence that the neural processes of sleep may contribute to nothing less than our creativity. Saletin's research brings to light the relationship between sleep and relational memory, or the ability to connect separate memories in novel ways. "Let's say you know how to get from Sacramento to Berkeley, and you know how to get from Berkeley to Los Angeles, but you've never actually been told how to get from Sacramento to LA," says Saletin. "You still know how to do that because you know how to combine the steps along the way. This is something that kids learn at an early age."

Saletin examines relational memory using transitive inference tests, which evaluate a person's ability to combine a set of learned inferences in new ways to solve unfamiliar problems. Subjects learn a series of premises—for instance, "choose A over B," "choose B over C," and so on (in his study, Saletin uses fractal images, rather than letters of the alphabet, to avoid biasing his participants). As in van der Helm's study, participants are separated into two primary groups: in the first group, participants are taught the premises in the evening, allowed to sleep overnight, and then presented with transitive inference tests the following morning; in the second group, participants learn the premises in the morning and then undergo the test 12 hours later, without an intervening period of sleep.

The test presents subjects with questions that require them to link the original premises in unfamiliar ways. The difficulty of the question depends upon the number of independent premises that must be combined in order to arrive at the correct answer. In some instances, participants must derive what are called "1-degree inferences"—for example, if asked to choose between A or C, a subject would have to combine the premises "choose A over B" and "choose B over C" to produce the right conclusion. More challenging are the 2-degree inferences, in which participants have to leap across two levels to figure out which option to choose; for example, to know that E is superior to B, subjects would have to link the premises "choose B over C," "choose C over D," and "choose D over E."

Saletin discovered that a full night's sleep selectively improves a person's ability to make the most difficult connections. "What happens when I give you B and D, which you've never learned before?" he asks. "After 12 hours, whether you've been awake or asleep, you get better at what we call inferential judgment, picking B over D, as if you're going through C. But after sleep, you're much better at the more distant pair of B and E, which requires two levels of relation jumping."

Based on these findings, Saletin suggests that sleep modifies our memories in more dynamic ways than previously suspected. "Traditionally, people have talked about memory in three stages: you learn it, you store it, and you recall it," he says. "But you actually do a lot more than that—you transform it over time and you integrate it. The transitive inference study leads us to suggest that sleep helps you build an infrastructure to connect pieces of information that you've never been explicitly told go together. This may be related to creativity, the emergence of an idea from parts that you've never put together before."

A stroke of genius while you sleep

In 1865, German chemist Friedrich August Kekulé was trying to determine the structure of benzene, a recently discovered molecule known to contain six carbon and six hydrogen atoms. At the time, the geometry of the molecule baffled scientists, who couldn't figure out how to arrange all 12 of the atoms such that each carbon atom possessed four bonds and each hydrogen atom possessed one. According to organic chemistry lore, a portion of the answer came to Kekulé while he dozed by a fire. After dreaming about a snake that circled about until it bit its own tail, he awoke and realized the solution—that benzene is a closed, hexagonal molecule with a carbon atom at each of its corners.

Other stories suggesting the creative force of dreams and their purported roles in historical events exist: Mary Shelley claimed that the monster in her book *Frankenstein* originated in a dream; Otto Loewi, a German pharmacologist, stated in a lecture that the idea for his experiment on frog hearts (which demonstrated the chemical transmission of nerve impulses and eventually made him a Nobel laureate) came to him in his sleep; and the melody for the Beatles song "Yesterday" apparently emerged from one of Paul McCartney's dreams.

With the "provocation hypothesis," dream researchers have proposed that on rare occasions, people may experience intense, highly vivid and memorable dreams that provide opportunities for insight and the birth of new ideas. Visiting scholar Kelly Bulkeley believes that such dreams exist, but he cautions that it's often difficult to validate the high profile reports of dream-based revelations. "It's always interesting to hear such stories, but it's a little dicey to rely too much on them. It's better to have a broader base of evidence to work with." In any case, keeping a dream journal might not be such a bad idea—especially if it leads to a Nobel Prize, emblazons your name on the walls of literary history, or produces one of the most beloved songs of all time.

"I dream my painting, and then I paint my dream."
- Vincent van Gogh

Using transitive inference tests to evaluate the effects of sleep on the ability to link memories in novel ways, psychology graduate student Jared Saletin has discovered that the construction of new ideas, particularly those of higher complexity, may occur while we sleep. In short, sleep may facilitate our creativity.

VINCENT VAN GOGH

So it was just a dream?

Aside from processing memories, the brain also happens to produce the most vivid and coherent dreams during REM sleep, as revealed by experiments in which subjects are woken up during various sleep stages. The coexistence of memories, emotions, and dreams during REM sleep has nourished speculation that dreams may have some unknown function, but very little is known about the biological basis of dreams, aside from the fact that most people appear to have them.

Although science remains unsure about them, humanity's fascination with dreams has proven powerful enough to bring forth a number of theories. Perhaps the most famous originated with Sigmund Freud, an early 20th century German psychiatrist who pioneered a psychological approach to dreams and viewed them as the "royal road to the unconscious," a means of accessing our innermost desires and neuroses. Today, dream theories like Freud's are largely ignored by cognitive neuroscientists, lingering at best as dusty, outdated ideas, and at worst as residents in the halls of pseudoscience.

In their place, physiological conceptions of the brain have taken hold. Rather than developing abstract conceptions of the mind, scientists now investigate the processes of cognition by searching for concrete links between anatomy and function and delving into the brain at the levels of tissue, neuron, molecule, and gene. But, according to Eleanor Rosch, a professor in the Department of Psychology, this approach doesn't paint a complete picture of the human mental experience.

Although her research career has not focused on dreams, she has maintained a long-standing interest in the topic and even taught a course on the psychology of dreams for several years. Her fascination with the subject grew out of her research into the psychology of Eastern religions, particularly Tibetan Buddhism, in which dreams play an important role. According to Rosch, psychology's neurophysiological models are difficult to apply to many of the mental processes that people utilize and experience every day. "Psychology is becoming more and more divorced from the way that people's minds function in daily life," she says. "Psychology has become very focused on the brain sciences, while anything that's difficult to approach from that perspective has been sidelined, especially in mainstream university psychology."

Rosch contends that because dreams are difficult to fit into current conceptions of the brain, they have largely been overlooked by neuroscientists. "Dreams are hard to fit into your prototype of what a scientific experiment is," she states. "If you work with a dream and you analyze it according to two different dream theories, you will come to very different conclusions that are difficult to compare, which makes testing the theories against one another hard." Rosch believes that the difficulty of developing mutually exclusive dream theories that are testable using conventional neuroscience techniques has made dreaming a taboo topic of research for modern day scientists. "This may be part of the allergy to actually studying anything about people's inner experiences," she says.

Dreams are also difficult to study because of the manner in which scientists must collect information about them. "You have to be awake to talk about your dream, and at that point, your brain is completely different in terms of neurochemicals and neurophysiology," says van der Helm. "So basically you're asking subjects to travel back in time, to a state where they were unconscious, and describe what happened. We have no idea what's happening during that transition from your dreaming brain to your waking brain. All you can rely on is the waking brain to recall it, and we already know that people differ dramatically in their ability to recall dreams."

In spite of the challenges inherent in dream research (or perhaps because of them), one hypothesis regarding the origin of dreams has become prevalent within the brain sciences—that dreams serve no purpose and actually originate from chaotic bits of images, sensations, emotions, or memories brought on by random stimulation of the relevant circuits as the brain goes about its nightly business. These jumbled, nonsensical fragments are then woven into a coherent narrative by the waking brain as it comes online again. "You can imagine that dreams are basically just an epiphenomenon—you're reactivating certain networks in the brain, and this is activating your visual and emotional areas," says van der Helm. "So you have these emotional feelings, and you see things, but perhaps the dream itself doesn't serve any purpose. Our lab doesn't necessarily think that dreams lack function, but this specific view is hard to disprove."

Top: This image depicts the Hindu god Vishnu as he sleeps on Ananta, the cosmic serpent, which floats on the cosmic ocean beyond space and time. In Hinduism, Vishnu is the divine dreamer and the world as we know it is his dream.

Bottom: In most cases, the only records of dreams from ancient times reside in religious texts. Visiting scholar Kelly Bulkeley uses his training in both religion and psychology to develop an interdisciplinary understanding of dreams. Drawn from the Bible, this scene depicts Jacob's dream of a ladder ascending to heaven.

FROM TOP: PHOTO © VICTORIA AND ALBERT MUSEUM, LONDON; COURTESY OF KELLY BULKELEY

Pointless? Maybe not…

At the Graduate Theological Union, a partnership of seminaries and graduate schools that focuses on interreligious collaboration and offers two affiliate PhD programs with UC Berkeley, visiting scholar Dr. Kelly Bulkeley spends his waking hours investigating the contents of dream journals, in which people record the details of their dreams immediately after emerging from sleep. Bulkeley, who suffered from recurrent nightmares as a child, began his academic journey as a student of psychology, but quickly discovered that he needed an interdisciplinary approach to understand the common elements of the overall human dreaming experience.

After studying philosophy and religion as an undergraduate at Stanford University, Bulkeley went on to divinity school, where he completed programs in psychology and religion. In particular, his exploration of world religions provided him with a wide perspective on the significance and nature of dreams. "The best historical records of dreams are often in religious texts or records of religious practices," he says. "We have only had psychology for the past couple hundred years. If we want to learn about dreams in the broader perspective of human history, you really have to have that bigger historical picture. The only way to get that was to understand world religions."

After sifting through both ancient and modern records of dreams, Bulkeley began to realize some common trends that transcended culture, ethnicity, and time. Such "psychological universals" suggested to Bulkeley that dreams are more than pointless offshoots of neurological babble. To investigate this hypothesis, Bulkeley needed to analyze the content of numerous dream journals produced by a large number of people. Unfortunately, the traditional approach to cataloguing dream content involves a tedious scoring process in which human readers pore over dream journals, searching for words that connote certain emotions, concerns, experiences, or activities. Although it has produced intriguing results, the human scoring system is highly subjective (the scoring of a particular word could vary between readers) and labor intensive, which has prohibited large-scale analyses of numerous dream reports.

> "The recurrent themes and content of dreams are accurate reflections of what's important in the dreamer's waking life. Dreams turn out to be much more mundane and normal than most people assume."
>
> *- Kelly Bulkeley, visiting scholar at UC Berkeley*

To address this issue, Bulkeley used word search technology, a data-mining technique that has been successfully employed by literary scholars to rapidly examine large swaths of works. Using 40 different categories of word strings partially constructed using words catalogued by human scorers, Bulkeley was able to quickly evaluate the content of several dream journals. The word search system reports the percentage of dreams that contain at least one word from a particular category, each of which represents something general like an emotion or use of a particular sense, such as vision or hearing. Using the automated word search system, Bulkeley demonstrated that a single person with access to a computer could quickly and reliably replicate the results of the human scoring system. The additional advantage of the word search approach is that researchers can conduct a blind analysis—that is, they can evaluate the content of a journal without ever reading (and becoming biased by) the dream narratives.

By employing the word search method, Bulkeley has shown that a dream journal can be used to accurately predict many aspects of a subject's waking life: religious convictions, the nature of personal relationships, jobs, hobbies, and more. When combined with the finding that most dreams contain relatively common scenarios—interactions with family and friends, walking and driving, going to work—rather than fantastical experiences like flying or falling from great heights, Bulkeley's studies suggest that our dreams may be more than neurological nonsense. "The recurrent themes and content of dreams are accurate reflections of what's important in the dreamer's waking life," Bulkeley says. "Dreams turn out to be much more mundane and normal than most people assume. Every now and then there's something odd, but if you look at the broad patterns of what people actually dream about, it tends to be about people we know, places we usually go to, things we often do in the day."

So do dreams mainly provide us with an opportunity to rehash the day-to-day occurrences in our lives? Possibly, but Bulkeley points out that dreams don't mirror our waking hours in every respect. "We seem to do less reading and writing and computer work in our dreams compared to the proportion that many of us, particularly in the academic world, do in our waking lives," he says. "Dreaming seems to have more of a bias towards social activities and less towards reading, writing, and arithmetic activities." According to Bulkeley, it's also plausible that dreaming, like play in young mammals, provides us with the chance to safely practice behaviors relevant to our survival. "We find recurrent patterns of fight or flight behavior, we find all sorts of sexual behavior, and we find all sorts of bonding behavior—kind of the basic stuff of human survival and reproduction," he says.

Pushing the boundaries

While varying cultural and religious beliefs about the significance of dreams abound, the underlying roots of dreaming continue to mystify non-scientists and scientists alike, even as they bind us together under the banner of universal experience. Are dreams inherently functionless, constructed piecemeal from random sparks released by the brain as it conducts the important work of processing our memories and emotions while we sleep? Or do they serve a purpose, providing us with the means to safely test the boundaries of existence? While proponents of either view may dismiss the competing idea as erroneous, dream research may actually benefit from the fertility of thought that can accompany controversy, especially if the answer lies somewhere between the two extremes.

"There may always be a horizon of skepticism, and that's fine—that's where we have the debates, and that's where we do the research," Bulkeley says. "We're pushing the edges, trying to figure out how far they extend and whether we do reach a point where maybe it is chaos, maybe it is random neural nonsense. I don't think we should stick to an ultimate psychological determinism, where every element of a dream means something. Maybe there is some crazy stuff in there, but we'll never know unless we look."

Naomi Ondrasek *is a graduate student in integrative biology.*

Access granted

Unlocking the scientific literature

by Jacques Bothma

When was the last time you searched online to find the answer to a question? Odds are you are one of the hundreds of millions of people who do this every day. Whether you're trying to find the closest café with a great cappuccino or the chemical structure of caffeine, you can easily satisfy your curiosity online—usually for free.

In today's open, digital world, it's surprising that the overwhelming majority of information contained in the scientific literature is not freely available online. The scientific literature is both an important repository of knowledge and a vibrant forum where the scientific community reaches consensus on the answers to difficult questions. Many of the findings contained in this literature have clear implications that reach beyond the scientific community to society at large, like those related to climate change and the impending energy crisis. However, access to this information is mostly restricted to a select few who pay for the privilege.

Scientific articles, the fundamental units of the scientific literature, are written by scientists and published in one of a large collection of journals and magazines. These journals and magazines are generally run by either a for-profit publishing company or a scientific society. Most of these entities make money by charging for access to articles through subscriptions, which are primarily paid for by university libraries that then provide access to students and faculty. "The way I describe it to students is that researchers on campuses do research, they then give that research away to publishers, and we buy it back from them," says Beth Weil, head librarian of the Marian Koshland Bioscience and Natural Resources Library at UC Berkeley. "That is the primary paradigm of scholarly publishing."

In recent years, the sustainability of this model of scholarly publishing has come into question. Meanwhile, a growing number of scientists are starting to publish their articles in open access journals, where authors pay publishing fees and subsequent online access to the research is free. During the last decade, this idea of open access publishing has evolved from an egalitarian ideal to a profitable business model which is now being adopted by many of the publishing companies that were once its staunchest critics.

OPEN ACCESS LOGO, PUBLIC LIBRARY OF SCIENCE

FEATURES Open access publishing

Questioning the status quo

In the last ten years, there have been a number of high-profile disputes between publishing companies and university libraries over licensing fees for subscription-based journals. In 2010, the University of California was asked to pay well over a million dollars—four times what they were already paying—for access to a subset of the journals published by the Nature Publishing Group (NPG). The dispute, "highlighted for both sides the serious need to find sustainable paths for scholarly publishing and scholarly communications, because clearly we are not on a sustainable path," says Ivy Anderson, Director of Collection Development and Management at the California Digital Library (CDL).

Publishers argue that the increased research output and corresponding number of paper submissions and publications have led to dramatically rising costs. The problem is that library budgets worldwide, which fund the majority of journal subscriptions, have been consistently shrinking. "So you have increasing research output, increasing research dollars, and decreasing funding of library budgets in institutions," Anderson explains. The University of California has felt the effects of this particularly acutely due to ongoing state budget cuts, but the picture is qualitatively the same around the world.

With the advent of site licensing, journals also began to see declines in personal and print subscriptions, further compounding the revenue problem as advertisers have grown even less likely to pay for ads in magazines and journals with lower print subscription rates. "Publishers have looked to libraries and institutions to make up their revenue shortfall," says Anderson.

As publishing revenue sources have dried up alongside library budgets, Anderson argues, "We really need a range of new techniques and publishing structures to address the problem." Open access publishing has the potential to form a large part of the solution to this crisis, a fact not lost on Harold Varmus, Patrick Brown, and Michael Eisen when they launched the Public Library of Science (PLoS) in 2000 and helped usher the open access publishing movement into the spotlight.

UC Berkeley professor Michael Eisen, pictured with part of an original data set showing how the expression of thousands of genes in yeast change when they start to reproduce. Restrictions imposed by journals on the reuse of scientific papers meant he couldn't mine the scientific literature to analyze this type of complex data. This is what led to his interest in open access publishing and eventually the formation of PLoS.

MAREK JAKUBOWSKI

A public library of science

The story of PLoS begins with a research question. As a postdoctoral fellow in Pat Brown's lab at Stanford in the late 1990s, current UC Berkeley molecular and cell biology professor Michael Eisen was analyzing data from genomic experiments looking at how gene expression patterns changed with cell behavior. In the past, people had done this with at most tens of genes at a time, but using new technology, Eisen and Brown were looking at many thousands of genes at once. The researchers were struggling to relate what was known in the literature to what they were observing in their experiments. "We were shifting from doing experiments on a small scale, where it was possible to know everything about the genes involved and the experiment we were doing, to a world where not even Pat, who has a photographic memory, could remember or even know every piece of relevant information," says Eisen.

They tried all sorts of ways of getting around the problem, but it quickly became clear that they needed to write some kind of program that could scan through the literature to find and organize relevant information. It just so happened that they were thinking about this when journals were starting to be published electronically. It also happened that the service doing the electronic publishing for most of the society journals at the time, HighWire, was basically part of the Stanford library, just down the road from the lab. "We felt that we could just go down there with a disk and ask them for all their papers. They would give them to us, and then we would be able to do all this cool stuff," Eisen says. "So we went down there, and they basically said, 'No, we own this stuff, and you can't use these papers.'"

Following this startling rebuff, Brown and Eisen became interested in the public, openly-accessible system used by the physics community, called arXiv. They started a conversation with Paul Ginsparg, arXiv's founder and professor of theoretical physics at Cornell University. From this conversation, Brown and Eisen began with the idea to clone arXiv for biologists, but even then they had some reservations about their idea. "We realized that if the publication forum was totally dissociated from the institutions that dominate biomedical research, as it is with arXiv and the dominant physics institutions, it was never going to work," says Eisen. "Where things were published was way more important to biologists."

Brown and Eisen then teamed up with Harold Varmus, director of the National Institutes of Health (NIH) at the time, along with a couple of other key people, to develop a plan for the NIH to run a freely accessible repository where all biomedical research papers could be posted not just for reading, but also for unrestricted reuse. This latter feature would allow researchers to perform their own analyses with previously published work. "Harold proposed this to the funding agency, and because it was the NIH, it had to go out for comment and review," says Eisen. "And it got eviscerated. Not just by the commercial publishers one would have expected, but by all of the non-profit societies, who, despite notionally representing science, are actually utterly dependent on the revenue from their journals for survival."

After the failure of their NIH proposal, Brown, Eisen and collaborators initiated a petition in the form of an open letter urging publishers to allow the articles that appeared in their journals to be distributed freely by independent, online public libraries within six months of their publication. The scientists who signed the letter pledged to only publish in and review for journals that complied with these demands, after a deadline of September 1st, 2001. "The open letter was hugely successful," Eisen says, alluding to the more than 30,000 signatures they received from scientists all over the world. "We thought it was very effective, but ultimately it didn't work." September 1st came and went, and nothing really changed. "We had argued for this open access model, where instead of having paid subscriptions, authors pay to publish," Eisen says. "The logic of the model was clear, we thought, but almost nobody believed it would work. So finally we realized that we had to just try and prove them wrong, and we were never going to have a chance if we worked within the existing publishing world." And just like that, the idea of PLoS as a publisher was conceived.

Rise of open access

The point of starting PLoS, Eisen explains, was to show that a successful publishing company could be based on an open access model. "The founders of PLoS had hoped that people would embrace open access just because it's the right thing to do, but we eventually realized that we first had to show them it worked." In the beginning, PLoS was not alone in trying to illustrate the viability of the open access model. BioMed Central, the brainchild of entrepreneur Vitek Tracz, was actually the first open access science publisher. Since these early days PLoS has grown significantly and has had a major impact on the publishing landscape.

One of PLoS's most successful journals is *PLoS One*. In 2006, the journal published a mere 138 articles, but the last four years have seen dramatic growth; in 2010, *PLoS One* published 6,749 articles, making it the world's largest peer-reviewed journal. In the beginning, PLoS was funded by grants from a number of foundations, but the company has now reached the point where it is self-sustaining. "*PLoS One* volume goes up every month and the community journals, like *PLoS Genetics*, are doing well. *PLoS Biology* and *PLoS Medicine* still require an investment but we are making enough on the other journals to sustain them," explains Eisen.

PLoS One's rapid growth has not gone unnoticed by other publishers, many of whom are now in the process of launching similar open access journals. In January 2011, NPG launched Scientific Reports, whose stated scope and purpose are almost identical to those of *PLoS One*. In the latter half of 2010 and early 2011, a range of similar announcements were made by many publishing companies and scientific societies including

What are the costs?

A 2008 Research Information Network report conducted by Cambridge Economic Policy Associates looked in detail at the costs involved in journals' publishing processes in the UK. It estimates the total cash cost of publishing the average journal article is $4,625. This breaks down to $840 in profit, $1,835 associated with producing the first copy of the article including managing peer review and editing, $982 associated with distribution, and $972 for publisher overheads. Subscription-based journals recover some of the costs by charging page or color charges. For example, Nature Publishing Group charges $1,210 for the first color figure and $432 for each additional color figure in a letter published in *Nature*. The rest come from advertising revenue, subscriptions, and site licenses.

The initial cost of publishing in an open access journal tends to be higher than publishing in a subscription-based journal. PLoS, for example, charges between $1,350 and $2,900 per article. BioMed Central, another open access publisher based in the UK, charges up to $1,875 per article. Hybrid journals tend to be more expensive, with some charging as much as $5,000 to make an article freely available online.

Regardless of where the work is published, doing the science that goes into a scientific publication is the dominant cost, requiring significant personnel, equipment, and monetary resources. Estimates of the average cost of the scientific investigations that go into producing an article range between $150,000 and $300,000.

The British Medical Journal, the American Institute of Physics, and the Genetics Society of America. There are also many primarily subscription-based hybrid journals that give authors the option of paying an open access fee to make their articles freely available online. "The fact that *Nature* and many other publishers are emulating PLoS is the great validation of what we've been saying for ten years," Eisen says.

There is, however, a subtle but important difference between the open access provided by more traditional publishing companies and that provided by PLoS. Many of the former place strict limitations on the use of articles through their licensing. PLoS's license, on the other hand, allows the unrestricted use of the contents of a paper as long as its authors are acknowledged. Restrictions through licensing are widespread and generally allow viewing of the material but restrict reuse.

However, the original motivation that kickstarted PLoS was Eisen's and Brown's inability to use the data in published work for their own analyses. As Eisen explains, "We had hoped that once the literature was available for people to access and manipulate, they would perform exciting new analyses. Unfortunately, that remains inhibited still by the unwillingness of the publishers to let go of their control over the papers."

Challenges for the new paradigm

Although the move to open access publishing has great potential, it still faces several serious challenges. As open access publishing becomes more widely adopted, a shift is occurring in who pays for publishing and providing access to articles. Instead of library budgets covering a large fraction of the costs and authors contributing to a lesser extent, the authors are now shouldering the entire financial burden. The money that pays for this will have to come primarily from research grants.

To publish a paper in an open access journal costs several thousand dollars; even though this is typically just a small fraction of the cost of doing the science itself, that cost is not insignificant. If funding bodies do not take the added publication costs into account, the amount of money available for research will decline. Furthermore, the variable amount of grant money available across different scientific disciplines could create a disparity in the ability to publish depending on one's scientific field. PLoS does have a policy of waiving the publication fee for people who can show that they really cannot afford it, and there are a number of institutional funding sources that have been set up to provide similar assistance. But it remains unknown how big a disparity might exist in an open publishing world.

Anderson points out that having this shift in who pays for publishing an article could actually streamline things. "Part of the open access experiment is seeing if you achieve more sustainability by placing the economic transaction where the true market relationship is, between the publisher and the author," she says. In open access publishing, the library is removed as the middleman between the authors and the publisher, allowing authors to decide where to publish based on how much a journal charges to publish an article and what services it provides the author in return. This in turn provides a clear and direct incentive for publishers to provide value for the costs they charge for publishing.

There are many researchers for whom the additional cost associated with publishing in open access journals is insignificant and who have a definite interest in maximizing the accessibility of their research. So what is preventing these scientists from publishing in open access journals? In a word: prestige. In the current system, the perceived worth of a paper is largely dependent on which journal publishes it. The scientific literature currently consists of a hierarchy of journals, where journals that accept only a small fraction of submissions sit at the top and those that publish most submissions are at the bottom.

The current belief is that the top journals, being far more selective, are only publishing the "best science": that which the editors and reviewers believe will have the highest impact. Therefore, where a paper is published is vital and the stakes are high—the perceived worth of a study and the scientists who performed it depend on it. David Hoole from NPG says this is why the journals at the top of this hierarchy are best served by a subscription-based system. "Highly selective 'top-tier journals' have high circulations, even larger numbers of readers, and relatively few authors," he says. "In such circumstances, it seems fairer to spread the costs across the large number of readers, rather than the much smaller number of authors."

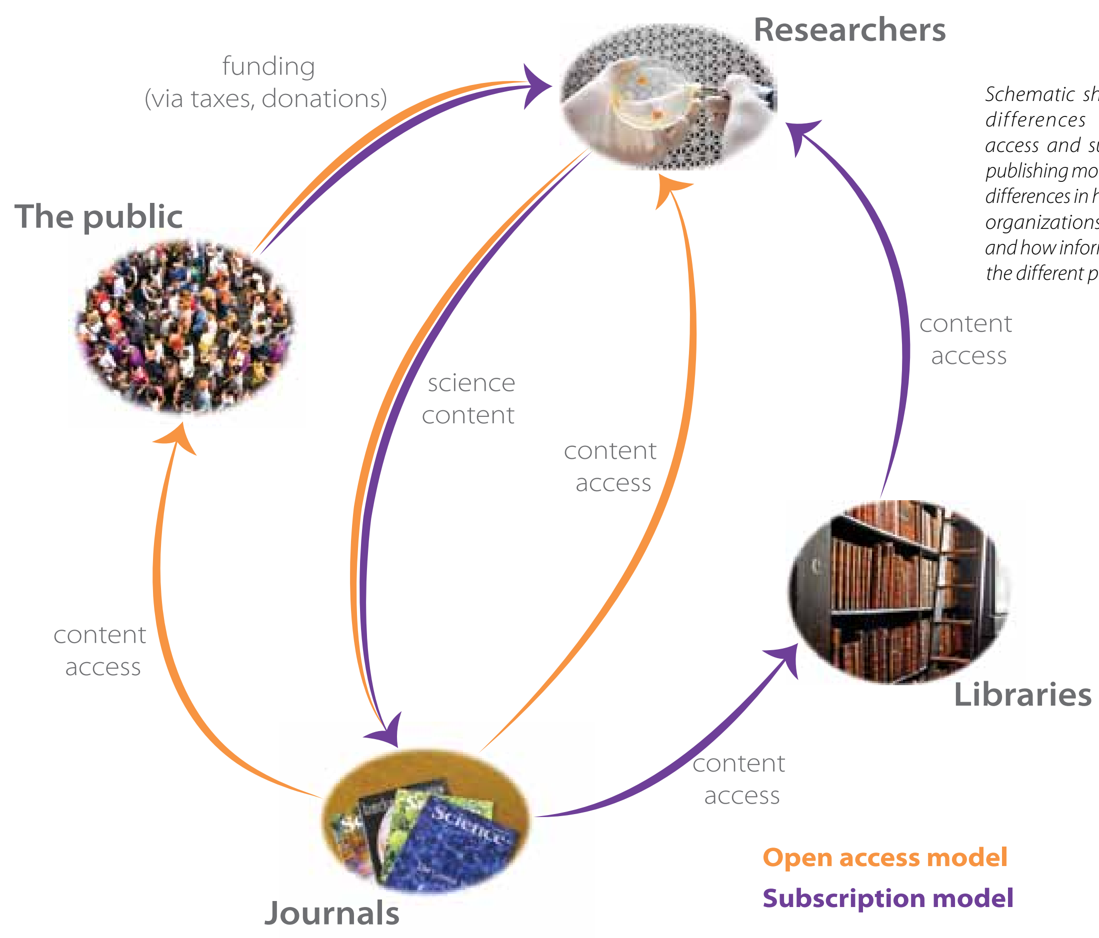
Most open access journals do tend to have lower rejection rates—*PLoS One*, for example, publishes around 70 percent of the submitted papers—putting them far down on the totem pole within the current paradigm. Thus, some scientists hesitate to publish in a journal like *PLoS One* because there is a sense that not everything published in the journal is necessarily great science. However, the disparity in acceptance rates between *PLoS One* and say, *Nature*, actually results from a different philosophy when judging the worth of a scientific paper. *PLoS One* will publish a paper if the work is novel and technically sound. *Nature* judges these factors as well, but places much more weight on a subjective assessment of the perceived impact of the work as determined by their editors and several scientists whom they ask to review the paper.

The open access community argues that the broader scientific community does a much better job of assessing the importance of a paper after publication than a handful of scientists working with journal editors before publication. Indeed, there are a number of high profile cases where Nobel Prize-winning work was rejected by journals like *Nature*, suggesting that maybe the PLoS philosophy is correct. In particular, *Nature* rejected the ground-breaking work on photosynthesis by Johann Deisenhofer, Robert Huber, and Hartmut Michel, as well as Hideki Yukawa's theoretical work on the existence of mesons.

The publishing world ahead

Once considered a small movement among scientists, open access publishing has become a significant part of the academic publishing landscape. Despite the challenges it faces, many signs are pointing towards open access journals playing a much larger role in the future of scholarly publishing. It is too early to predict how all these changes in publishing will influence scientific research, but many are hopeful that they will facilitate future discoveries by enabling open sharing of information and allowing new and powerful analyses of published works. With the prospective opening of the science literature, in the near future anyone with internet access and a strong sense of curiosity will be privy to the latest scientific discoveries and have unrestricted access to much more of humankind's scientific knowledge than ever before.

Jacques Bothma *is a graduate student in biophysics.*



Schematic showing the major differences between open access and subscription-based publishing models. It illustrates the differences in how the groups and organizations involved interact and how information flows under the different publishing models.

DESIGN: AMY ORSBORN; PEOPLE: GUILLAUME BURET; RESEARCH: PONTIFICIA UNIVERSIDAD CATÓLICA DE CHILE; LIBRARY: NIC MCPHEE; JOURNALS: AMY ORSBORN

- 1991 — Physics publication forum arXiv founded
- 1999 — PubMed Central proposed
- 2000 — PLoS founded
- 2001 — Open letter to Scientific Publishers deadline passess
- 2002 — First BioMed Central publication
- 2003 — First PLoS publication; UC and Elsevier price dispute
- 2006 — *PLoS One* founded
- 2008 — NIH open access mandate takes effect
- 2009 — Federal Research Public Access Act introduced to Senate
- 2010 — UC and Nature Publication Group price dispute
- 2011 — PLoS breaks even

Mina Bissell

FROM LEFT: ROY KALTSCHMIDT, LBL; PEZCOLLER FOUNDATION

"They're the sort of questions that are almost too big for people to take on," Mina Bissell muses as our interview gets started. And, for over thirty years, that is exactly what she has been doing—tackling the questions that seem too big to answer. After differentiating to become part of a particular organ, how does a particular cell remember to maintain its identity? Why do some cells forget the rules and become cancer cells? What exactly has gone wrong?

Mina Bissell's background is anything but ordinary, and it is her unique experiences, she says, that have molded her success. She was born in Tehran, Iran, and graduated as the country's top high-school student. She then ventured to the United States by herself at barely eighteen and began her undergraduate studies at Bryn Mawr. After two years, she transferred to Radcliffe, graduating with honors in chemistry. She did her PhD studies at Harvard Medical School studying bacterial genetics and moved to UC Berkeley in the 1970s for a postdoctoral fellowship. Bissell has since received numerous awards and served as the director of the Life Sciences Division at Lawrence Berkeley National Laboratory (LBL), where she is currently a Distinguished Scientist.

AG: What were some challenges you faced at the start of your science career?
MB: I was very young when I first came to this country. I had no idea that, even in the 1960s, women were discriminated against in this country. When I got to graduate school, I began to realize that there was this very complex relationship with how people treated women—especially outspoken and assertive women. It never occurred to me not to speak up. You know, I was fearless and that scared people. I know everybody has to prove themselves. I just found this surprising and very challenging. The other thing that was very challenging for me was how conventional people are in science. You would think that in science you would want people that are really open to new ideas. I found out that was not the case. And again I had to prove myself just because I wasn't doing what everybody else was doing, and I was doing it in a different way with my own ideas, and very few people would open their minds to it. Luckily that has changed, and we have opened up a new way of thinking about tissue specificity and cancer.

AG: What is the main focus of your research now?
MB: The question is—how do cells not only organize themselves into different organs and tissues, but how do they remember to behave like an organ or tissue? There are many different steps that come together to make your nose your nose, your mouth your mouth, and your elbow your elbow. When you take these cells out of their three-dimensional environment in an animal and put them in a flat dish, they forget where they come from. That tells you that noseness, mouthness and elbowness are not absolute. It says that there has to be something *in vivo* that is giving the signal that we took away. Part of that signal is the extracellular matrix (ECM), but the fundamental regulator of organ and tissue specificity is the spatial environment generated by the organ itself. In other words, the organ and tissue's architecture has information and is telling the cells what to do. When you take away that organization, cells behave very differently. So we argue that context and architecture matter—there is wisdom in your nose and wisdom in your liver and that evolution has made these things the way they are.

AG: You study cancer, too. How does that relate to this idea about the importance of environment in tissue differentiation?
MB: When we treat patients with a given drug we shouldn't be just treating the tumor alone—we should be treating both the tumor and the microenvironment around it. We now know that the microenvironment is not just the ECM or the other cell types but also factors like the immune system. All of these things go on to say that context is important.

AG: I heard that you considered studying literature as an undergraduate.
MB: When I was at Bryn Mawr, I wanted to major in literature. I had a magnificent English professor, and I love literature and poetry, so it was a fight between chemistry and literature. But chemistry won!

In 1959, Mina Bissell was given a medal by the Shah of Iran, Mohammad Reza Pahlavi, commemorating her position as top high school graduate in the country.

AG: Who are some of your favorite poets?
MB: I grew up immersed in poetry, as all Persians do. I really love the very famous poet from Iran that Americans don't know much, Hāfez. He is probably our greatest poet. Another poet I've always admired is Yeats—I love Yeats! Of modern American poets, I like Billy Collins. I also read the poems in *The New Yorker* and, back in the old days, I used to go to the Black Oak Bookstore and hear the young poets.

AG: Do you have any words of wisdom for current graduate students in science?
MB: Nothing is easy. You have to have your own independent way of keeping your dignity. There is dignity in work and it's very important to be independent. There is a lot of good science we know nothing about. There's so much to learn and there's so much to do—you just have to open your eyes to your data. Don't just try to satisfy your professor—challenge authority. And exercise! Exercise and challenge authority and stick with it! Do something good with your life. It doesn't matter what you do—but do something good and important. Do something that will make you feel good about yourself and about humanity. And, for crying out loud, get involved in politics! Vote! It matters! It matters a lot!

Adrienne Greene *is a graduate student in molecular and cell biology.*

book review

Kids First

by David L. Kirp
PublicAffairs Books
288 pages, $24.99

You have a million dollars to apportion for the public good, and want to leverage this capital to create the greatest possible benefit. Do you invest in health care or business? Social welfare or crime reduction? Given the broad range of worthy causes, how do you decide where to spend the money? Answering this question—as we implicitly do when we vote or donate our time and money—can spark extensive and passionate debate, and I highly recommend arming yourself with David Kirp's recent book *Kids First* (March 2011, PublicAffairs Books). A professor at UC Berkeley's Goldman School of Public Policy, Kirp critically synthesizes a body of extensive research suggesting that investing in children's education and development generates quantifiable and far-reaching economic and social benefits.

While we all have an intuitive sense that it's important to look after children, I found that *Kids First* reshaped and expanded my understanding of the unique benefits of child education. Kirp discusses five especially effective proposals in detail: parenting programs, preschool education, mentoring, education-focused savings accounts, and community schools. He evaluates empirical studies and insightfully probes specific programs to understand which policies are most effective and least expensive, details the profound effects of the best programs on children's later success, and quantifies the economic gains reaped when money is invested in children.

Kids First demonstrates how investing in evidence-based policies for child education satisfies two typically conflicting goals. It promotes social justice and equity by providing opportunities to all children, as captured in Kirp's kids-focused Golden Rule: "Every child deserves what's good enough for a child you love." It also reflects "enlightened self-interest" because it yields financial payoffs for governments and businesses. Early nurturing

PUBLICAFFAIRS BOOKS

of kids averts trajectories into delinquency and helplessness—which impose costs on public services and constitute squandered resources for a private sector—by instead developing successful adults who have the motivation and competence to hold skilled jobs and furnish taxes, contributing to society and GDP.

If you have to choose one, Kirp's analysis of the effects of high-quality preschools provides a concrete example of the benefits of investing in children. The reader is given an enjoyable and inspiring tour of high-quality preschools—journeying through Los Angeles, Oklahoma and New Jersey—along with a critical discussion of studies that satisfy gold-standard social scientific standards like experimental manipulations and random assignment. These pinpoint the factors that produce tangible changes in kids' lives: evidence-driven curricula and teaching strategies, properly trained teachers with few students, and effective management policies for implementing proven programs. The outcomes can be eye opening. One research effort, the Perry Preschool study, randomly placed a group of 58 highly disadvantaged children into one of these high-quality preschools for two years and followed their development into adults. Compared to a control group of similar children who stayed in their normal environment, students in the preschool were 50 percent more likely to graduate from high school as adolescents, had substantially higher IQ scores, earned better salaries, and were less likely to be in prison as adults. Kirp points out that these real-world findings converge with basic research in psychology and neuroscience, which emphasizes the importance of stimulating instruction during the critical period when children's brains and minds are being formed. How much would we pay for a medical treatment or drug with similar outcomes?

Kirp's discussion of the economic bottom line of this study—a signature feature of the book—is particularly compelling. Under some estimates, a high-school dropout can cost the American economy about $250,000 and a career criminal $1.5 million. Kirp reviews analyses that place the benefit-cost ratio of the Perry Preschool at seventeen-to-one, which translates to an annual return of 11 percent on the initial preschool cost. As a long-term investment, this beats the stock market by almost two-to-one.

Although Kirp presents evidence for the effectiveness of his five proposals, I appreciated that he was balanced in assessing his argument. He compares the relative effectiveness of different programs within each proposal and is honest about what does not work, such as pointing out how preschool education programs may not produce large benefits if improperly implemented. The book also emphasizes that its goal is to spark discussion on kids-first policies, leaving open the possibility that new research and ideas will enhance its proposals.

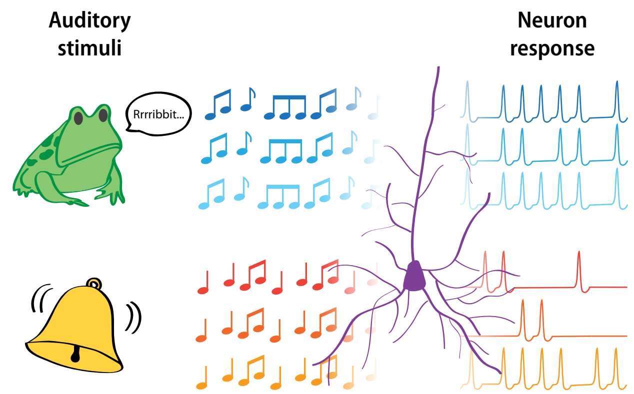
Kids First exposed me to a novel perspective on the tremendous social and economic advantages of investing in people when they are most open to change—as kids. If you don't have a million dollars, but just a small sum to donate, one vote, and a few hours to volunteer, how can you get the best returns on your capital?

Joseph Williams *is a graduate student in psychology.*

toolbox

We are living in a world of information. In a matter of seconds, I can access and transmit vast quantities of information ranging from the important (a 911 call) to the not-quite-vital ("every1 should see da @justinbieber movie"—Shaquille O'Neal via Twitter). But what is information? A satisfying answer eluded most thinkers until a single paper, published in 1948 by Claude E. Shannon, a researcher at Bell Laboratories, laid out an incredibly far-reaching framework for thinking about information, uncertainty, and communication.

By that time, engineers had already developed sophisticated ways of communicating—telegraph, telephone, Morse code, radio. Lacking, however, was a way of thinking about all of these communication systems that described them in comparable terms. How is the information from a dot of Morse code like that from a letter in a telegraph? Shannon noticed the unmistakable similarity of all communication systems—an information source draws symbols from a symbol set and transmits them to a receiver, who then decides which symbols the transmitter sent. Systems might use different symbols, like dots and dashes or letters, but they are bound by Shannon's underlying theory.



AMY ORSBORN

Information and uncertainty are inextricably linked. Consider an alphabet consisting of only one letter. Any message you could possibly write using this alphabet will always end up transmitting exactly NO information. Because the receiver is always 100 percent sure of the identity of the next letter, there is no uncertainty that can be reduced, and thus, the message is information-less. Now, add just one more symbol to the alphabet and the receiver is no longer so sure. Simply adding one symbol bestows the uncertainty needed for communication. Wherever there is a reduction in uncertainty, you can be sure it was information that did it—uncertainty is the Joker to information's Batman, and the Dark Knight can't exist without someone to vanquish. Shannon termed his mathematical formulation for uncertainty "entropy."

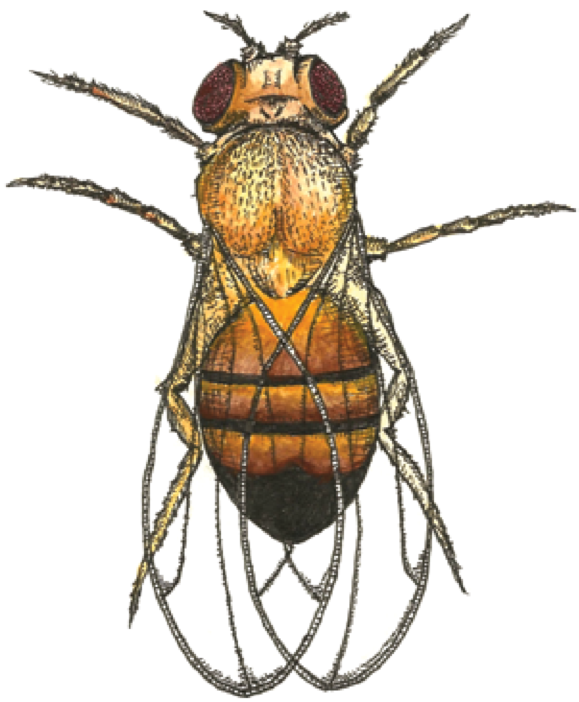
Almost as soon as Shannon proposed his theory, it was adopted to study the brain, the undisputed champion of communication. Brain cells, or neurons, are highly interconnected, sending and receiving vast numbers of messages in the form of electrical impulses, or "spikes." Their signal starts at the information source, the world. The world is very uncertain; even if you only consider only one sense, like vision, there are a nearly endless number of things that appear before you and the brain would like to acquire information about which one it is seeing. Neuroscientists can use information theory to ask how much information about various stimuli is located in particular neurons by observing their activity and asking, do spikes in this neuron reduce my uncertainty about which stimulus is present?

In one such experiment, scientists play sounds to a bullfrog as they record activity from its neurons. At any given time, the neuron could send one of many unique spike train "messages." That means there is entropy, but is the neuron taking advantage of it? On one extreme, it's possible that all of the unique spike trains are just random messages that tell us nothing about the stimulus; on the other end, perhaps each spike train unambiguously tells us which stimulus was played. Where a neuron lies on this continuum is related to its information efficiency, and research has shown that it depends a great deal on the type of stimuli the frog encounters.

The figure shows hypothetical responses to three presentations of one frog-like and one noise stimulus. By observing the reliable responses to the frog-like sound (bluish notes), we learn that the blue sound was played. You can imagine that the response to another frog-like sound would elicit a different but consistent response (not shown). A noise stimulus (orangish notes) on the other hand, elicits unreliable responses, giving us less stimulus information. Information theory serves as the unbiased adjudicator that allows us to quantify the information and information efficiency of neural responses to the two sets of stimuli. For noise stimuli, the efficiency is low—between five and 20 percent. But for stimuli resembling natural frog calls, the efficiency is astoundingly high, approaching 100 percent, meaning nearly all of the entropy in the neural signal is being used to convey stimulus information. Work like this supports the idea that neurons don't simply represent everything around them equally, but are exquisitely specialized to convey information about stimuli that are relevant to them, like a frog call to a frog.

To put information theory most generally, you would say something like, "Wherever you have something affecting the probability that another thing does something, you have information." While this sounds trivial at first, the ability of information theory to detect changes of the most general nature has allowed us to use it in contexts where we ourselves are not sure what the meaning is. That is certainly true of the brain, and many more places including the genome, Wall Street (two areas area that Shannon himself tackled with his theory), and, in short, the world.

Robert Gibboni *is a graduate student in neuroscience.*



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