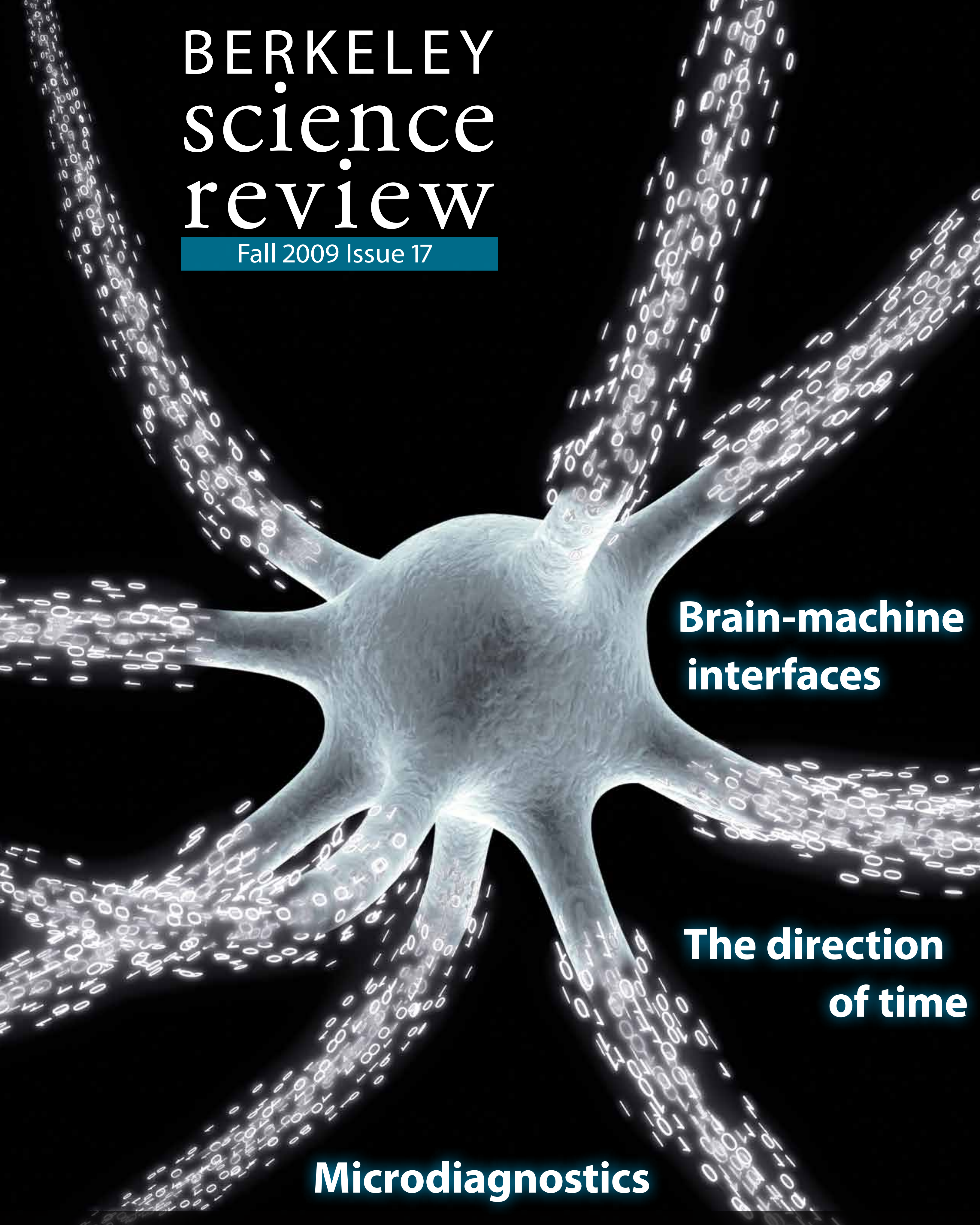
BERKELEY science review

Fall 2009 Issue 17

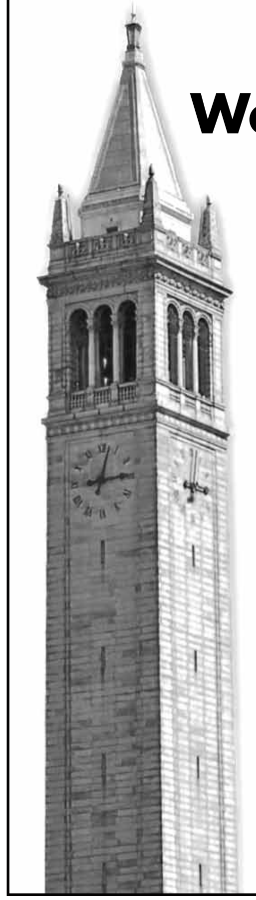


Brain-machine interfaces

The direction of time

Microdiagnostics

Obese mice • *More than a feeling* • *Quantum dots* • The Triple Bind • *Science policy and outreach*



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Dear Readers,

Welcome to the 17th issue of the BSR. Here at the magazine, we are constantly striving to share our excitement about science—UC Berkeley science in particular—with you, our readers. We're trying to do our part to keep the public abreast of university science for a few reasons. First, our livelihoods depend on it; keeping the public involved with our research helps ensure continuing support for the basic research funding that pays the bills around most of our labs. Less selfishly, the public must be adequately informed about the scientific topics of the day to make good decisions about important issues such as combating global warming or ensuring appropriate health care. Equally as important, we just think science is really interesting, and we want everyone else to have the chance to enjoy it too! While we like to think we do our part to spread the science gospel, we're happy to report in this issue a few other ways that UC Berkeley scientists are involved in these sort of scientific outreach efforts. On page 27, Alec Sexton and Seychelle Vos report on two such projects: a course co-sponsored by UC Berkeley and Lawrence Hall of Science that teaches scientists how to teach science and a program that sends graduate students to area elementary schools to share their skills and knowledge with eager students.

Teaching students to appreciate science at a young age should help to increase the science literacy of the general population, but we can't leave it all in the kids' hands. A number of UC Berkeley scientists, such as Secretary of Energy Steve Chu and White House Fellow Daniel Fletcher, have become involved with the policy side of the conversation—Lee Bishop and Elena Spitzer describe some of their experiences on page 22. Aside from education and policy, scientists can reach out to the community by action, actually bringing the benefits of research to improve our quality of life. Allison Berke writes about a number of groups on campus that are working to use technology to bring better medical treatment to inhabitants of the third world (p 30).

On a lighter note, this issue of the BSR is also filled with articles about things that are just plain cool—vibrantly colored shrimp so strong they are known as thumb-splitters that can detect circularly-polarized light (p 8), a study on space tornadoes and their connection to the aurora (p 6), and new ways to connect brains and machines with implications for paralysis patients (p 34). We also introduce a new back page feature called Time Machine that shows a snapshot of research life on campus 25 and 50 years ago.

As always, it has been a great privilege to work with so many talented and dedicated authors, editors, and layout editors. Putting the magazine together each semester requires a tremendous amount of effort, and I am genuinely thankful for the dedication of all of the people involved in creating this final product. If you feel like you have too much free time and are passionate about sharing science with the public and want to join our staff, we'd love to hear from you at sciencereview@gmail.com. These two semesters as editor-in-chief have been challenging in ways that I hadn't imagined when I originally signed up for the job, but the rewards have been great as well. Now it's time for me to pass on the mantle of responsibility, so I will leave you with a fond farewell.

Enjoy the issue,

Rachel Bernstein

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Cover: UC Berkeley scientists are coming closer to bridging the gap between brain and machine. Image courtesy of Nicolas Rougier.

Berkeley Science Review

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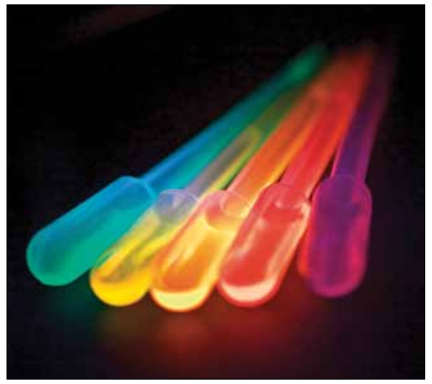
Berkeley, November 2009 No. 17



DEPARTMENTS

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COUNTERCLOCKWISE FROM TOP-LEFT: ARGONNE NATIONAL LABORATORY; ROY CALDWELL; KEN CATANIA; MATTHEW VAN DAM; MATTHEW VAN DAM; ROY CALDWELL; GREG SELLEK; MAREK JAKUBOWSKI; SCIENCE MUSEUM/SCIENCE & SOCIETY PICTURE LIBRARY; TONI VERDU CARBO; CEZARY PIWOWARSKI

labscopes

Strike a pose!

The lights are angled and adjusted to highlight contours and curves. A diffuser softens the colors. On the third floor of Mulford Hall, a graduate student is hard at work in a tiny microphotographic studio. Minute forceps adjust appendages with artistic precision and finely trimmed camel hair paintbrushes dust off even the slightest speck, which, at magnifications of more than 50x, can look like a meteorite. Part art, part science, the custom-built Microptics facility in Professor Kip Will's Environmental Science, Policy, and Management Lab is enabling researchers to generate fantastic images at a fraction of the cost (and without the learning curve) of some other high resolution technologies. Anyone who has looked at a small object under high magnification knows it is impossible to see the entire object in focus; you have to examine one layer at a time, scanning up and down to create a complete picture. Will's Microptics lab overcomes this hurdle with photographic seaming software that melds together more than 100 snapshots to create a singular, perfectly focused three-dimensional representation of a small beetle, caddis fly, or bee. The images taken with high-resolution microphotography can be used in the place of scientific illustrations, providing an exact representation of anatomical structures in true-to-life colors ideal for species descriptions or taxonomic reviews. These highly detailed images can also be used for public education and outreach in K-12 classrooms so that a younger generation of scientists can get a closer look at micro-biodiversity. What's next for the images coming out of the Will Lab? The cover of *Science* or the next issue of *Vogue*?

—Victoria Wojcik

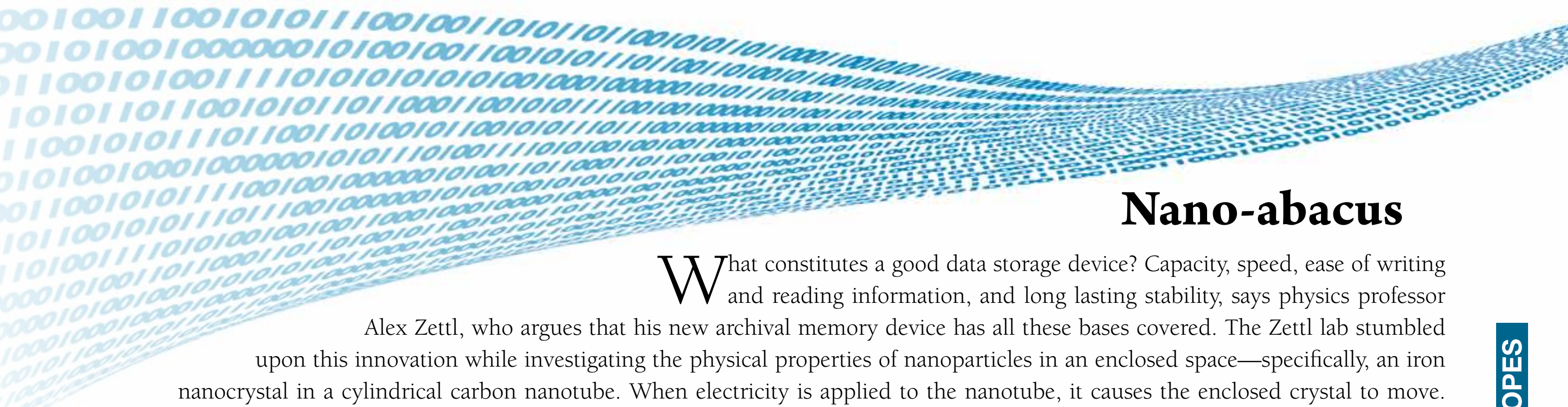
Space tornadoes!

On a hot day, it's clear how the Sun influences the Earth's environment. But how does the Sun affect our space environment? Astrophysicists aim to answer this intriguing question using five probes operated by UC Berkeley, in conjunction with NASA and a number of international institutes, as part of the THEMIS (Time History of Events and Macroscale Interactions during Substorms) project. THEMIS and UC Berkeley scientist Andreas Keiling, along with colleagues Karl-Heinz Glassmeier of the Institute for Geophysics and Extraterrestrial Physics in Germany and Olaf Amm of the Finnish Meteorological Institute, recently detected the existence of vast space tornadoes. "Large enough to envelop the Earth and rotating at more than a million miles per hour, these funnel-shaped solar windstorms are many-fold faster and larger than terrestrial tornadoes," says Keiling. The space substorms, as they are called, were detected by THEMIS probes that measure the speed and direction of solar winds. Solar winds, including space tornadoes, are not the same as wind as we know it on Earth; they involve the movement of charged particles (mostly protons and electrons) ejected from the Sun. These particles can collide with and excite gas molecules in the upper atmosphere; subsequent energetic relaxation of the gas molecules gives rise to bright and colorful auroras such as the Northern Lights. The researchers found that space tornadoes, which carry electrical currents of more than a hundred thousand amperes (roughly ten times that of an average lightning strike), are likely the hidden power behind these beautiful, mysterious polar light displays. "It's the most beautiful result," says Keiling, "when you can look at the intense aurora and say, 'Wow, look, there must be a space tornado out there.'"

—Sharmistha Majumdar

FROM TOP: MATTHEW VAN DAM; GREG SELLEK

ALISTAIR BOETTIGER



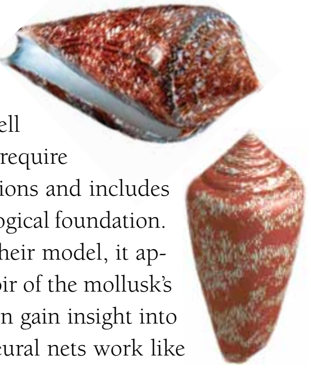
Nano-abacus

What constitutes a good data storage device? Capacity, speed, ease of writing and reading information, and long lasting stability, says physics professor Alex Zettl, who argues that his new archival memory device has all these bases covered. The Zettl lab stumbled upon this innovation while investigating the physical properties of nanoparticles in an enclosed space—specifically, an iron nanocrystal in a cylindrical carbon nanotube. When electricity is applied to the nanotube, it causes the enclosed crystal to move.

This nanocrystal shuttling mimics counting on an abacus, where each count is recorded by physically moving a bead. In the nano case, a '0' or '1' value can be assigned to specific positions of the iron particle in the tube. This position can be read directly by visualizing the tube with an electron microscope, but this strategy is expensive and impractical. A simpler alternative is to measure the electrical resistance at one point on the tube, since this value is directly correlated with the crystal's position. The simplicity of such a device is appealing, but to be truly useful, a storage device must be highly stable as well. CDs and DVDs tend to wear out over a decade, which is simply not long enough for long-term storage of important files like financial information or research data. The Zettl lab has used simple models to predict the lifetime of their nanodevice and is confident it can last a few centuries, if not longer. This stability is preserved even when numerous nanotubes are grouped together to form a high-density device. Another advantage of the device: "It is easily made into conventional architectures [of a chip], and it wouldn't have to be modified too much to take advantage of," says Zettl. It seems like gadget geeks can expect a new groundbreaking data storage system if this device is commercialized in a few years.

—Sharanya Prasad

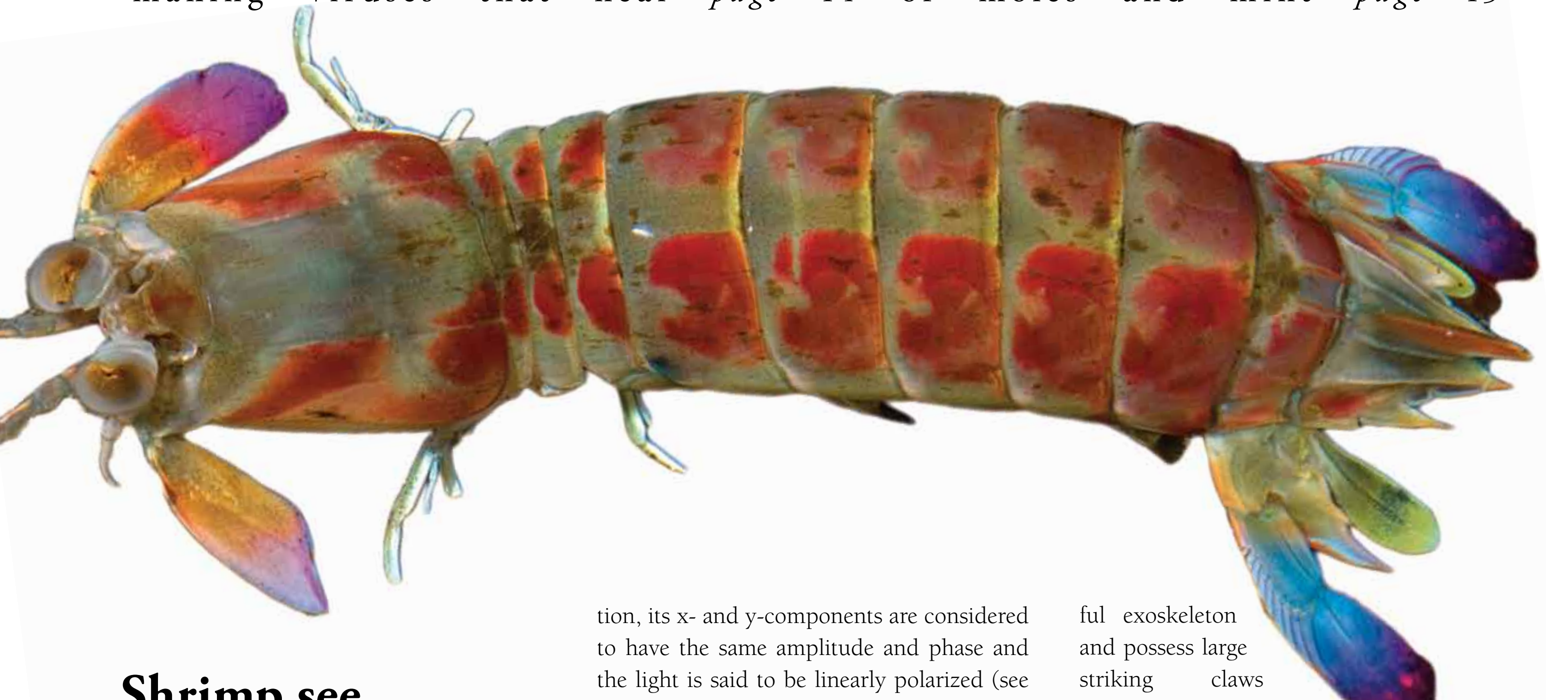
Memoirs of a mollusk



Remember combing the beach for seashells as a kid? All those pretty shells have a story to tell. Alistair Boettiger, a graduate student in biophysics, and Professor George Oster of the Department of Environmental Science, Policy, and Management have created a mathematical model to describe the highly diverse nature of both seashell shapes and patterns across a wide range of aquatic snail species. Unlike previous chemical diffusion models, which require multiple equations to explain shell patterns, Boettiger's model is based on knowledge about actual neural connections and includes nine different biological parameters in a single equation. As Boettiger puts it, "The previous models didn't have a biological foundation. I have a very simple rule, but I actually generate something with a very high degree of complexity." According to their model, it appears that the elaborate markings on the snail shell are actually a record of its neural activity, in effect a sort of memoir of the mollusk's experiences. Being able to describe and predict these patterns with mathematical modeling means that scientists can gain insight into how neural networks function, giving researchers a foundation for deciphering more complex neural systems. "Neural nets work like neural nets, and if we understand how they work in a lower organism, the same thing's probably happening up here," Oster says as he taps his head. "You want to study simple neural nets and then work your way up. The brain is built like an ice cream cone. You put scoop after scoop on top of it, and evolution finally produces a neo-cortex that can think."

—Lauriebeth Leonelli

current briefs



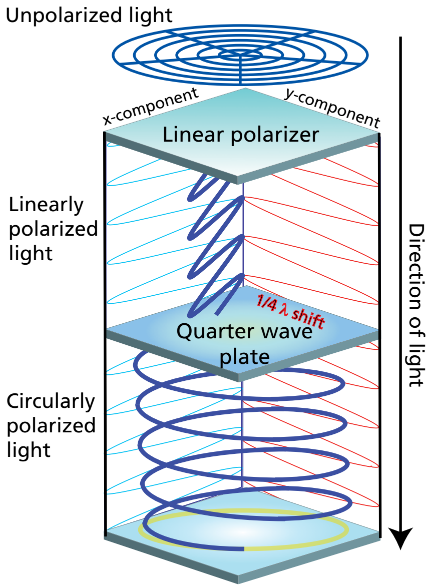
Shrimp see the light

Private communication under the sea

If you have been to the Cineplex in the last year, you may have noticed an increasing number of 3-D films on the marquee. Unlike the monster movies of yesteryear, which required those funny red and blue glasses to make the pictures pop, today's more sophisticated 3-D movies require audiences to wear glasses that take advantage of a property of light invisible to the naked eye: polarization. Modern digital projectors seamlessly interweave alternating left- and right-circularly polarized images onto the screen to create a stereoscopic 3-D effect. While all of this has only recently become possible with the advent of modern technology, it just so happens that humans are not the only animals to capitalize on circularly polarized light.

Light is an electromagnetic wave that oscillates as it passes through space. If this oscillation goes up and down in one direction, its x- and y-components are considered to have the same amplitude and phase and the light is said to be linearly polarized (see diagram). Linearly polarized light can be converted to circularly polarized light by passing it through any material that will shift the wave's x- and y-components out of sync by a quarter of a phase. Such a material is aptly termed a quarter-wave plate and can also convert circularly polarized light into linearly polarized light. Ambient light is a mixture of un-polarized light and varying degrees of polarized light. Take a polarizing filter from a camera lens and hold it up to the sky and you will notice dark patches where linearly polarized reflections are blocked. Many animals possess some sort of vision able to detect linear polarization, but until now, no animals were known to recognize circularly polarized light.

Professor Roy Caldwell in the integrative biology department at UC Berkeley, along with scientists in the labs of Justin Marshall of Queensland University and Thomas Cronin of University of Maryland, Baltimore County, has discovered that two species of large marine shrimp known as stomatopods possess the ability to see circularly polarized light. These fearsome creatures, also known as mantis shrimp, are decorated with a colorful exoskeleton and possess large striking claws capable of smashing open the rock homes and shells of their prey. Stomatopods are one of the fastest-swimming marine organisms, and their claws can strike with the force of a 0.22 caliber bullet, earning these aggressive animals a nasty reputation with divers, who refer to them as "thumb splitters." Despite the bright red markings along their bodies, color alone is not sufficient as a distinguishing feature. "Most of the species we've been studying occur from 10-40 meters below the surface," says Caldwell. "If I'm looking at a stomatopod that has an antennal scale that goes from red to clear to red, and that animal lives at 30 meters, there's no red light. Basically, what we're looking at is a bright/dark signaling." This may be why stomatopods have evolved to possess polarized vision.



Different light polarization states; note that a quarter wave plate converts linearly polarized light to circularly polarized light.

DIAGRAM ADAPTED FROM AMERICAN POLARIZERS, INC. BY HECTOR HUANG

SHRIMP PHOTOGRAPHS BY ROY CALDWELL

One of the initial clues that stomatopods could see circularly polarized light came from the anatomy of the animals' eyes. Like many insects, stomatopods have compound eyes made up of thousands of individual facets. Unlike insects, however, the middle of the stomatopod's eyes contains six specialized rows of facets called the midband. The photoreceptors of two midband rows are arranged to act as crossed polarizers, allowing most species of stomatopods to distinguish linearly polarized light. Caldwell and his collaborators noticed in two species of stomatopods an odd placement of another photoreceptor, known as the R8 cell, which sits on top of the polarizing photoreceptors and seems to act as a quarter-wave plate.

This configuration of photoreceptors was initially confusing, as it essentially knocks out the eye's ability to detect linearly polarized light. As Caldwell recalls, "For a long time it just didn't make sense to us. Here evolution had gone to all this work to produce a beautiful system for detecting linearly polarized light, and they put in a little piece in front of it that knocks it out." However, Caldwell credits famed visual physiologist Dr. Horace Barlow of Cambridge University for recognizing the significance of the R8 cells a couple of decades earlier, when Barlow noted, "That's the way you would detect a circular signal," meaning that the R8 photoreceptor converts circularly polarized light into linearly polarized light, to which the eye responds. The researchers extracted the R8 cell and observed the sample on a darkfield microscope, which is capable of measuring light polarization, and saw that the R8 cell induced a phase shift in the light of about a quarter of a wave.

They then showed that these stomatopods can actually distinguish left- and right-handed circularly polarized signals. By shining circularly polarized light on the specialized photoreceptors and recording the electrical impulses from the eyes, they demonstrated different handed sensitivities in different photoreceptors. Researchers can also train stomatopods to associate either left- or right- circularly polarized light signals with food reward.

So why would shrimp have evolved such a rare and complex visual modality? It turns out that one of the stomatopod species has a tail region that reflects circularly polarized light. Importantly, this trait is sexually dimorphic, meaning, in this case, that the tail region is larger in males than in females. "We really don't know what they're using it for. I suspect that it allows them to recognize species quite well, and it probably allows males and females to tell one another apart at a distance, as opposed to up close, where they can use chemical cues," posits Caldwell.

The stomatopod eye has a specialized region that acts as a quarter wave plate, converting circularly polarized light to linearly polarized light, which can be detected by the eye.

Undoubtedly, this system gives these solitary animals unrivaled speed in profiling situations. Visual cues go directly to claws for fighting or the tail for swimming, bypassing higher-order processing in the brain. In light of this sort of shoot first, ask question later behavior, it makes sense that evolution has endowed mantis shrimp with one of the most complex and advanced visual systems around. A signaling system that no one else can detect has other benefits as well. "It is, without a doubt, the most private communication system out there," says Caldwell. He and his collaborators speculate that circularly polarized communication prevents predators tuned into linearly polarized communications from picking up on private mating calls. If this makes you feel insecure about your own visual abilities, don't distress. At least you can still go to a Cineplex and pay $13 to see a 3-D movie.

Hector Huang *is a graduate student in molecular and cell biology.*

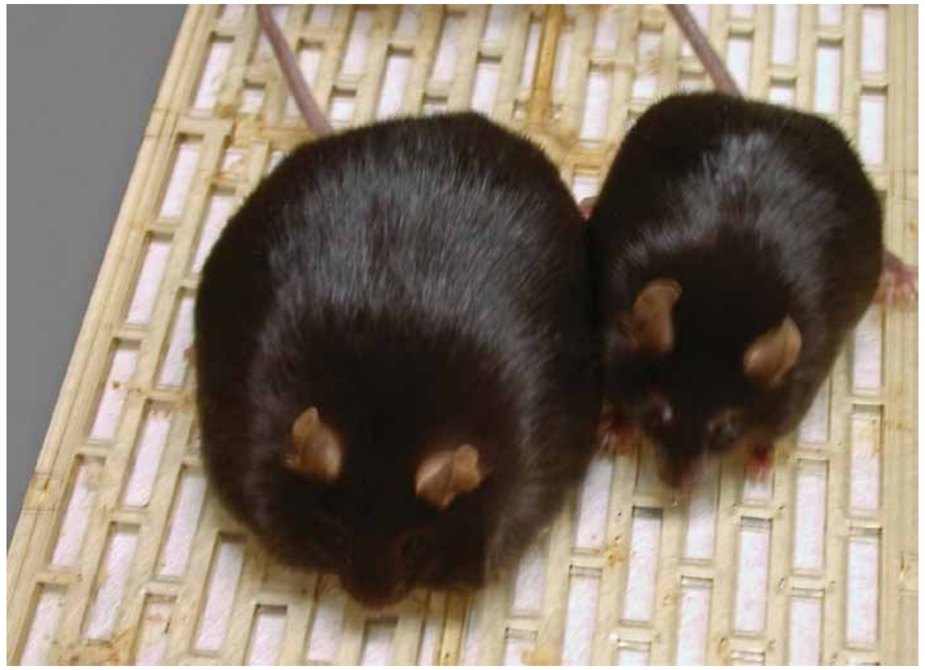
Fat mouse, skinny mouse

Investigating metabolism with genetic engineering

For our ancient ancestors, the ability to store fat was critical to survival. They were hunter gatherers whose food supplies were unpredictable and could fluctuate widely depending on season, drought, competition with animals, and many other factors. Humans evolved the ability to store fat efficiently when food was plentiful so that its energy could be used in leaner times. Our modern lifestyles, however, are frequently at odds with the way our bodies have evolved. Constant access to abundant food and a lack of physical activity means that many of us are consuming and storing much more fat than we are likely to need, and this is having a dramatic effect on our bodies.

According to the National Institutes of Health, approximately two thirds of adult Americans are overweight. Of those, half are obese. Excess weight puts people at risk for a myriad of health problems such as heart disease, type II diabetes, and hypertension. A 2002 study estimated that approximately \$92 billion was spent annually on health care costs related to weight problems, or about 9.1% of all health care costs. Clearly, understanding and controlling weight are critical to improving health and reducing health care costs. Recently, researchers in Hei Sook Sul's laboratory from the Nutritional Science Department at UC Berkeley discovered an enzyme called AdPLA that plays a critical role in fat metabolism.

The body regulates fat with two opposing processes: it can either burn it or store it. When a person consumes fat, carbohydrates, or other foods, the molecules are broken down and transformed into lipoproteins, centers of fat molecules surrounded by proteins. In this form fat can be circulated through the blood stream. Excess fat in the blood is taken up by fat cells, broken down again and stored in what is called white adipose tissue. When the body requires more energy, the fat in the adipose tissue is broken down in a process called lipolysis. It is then reformed into lipoproteins and released into the blood stream. These two processes are in constant balance. When a person eats, levels of signaling molecules that prevent lipolysis increase, allowing fat to be stored. When food is not being consumed, levels are low and fat is burned.



These mice were both fed the same high-fat diet. The mouse on the right remains normal-sized despite this enriched diet because it does not have the AdPLA gene, while the genetically normal mouse on the left becomes obese.

MARYAM AHMADIAN

The enzyme AdPLA, short for adipocyte phospholipase A, plays a critical role in lipolysis. AdPLA is at the beginning of a chain of protein interactions that eventually leads to the breakdown of fat. AdPLA is inhibitory, meaning that it prevents lipolysis. AdPLA is abundant during feeding, so when an animal eats, AdPLA prevents fat from being broken down and allows for fat storage.

Using a process called knockout cloning, the lab created a mouse in which the gene for AdPLA was removed from the animal's DNA so the enzyme would no longer be produced. They found that animals with this mutation did not gain weight, even when fed a high-fat diet. Graduate student Maryam Ahmadian further explains, "We found that even when AdPLA knockout mice have another mutation that causes extreme overeating and obesity, these mice still remained slim." Without this enzyme present to prevent lipolysis, fat was constantly being burned, even at times when the body should have been storing it.

The researchers believe AdPLA could be an ideal drug target. A drug that binds to the enzyme could temporarily disable it, thereby increasing lipolysis and helping a person lose weight. AdPLA has some unique features that the researchers believe may make it a far better target than other known regulators of fat metabolism. First, the absence of AdPLA causes fat to be burned in a unique way. In lipolysis, fat is usually released straight into the blood stream. However, the fat has to go somewhere, and what isn't used for energy will collect in other places in the body. "When lipolysis happens [in the absence of AdPLA], fatty acid is not released into the blood," explains Hei Sook Sul, "it mostly burns inside the adipose tissue." Thus, a patient taking an anti-AdPLA drug should not develop complications from excess fat circulating and collecting in the body. Second, AdPLA is made exclusively in adipose tissue and has only this one known function. Other molecules involved in fat metabolism are found throughout the body and have multiple functions. For example, insulin is a hormone produced in the pancreas and circulated throughout the body. In addition to its ability to inhibit lipolysis, insulin also regulates blood glucose and other physiological processes. While a drug targeting insulin would affect all these processes all over the body, essentially mimicking type I diabetes, a drug targeting AdPLA would only affect lipolysis in adipose tissue.

The discovery of this gene may also aid scientists in studying how fat metabolism differs among individuals. Weight is influenced not only by food intake and activity level, but also by genetics. Some individuals seem prone to being heavy, while others seem to never gain weight no matter how they behave. By analyzing the genetic variations in AdPLA and other critical fat metabolism genes, researchers hope to learn what mutations might put a person at risk for becoming overweight.

Melanie Prasol *is a graduate student in molecular and cell biology.*

Quantum dots light up

Seeing inside cells more clearly

The British newspaper ***The Telegraph*** once defined nanotechnology as "the science of invisibly tiny things." Visualizing invisible tiny things can prove quite a challenge, and a major research area in nanoscience is indeed the search for ways to make the "invisibly tiny" visible. Recently, a team of researchers at Lawrence Berkeley National Laboratory's Molecular Foundry made a new advance in this field that will help in imaging single molecules under the microscope, a subject of great interest to biologists and medical researchers.

To understand how cells work, it is very useful to be able to visualize the locations of molecules within a cell and track their movements in real time. However, cells are mostly transparent and it's not easy to distinguish their components under a microscope. The centuries-old method biologists have used is to apply stains that bind to the structures within a cell and make them different colors. More recently, they have turned to fluorescent tags that greatly increase the contrast and allow targeting of particular molecules. In the fluorescence process, light of a specific wavelength is absorbed, "exciting" the molecule, and is re-emitted as lower-energy light as the molecule relaxes. Usually, ultraviolet (UV) light from a mercury lamp in a microscope is used to excite the tag because it results in emitted light in the visible range. Fluorescent molecules are attached to the target molecules the researchers want to study, and then they show up against the dark background as bright spots of colored light that reveal the location of the targets in the cell.

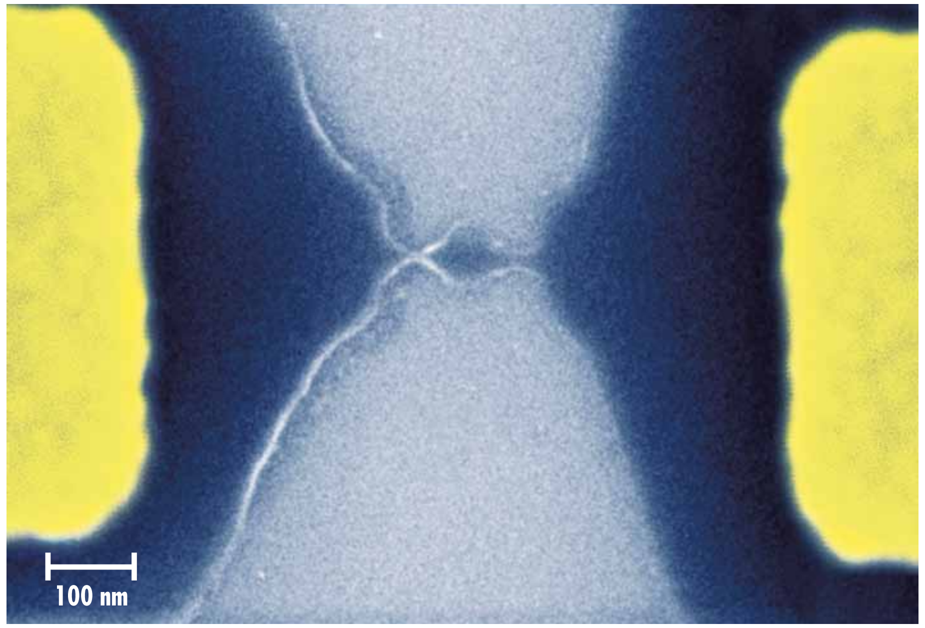
Various small organic molecules can be used as fluorescent tags, and another commonly employed choice is green fluorescent protein (GFP), whose discovery was the subject of the 2008 Nobel Prize in Chemistry. However, these all have a fatal flaw: if you leave the UV lamp shining on them for even a few seconds, the fluorescence dies away, a process known as bleaching. This susceptibility to bleaching makes it difficult to track objects over time. A solution came in the form of semiconductor nanocrystals (also known as quantum dots), little bits of inorganic materials whose fluorescence is brighter and more resistant to degradation by light.

Nevertheless, there is still an irritating problem with quantum dots: they blink. Imagine trying to watch quantum-dot-labeled proteins moving around a cell, and having their fluorescence occasionally disappear. Even when they turn on again, you can't match them with the proteins you were tracking before to have the full trajectory. The underlying mechanism of blinking is still hotly debated; regardless, blinking has been a significant limitation for researchers using quantum dots.

Now, Foundry researchers have synthesized a new kind of nanocrystal that does not blink. "Our results show a single nanocrystal is stable and bright enough that you can go out to lunch, come back, and the intensity remains constant," said Jim Schuck of the Foundry's Imaging and Manipulation Facility, who led the research team.

Their new quantum dots are made of an inert matrix of sodium yttrium fluoride ($NaYF_4$) embedded with ytterbium (Yb) and erbium (Er) atoms, dopants from the bottom of the periodic table, where elements have strong fluorescent emission of visible light. Rather than using UV light, which is higher in energy than visible light, these quatum dots are excited by infrared light, which is lower in energy. First, one of the atoms of Yb in the dot absorbs an infrared photon. It then transfers its energy to a neighboring atom of Er, which can then absorb another infrared photon, providing enough energy to finally emit a photon of either green or red visible light. This novel infrared-to-visible imaging process led the researchers to term their creation "up-converting nanoparticles," or UCNPs (in a—perhaps unconscious—allusion to their employer).

In traditional quantum dots, all of the atoms in the dot participate together in fluorescence, causing the dot to blink on and off as a whole. The crucial difference with the UCNPs is that each Yb and Er atom in



Quantum dots can be made of a variety of materials. A quantum dot carved out of a graphene sheet is shown above.

ANDRE GEIM

the quantum dot absorbs and emits independently. Therefore, even if the individual atoms are blinking on and off, there will still be light produced overall and the average amount won't change much. The Foundry team determined there were 7000 Yb atoms and 700 Er atoms per dot, so there are plenty to ensure continual light emission.

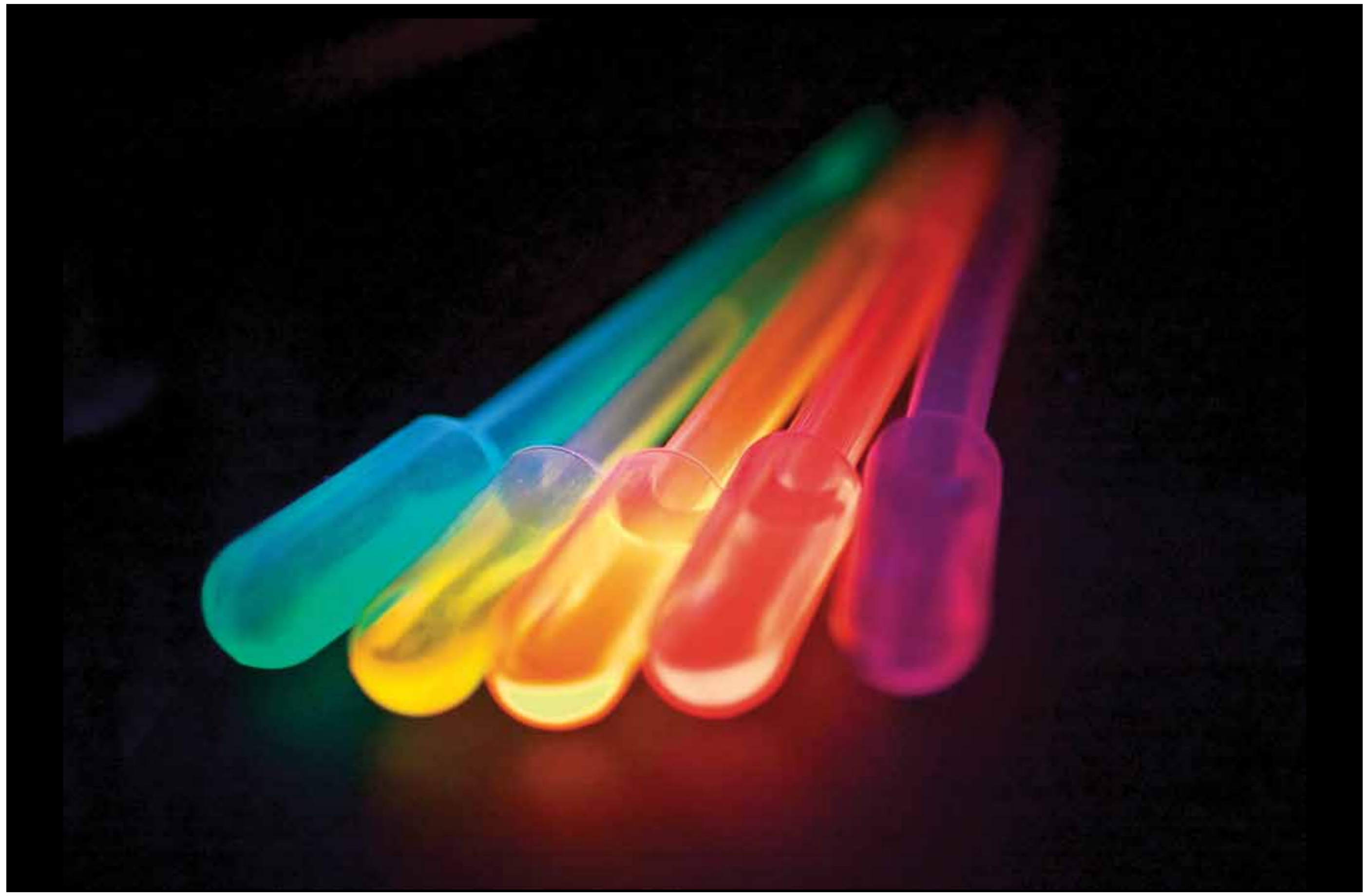
This way of suppressing blinking is actually much like the twinkling of stars. When you look at a distant star at night, you see it as a single point of light, which can change rapidly in brightness due to fluctuations of the atmosphere. By contrast, planets are closer to us and appear as a bigger disk of light. They don't twinkle because the fluctuations of their many individual points of light are averaged out, just as they are in UCNPs.

The researchers note that conquering blinking also endows their quantum dots with two other interesting advantages. With ordinary quantum dots, the contrast against the unlabelled parts of the cell is limited by the fact that excitation with UV light can cause some natural molecules in the cell to fluoresce slightly themselves. However, nothing naturally present in the cell can undergo infrared-to-visible up-conversion, so the dark background of the cell becomes darker yet and makes the imaging method more sensitive. Also, since the process needs two photons, if two infrared beams are directed at a cell, the most intense emission is at the crossing point. By moving the beams, the crossing point can be scanned to different depths, allowing generation of a three-dimensional image.

The team demonstrated the effectiveness of their UCNPs as imaging probes by coating them with biomolecules to render them water-soluble and biocompatible, putting them in mouse cells, and showing that the nanoparticles retained their optical properties. In future work, they plan to use them for uninterrupted tracking of proteins moving around the cell over long times. In the process they will also work to improve the stability of the coatings on the quantum dots, which tend to degrade over time in the cell.

Bruce Cohen of the Foundry's Biological Nanostructures Facility said this work has helped to make quantum dots more effective and easier to use, which will lead to wider use by non-specialists in the biology community. He jokes, "We're making them not just bio-compatible, but 'biologist-compatible.'" And so the frontier of the "invisibly tiny" has been rolled back a little further.

David Strubbe *is a graduate student in physics.*



These plastic pipets are filled with solutions of quantum dots, which are small semiconducting nanocrystals that can produce a rainbow of colors depending on their size. The UCNPs developed at LBL are currently only available in red and green but are still useful in many imaging applications.

ARGONNE NATIONAL LABORATORY

Change one, change all

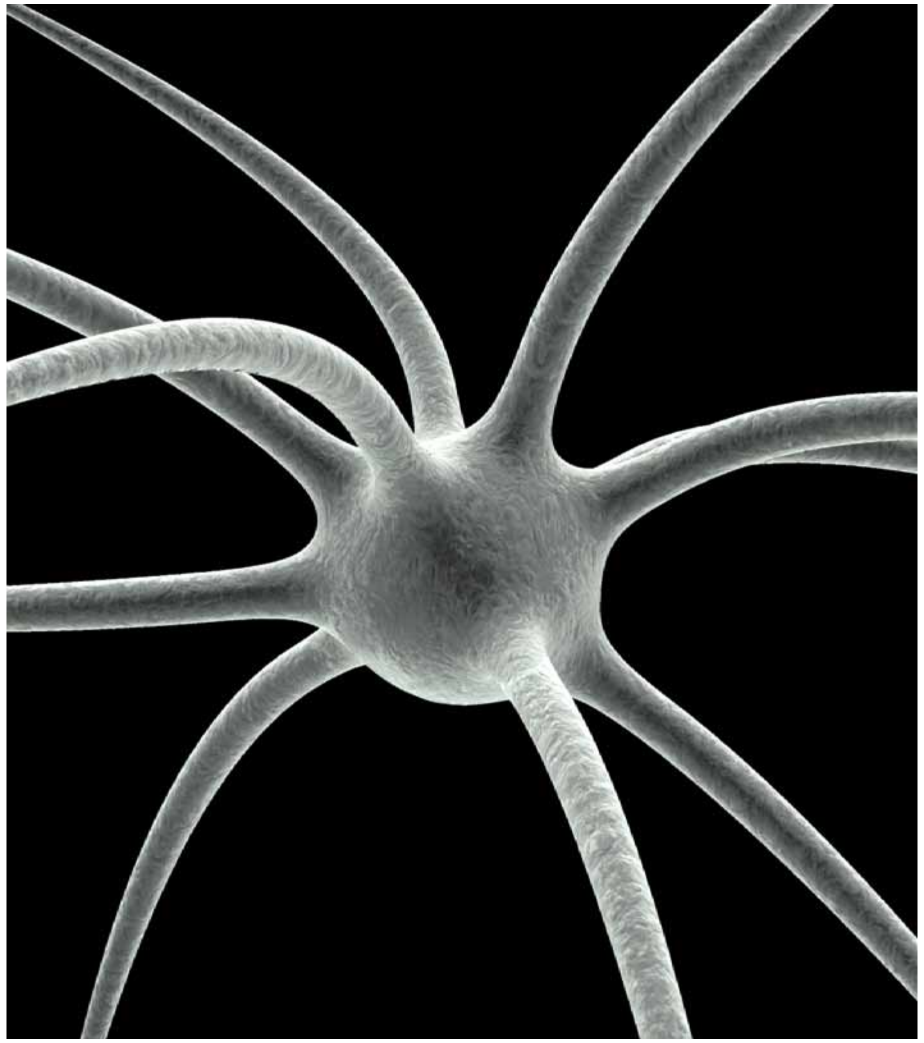
A single neuron switch

Activating a single neuron, or nerve cell, can cause a rat's whisker to twitch. Find that hard to believe? Try this then: UC Berkeley researchers have found that exciting a single neuron can cause a cascade of signals to shoot through the brain, shifting the overall state of the rat brain from a state closely resembling sleep to one resembling wakefulness. Studying how this happens may help shed light on the mystery of connectivity in the brain.

Signals in the brain are transmitted as small electrical currents sent from one neuron to another. The currents from all neurons in any given area of the brain add up to create an electric field, which can be measured by recording changes in voltage between two points in the brain. Different brain states are characterized by different patterns in the electric field. For example, sleep is characterized by electrical waves that oscillate slowly upwards then downward, in a typical horizontal S-shape, while waves that spike rapidly upwards, forming jagged teeth, occur during wakefulness.

Tony Li, a postdoctoral fellow in Professor Yang Dan's lab in the Department of Molecular and Cell Biology, was using microscopic electric currents to activate a single neuron in the brain of an anesthetized rat as part of an unrelated study. He was also recording the global state of the brain some distance away. He noticed that activating the single neuron caused the brain state to change from sleepy, slow oscillations to fast, jagged waves more like wakefulness.

Li was surprised that activating a single neuron could have such a dramatic effect on brain state. "Brain state is really global, and depends on the activity of millions of neurons," he says. Sleep and wakefulness, in particular, are highly complex processes that are governed by many parts of the brain working together. The hypothalamus, a region located deep inside the skull roughly behind one's nose, keeps the brain awake, and once it shuts down, a region at the base of the skull called the brain stem takes over, controlling the shift between rapid eye movement (REM) sleep and deeper sleep. The neuron Li activated was in the cortex, which is many layers of neurons away from both the hypothalamus and the brain stem—the distance between the top of one's head and the base of the skull.



A single neuron can connect to hundreds of thousands of other neurons via a vast array of dendritic processes.

GRAPHIC BY NICOLAS ROUGIER

Li also found that it took a particular kind of firing from the initiating neuron to cause this change in brain state. Only a neuron firing high frequency bursts—almost continuous, repeated spikes—could pass the message along. Neurons usually fire at much lower frequencies than that of the high frequency bursts he triggered in this study, and these high frequency bursts are not likely to happen naturally in the particular area of the cortex Li studied. Instead, it's more likely that a small number of cells in a given area are activated and start to fire, cumulatively giving rise to a high frequency burst that sends signals running through the cortex, finally waking up the brain stem.

An enduring mystery in neuroscience concerns exactly how neurons connect to each other. Each neuron in the brain can be connected to between 5,000 and 250,000 other neurons, forming billions of circuits throughout the brain. Current technology allows for measuring the activity of single cells, and activity across the brain as a whole, but there really isn't a good way to record what individual circuits of neurons are doing. Tracking down the path by which one activated neuron ends up modifying brain state could provide a way to map some of those elusive brain connection circuits.

"The most important part is the mystery of connectivity in the cortex," says Li. What paths do these signals follow through the cortex, and how do they eventually reach the hypothalamus and brain stem? These are questions that he hopes to answer with his research in the future, answers that may unlock some of the mysteries of connection in the cortex.

Niranjana Nagarajan *is a postdoctoral fellow in molecular and cell biology.*

Making viruses that heal

Evolution breeds new treatment options

Life is brutal in David Schaffer's lab, especially if you are a virus. Researchers in the Schaffer lab have been forcing millions of viruses to race each other to infect flecks of human lung tissue, creating a viral gladiatorial games where the winners advance to the next level and the losers die in the fight. The point of this competition is not merely sadistic entertainment. Rather, it is to pick out the most infectious viruses, isolating them from a haystack of hopefuls. In a recent paper Schaffer and his collaborators reported the final result of this process: one mutant that not only rapidly infects lung cells, but could, in the process, deliver a gene with the potential to cure cystic fibrosis.

Cystic fibrosis is a chronic, life-shortening disease that results from a defect in a single gene known as the CFTR gene. This CFTR mutation causes mucus thickening in several organs, which can trap bacteria and lead to infection. These infections are particularly deadly in the lungs. "Cystic fibrosis is an uncured disease. It's devastating for those who have it," says Schaffer. "Hypothetically, though, if you can deliver that one gene to that person's lung, you can cure it." This approach is the goal of gene therapy: to replace malfunctioning genes with working copies, inserted directly into cells.

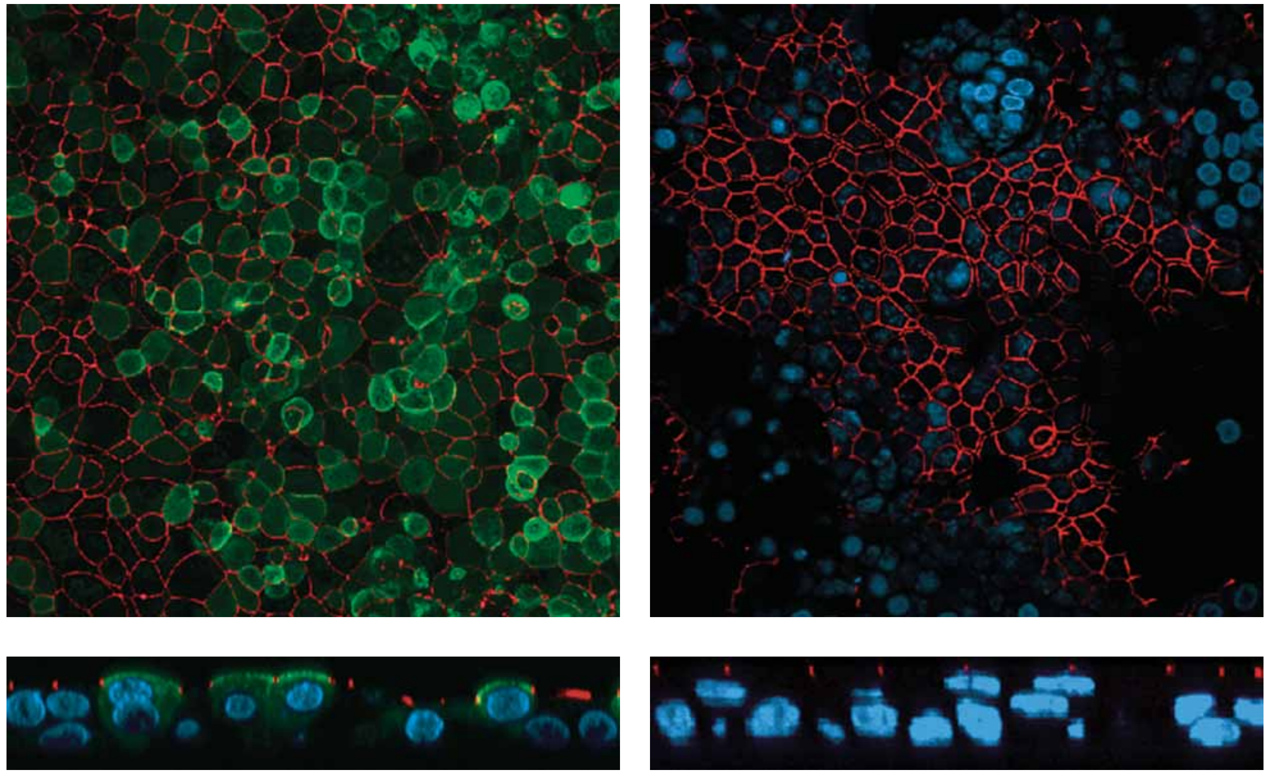
Getting new genes into a cell, however, is not so easy. Viruses, which inject their DNA into cells and hijack cellular machinery to reproduce, are in principle well-suited to the task. For decades, researchers have been trying to harness this viral DNA delivery system. By replacing the DNA in a relatively harmless virus, such as adeno-associated virus (AAV), with specialized therapeutic genes, they hoped the virus would seek out relevant cells and deliver the curative goods. But, as Schaffer explains, "While AAV is a terrific and safe vehicle for carrying genes to a cell, it's not very efficient." In other words, the virus does not infect enough cells to make a difference.

To find a more infectious virus to carry the CTFR gene into lung cells, Schaffer used a common tool in his home field of chemical engineering: a competition for survival, also known as directed evolution. Researchers in his lab first created massive libraries of mutants from the nine known types of AAV. They then exposed the millions of resulting AAV variants to human lung tissue in a dish, where the viruses had to either infect cells or be washed away in the swirling media. Viruses that managed to get into lung cells made it to the next round, where those that infected the largest number of cells had a competitive advantage. After several such rounds, a single champion emerged. When the researchers loaded that winning variant with copies of the CFTR gene, they found that the CFTR gene worked its way into lung cells and was readily expressed. The secret to this virus' success seems be a mutation that makes it stick particularly well to the target lung cells before unloading its genetic cargo.

AAV was not always the virus of choice for gene therapy. In the 1990s, most research focused on adenovirus, which did a better job of delivering genes than AAV. But adenovirus fell out of favor after a severe immune reaction to it killed an 18-year-old research subject in 1999. AAV, which is naturally found in a substantial portion of the population and has been used in hundreds of clinical trials, seems to be a safer alternative. Schaffer's directed evolution techniques may give us the best of both worlds, then: good gene delivery like adenovirus with the proven safety of AAV.

Directed evolution methods are "a huge leap forward" for gene therapy, according to John Flannery, a professor of neurobiology here at Berkeley, and they could improve gene therapy treatments in many parts of the body. Using directed evolution with retina rather than lung tissue, for example, Flannery has collaborated with Schaffer to find a virus that can deliver an important neurotrophic factor—a kind of food for neurons—to support injured or diseased photoreceptors in the eye. When testing this virus on rats with retinal degeneration, Flannery found a 50% slowing of photoreceptor death. "These animals usually go blind in three or five months," says Flannery. With this virus treatment, "you can slow it by half." Schaffer hopes the directed evolution approach will continue to help create new virus variants in many different tissue types. "The off-the-shelf AAV variants we get from nature are simply not good enough," he says. "They get us 60% of the way there, and I think these tools can get us the other 40%."

Liz Kirby *is a graduate student in neuroscience.*



These images show lung cells with the cystic fibrosis mutation in the CFTR gene. Each cell is outlined in red and the nuclei are labeled in blue. The cells on the left have been treated with Schaffer's mutant virus carrying a healthy CFTR gene. The resulting protein, which protects the cells from the disease, is labeled in green. The extensive green coloration seen in these cells indicates that Schaffer's treatment has been effective. On the bottom is the cross section of the cells, showing that the CFTR protein is found in the cytoplasm surrounding the nucleus, where it can effectively prevent the disease.

AVID SCHAFFER

DIANA BAUTISTA

Of moles and mint

The molecular basis of sensation

Chili peppers, mint, mustard seed, peppercorns, garlic, wasabi: the shelves of Diana Bautista's lab are a veritable spice rack. But Bautista, who joined the UC Berkeley faculty as an assistant professor of molecular and cell biology in 2008, is not a chef in her spare time. Instead, she's using these spices to study how we sense the world through our skin.

"We are interested in identifying the molecular and cellular mechanisms underlying touch and pain," explains Bautista. "So if you get stuck with a pin or are lightly brushed with a feather, we want to identify the receptors that convert these physical signals into the electrical signals that travel along your nerves."

Our skin is filled with a variety of different nerve cell types whose surfaces contain specific receptors (specialized protein molecules) through which we sense our environment. Some of these receptors detect painful stimuli, some detect different types of touch, such as light touch, vibration, or texture, and some detect heat or cold.

"There are many different types of touch receptors that detect distinct types of tactile stimuli, and we would like to isolate them from one another so we can find the mechanisms underlying these different types of sensations," says Bautista. However, not only are the receptor-containing nerve cells spread diffusely throughout your skin, they're also all jumbled together with cells of different types, making them a nightmare to separate and thus difficult to study.

That's why Bautista turned to natural products—chemicals derived from living organisms, usually plants. Compounds like menthol (which creates the curiously strong cooling sensation we feel when we eat an Altoid breath mint) and capsaicin (which makes chili peppers spicy) both bind to and activate different temperature-sensitive receptors, which is why we feel them as "cold" and "hot." By searching for the targets of these and other natural products, whose effects on the senses are well known thanks to thousands of years of human experimentation, researchers have been able to find and study new receptors that would have been difficult to identify otherwise.

Bautista's lab primarily uses the mouse as its model organism, studying both cultured nerve cells and live animals. For example, in a paper published in the journal *Nature* in 2007, Bautista (then at UCSF) and colleagues describe an experiment in which a genetically engineered mouse was placed in a chamber heated to 30°C (86°F), which was connected to an adjacent chamber cooled to 20°C

Sichuan peppercorns contain the compound hydroxy-alpha-sanshool, which the Bautista lab uses to study the sensation of light touch.

(68°F). While a normal mouse was hesitant to even poke its head into the cooler chamber, this mouse walked right in and sat down to clean itself. It continued to explore both chambers, seeming to show no preference for one or the other. "Mice are really sensitive to cold, and the TRPM8 knockout would just sit comfortably on a cold plate," recalls Bautista. "It had little cold sensitivity. That was really striking."

The mouse in question was a "knockout mouse." It developed from an embryo that the researchers had cleverly manipulated so as to remove a specific gene—in this case, the gene encoding TRPM8, a cold receptor that was initially identified because it is also activated by menthol. Without this gene, the mouse could not sense cold until the temperature dropped below 15°C (59°F). Before Bautista's study, researchers disagreed about the importance of TRPM8 in detecting cold. However, the cold insensitivity of the knockout mouse was solid proof that TRPM8 is the principal cold receptor in mice, and likely in humans as well (though there seems to be another receptor, as yet undiscovered, that detects painful cold below 15°C).

Currently, the Bautista lab is using natural products to study the sensation of touch. "We're interested in identifying other temperature-sensitive receptors as well, but I'd say about 75% of the lab is interested in finding receptors involved in touch—that's really the holy grail of the pain field right now," says Bautista. However, touch is a particularly difficult sense to study. "How do you mimic touch in the lab? It's really hard to do. You could poke cells, and stretch cells, but you don't know if that really approximates what's going on in the skin," she explains.

So, for these studies, the lab uses a product derived from the Sichuan peppercorn. This spice is not related to chili peppers and does not contain capsaicin; rather, it contains a chemical called hydroxy-alpha-sanshool that elicits a tingling, numbing sensation Bautista describes as "akin to the experience of touching one's tongue to the terminals of a nine-volt battery." By bathing cultured nerve cells with purified hydroxy-alpha-sanshool, Bautista has been able to determine the subsets of neurons activated by the compound, and has even identified a new class of receptors that she thinks is important for our sense of light touch.

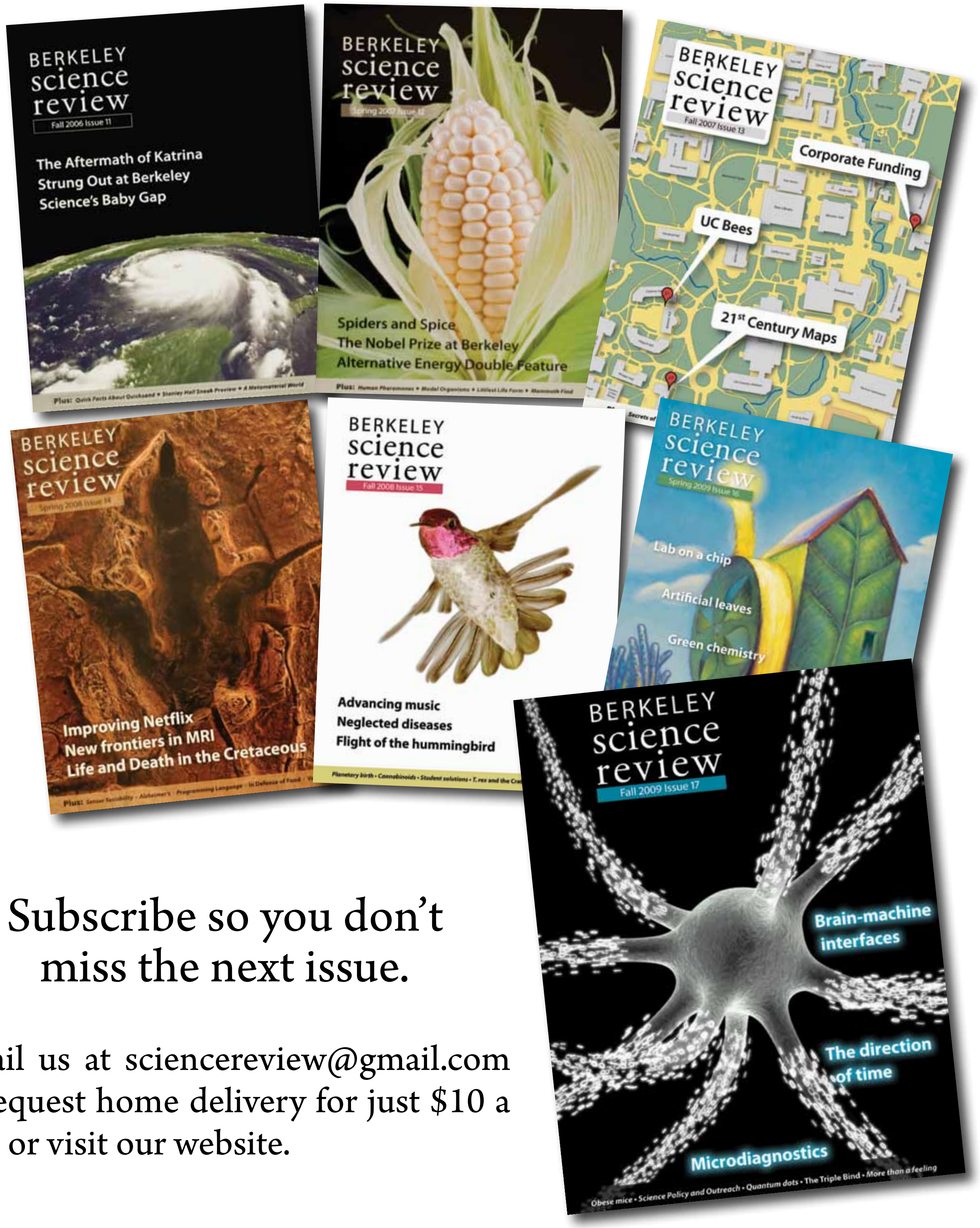
Surprisingly, a mole has also come in handy for Bautista's studies of touch. The nose of the star-nosed mole is the most sensitive touch organ known, making it of particular interest to Bautista and her collaborator Ken Catania at Vanderbilt University. The "star" is a large, pink appendage with 22 sensitive projections that the mole uses to detect food as it scoots through its underground tunnels. Not only is the star packed with ten times more nerves than the human hand, it also has only three nerve types, all light-touch sensors. By isolating these nerves and finding the receptors expressed in each, Bautista hopes to learn more about how we detect light touch.

When she first started her research, Bautista was surprised at how little was known about such an essential part of our physiology. "I'm very interested in sensory neuroscience and how we interact with the real world, and one thing that shocked me was how little we know about touch and pain at the molecular level." She hopes that her studies will not only add to our knowledge of how we sense the world, but also help us better understand medical disorders such as chronic pain.

Meredith Carpenter *is a graduate student in molecular and cell biology.*

The nose of the star-nosed mole is the most sensitive touch organ known. The Bautista lab studies the star-nosed mole to better understand how we detect touch.

KEN CATANIA



TONI VERDU CARBO

TIME *TWISTER*

The strange world of small things

by Gary Clark

Which way is time flowing? To a human being in the macroscopic world, the answer to this question appears obvious. Our sense of time is intuitive: the past, the present and the future are distinct. However, like many other observables, such clear distinctions become murky when we consider processes at scales far away from those of our everyday experience. At the molecular level, on the length scales of molecules, the distinction between the past, the present and the future—the direction of time's arrow—is not always apparent. This is just one extreme example of how our intuition can fail us when we attempt to understand systems consisting of a relatively small number of molecules. It happens that many systems that are particularly interesting, such as the cells that are the core units of living things, inhabit this molecular regime. This article explores this counterintuitive world, highlighting ongoing theoretical and experimental efforts at UC Berkeley to understand the physical rules that govern it.

Thermodynamic fluctuations and the direction of time's arrow

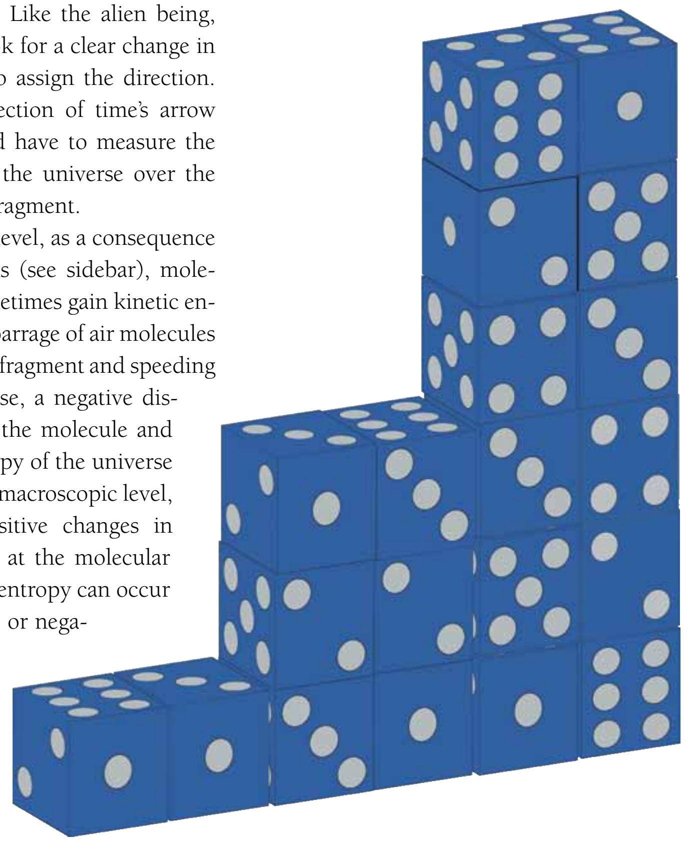
In recent work, a team of scientists led by Gavin Crooks of the Physical Biosciences Division at the Lawrence Berkeley National Laboratory derived a relationship between the direction of time and changes in energy at the molecular level. The relationship follows from other work by the Crooks lab that has allowed scientists to investigate the thermodynamic properties of single biological molecules. The properties of these molecules are important for understanding how cells work and ultimately for designing and building machines on the molecular scale. Crooks explains, “We would like to understand how our bodies work, how cells convert energy into work, and we would like to design and build our own machines similar to those in our body that work at the same length scales and under the same types of conditions.”

To understand systems at the molecular scale, we require an understanding of their thermodynamics, the study of how energy is converted into mechanical work and heat and the relationship of these quantities to variables such as temperature and pressure. Of particular significance is the second law of thermodynamics, which is the only fundamental law of physics to pick a direction in time. The second law states that, on average, the entropy of an isolated system is increasing—in other words, a change in entropy (see sidebar) of an isolated system over some period of time will be positive. The universe is taken to be an isolated system: both mass and energy are constant. Since the entropy of the universe is increasing, the arrow of time clearly points from the low-entropy past into the high-entropy future.

In accordance with the second law of thermodynamics, at the macroscopic level only large and positive changes in entropy are observed. If a vase falls off a table, we rightfully expect that in a few moments it will smash into many pieces on the floor. Behind the scenes a large positive change in entropy is observed as the universe proceeds from a low-entropy ‘vase’ state to a high-entropy ‘broken vase’ state. Imagine if the breaking of the vase were filmed and shown backwards to a being with no experience of gravity or the breaking of vases, and therefore without our human intuition. How would this being assign a direction to the arrow of time? If it understood the second law of thermodynamics, it too would arrive at the same conclusion based on the large increase in entropy of the universe between the two states, without the need to invoke experience.

While at the macroscopic level assigning a direction to the arrow of time is something intuitive, this is not the case at the molecular level. We could make a new movie in which we only film a tiny fragment of the vase, the size of a few molecules, after the impact of the vase on the floor and before the fragment lays to rest as part of the final ‘broken vase’ state of the universe. If we randomly oriented the film before playing the movie, we would see the fragment moving through the air, but with no discernable difference between the initial and final states of the fragment (and therefore the universe). With no experience of these time and length scales, it is almost impossible to ascertain the direction of time's arrow using intuition. Like the alien being, however, we could look for a clear change in entropy with which to assign the direction. To determine the direction of time's arrow for this clip we would have to measure the change in entropy of the universe over the trajectory of the vase fragment.

At the molecular level, as a consequence of thermal fluctuations (see sidebar), molecules can lose and sometimes gain kinetic energy—analogous to a barrage of air molecules bumping into the vase fragment and speeding it up. In this latter case, a negative dissipation of energy by the molecule and a decrease in the entropy of the universe may occur. Unlike the macroscopic level, where only large positive changes in entropy are observed, at the molecular level small changes in entropy can occur that are either positive or negative (although on average positive). These fluctuating changes in entropy on short timescales result in ambiguity in the direction of time's arrow. In their study Edward Feng (now at the Sandia National Laboratory) and Gavin Crooks have developed a relationship between energy dissipation (or the change in entropy of the universe) and the direction of time. They relate the probability of observing a particular change in entropy in a forward experimental protocol, going from an initial state to a final state, to the probability of observing a negative change in entropy of equal magnitude in the reverse experimental protocol, going from the final state back to the initial state. From the relationship between these two protocols and the energy dissipation measurements, they derive a probability of being able to assign a direction to time.



GARY CLARK

Entropy is an important physical observable required in the understanding of the direction of time. This image shows a representation of some of the entropy states (see sidebar) of a system of two dice. There is only one way in which to roll a two, so this corresponds to the lowest entropy state of the system, while there are six ways to roll a seven, so this represents the highest entropy state of the system.

The recent work of the Crooks group highlights that contrary to our experiences in the macroscopic world, the direction of time is not an absolute quantity but instead is dependent on environment and perspective. This phenomenon is highlighted at the molecular level where thermal fluctuations lead to ambiguity in the direction of time at this scale. While this theory yields an interesting insight into the nature of time at the molecular level, it has not yet found application in

Entropy and Thermal Fluctuations

Entropy is a physical observable and can be thought of as a measure of the number of possible ways in which to arrange a system. The greater the number of ways to arrange the system the larger the entropy. For example, if a system is composed of two dice and a state is the sum of the values of those dice then there are 11 different states, 2, 3, 4, ... ,12. The lowest entropy states are 2 and 12, as there is only one way in which each of these states can be obtained, by throwing 1-1 or 6-6. The highest entropy state is 7, as there are six ways in which this state can be obtained, by throwing 1-6, 2-5, 3-4, 4-3, 5-2, or 6-1. Thus state 7 has the highest entropy compared to the other states, as it has the largest number of ways in which it can be arranged.

Thermal fluctuations refer to the change in the random thermal motion of particles, observed as a change in the frequency of collisions between particles and the kinetic energy of colliding particles. On average all of the particles in an isolated system will be moving at the same velocity and have the same kinetic energy, but subsets of these particles will be more or less energetic. The number of particles that inhabit these states distant from the average energy changes from moment to moment, although over the long periods and large spatial scales relevant to human experience the average remains constant. Thus, if we sit in a room the temperature feels constant as millions of air molecules collide with us each second. However, a single protein molecule dissolved in water will be subject to varying numbers of collisions at any given moment, and thus processes that it may undergo, such as unfolding, are subject to thermal fluctuations.

Thermodynamic Equilibrium

Equilibrium can be defined as a state of balance, whereas non-equilibrium is defined as a state of flux. For instance, two systems in contact with one another and with the same temperature are said to be in thermal equilibrium. There is no heat energy exchanged between the two systems. If the temperatures of the two systems are different, then heat energy will flow from the hot system to the cold system. For example, if a glass of water is placed in a fridge, initially it will be out of equilibrium with the inside of the fridge as heat energy flows from the glass of water to the air molecules inside the fridge. This flow of energy, or energy dissipation, will stop when the glass of water and the inside of the fridge are at the same temperature.

For a system to be in thermodynamic equilibrium, three conditions must be satisfied: thermal equilibrium (as we have just discussed), mechanical equilibrium, and chemical equilibrium. A system is in mechanical equilibrium when the net force acting on it is zero. For instance, a glass of water is in mechanical equilibrium if it is at rest, but if the glass sprang a leak then the water would no longer be in equilibrium, but would instead accelerate to the floor in a state of flux under the influence of gravity. The final condition, chemical equilibrium, concerns the concentration of matter in a system. In the example of the glass of water, the water is in chemical equilibrium as long as there is no net change in the number of water molecules. If water vapor were to condense into the glass at a rate faster than that of water evaporation from the glass then the glass of water would no longer be in a state of chemical equilibrium.

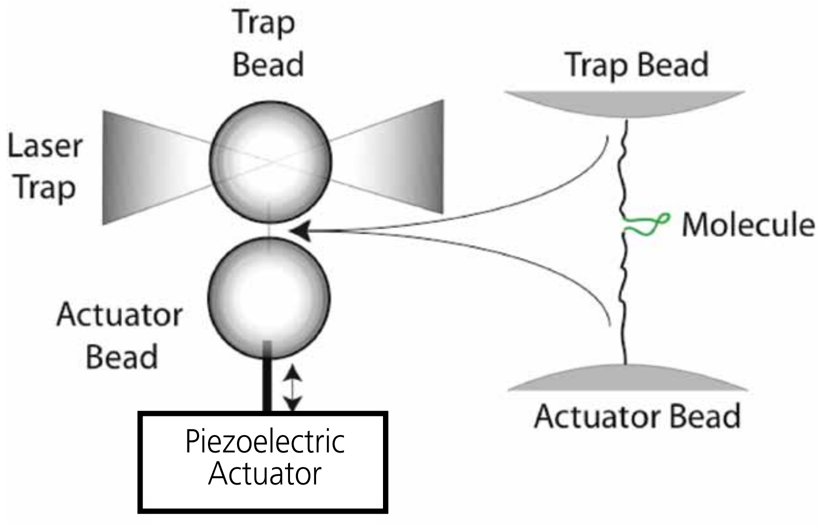
In reality, things are rarely in equilibrium, but are instead in a state of flux; water flows down hill, compounds react and change, and the continents drift. Sometimes the approximation of a nonequilibrium system being at equilibrium can be made. For instance, over a short enough period of time the continents can be considered to be in a state of mechanical equilibrium.

experiment. However, previous work by the Crooks group, on which this theory is based, has proven critical for the interpretation of single-molecule experiments.

Single-molecule experiments: deviating from a set path

In a typical experiment to probe the thermodynamics of a single molecule, a macromolecule such as a protein or RNA is attached between two beads. One of the beads is attached to an actuator, which is used to move the bead up and down, and the other is captured in a laser trap, which measures the force applied to the molecule. This set-up is referred to as an optical tweezer. The actuator is used to change the separation between the two beads. If the beads are close enough together, the molecule can exist in its proper compact, or folded, structure. When the beads are pulled farther apart, the molecule is stretched until it loses its structure and becomes roughly linear, or unfolded. Throughout this process of folding and unfolding the force applied to the molecule is measured, from which the amount of energy put into folding or unfolding the molecule can be calculated.

Jesse Dill, a biophysics graduate student in the Marqusee and Bustamante labs, uses optical tweezers to investigate the folding and unfolding of proteins. Dill explains, "In the world of proteins there are a couple of very basic building blocks: the protein can zigzag back on itself to create a beta sheet, or it can spiral around to create alpha helices. We are interested in how the organization of these structural motifs, these building blocks, defines the mechanical properties of the proteins." A key measurable property in biochemistry is the change in free energy upon folding a molecule from its unfolded, or denatured, state to its folded, or native, state. In its folded state, a protein is in a functional form, whereas in its unfolded state, it can no longer carry out its function. The change in free energy between these two states can be calculated from the force applied to the protein and its measured end-to-end extension as it folds and unfolds.

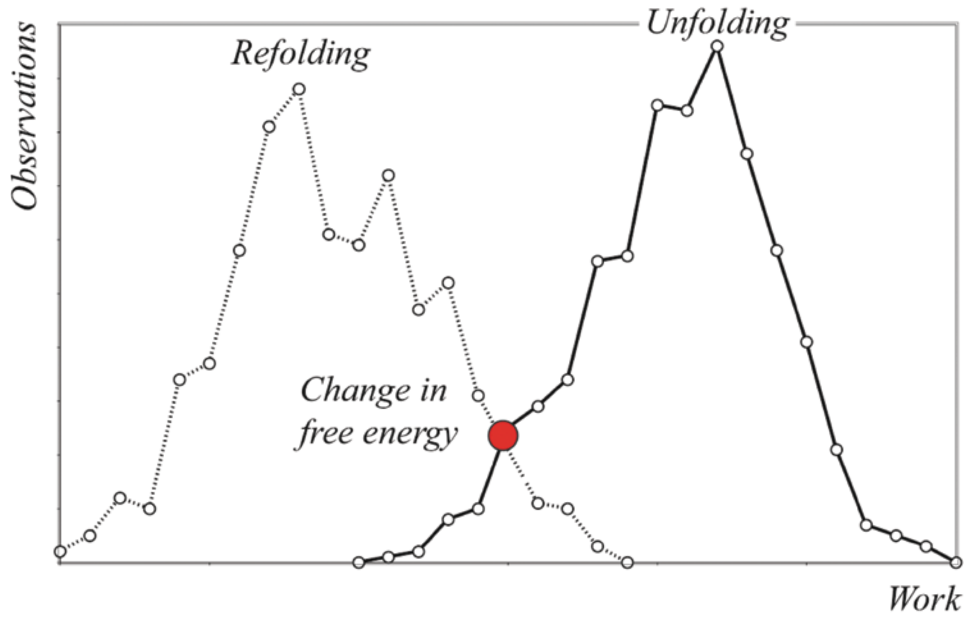


A cartoon of the setup for a single-molecule experiment. A molecule is tethered between two beads, one of which is trapped by a laser, while the other is attached to an actuator, which can be used to move the bead and stretch or compress the molecule. The force acting on the molecule can be measured by the movement of the bead trapped by the laser.

GAVIN CROOKS

To measure a free energy change for a molecule we require it to be in equilibrium with its surroundings (see sidebar). For some systems this measurement is not a problem; the molecule can be folded or unfolded very gently, allowing equilibration of the molecule with its surroundings. In this regime, thermal fluctuations observed at the molecular level are small, allowing the change in free energy to be calculated directly. When the experiment is repeated, the same value for the change in free energy is always obtained. For some experiments, however, even when given the same starting conditions, the energy required to fold or unfold the molecule varies from one experiment to the next. Dill explains, "If you measured the amount of energy it takes to unwind a spool of thread, and then you did it again, you would get the same number. If you measured the amount of energy it takes to pull apart a clump of velcro, and then you did it again, you would get a different number." It turns out that, in these velcro-like systems, at certain points the protein or RNA structure is not in equilibrium with its surroundings. In this regime the required rate of pulling is too fast for equilibration to occur. Thermal fluctuations then lead to energy dissipation, which varies for different repetitions of the experiment. After a series of experiments, distributions of the work required to both fold and unfold the molecule are obtained.

Until recently, it was almost impossible to resolve the change in free energy for protein systems out of equilibrium due to the variation in work measured for each experiment.



An example of the work diagram obtained from the folding and unfolding of a protein molecule in a single-molecule experiment. From the Crooks fluctuation theorem, the point at which the folding and unfolding trajectories intersect gives the equilibrium change in free energy between the folded and unfolded states of the protein.

GAVIN CROOKS

This changed in 1999 however, with the application of a theoretical discovery by Crooks to these single-molecule experiments. Crooks' discovery—the Crooks fluctuation theorem—showed that the intersection of folding and unfolding work distributions gave the equilibrium change in free energy between the folded and unfolded states of a molecule.

Similar to the velcro clump, a compact RNA or protein structure is hard to pull apart—and when it unfolds, it can often do so in a number of different ways, referred to as pathways. For a velcro clump, the pathway depends, in part, on the technique used to pull it apart. For a single molecule, the pathway depends on thermal fluctuations in its local environment. These fluctuations are the same as those that affected our molecular vase particle. In the optical tweezers experiments, though, it is water molecules bumping into the molecule and transferring kinetic energy that causes these fluctuations. For each repetition of the single-molecule experiment, the local environment around the molecule will change. The result is that the molecule will sample different pathways, each of which requires a different amount of work to be done. Like the clump of velcro, which sometimes unfolds easily but at other times forms a tight knot, there will be some folding and unfolding pathways that are easier to access than others. If the experiment is repeated many times, a distribution of folding and unfolding forces will be obtained. The experimentalists measure the force exerted on the molecule as it unfolds each time, and use that information to calculate the distribution of work it takes to repeatedly destroy the folded structure.

For the folding and unfolding of a molecule, the Crooks equation shows that the point at which the two work distributions intersect gives the information change in free energy between their folded and unfolded states, a key insight which makes these experiments interpretable. The next challenge for experimentalists is to see if the theory that postulates the ambiguity in the direction of time can aid in understanding observed phenomena on the molecular scale.

Gary Clark *is a postdoctoral fellow in bioengineering.*

Molecular Machines

In recent years the development of single-molecule experiments has enabled scientists to investigate the properties of molecular motors. These motors are responsible for a multitude of different tasks; the motor protein myosin, for example, is responsible for muscle contraction, while others, dyneins and kinesins, "walk" along the cytoskeleton of a cell transporting cargo. Gheorghe Chistol, a graduate student in the Bustamante Group in the Department of Physics, uses optical tweezers to investigate the ATPase molecular motor on a phi 29 bacteriophage (phage), a common virus that infects bacteria in the soil. The phage infects bacteria by injecting its viral DNA into a bacterial cell, hijacking the cell to build a new phage. The phage uses the ATPase motor to grab onto and load its DNA into a basket, or capsid, which it uses to carry the DNA to its next victim. The ATPase motor is powered by chemical energy carried by the ubiquitous adenosine triphosphate (ATP) molecule. Molecular motors from the ATPase family are found in almost all organisms.

The work of Chistol is concerned with the understanding of the mechanism, or mechanochemistry, by which ATPase works. For example, optical tweezers can be used to measure properties such as the rate at which the motor packs DNA into the capsid, or the maximum amount of force that the motor can work against. Thermodynamic properties may also be of interest in the future. According to Chistol, the human body runs at about 50-60% efficiency, while a car engine may run at only 10-20% efficiency. An understanding of the mechanochemistry and thermodynamics of molecular motors may help us develop machines at the molecular scale and may yield gains in efficiency in macroscopic machines.

SCIENCE IN THE HOUSE

UC Berkeley faculty brings expertise to Washington

CEZARY PIWOWARSKI

By Lee Bishop and Elena Spitzer

"Science forces us to reckon with the truth as best we can ascertain it," said President Obama in his April address to the National Academy of Sciences (NAS). "Science cannot supplant our ethics or our values, our principles or our faith. But science can inform those things and help put those values…to work—to feed a child, or to heal the sick, to be good stewards of this Earth."

Obama is the first sitting president since John F. Kennedy to address the annual meeting of the NAS, where he stressed the importance of science to society. Perhaps a more concrete demonstration of his belief that scientists have a role to play in public life is his appointment of a number of highly regarded scientists to posts in his administration. Among them are two former UC Berkeley scientists: physicist and Nobel laureate Steven Chu, now Secretary of Energy, and environmental policy professor John Holdren, now Director of the White House Office of Science and Technology Policy. Chu and Holdren have left the university to fill these critical positions in the administration, but UC Berkeley still has many faculty members who are actively involved in both scientific research and public policy. We spoke with five such professors about their views on scientists getting involved in public policy and explored with them some of the mechanisms, motivations, and mishaps of scientists' involvement in policy.

Why scientists get involved in policy

John Harte, who currently holds a joint professorship with the Energy and Resources Group and the College of Natural Resources, began his career as a particle physicist. His transition to a politically and socially active scientist began in 1969, when, as an assistant professor at Yale, he helped organize a teach-in about the Vietnam War. The idea was to educate the campus community about the US involvement and the nature of the war by inviting experts from around the country to speak. A representative of the NAS participated in the teach-in, and it just so happened that he was also recruiting physicists to join a study investigating environmental problems in the Everglades. He met Harte and persuaded him to join the project. Harte didn't know it then, but this chance meeting would have a large impact on his future work and career.

Harte applied his physics training to develop models of what would happen if a particular large Cypress swamp area near the Everglades was drained to make way for a new Miami international airport. His study concluded that this would result in salt contamination of the drinking water for half a million Gulf Coast residents. These results and others from the study helped halt construction on the airport, and the area is now federally protected land known as the Big Cypress National Preserve. Harte says he wasn't looking for a career change, but that "the success of that work, the fact that it had an impact, really persuaded me that this was terribly exciting and important." And so he moved from the Yale physics department to UC Berkeley's newly formed Energy and Resources Group, whose stated mission is to "enable a future in which human material needs and a healthy environment are mutually and sustainably satisfied."

"More and more people from more and more fields are realizing that they can't just confine their science to the laboratory," insists Harte. Indeed, the desire to use their scientific training and research to have a direct, positive impact on society is a common motivation among university researchers for becoming actively involved in matters of public policy. Alastair Iles, an assistant professor in the Department of Environmental Science, Policy and Management, is a policy analyst who works on environmental health issues. He says his primary motivator is a concern for "the human needs of people worldwide, and how their lives are affected by environmental degradation." Iles is a co-founder of the online start-up GoodGuide.com, which provides information to consumers about the environmental and social impacts of common household items. He believes it is crucial for "scientists and policy analysts to use and communicate their insights in ways that make a difference."

"It has been a long-standing interest of mine to be engaged in making a difference in terms of policy," says Professor Catherine Koshland, whose career began in Washington, DC, as a Management Assistant at the Office of Coal Research in the Department of the Interior. During the height of the energy crisis of the 1970s Koshland realized that in order "to credibly impact public policy, I needed a stronger technical background." She subsequently obtained her PhD in mechanical engineering from Stanford and came to Berkeley in 1984. She currently combines appointments in the College of Engineering, School of Public Health, and the Energy and Resources Group. Her research focuses on energy, air pollution, and environmental and human health, with an emphasis on the mechanisms of formation and effects of combustion-derived pollutants.

Daniel Fletcher, a professor in the bioengineering department, has spent this past year as a White House Fellow in the Office of Science and Technology Policy, where he participated in the work of that office, advising the White House on all science and technology issues. Fletcher says he prefers the halls of UC Berkeley to the halls of the White House—he is just too enamored with the biophysics of cell motility to leave the lab behind. However, he still believes it is important for scientists to be actively engaged with policymakers. He says that influencing the government is "the most powerful way to improve the lives of people and to ensure that we have a positive outcome on everything from energy to the environment to the survival of academic research."

Where political priorities go, funding follows. Even when a scientist is doing basic research, aligning that research with public policy priorities can help him keep his supercomputers current and graduate students funded. Fletcher notes that academic scientists have a vested interest in communicating with lawmakers in order to ensure continued financial support. At the same time he worries about the tone of this interaction—if scientists simply band together to insist on increased funding, they could "easily slip into being just another lobbying group, which would be nothing new in DC." The most important thing, Fletcher says, is for scientists to show the public and policymakers how basic research can lead to technical advances and to communicate the many benefits of applying the scientific method to questions that need to be answered. "The money will come if our contributions are valued," says Fletcher. Not only does he urge scientists to show the public and policymakers the value of fundamental research and the scientific method, but he also believes scientists can make more of an effort to conduct and promote their research such that it can be applied to everyday issues. "We've got to have a plan for solutions to problems, not just a plan for how to spend more money."

Ways to get involved

One important avenue for scientists to analyze issues facing the nation and to propose solutions is through National Research Coun-

Kirk Smith, professor in the School of Public Health, holding an inexpensive air pollution monitor developed for use in village households.

cil (NRC) consensus studies. The NRC is part of the National Academies, an organization that brings together experts to advise the nation on science, engineering, and medicine. In 1863, President Abraham Lincoln founded the first National Academy, the National Academy of Sciences, with the following directive: "The academy shall, whenever called upon by any department of the government, investigate, examine, experiment, and report upon any subject of science or art." Indeed, the NRC provides a forum for scientists to advise on issues as wide-ranging as national security, transportation infrastructure, sustainability in the chemical industry, and the status of pollinators in North America. The NRC reports aim to provide politically neutral, scientifically credible analyses of complex issues about which one often hears conflicting reports from the popular media. Kirk Smith, a faculty member in the School of Public Health, has participated in a number of NRC panels and notes that the NRC is "the biggest apparatus in the world in terms of a science-policy interface. With hundreds of committees in operation at any one time preparing reports, no other country has anything of this scale."

Smith has also been involved in scientific consensus-building efforts at the international level through his participation in the Intergovernmental Panel on Climate Change (IPCC) and the International Agency for Research on Cancer (IARC), among other activities. At this level, scientific consensus-building becomes extremely complicated, owing to the requirement in many of these organizations that governments themselves sign off on the document. "We're struggling with how to do this as a planet," explains Smith. "Saudi Arabia looks at energy differently than Bolivia," and so creating a document that represents the consensus of a variety of governments on a given issue and is still scientifically credible poses an enormous challenge. Issues surrounding the peer review process and conflict of interest policies must be carefully handled to ensure the validity of the output. "Some would criticize the IPCC for being too conservative because it has to persuade the US and Saudi Arabia, which tended to be conservative on climate change issues, to sign up. On the other hand, the fact that the IPCC eventually produces something that is a consensus document is a very strong statement in the end," says Smith.

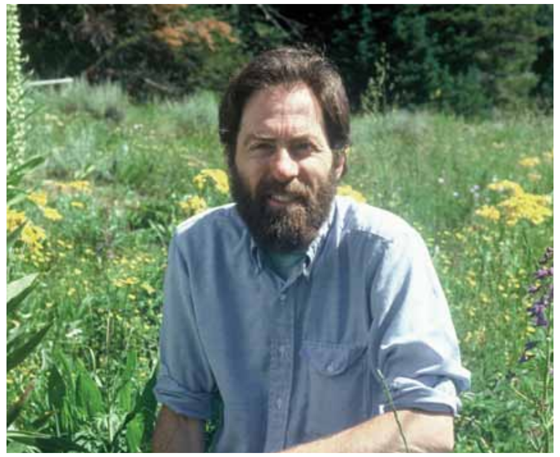
During his fellowship at the Office of Science and Technology Policy, Fletcher realized how difficult it is for politicians to stay current on the huge number of scientific advances that might influence policy decisions. One way active researchers can participate in public policy is "to make sure our lawmakers and policymakers are aware of the changing landscape" of science. NRC reports alone aren't enough, since the report on a single issue can sometimes take a number of years to complete, during which time advances or changes in scientific knowledge are all but certain to occur. How to keep the government informed on a more rapid timescale "is not a solved problem," according to Fletcher, "but it's one where we need creative scientists and engineers to be active."

Scientists can also exert a significant impact on public policy by educating the general public—an area in which Professor Harte has been particularly active. On the topic of toxic substance in our bodies and the environment, Harte found that "there were some technically excellent sources of information but no way even a well-educated layperson could have waded through them." In response, he co-authored the book *Toxics A to Z: A Guide to Everyday Pollution Hazards*. His goal was to create something that was "scientifically reliable but also accessible to the general public," he explains.

Harte spoke to us from the Rocky Mountain Biological Laboratory in Colorado, where he has been pursuing research relevant to climate change for the past few decades. Harte and his wife, a biologist, have recently written a free, downloadable book entitled *Cool the Earth, Save the Economy: Solving the Climate Crisis is EASY*. In the book, they outline how US carbon emissions can be cut 75% by the year 2030 through energy efficient appliances, buildings, industry, and transport, as well as investment in solar and wind-based electricity. However, proposing a solution to a problem doesn't guarantee your advice will be taken. Harte expresses deep frustration that the ideas he has outlined in his book have not found their way into the energy bill that is winding its way through Congress. "We know how to save the US one trillion dollars between now and 2030, and you'd think we would leap at such an opportunity. But the ideas we present in the online book are just not getting discussed."

Steven Chu, Secretary of Energy and UC Berkeley physics professor

FROM TOP: KIRK SMITH; THE CENTER FOR AMERICAN PROGRESS ACTION FUND



UC Berkeley Professor John Harte has been studying the effects of experimentally-manipulated climate change in a Colorado rockies meadow.

DENNIS JOHNS

Not for everyone

All five of the professors from our rather unscientific sample are involved in public policy in different ways and to varying degrees, but many scientists hesitate to get involved at all. Some simply are not interested in the issues or the process of politics. Instead, their passion might lie, for example, in the nuances of particle physics, gene signaling, or the ecology of riparian communities, regardless of how these fields intersect with politics or even with daily life. Fletcher reasons that policy work may fall uncomfortably outside of many scientists' preferred world view—"It's so different from how we're trying to understand the world through a logical framework." Fletcher points out that science is often appealing because it is structured and methodical, while politics can be quite the opposite. There are no compromises among subatomic particles, no lobbying genes or proteins.

Apart from personality and intellectual preference, there are other reasons that scientists might shy away from policy involvement. In a world where promotions and grant funding are often based on peer-reviewed publications, public policy can be an unwelcome, or at least an unproductive, distraction. Kirk Smith, a senior faculty member in the School of Public Health, says that publications are key for obtaining tenure. Consequently, he says, "we try to protect the younger professors from too much policy stuff to give them time to publish." A scientist's primary job is to do good science, and "the bottom line is that it's hard to do both [science and policy work]," says Fletcher.

One way to lessen the impact of time spent working on public policy instead of bench work is to invest your time strategically. Koshland maintains that it is possible and important to engage in public policy. "Part of it," she cautions, "is about being smart about what one agrees to do. Don't say yes to everything. You have limited resources and limited time, so you've got to align things." Koshland has apparently mastered the art of time management, as she holds faculty positions in three departments, as well as serving as the Vice Provost of Academic Planning and Facilities.

All five of the professors we spoke with emphasized the importance of initially building a solid scientific reputation through research, socially relevant or otherwise, in order to be a successful faculty member and to successfully engage in policy. Sometimes, however, policy work can be a helpful distraction. Understanding the political landscape can help a scientist do work with a bigger scientific and social impact. As Fletcher points out, "You can do even better science by being informed about what the needs are. You can do good science by addressing problems that have a large impact."

Some scientists shy away from involvement in political matters because they fear being viewed as biased or having their scientific integrity questioned. Harte, an active participant in climate change debates, has heard these fears expressed many times. However, he contends that the reasoning is fallacious: "Being partisan doesn't mean being unobjective or biased. The fact that your science leads you to certain conclusions that have policy implications doesn't mean you

Dr. Chu goes to Washington

UC Berkeley professor Steven Chu was sworn in as Secretary of Energy on January 21, 2009. Prior to his appointment, the physicist and Nobel Laureate was director of Lawrence Berkeley National Lab (LBL) and professor of physics and molecular and cell biology. According to the Department of Energy, he is now charged with "helping implement President Obama's ambitious agenda to invest in alternative and renewable energy, end our addiction to foreign oil, address the global climate crisis, and create millions of new jobs."

Over the course of his scientific career, Chu's research has focused on atomic physics, quantum electronics, and biophysics. His research in cooling and trapping atoms with laser light won him the Nobel Prize in 1997. More recently, Chu has been devoted to the search for new solutions to our energy challenges and stopping global climate change. He is one of the nation's foremost and outspoken advocates for scientific solutions to the twin problems of global warming and the need for carbon-neutral renewable sources of energy. He has called these problems "the greatest challenges facing science" and has rallied many of the world's top scientists to address it. Chu has said, "The path to finding solutions is to bring together the finest, most passionate minds to work on the problem in a coordinated effort, and to give these researchers the resources commensurate with the challenge."

Chu is internationally recognized as a proponent of increased government investment in advanced energy research. And, in his new role as Secretary of Energy, Chu now has the heft of the US government behind his ambitions to find scientific solutions to combat global warming. As a part of the 2009 Recovery Act, the Department of Energy has already authorized $32 billion worth of spending, with a focus on research in the areas of energy efficiency and renewable energy. "We will reduce our carbon emissions and create entire new industries based on America's resources, America's ingenuity, and America's workers," says Chu. And, with his unique blend of scientific and administrative proficiency, he is the man to lead the way to a more sustainable future.

Adapted from www.lbl.gov and www.energy.gov are being unobjective." Harte points out that intense scrutiny of results is an inherent part of the scientific process and is not particular to policy-related science.

What it takes

Involvement is not for everyone. It requires interest and a certain personality. But even those are not enough. Policy issues are broad in scope and often require an understanding of multiple scientific disciplines as well as the political and social landscape. Otherwise, a scientist might end up in a situation similar to one described by Harte, where a well-respected physicist proposed the disposal of radioactive waste by dumping it into the oceans. The idea was that the waste would be diluted enough to become harmless. However, this solution failed to account for biomagnification, the process by which toxic chemicals become increasingly concentrated as they move up the food chain. Small concentrations in seawater would lead to higher concentrations in plankton and so on down the line until we end up with dangerously radioactive tuna. "It is very easy to go astray when you know a lot about one field and make pronouncements that require insights from many fields," says Harte.

Advanced scientific training tends to be exceptionally deep, explains Harte, but also narrow, creating a challenge for the scientist who hopes to affect policy. A strong scientific background provides a source of authority in matters of science policy, but science graduate programs often don't include training in other areas relevant to policy. Instead, science graduate students are typically expected to spend their time in the laboratory pushing the boundaries of science. Some graduate training in science, however, does incorporate training in preparation for public involvement. Harte describes how Berkeley's unique Energy and Resources Group provides both depth and breadth by requiring coursework in a variety of disciplines. The doctoral seminar in environmental health sciences has occasionally been organized to give the students the experience of participating in mock NRC committees. Graduate students in Koshland's group have been funded through the NSF's Integrative Graduate Education and Research Traineeship (IGERT) grants that specifically target interdisciplinary study.

Professor Iles started out in environmental law and has more recently been focused on green chemistry and environmental health, so he is very familiar with interdisciplinary work. Besides being knowledgeable in a variety of disciplines, it is also essential to obtain a certain level of authority to effectively engage in the policy arena. Iles says, "Participating in public policy is very much about creating your credibility as a resource and participant through a series of ongoing contributions over time." As an assistant professor, Iles is currently attempting to do just that, so that when future public policy decisions relevant to his area of expertise are being made, he can play a larger part in the discussion. A scientist can have a greater impact on policy by gaining the respect of the scientific and political communities, resulting in more opportunities to participate in relevant research and policymaking activities such as NRC reports or Senate hearings.

Science for policy and policy for science

When science and policy inform each other, society stands to benefit, says Catherine Koshland. Consider how lost scientists or policymakers alone would be on an issue such as climate change—each standing helpless with his inert facts or political acumen, respectively. "You can't assume that technology is going to answer a problem. You can't assume that a policy is going to be able to be implemented without a solid grounding in science if that's the kind of policy that you're working with. You cannot separate the two; it is an artificial barrier," says Koshland. Science provides a special kind of insight into the physical world, but scientific facts alone will only get us so far. Public policy has the unique ability to effect significant social change, but it can lack insight into the short and long-range effects of any such changes.

Policymakers can use science to develop more well informed policies. Understanding policy helps scientists secure funding and do work with a broader impact. Fletcher hopes that the Obama administration's call to scientific arms will help to bring together scientists and policymakers. He hopes it will help to get scientists out of the mindset that "the government is there to give us money and then that's it," as he puts it, and to make the political process more open to input from scientists. Scientists can contribute by participating in science for policy and policy for science: doing scientific research that will help to inform political decisions and encouraging policies that support continued scientific discovery.

Lee Bishop *is a graduate student in chemistry;* **Elena Spitzer** *is an alumna currently working at Google.*

Teaching public policy to scientists

"If scientists are to make a meaningful contribution to societal challenges, they need to be willing to be entrepreneurs and to learn more about the realities of policy-making processes," says Professor Alistair Iles. However, a scientist sticking his or her head out of the lab for the first time may not know which way to turn.

Jaime Yassif, president of UC Berkeley's Science Technology & Engineering Policy Group (STEP), is familiar with this predicament. "There is no clear set of hoops for a scientist [interested in public policy] to jump through," she says. STEP is a student-run organization that aims to address this lack by creating a venue for students with diverse backgrounds to discuss a wide-range of scientific issues through a seminar series, journal club, and an annual white paper competition. The 2009 white paper finalists included proposals for the implementation of a new malaria diagnostic device in southern Benin and the reduction of overharvesting of marine fisheries.

Scientists can also gain hands-on public policy experience through science policy fellowship programs. The American Association for the Advancement of Science, National Academies of Science, and other scientific associations such as the American Chemical Society offer such programs, which place newly minted PhDs in governmental offices. These fellowships act as a stepping stone from which a scientist can return to academia, move into industry, or continue working for the government. Finally, scientists can stay informed, write letters, share their research results with the general public, and forge relationships with colleagues who are already active in the policy-making process.

MAREK JAKUBOWSKI FOR BSR

FIELD TRIP!

Scientists inspire the public

by Alec Sexton and Seychelle Vos

In a 2007 survey, UC Berkeley's Lawrence Hall of Science found that 80% of Bay Area elementary school teachers spent less than one hour per week on science education and fewer than half of Bay Area fifth graders met state standards for science. Results like this show that scientific illiteracy is an enormous problem, especially in our increasingly technological world. In response to the clear need for improved scientific communication and outreach, a number of UC Berkeley institutions are coming up with innovative solutions that bring the expertise—and excitement—of Berkeley scientists to the public.

Museums lead the way

Lawrence Hall of Science (LHS) may be the most well known museum affiliated with UC Berkeley, but there's another institution that has been a pioneer in science outreach: Cal's Museum of Paleontology. The museum was one of the first in the world to create its own website, and, following in this tradition, it continues to develop innovative methods to disseminate science to a broad audience throughout the world. Websites such as the *Paleontology Portal*, *Understanding Evolution*, and *Understanding Science* give educators, students, and the general public access to interactive materials aimed at a broad range of age groups, from kindergarten to undergrad levels. "They're extremely popular because they're robust, they're accurate, they're current, and they're also engaging," says Judy Scotchmoor, the museum's director of education and public programs. In fact, demand for the websites is so high that Understanding Evolution has been translated into Turkish, with German, Spanish, French, Portuguese, and Tibetan versions coming soon.

The Internet provides a great tool to help institutes like the Museum of Paleontology reach a broad audience, but simply making information available is not enough. The Museum of Paleontology website is an effective learning tool because it communicates science in a captivating and informative way—no small task, as any scientist will tell you. LHS, with its rich history of leading science education, has successfully achieved this balance as well. Aside from the 200,000 people who visit the museum every year, about 350,000 students across the country benefit from science curricula and programs developed at LHS, and an additional 22,000 science teachers attend LHS professional development workshops every year. The long hours spent putting these curricula together, as well as the countless exhibits the museum has hosted in its forty years of existence, mean that curators at LHS have some pretty good ideas about effective science communication. And in the past few years, they have started sharing this expertise with other scientists.

A scientist's training generally focuses on the complexities of the atom or the nuts and bolts of mouse metabolism rather than the skills to share scientific discovery with a non-specialist public. LHS is working to help bridge this gap through a partnership with UC Berkeley by hosting a course called Communicating Ocean Sciences to Informal Audiences (COSIA). This course uses ocean sciences as a model to teach aspiring scientists how to share their findings with the public. "I think scientists owe it to society to let them know, in language they can understand and relate to, what it is we do and why it is important," says UC Berkeley Professor of Earth and Planetary Sciences and COSIA instructor Lynn Ingram, explaining the motivation for the course. "We also have a vested interest in keeping our society literate in science, and that means we really need to be involved in science education at the K-12 level. This is the time that kids are still so excited and curious about the natural world. Kids need to be engaged by science, and feel that they too can think like a scientist—make hypotheses and test them—even if that isn't their profession."

Ocean sciences may seem like an odd topic for such a course, but increasing awareness of climate change and rapidly diminishing populations of ocean life have led people to care more about what is happening in the sea. Furthermore, "it is important to know about the ocean and understand ocean concepts in order to be science literate," says Catherine Halversen, director of COSIA at LHS, "not just ocean science literate, but science literate. Ocean sciences are intrinsically important and highly relevant, especially to understanding climate change, and are a motivating and integrating context for learning biology, chemistry, physics and earth science. All the disciplines of geosciences (ocean, atmosphere and earth) are growing in importance at a rapid rate as research related to climate and climate change becomes increasingly prominent and critical."

In the course, about 40 UC Berkeley undergraduate students learn how to communicate science by focusing on science's experimental framework instead of fact memorization. In one experiment, for example, students must determine which of two unknown water samples is saltwater and which is fresh without tasting the water. One solution uses the different buoyancies of saltwater and fresh water: if something floats in the first sample but not the second, the first must be the saltwater. Then, in an important and recurring motif of the course, the students discuss what they learned and how they learned it to better understand the variety of learning styles that they may encounter on the floors of science centers.

Chemistry graduate student Laura Miller explores states of matter with first graders at Berkeley Arts Magnet during a CRS visit. The students tested whether different solids floated or sank in water to determine their relative densities.

Fifth graders at Bella Vista Elementary in Oakland eagerly dive into the CRS experiments brought to their classrooms.

"Reading and writing are not the only ways that people learn," says COSIA instructor and LHS research specialist Lynn Tran. "Talking is part of the learning process, engaging and interacting with their peers is part of the learning process, and this idea of people constructing knowledge of the natural world around them based on their experiences is a huge part of learning that is a revelation to the students." Activities in the COSIA course are meant to teach students about these multiple learning styles and prepare them for trips onto the floor at LHS, where they practice their newfound skills by talking with guests.

Museum visitors benefit from the skills COSIA students learn as much as the students do themselves. Having scientists, especially young ones, interact with visitors at science institutions is hugely effective. In a preliminary evaluation conducted for the COSIA program, responders said that their attitude towards science changed positively as a result of their interaction with COSIA students. According to Tran, "In interacting with these college students they realize, 'wait a minute, scientists actually care about me and will talk to me and teach me about work that they do.'"

The success of COSIA at LHS promises to extend well beyond Berkeley. Halversen reports that LHS has already received inquiries from other institutions that would like to be involved in the program. To meet this need, course organizers are developing a manual that can be used by other institutions to teach more future scientists about effective science communication, making portable the expertise of COSIA's course instructors. There is also a desire to expand the scope to teach established scientists how to convey their findings and to share the most recent scientific advances with science educators. The program appears poised to receive additional funding to create courses that would meet both of these aims and help further bridge the gap between educators and research scientists.

Taking it to the classroom

While Berkeley undergrads are making a splash at LHS, there is always a need for more involvement with young students in the classroom. "Science education needs to undergo a sea change, empowering children to learn through their own experiences of making observations, formulating and testing hypotheses by gathering evidence, and objective reasoning," says Ingram. Berkeley graduate students are answering this call to service in droves. Through a program called Community Resources for Science (CRS), every week they reach out to students in their own classrooms with science demonstrations meant to excite and stoke latent curiosity.

CRS is a non-profit organization founded by two parents in 1997 that brings hands-on science experiences into elementary school classrooms, mainly in Alameda County. The founders, Nicki Norman and Anne Jennings, created the organization in response to elementary school teachers' desire to teach science more effectively. With this in mind, they held town hall-like meetings to find out what teachers thought would make science more accessible in the classroom. As CRS Program Coordinator Heidi Williamson recounts, the teachers responded, "What we really need are '-ologists.' We don't care what kind, we just want scientists to come in and talk to our kids to show them that we are not the only ones who find science exciting."

HEIDI WILLIAMSON

In 2003, CRS enlisted Professor Robert Bergman of the College of Chemistry, who became a key force for the development of Chemistry in the Classroom. From a small group of chemistry students, the program has mushroomed in the past six years to Community in the Classroom, with students from over 20 departments on campus, including Plant and Microbial Biology; Molecular and Cell Biology; and Environmental Science, Policy, and Management. Last year, approximately 150 UC Berkeley graduate students, with the help of about 30 outside volunteers, taught over 230 lessons. Interest has been so high that the program has expanded to include areas beyond its original reach in Alameda County. Local scientists working in government or industry also assist the organization, and the College of Chemistry now offers a graduate course affiliated with Community in the Classroom. In recognition of the impact the program has had on the local community, Bergman and CRS were awarded the UC Berkeley Chancellor's Public Service Award for Campus-Community Programs in April.

"A main goal of the program is to inspire kids from a young age to pursue science," says Stavroula Hatzios, a chemistry graduate student involved in Community in the Classroom. The tools for this inspiration: hands-on science lessons that give students the opportunity to play and to explore the excitement of discovery. Teams of graduate students teach one-hour lessons, developed with CRS assistance to ensure that they are age group appropriate and meet California State science standards, in different elementary school classrooms throughout the year. The lessons cover a broad range of scientific principles, ranging from proper controls to recognizing trends to forming hypotheses. In one of the fifth grade lessons, candy has been stolen from the classroom and the thief has left a ransom note. The students are asked to determine who stole the candy based on the note. Each student is given a different pen, and basic chromatographic techniques are used to determine which pen was used to write the note.

The materials are simple, affordable household products, and elementary school teachers can easily repeat the experiments. The lessons give teachers confidence that they too can perform simple yet interesting scientific experiments with their students, empowering the classroom for further scientific investigations. Perhaps most importantly, the kids really enjoy the lessons. "Overwhelmingly the kids are very excited," Hatzios says. "They are very easily engaged. They are always excited to have someone new, a fresh face come into the classroom."

Thank you notes written to Community in the Classroom illustrate the program's effectiveness and the kids' enthusiasm. In one such note, a child drew a picture of herself with a pillow over her head and her sister standing beside her and titled the picture "potential energy." In the next frame, she drew the pillow hitting her sister and titled the picture "kinetic energy." This playful depiction of a scientific concept shows both the effectiveness of the teaching as well as the enthusiasm that graduate students are able to elicit in young students who otherwise might shy away from science, perhaps viewing it as too difficult or too boring.

Aiming For The Stars

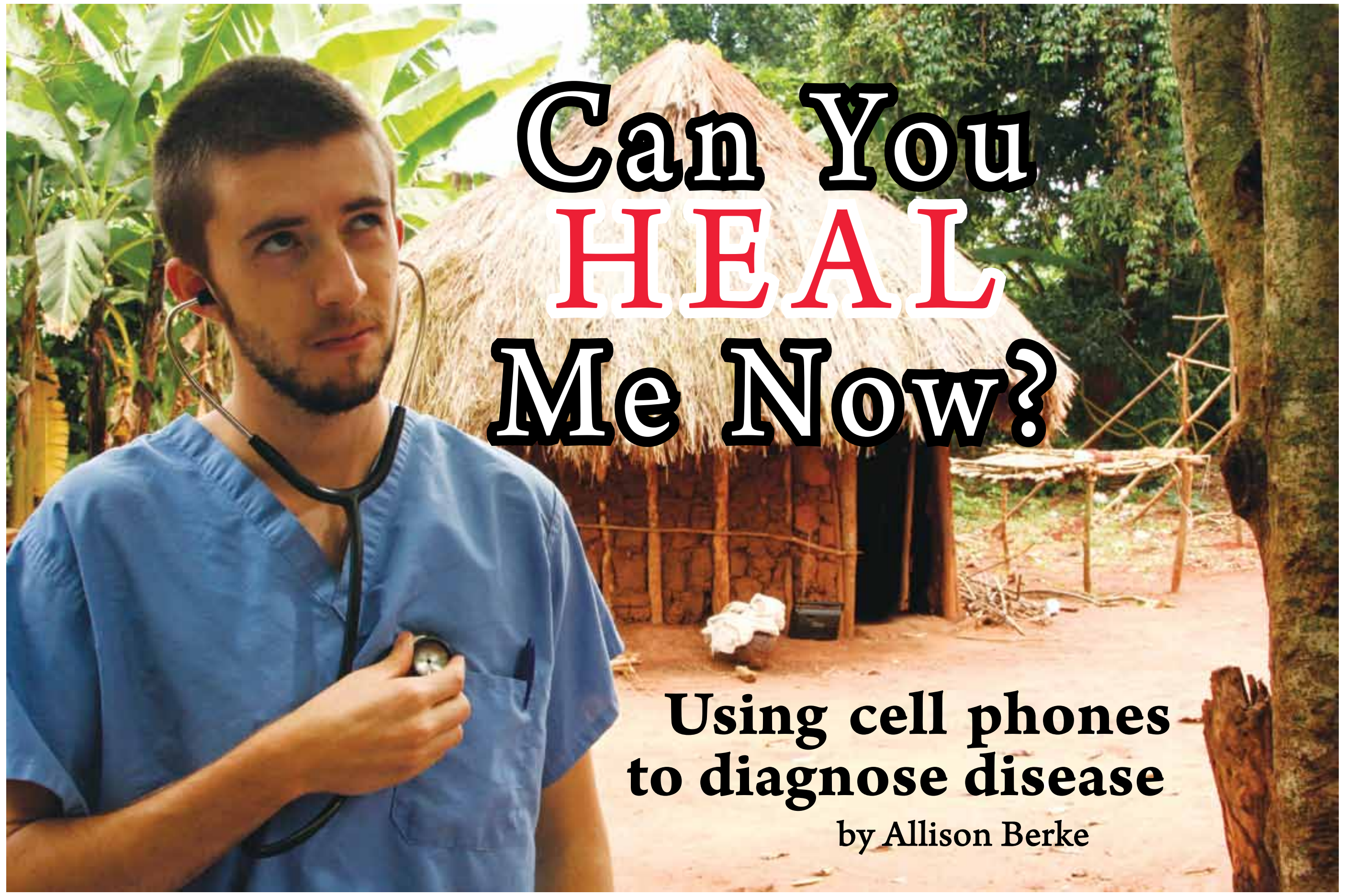
2009 was named the International Year of Astronomy in honor of the 400th anniversary of Galileo's first observations of the sky with his simple telescope, and groups across the world are celebrating, including UC Berkeley's Department of Astronomy. Berkeley's department arranged a special lecture series to take place over the year; talks ranged from astronomy professor Geoff Marcy's search for habitable planets to history professor Roger Hahn's discussion of Galileo to a joint talk between astronomy postdoctoral fellow Steve Croft and Integrative Biology Professor David Lindberg discussing the connections between astronomy and evolution. "As scientists," says Croft, "the public are paying our salaries and we need to do some outreach to make sure that people support funding what we are doing because they understand what we are doing. But I also think it is our duty simply to give back to some extent, to give back to society the fruits of our labor in terms of what we are learning." The lecture series aimed to do just that, highlighting current research and informing the public of many of the interesting faces of astronomy today.

"Grad students are fabulous," Williamson says. "They are really enthusiastic. They are really good at communicating at the level of the students and they are really excited to do something like this. They show the students that lots of different people are scientists. Graduate students really drive home that idea because they are so diverse, they are young, and they are usually hip. It is great for the students to be able to see people who they feel they would want to be like, who are scientists and who are excited about science." Bergman goes further, saying, "It's not just old people like me who are going in and doing these things, its people who are much closer in age to the students, and I think the kids relate to that. They have the sense that it won't be too long before they reach the age of the grad students and they have some chance of becoming a scientist too."

A sea change

According to the Pew Research Center, 84% of the public considers science to have a positive impact on society, yet a disappointingly small number of adults can be considered scientifically literate. Scientists themselves are partly to blame for this shortcoming, as many aren't doing their part, either because they lack the skills or simply lack the energy to communicate complex ideas to a non-specialist audience. The Bay Area is in a singular position as one of the world's most dynamic scientific research hubs to overcome some of these hurdles and provide unique opportunities for interaction between scientists and the public. As the educator Francis Keppel put it, "education is too important to be left solely to educators." In some cases, the scientists themselves must become the educators, and programs like COSIA and Community in the Classroom are making promising headway toward this goal.

Alec Sexton *and* **Seychelle Vos** *are graduate students in molecular and cell biology.*



LASTBEATS

Can You HEAL Me Now?

Using cell phones to diagnose disease

by Allison Berke

A patient comes into a rural health clinic, coughing and complaining of trouble breathing. The doctor collects a sample of material from the patient's lungs, commonly known as sputum, and drops it on a slide, which he then loads into a device about the size of a cell phone. The slide is tested for a few common illnesses—say, tuberculosis and influenza—and the results are transmitted wirelessly to a secondary location for confirmation and interpretation. Within minutes, data is sent back to the device, and the doctor has an answer. The whole process doesn't seem too farfetched, until you imagine that the rural health clinic is in a small village in Uganda, the doctor is actually a Peace Corps volunteer or the patient's relative whose only training is the instruction manual that comes with the device, and the device actually is a cell phone, or an attachment fitted to it. Now we're in the realm of the latest UC Berkeley projects designed to automate and expedite diagnostic healthcare in the developing world.

Portable, low-cost diagnostic devices will be implemented frequently in communities that are large, sprawling, and densely populated. Part of the need to automate diagnostics arises from insufficient access to trained healthcare personnel: the UN estimates that in countries such as Nigeria and South Africa, there are fewer than two doctors for every 10,000 people. In comparison, the United States has about ten times as many. One thing that most people in developing countries do have access to is a cell phone. According to the telecommunications branch of the UN, six out of 10 people world-wide have cell phones, and 80% of the world lives in an area with cell phone network coverage. Cell phone companies aren't ignoring this developing-world market—Vodafone has particularly extensive contracts in the Democratic Republic of the Congo (DRC), a country also classified as a tuberculosis hotspot. UC Berkeley inventors, concerned with getting better healthcare to more parts of the globe, are also taking notice.

Turn your cell phone into a microscope

One of the most publicized UC Berkeley diagnostic tools is CellScope, a cell phone microscopy project spearheaded by Dan Fletcher, an associate professor in the Department of Bioengineering. He and a group of undergraduates developed the cell phone attachment in a microscopy class he teaches. He then brought it back to his lab, where a team of graduate students and postdocs have refined and added to the original model. The group is now rolling it out for field testing with the help of grant money from Intel, CITRIS (Center for Information Technology Research in the Interest of Society), Microsoft, and Vodafone, which is also working to provide CellScope users with a free network number. This would allow data obtained on a phone using CellScope to be sent to other users or to centralized medical facilities in the United States for sample verification and analysis.

CellScope is essentially a 60x objective lens coupled to a 20x eyepiece lens and a 16 centimeter optical tube, all parts of a microscope that magnify a sample, explained Erik Douglas, a post-doc in Fletcher's lab who has been heavily involved with the project. Together with the optics built into a cell phone camera, the attachment delivers three megapixels of resolution, which is sufficient to image at 20 frames per second, with each frame the size of a standard laptop display screen. The phone itself will use software, currently under development, that can perform a number of automated functions, including moving through fields of view, identifying cell shapes, and counting bright spots. Each of these functions, described in greater detail in a *PLoS ONE* paper, corresponds to a step in a diagnostic procedure used to identify diseases like tuberculosis, sickle-cell anemia, and viral infections.

When a patient comes in with an unidentified illness, a blood or sputum sample is placed on a disposable glass slide. Depending on whether the slide has been treated with a disease-specific stain or not, the slide is viewed with bright-field microscopy (microscopy in which the sample is illuminated from behind by an outer light source) or fluorescence microscopy (requiring another attachment to provide illumination, and a filter to admit only certain wavelengths of light). The standard tuberculosis assay used in developing countries stains each bacterium with either a red or fluorescent dye. The threshold for diagnosing tuberculosis is at least one bacterium per one hundred fields of view, equivalent to 10,000 bacteria per milliliter of sputum. Three negative tests are required before a patient can be declared free of the disease, and the process of switching through hundreds of fields of view, looking for even one red-stained particle two micrometers in length, can take hours and is subject to human error and fatigue. With the CellScope and automated software, the time required decreases to a matter of minutes, and error rates plummet to the level of the most up-to-date laboratory detection methods.

Douglas estimates that a bright-field setup would cost $100, and a fluorescent one $500, but these costs may be defrayed through partnerships with global healthcare organizations. Initial testing has been done with help from a local organization, Heal Africa, which brought Douglas along on a recent trip to Goma, a city in the DRC. He and his colleagues have also arranged trips to Benin and Uganda to test their device's tuberculosis detection in the field. "Wherever we go, they're eager to try it out," Douglas says. "If we can get [the devices] to the local clinics, they'll use them."

Handheld tuberculosis screening

Another UC Berkeley-led effort is entering the tuberculosis diagnostics race in the form of the company AutoTB, led by CEO Kelly Karns, a bioengineering graduate student in the lab of Professor Amy Herr. She and four co-founders, with expertise spread among the fields of medicine, engineering, law, and business development, started AutoTB a year and a half ago, looking to meet the growing need for cheap, automated, and reliable tuberculosis diagnostics that could be used in the developing world without medical training or extensive equipment.

ERIK DOUGLAS AND CELLSCOPE

The CellScope fits on the back of a standard cell phone, and uses the phone's built-in camera to capture magnified images of a slide clipped to the end of the CellScope. Software on the phone can analyze the image immediately, or send it via satellite to off-site collaborating doctors.

What they came up with was software that can be used to detect a variety of disease- and contamination-causing agents, from tuberculosis bacteria to *streptococcus* and malaria-infected cells. The software relies on image processing algorithms that can identify and outline individual cells in a sample and detect varying levels of dye within those delineated cell bodies. The software interface allows users to view either the sample itself or graphs of detection results, including the number of positively stained particles detected, the number of fields of view analyzed, and a diagnostic yes or no for the disease in question.

The device, about the size of a shoe box, has a slot in the front for a slide and a large GPS-like display screen. Building off of recent trends in sleek gadgetry, the simplified interface only uses two buttons: one to insert and retract the slide, and one to scroll through on-screen menu options. Like CellScope, its machinations are completely automated and reduce human error and time investment. "How long can you sit in front of a microscope and look at a slide?" Karns asks. "I could only do that for maybe three, four hours without it starting to affect my ability to recognize the bacteria. In the field, technicians are looking at slides for up to 10 hours a day. As a result, their accuracy levels are close

Methods of pathogen detection: the ELISA assay and TB skin test

The detection method upon which Silicon BioDevices (see page 33) relies is based on a standard laboratory technique that has been miniaturized and automated. Florescu's sensor uses a novel system of magnetic beads to attach to and move antigen fragments, but it is based on the methodology of the ELISA, a common means of identifying antigen in a mixed sample. The ELISA, or Enzyme Linked ImmunoSorbent Assay, is an immunohistochemical detection technique that relies on multiple antigen-antibody interactions. First, a specific antibody coupled to an enzyme binds to an immobilized antigen or antigen fragment; then the unbound antibody is washed away and the enzyme is activated, changing color or emitting fluorescence to aid in detection. Florescu's device represents a form of automated ELISA, which is why this test is used to compare its efficiency and functionality. If you received a TB test when you were a child, it was probably a skin test for a latent infection. The most common of these tests is the Mantoux test in which, similar to an immunization, purified and non-infectious *Mycobacterium tuberculosis* fragments are injected under the skin and observed for signs of an inflammatory immune response. Such a response would indicate prior infection, which, when latent, may not cause disease symptoms for months or years. AutoTB and CellScope both use the only definitive method of tuberculosis detection, the auramine-rhodamine stain, which causes red or yellow fluorescence in bacteria with highly acidic cellular walls like *Mycobacteria*, a strain of which causes tuberculosis. These bacteria cannot be labeled by Gram staining, which separates bacteria by the number and thickness of their cell walls, due to this acidic resistance. While fluorescing bacteria are easy to pick out of a sample, another stain, known as the Ziehl-Neelsen stain, uses a three-step process of staining, acidifying, and counter-staining to dye *Mycobacteria* red against a background of blue.

to 30% and a correct diagnosis almost never happens until patients are very sick." While 100 fields of view at 100x magnification are required for a single sample, AutoTB's device can cycle through ten times that many in a matter of minutes and provide statistics on its readings.

Although AutoTB's software is fully developed, Karns admits that the device itself is still on the drawing board; a mock-up AutoCAD drawing is used in presentations and promotional material. AutoTB is looking for $2 million in initial investments, though Karns estimates that the global market for TB diagnostics, encompassing NGOs, foundations, governments, and health departments, approaches $1 billion. The group has received approximately $45,000 from business-plan competitions at UC Berkeley and Cambridge University and recently competed at the World Innovation Summit in Barcelona but is still looking for a corporate sponsorship deal similar to CellScope's. AutoTB has the software and is developing a device, while CellScope has a device ready to ship and is working on software. Have the two considered a merger? Both are open to the possibility, but at the time of their interviews had not formally discussed it and are planning to move forward separately.

For the home diagnostics market, Silicon Biodevices is testing a hand-held prototype that reads the results of antibody detection from single-use microchips that couple together sample processing and reporting.

OCTAVIAN FLORESCU

Home-made tumor detectors

Another project that might make use of a software platform like that of AutoTB or CellScope is Mechanical Engineering Professor Boris Rubinsky's tumor-detecting cell phone electrical impedance tomography (EIT) device. Emphasizing the lack of imaging technology in the developing world, which includes processes like X-rays, MRIs, and CAT scans that we have come to take for granted, Rubinsky explains that his devices decouple image gathering from image processing.

The principle behind EIT is that electrical impulses travel differently through tissues with different densities. Each type of tissue in the body has a different known density, from high-density bone to low-density fat. Tumors are denser than healthy soft tissue but less dense than bone. Measuring the voltage drop across tissue is really measuring its electrical conductivity and permittivity, which vary with the type and density of tissue. Air-filled tissue in the lungs is less dense than fluid-filled tissue, and this difference can be measured as a smaller or larger drop in voltage. Rubinsky's device measures the voltage drop at various positions across a tissue sample and at different frequencies (at voltages low enough to be used on the body) and records these measurements in a small data file. The data file is sent to a computer back in the United States, which analyzes the measurements and returns an image file with densities arranged and color-coded like a topographic map. By outsourcing the brunt of the diagnostic work, hospitals and clinics in underserved areas can get results similar to those from expensive machines using the cell phones they already have.

The resolution and thus the accuracy of Rubinsky's device in pinpointing areas of locally increased or decreased density only depend on the number of measurement points. EIT devices used in fully-equipped hospitals will attach twenty to forty electrodes across a patient's midsection, while Rubinsky's device will use as many as the rural hospital can scrounge up, down to even two. These electrodes are attached to a source of current, and Rubinsky's device measures the resultant voltages and stores them for data transmission and analysis.

With help from the National Institutes of Health (NIH), Rubinsky and his students are working on fine-tuning the capabilities of various low-cost devices designed to gather data that will emulate the data gathered by X-ray machines and MRI scanners, as well as the EIT device mentioned, before deploying them for use in developing regions. Additionally, Rubinsky's device has the advantage of being adaptable to a number of platforms. If software from a UC Berkeley group doesn't work, other university groups are working on similar open-source software platforms for cell phone-based medical diagnostics and imaging processing, like Moca Mobile, software developed by a collaborative MIT-Harvard team.

Funding for TB diagnostics

It can be difficult to pin down the exact amount of money available to a group like AutoTB, CellScope, or Silicon Biodevices looking to market a new diagnostic when nearly all of the non-governmental agencies offering funding are also in the business of soliciting funding and proving to governments and financiers that the current amounts they are able to provide will not meet growing demands. In the field of tuberculosis prevention alone, the World Health Organization (WHO) has the most clout, and coordinates funding from governments directly. It estimates that in 2009, three billion dollars are available worldwide for tuberculosis control, 87% of which come from governments, 9% from Global Fund grants, and 4% from other donors. The WHO also identifies $1.2 billion in funding gaps, areas of research, diagnosis, and treatment which are underfunded, most of which occur in Southeast Asia. There are also separate agencies directly offering grant money for research into new TB diagnostics, such as the European and Developing Countries Clinical Trials Partnership, which is offering eight million euros for two to four projects aimed at diagnostic innovation. In general, startups backed by clinical evidence or the clout of a lab at a major research university can directly apply for funding to the NIH or the WHO's umbrella of initiatives; startups in the earlier stages of development may aim for business plan competitions, as AutoTB has, or corporate donors and private "angel investors," like CellScope.

Five diseases on a single microchip

Another diagnostic device coming from a UC Berkeley engineer may be the closest to public use. Silicon Biodevices is a company started by Octavian Florescu, a graduate student in Bernhard Boser's lab in the Department of Electrical Engineering and Computer Science. Under Florescu's guidance, the company plans to manufacture sample readers that interface with silicon microchips, resulting in a device the size of a remote control that uses an integrated microchip circuit to detect miniscule amounts of antigen in a drop of blood, urine, or saliva.

For developing markets, Florescu says the device costs only $15, plus about one dollar per disposable cartridge, which is used for a single patient but can run multiple tests on one sample. An LCD screen on the reader provides directions equally appropriate for a patient as for a doctor, eliminating the need for training or sample preparation. The device operates on the same principle as an ELISA assay (see sidebar): liquid elutes through a membrane atop the sample tube and mixes with antibody-coupled magnetic beads, which wash down into wells of secondary antibodies along the length of the chip. Beads that have bound target proteins will couple to the antibodies in the wells, holding them in the wells for a magnetic sensor to detect. With the subsequent application of magnetic fields along the walls of the chip, these beads remain stuck in the wells while unbound beads are drawn to the side. (For more detail, see "Lab on a Chip," *BSR* Spring 2009.) Initial results show a detection threshold of one nanogram per milliliter of target protein in liquid sample, equivalent to that of the standard ELISA assay. This means the device is as sensitive as currently used laboratory tests, requires only one drop of blood, and needs only 15 minutes to deliver results.

Understandably, Florescu's plans for his device extend not only to developing-world clinics, but also into the field of personal and home-use healthcare diagnostics. Because device sensitivity depends only on the type of antibody conjugated to the magnetic beads, the same platform can be used to detect many different solutes found in blood, such as cholesterol, along with disease indicators. Silicon Biodevices has developed a multi-channel version of their screening chip that can perform several detections at once, including HIV and various strains of influenza. Because results are supplied digitally, the device can also interface via USB port with a laptop or cell phone to provide data transmission. Having received some start-up funding, Silicon Biodevices is in the market for more, looking to corner part of the approximately four billion dollar market for molecular diagnostics.

The AutoTB device integrates slide viewing and diagnostic software into a one-step device: users load a sample slide into a slot in the front, and navigate through fields of view on the GPS-like screen.

Octavian Florescu's microchips manipulate antibody-coupled magnetic beads into wells for detection. Each of the chips shown here is attached to a sample collection tube containing a solution of the beads, and the solution in each tube can contain different antibodies, allowing for greater diagnostic versatility.

FROM TOP: KELLY KARNS; OCTAVIAN FLORESCU

Funding for developing world diagnostics

With the billions of dollars and vast scales of improvement being discussed in the lab, one remaining question is how amenable to—and, indeed, how capable—the developing world is of accepting and actually using this projected technological bounty. Much of the developing-world healthcare market is composed of NGOs and the World Health Organization (WHO) in a multipronged effort to aggregate healthcare data, control outbreaks and the spread of deadly diseases, and, of course, provide healthcare to the poorest nations of the world and alleviate some of the most preventable forms of suffering. As is reflected in business plans from the startups interviewed here, any device aiming for third-world markets has to pass the WHO's tests and receive NGO or governmental distribution contracts.

Researchers like Douglas who travel to the DRC and Uganda can distribute their devices somewhat outside of these channels, but any sort of broad, comprehensive scheme has to go through a larger organization first. Additionally, many devices depend on initial, smaller steps of sample-prep—staining with dye, for example, or hooking up an electrode to a power source—that, while not cost-intensive, present more hurdles for a local clinic hoping to set up one of these devices for regular use. Elizabeth Starr, who works at a halfway house in Dakar, Senegal, described the state of medical care in that part of Africa. Some of the primary concerns in using a foreign-made medical device in Africa are reusability (what disposable parts does the device have, how easy are they to order and how much does it cost to restock them) and adaptability (most countries have more than one dialect, as well as an official language, and a device has to be usable by someone who may not be able to read the instructions). Hospitals in the areas where she has worked vary widely in the availability of trained personnel and disposable equipment like syringes, gloves, and slides. Because regions without much industry rely so heavily on import, usually only the hospitals and clinics with direct connections to the WHO are reliably stocked.

The general attitude toward receiving and using the devices described here is optimistic but cautious. In the excitement of generating a new technology, practical concerns can often be neglected, reappearing to cause problems or delays in manufacture later on. The real test of these devices won't happen in UC Berkeley labs: it will come from field reports from clinics in Africa and from NGOs using the devices, to prove that they do treat patients more quickly, more effectively, and more cheaply.

Allison Berke *is a graduate student in bioengineering.*

PLUGGING BACK IN

Can brain-machine interfaces empower paralyzed patients?

by Janelle Weaver

PEG SKORPINSKI

"May the force be with you," says Lavi Secundo, a UC Berkeley graduate student, to a patient as she attempts to control a computer cursor using her thoughts alone. Surgically implanted with electrodes that record electrical activity from her brain, the patient simply has to think about moving her hand in a certain direction, like she's Luke Skywalker in *Star Wars*, to get the cursor to go the right way. Scientists at UC Berkeley hope that moving cursors is just a precursor to more meaningful independence for paralyzed patients: controlling a wheelchair, feeding themselves, and checking email may one day be within their grasp.

Nearly six million paralyzed Americans stand to benefit from such technology. Despite enhanced national awareness of the plight of paralyzed people and decades of research across multiple fronts, there is still no "cure." Once cells in the brain or spinal cord die, they generally do not recover. "Perhaps one day stem cell research may move us closer to a cure, but in the short term, the best we can do is improve patients' quality of life with brain-machine interfaces," says Secundo.

What is a BMI?

Brain-machine interfaces (BMIs) are devices that bypass damaged neurons, allowing intact cells to control computers and robots. They come in a variety of flavors, from invasive surgical methods to non-invasive electrode skull caps. Although non-invasive approaches can be used to control computer cursors and spell words (albeit slowly), invasive methods may be more powerful, since proximity to neurons yields a stronger signal. Some scientists believe that invasive approaches are necessary to achieve complex, natural movements with minimal training.

Currently, invasive BMIs are carefully restricted in human clinical research trials. Despite the scarcity of opportunities to employ invasive approaches in humans, there are already promising signs of their effectiveness. In a landmark 2006 study, John Donoghue and colleagues at Brown University demonstrated for the first time that a quadriplegic patient could check email, draw a circle, operate a television, play computer games ("Neural Pong"), and control a prosthetic hand and robot arm using an electrode array implanted into his primary motor cortex, a part of the brain that controls movement.

Scientists at UC Berkeley are also experimenting with invasive BMIs, but their approach is slightly different. Rather than working with paralyzed patients, who must agree to have electrodes implanted into their brains for research purposes, Secundo performs tests on epilepsy patients who already have electrodes on the surface of the brain.

Access to brain signals

Severe cases of epilepsy can require the removal of the brain's seizure "epicenter." In order to precisely localize the area to be lesioned, neurosurgeons first implant an electrode array to continuously monitor brain activity—a procedure known as electrocorticography (ECoG). Surgeons typically wait seven to ten days for a seizure to occur. This window provides the unique opportunity for researchers to record high-quality brain signals from humans as they perform cognitive tasks involving language, memory, attention and motor control.

Despite the challenges they face, patients are generally excited to contribute to the research effort. "We sometimes give them very boring tasks—they have to press buttons when they hear 'beeps' and 'boops'," says Secundo. "But the patients and families are very motivated and engaged, and we do try to make it fun for them, like a computer game," he adds.

Robert Knight is a professor of psychology, the Evan Rauch Professor of Neuroscience and director of the Helen Wills Neuroscience Institute. "BMI is a new area for my lab," he says. "We started three years ago, and now we have an active ECoG program."

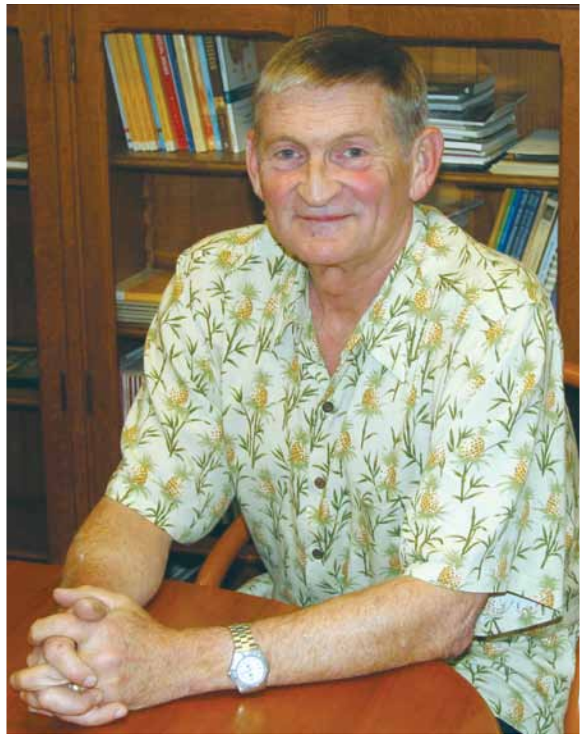
Their preliminary results show that ECoG could be used to control language and simple motor actions. In some tasks, for instance, patients are instructed to discriminate amongst auditory and speech sounds; they are able to use their thoughts alone to select a "beep" instead of a "boop", or "pa" instead of "ba"—building blocks of language. Eventually, patients may be able to choose sequences of these building blocks, allowing them to form words and sentences—all through simple imagination.

To demonstrate how brain signals can control neuroprosthetics, Knight holds up a water bottle in front of me. "Take a good look at this, and then close your eyes. Can you see the water bottle in your head?" he asks. Then he waves his hand back and forth in the air and instructs me to do the same. "Now close your eyes and imagine that you're moving your hand the same way. Can you imagine your hand moving?" I certainly could.

"The same brain regions are activated when you see or do something and when you imagine seeing or doing the same thing," says Knight. In order to construct BMIs that can mimic complex movements in natural settings, Knight believes it will be crucial to first gain a thorough understanding of how the brain generates signals that control movement.

"It's a baby field with lots of promise. The challenge is to understand the motor-control signals better and to make a wireless device that will translate these signals into complicated 3D actions, like controlling a wheelchair, feeding oneself, and grabbing objects," says Knight.

To investigate these movement signals further, Knight is collaborating with BMI expert Jose Carmena, assistant professor in electrical engineering and computer sciences, cognitive science and neuroscience,



Professor Robert Knight would like to develop a world-class neuroprosthetic program at UC Berkeley and UC San Francisco, with the goal of restoring language and motor functions to paralyzed patients.

and according to Knight, “the guiding light in the operation.”

BMI breakthroughs at UC Berkeley

Across campus, Carmena is making important new discoveries about how the brain orchestrates movement. In a paper that was published in *PLoS Biology* in July, he demonstrated that the brain can develop a motor memory for prosthetic control. That is, it is possible to train neurons in motor cortex to gain stable control of a prosthetic device, and, most importantly, these neurons are able to retain this knowledge day after day.

“We showed that long-term use of a neuroprosthetic device is associated with the formation of a mental representation of prosthetic function that is stable across time, readily recalled and resistant to unlearning,” says Carmena.

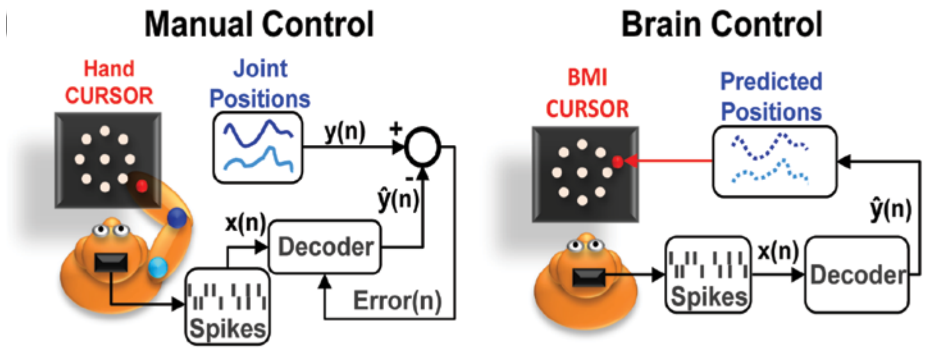
Typically in BMI studies, scientists first record from a set of neurons while subjects perform predetermined movements, such as moving a hand towards circles on a screen in front of them. They then correlate activity from these neurons with specific movement elements, like hand velocity and the relative positions of the hand, elbow and shoulder. These statistical relationships help them construct a decoder that translates neural signals into movements of a robotic arm, or movements of a cursor on a computer screen. Finally, they put the decoder to the test: subjects must use their thoughts alone to control a robot’s or cursor’s movements. Based on information collected during the recordings performed earlier that day, the decoder takes the neural activity and translates it into movements of the robotic arm or cursor on a computer screen.

Unfortunately, because of tiny movements in electrode position, it has been challenging to guarantee that recordings come from exactly the same neurons every day, so decoders must be retrained before every session. In his latest study, however, Carmena took great care to ensure that he was recording from the same neurons every time. He found that these neurons were quickly able to remember how to control the BMI each morning. The neurons formed a stable activation pattern to control a cursor’s movements toward targets on a computer screen.

Once neurons settled on this pattern, Carmena decided to scramble the decoder into a nearly random translation. That is, he took each neuron’s activity and translated it into a random arm position, unrelated to the arm position that the neuron originally encoded. Amazingly, he found that these same neurons were able to figure out the new “code” for controlling the computer cursor within just a few sessions.

In addition to demonstrating the brain’s impressive plasticity, Carmena’s study yielded other valuable insights. He reintroduced the original decoder (decoder A) to the same neurons to see if they still remembered the original code, and he found that they did. “A small set of neurons could hold on to many different motor memories,” says Karunesh Ganguly, a postdoctoral fellow in the Carmena lab and first author of the *PLoS Biology* paper.

Scientists at other institutions are taking notice. “Carmena clearly demonstrated for the first time that if you can record the same neurons over many days, you could then track how they learn different motor skills and readily switch between them,” says John Kalaska, professor of physiology at the University of Montreal. The same small number of neurons were able to perform multiple tasks: they were able to learn decoder A, retain that skill, learn decoder B, and then switch back to decoder A. “Neurons are not locked into certain patterns,” he adds. The results show that the brain can use many different solutions to solve problems.



A schematic depicting how brain-machine interfaces work. Scientists record brain activity of subjects reaching toward circles on a screen in front of them. They then correlate neural activity with elbow and shoulder positions to develop a decoder, which later translates neural signals into movements of a computer cursor based on brain signals alone.

JOSE CARMENA

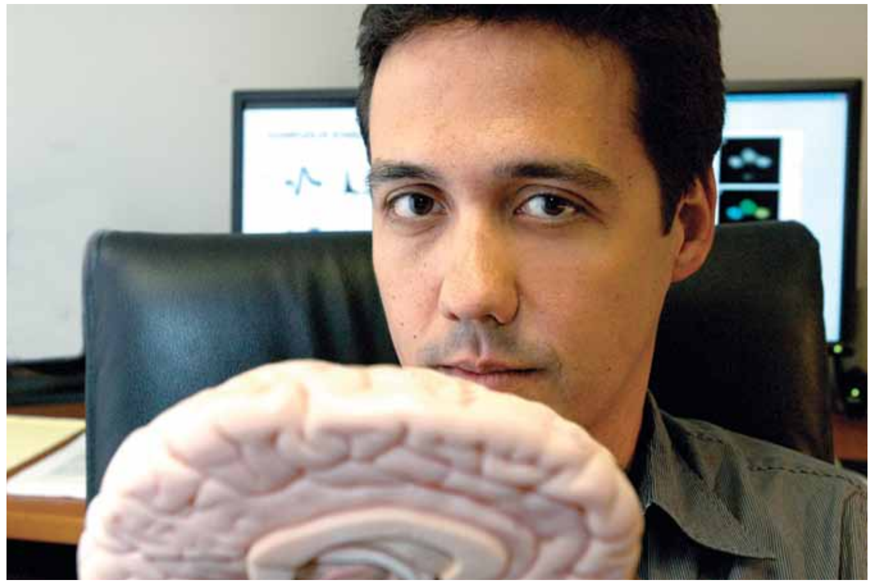
Kalaska, an expert on motor control and motor learning, likens these findings to prism adaptation experiments. When human subjects first put on a pair of prism glasses that shift their entire visual field, they cannot accurately reach out and grab an object, like a cup of coffee. Initially, their arms reach out in the opposite direction, to a degree that depends on how much the glasses distort their visual field. Over time, however, they learn to adjust their arm movements when wearing the glasses—that is, they learn the new code or translation—and eventually they can accurately pick up a cup of coffee. Similarly, when the glasses are suddenly removed, they initially reach in the wrong direction before finally relearning the correct motor code.

In essence, Carmena showed that a similar type of motor learning can be accomplished very quickly by a small number of neurons in motor cortex, and that this motor learning can be used to gain impressive control over BMIs. “This is pioneering work that demonstrates how new technology can provide insights into fundamental issues of how the brain works, separate from helping paralyzed people,” says Kalaska.

But the impact for patients cannot be overstated. These findings support the idea that the same neurons could learn to execute many tasks using a variety of neuroprosthetic devices. “This would greatly improve paralyzed patients’ quality of life and ability to live independently,” says Kalaska.

Moving naturally with BMIs

Across the bay, Carmena’s latest discoveries elicit enthusiasm from a long-time friend and fellow BMI expert Krishna Shenoy, associate professor of electrical engineering, bioengineering, and neurosciences at Stanford University. Shenoy congratulates Carmena on “very innovative thinking and hugely important explorations of what the brain is capable of doing.”



Professor Jose Carmena recently discovered that brain cells can quickly form a stable motor memory to control prosthetic devices.

UC BERKELEY DEPARTMENT OF PSYCHOLOGY

From a clinical perspective, Shenoy agrees with Knight that the best performance could be achieved by BMIs that mimic normal brain behavior. Shenoy likens it to learning a foreign language. You could try to teach someone a random foreign language, and they will eventually learn some of it. Or you could first ask them which languages they already know, and then pick a foreign language that is most similar to those. When starting from a more familiar language, they would immediately begin to perform better.

“Imagine that you go into a 7-11 and want to press the Coke button, not the Pepsi button, or swing a bat, or pick up your kids. Many neuroscientists believe that this kind of precise control can only be achieved through activation of the brain’s natural patterns. The biggest challenge is to understand enough about how the brain actually works under natural conditions,” he says.

Carmena admits that it may be challenging to build a BMI that responds and adapts to events in the environment strictly by mimicking natural brain patterns. “When you ‘close the loop’, or provide environmental feedback to the BMI, you are changing the inputs to the brain, and as a result, changing motor responses. It’s very difficult to keep the same patterns of brain activity under these conditions,” he says.

However, he and his students are exploring new ways of optimizing BMI performance under natural conditions. “A standard problem in the field is to design a BMI that can grab a glass of wine,” says Carmena. To pick up a glass of wine without dropping it, crushing it, or missing it entirely, you need to have precise sensory feedback from multiple channels, such as touch, vision and proprioception, which is used to keep track of your body’s movements and positions. “We plan on stimulating neurons in sensory parts of the brain to mimic natural feedback from many sensory modalities,” says Carmena.

Slip-sensors, for instance, could be used to detect when the wine glass is slipping and trigger a robotic hand to squeeze tighter. “Although it is possible to design a robot that does this automatically, we believe you can get better control by using the brain,” says Subramanian Venkatraman, an electrical engineering graduate student in the Carmena lab. His latest research shows that microstimulation can actually evoke a sensation similar to natural touch. However, he quickly points out that it is not necessary to exactly mimic natural sensation to get accurate control with BMIs. “You could learn to use sensory feedback from microstimulation even if you don’t stimulate the precise neural circuitry that’s naturally involved; it would just feel a little artificial,” says Venkatraman.

The future of BMIs

It’s not likely that patients will be using BMIs to pick up wine glasses anytime soon. Currently, the risks from surgery and unreliable electrodes outweigh the benefits, except for three types of patients: those with damage to the high cervical part of the spinal cord, which causes quadriplegia; those with Amyotrophic Lateral Sclerosis (Lou Gehrig’s disease), a neurodegenerative disorder that causes motor neurons to die and later leads to complete paralysis; and those with “locked-in syndrome,” a condition, typically caused by a stroke in the brainstem, that causes patients to lose control over all muscles except for the eyes. To increase BMIs’ potential benefit to a wider spectrum of patients, it will be necessary to improve the performance of BMIs, decrease their invasiveness, or both.

University of California scientists are on the path to achieving this goal and eventually restoring language and motor functions to paralyzed patients. Knight is committed to developing a joint, world-class neuroprosthetic program with UC San Francisco (UCSF), in collaboration with two neurosurgeons who have been instrumental in his experiments: Mitchel Berger, neurosurgeon and chair of neurological surgery at UCSF, and Nicholas Barbaro, neurosurgeon and co-director of the Functional Neurosurgery Program at UCSF. “We’ve received supportive feedback from deans on campus, but what we really need now are some large donations to help jumpstart the center,” says Knight.

Although ubiquitous neuroprosthetics may seem like a farfetched fantasy at the moment, Carmena and Knight expect they will follow the same successful path as previous cutting-edge medical implants. “In the 1970s, defibrillators were an experimental treatment for cardiac arrhythmia; now they’re widely used. In the mid-1980s, cochlear implants were approved by the FDA to restore hearing. More recently, deep brain stimulators were introduced as an experimental treatment for Parkinson’s disease and other neurological disorders. All of these were once crazy ideas that are now accepted, because they work,” says Knight.

In the meantime, debates about the most promising approaches—invasive or noninvasive, or those that mimic or bypass natural circuitry—continue to rage on. “Scientists are working in parallel to accelerate discoveries in the field,” says Carmena. Shenoy agrees that the multifaceted approach is optimal. “Show me a medical technology where it’s not better to have more options,” he says. One day, patients may be able to walk into a clinic and choose from a suite of BMI options that cater to their individual needs.

Janelle Weaver *is a graduate student in science communication at UC Santa Cruz.*

REINVENTING THE TRANSISTOR

Breaking the silicon barrier

By Brian Lambson

In *The Matrix*, good-guy-turned-traitor Cypher was so attuned to reading huge arrays of ones and zeroes on his monitor that he could interpret them as sights, sounds, and smells in real time. While his feat is impossible for ordinary people, computers interpret ones and zeroes all the time. In fact, computer processors deal exclusively with binary data, or bits, when performing calculations and restore information to a form useful to people (e.g. visual, audio, or mechanical) only as a final step.

Transistors—tiny electronic switches that are connected together to build microprocessors—are the key to manipulating bits in computers. For example, they do the physical work inside laptops, cell phones and iPods. However, just as we tend not to think about brain cells while using our brains, few consider transistors while using a computer. And why should we? Since the 1970s, when the metal-oxide-semiconductor field effect transistor (MOSFET) became the transistor design of choice in digital technologies, the underlying physics inside microprocessors has remained essentially unchanged. Sure, transistors have become smaller, faster, and more energy efficient over the last three decades, fueling remarkable progress in digital gadgetry, but such progress has primarily been driven by advancements in fabrication and processing technology. The underlying MOSFET design has remained basically unchanged.

Now that the ubiquitous MOSFET is approaching fundamental limits to further improvement, transistor research has returned to the cutting edge. Researchers in the Electrical Engineering and Computer Sciences Device Group at UC Berkeley and elsewhere are experimenting with new transistor designs that may replace the MOSFET in certain applications within a decade. In particular, their new designs seek to improve on the primary weakness of the MOSFET: power consumption. The development of low-power transistors is crucial for applications such as data storage, wireless sensor networks, and biochips. In addition to enhancing the performance of existing technology, highly energy efficient transistors are likely to open up unforeseen product spaces.

In their effort to improve transistors beyond the physical limits of the MOSFET, researchers are drawing from a number of scientific fields not traditionally associated with transistors. Three new transistor designs being developed at Berkeley exemplify this trend: the tunnel field effect transistor (TFET), nano-electromechanical (NEM) relay, and negative capacitance field effect transistor (NC-FET).

BELL LABORATORIES

The ones and zeroes of computers

Bits in electronic circuits are manifested as electric charge on conducting surfaces called capacitors: charged represents a 1 and uncharged represents a 0. To perform a computation, the states of one or more input capacitors are used to determine whether an output capacitor should be charged or discharged. Transistors, which turn "on" and "off" like a household light switch depending on the state of an input capacitor, turn out to be the most direct way to translate information from input capacitors into output behavior. Typical output behavior includes driving the input of another transistor, writing bits to memory, and illuminating pixels in a display. In general, the functionality of a chip is determined by the number of transistors and speed at which they switch.

A microprocessor contains little else besides capacitors, transistors, and wires—an astonishing testament to the utility of electronic switches. Properly arranged, transistors can be made to perform any logical operation involving one or more input bits and a single output (called a Boolean logic function). Boolean logic gates serve as building blocks for simple calculations such as adding two numbers together. More complex operations require linking inputs and outputs to memory and a clock. Finally, programs and user interfaces give rise to the many computer applications familiar to the end-user.

Given that today's MOSFETs cost only a few millionths of a cent each, I wouldn't recommend making one yourself. That said, the most important step in making a transistor is to choose the right materials. Electrical engineers normally classify materials as conductors—those that allow electric current to flow through them—or insulators—those that do not. Although conductors and insulators are useful for a great many electronic applications, building an efficient transistor is not among them. What a transistor needs is a material that can be either conductive or insulating, along with a convenient way to switch between the two.

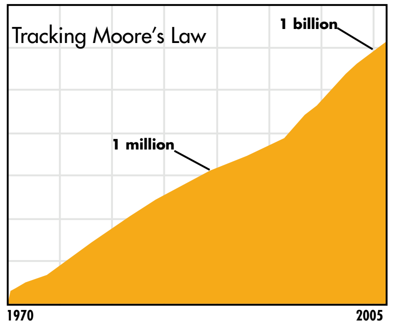
Enter semiconductors. A semiconductor is ordinarily an insulating material, but when positive or negative charge is placed on a nearby capacitor plate, it can be made conductive. This is due to the so-called field effect in which mobile electrons are attracted to the region close to the capacitor plate when it is charged and depleted from the same region when the capacitor plate is uncharged. In a MOSFET, the semiconductor region that switches between conductive and insulating is called the channel, the capacitor plate that controls the state of the channel is called the gate, and the two electrical contacts that connect the channel to the rest of the circuit are called the source and the drain.

The primary goal of transistors in digital applications is to transition between on and off states as abruptly as possible. The mechanism used to control the number of free electrons in the channel determines how abrupt the switch is. In the MOSFET on-state, free electrons are supplied to the channel by the source through a process called diffusion. While diffusion does not quite provide ideal on/off switching characteristics, it is close enough that it is used in all of today's computing applications. On the other hand, designers trying to improve on the MOSFET often turn to mechanisms other than diffusion to control the supply of free electrons to the channel.

Silicon has proven over many years to be the semiconductor material that best balances cost and performance and is the channel material for almost all commercial chips. In fact, due to processing considerations, a typical MOSFET is made entirely of silicon-derived materials: a conductive form of silicon known as polysilicon is used in the gate; silicon dioxide, an insulator, is used to physically and electrically separate the gate from the channel; and silicon doped heavily with conductive ions is used to construct the source and drain. The remaining challenge for electrical engineers has been optimizing and shrinking the MOSFET as far as technology and physics allow.

The mighty Moore

Consider a simple math trick. Start by placing a single penny on a table. Next to it, stack two pennies. Continue building stacks of pennies, each one twice the size of its neighbor, until there are 28 stacks. Done? Congratulations! You're a millionaire. Here's another: the year is 1965, and the latest chip produced by the electronics company you co-founded has 50 transistors. Based on the last four years of data, you predict that every two years the number of transistors on a cost-competitive chip will double. The catch is that the chip size and cost must remain constant, so the transistors themselves have to become both smaller and cheaper. Intuition from the penny example suggests that maintaining an exponential rate of scaling for almost 50 years



Moore's Law states that the number of transistors in computer microprocessors doubles roughly every two years. The y-axis of the plot is logorithmic.

(corresponding to a scaling factor of over 10 million) would be impossible. Yet incredibly, this is not a trick. The prediction was made by Gordon Moore, co-founder of Intel, and has accurately described one of the most remarkable feats of scientific and technological innovation of all time.

Moore's Law, as his prediction has become known, does have limits. An obvious example: no transistor can be smaller than a single atom. Already, the latest generation of MOSFETs has channel lengths of several hundred atoms, soon to be in the tens. However, even as the MOSFET approaches fundamental scaling limits, engineers are wary of predictions that Moore's Law is coming to an end, and for good reason. Every decade, researchers have predicted that seemingly insurmountable obstacles would prevent the continued scaling of transistors, only to make breakthroughs that allowed Moore's Law to continue unabated.

Currently, the principal challenge facing Moore's Law is power density, defined as the amount of power dissipated per unit area of chip during computation. The more power a chip dissipates, the more it heats up. As chips pack more and more tiny transistors together it gets harder to conduct that excess heat away. In the worst case, transistors have to be operated at slower speeds to give them more time to cool between operations. The only way to avoid such a tradeoff and increase overall functionality is to decrease the energy dissipation per operation in the transistors themselves.

As it turns out, a nano-size MOSFET has only a limited ability to scale up energy efficiency while decreasing size. The limit arises from undesired leakage current, which is the current that flows through a transistor when the channel is supposed to be insulating.

Even when logical operations are not being performed, the chip still produces heat (and, in mobile devices, drains power from the battery) in significant quantities. To overcome these limitations, researchers are looking beyond MOSFETs to find devices that are more energy efficient at the nanoscale.

Tunnel FET: A quantum leap

For the most part, walking through walls doesn't work, unless you're an electron. Via quantum tunneling, electrons are able to defy classical physics and pass through thin barriers at an appreciable rate. Now that transistors have become nano-size, tunneling has become a significant source of leakage current and a major reason that the energy efficiency of transistors is failing to keep pace with Moore's Law. However, a group of EECS professors has shown that tunneling can be harnessed to build a transistor that is in fact more energy efficient than the MOSFET. Tunnel FETs come in many shapes and sizes: at Berkeley alone, at least three separate designs are under investigation.

Professor Tsu-Jae King and her graduate students are studying a design called the germanium source TFET. In this design, germanium, rather than silicon, is the semiconductor material that is switched between conducting and insulating via the field effect. Although the germanium source TFET is similar to a MOSFET in structure, free electrons in the TFET do not enter the channel by diffusion. Rather, the field effect sets up a thin barrier in the source through which electrons tunnel to reach the channel. Compared to a MOSFET, the transition between conducting to insulating states in a TFET is very abrupt. As a consequence, the TFET allows very little leakage current when turned off and is attractive for energy-efficient applications.

King chose germanium as the active material in the TFET for its ability to sustain higher tunneling current than silicon TFETs. Higher current means charges move more quickly through the circuit, allowing for higher operating speeds. "Tunneling current is described by a formula that gives us various 'knobs' that allow us to enhance the transistor's on-state current," she explains, one of which is to decrease the width of the barrier through which electrons tunnel. Germanium has thinner tunneling barriers than silicon, so it was natural to incorporate it into a TFET.

Because silicon has been the dominant semiconductor material for such a long time, many research labs are not well-equipped to process less common materials such as germanium. Therefore, fabricating high quality devices using germanium can be challenging for many groups. But King has been working with germanium since she was in graduate school, so when the opportunity to improve the performance of TFETs using germanium came along, she explains, "the experience of my group in the past with germanium was leveraged to obtain the best reported tunnel transistors to date."

At a recent conference, King's students reported a germanium source TFET with the highest ratio of on-current to off-state leakage current, known as the on/off ratio, in a tunnel transistor. "In the past," King says, "people were focused mainly on the speed of their devices, so they would compare only the on-current. However, for energy efficient electronics, the key metric is not simply the on-current but the ratio of on-current to off-state leakage current." Going forward, King hopes to further improve both the on-current and on/off ratio in her group's devices. With the semiconductor industry watching closely, the germanium source TFET is now positioned as one of the prime candidates to overtake the MOSFET in energy efficient applications.

NEM relay: flexing some muscle

Not all low-power transistor designs currently on the table rely on exotic physical phenomena like quantum tunneling. In fact, one idea Berkeley researchers are working on is rather old-fashioned: a mechanical switch. From the mid-19th century until the advent of modern electronic computers, scholars, engineers, and inventors devised intricate machines that used small mechanical switches to perform calculations and derive mathematical tables. Few were actually built, though. Mechanical computers were too unreliable, slow, and expensive for any practical purposes, and it was not until electronic switches were developed that computers achieved widespread use.

Given the disadvantages of a computer with moving parts compared to electronic switches, it might seem strange that anyone would want to revive the concept, especially to use in an ultra-low power computer. But King and her students have done exactly that with a pioneering new device called the nano-electromechanical (NEM) relay that they believe will require much less energy per operation than a MOSFET. The secret to its success is its small size. In a mechanical system, King explains, "reliability; operating voltage, which is closely tied to energy efficiency; speed…all these things are helped by miniaturization. Interestingly, it is because of advances in processing technology driven by the MOSFET that we are able to fabricate mechanical devices that are in fact small enough to be more energy efficient than the MOSFET."

The reason the NEM relay can achieve higher energy efficiency than a MOSFET is that it has zero leakage current; by physically

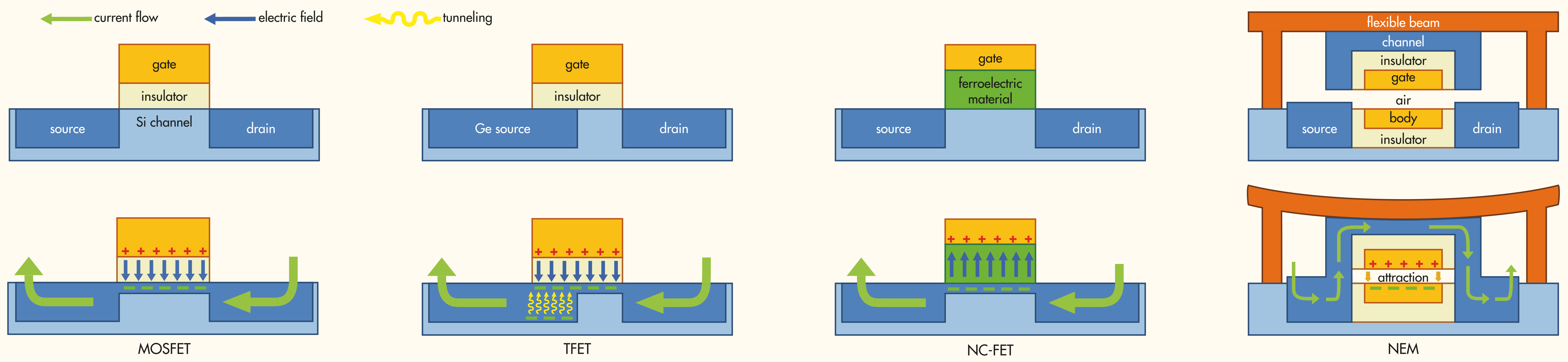
Quantum Tunneling Heats Things Up

One of the strangest implications of quantum physics is that of tunneling—the notion that a particle will occasionally pass through a barrier that it should not be able to penetrate according to classical physics. There is a reason no classical theories predict tunneling: it is negligible across barriers with thicknesses greater than about one nanometer. That's more than ten thousand times smaller than the diameter of a single strand of hair!

Despite its existence across only extremely small distances, tunneling plays a major role in daily life thanks to—you guessed it—transistors. In today's MOSFETs, the distance between the gate and channel is just about one nanometer, meaning that some of the electric charges that are supposed to be confined to one of the two regions leak across the barrier that separates them via a tunneling process. The electric current that flows into the gate as a result of tunneling is highly detrimental to transistor operation and has become quite a nuisance for device engineers.

However, engineers are well trained to turn lemons into lemonade, so although tunneling between the channel and gate of a MOSFET is harmful, its existence in other regions of the device is exploited. For example, the TFET uses tunneling to supply free electrons to the channel of the transistor so the device can turn on. The diagram below shows the various locations of tunneling in a TFET (the yellow arrows signify movement of electrons). The good kind of tunneling between the source and the channel is the primary mechanism by which the source provides free electrons to the channel. The bad kind of tunneling prevents those electrons from reaching the drain by extracting them into the gate. Note that for the most part, the bad kind of tunneling is kept to a low enough level that the transistor still works as expected.

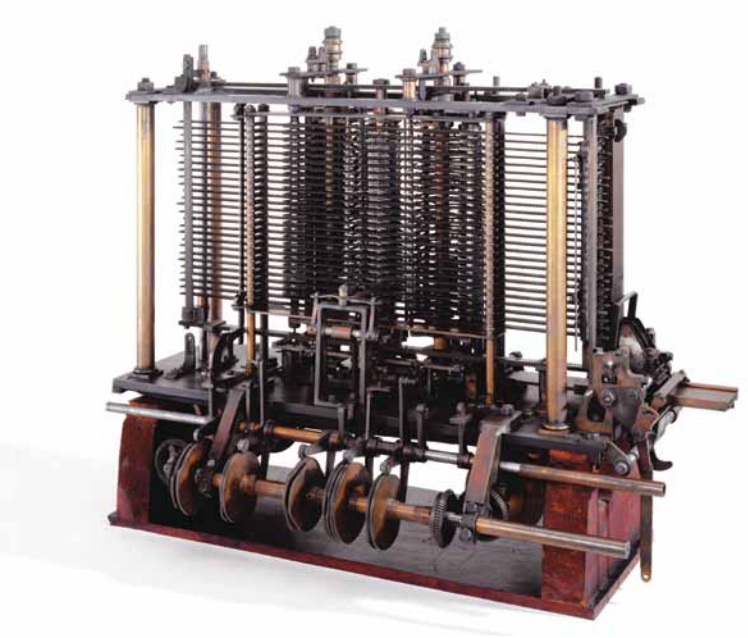
Because the dimensions of semiconductor devices are just now reaching nanometer scale, tunneling is a rather new tool for device engineers. Many designs are still under consideration for the TFET and other devices that seek to utilize tunneling. As our understanding progresses, the hope is that devices with characteristics vastly superior to those using traditional charge transport mechanisms will be discovered. After just a few years of trying, a number of promising experimental results have been obtained; many more are sure to follow.



All transistors, no matter how they are implemented, provide three terminals: the gate (orange), the drain, and the source (both dark blue). The TFET and NC-FET operate on the same basic principle as the conventional MOSFET: the electric field effect from the gate draws free electrons from the source into the semiconductor channel of the device, directly under the gate. The extra electrons make the channel more conductive, allowing current to flow. The TFET improves on the MOSFET by using tunneling rather than diffusion to draw electrons into the channel. The NC-FET operates via diffusion like the MOSFET, but the permanent field of the ferroelectric material amplifies the strength of the field effect. The NEM relay does not rely on the field effect at all. Rather, it uses the attractive forces between positive and negative charges in the gate to physically connect the source and the drain.

separating the conductive components of the transistor in the off-state, current through the transistor is completely blocked. In contrast, the current through a MOSFET becomes merely “low” due to small but significant leakage currents.

Building a nano-scale mechanical switch is a challenging task, requiring three dimensional fabrication techniques rarely used in transistors. In this respect, the NEM relay borrows heavily from techniques developed for the field of micro-electromechanical systems (MEMS) over the last few decades. To create an air gap under the gate and channel of the NEM relay, part of the device initially sits on a temporary spacer that is later removed. Hei Kam, a graduate student in King's group, notes that “we are limited in the materials we can use because we need to remove one layer of material without affecting any of the structural materials.” In particular, this limits the options for a contact material. “What we found,” says Kam, “is that the only material we can use for the contact is tungsten; it can withstand the removal of supporting materials, it is a good conductor of electricity, and it is a hard material, improving reliability.”



The 19th century mathematician Charles Babbage designed the mechanical Analytical Engine to perform programmable computations. Recent work on microscopic NEM relays on campus may resurrect the mechanical computer.

SCIENCE MUSEUM/SCIENCE & SOCIETY PICTURE LIBRARY

Still, Kam says, “I am often asked about the reliability of the NEM relay, because the device must physically open and shut billions of times without breaking or welding shut.” Welding is a particular concern because high electrical current in the relay can cause a significant temperature increase. However, Kam says that the contacts are designed not to allow the levels of current that would cause welding. “The on-state current we are shooting for is relatively low, and when we operate the device in the low current regime, reliability takes off.”

To exploit the energy-savings of the NEM relay with a minimal loss of functionality, Kam collaborated with EECS Professor Elad Alon to design circuits specifically suited to the NEM relay's strength: zero leakage current. “As you can imagine, the NEM relay switches slowly because it involves physically moving parts, which is inherently slower than electron transport,” Kam explains, “so what we do is parallelize the mechanical motion such that all the computation is done within one mechanical switching cycle.” Parallelism involves breaking up a computation that is normally done sequentially—long division, for example—into pieces that can be executed simultaneously. Because the NEM relay is well-suited for parallelism, Kam and Alon show it is possible to realize most of the energy gains of the NEM relay while retaining high speed in parallel applications.

Negative capacitance FET: Supercharging the field effect

While King and her students are working on devices that are fundamentally different from the MOSFET, EECS Professor Sayeef Salahuddin has proposed a device that seeks to retain the MOSFET's key features as much as possible. “The negative capacitance FET I am working on is essentially an external device to the MOSFET itself, equivalent to putting a small electrostatic transformer at the gate,” says Salahuddin. “The operating principles of the MOSFET are left intact.” An electrostatic transformer serves to amplify the field effect, making the channel more conductive than a MOSFET's when turned on and more insulating when turned off. As a result, the negative capacitance FET dissipates much less energy than a conventional MOSFET.

In Salahuddin's design, an electrostatic transformer is implemented by replacing the insulator between the gate and channel of a MOSFET with a ferroelectric material. Ferroelectric materials have a permanent internal electric field caused by asymmetry in their crystal structure. When placed below the gate of an otherwise typical MOSFET, this permanent electric field adds to the electric field induced by charging the gate.

Ordinarily, the internal electric field of a ferroelectric material has no net effect on a transistor because it is the same for both the on and off states. However, Salahuddin hypothesized that under a particular set of operating conditions, the internal fields can be functionalized to counteract any electric fields between the gate and channel. In this special state, the strength of the “permanent” field in the ferroelectric material changes in response to the amount of charge on the gate capacitor. The net effect on the device is to increase the number of free electrons in the channel in the transistor's on-state without increasing its off-state leakage current.

In order to describe the behavior of the NC-FET mathematically, Salahuddin noted that equations that describe current flow in a MOSFET were left intact if he replaced the value of capacitance between the gate and channel—normally a positive number—with a negative value. Therefore, one way to express how his proposed device works is that it introduces an effective negative capacitance between the gate and channel.

Currently, Salahuddin and his students are looking to experimentally verify the key principles of the NC-FET. An investigation is underway to demonstrate effective negative capacitance in a two-capacitor structure. Salahuddin explains, “Ordinarily when you have two capacitors in series, the total capacitance should be smaller than either one of the capacitors individually, but if one of them is negative, then the total capacitance can be larger. To show this would be almost a definite proof that the effect we are looking for is real.” Once negative capacitance is demonstrated, the semiconductor industry will look to take the device to market. Since the NC-FET is notable for not requiring a major redesign of the MOSFET, integration into mainstream technologies could be substantially faster than other low-power devices.

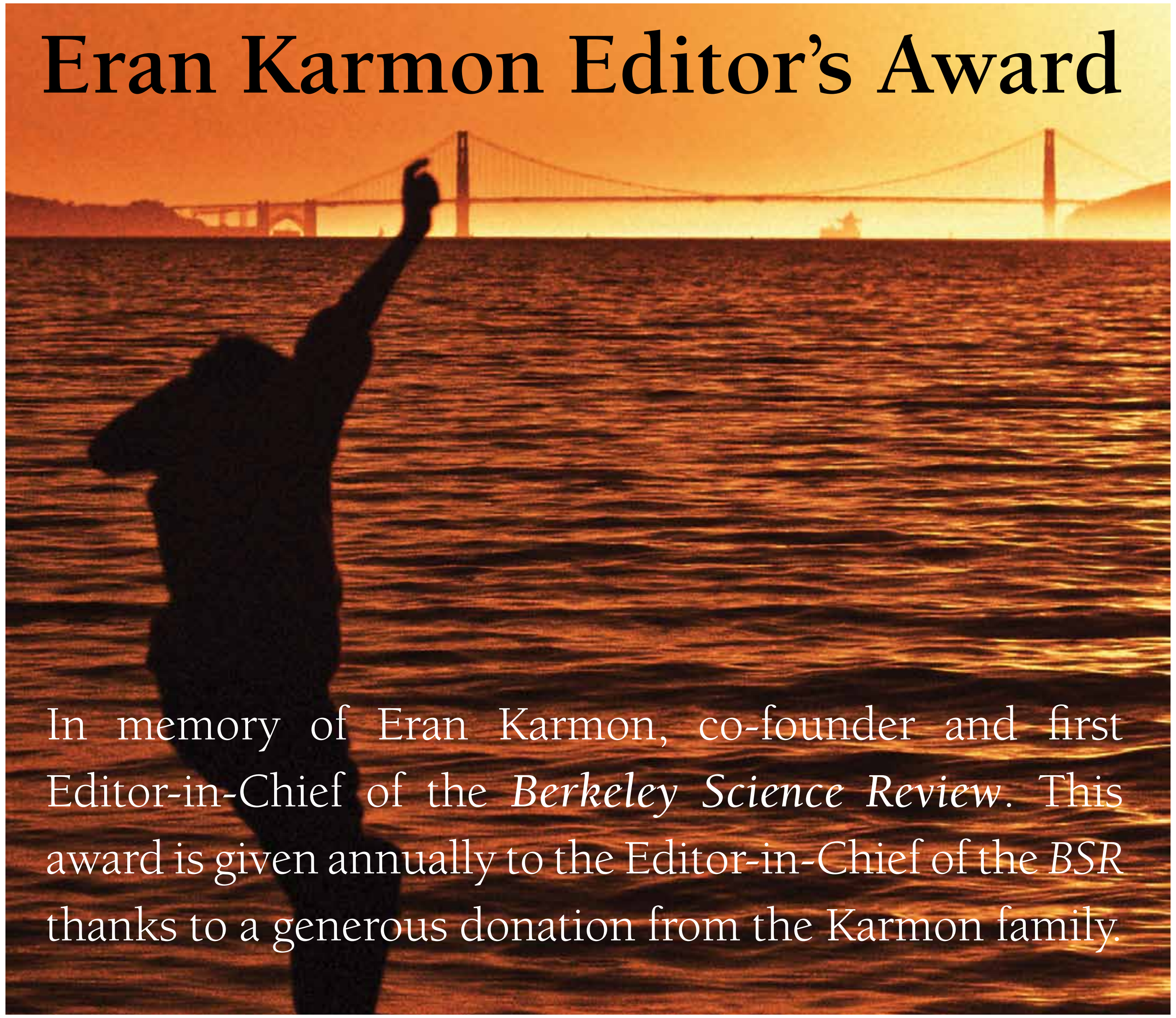
Powering through the MOS roadblock

In a recent lecture given at Berkeley, Intel chairman Craig Barrett was asked when he believed Moore's Law would end for the MOSFET. He responded, “June 27, 2024.” Despite his tongue-in-cheek precision, Barrett was in fact giving a sincere approximation based on what Intel researchers are currently able to achieve in the lab.

For device researchers, this relatively short time scale means that exploratory research with basic science in mind is no longer the primary goal of many projects. Researchers working on devices such as the TFET are already seeking to optimize performance-based metrics rather than introduce new physics into the device, and circuit designers are beginning to come up with layouts that optimize the new functionality introduced by a device such as the NEM relay. In other words, the kind of research that went into making the MOSFET such an unambiguous success over the last few decades is beginning to be applied to new devices as well. This represents a distinct shift from answering basic science questions about nanoscale devices to actually working on the implementation of the devices in mainstream technology.

Over the next few years, researchers expect further improvements in nanoscale fabrication techniques, spurred by progress in such diverse fields as biology, chemistry, materials science, and physics. The new developments will ultimately determine which devices will be best suited to replace the MOSFET in low power applications. Because the TFET, NEM relay, and NC-FET represent only a small fraction of devices being explored right now, it is very much possible that an entirely different technology will take the throne. What is clear, however, is that the lines have been drawn for what promises to be an intriguing battle to replace one of the most important devices in modern society.

Brian Lambson *is a graduate student in electrical engineering and computer science.*

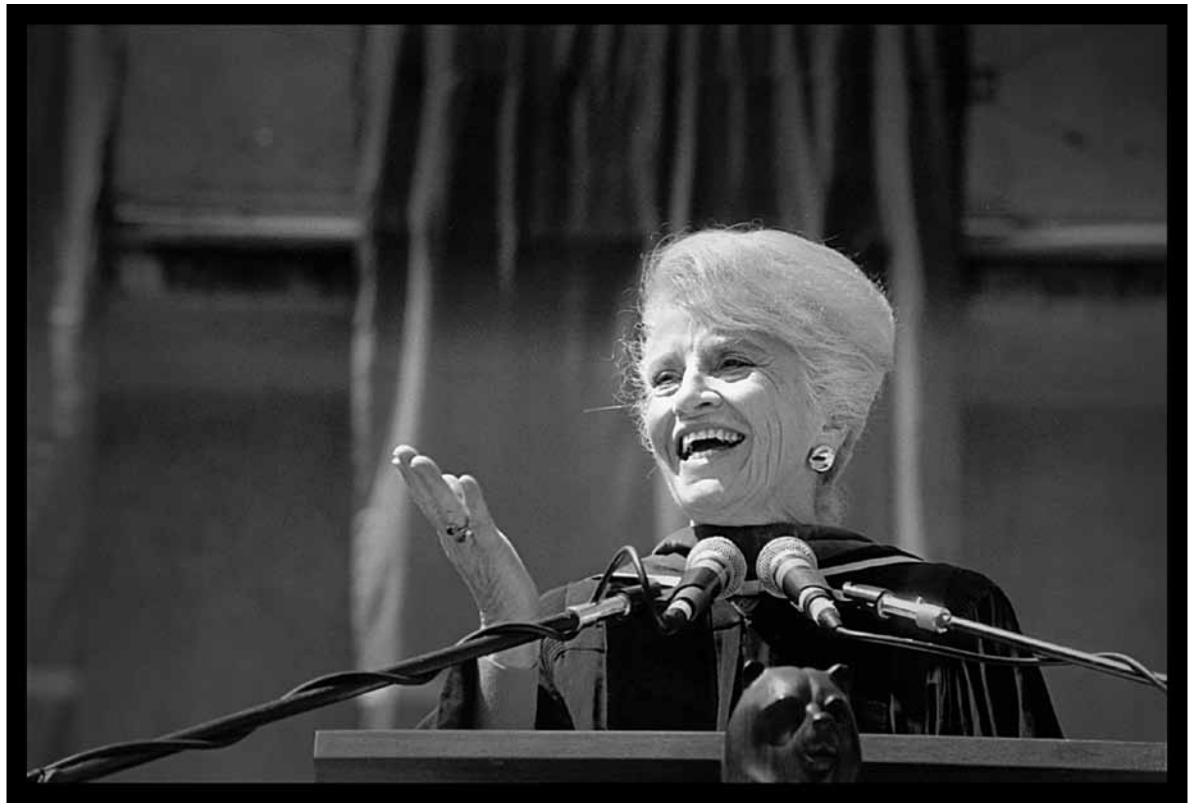


MAREK JAKUBOWSKI

Eran Karmon Editor's Award

In memory of Eran Karmon, co-founder and first Editor-in-Chief of the *Berkeley Science Review*. This award is given annually to the Editor-in-Chief of the *BSR* thanks to a generous donation from the Karmon family.

Faculty Profile:
Marian Diamond



JONATHAN KING

Marian Diamond is a professor of neuroanatomy in the integrative biology department. Over the span of her career she has held numerous distinguished positions, including Director of the Lawrence Hall of Science. She is a fellow of the American Association for the Advancement of Science and a member of the California Academy of Sciences. She received her PhD in anatomy at Berkeley and later returned to join the faculty in 1965. She has been teaching for more than 40 years, has received the Outstanding Teaching Award and Distinguished Teacher's Award, and is a member of the American Association of University Women Hall of Fame.

Professor Diamond's research revolutionized the way we think about aging, showing that with proper stimulation the brain can continue to develop at any age. She stresses the importance of an "enriched" environment (for rats, her model system, this consists of 12 rats living together in a large cage with a changing array of objects to explore) compared to an "impoverished" environment (one rat living alone in a small cage with no objects). Her work has also demonstrated significant differences between male and female brain structure. Our conversation reflects the breadth of her career, ranging from what it was like to study Einstein's brain to her current work with impoverished children in Cambodia.

When you were a graduate student here at Berkeley, you were the only female graduate student in the anatomy department. What was that like?

Well, I wasn't paying much attention to that, because I was so eager to learn. I was very enthusiastic and very hard working, because I had a goal. At first the men in the department didn't know what I was doing there, and I had to put up with a lot of sexist remarks which no woman would have to put up with today. But that was the way it was. I knew what I wanted, and I wasn't going to let them deter me or hurt me. And so I proceeded accordingly.

In the time that you've been here have you seen changes in the department that are encouraging to you?

Oh, of course. A woman can come in and she can be associate professor within a few years. That would have never happened previously. When I started to write my papers one of my friendly collaborators, David Krech, put my name in parentheses. I said "David, what are you doing? I did all that work," and he said "But I've never worked with a woman before." So it was a matter of education. It wasn't a prejudice; it's just what male scientists were used to. But I really think in today's world all of this is gone. Unless you're in their field and you're doing better than they are, then they're not too happy about that. They probably wouldn't be happy with you if you're a very good competitor, no matter what gender you are.

You are best known for your work showing that the environment alters the structure of the brain, and that can happen at any age. How did this study come about?

When I started, the group was working on the biochemistry and showing that a neurotransmitter-processing enzymze called acetylcholinesterase was increasing in enriched animals compared to impoverished animals. I was interested in anatomy and the structure of the brain, and so I had the hypothesis that the structure should be changing too. And that's when we first found that the anatomy of the cerebral cortex could respond to the environment. Nobody was working on any of this; this was brand new. Competition didn't come until about 10 years later.

Another of your significant findings is that the male and female brains have anatomically distinct structures. How did you decide to look at that?

I worked with three men, and they only wanted to work with male brains. They didn't want to work with the female brain and get caught in the esterus cycle, because the fluctuations in hormones could possibly be changing the brain. In short, the male is easier to work with.

KATHRIN MILLER

I actually broke away from the group to follow my interest in the male/female differences, and that's when I found that the male is what we call lateralized. His right hemisphere has a thicker cerebral cortex than his left. And it's highly statistically significant in most areas. The female does not have that; she has what we call a symmetrical thickness. There's no statistical difference between the thickness on the right and left. The differences are sex steroid-derived—you can take out the testis or the ovaries and change the pattern.

Is it known why?

Well, we had to hypothesize because nobody had seen this before. In fact I remember the day I was reporting this to the graduate students up at UC Davis. I said, "These are our most recent data. We show that the male has asymmetric thickness of the cortex and the female does not." "What does it mean?" someone asked. I said, "I don't know, these are new data, and I haven't had time to learn more. If you want an off-the-top hypothesis I would say look at the phylogenetic picture. What's the major function for the males? It's to find territory, defend territory, find a female—all very specific, focused functions. And the female? What's her major function? To produce and raise young. She has to be ready to go in all directions. If she were lateralized it might be a hindrance, but here she can have information going back and forth between the hemispheres more readily." I put that out as a hypothesis then and nobody has refuted it all these years.

Your work now involves teaching children in Cambodia. How did you become interested in this project?

Everybody wants a better brain. We finally figured out five factors that affect the brain—a good diet, exercise, challenge, new things, and love. These five things all affected our rats' brains and that's what we'd love the world to practice. So I wanted to find the most impoverished children in the world and see if we could reach them because that, to me, was the epitome of good enrichment. I started this project in Cambodia 10 years ago and it's been extremely sucessful.

I am intrigued by your study of Einstein's brain. How did you become interested in that? Was it hard to get the sample?

We had shown that animals with enriched environments had an increased number of glial cells, and so I wondered whether Einstein would have more glial cells per neuron than the average male. I was by myself in my husband's office with nothing to do when I remembered that *Science* magazine had shown a picture of a box with Einstein's brain in Kansas. So I called University of Kansas and learned who had Einstein's brain. Three years later I got four chunks of his brain to slice and study. I found that in all four he did have more glial cells per neuron than the average male, but in his inferior left parietal, a multifunctional brain center, he had significantly more.

I think it's so cool that you got to study Einstein's brain.

I can show you a picture if you'd like; it's my screensaver.

Orapim Tulyathan *is a graduate student in biophysics.*

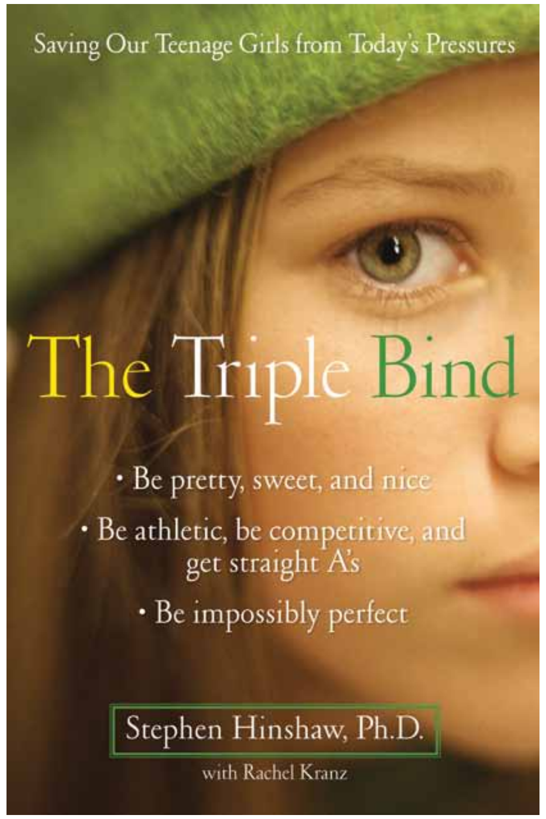
Troubled teens

The Triple Bind

by Dr. Stephen Hinshaw with Rachel Kranz
Ballantine Books
256 Pages, $25.00

By all outward appearances, young women growing up in the 21st century have the world at their feet. Previous generations of women have seemingly broken the proverbial glass ceiling, and opportunities abound for today's teenage girls to fulfill their dreams. If this is the case, then why are a full 25% of these girls at risk for self-mutilation, eating disorders, violence, depression, or suicide? Why are rates of aggression and violence among girls eighteen and under rising while those among boys in the same age group are falling? Moreover, why are rates of depression and suicide rising nationwide, and why are these mental health problems presenting at earlier ages?

These alarming questions led Stephen Hinshaw, UC Berkeley professor and chair of the Department of Psychology, to examine the cultural climate girls face as they grow up today. His findings, presented in his latest book, *The Triple Bind: Saving Our Teenage Girls from Today's Pressures*, implicate a set of unhealthy societal pressures facing contemporary teenage girls. He argues that the very opportunities meant to liberate women have instead shackled them by defining a new set of restrictive gender expectations. In addition to fulfilling the traditional female expectations of building strong relationships, being empathetic and nurturing, and looking pretty, girls must now also succeed in school, sports, extracurricular activities, and careers, arenas once dominated by boys. Finally, all of these expectations are circumscribed by a set of uncompromisingly narrow cultural standards of how a young woman should look and behave: thin, sexy, and effortlessly poised. Hinshaw terms these three-pronged pressures facing today's teenage girls the "Triple Bind."



Perhaps Hinshaw's most powerful observation is just how insidious this last aspect of the Triple Bind is, as it affords virtually no room for escape. Formerly, girls had "gender bending" role models such as Janis Joplin, Cyndi Lauper, and Mary Tyler Moore, who defied conventions of femininity by assuming such alternative identities as beatnik, tomboy, hippie, punk, or goth. These role models, and the ideals of feminism they represented, allowed girls an escape from the traditional expectations of what it meant to be feminine. In comparison, today's girls are confronted with only one over-sexed model for success, according to Hinshaw. Even cultural icons who seemingly break the mold are not exempt from these expectations. The first female Indy 500 driver, Danika Patrick, still poses for *Playboy* and is judged by her "hotness." The message, at the end of the day, is that girls must "do it all."

Hinshaw examines in detail how different biological and environmental factors have conspired to contribute to the Triple Bind and why teenage girls are especially at risk. Today's overworked society has created a demanding, stressful lifestyle. Not only are women at a higher genetic risk for depression than men, but Hinshaw also contends that they are socialized from an early age to please others and therefore bear the brunt of demanding expectations from school, work, and loved ones. And, while only a fraction of the girls will be diagnosed as clinically depressed, Hinshaw points out that the cultural environment will influence each and every girl in our society: "Some might become seriously ill while others would escape with low-grade symptoms, but all would reveal, in a variety of ways, the toll taken by their toxic environment."

In accordance with his stated goal of dispelling myths about mental health issues and increasing public awareness, Hinshaw writes mainly for the parents, teachers, guidance counselors, and mentors in the lives of teenage girls. He aims to shed light on their plight and the cultural environment that has made for widespread physical, emotional, and mental health problems amongst teenage girls. To this end, the writing style is casual and accessible to a broad audience. Hinshaw's intention to inform the general public is best kept in mind while reading the introduction to the biological basis of depression and mental illness, which otherwise may seem overly simplistic to a reader familiar with the material.

In *The Triple Bind*, Hinshaw paints a distressing picture of the world encountered by teenage girls and the frightening reality of the damaging pressures they face. On a hopeful note, however, the final chapter provides examples of girls who have successfully faced and overcome the Triple Bind and gives some useful approaches to counteract its effects. By bringing attention to these issues, *The Triple Bind* will hopefully help to reverse an alarming societal trend.

Shirali Pandya *is a graduate student in molecular and cell biology.*

With this issue we kick off a new back page series, the Time Machine. We'll explore major scientific achievements at Cal throughout the years and investigate how different scientific fields have progressed in response to these discoveries.

UNIVERSAL PICTURES

50 years ago

This year, RCA begins selling the first color televisions and newspapers are still discussing the admittance of Alaska and Hawaii into the United States. The UC Medical Center is located in San Francisco, but it is still under the auspices of UC Berkeley and there is a raging debate about whether the campuses should be consolidated. It will be another five years before the medical center is granted autonomy.

Before the split, the Medical Center already had several specialized research facilities. One of these was the Cardiovascular Research Institute, which in December of 1959 announced the results of a new study: cigarette smoking decreases air intake. The previous decade witnessed a flurry of studies linking cigarettes to cancer, but cigarette manufacturers began to add filters to their cigarettes to sidestep health concerns. They claimed that filters removed cancer-causing substances from smoke. The Cardiovascular Research Institute study, however, showed that smoke caused more than just cancer and was critical evidence for later campaigns against smoking. Despite the study's findings, it would be nearly another decade before Congress would force cigarette companies to stop touting the health benefits of filtered cigarettes. "The tobacco industry has huge clout in state and federal government, so it's hard to push through any meaningful legislation" says Joel Moskowitz, director of the Center for Family and Community Health in the School of Public Health.

These days, it is universally accepted that cigarettes cause a host of health issues. Tar occludes the lungs of smokers and can kill cells, and nitric oxide, a chemical unaffected by filtering, causes restrictive mucus buildup. However, people continue to smoke. Moskowitz says, "You can throw all kinds of studies at people, but lots of decisions are based upon social norms. We like to think people make logical decisions, but marketing research shows that's usually not the case." The future of smoking research is in examining these decisions, but it's hard to study peer pressure and marketing effects in rats.

25 years ago

Generally, the 1980s are known for *We Are the World* and Ronald Reagan. Scientifically, though, the topic of the day was recombinant DNA. Much like modern-day stem cells, transgenics as a science was welcomed by some as the wave of the future and reviled by others as a danger to nature. After all, what would happen if genetically modified organisms escaped and began mating with their wild cousins? We could be overrun by a race of genetically engineered super-mice.

Imagine the outcry, then, when a Berkeley professor announced his intent to spread genetically modified bacteria over a plot of potatoes. Steven Lindow, currently a professor of plant pathology in the plant and microbial biology department, intended to spread so-called ice-minus bacteria (microorganisms that make it more difficult for ice to form on plant surfaces) over an agricultural field. Lindow had been studying a bacterium known as *Pseudomonas syringae*, which normally produces a protein that nucleates ice crystals on plant surfaces. These ice crystals damage the plant's surface and make its nutrients available to the bacterium but can also wreak havoc on crops. Removing the gene responsible for creating this protein resulted in the ice-minus bacteria. According to Lindow, "I was really just interested in how a loss of this gene would affect bacterial ecology. The commercial promise was just an added bonus." Unfortunately, public outcry caused a storm of litigation and regulatory involvement.

After nearly five years in court, Lindow was allowed to conduct his experiment, resulting in the first ever release of genetically modified bacterium. Thus, the experimental and political hurdles were momentous. "The EPA brought in a lot of equipment from an old bioweapons lab to monitor our bacterial spread, and we also had vandalism. Someone pulled up all of our potatoes, so we had to replant them and guard them in shifts," says Lindow. Today, many farmers embrace transgenic crops: 80% of American corn, soybeans, and cotton are genetically modified. As Lindow says, "Plants aren't so bad for most people because you can see them, but bacteria, they still think, 'They're the bugs that make us sick,' and that can make things difficult."

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