BERKELEY science review

Spring 2009 Issue 16

Lab on a chip

Artificial leaves

Green chemistry

Digging in the past • *Spam* • *HHMI Investigators* • Born to Be Good • *Bending light* • *Brain magnets*

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Dear Readers,

Spring has arrived in Berkeley: the grass is growing, seasonal allergies are blooming, and a new issue of the *Berkeley Science Review* is here. This springtime weather has me thinking green (along with the rest of the country), and thus I'm happy to unofficially dub this issue of the *BSR* "The Green Edition." Politicians are focusing on new plans to carbon taxes and caps, but here at Berkeley researchers are thinking about green in more creative ways. Photosynthesis, the original green technology, produces a tremendous amount of energy, and Tracy Powell explores how researchers are investigating its mechanisms and applying those lessons to a new generation of solar energy panels (p. 16). Other groups are working to create power from more unlikely sources. One project is turning up the efficiency for converting heat energy into electricity, as Jasmine McCammon describes on page 6, and Susan Young's brief, "Poo Power," will tell you all about how microbial fuel cells can turn organic waste into electricity (p. 13). With Berkeley's own Steven Chu as President Obama's Secretary of Energy, it probably comes as no surprise that Berkeley researchers are working on alternate energy sources, but going green also means decreasing the footprint of toxic chemicals we leave on the planet. On page 27 Lee Bishop and Mitch Anstey write about a new green chemistry movement taking shape on Berkeley's campus. Even Hanadie Yousef's archaeology feature uncovers sustainable farming techniques from Hawaii (p. 41).

Does it sound like we've got green on the brain? Well, there are researchers looking into how our minds work, too. Colin Brown writes about a controversial technique that can induce temporary brain lesions for both research and patient treatment (p. 23), and if you've ever wondered how all those video games affect your intelligence, it turns out that some games can actually train your brain and improve your IQ–Katie Hart has the full story on page 12. Finally, on our back page Louis-Benoit Desroches debunks the myth that we only use 10% of our brain. And, of course, although this may be the green edition, you can also read about materials that bend light backwards (p. 8), the deluge of spam that shows up in your email inbox (p. 49), and what a canyon in Idaho might tell us about water on Mars (p. 7).

Speaking of green, we have an almost entirely new editorial staff for this issue. While it was sad to see so many of our seasoned veterans leave us for greener pastures (or, in some cases, to focus more on their research) and daunting to think about training a new editorial board, it has been exciting to have so many fresh faces and new ideas. I'd like to thank the entire editorial staff for their enthusiasm and willingness to commit precious hours to this magazine, and also the former members of the staff who have provided so much support during this transition. If you're interested in getting involved, or if you loved–or hated–one of our articles, we'd love to hear from you at sciencereview@gmail.com.

Enjoy the issue,

Rachel Bernstein

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Cover: Chemists, engineers, physicists, and other experts are cracking the secrets of photosynthesis to harvest the sun's power to meet our increasing demands for energy. Painting by Micheal Hagleberg.

Berkeley Science Review

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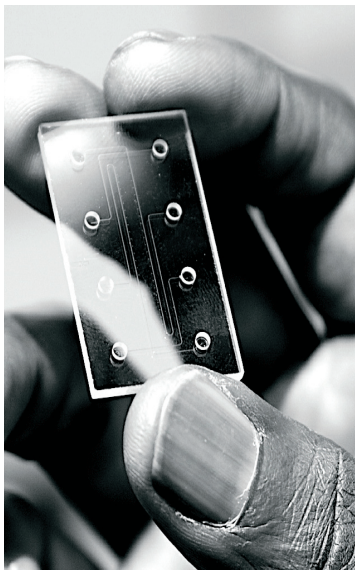

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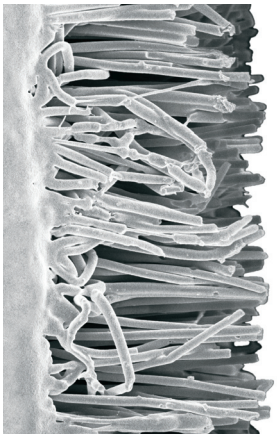
labscopes

Sticky fingers



Thanks to recent work from UC Berkeley engineers, the makers of Scotch Tape may have to rethink their product line. Taking a cue from geckos—which can climb nearly any surface with their sticky but self-cleaning feet—Jongho Lee, a postdoc in Ronald Fearing's lab, has developed a material that can stick to both dry and wet surfaces, and even gets stickier with repeated cycles of adhesion and release. This sticky surface, made out of polypropylene, is covered with millions of microscopic "fingers" about 20 microns long (approximately one-fifth the thickness of a sheet of paper) and just 300 nanometers in diameter (about one-hundredth that of a human hair). If the material gets dirty, just stick it to a clean, dry surface. More of the contaminating particles' surface area is in contact with the glass than with the tiny hairs, so when the adhesive is pulled away, the particles stick preferentially to the glass, leaving a newly clean adhesive surface. Larger particles make more contact with the hairs than small particles do, so the larger the particle, the harder it is to shake off, but Fearing's material has shown great success getting rid of particles with a two micron diameter. This technology won't keep you from tracking mud into your house on a rainy day, but it might make its way into space travel, medical equipment, climbing robots–or maybe, someday, all three.

— Jesse Dill

Images courtesy of Jongho Lee and NASA

Looking for Bosons

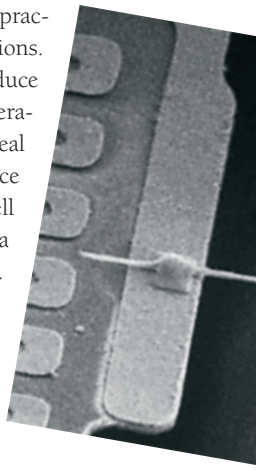
The Large Hadron Collider (LHC), powered up for the first time last fall by the European Organization for Nuclear Research (CERN), is the largest and most complex machine ever built. Its primary purpose is to smash beams of particles together, traveling in opposite directions inside a 17 mile underground tunnel at tremendous velocities. The much-hyped ATLAS experiment aims to support or disprove a quantum theory involving the Higgs boson, which would help explain how massless particles can have mass. As part of a huge international collaboration, scientists at the Lawrence Berkeley National Laboratory (LBL) designed and partially fabricated the distribution feed box (DFBX), connecting the LHC's cryogenic, electrical and vacuum systems to the different colliders and to the CERN control center. The DFBX plays a role in all four major collider experiments: ALICE (A Large Ion Collider Experiment), ATLAS (A Toroidal LHC ApparatuS), LHCb (Large Hadron Collider beauty), and CMS (Compact Muon Solenoid). Growing anticipation was put on hold, however, as a faulty connection led to a helium leak that will delay a restart until September, 2009.

— Laura Erickson

Images courtesy of CERN and Austin Roorda

Hotwired

Fossil fuel combustion produces about 90% of the world's power, but in the process, 60 to 70% of the energy stored in the fuel is lost as heat. Devices to scavenge this heat and turn it into electricity, called thermoelectrics, have been around for decades–providing power for the deep space probes Voyager I and II, for example–but their efficiency is generally too low to compete with conventional electricity, making them impractical for most applications. Thermoelectrics produce electricity from a temperature difference, so the ideal material for such a device conducts electricity well but can also maintain a temperature gradient. Unfortunately, good electrical condu ctors also tend to conduct heat well. To solve this-



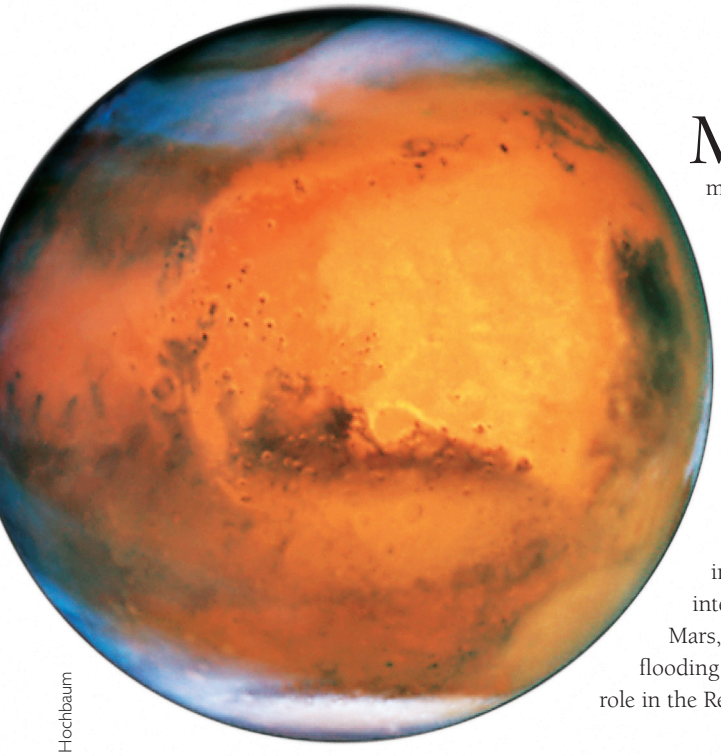


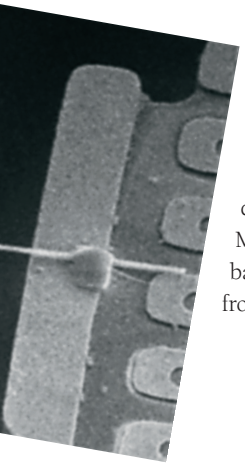
Image courtesy of Allon Hochbaum

Mars in your backyard

Most canyons result from gradual geological processes over millions of years, but short, massive deluges of water can also scoop out a chasm. For example, geomorphologist Michael Lamb and his colleagues from the UC Berkeley BioMARS project believe that a sudden megaflood carved the amphitheater-headed Box Canyon in southern Idaho. Amphiteater-headed canyons, so named because they end in round, steep walls, are usually found in soft, sandy conditions and are thought to result from groundwater emerging as springs to erode the canyon walls, but Box Canyon is carved into much harder basalt, which made Lamb and his coworkers give it a second look. The canyon currently has no surface water flow, but Lamb believes that the many depressions, or "plunge pools," at the canyon's base were formed by ancient waterfalls. Its head also has telltale scour marks likely left by surface water. And the team's calculations indicate that only vast amounts of very fast-flowing water could have moved the massive boulders downstream to their current resting places. They estimate that the canyon, up to 70 meters deep in some places, was formed by a flood lasting only 35 to 160 days. Of particular interest are the similarites between Box Canyon and amphitheater-headed canyons on Mars, also carved into basalt. If the Martian canyons evolved in the same way, through flooding rather than erosion, this could shed light on unanswered questions about water's role in the Red Planet's past.

—Sharmistha Majumdar

problem, professors Peidong Yang and Arun Majumdar turned to silicon nanowires that decouple electrical and thermal conductivity. The nanowires are so tiny (about 100 nanometers in diameter, or one-thousandth the diameter of a human hair) that they cannot sustain the vibrations that would result in heat transfer, and etching the nanowires to roughen their surface restricts the vibrations even further. While the heat conductivity is greatly restricted, the electrical conductivity remains relatively robust, leading to an efficient thermoelectric device. While these devices are not yet ready for large-scale use, they may bring us one step closer to the thermoelectric dream; as graduate student Michael Moore says, "You're basically getting something from nothing."

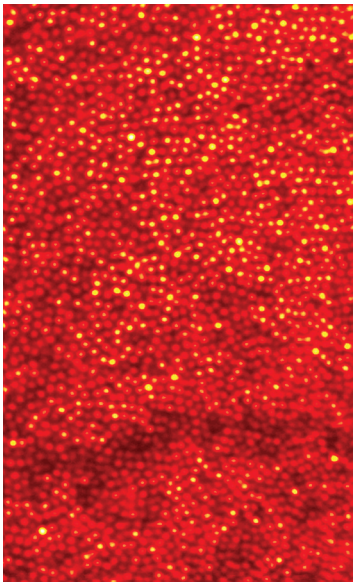


—Jasmine McCammon

Look both ways

Not satisfied with your 20/20 vision? How about 20/8? Austin Roorda can give it to you, as long as you're looking into his machine. Roorda, chair of the UC Berkeley Vision Science Graduate Group, has developed the Adaptive Optics Scanning Laser Ophthalmoscope, or AOSLO, a machine that allows him to see your retina—and you to see images—with unprecedented clarity. Adaptive optics was originally developed by astronomers to eliminate distortions in their images by measuring and correcting for fluctuations in the atmosphere between the stars and their telescopes.

For Roorda's application, he says, "adaptive optics is a way to remove the blur caused by imperfections in the eye's optics," including the lens, cornea, vitreous humor, and even the film of tears that covers the eye, all of which are constantly changing. AOSLO uses a laser to detect aberrations in the eye and then corrects the image—or adapts—in real time. The correction works both ways: Roorda sees clearer images of patients' retinas, and patients see extremely crisp images projected by the laser directly onto their retinas. Roorda's first goal is to screen patients for eye diseases by examining the retina on a cellular level. He also aims to test the limits of human vision. Theoretically the retina limits our visual acuity to roughly 20/8, and one subject, with the help of the AOSLO, has achieved this limit. Whether it's peering into the furthest skies or depths of eyes, adaptive optics provide great insight.



—Chat Hull

current briefs

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Image courtesy of Lempismatt

Fishy Physics

Metamaterials bend light backward

Bending light is nothing new; anyone who wears glasses is grateful for this phenomenon. Physicists use microscopes to guide light and achieve remarkable focus of the microscopic world. But their tools have an unavoidable limit in resolution set by the wavelength of visible light: a typical optical microscope cannot resolve details smaller than 200 nanometers (billionths of a meter) in size. To achieve resolution beyond this limit, large and costly devices are necessary. But Professor Xiang Zhang of the UC Berkeley Nanoscale Science and Engineering Center and Department of Mechanical Engineering thinks there is an easier way to beat this diffraction limit: gain complete control over the movement of light.

The direction light bends when passing between two surfaces (e.g., water and air) depends on how each material interacts with light, measured by a value called the index of refraction. For example, water has an index of about 1.33 and air has an index of 1.0. Since water has a higher index, reflected light off an underwater fish always bends toward the surface of the lake. Similarly if someone were to shine a flashlight on the lake, the light would always bend towards the line perpendicular to the surface of the water. All naturally occurring materials have a positive index, making light limited in the number of possible directions it can travel.

Zhang has overcome this limitation by engineering negative index materials. In this case the light appears to bounce off the perpendicular line and bend backwards. If water instead had a negative index, the fish would appear to be flying through the air.

These often-called "metamaterials" gain their properties from their nanoscale structure rather than their molecular composition. As described in the August 2008 edition of Science, Prof. Zhang and co-workers uniformly arranged straight silver nanowires in non-conducting aluminum oxide to achieve a negative index for red light. The nanowires are spaced 100 nanometers apart, a thousand times smaller than a human hair and nearly seven times smaller than the wavelength of red light. Since the incoming wave is larger than this spacing, it is "unaware" of this structure and sees a uniform material. "The light effectively sees a material composed of nanosized 'meta-atoms' that we can engineer to control the path of light" says Jie Yao, a

Image courtesy of Luis Argerich

Refraction, the redirection of light by a surface or material, is getting put to new use by wrapping photons like a major league pitcher throwing curve ball.

graduate student of Zhang's lab and co-author on the Science paper.

Fabricating negative index materials for visible light has been a challenge due to its short wavelengths. Previous metamaterials have achieved negative indices only at microwave and infrared wavelengths, which are at least one and a half times that of red light. These metamaterials have also been relatively thin, consisting of a single to a few meta-atomic layers. Increasing the thickness of the material resulted in considerable energy loss due to absorption in the material. Zhang has also overcome this limitation and achieved effective three-dimensional metamaterials measuring tens of meta-atomic layers thick.

Previous metamaterials were constructed so electrons in the metamaterial would oscillate at the frequency of the incoming wave (see "Metamaterials World," BSR Fall 2006). This allowed the wave to be absorbed and reemitted in another direction. Zhang's metamaterial takes a new approach by relying on silver's conductive properties. Light is an electromagnetic wave, consisting of an oscillating electric field with a perpendicular magnetic field. The incoming electric field, when aligned with the silver wires, induces a current in the wires that emits a new electric field propagating in another direction. The incoming magnetic field is unaware of the wires and follows the new electric field, resulting in a new electromagnetic wave. Since the magnetic field is not absorbed in the process, less energy is lost as the wave moves through the material.

An alternative optical metamaterial was devised by stacking alternating layers of silver and insulating magnesium cut into a nanoscale fishnet pattern. As described in their August 2008 Nature paper, these layers form small circuits that induce an electromagnetic wave moving in the opposite direction as the original. "This new design has incredible flexibility and it is simple," says Jason Valentine, graduate student and co-author of the Nature article. "You want the simplest design possible when dealing with fabrication." This design also demonstrated better energy efficiency compared to previous metamaterials.

Such metamaterials can enable researchers to overcome the diffraction limit and resolve details smaller than the wavelength of the incident light. When light waves impact a material, a pattern of waves is formed near the material's surface. Details smaller than the wavelength of light are in these waves, yet they decay and vanish almost instantly. Negative index materials placed close to the object can amplify these evanescent waves, allowing them to propagate far enough to be resolved. Zhang's group demonstrated a working "superlens" in 2005 ("The Sharpest Image," BSR Fall 2005), being able to resolve two lines separated by one-tenth the wavelength of red light. Superlenses could lead to inexpensive optical microscopes that would be able to resolve structures as small as living viruses. "The idea is simple enough that it could one day be used even in high school biology classrooms," explains Leo Zeng, post doctoral researcher and lab manager of Zhang's group.

In fact, overcoming the diffraction limit is just one of several applications achievable by mastering the manipulation of light. These materials may one day play a role in high speed optical computing, cavities that can trap light in a way that mimics the environment around a black hole, and cloaking devices. Prof. Zhang's remarkable achievement of bending red light the "wrong" way has laid the necessary groundwork for the development of practical application of metamaterials. "The results demonstrated in these two papers seemed impossible in 2003, but we did it," says Zeng. "We are limited only by our imaginations of what is possible."

Aaron Lee *is a graduate student in astronomy.*

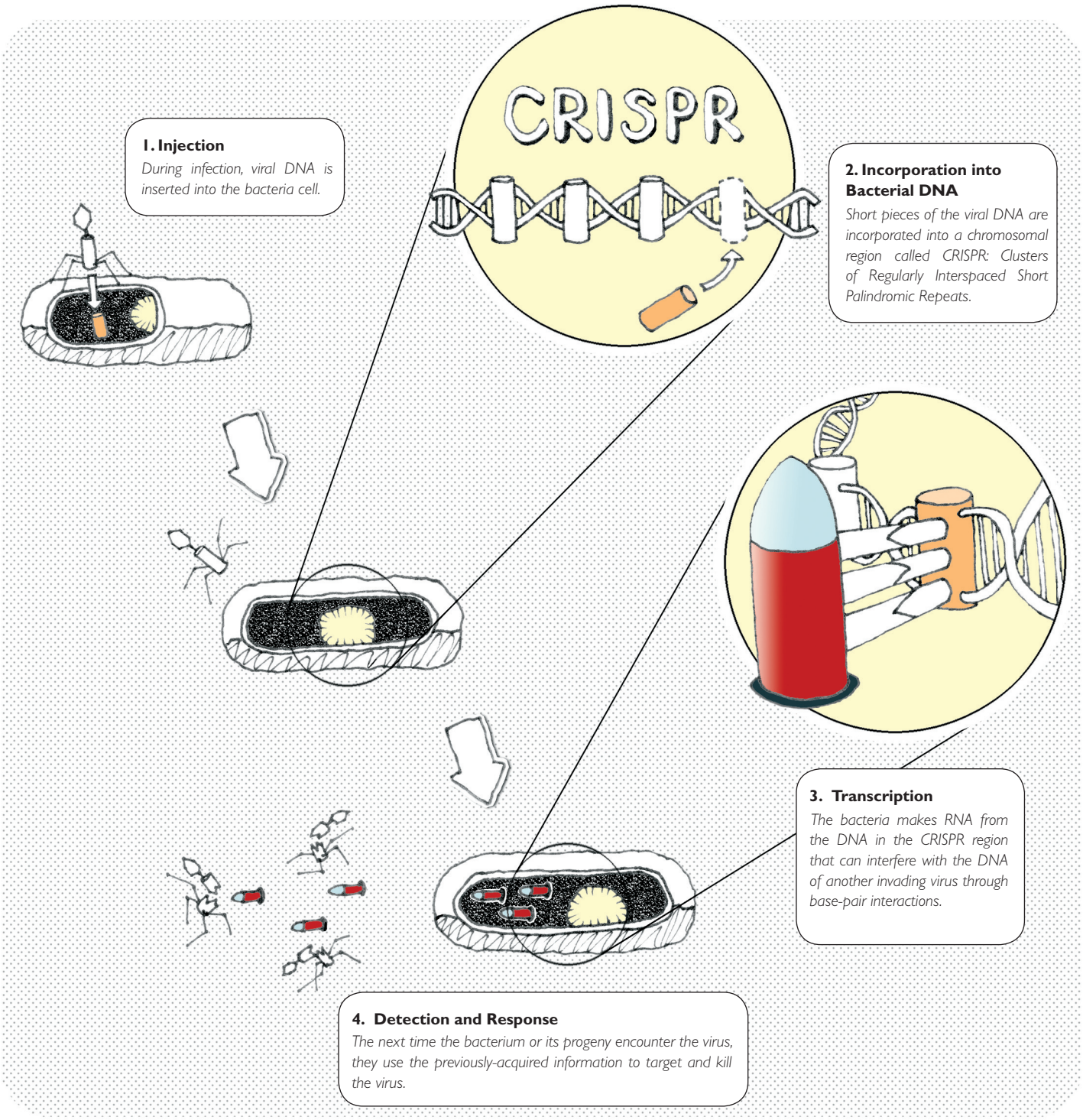


Illustration by Tony Le

Battle Of the Bugs

The evolution of bacterial immunity

It is war. Every two weeks, half of the population is destroyed. The survivors adapt to outsmart the enemy, but the enemy quickly evolves its strategy and will continue to kill. This is the largest arms race on the planet: the epic battle between bacteria and the viruses that infect them. Scientists have long known that bacteria can be infected by viruses called bacteriophage (from the Greek for "bacteria-eaters"). There can be no quarter in the conflict between these foes, as the phage cannot reproduce without infecting the bacteria, while the bacteria will not survive to propagate if the phage infection is successful. "It really is a tug-of-war," explains Blake Wiedeheft, a postdoctoral fellow in Jennifer Doudna's laboratory in the Department of Molecular and Cellular Biology. "That's what evolution is. The bug responds and then the virus responds in kind, as a consequence of that selective pressure."

Scientists had believed that bacteria evade viral pathogens primarily by systematically eliminating any foreign DNA that they find inside of themselves, which is often injected by viruses. Recent findings over the past four years, however, suggest that bacteria are capable of much more complex ap-

proaches to warding off viral invaders. "What we're beginning to realize," says Wiedenheft, "is that bacteria have an immune system that adapts to viruses. It will recognize those viruses, and it will be prepared to defend itself against them." This notion of adaptive immunity is conceptually very similar to the way the human immune system works. Once we've been exposed to a particular pathogen, either by a vaccination or by prior infection, we are much less likely to be infected a second time. Our bodies remember the infectious agents that have previously been encountered and maintain an arsenal of countermeasures against them, like antibodies, proteins that bind to these invaders and target them for destruction.

Despite this similarity to human adaptive immunity, the newly discovered bacterial immune system has a completely different mechanism. It is based on nucleic acids and is centered around a region of the bacterial chromosome that goes by the descriptive acronym CRISPR: Clusters of Regularly Interspaced Short Palindromic Repeats. These repetitive sequences were noticed in the DNA of many bacteria when their genomes began to be sequenced twenty years ago, but nobody was sure of their purpose. It was only four years ago that researchers recognized with excitement that the "spacer" sequences in between the repetitive elements actually match sequences from the genomes of viruses that infect the bacteria.

It appears that when bacteria recognize the DNA of an invading virus, they cut it up and incorporate a short piece of the virus' genetic material into their CRISPR region between the repetitive sequences. Exactly how this leads to immunity is still a subject of active research. Recent reports suggest some similarity to the mechanism of RNA interference (RNAi) in higher organisms. It seems that bacteria make RNA from the DNA of the CRISPR region, which is then diced into small pieces that are hypothesized to interfere with either the DNA genome or the messenger RNA of an invading virus through the same sort of base-pairing interactions that stitch together the double helix of DNA. While the mechanism of CRISPR-based immunity still remains hazy, what is clear is that the next time the bacterium encounters that virus, "it uses the information it just acquired from the parasite to target that parasite to kill it," explains Wiedenheft. Essentially, it's a flu shot for bacteria.

The realization that microorganisms show such sophistication in their defense against viral parasites has sparked significant scientific interest, and multiple laboratories at Cal have begun to explore the CRISPR-based immune system. Jennifer Doudna's lab is trying to sort out the mechanisms of the CRISPR immune system by deducing the structure and function of its constituent proteins. Her lab has recently determined the three dimensional structure of the only protein common to all eight versions of the immune system discovered in different species of bacteria. This protein has the ability to degrade DNA in a test tube, supporting the group's hypothesis that it is involved in early stages of CRISPR based immunity, such as viral DNA recognition and processing into the CRISPR region. Studying this mechanism sheds light on the tactics employed by bacteria in their ongoing battle with viruses, but understanding the full extent of the war requires studying the entire microscopic ecosystem in action.

Jill Banfield's lab, in the Departments of Earth and Planetary Science and Environmental Science Policy and Management, is addressing this question by studying the interdependent population dynamics between bacteria and viruses in the environment. Christine Sun, a graduate student in the Banfield lab, explains their interest in a particular model ecosystem known as "acid mine drainage," the result of erosion from metal or coal mines. "It's a really acid rich environment, where the pH can go down below 1, and so very few organisms can thrive in these areas." Because this niche ecosystem is so inhospitable, the lab can sequence samples of DNA from the environment, determine exactly which microorganisms were present, and even reconstruct complete genomes for many of them. "Over the years Jill has characterized the microbial community," says Sun, "and now we're looking at how viruses and microbes co-evolve."

The Banfield lab is excited about the CRISPR system because it provides a "historical" genetic record of which viruses have infected which bacteria. This information is enabling microbial ecologists to study the interplay between these populations in their native environment, eliminating the need for cultured samples in the laboratory. By sequencing samples taken from the ecosystem at different times, the group's research has uncovered that both the viruses and bacteria have been evolving at an incredibly rapid rate. Once bacteria have targeted a viral sequence in their CRISPR region, the selective pressure to survive drives the viruses to change the sequences of their genome to avoid destruction by the bacterial immune system. Thus, the CRISPR system is actively influencing the diversity of the microbial population and driving the evolution of the ecosystem.

How could the revelation that bacteria use adaptive immune systems to ward off viral pathogens impact higher organisms, like people? "We're studying this CRISPR-virus interaction in acid mine drainage, but it could be applied to any system in which you have microbial communities," says Sun. Bacterial communities involved in commercial processes such as yogurt production and biofuel generation are of particular interest. "That's going to require that they're grown in high density and confined situations," says Wiedenheft. "And what happens in those situations, just like in human populations, is that a virus can really spread and wipe out an entire population. It can shut down your whole operation. If we can immunize bacteria against the viruses that infect those bugs that we're exploiting, then that has obvious economic consequence and benefit." Thus, as we gather new intelligence about the CRISPR immune system, humans stand to become beneficiaries in the ongoing war between bacteria and phage.

Katie Berry *is a graduate student in chemistry.*

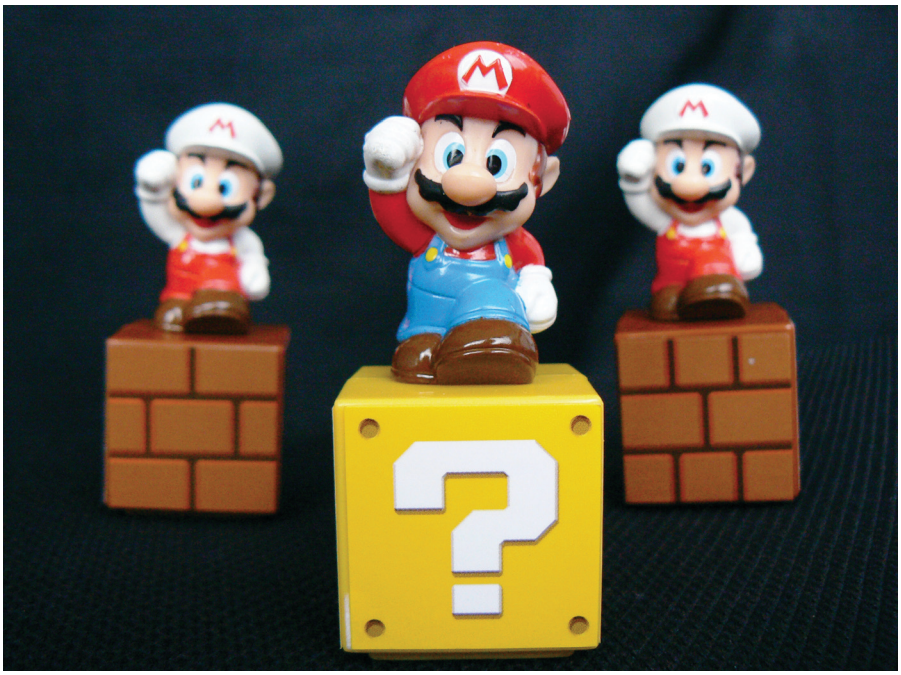
Train Your Brain

How video games can be good for you

We largely accept that we can manipulate our bodies by changing our exercise and eating routines—but what about our brains? Because the brain is traditionally viewed as the locus of our true "self," too often we treat it as immutable. But just as our bodies grow and change, so do our brains. Mounting evidence from the field of neuroscience suggests that our environment molds our brains, and that we can exploit this plasticity through directed training, perhaps even to increase our intelligence.

"Intelligence is perceived as a unitary phenomenon, but a lot of this can be attributed to culture," says Mark Kishiyama, a postdoctoral fellow in Professor Robert Knight's lab in the Helen Wills Neuroscience Institute. "Americans tend to attribute intelligence to something innate, whereas Asian cultures perceive it more as discipline and hard work."

Kishiyama and others in the field of cognitive neuroscience are challenging this view of intelligence as a unitary, innate phenomenon with evidence that IQ, and other metrics of general "intelligence," actually measure the output of many discrete brain functions which can be improved with training. Ongoing studies in Assistant Professor of Psychology Silvia Bunge's lab have recently marshaled support that this is, indeed, the case. "We did a training study to see if we could train up reasoning ability in kids," Bunge explains. "After only 6 weeks, the training led to an improvement in IQ of, on average, 11 IQ points and as high as 20 points." Ten to twenty IQ points is considerable when you consider that the average person has an IQ of 100, and an IQ of 136 puts you in the 98th percentile, approaching genius status.



While all those hours you spent mastering Super Mario probably won't boost your SAT score, other video games may help improve IQ scores by honing discrete brain functions.

Image courtesy of Oscar Mota

The unpublished study used two types of training on kids in an Oakland Elementary school. One group played reasoning games such as Towers, a game in which players must strategically plan several moves ahead to transfer rings from one post to another. The other group played games intended to increase processing speed, like Blink, a card game based on matching shapes and colors as quickly as possible. The games themselves were not exceptional: Blink and Towers are both commercially available. But the results were intriguing. "Keep in mind it's a fairly small group of kids so far, and we're going to run the study again this semester," Bunge cautioned. "But there was a double dissociation between the two groups. The cognitive speed group got better on tasks that required them to think quickly. And the reasoning group got better at tasks that required them to plan."

Playing games with UC Berkeley graduate students twice a week might be sufficient in and of itself to improve IQ across the board, but the targeted improvements in Bunge's study suggest that training can actually boost specific aspects of IQ test performance. Bunge explains that because IQ measures the combined contributions of many interconnected cognitive functions, improving specific skills can lead to an overall increase in IQ. "We think of both reasoning and processing speed as being really important components that subserve cognition," Bunge says. "Your mind has to be quick enough to be able to think through problems, otherwise you're going to lose the thread and you won't be able to, for instance, do a mathematical calculation. So, processing speed is really important. And on the other side, being able to plan out, strategize and tackle a novel problem, as in the reasoning, is also important."

Bunge's study highlights the significance of growing up in a cognitively enriched environment, where children play games and interact with adults, for performance on tests that measure intelligence. Unfortunately for less privileged children, other research suggests that the converse is also true: Kishiyama and Professor Knight published a study earlier this year which suggests that kids from lower socioeconomic backgrounds have reduced function in a region of the brain associated with higher-order cognition.

Using electroencephalography, or EEG, measurements, the researchers recorded electrical activity in the prefrontal cortex. Responses to visual stimuli were found to differ between kids from low versus high socioeconomic status (SES) in ways that suggest differences in attention, one established function of this brain region. Kishiyama observed that the reduced responses in low SES children were similar to those seen in some stroke patients, but was quick to point out, "That's where the similarity is, but that's where the similarity ends. Stroke patients will have a certain amount of recovery because the brain is plastic, but they're not going to get complete recovery. The thing with these kids is that because there is no structural brain damage, just a functional disruption, it's something that can be reversed. That's

what argues for the next step in terms of intervention."

Both Bunge's and Kishiyama's studies are preliminary, with limited sample sizes that temper the strength of their conclusions. What these studies truly represent is a jumping-off point: they offer a set of testable hypotheses about problems with large social implications. And indeed, powers beyond the confines of the scientific community are already taking those implications seriously. Bunge and Knight are involved in the Law and Neuroscience Project, an initiative funded by the MacArthur Foundation that was created to address the issues of criminal responsibility in light of modern understanding of the human brain. "There are all kinds of things that we're thinking about in terms of frontal lobe immaturity potentially being a mitigating factor for sentencing," says Bunge. Research with adolescent brains, for instance, suggests that prefrontal cortex, and thus some higher cognition, is still developing into the early 20's. Why then, Bunge wonders, are children under the age of 18 locked away for life, especially given that brain function is trainable? Bunge says she is hopeful that her work and that of her colleagues will help bring reform to the legal system. "The judges that I have been speaking to find it heartening to know that there's at least some evidence that your brain function can change."

Katie Hart *is a graduate student in chemistry.*

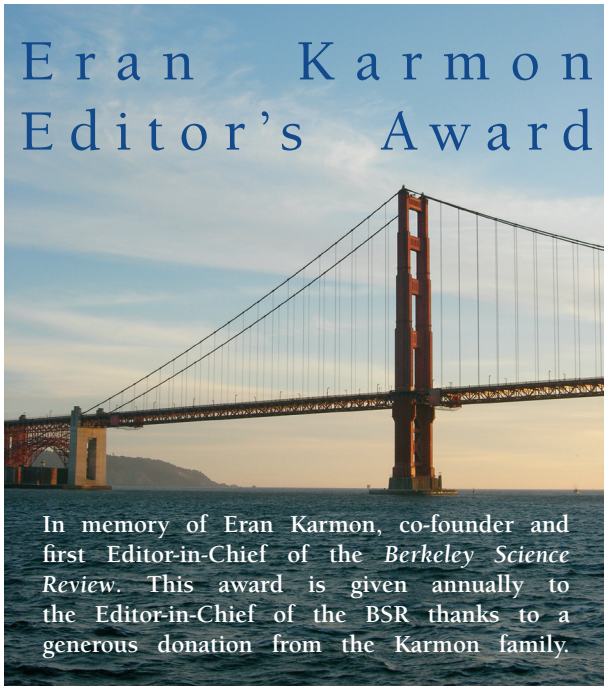
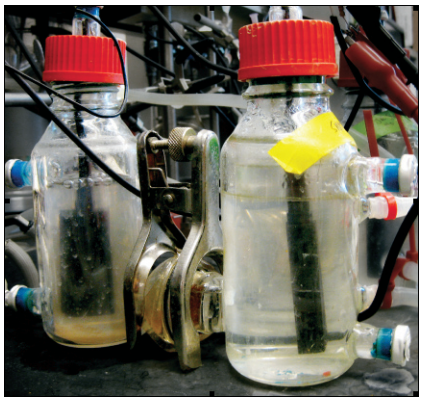


Image courtesy of **********

Poo Power

Harnessing the energy of waste

Like spinning straw into gold, microbial fuel cells (MFCs) can create electricity from seemingly useless organic wastes like sewage or farm runoff. Poo-power may sound like the answer to our current energy crisis, especially given that the wastewaters that fuel them are abundant and essentially free, but these devices aren't efficient enough to suit most energy needs. In MFCs, bacteria act as living catalysts to drive energy production, but despite this, most efforts toward improving the efficiency of MFCs have not focused on the biological details of the waste to wattage conversion. A recent report from Dr. John Coates' group in the Department of Plant and Microbial Biology, however, demonstrates that focusing on the bacteria that power MFCs can not only bring to light the biological mechanisms behind MFC energy production but can also lead to the discovery and isolation of bacteria that are especially proficient at energy production.



A microbial fuel cell. Electrons flow between the anode chamber (right side), where bacteria grow, to the cathode chamaber (left side).

Fuel cells are devices that convert chemical energy into electrical energy. In a conventional hydrogen fuel cell, a negatively charged electrode, the anode, is the site of a chemical reaction that splits hydrogen into hydrogen ions and electrons. The released electrons flow through an external circuit that lies between the anode and the positively charged electrode, the cathode, creating an electric current. In MFCs, on the other hand, bacterial metabolism acts as the electron source: bacteria release electrons from organic food sources and transfer them externally to the anode of the fuel cell, thereby creating the electric flow.

All organisms must get rid of the electrons generated by metabolism, but not every organism does it the same way. "We breathe in air and oxygen is our electron acceptor. These bacteria breathe iron and it is their electron acceptor," says Dr. Coates.

Iron-breathing bacteria may sound exotic but you would probably find some of these microbes in soil from your own back yard, as did Dr. Coates' son for a science fair project. The bacteria in MFCs often come from a sewage treatment "sludge" so most MFCs are powered by a complicated mix of unidentified bacterial species. "We wanted to make [the bacterial community] as simple as possible so we'd have the best chance of isolating those key players responsible for the electron transfer on the electrode," says Kelly Wrighton, a graduate student in the Coates lab and lead author in this study.

To cultivate a simplified community, Wrighton and co-workers set up a restrictive growing environment within their MFCs. First, they maintained their fuel cells at 130oF, a higher temperature than most, which favored thermophilic (heat-loving) life while preventing the growth of bacteria that prefer more moderate temperatures. Second, they established an oxygen-free environment within the MFC to select for microbes capable of 'iron-breathing' respiration. Finally, a non-fermentable carbon source facilitated external electron transfer to the anode by the microbes. After 100 days of monitoring the current produced by the MFCs, Wrighton and co-workers removed the anode to see who was growing on its surface.

With the help of recent innovations in DNA-based 'fingerprinting' of bacteria, they found the reactors that produced electricity contained a different collection of bacteria

than the control reactors that did not. Overall, the absolute numbers of bacteria cells in current-producing systems had decreased as compared to the more dense starting culture; however, certain members of the starting community had actually grown in number--and their identities were surprising.

The cellular proteins we know to be capable of transporting electrons are found in cell membranes. Before this study, all bacteria known to be capable of external electron donation belonged to a single major branch of bacteria that have an outer membrane surrounding their cell wall that plays an integral role in electron transfer. Surprisingly, many of the bacteria enriched in the thermophilic MFCs were from the branch of the family tree that lacks an outer membrane. Exactly how these bacteria are transferring electrons to the anode without an outer membrane is somewhat of a mystery. Wrighton speculates that perhaps these bacteria have a conductive cell wall or their electron transporting proteins might be attached to the cell wall via some molecular tether.

Wrighton and co-workers next set out to isolate a single member of the bacterial community growing on the anode so they could learn more about the biological processes governing external electron transfer. From a scraping of the anode, they developed a pure culture of a strain of Thermincola bacteria they dubbed "JR." Strain JR produced more current than any organism previously studied in traditional MFCs. A Thermincola genome project is underway that will allow Wrighton and co-workers to look for clues as to which genes make external electron transfer possible. Once determined, the molecular details of the cell-to-anode electron transfer could guide improvements in the design of anode materials that are better suited for MFCs.

Strain JR is the first member of its phylum we know to be capable of directly transferring electrons to an anode. Given that strain JR is so proficient at converting organic materials into electricity, this certainly suggests that there may be a number of other bacteria not only capable of this electrical alchemy, but perhaps even more adept.

Susan Young *is a graduate student in molecular and cell biology.*

Science Reaches Out

Cultivating a stem cell dialog

A 2008 poll by the Pew Research Center for the People and the Press found that although 77% of respondents believed in climate change, only 47% acknowledged that it is the result of human activity. People who don't believe humans are the source of global warming are unlikely to change their behavior or support policies and politicians that aim to counteract this threat. Regarding this and many other issues, a lack of understanding in science could potentially hinder progress. So how do we promote understanding and bridge the gap between science and society? There are a number of people and organizations in the Berkeley community that seek to address this problem.

One approach is to better educate scientists in the policy process and to teach them to communicate effectively with non-scientists. The Science, Technology, and Engineering Policy Group (STEP) is a student-run organization that brings together students from various backgrounds to discuss a wide range of science and technology issues. Unlike more traditional disciplines such as molecular biology or law, there is no firmly established path to a career in science policy. STEP president Jaime Yassif explains, "Berkeley is a world-class science research institution and has very strong departments in law, business and public policy, but we need to work harder to build connections across department lines. STEP is working to do this while helping students educate themselves in the process."

Members participate in a journal club where articles written by scientists and policy experts are presented and discussed. Experts are also invited to give talks, which allows students to simultaneously learn about science policy and make connections in the field. The flagship program is the annual white paper competition, in which students

identify a technology or science policy issue, analyze that problem, and propose a solution. Participants develop communication skills not commonly practiced in academic science and learn how to approach a technical problem from a different vantage point. Topics in 2008 included privacy issues in personal genomics, constraints on pharmaceutical research, and utilization of alternate energy sources. For students who plan to pursue a career in science, these skills will hopefully prove useful in communicating effectively with the public and in considering broader issues when conducting research. "I think STEP is important because we need people with an interdisciplinary skill set," explains Yassif, "individuals who are trained in science and engineering but who also understand the policy-making process. We need people who can use their technical skills to analyze policy challenges and help develop solutions".

Government officials decide most policy issues, but sometimes the public becomes directly involved. In 2004, California voted by 61% to approve ballot initiative Proposition 71. This allocated $3 billion to stem cell research, primarily on human embryonic stem cells. Yet there are wide misconceptions about stem cell research. A pilot survey by the Stem Cell Initiative at Berkeley found that about 20% of surveyed people incorrectly thought umbilical cord blood was a source of embryonic stem cells. This belief has been used as a justification that cord blood, not human embryos, should be used as a source of stem cells. Cord blood, however, is a source of a more mature cell type that does not afford the same therapeutic potential as embryonic stem cells. Equally concerning is a misapprehension that stem cells will help cure a variety of diseases overnight. The first, and only current, clinical trial of a human embryonic stem cell therapy was just approved on January 23, 2009, and many more years will likely pass before any such therapies become available to the public. To ensure continued support for bills like Proposition 71, it is critical to communicate the pace of science and to instill realistic expectations that can be met by researchers.

The recent deliberations over the stem cell bill in California illustrate an important question at the intersection of science and society: Should the general public have a good understanding of stem cell research when they are being asked to make decisions about stem cell policy? Laurel Barchas, a former undergraduate and current laboratory technician at UC Berkeley, believes that public understanding is critical. Together with Professors Charis Thompson and Irina Conboy from the Gender and Women's Studies and Bioengineering Departments, respectively, Barchas received a $25,000 grant from the Edmond D. Rothschild Foundation to establish the Stem Cell Science and Values Education Initiative. This includes an outreach program for middle and high school students, the Stem Cell Education Outreach Program, which has conducted presentations to over 1000 students in the Bay Area. The goal is educate people who will soon be voters and help them understand the science and policy of stem cell research, as well as possibly spark and interest in science. An important component of the program is to acknowledge the ethical debate concerning human embryonic research. As Laurel explains, "The point of these presentations is to give the students information on this very interesting and complex topic and let them choose for themselves. We try for an unbiased approach and to tell the whole spectrum." She is currently trying to expand the program statewide.

Another important aspect of the interface between science and society is how well the scientific community understands the public's interests. Kelly Rafferty is a doctoral candidate in Performance Studies and also a predoctoral fellow with the Berkeley Stem Cell Center. In her studies, she draws on information from multiple fields, such as performance art, political discourse, and scientific research, as well as the ideas of other scholars to develop theories on how society and science influence each other. Rafferty describes her work as examining "what it means to have a body." Modern technology allows people to dramatically alter their bodies in a variety of ways, from organ transplantation and prosthetic limbs to cosmetic surgery. Part of Rafferty's work is examining how these medical technologies change the way we define the human body and how society responds, particularly through art. She is also interested in how society drives scientific work. She asks, "How do our fears of difference or our deep adherence to certain cultural ideals determine which things get researched or which 'conditions' get treated?" For example, deaf children can receive cochlear implants to restore hearing, but this procedure is extremely controversial within the Deaf community. As Rafferty explains, "Some Deaf people would argue that Deafness is not a disability, but its own valuable culture and should not be eliminated."

Politicians, scientists, and the public are inextricably intertwined. The public votes for government officials and those officials act based on the ideals of their constituents. From debates about global warming and privacy concerns in personal genomics to discussions about stem cells, many modern issues have strong scientific and technological components. How much government officials and the public know about the underlying science, as well as the effectiveness of the scientific community's communication with both groups can have large ramifications on legislation and policy. Programs like STEP and the Stem Cell Education Outreach Program, as well as the individual efforts of scholars like Kelly Rafferty, are facilitating that much-needed discourse.

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

Photosynthesis

by Tracy Powell

Image courtesy of ViVien Muller

You've seen them: matte black, arrayed in regiments, and mushrooming up on what seems like every available outdoor Bay Area surface. From rooftops to traffic signals, solar panels have colonized the landscape—visible symptoms of inexorably rising energy prices and atmospheric CO2.

As this profusion of panels attests, solar energy is booming. Over the past 15 years, demand for solar energy has grown by 30% per year; in 2008 alone, nearly six gigawatts of solar energy-generating capacity were installed worldwide, more than doubling the previous year's installations. Unsurprisingly, as the market for solar energy has expanded, scientists and engineers have intensified their efforts to develop better, more efficient photovoltaic (PV) materials that can convert solar radiation to usable electricity.

To date, the ubiquitous, silicon-based arrays have been the industry standard in solar technology. However, many of these commercial PV materials are bulky, inflexible, and—their cardinal sin—expensive to produce. Better, less costly technologies are needed for solar power to compete with traditional, pollution-generating energy sources.

In pursuit of this goal, some researchers are seeking inspiration from the cheapest, greenest solar-power systems around: plants.

Lean, mean, green machines

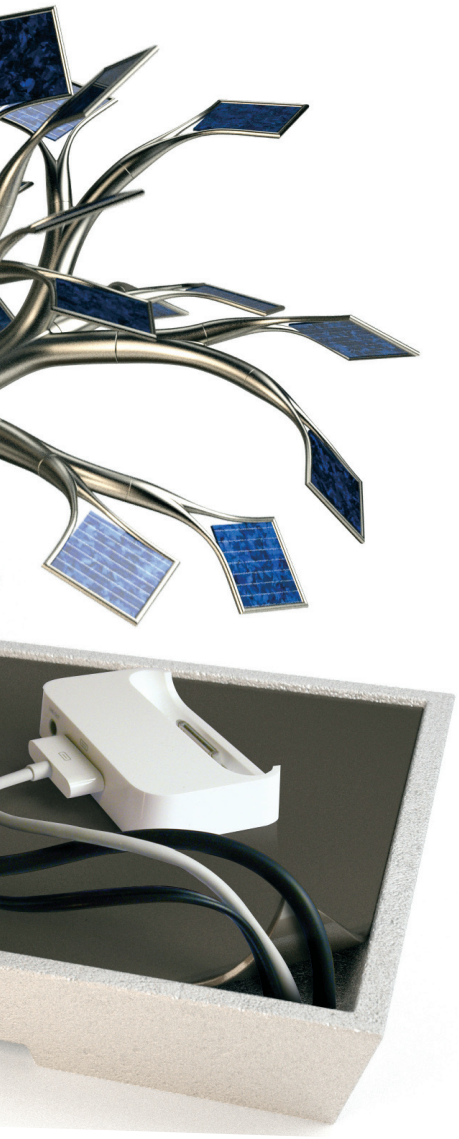
Plants have long been central to alternative energy schemes, the push to fill the nation's gas tanks with plant-derived ethanol being a recent example. However, plants' energy significance goes beyond pumping out carbon compounds to be refined into liquid biofuel. Honed by millions of years of evolution, photosynthesis (the process by which plants use solar energy to transform water and carbon dioxide into oxygen and sugars) is a model system for the efficient capture and use of renewable energy. In particular, the efficiency, durability, and flexibility of photosynthetic light-harvesting systems have attracted increasing attention from solar energy researchers.

A leaf may not look a whole lot like a solar panel, but the functional parallels between photovoltaic devices and the early, light-harvesting steps of photosynthesis are profound. Both processes begin with sunlight spilling into the atmosphere. That light, made up of a mixture of different wavelengths, shines onto a reactive surface—a leaf on a houseplant, say, or one of the PV panels encrusting the MLK Student Union.

Upon striking the reactive surface, a few units of solar energy (called photons), carried by light of just the right wavelength, are absorbed. This absorbed energy jolts loose an electron from the reactive surface, and the electron is then harnessed to do work. In a solar cell, it is diverted into a current of similarly liberated electrons, funneled through wires, and eventually used to power all manner of indispensable gadgets that blink and go beep. In photosynthesis, the loose electron instead interacts with a series of biological molecules, eventually driving the chemical synthesis of sugar. Plants and solar energy scientists therefore face a similar task: efficiently transforming light energy into a flow of electrons that can be harnessed to power downstream processes.

At first glance, Mother Nature is no match for the engineers. Commercial silicon PV panels typically convert around 15% of available photons into usable electricity (a statistic called "photon conversion efficiency"); next-generation silicon technologies can exceed 40%. How do plants measure up, those photosynthetic paragons and evolutionary pinnacles of light-harvesting prowess? It is difficult to pin down a parallel estimate, but research generally suggests that photosynthesis converts at most 1-10% of available photons into electrons—and this efficiency decreases dramatically under intense

Illuminating alternatives for solar energy research



light or adverse environmental conditions. However, on closer analysis, plants' lackluster overall efficiency conceals some very real advantages.

Converting photons into electrons is a multi-step process, the first stage of which is to absorb as many photons as possible from sunlight. Plants are confined to absorbing light from the red and blue portions of the spectrum, while photovoltaic materials absorb energy from a wider range of visible wavelengths. (This is why plants look green, while solar cells appear black.) PV materials can therefore reap a bumper crop of photons from each unit of available sunlight, while plants trap a much smaller fraction of available energy. This difference accounts for much of plants' photon conversion inefficiency.

Once photons have been trapped, the absorbed energy must travel to sites where electrons are actually generated and exported. In these later steps of energy conversion, plants can actually outperform solar cells, transporting absorbed energy with near-perfect efficiency. Scientists are therefore probing photosynthetic mechanisms of energy transport, with the goal of using their discoveries to improve the overall efficiency of photovoltaic materials.

In addition to their energy transport efficiency, plants also excel at doing their job on the cheap. They are made out of water, carbon, and a few minerals—all inexpensive, plentiful materials—and they essentially assemble themselves. In contrast, commercial solar panels are constructed of exquisitely pure silicon crystals, whose manufacture is both energy-intensive and expensive. The thin sheets of silicon on which PVs are produced currently cost around $250 per square foot. At that price, manufacturers are happy to incorporate silicon slivers into consumer electronics; tiling the nation's roofs with the stuff, however, is less feasible. To make solar power competitive, it is widely believed that the retail price of photovoltaic units must drop by 70%.

Many next-generation PV technologies are therefore aimed at reducing manufacturing costs. These advances range from developing cheaper ways to manipulate silicon to replacing it with other inorganic compounds, such as copper or even iron pyrite (fool's gold). Other strategies include using organic dyes, exploring the PV properties of novel nanomaterials, or replacing inorganic solar materials with organic compounds. (Here, organic refers not to your local farmer's market, but to materials made mostly of carbon and hydrogen atoms.)

Though these new PV materials may succeed in dropping manufacturing costs, they have so far been less efficient at converting photons into electrons than traditional, silicon-based devices—organic solar cell researchers, for example, recently trumpeted an all-time efficiency high of just over 6%. Such reduced efficiency might be an acceptable tradeoff for a significantly cheaper technology, so long as the overall cost of generating electricity was lower. Unfortunately, organic and other next-generation PV materials suffer from other problems which have prevented them from realizing their cost-saving potential.

Foremost among their faults, novel PV materials are not durable. Customers would likely object to the hassle of replacing their PV panels (even cheap ones!) on a daily or monthly basis, and continual replacement fees offset any savings gained from using inexpensive materials. Researchers must therefore find ways to extend the lifetime of these novel PV materials. Additionally, even the most promising solar technologies will require innovations in large-scale manufacturing techniques in order to minimize production and assembly costs.

It is here, in the design and assembly of cutting-edge solar cells, that understanding the biology of photosynthesis becomes relevant. How do biological systems use free, nonpolluting ingredients to produce effective photochemical devices? How do they assemble complex light-harvesting systems under everyday conditions, without elaborate manufacturing techniques? How do they maintain and repair these systems for indefinite periods of time? Researchers are seeking to answer these questions, and hope to one day apply lessons learned from Nature to the rational design of solar energy tools.

Some (self-)assembly required

Cost of manufacture is a major hurdle to commercializing any photovoltaic technology. It's generally safe to assume that if a manufacturing process demands 99.999999999% pure reagents, ultra-high vacuum chambers, and temperatures of 1500° Celsius, it's probably not cost-effective (these, incidentally, are some of the traditional requirements for making silicon wafers). On the other hand, if a PV material can put itself together in a simple, water-based buffer, even die-hard penny-pinchers are likely to give it a big thumbs-up. Such is the logic behind Rebekah Miller's research, which investigates how to exploit the self-assembling properties of biological mol-

ecules to build inexpensive light-harvesting structures.

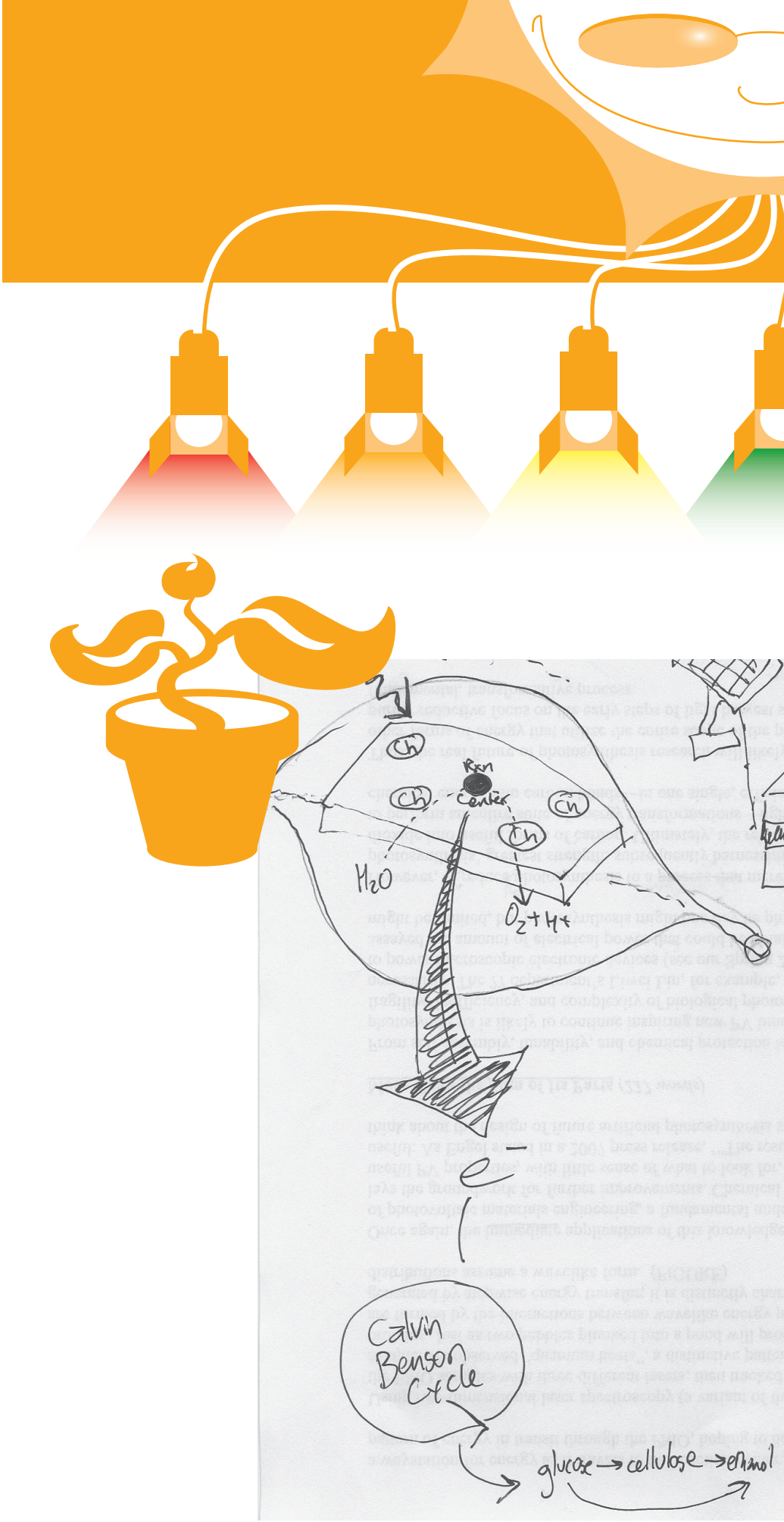
As a doctoral student in Matthew Francis's lab in the Department of Chemistry (she recently graduated and is now at MIT), Miller began her research with tobacco mosaic virus coat protein (TMVP), a simple biological unit that can aggregate into organized structures. Using basic, benchtop reactions, she chemically attached light-absorbing dye molecules to each protein. Once placed in the proper solutions, these modified TMVP proteins assembled themselves into either disks or long, rodlike filaments studded with dye molecules (FIGURE). Because the protein scaffolds fix the dye molecules in close proximity to one another, light energy absorbed by one molecule can easily transfer to a neighbor, allowing the structures to function as light-harvesting, energy-transmitting antennae. Miller's biological self-assembly process had generated functional photovoltaic components.

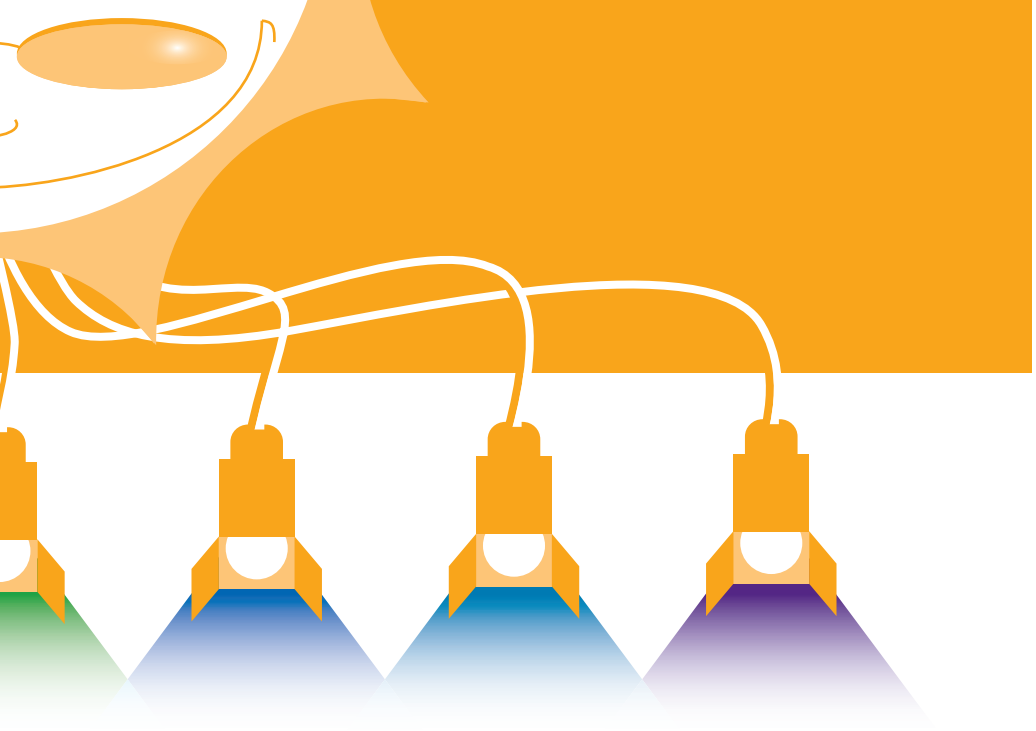
Miller also showed that combining the dyes in different ratios or changing the combination of dyes used could improve energy transfer efficiency. These results were especially encouraging because they suggested that in addition to successfully harvesting and transmitting light energy, the protein assemblies might offer another benefit associated with biological systems: tunability.

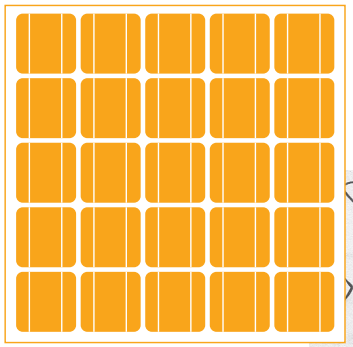
Collectively, plants, algae, and photosynthetic bacteria have evolved a broad repertoire of light-absorbing pigments, including multiple forms of chlorophyll and a large family of molecules called carotenoids. Each pigment absorbs a unique combination of wavelengths, and by combining multiple pigments, an organism can "tune" its ability to absorb light from a preferred range of the spectrum.

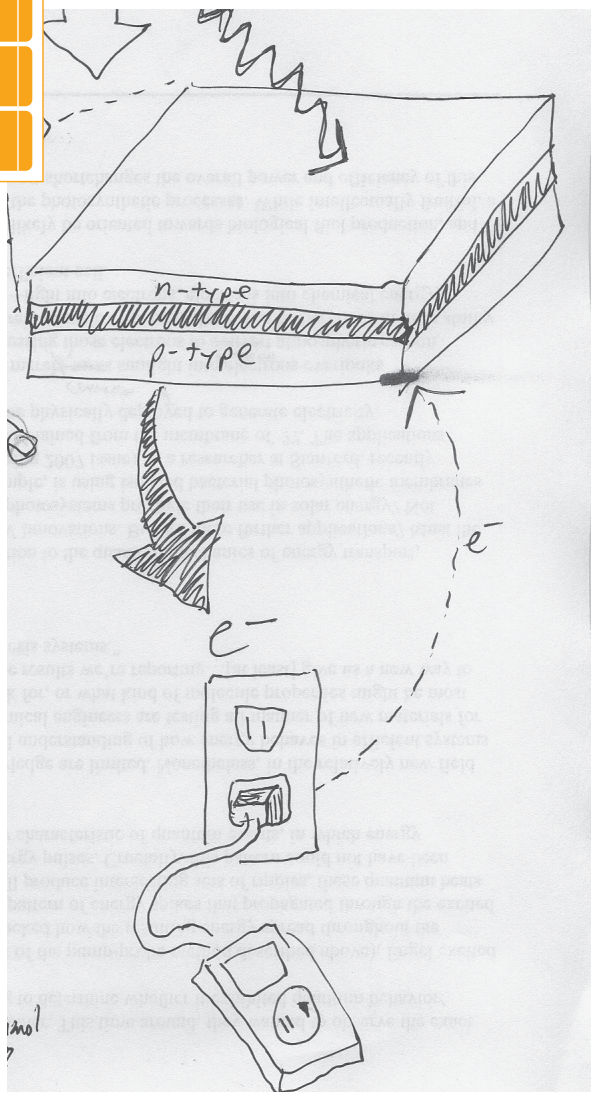
Seaweed is a classic example. Millennia of evolution have endowed shallow-water species with green pigments that absorb the red and blue wavelengths abundant in light-rich, surface waters. The red and purple pigments of deep-water species, however, have evolved to absorb the meager, blue-green wavelengths that penetrate the depths. Each species' pigment content has been optimized to absorb wavelengths of light available in their environment. Similarly, to cope with changing light quality on a shorter timescale, many plants can adjust the ratio of different forms of chlorophyll present in their leaves, maximizing efficient light use.

This flexible approach to light absorption appeals to engineers. Just as photosyn-









thetic organisms rely upon a variety of biological pigments, researchers have developed many synthetic pigments, each of which absorbs a unique spectrum of light. By mixing and matching the pigments shackled to her TMVP structures, Miller's assemblies could one day be optimized to expand the range of wavelengths from which they can harvest light, greatly enhancing their flexibility and efficiency.

Currently, researchers in the Francis lab are working to combine TMVP light harvesting antennae with small molecules that can conduct electricity, with the goal of designing functional electronics that operate like biological systems. On a more basic level, studying the behavior of these assemblies could help improve our understanding of how light energy is transmitted on small spatial scales.

However, despite the potential advantages in cost, tunability, and manufacturing simplicity, directly incorporating biological components into photovoltaics would also bring special challenges. Primarily, biological molecules tend to degrade quickly, particularly under high-intensity light. According to Miller, preliminary evidence suggests that the three-dimensional structure of the TMVP scaffold may help to stabilize it, protecting the assembly against light-induced decay. The overall vulnerability of organic PV components has led scientists to search for better mechanisms to protect them—a search which has led to closer examination of how biological systems maintain themselves under challenging environmental conditions.

Do-it-yourself fixer-upper

It doesn't matter whether you're a plant or a PV engineer—if you lavish time, effort, and precious resources on constructing a light-harvesting system, you want it to last. Unfortunately, components in both natural and manufactured photosystems degrade over time. Organic solar cells, for instance, rarely last more than a single day. The chemical reactions that lead to this decay are not always well-understood, but oxidation (the same oxygen-dependent process that rusts your car and browns your apples) is a likely culprit. Simply by isolating it from oxygen, an organic PV's lifespan can be extended from days to weeks.

Similarly, in plants, key photosynthetic proteins can be damaged or destroyed by oxidation within minutes of activity. At noon on a sunny day, for instance, plants are bombarded with high-energy photons. This light

energy is temporarily absorbed by chlorophyll molecules, rendering them chemically volatile until they have passed the energy off to other acceptor molecules. Under low-intensity light, this handoff is rapid: Energy is immediately siphoned away and expended in controlled, downstream chemical reactions. But when light is intense, the plant's photosynthetic machinery can be overwhelmed. A backlog of absorbed energy builds, and excited chlorophylls have nowhere to expel their excess energy. These dangerously reactive chlorophylls can then spawn destructive oxidative reactions that cripple proteins, damage membrane components, and generally wreak havoc in the cell.

Fortunately, plants have evolved an array of clever mechanisms to shield themselves from the oxidative dangers of photosynthesis. To learn more about these protective strategies and whether they might be adapted for solar cell design, engineers are collaborating with biologists to understand fundamental protective mechanisms. Of particular interest is a pigment called zeaxanthin (pronounced zee-uh-ZANTH-un).

Zeaxanthin has long been known to stifle (or "quench") chlorophyll's hazardous chemical reactions under high-intensity light. However, "the exact mechanism for this kind of quenching was not well-studied," explains Tae Ahn, a postdoctoral fellow in Professor Graham Fleming's chemistry laboratory. Frustrated by the fragility of organic photovoltaics in his graduate research, Ahn became interested in zeaxanthin as a potential model for protective energy quenching in next-generation PV materials.

To better understand how zeaxanthin protects the plant, Ahn first wanted to identify exactly where its quenching activity occurs. This was no trivial task. Textbook diagrams may reduce photosynthesis to a parade of comfortably spaced cartoon blobs, but in reality this process transpires in dense, dynamic rafts of proteins, swaddled in membrane and cloistered in the deepest recesses of the chloroplast. Zeaxanthin could be interacting with any of hundreds of these molecules. Furthermore, its quenching reaction lasts mere trillionths of a second. Pinpointing the exact site of this ephemeral process required some serious sleuthing.

To narrow the hunt, Ahn collaborated with Roberto Bassi, a biochemist at the University of Verona, Italy, who had purified several photosynthetic proteins suspected of interacting with zeaxanthin. (This in vitro approach removed much of the biological bric-a-brac that obscures quenching behavior in the plant cell itself.) Ahn then used a technique called ultrafast pump-probe spectroscopy to identify which of the purified protein candidates facilitate zeaxanthin's protective quenching. In keeping with its impressive name, this method offers the ultimate in laser-light machismo: fast, powerful, exquisitely controlled lasers bombard a sample with light. An initial "pump" pulse of laser light triggers a chemical reaction in the sample—in this case, exciting a chlorophyll molecule bound to a sample protein. Subsequent laser pulses (the "probes") are delivered a few trillionths of a second later, and allow researchers to collect information about how the sample has changed as a result of the initial pump stimulus. Because data can be collected over minute increments of time and space, researchers can actually track physical and chemical reactions as they occur. Ahn's spectroscopy experiments therefore allowed him to watch photosynthetic proteins absorb light energy, then measure whether or not zeaxanthin could stabilize the excited chlorophylls in a quenching reaction.

Using this method, Ahn first narrowed down which of several protein clusters participated in quenching. He showed that the major light-harvesting antenna (one important complex of photosynthetic proteins) did not undergo quenching after laser excitation and the proteins that comprise this complex did not participate in zeaxanthin's protective efforts. However, after an initial zap with the laser, three proteins from a second cluster, called the minor light-harvesting antenna, did facilitate quenching. From a daunting lineup of potential candidates, Ahn had identified three proteins responsible for quenching: CP26, CP29, and CP43.

Working from this preliminary identification, Ahn collaborated with Tom Avenson, then a postdoc in Krishna Niyogi's lab in the Department of Plant and Microbial Biology, to further pinpoint the mechanism of quenching. Focusing on CP29 as a case study, Ahn determined that in order for quenching to occur, the protein must be able to bind two chlorophyll molecules immediately adjacent to zeaxanthin. This suggests that, in periods of high-intensity light, physical proximity allows zeaxanthin to donate an electron to this nearby pair of over-excited chlorophylls—a chemical mechanism which could stabilize its chemically volatile neighbors.

When asked about immediate applications of this knowledge to PV design, Ahn acknowledges that practical implementation is a distant prospect. However, he suggests that solar energy researchers might one day mimic plants' protective mechanisms by seeding PV materials with molecules that prevent degradative chemical reactions (like zeaxanthin).

In a more general sense, a better understanding of how photosynthetic energy conversion can be controlled at such small scales could also improve PV design. Fleming, for instance, has likened zeaxanthin's quenching activity to a protective dimmer switch. By clarifying how this molecule regulates the flow of energy through the photosynthetic protein complex, his group hopes to improve scientists' control over the behavior of energy generated by PV devices. Indeed, to better understand energy fluxes in plants, researchers in the Fleming lab have looked beyond purely protective mechanisms and applied their advanced spectroscopic techniques to other important steps of photosynthesis.

A quantum of sol

One question to which Fleming and his collaborators have applied their expertise is understanding what happens to solar energy once it has been absorbed by the plant. Based purely on photon absorption efficiency, plants do a relatively shabby job of harvesting the photons available in sunlight. However, once a photon is absorbed, its energy is transformed into electrons with remarkable efficiency—approximately 97%. By comparison, PV materials typically only achieve 50-90% energy transport efficiency. Understanding how biological systems manage such energy thrift could therefore inspire efficiency breakthroughs in artificial photosynthetic systems.

Plants have evolved a specific architecture to support efficient energy transfer, packing light-absorbing chlorophyll pigments into protein clusters called antennae. Photons of light are absorbed in the antennae, and the resulting energy hopscotches from one chlorophyll molecule to the next until it reaches another protein complex called the reaction center. Here, the energy finally escapes to power downstream chemical processes like making sugars.

To make solar energy conversion as efficient as possible, absorbed energy must seek the shortest, speediest escape route from the antenna to the reaction center. Until recently, researchers usually depicted this escape as you would any normal biochemical phenom-

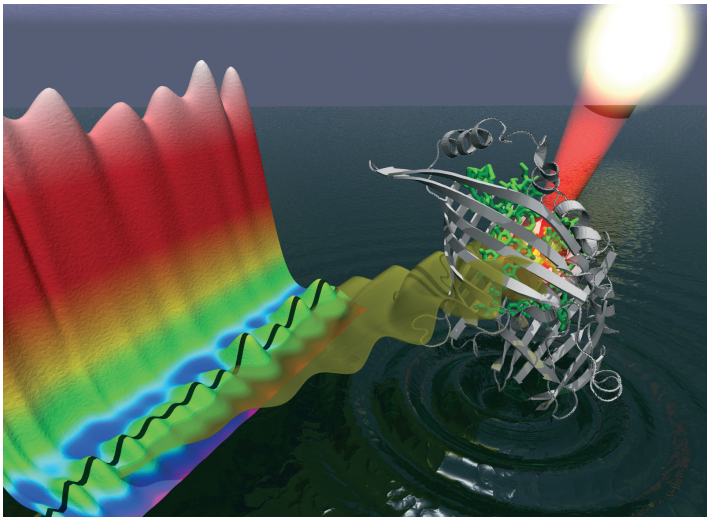


Image courtesy of Tae Ahn

Ultrafast pump probe spectroscopy is used to study photosynthetic, energy transfer reactions in proteins. These reactions that occur on the femtosecond (10^{-15}) timescale.

enon: as a linear, stepwise process. Like a mouse in an unfamiliar maze, they believed the energy of an absorbed photon would make arbitrary "decisions" about which nearby chlorophyll to jump to, arriving at the reaction center only after a series of twists, turns, and backtracking.

However, this assumption never entirely made sense. Photosynthetic energy capture is simply too efficient for energy to aimlessly meander between chlorophylls. In a sequential process like that, energy would leak away at every step. How could such inefficient hopping permit near-perfect energy efficiency?

In a 2007 paper in Nature, Greg Engel, then a Miller Postdoctoral Fellow working with the Fleming laboratory, presented evidence favoring an alternative explanation. What if, instead of the traditional stepwise model, quantum physics could explain photosynthetic energy efficiency?

In the weird, subatomic world of quantum physics, energy doesn't behave as a single, concrete unit—energy doesn't bumble sequentially from one place to the next. Rather, it simultaneously inhabits a variety of locations, its distribution smeared across many probable sites. Only when a particular event, such as a chemical reaction, forces it to attend a defined location does it manifest at that site.

According to this model, excitation energy absorbed by a light-harvesting antenna would spread out to simultaneously occupy all of the intervening chlorophyll molecules en route to the nearest reaction center. Only when chemical events at the reaction center require the energy to be located right there, just then, does this fuzzy distribution snap into a single, linear path—the shortest distance between antenna and reaction center. It is as if the most efficient path is calculated retroactively. Engel sought to discern whether this sort of quantum process permitted the efficiency of photosynthetic energy transfer.

To test whether the quantum model was correct, Engel and his collaborators purified a glob of proteins normally sandwiched between the antenna and the reaction center of photosynthetic Chlorobium tepidum bacteria. The group had previously shown that these proteins act as a biological wire, conducting energy as it travels to the reaction center. This time around, they wanted to stimulate the proteins with light and then observe the exact pattern of energy in transit, hoping to determine whether it exhibited quantum behavior.

Using a variation of the same laser spectroscopic technique used by Ahn, Engel and his colleagues tracked how energy spread throughout the sample. They observed "quantum beats", a distinctive pattern of energy spikes that propagated through the excited proteins. Just as two pebbles plunked into a pond will produce intersecting sets of ripples, these quantum beats are formed by the interactions between wavelike energy pulses of absorbed photons. Crucially, this pattern could not have been generated by stepwise energy transfer; it is distinctly characteristic of quantum events, in which energy distributions assume a wavelike form.

Since these findings were published in 2007, coauthor and Fleming lab graduate student Tessa Calhoun has continued the project. Using the same spectroscopic approach, she has observed quantum energy transfer in the light-harvesting complexes of higher plants, which are significantly more complicated than the simple bacterial clusters used in the initial study.

Such fundamental understanding of how biological systems promote efficient energy transfer lays the groundwork for vast improvements to solar technology. Today, for example, solar cells rely on simple diffusion of charged particles to transport absorbed solar energy to a conductive surface. Future PVs might instead mimic plants' separation of light-harvesting and electron-donating functions—improving performance by efficiently shuttling energy from antenna structures to a synthetic reaction center.

This sort of advance could redefine the very nature of photovoltaic materials. "Traditional photovoltaic materials, such as silicon, tend to be very ordered," explains Engel, now an assistant professor at the University of Chicago. "In contrast, photosynthetic systems are very disordered, with much more elaborate architecture at the molecular level. Using what we're learning about how such biological complexity supports energy transfer, we're now attempting a more sophisticated approach to designing photovoltaics."

Going green (literally)

From self-assembly and protective quenching, to the quantum mechanics of energy transport, photosynthesis is poised to inspire PV innovation in many different ways.

Some researchers embrace photosynthetic processes as an inspiration, but suggest that the fragility and complexity of biological photosystems preclude their direct use in large-scale solar power endeavors. Both Ahn and Engel, for example, embrace photosynthetic processes as inspiration for next-generation photovoltaic design principles.

In contrast, other researchers have sought to exploit biological materials despite their shortcomings. The Francis lab, for instance, continues to build upon Miller's work with TMVP light-harvesting assemblies. In another example, the mechanical engineering department's Liwei Lin has used isolated bacterial photosynthetic membranes to directly power microscopic electronic devices (see our Spring 2007 issue).

In the crowded field of next-generation photovoltaics, it is yet unclear which technologies will prevail. Nonetheless, one thing is certain: From plant-inspired designs to solar devices that actually derive power from photosynthetic proteins, the future of solar energy has never looked greener.

Tracy Powell *is a graduate student in plant and microbial biology.*

The machine makes a loud clicking sound, and a powerful pulse of magnetic energy is zapped across the skull, scrambling the signals in the brain and changing how the subject thinks. At first glance, it might seem a bit like mad scientist technology or the plot of a James Bond film, but the machine, called a Transcranial Magnetic Stimulator, is very real, and is being used in hundreds of universities and psychiatric clinics around the globe. Far from a a malevolent mind-control device, it is allowing neuroscientists to tease apart how the brain works with a level of safety, control, and precision never before possible. Originally developed in the mid-eighties by neurologists as a diagnostic tool for patients with nerve damage, it has since been developed into a powerful method for probing the wiring of the human brain. Unlike brain imaging technologies such as functional Magnetic Resonance Imaging (fMRI), TMS allows neuroscientists to directly manipulate, rather than simply observe, brain function. At Berkeley and elsewhere, TMS is being used to address basic questions about the neural basis of memory, attention, and movement, and it has shown promise as a treatment for a wide variety of disabling psychiatric disorders. But many questions still remain about the technology, not the least of which is: exactly why does it work?

A stimulating experience

According to neuroscience lore, the Italian physician Luigi Galvani first discovered that nerves transmit electrical signals in 1783 when his assistant touched a charged scalpel to an exposed nerve in a dissected set of frogs legs, causing them to twitch. TMS operates on a similar principle, but instead of applying a current to neurons directly, it uses a magnetic field to generate electrical flow in the cells by electromagnetic induction, the same principle used in electrical generators. In the simplest application, a single pulse is applied over a part of the brain for a few milliseconds, causing nerve cells in the region to shoot off randomly. The subject might experience a muscle twitch or see a brief flash of light, depending on the location of the pulse.

However, when a pulse is applied over a region involved in more complicated cognitive processes, the haphazard neuronal firing induced by TMS can scramble the carefully orchestrated sets of signals present during normal function. The result is a very brief, targeted disruption of information flow

...P!

...RIP UP BRAIN ...CTION

By Colin Brown

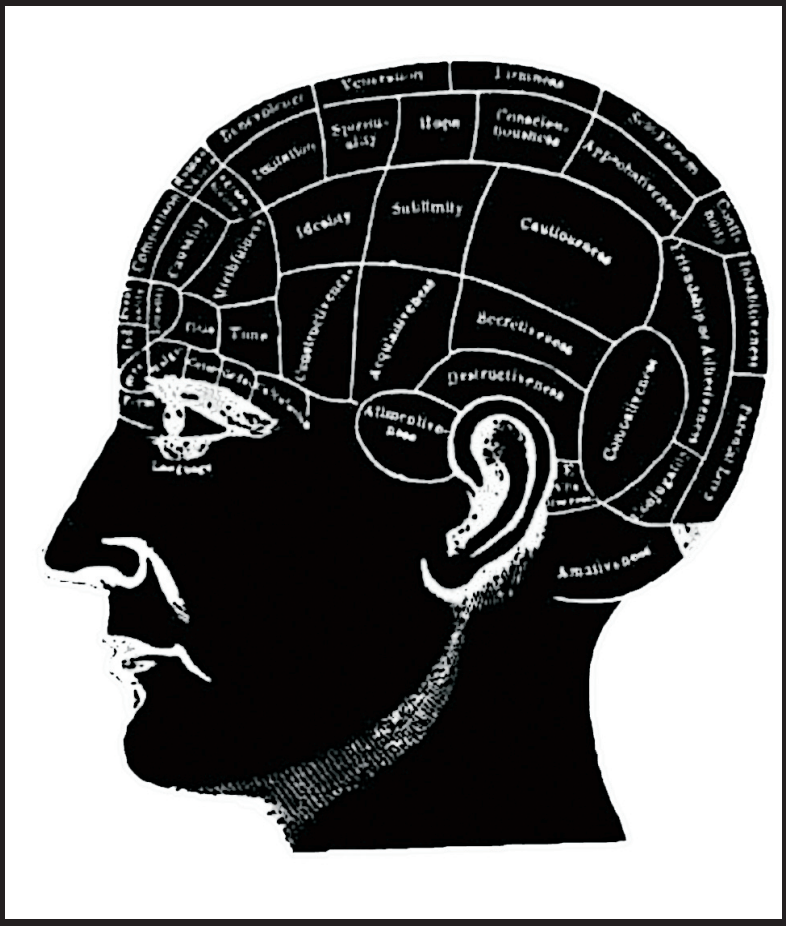


Image courtesy of Terry Yen and Indiana Medical History Museum

through that region. If the area targeted by the pulse is involved in a particular cognitive task, this disruption will manifest itself through subtle behavioral effects, such as an increased error rate when reading letters from a screen. By pairing behavioral measures with carefully timed TMS pulses, researchers can establish a causal role for a region in a particular task.

"Essentially, you're introducing transient noise to a region, and if that region is critically involved at that time, it's not going to perform that function as efficiently", said TMS researcher Brian Miller, a recent graduate from Mark D'Esposito's lab at Berkeley.

The disruption of a region after a single TMS pulse lasts for a very short time, usually just a fraction of a second after the pulse is applied. While even these short pulses can be useful for some applications, a far more common and powerful technique is repetetive TMS or rTMS, where a train of pulses is applied over several minutes. This leads to more extended "offline" disruptions that can last as long as half an hour after the treatment. Depending on where the pulse is applied, the effects of rTMS treatments can mimic those seen in so-called "lesion" patients who have experienced damage to the region from stroke or other brain injuries. Since the effects of rTMS are controllable and fade after a few minutes, researchers can create temporary "virtual lesions" to disable almost any brain region at will. Examining real lesion patients can yield profound insights into the function of healthy brains, but the size and severity of the damage can vary widely among individuals, and the reorganization that takes place as the brain heals itself following an injury can obscure its effects. According to Miller, "with lesions you have no control over the location or the extent of the damage. TMS gives you that very focal control over the region of disruption...you can take someone who is otherwise totally normal, and very transiently disrupt the region you're interested in."

Virtual lesions

Miller's work used this rTMS lesioning approach to study a brain process called "refreshing", which allows the brain to pick out interesting bits of information from the swamp of sensory data that passes through its visual and auditory systems. When Miller and his colleagues used fMRI, which maps regions of neural activation, to scan the brains of people during a task that involved refresh-

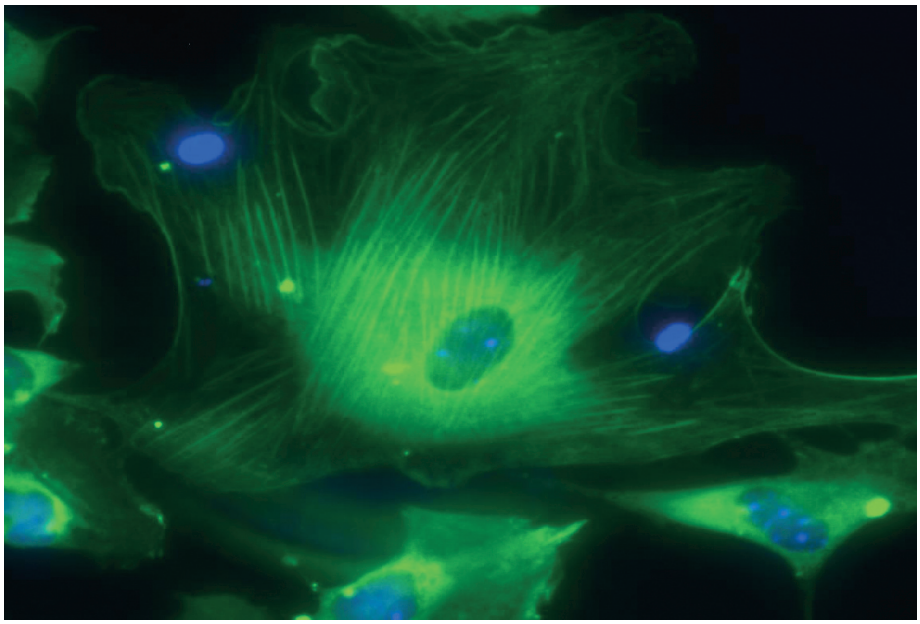


Image courtesy of the California Institute of Regenerative Medicine

Smooth muscles cells derived from human embryonic stem cells showing the nuclei (blue) and proteins of the cytoskeleton (green).

ing, they ran into a problem—they found two different regions, one in the prefrontal cortex and one in the parietal lobe, which lit up almost simultaneously.

"The key complement [TMS] makes to techniques like fMRI," said Miller, "is that you can really get at the causality. You can see different areas are active in an fMRI scan, but you can't really say that those regions are necessary for a cognitive function."

Using rTMS like a temporary scalpel, they were able to focus on each region individually. When they disabled the prefrontal cortex, subjects showed significant defects in refreshing, but when they disabled the parietal region the subjects were essentially normal. The conclusion was that the prefrontal cortex was not only involved in refreshing, but was actually the source for the refreshing signals.

Another Berkeley neuroscientist, psychology professor Lynn Robertson, used rTMS to examine how people with a perceptual quirk called synesthesia process visual information. These individuals see certain letters or numbers as always having a specific color. A's for instance, might always appear as purple, even when printed on a black-and-white newspaper page. While the causes of synesthesia are complex, Robertson suspected that it might have something to do with a brain process called "binding." The first thing the brain does when receiving a raw image from the eyes is break it down into its most basic features, such as motion, color, and shape. Before binding occurs, a basketball flying toward the rim is just an unassembled medley of concepts: orange, round, movement. When we focus attention on the ball, the brain's binding circuits reassemble these separate parts to form a complete object (the ball) at a specific position in the visual field. Robertson suspected that synesthesia results from a permanent, incorrect binding of a color that is not present in a visual field to letters or numbers that are. To test this, she and her team used rTMS on two syneasthetic individuals to disable a part of the brain known to be critical for binding in normal people. Remarkably, this caused them to temporarily lose their synaesthesic associations, confirming that normal binding and synesthesia share a common mechanism in the brain.

The excitement of competition

Inducing lesions in healthy patients, however, is only a part of what TMS can do. By applying a brief TMS pulse over a region of the brain called the motor cortex, researchers can trigger electrical signals that travel down the nerves of the spinal cord and produce a brief muscle twitch, called a motor evoked potential. By measuring the strength of these twitches in various muscles as pulses are applied over different parts of the cortex, researchers can generate maps of the complex wiring that connects the brain to the body. Although these connections are generally hardwired, the regions of the motor cortex that connect to a particular muscle can change in both size and "excitability" - how likely they are to trigger a movement - over time. For example, the area in the cortex corresponding to the hands often becomes larger in musicians or athletes who spend a lot of time practicing fine-scale movements. Researchers can map these changes by applying TMS pulses over a region and measuring the strength of the muscle twitches that result - the stronger the twitch, the greater the excitability of the stimulated region.

This mapping technique is useful in clinical settings, for example when doctors want to know the extent of nerve damage in stroke or Parkinson's patients. It is also used by cognitive neuroscientists like Dr. Rich Ivry in the Berkeley psychology department to study how the motor cortex is involved in conceptualizing movements. When we think about reaching for a coffee mug or we watch Tiger Woods swing a golf club on TV, the same parts of the brain that would be involved in executing those movements light up with neural activity. However, since we don't jump up and start swinging every time Tiger does, some process must block the signals that are generated when we are only thinking of a movement rather than actually doing it. Researchers in Ivry's lab were able to use the strength of muscle twitches generated by TMS to measure the extent of this blockage. When a subject thought about making a movement, they found that the strength of the twitches generated by regions involved in that movement went down. Based on fMRI, they suspected that a particular region of the brain's prefrontal cortex might be involved in generating the blocking signal. When they measured muscle twitches in people who had had this region disrupted by rTMS, they found that the blockage was lifted.

Ivry's lab has also investigated how the brain selects whether to use the left or right hand for tasks where a choice is possible. For instance, what if that coffee mug we're reaching for is directly in the middle of the table?

"It seems to us like it's an automatic, effortless choice," said Ivry, "but really there's a sort of competition there that gets resolved."

Ivry and his lab peered into this battle by using TMS to measure excitability in the right and left cortices as subjects were asked to plan movements using one or both of their hands. The hypothesis was that the side responsible for controlling the selected hand would stifle the other. But surprisingly, they

Image courtesy of Colin Brown

Dr. Rich Ivry from the UC Berkeley Psychology department shows off a TMS coil used by his lab.

found more inhibition in the side involved in the actual movement.

An ongoing project in Ivry's lab is even trying to use rTMS to influence how subjects make these left-versus-right choices. By creating a lesion in the region containing information about the right half of a subject's visual space, the researchers are able to skew their preference toward the left.

"We think we're disrupting the representation of where the object is [in space] in the left hemisphere, which is needed for a person to plan a right-hand movement," said Ivry.

How does it work?

Although TMS is growing rapidly in popularity, both in basic research and in clinical settings, there are still many open questions about exactly how it works, and why it has the effects it does.

"TMS, in the grander scheme of things, is still a young technology," said TMS researcher Brian Miller. "People are still trying to figure out exactly what it's doing to the underlying physiology."

In some sense, the greatest strength of TMS - its ability to easily and reversibly affect brain function in human subjects - has also been a barrier to understanding more about its basic mechanisms. Since most studies have focused on humans, there has been little drive to do experiments in animal models that allow much closer inspection of the physiological, neural, and molecular changes that occur following a TMS pulse.

As the uses of TMS in both the clinic and lab have become more complicated, the need for better information about the specific physiological effects of TMS has become even more pressing. Brian Pasley and Elena Allen, graduate students in Ralph Freeman's lab in the Berkeley School of Optometry, began to clarify some of these issues in a study published in the journal Science in 2007. One fundamental question in the field is whether the alterations in brain function induced by TMS can be measured directly by imaging technologies like PET scans and fMRI, which detect changes in oxygen usage and blood flow. If this is the case, it would allow researchers to know not just the location where a pulse was applied, but also the specific effect it had on the network of nerve cells in that region. Pasley and Allen used anaesthetized cats as an animal model, and simultaneously measured electrical activity, blood flow, and oxygen levels, in the animals' visual centers as rTMS was applied at several different frequencies. They found that all three measures were highly correlated, confirming what most in the field had suspected and opening up the possibility of combining powerful brain imaging methods with TMS.

Pasley and Allen also found that the physiological effects of the rTMS pulse lasted longer than expected in comparison to the known behavioral effects. They saw cellular disruptions lasting several minutes after a pulse of just a few seconds. In addition, they found peculiarities in the measured input and output of brain regions affected by TMS, pointing the way for others to delve deeper into its cellular mechanisms.

Safety Issues

In spite of the seemingly profound changes that TMS can induce in the brain, all evidence indicates that the technique is remarkably safe for most people. The most common complaints are aimed at the secondary effects of the coil itself, which makes a loud clicking noise when a pulse is applied and can produce momentary pain or tingling in the skin of the scalp. rTMS can sometimes cause headaches, but these respond well to over-the-counter pain killers and usually only last as long as the treatment is applied.

In a small number of cases, it is possible for high-frequency rTMS to cause seizures in healthy subjects, although a careful screening process has kept the number of these incidents remarkably low (fewer than ten out of the many thousands of people who have undergone the procedure).

The safety issues are less clear for some clinical applications, where patients often receive daily TMS treatments over several weeks, far more than are used in most basic research applications, Even here, though, TMS's track record is remarkably clean, and the use of TMS to treat patients suffering from drug-resistant depression was recently given the nod by the FDA Currently, the area of greatest concern is treatment of people with known neurological conditions. Patients with epilepsy are believed to be more prone to seizures when undergoing TMS, and the safety of using TMS in patients with brain damage, such as stroke patients, still needs further study. For now, patients with these types of conditions are excluded from most TMS studies and treatments. In general, doctors and researchers agree that better information about the physiological underpinnings of TMS is needed before the concerns about its safety can be completely dismissed. However, given the immense promise of TMS as both a clinical and research tool it will likely only be a matter of time before these issues are addressed in detail.

TMS in the clinic

The ability of rTMS to noninvasively alter brain function with few apparent side effects makes it particularly appealing as a treatment for psychiatric disorders. By far the most successful example of this strategy is for depression, especially in patients who don't respond well to antidepressant drugs. TMS may even be able to take the place of electroconvulsive treatments (commonly known as "shock therapy") for some. Most of these treatments try to correct imbalances between the left and right halves of the brain's prefrontal cortex. Functional MRI studies have shown that the right half of this region is often hyperactive in depressed patients, while the left half often shows decreased activity. In order to produce an elevated mood in depressed patients, rTMS treatments try to either impair function of the right side by using low frequency pulses, or boost function of the left side using higher frequency pulses that can in some cases excite neural function. The effects of stimulation applied to the cortex can then spread to other brain regions also involved in mood regulation through neurons connecting them to the cortex. How the short-term changes induced by TMS treatment translate into a lasting elevation of mood is still unclear, however..

Although the antidepressant properties of TMS have been a topic of research since the 90s, its widespread use as a therapy was hampered by questions about exactly how it works and how effective it actually is. A major problem has been the difficulty in creating properly controlled and blinded trials. The coils used for TMS produce a loud click and a noticeable tingling sensation when a pulse is applied, both of which are difficult to mimic in a double blind trial where both the patient and the researcher can't know whether a placebo is used. This problem was so pervasive that special "sham" coils had to be designed before proper trials could be conducted. Also, many early trials showed inconsistent results, likely due to problems with targeting the proper region of the brain (see sidebar "targeting TMS") and differences in the effectiveness of the treatment among patients with different types of depression. As more trials were performed, however, a consistently beneficial effect began to emerge, and last fall the FDA finally approved a TMS device, marketed by the company Neuronetics, for general use as an antidepressant.

The therapeutic usefulness of TMS for other psychiatric disorders, however, is still unclear. Since TMS is relatively easy to apply and has few side effects, researchers have tried using it to treat all types of disease, including mania, obsessive-compulsive disorder, post-traumatic stress disorder, and schizophrenia. Results from most of these trials have been mixed, however, and it is likely that a deeper understanding of both the neural basis of these disorders and the physiological mechanisms of TMS will be needed before it is widely used to treat these conditions.

A better brain by magnetization

One of the most intriguing possible uses for TMS is as a tool for neuroenhancement, that is, boosting mental function in otherwise healthy individuals. In fact, a small number of studies have already claimed substantial improvements in cognitive function using TMS. The best known of these, and also one of the most controversial, was conducted by an Australian neuroscientist named Allan Snyder. By applying rTMS to a region of the prefrontal cortex, Snyder claimed to actually induce enhanced artistic abilities in otherwise normal subjects (including a New York Times reporter), essentially turning them into what he referred to as "savants" for the duration of the treatment (see illustration - drawings?). While many in the field are skeptical of these particular results, the thorny ethical implications raised by the possibility of using TMS for neuroenhancement are still there.

"If these things do turn out to have some truth to them, people are going to use them."

But many researchers who use TMS in the lab are cautiously optimistic about the possibility of enhancement. Some have pointed out that there is little physiological difference between the changes in the brain resulting from TMS and those resulting from more "natural" methods such as learning. In a 2003 article, TMS researcher Dr. Alvaro Pascual-Leone argued that "all environmental interventions, and certainly educational approaches, represent interventions that mold the brain of the actor. Given this perspective, it is conceivable that neuromodulation with properly controlled and carefully applied neurophysiological methods could be potentially a safer, more effective, and more efficient means of guiding plasticity and shaping behavior." The Berkeley researchers consulted for this story agreed that studies of neuroenhancement should be pursued, if for no other reason than to allow these techniques to be applied safely. "We shouldn't close the door out of hand," said Rich Ivry. "If these things do turn out to have some truth to them, people are going to use them. Science's best guide here is to make sure that they're properly evaluated."

Where does it go from here?

The Berkeley researchers agree that the future of TMS as a tool for cognitive neuroscience seems bright. New advances in coil design are allowing TMS to be joined with imaging technologies like fMRI to give researchers unprecedented access to the inner workings of the brain. Special ceramic coils can now even be used while a subject is inside the giant magnets of an fMRI scanner, to image the changes induced by TMS in nearly real time. This should allow for better targeting of TMS pulses, and also opens up entirely new types of experiments for researchers interested in understanding the connections between the brain's various processing centers and subnetworks. By applying a pulse to activate one structure using TMS and then using fMRI to follow the tracks of activation through the brain, researchers hope to be able to construct incredibly detailed maps of entire networks of neurons. Better coils may also allow disruptions to be generated deeper inside the brain, allowing researchers and clinicians to study structures controlling memory and emotion.

Much of the future of the technology, especially in the clinical arena, may hinge on how well scientists are able to understand its fundamental mechanisms. An improved understanding of the principles of TMS, combined with better knowledge of how treatment outcomes vary among patients, may allow doctors to predict a specific treatment regimen's effects on a given person. This could reveal an unprecedented array of treatment options for people suffering from psychiatric disease.

Colin Brown *is a graduate student in molecular and cell biology.*

From 1961 to 1971, over 20 million gallons of the powerful defoliant Agent Orange were sprayed across the jungles of South Vietnam. The herbicidal active ingredients destroyed millions of acres of forests, but perhaps even more tragically, the contamination of Agent Orange with the carcinogen dioxin caused hundreds of thousands of deaths and continues to affect the people of southern Vietnam to this day. Dioxin is now infamous as one of the world's most potent cancer-causing chemicals.

Chemists clean up their act

Green Chemistry

By Lee Bishop and Mitch Anstey

Burning chlorine-containing organic materials produces dioxin, and oftentimes the chlorine is present only as a contaminant and not as the crucial component of the material, making dioxin production difficult to control. Coal fire plants, waste incinerators, and even forest fires are implicated in dioxin production, and until recently, engine exhaust from ships and trains also contributed to the problem. In response, the California Environmental Protection Agency began investigating how chlorinated chemicals could be contaminating these vehicles' fuel. They found that the automotive repair industry was using two chlorine-containing compounds, methylene chloride and tetrachloroethylene, as brake and engine cleaners. These chemicals were then combined with used car oil that was recycled into a cheap source of fuel for dioxin-spewing tankers and trains.

These findings prompted well-intentioned regulations to prohibit the use of those chlorinated chemicals in degreasers in California, and the automotive repair industry adopted a mixture of the chemicals hexane and acetone as a substitute. Tragically, auto mechanics began experiencing numbness of their hands and feet, and some were even rendered wheelchair-bound. It was eventually determined that hexane was being metabolized into a potent neurotoxin in the mechanics' bodies, causing nerve damage. This so-called "regrettable substitution" illustrates the difficulties inherent in designing and regulating chemical tools, weighing their benefits against often unknown environmental and health impacts. It is becoming increasingly apparent that the current chemical production and regulation system is flawed, and the field of green chemistry aims to provide the solution.

The meaning of greening

The term green chemistry was first coined in 1998 by Yale professor Paul Anastas and John Warner of the Warner Babcock Institute in their book "Green Chemistry: Theory and Practice." They defined it as "the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products." In other words, the green chemistry campaign seeks to reform just about every aspect of chemical production and use. Its principles would equally be embodied by a laboratory chemist who invents a new biodegradable plastic as by a business that discovers how to manufacture that plastic using chemicals that minimize the risk to their workers' health. And it doesn't just apply to people in labcoats; the plastics in water bottles and kids' toys are also potential risks that need to be assessed. The diverse ways that chemicals affect individuals and the environment means the success of the green chemistry movement will require chemists working together with an array of other professionals to ensure that chemicals are created, tested, treated, and disposed of properly.

The green chemistry movement is beginning to take hold at UC Berkeley. An important recent step was a 2008 report commissioned by the California EPA entitled "Green Chemistry: Cornerstone to a Sustainable California," which includes among the authors Drs. Michael Wilson and Megan Schwarzman, research scientists in the UC Berkeley School of Public Health. The wide-ranging report outlines some of the major environmental, health, and economic impacts of California's current approach to regulating chemicals. Over 100 synthetic chemicals and pollutants have been found in umbilical cord blood, breast milk, and adult tissues, and, according to the report, many of these chemicals are "known or probable human carcinogens, reproductive or neurological toxicants, or all three." Thousands of new chemicals are introduced to the marketplace each year and global chemical production is doubling every 25 years. The report highlights the need for comprehensive policy solutions to avoid the potentially disastrous consequences of releasing these chemicals into the environment.

The Carbon Connection

The linkage between two carbon atoms is one of the most common bonds in nature, seen in everything from petroleum to perfume to proteins, and organic chemists often want to create bonds between carbons on different molecules to form a new product. However, forming these bonds in the lab can prove quite difficult. Creating carbon-carbon bonds usually involves preparing two carbon-containing precursors with fairly active chemical elements to aid in the joining of the two carbon atoms. The highly reactive elements used in these "prefunctionalization" steps will not end up in the final product, creating waste, so chemistry professors Robert Bergman and Jonathan Ellman have developed methods that avoid these additional steps and allow bonds to be formed directly between two carbon atoms. The majority of carbon atoms are linked to hydrogen atoms in stable bonds that are very difficult to break (thus, the necessity for prefuctionalization). "Carbon-hydrogen bond activation" is a solution to transform the ubiquitous but difficult to manipulate carbon-hydrogen bond directly into a carbon-carbon bond. These approaches typically involve rare metal catalysts and other extreme conditions to make the reaction occur, but the researchers are able to create new carbon-carbon bonds.

Since most organic chemicals already have an abundance of carbon-hydrogen bonds, Bergman and Ellman are now attempting to target one carbon-hydrogen bond in the presence of all the others. Most organic molecules, and specifically pharmaceuticals, contain elements such as nitrogen and oxygen, and the current strategy to selectively "activate" carbon-hydrogen bonds exploits these common atoms as "directing groups" to guide their catalysts to the desired location on the molecule. Little to no modification of the molecules is necessary, but the list of useful molecules is limited to those that have the correct "directing groups" already built in. Nevertheless, the method has proven successful in the synthesis of incarvillateine, a molecule with potent analgesic properties, as well as possible anti-inflammatory, anti-malarial, anti-tumor, and anti-HIV drugs. As this technology matures, its application in the large-scale synthesis of pharmaceuticals and other molecules of interest could dramatically decrease the amount of waste generated by the chemical industry.

Most consumer product manufacturers are not required to assess the safety of chemicals in their products, so this vast responsibility is left to government agencies. With the current costs of a full toxicological screen approaching five million dollars, the government does not have the resources to screen each new chemical as it comes to market. This means there just isn't enough information about the potential health or environmental hazards of chemicals currently in production, and this lack of data is the first of three main challenges cited as an obstacle to a comprehensive policy solution (see "sidebar" for more information about a means of addressing this issue). The second is that most companies are not required to assume full responsibility for the health and environmental impacts of their products. This means that producers have little impetus to design safer chemicals or processes, and government agencies must wait until harmful effects are observed to take action instead of instituting preventative measures. The final obstacle is a lack of public and private investment in green chemistry research and education. Without investment in the chemicals and processes of the future, the field of green chemistry will be relegated to banning old harmful chemicals instead of creating new benign ones.

Green making green

Early on, chemical companies were thinking creatively about waste disposal for financial reasons – why throw something away when it can be made into something you can sell? In the 1930s, the chemical company I. G. Farben began converting styrene, a by-product of the oil and gas industry, into polystyrene, one of today's most widely used types of plastic. Polystyrene may not be a sustainable material by today's standards, but producing a valuable product from a chemical that would otherwise have to be disposed of is certainly a step in the "green" direction.

Despite this example, industry and the environment have had a historically rocky relationship. In the past, manufacturing plants were strategically placed along bodies of water so that they could be used as dumping grounds for unwanted waste. "One could say that was economically advantageous at the time because it was cheap," says chemistry professor Robert Bergman. "But if those costs to the environment had been assigned to the company, instead of having to be picked up by society, then a much different economic situation would have occurred. The whole problem with how our economy operates is not that some things are cheap and some things are costly, especially in the chemical arena. The problem is the costs are not assigned in the right place."

As waste disposal prices and regulations have grown, this "cost assignment" has begun to shift, and corporations are becoming keenly aware that green chemistry can be a huge benefit for the bottom line. "Companies don't want to create waste and don't want to create emissions," says Tony Kingsbury of the Haas School of Business. "You can't, literally, from a dollars and cents standpoint, afford to send it to a landfill, hazardous waste site, or dump it in the ground." For modern companies, it's a combination of economic and social advantages. "Dow is very interested in green chemistry for economic reasons, but I think also for societal reasons as well," explains Professor John Arnold of the College of Chemistry. "They do want to be stewards of the environment, and it makes sense economically for them to do that."

Interdisciplinary troubles and triumphs

While businesses may be making strides in the right direction, they can't do it alone. According to Schwarzman, tackling the obstacles to green chemistry will take "a blend of many different fields working together." To this end, staff and faculty from across campus have begun roundtable discussions under the auspices of the Berkeley Institute of the Environment towards the creation of a center for green chemistry at UC Berkeley—one that brings chemists, toxicologists, health scientists, public policy experts, and business experts to the same table. "The basic purpose of the center is to bring all these disciplines to bear on these problems," Schwarzman says.

In assembling a faculty panel, the center is already confronting scientists' hesitance to become involved in matters of policy. Of speaking to the press, Bergman says, "Have you ever talked to a reporter and then read what they wrote about what you said? It's a scary experience." Misrepresentation of scientific results or opinions can compromise a researcher's integrity and lead to confusion about what the scientific facts really are. Professor Dale Johnson in the School of Nutritional Science and Toxicology explains another cause of apprehension. "As a scientist, when you know that policy decisions will be riding on your research, you run the risk of introducing bias. And this bias can potentially cause you to skew your results and scien-

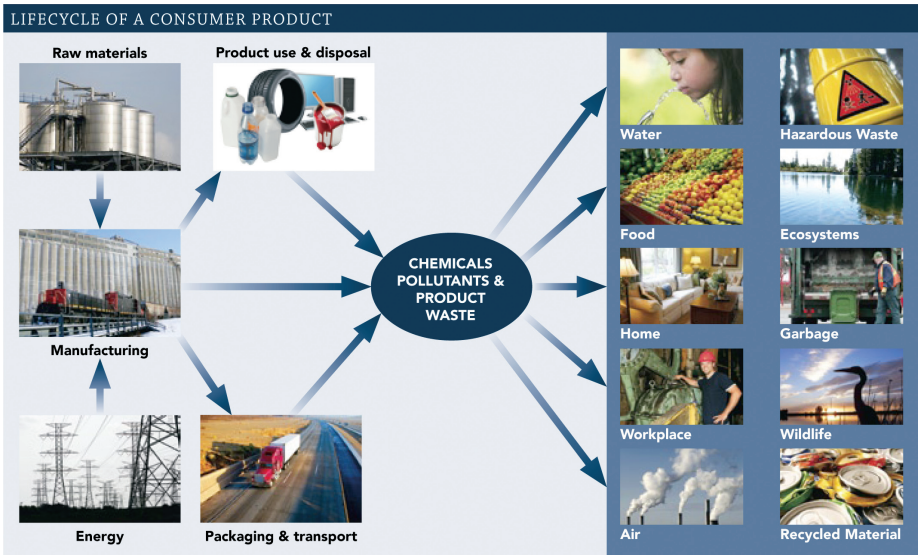
tific conclusions." Schwarzman outlines a third cause, saying, "Scientists shy away very quickly from something that's being dealt with in the public arena because then it feels like they have to take sides or be an advocate just because there are advocates in the process."

In some cases, chemists shy away from the concept of green chemistry because they don't understand what it means. "I think from a lot of academic chemists' perspectives, the situation is a little confused by what people mean by green chemistry," says Arnold. Chemists often view green chemistry negatively, seeing it as a list of "bad chemicals," the avoidance of which merely narrows the field of scientific possibilities. While policymakers may be primarily interested in removing toxic chemicals from the environment, chemists are more excited about green chemistry as an opportunity to make new, environmentally friendly discoveries. Importantly, these two goals are not mutually exclusive. Schwarzman strikes a conciliatory note, explaining that green chemistry is "science in the service of precaution," and should not be misinterpreted as "precaution versus science." "Any sort of initiative that's going to get chemists behind it has to be framed in the positive," says chemistry graduate student Marty Mulvihill. You can't talk about bad chemicals and sick babies, you have to talk about saving the earth and doing fundamentally new and interesting chemistry."

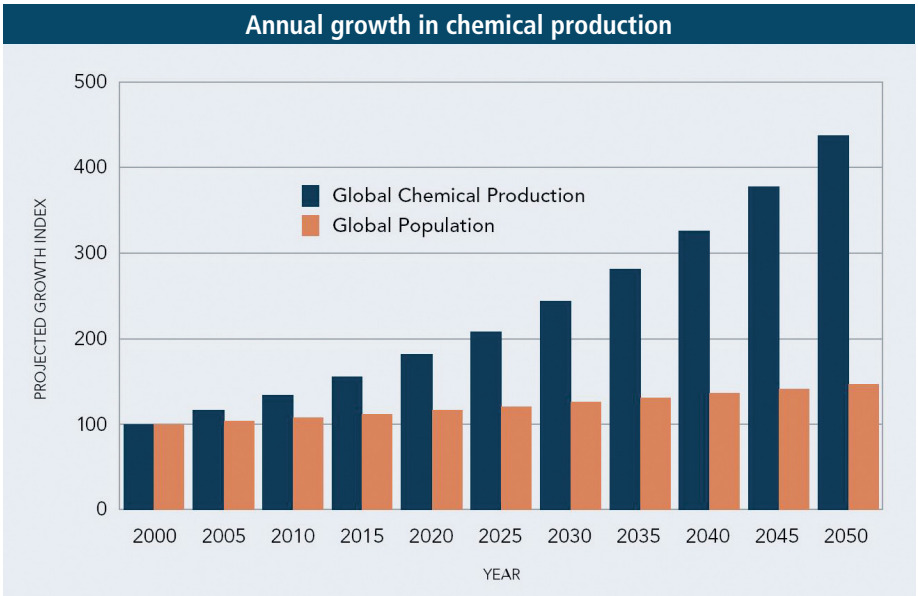
The good news is that voices remain optimistic about the future of this field. "It's rare in my experience that talking about things and getting information is bad. I nearly always see good come out of that," says Arnold. Creating the center for green chemistry represents a crucial step towards solving the communication difficulties between its constituent disciplines.

One benefit of scientists interacting across fields is that it helps them gain a new perspective on their research. "I think that it is important for scientists to be aware of the broader implications of what they do," says Professor Richard Mathies, dean of the College of Chemistry. "There's no reason why a chemist shouldn't think about what's going to happen to his or her product after it gets made," Bergman agrees.

The general sentiment in the department is that chemists and chemical engineers can provide the ultimate solutions to problems caused by toxic chemicals in the environment because they understand how these molecules are designed and produced in the first place and therefore are the most capable of improving them. Not only will this work help the environment, but it will also provide chemists with fresh challenges to tackle in their research. "Chemistry will play a very important role in the overall concept of sustainable development," Arnold says. "It will require new chemistry, which is why I'm interested in it. We will have to do things in new ways, so there will be new processes, new reactions that need developing, and that's what I like."



Green chemistry strategies target each stage of a product's lifecycle to continually improve its biological and ecological safety, reduce its energy consumption, and eliminate the prodution of hazardous and product waste. (Data and text courtesy of the California EPA Cornerstone Report).



Growth in chemical production outpaces population growth. Global chemical production is expected to grow 3% per year, while global population will grow 0.77% per year. On this trajectory, chemical production will increase 330% by 2050, compared to a 47% increase in population, relative to the year 2000. (Data and text courtesy of the California EPA Cornerstone Report).

Education for a green generation

Though the green chemistry movement at Berkeley is still in its early stages and its adherents varied in their approaches, everyone seems to agree that education is a central component of addressing the sustainability problem. Within the Department of Chemistry, Mulvihill has been on the forefront of the current educational effort. "Throughout graduate school I've been trying to organize graduate students to realize that the work we do here does have a broader social impact," Mulvihill says. Most chemists are not offered any formal training in toxicology, so even if they are interested in decreasing the toxicity

Images courtesy of California EPA

Modeling Molecules

The linkage between two carbon atoms is one of the most common bonds in nature, seen in everything from petroleum to perfume to proteins, and organic chemists often want to create bonds between carbons on different molecules to form a new product. However, forming these bonds in the lab can prove quite difficult. Creating carbon-carbon bonds usually involves preparing two carbon-containing precursors with fairly active chemical elements to aid in the joining of the two carbon atoms. The highly reactive elements used in these "prefunctionalization" steps will not end up in the final product, creating waste, so chemistry professors Robert Bergman and Jonathan Ellman have developed methods that avoid these additional steps and allow bonds to be formed directly between two carbon atoms. The majority of carbon atoms are linked to hydrogen atoms in stable bonds that are very difficult to break (thus, the necessity for prefuctionalization). "Carbon-hydrogen bond activation" is a solution to transform the ubiquitous but difficult to manipulate carbon-hydrogen bond directly into a carbon-carbon bond. These approaches typically involve rare metal catalysts and other extreme conditions to make the reaction occur, but the researchers are able to create new carbon-carbon bonds.

Since most organic chemicals already have an abundance of carbon-hydrogen bonds, Bergman and Ellman are now attempting to target one carbon-hydrogen bond in the presence of all the others. Most organic molecules, and specifically pharmaceuticals, contain elements such as nitrogen and oxygen, and the current strategy to selectively "activate" carbon-hydrogen bonds exploits these common atoms as "directing groups" to guide their catalysts to the desired location on the molecule. Little to no modification of the molecules is necessary, but the list of useful molecules is limited to those that have the correct "directing groups" already built in. Nevertheless, the method has proven successful in the synthesis of incarvillateine, a molecule with potent analgesic properties, as well as possible anti-inflammatory, anti-malarial, anti-tumor, and anti-HIV drugs. As this technology matures, its application in the large-scale synthesis of pharmaceuticals and other molecules of interest could dramatically decrease the amount of waste generated by the chemical industry.

of the chemicals they work with, they generally do not possess the requisite knowledge. To address these issues, Mulvihill and some graduate student colleagues started the Green Chemistry and Sustainable Design seminar series, offered for the first time this past fall. The series covers toxicology, as well as green chemistry in academia, industry, and public policy. Experts in these fields were invited from within the university and across the country, and in demonstration of support for the seminar, many speakers even offered to pay for their own travel expenses. Mulvihill was pleased by the response to the seminar series; according to surveys, student interest in green chemistry and sustainability dramatically increased after participating (see figure). "Students are more and more interested in pursuing research that relates to issues of importance in our society," Mulvihill says.

This seminar series was the first significant effort to introduce elements of green chemistry into the chemistry department's curriculum. Tony Kingsbury, executive-in-residence of the Sustainable Products and Solutions Program, a collaboration between the Dow Chemical Company Foundation, the Haas School of Business, and the College of Chemistry that provides the primary funding for the green chemistry seminar series, remarks that he is seeing increased interest in sustainable chemistry all the way up to Dean Mathies. "What this college should be doing," says Mathies, "is providing the knowledge and information and education necessary to put people out there who can work for chemical companies, who can work for the government, who can work with advocacy groups and so on, such that they all have an understanding of chemistry, chemical principles, sustainability, and toxicology." He feels that students educated in this way "can improve the processes in chemical companies, improve the way chemicals are handled, and improve the legislation that is put forward."

Toward this end, as part of the college's effort to revamp the undergraduate laboratory courses, Mathies plans to make sustainability an integral part of the undergraduate chemical education. He feels that broad promotion of sustainability concepts has been hampered by the lack of a common language and understanding to allow communication between groups with diverse interests. Citing the fact that 54% of the students that pass through this university will take at least one course in chemistry, Mathies feels that the college can provide that "common language and common understanding that allows people to communicate better and achieve solutions." Furthermore, laboratory spaces are being renovated to operate in a more environmentally friendly fashion and experiments are being updated to use greener chemicals. Mathies hopes to incorporate the 12 principles of green chemistry, as outlined by Anastas and Warner, into the laboratory curriculum in an effort to illustrate to the students the kind of careful, integrated thinking involved in evaluating the sustainability of a chemical or a reaction.

"Our world is becoming a chemical world, and it affects every natural resource we have."

Where do we go from here?

The challenges posed by the principles of green chemistry cannot be addressed through legislation, business practices, or research alone. Our society and economy depend on chemicals that often pose hazards to ourselves and our environment. "Our world is becoming a chemical world, and it affects not only the environment but every person and natural resource we have," says Johnson. If no green alternative to a given hazardous chemical or process exists, then one has to be created, which requires focused research with sustainability as an explicit goal. Creating a society that fosters that kind of research and its translation into economically viable products will require a population that is educated in the principles of green chemistry and other aspects of sustainability. Appreciation of this is beginning to take hold at UC Berkeley, leading to dramatic changes in the way students are educated and research is carried out. On the potential impact of these changes, Mathies says, "If we train the students properly, then they will go out into the world and we will see a transformation."

Mitch Anstey and Lee Bishop *are graduate students in Chemistry.*

FUNDING THE FUTURE

The Howard Hughes Medical Institute contributes millions to Berkeley research

by Meredith Carpenter

It's a scientist's dream: at a time when funding is scarce and many take the safest research route to guarantee results for that next grant application, you're given a million dollars a year and instructed "to take risks, to explore unproven avenues, to embrace the unknown—even if it means uncertainty or the chance of failure." Want that new $500,000 microscope? Buy it. Have an idea for an experiment that might take several years of troubleshooting? Hire a new postdoc and go for it. This scenario, while fantasy for most, has become reality for the 13 Howard Hughes Medical Institute (HHMI) Investigators at UC Berkeley.

From Spruce Goose to lab use

In 1953, the eccentric aviation magnate Howard Hughes founded a charitable research organization. He was the sole trustee of the organization and transferred all of his stock from the Hughes Aircraft Company into its coffers. As a result, the major aerospace and defense contractor effectively became a tax-exempt charity, albeit one whose goal was "to probe the genesis of life itself." The Internal Revenue Service, understandably dissatisfied with this arrangement, soon challenged the organization's non-profit status. So, in the late 1950s, the Howard Hughes Medical Institute began funding 47 medical investigators at nine different institutions.

As of 2008, the HHMI's endowment had grown to a whopping $17.5 billion that funds 354 investigators at 71 host institutions, as well as a myriad of grants that support teaching programs, international researchers, and research opportunities for predoctoral and premedical students. It is one of the largest philanthropic organizations in the United States, second only to the Bill and Melinda Gates Foundation. There are currently 13 HHMI Investigators at UC Berkeley, of whom five were appointed in 2008. In addition, in April 2009, Professor of Molecular and Cell Biology Robert Tjian was appointed the organization's new president, one of the most prestigious leadership positions in science.

The HHMI's motto is "people, not projects"—that is, it appoints scientists as "investigators" instead of awarding grants based on a specific research proposal, which is the method used by government agencies like the National Institutes of Health (NIH) and the National Science Foundation. "The main goal is to identify the best scientists doing the most original and creative work and give them enough resources for a long enough period of time to allow them to pursue their scientific curiosity," says Tjian.

Robert Tjian, Professor of Molecular and Cell Biology at UC Berkeley and HHMI investigator for 20 years, is the new president of the HHMI.

Photo by Niranjana Nagarajan

HHMI Investigators are awarded a renewable, five-year appointment. They remain at their host institution, but they also become employees of the HHMI, which pays their entire salary and benefits and even compensates the host institution for their laboratory space. In addition, they receive about one million dollars in funding a year and administrative support for their labs. "We're in this incredibly privileged situation where we can give pretty substantial amounts of funding for pretty long periods of time," Tjian explains. "I've been a Hughes investigator for over 20 years—that's extraordinary generosity for any organization."

Investigator rising

Since the early 1990s, the HHMI has held periodic national competitions to search for new investigators. Prior to 2006, they would invite about 200 research institutions—universities and academic health centers—to nominate two to four researchers "in the ascending phase of their career" for each competition. Starting in 2006, however, the competitions have been "open," mean-

Continued on page ...

Cal's newest HHMI Investigators

Christopher Chang

Assistant professor of chemistry and faculty scientist in LBNL's Chemical Sciences Division

Photo by Noah Berger/AP, ©HHMI

To Christopher Chang, copper isn't just the stuff pennies are made of. In fact, trace amounts of copper, as well as other metals like iron and zinc, are required for proper functioning of the human nervous system, though the reasons for this are still poorly understood. "It's interesting to us because brain tissue actually contains more of these metals than any other part of your body," says Chang. The Chang lab uses chemistry to study neurobiology, with the goal of better understanding how the brain works on the molecular level.

To study the role of copper in the brain, the lab is working on ways to visualize the metal in living cells, particularly under conditions of neural activity, neural stem cell development, injury, and disease. "We're approaching it from a chemical point of view, where we develop a fluorescent probe that will selectively detect copper, and use that new tool to do experiments that were previously inaccessible due to experimental limitations," says Dylan Domaille, a graduate student in the Chang lab. "It's been observed that copper is released during synaptic activity, and recent evidence suggests some sort of neuroprotective effect," he explains. "That's probably one of the predominant hypotheses now in terms of what's happening in the brain, but we want to know what's happening on the molecular level at a higher resolution."

One complicating factor is that copper can actually exist in two forms depending on its number of electrons—while it mainly takes the form of copper(II) in nature and outside the cell, it is changed into copper(I) at the cell membrane, and this is the predominant form inside the cell. "We've got a few copper(I) detectors, but copper(II) is more difficult," Domaille explains. "It's easy to make a molecule that fluoresces and then turns off when it binds copper(II). But practically, that's difficult to use because you're looking for a dark spot in a bright background, and you'd rather look for a bright spot on a dark background. We're still working on that."

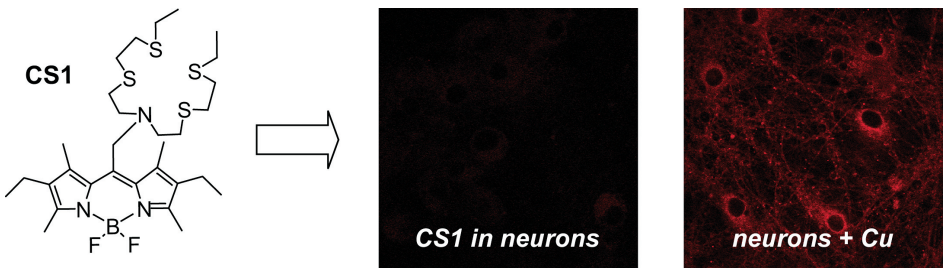
Domaille plans to use these sensors to study the distribution of copper in cells in culture, and eventually even in live animals, to understand more about its function, storage, and distribution in the brain. "We're looking at what I'd call waves or packets of metal pools moving around," says Chang, "things you wouldn't normally think that copper would do, so it must have its own channels, transporters, and targets." Misregulation of copper pools in the brain has also been linked to diseases such as Alzheimer's and Lou Gehrig's, so work in the lab may aid in the understanding of those disorders.

The Chang lab is also looking into the role of reactive oxygen species, and particularly hydrogen peroxide, in normal brain function. Reactive oxygen species are molecules that can produce free radicals, which can damage DNA and other cellular components. However, "we've been interested in this idea that in certain places, generated at certain times and at certain levels, hydrogen peroxide has a role in neurotransmission and stem cell growth and development in the brain," says Chang.

> "Because it's so complex, it makes sense that it would need different chemistry than you would find anywhere else."

To study the role of hydrogen peroxide, members of the lab are taking a similar approach to how they study copper—designing fluorescent sensors that can report on the presence of the molecule. "We have a small molecule that fluoresces in the presence of hydrogen peroxide, so it's a way of asking if there's any hydrogen peroxide in what you're looking at," explains Evan Miller, another graduate student in the lab. "We're particularly interested in living systems because hydrogen peroxide is part of how cells talk to each other." In fact, Miller has already used one of these molecules to map molecular pathways of hydrogen peroxide production in living brain cells.

Ultimately, these studies have implications for understanding aging and neurodegeneration, in addition to illuminating how the brain works on a basic level. To Chang, the existence of signaling pathways unique to the brain is not surprising. "You have something that's really unique in terms of controlling senses like sight, hearing, thought, memory, and motor skills," he says. "So because it's so complex, it makes sense that it would need different chemistry than you would find anywhere else."



A probe designed by the Chang lab for detecting copper(I) in neurons. Coppersensor-1 (or CS1, the chemical structure depicted at left) only fluoresces in neurons when copper (Cu) is present.

Image courtesy of Chris Chang

Cal's newest HHMI Investigators

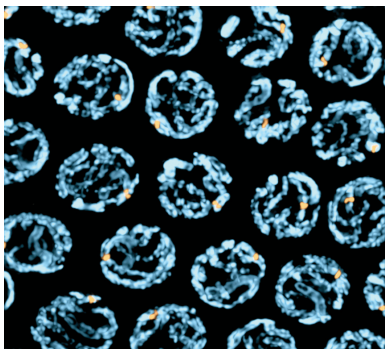
Abby Dernburg

Associate professor of molecular and cell biology and faculty scientist in LBNL's Life Sciences Division

Photo by Noah Berger/AP, ©HHMI; Image courtesy of Abby Dernburg

Abby Dernburg studies a type of cell division called meiosis, which produces gametes (eggs and sperm) in sexually reproducing organisms. Gametes contain half the genetic material of the parent—in humans, one set of 23 chromosomes. That way, when two gametes are combined at fertilization, the complete complement of genetic material (in humans, two sets of 23 chromosomes, one from each parent) is restored, resulting in new genetic diversity. A key step in meiosis is the exquisitely controlled pairing of the two sets of chromosomes, each with its so-called "homolog." This step ensures that when the chromosomes are distributed to the gametes, each gamete gets one copy of every chromosome. Errors in this process, which result in missing or extra chromosomes in the offspring, can cause problems ranging from Down syndrome to miscarriage.

Using the nematode worm ***Caenorhabditis elegans*** as a model organism, members of the lab study the mechanisms underlying the pairing of homologous chromosomes. Worms are especially useful for these studies because they are transparent, giving researchers a convenient window for watching the stages of meiosis in the live organism. The Dernburg lab has already discovered that, in worms, specific sequences of DNA on each chromosome are required for the pairing of homologs during meiosis [see BSR Issue 12]. Without these sequences, the chromosomes are unable to find each other and are segregated incorrectly. In addition, Dernburg has identified proteins that bind to the sequences and help bring the two homologs together. Now, members of the lab are investigating the steps of the ***pas de deux*** that culminates in the physical pairing of each set of chromosomes. In addition, they are studying how the cell checks whether chromosomes have paired before allowing meiosis to continue.



Gamete precursors undergoing meiosis in a nematode worm, stained to highlight the chromosomes (blue) and one of the specific sequences that helps homologous chromosomes pair (orange).

Jay Groves

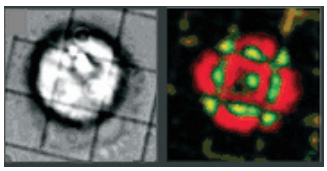
Associate professor of chemistry and faculty scientist in LBNL's Physical Biosciences Division

Photo by Noah Berger/AP, ©HHMI; Image courtesy of Kaspar Mossman

Jay Groves' research defies placement in a single department. A biophysicist by training, he is a professor in the chemistry department who studies cell membranes. Groves is interested in how large-scale collective interactions, such as the association of individual lipid molecules and proteins that make up the cell membrane, affect the overall properties of the system without changing its chemical make-up. For example, signaling across the cell membrane (i.e. relaying a signal originating from outside of the cell to the inside) occurs through specific proteins embedded in the membrane. However, in some cases, it is not simply the action of a single signaling protein that matters, but also the clustering of those proteins into patterns.

One example of this phenomenon, and a focus of research in the Groves lab, is the T cell receptor [see BSR Issue 10]. When a cell is infected by, for example, a virus, it takes pieces of proteins from that virus and displays them on receptors on its surface—a signal that helps to draw the attention of immune cells. One of these immune cells is the T cell, which uses its T cell receptor to bind to the receptors on the infected target cell. During this interaction, the bound receptors cluster into a bulls-eye configuration, and the T cell is activated to kill infected cells or help mobilize other immune system cells.

It would be difficult to study this interaction and clustering using traditional molecular biology methods, so Groves takes a very different approach. He uses live T cells, but the interacting cell is replaced by an artificial cell membrane, complete with receptor proteins, on a nanostructured surface that allows Groves to guide the movements of the interacting proteins. He then constrains the movement of the bound receptors in certain ways, creating "spatial mutations" in otherwise chemically equivalent cells, and watches how these changes affect T cell activation. Using these tools, Groves and his former student Kaspar Mossman found that the radial positioning of the receptors is required for proper signaling activity. Currently, in addition to continuing his studies of the T cell receptor, Groves is using his hybrid cell system to investigate mechanisms of cell signaling in cancer.

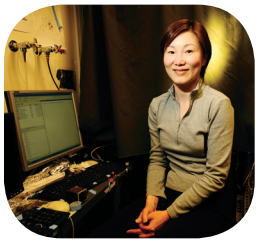


(Left) A T cell bound to the artificial cell membrane. (Right) The same cell, with its T cell receptor fluorescently labeled in green and the receptors on the artificial membrane labeled in red.

Cal's newest HHMI Investigators

Yang Dan

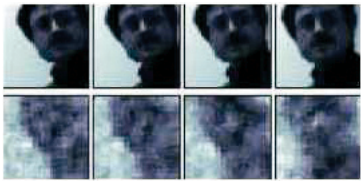
Professor of molecular and cell biology



Few UC Berkeley professors can claim to have a YouTube video of their research findings. But Yang Dan's video is understandably popular—it shows the viewer what it's like to see through the eyes of a cat. Dan studies the neurobiology of vision, specifically how visual information is encoded and processed in the brain, and how neural circuits are shaped by visual experience. "We think about coding—how do you take visual input to turn it into electrical signal?" explains Dan. "And then you can also go backwards and ask how you decode information. So if you observe the neural response, can you guess what stimuli were out there?" She studies these questions on multiple levels, using mathematical models and measurements of neural activity in both individual neurons and live brains to develop models for different aspects of vision.

Dan made the video now on YouTube by recording the electrical activity of 177 neurons in the cat's thalamus, a region of the brain that receives signals from the eyes. With knowledge of how these neurons responded to light and dark, she and her collaborators then used sophisticated computer programs to translate the cells' firing into a two-dimensional recapitulation of the animal's field of vision. Though fuzzy (due to the small number of neurons sampled and the bypassing of any processing by other areas of the brain), a human face crossing the field of vision is clearly discernible in the resulting movie.

This study was actually performed about 10 years ago, but the lab continues to study similar problems. "At one level we're interested in microcircuitry—at the single neuron level, who connects to who," says Dan. "But the other half is a very new direction that has to do with the global brain state." She is interested in how the brain switches from one brain state, such as sleep or attentiveness, to another. Neuroscientists already know that in the brain, individual neurons don't fire independently; instead, they tend to fire in a coordinated way with other neurons in their circuit, and it is the overall pattern of these oscillations that determines the brain state. "We know that in the brain stem and the basal forebrain and hypothalamus, there are all these neuromodulatory circuits controlling the brain states," Dan explains. The patterns of activity (often measured by electroencephalogram, or EEG) in different areas of the brain have been correlated with different brain states. "But that's only a preliminary understanding based on the anatomy. We want to know the exact mechanism of how these neuromodulatory circuits interact and control the brain states." To answer these questions, the lab is using a combination of multi-electrode recording and imaging experiments in live animals. Although this research is relatively new in the lab, Dan says the HHMI funding will allow her to move forward faster. "When you're struggling for funding, and write grants one round after another, you're much more conservative—you don't want to branch out too fast," she says. "But with this, we can be bolder in terms of taking more risks. For me, it's about how fast you can move."



A series of frames from Dan's cat vision video, showing the actual image (top) and the reconstructed image (bottom).

Photo by Noah Berger/AP, ©HHMI; Image courtesy of Yang Dan

Michael Eisen

Associate professor of molecular and cell biology and faculty scientist in LBNL's Genomics Division

A major question in evolutionary biology today is how small changes, or mutations, in the DNA sequence of an organism can translate to larger changes that eventually result in new species. Most mutations are either neutral (have no effect on the organism either way) or harmful. While these do play a role in evolution, researchers have recently turned to changes in gene regulation—controlling when and where a certain gene is expressed, or activated to produce the protein it codes for—as a previously underappreciated source of evolutionary change. This idea is especially attractive because differences in the timing or distribution of expression of a gene, especially during development, could have major effects without interfering with the resulting protein itself.

Sequences of DNA flanking a gene usually contain the regulatory information for that gene, including sites for proteins to bind that enhance or reduce expression of that gene. The Eisen lab studies these regulatory sites in various species of fruit fly, one of the classic model organisms for genetics, using both computational and experimental techniques. The complete genome sequences of 12 different fruit fly species have been determined, an effort spearheaded by Eisen, allowing members of the lab to find and compare the regulatory regions of the same genes between species. In some cases, differences in these regions have been found to be directly responsible for physical differences. However, Eisen is especially interested in the regulatory regions that have retained the same function despite numerous sequence changes. As they explained in a 2008 paper in the journal *PLoS Genetics*, "We believe that identifying divergent [regulatory sequences] that drive similar patterns of expression, and distilling the common principles that unite them, will allow us to decipher the molecular logic of gene regulation." Ultimately, Eisen hopes that his research on fly gene regulation will shed light on not just evolution, but also on the sources of variation in the human genome.

Photo by Noah Berger/AP, ©HHMI

ing researchers from 121 top institutions can apply directly, although institutions can still nominate researchers who do not nominate themselves. "I think it's a much more democratic way of doing it, because you don't have this middle layer of people making decisions about who should be nominated and who shouldn't," says Tjian. "I was very happy to see that happen."

Competitions usually take place every three years, but they are sometimes held more frequently, with each one focused on a particular research area or investigator career stage. The most recent completed investigator competition was held in 2007, which resulted in the appointment of 56 new investigators—including five from Cal—in 2008. "I think it's fantastic that Berkeley got five new investigators. MIT is the only other university that got five, and everybody else got three or less, which is a real statement for Berkeley's quality," Tjian says. "Another thing I like about the Berkeley group is they're very diverse in their fields—they cover not just molecular biology, but also bioengineering and chemistry."

The 2007 competition specified that applicants be between years four and ten of tenure-track faculty appointments. In contrast, the recent 2009 competition focused on early career scientists who have been faculty for only two to six years. And unlike in previous competitions, applicants for the 2009 competition were not required to already be receiving one or more active national research grants. The goal, according to the competition announcement, was "to identify the nation's best biomedical scientists at a critical early stage of their faculty careers, and to provide them with flexible funding to develop scientific programs of exceptional merit." The award recipients, announced in late March, included Associate Professor of Molecular and Cell Biology Kristin Scott, who studies the biology of taste perception.

For all investigator competitions, applicants must submit a *curriculum vitae*, a summary of their research plans, and five publications reflecting their most important scientific contributions. The selection process takes about a year. "If you start at 1,000 and you need to choose 50, you can imagine it's a really rigorous review process," says Tjian. Once the list is narrowed to a few hundred, it is sent to the HHMI Scientific Review Board, which consists primarily of non-HHMI scientists. This group creates lists of the top applicants; however, the final decisions are made by the President and one or two of the Vice Presidents of Scientific Research.

Kicking it up a notch

For those lucky few who are selected, how does the money actually change their research? "The really big difference the Hughes can make is that if you have one or two NIH grants, and they're limited to $250,000 each, you're at half a million and you're pretty much tapped out," Tjian explains. "Well, our research might really need $1.5 to $2 million, if you run a really aggressive research operation. The Hughes was that lifeline that allowed me to buy instruments and get into a kind of science I couldn't do otherwise. It kicked me up a couple of notches, and I think most people's experiences are like that."

Tjian also emphasizes that the HHMI hopes the funding will not benefit the recipient lab alone. "It allows you to hire the right people, get the right kind of equipment, and then make the equipment available to your colleagues. The whole idea is that within any given department, only a small percentage are Hughes investigators, but we hope that the Hughes funds get used in a more equitable way." For example, several years ago Tjian used his HHMI funds to start a mass spectrometry facility, which consists of a set of instruments used to determine the exact mass or sequence of amino acids in a protein (among other tasks); this facility is now open to the university community.

In his new role as HHMI President, Tjian is contemplating his goals for the organization, especially in light of the recent economic downturn. "A lot of it is trying to figure out where we can make the most difference—what fields and which scientists should we be supporting that we're not supporting today, and how much should we be doing outside of the borders of the United States in the international scene," he explains. "There's no doubt that there's tremendous talent all over the world that the Hughes has not supported, and how much should we be viewed as an international organization rather than a national one? That's something I'm going to be thinking about hard."

Clearly, the HHMI has been a major force in biomedical science, particularly in the last few decades. The idea of awarding grants to people instead of specific projects is still unique in the realm of research funding. Regardless, the strategy seems to be working—12 of the current HHMI investigators are Nobel laureates. "We don't know where the discoveries are going to happen," says Tjian. "So you just have to find people who are really passionate about what they're doing. They don't really see it as work—they see it as their life, and all they need are the resources."

Down On the Farm

A new crop of scientists is being cultivated at Janelia Farm, the HHMI's "freestanding laboratory" located in Ashburn, Virginia. The farm—named for Jane and Cornelia Pickens, whose parents originally owned the property—is modeled after AT&T's Bell Labs, which was famous for its basic research programs that produced such innovations as radio astronomy, the transistor, the UNIX operating system, and UC Berkeley Professor/Secretary of Energy Steven Chu's work on laser cooling that earned him the Nobel Prize in Physics in 1997.

According to the HHMI's website, the objective of Janelia Farm is to allow scientists to "pursue fundamental problems in basic biomedical research that are difficult to approach in academia or industry because they require expertise from disparate areas, they are too long-term for standard funding mechanisms, or they are outside the current priorities of other funding agencies." However, rather than hosting researchers working on many unrelated topics, the Janelia Farm senior staff chose to concentrate on two main areas: the identification of general principles that govern how information is processed by neuronal circuits, and the development of imaging technologies and computational methods for image analysis.

The labs at the research center are fully funded by the HHMI and are supervised by group leaders, who, because they are not required to perform administrative duties or submit grant applications, are expected to play an active role in research in the lab. Postdoctoral fellows and graduate students can also undertake research at Janelia Farm, though the latter must first attend either the University of Chicago or Cambridge University for a year before completing their PhDs at the Farm. "The junior faculty at Janelia Farm have groups of three people only, and the senior faculty have groups of eight, so they're very small," says Robert Tjian, HHMI President. "The idea is that you have no other distractions—no teaching, no writing grants. Just do your research and train your people properly."

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

Lab on a Chip

Tiny Technologies Offer Big Possibilities

Image courtesy of Niranjana Nagarajan

by Paul Hauser

What do the next Mars rover mission, an infectious disease testing unit, and a mobile forensics van have in common? In the very near future, a group of UC Berkeley scientists hope to equip all of these with diagnostic biological "chips" that can run batteries of tests on microscopic samples -- from Martian ice crystals to minute drops of blood. The chips, some as small as dimes and some as big as compact disks, harbor integrated technologies to manipulate and characterize biological samples, allowing the work of an entire clinical lab to be done on a single, portable biochip. With their size, accuracy and time-saving advantages, these mobile testing units are fast becoming the weapon of choice for diagnosing and fighting diseases ranging from equatorial Dengue fever to rare genetic disorders.

These so-called "labs-on-a-chip" get their name from the fact that they integrate laboratory procedures for sample preparation, reagent mixing and biochemical analysis on a single chip, essentially replacing much of the bulky instrumentation or manual operations found in a traditional laboratory setting. Because the elements contained within these chips are highly variable, the chips can be designed to monitor everything from food and beverage contamination to the spread of HIV. And much like the microprocessor chip powered the computing revolution, these researchers hope to seed the next wave of biological discovery and diagnostics with their surprisingly small and elegantly powerful devices.

Expanded scope, shrinking size

Spurred on by the potential of combining the physics of fluid dynamics with the power of materials fabrication and design, as well as the hope of using modern biological tools to solve complex problems, UC Berkeley researchers are working to create integrated solutions in the form of biological microchips. "These small chips give significant performance advantages compared to larger devices, making analysis a lot faster while still retaining the capacity to achieve very high resolution data," says Professor Amy Herr of the Department of Bioengineering. Much of the improvement in data quality is a direct result of the chips' size, since the engineering and physics principles governing microchips are markedly different from those that limit analogous large-scale laboratory instruments. Couple the increased resolution with the extremely small amount of liquid necessary to run such chip analyses and it becomes clear why these devices are making a big impact in diagnostic applications where samples, man-hours and time are all in limited supply.

As the lab-on-a-chip field races to innovate ever more integrated, more automated and higher precision chips, biochip engineers are faced with a host of engineering challenges and opportunities. This is where creativity can flourish, because creating microchips that combine multiple laboratory manipulations presents nearly limitless possibilities for design, implementation and testing. To accomplish these specialized tasks, scientists engineer chip components that filter, purify, sort, distribute, catalogue, and even make copies of biological elements. The fundamental physical and chemical properties of the chip system simply provide the jumping off point for implementing the appropriate combination of intricate design strategies that solve the problem at hand.

Putting cells in their place

So what do these miniaturized on-chip devices look like? In Professor Luke Lee's bioengineering lab, the chips commonly take the form of an array of small moldable polymer "traps" that capture cells from a microfluidic flow. Imagine a glass-encased microchip that looks strikingly similar to the Pac-Man game of yesteryear, with cells maneuvering through a maze of paths and barriers. Pressurized flows push the cells along while single or multi-cell mechanical barriers trap or gather cells, preventing them from flowing out the other end of the chip and housing the cells for downstream manipulations. The

trapping wells can be manufactured to vary in size ranging from large wells designed to collect clusters of cells to microscopic traps that capture single cells.

In addition to the maze of capture wells, the lab has developed an on-chip procedure to break trapped cells apart using a targeted electrical current, releasing the cells' internal contents for further analysis. Under an alternative scheme, an electric pulse briefly compresses the cells' outer membranes to allow external genetic material to enter the cell and become incorporated into the host genome. This on-chip genetic trick can be combined with on-chip cell culture in which a temperature-controlled chamber is used as an incubator to proliferate single cells after applying the genetic modifications. Lee's lab is now using these basic cell manipulations to create chips that test and validate current models of cancer cell adhesion, tumor formation and nerve cell function.

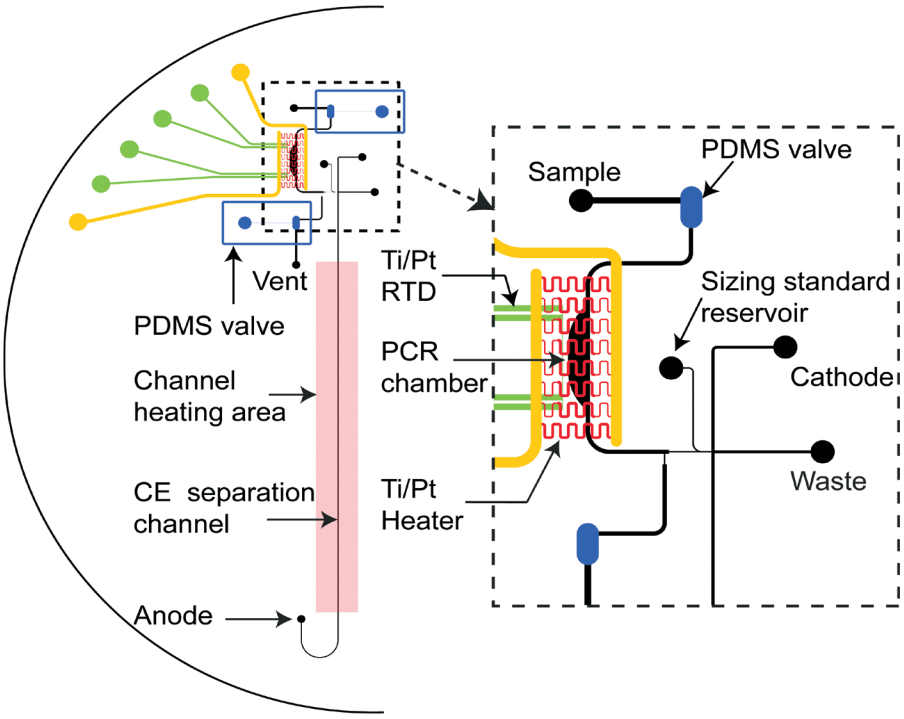
From cells to genes

While Lee's group manipulates whole cells, chemistry Professor Richard Mathies focuses on manipulating the biological molecules that comprise the genetic basis of cells, namely the cellular nucleic acids, DNA and RNA. The idea to focus on nucleic acids started rather unexpectedly from his groups' early explorations of a simple valve system that precisely gates and controls the on-chip flow. "What started as a very fundamental exploration of the power of a simple valve to control fluidics expanded to meet the many needs of a wide variety of practical problems," explains Mathies. The valves, which can control fluids with very high precision, have allowed Mathies' group to think creatively about the management of biological molecules with sensitivities and scales unheard of just a decade ago – an approach that has proved particularly powerful for manipulating molecules like DNA and RNA.

The microvalves are manufactured by sandwiching a thin piece of rubberized polymer between the two etched glass plates or wafers. On the glass plate above the membrane, a thin glass obstruction blocks the flow of liquid while the plate below contains an etched depression that is connected to a vacuum pump. Any time a vacuum is administered from beneath the depression, the rubber is displaced down and away from the glass barrier to allow fluid to flow through the valve as long as suction is applied. This elegant control mechanism has given biochips the capability to precisely measure and control nanoliters of fluid (one billionth of a liter), allowing for more efficient fluid control and thus more sensitivity for on-chip measurements. As a result, chips can contain capillaries where, as Mathies describes, "one microliter of fluid [one thousandth of a liter or close to the smallest visibly discernable drop of liquid] would now be nearly two meters long on-chip". With this kind of accuracy and control, standard manipulations are transformed into entirely new dimensions of distance, time and efficiency.

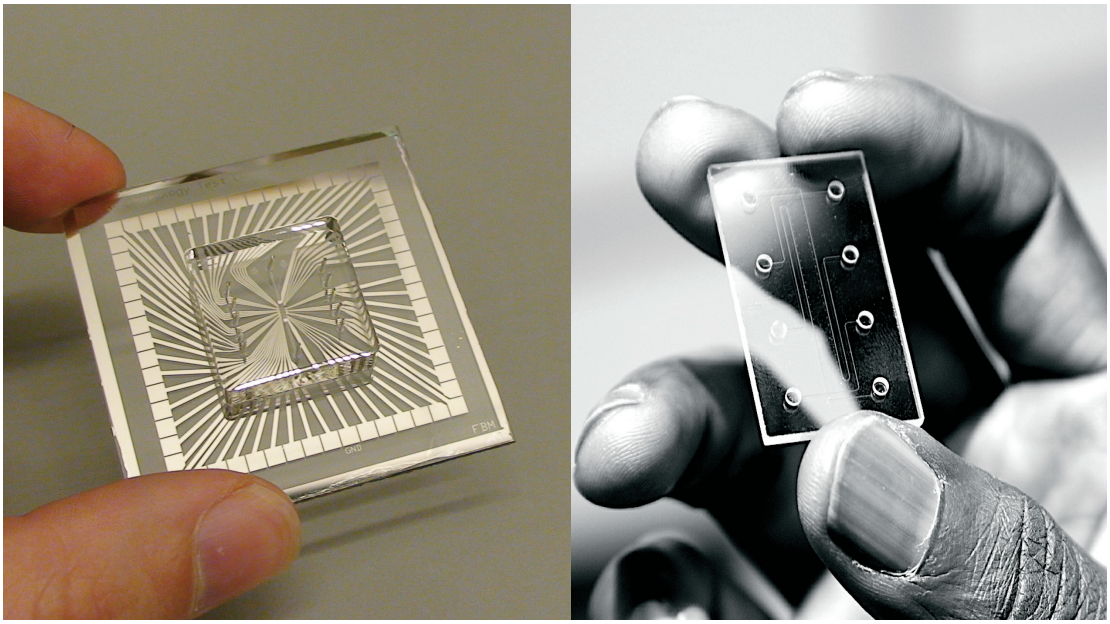
One traditional laboratory process that has benefitted tremendously from the reduced scale and integrated fluid management is the polymerase chain reaction (PCR), a process that uses repetitive synthetic reactions to make millions of copies of identical DNA sequences. The on-chip equivalent of PCR now uses only hundreds of nanoliters of liquid instead of the classical instruments that use a thousand times more volume. Because PCR requires successive heating, cooling, and mixing cycles, the chip can automate this process and the reaction time is reduced to less than 30 minutes, compared to the two or more hours needed for the standard, lab-scale procedure.

In more advanced experiments, the lab has expanded technology developed for the Human Genome project to form rapid sequencing and genotyping chips that read each "letter" of the genomic material within a minute biological sample. In collaboration with Matthew Francis and Carolyn Bertozzi, also in the Department of Chemistry, the Mathies group developed a single chip that combines single cell capture, PCR amplification of unicellular DNA or RNA, and a genetic screen to compare that cells' DNA or RNA with other cells in a mixed population. Each of these steps involved significant testing and validation in isolation. More such collaborations are in the future as single-cell genotyping experiments are seen as a necessary tool for stem cell biologists, tumor and cancer researchers and geneticists alike.



A schematic diagram depicting the contents and construction of a DNA forensics chip that was developed by the Mathies lab. A small fluid sample is loaded ("Sample" port) and it's flow is controlled at the valves ("PDMS valve") such that the correct amount of DNA is loaded into the PCR chamber for replication by successive heating and cooling reactions. After replication by PCR, the sample is separated and 'read' by laser light measurement.

Image courtesy of Peng Liu



An example of the cell lysis chips being designed in the Lee lab (left). Cells are delivered to and captured in the central chamber (in the center of the chip) and an electrical current is passed via the silver electrodes (radiating out from the chip's center) to break apart the cells and release the cell contents for further analysis and processing.
An example of the type of glass-etched chips being used in the Herr lab (right) to manipulate and analyze protein samples from small biological samples. Fluids containing dissolved proteins or solutions to be mixed with the proteins are loaded using the small circular ports and the fluid flow is passed through the microchannels seen as the lines connecting the input ports.

Image courtesy of Frankie Meyers (left) and Niranjana Nagarajan (right)

Prototyping protein chips

Efforts such as the Human Genome project and large-scale genetic screening for heritable diseases have provided compelling reasons to pursue DNA-based microchip analysis, but Herr and other researchers are keenly aware that protein analyses are equally powerful for disease diagnostics. It is proteins that really do the work of keeping cells healthy and fighting off disease. Accurate and real-time measures of such processes through protein profiling affords great power for improving treatment regimes and individualized drug development. Herr and her students are primarily interested in harnessing the advantages of the reduced-scale chips to arrive at new and more effective protein manipulations with the hope of improving both laboratory and clinically relevant measurements. As a first step in this direction, they have introduced protein separation, labeling and detection systems into their glass-etched chips.

On-chip protein separation gels are one of the many customizable tools in Herr's on-chip arsenal. These homogenous polymer gels start as a liquid that is introduced into an empty chip and solidified into place with the aid of laser light. Once the gel is in place, an electrical field is applied to the chip to drive charged proteins through the gel in accordance with their molecular charge and size. Additional membrane-like elements that filter or concentrate proteins from a microfluidic solution also add separation power. These complementary elements are used in concert through a combination of fluid flow and electric current to move and enrich proteins in a prescribed way.

This technology is only useful if the proteins can be visualized, which is usually done by some sort of labeling procedure. In the lab and on-chip, researchers use purified antibodies that have light emitting molecules attached to them to bind to and visualize proteins that they are interested in following. While long available on the lab scale, the reduced scale environment of the chip allows Herr to concentrate and then label proteins to measure samples of very low abundance. These measures are then used to distinguish normal and disease-associated protein profiles in just a single drop of liquid, such as from a tear, a drop of saliva or spinal fluid ex-

One Cell, Two Cell, Red Cell, Blue Cell

There are all kinds of different cells, and often the number and type of cells in a sample can provide a lot of information about the health of a patient or the success of an experiment. Wouldn't it be great if there were a quick and easy way to count and characterize cells? Mechanical engineering professor Lydia Sohn's lab designs microscopic pores, hardly wider than a single cell, to do just that.

The pores are millimeter-long channels, through which liquid flows and conducts a current. Foreign objects (including cells) entering the pore block the flow and thus cause a drop in conductivity. To actually characterize specific cells that pass through, the pores are lined with antibodies that interact with markers on the cell surface, slowing cells with the marker of interest. By measuring the duration of the conductivity drop, it is possible to distinguish between cells with the marker (long drop) and those without (short drop). Dr. Sohn published a paper in the August 2008 issue of *Lab on a Chip* demonstrating proof-of-principle for this system.

The potential medical applications of these pores were the driving force in their creation. Professor Lucy Godley of The University of Chicago, a co-author on the Lab on a Chip paper, is interested in developing a means to quickly diagnose acute promyelocytic leukemia (APL), a blood cancer that usually afflicts adults and can cause fever, fatigue, weight loss, and other unpleasant symptoms. APL is readily curable, but treatment must be administered quickly, often within 24 hours of admittance, and is dangerous when given to non-APL patients. APL patients admitted on nights and weekends are sometimes not diagnosed quickly and may die as a result. Godley believes a device based on the pore system could provide a quick and simple method of detecting APL-associated cell types, allowing a faster response and hopefully saving lives. The portability and low cost of the system should make its incorporation into the medical field relatively easy. The devices themselves cost less than a penny each, and the handheld box to monitor pore conductivity costs only $1000.

tractions, creating "a cleaner format through which standard clinical measurements can be done in an automated or hands-free way," as Herr says.

Beyond the halls of science

While careful not to overstate the impacts of their work that is, at the moment, still largely performed within the confines of the lab, UC Berkeley-based lab-on-a-chip researchers all have visions of developing and validating chip systems with broad applicability to real world problems. As Herr notes, "most of my lab right now is working on the basic material science, systems engineering, and electrophysics of what's happening inside the integrated chips but all of them have the goal of making quantitative measurements of clinical relevance." And why not, since the microchip platform can address problems that in some cases other methods cannot. In addition, many of the on-chip assays are faster, more portable, sparing in their sample usage, and often more sensitive than their traditional counterparts. While cost can be a barrier for the one-of-a-kind chips, options for large-scale manufacturing are being pursued that may soon create chips that can be produced cheaply enough to be disposable. With this as a future paradigm, UC Berkeley groups are eager to show that biochip assays can provide immediate solutions for diagnostic and industrial needs.

In a recent proof of principle study, Herr and collaborators from the UC Berkeley-affiliated Joint BioEnergy Institute (JBEI) and the University of Michigan School of Dentistry published a paper showing that on-chip microfluidics can be used to accurately test saliva for proteins that have clinical importance for oral health. This so-called point-of-care diagnostic study shows that fluorescence-based measurements of a saliva protein known to be associated with progressing gum disease can be used to accurately screen patients for their relative risk of advancing oral disease. And while the results are highly significant themselves, the added benefit is that Herr had only to "ask for small samples and could get out meaningful results, making their clinical collaborators very happy." Additionally, she says, "if we can do it fast and in an automated way they are even happier because they don't have to dedicate their time and resources examining these samples."

Another project currently in the early stages of testing and development in her lab is a diagnostic measurement of traumatic brain injury using protein assays of cerebrospinal fluid and serum. While the details of which proteins will be measured in the study are still under consideration, she and her collaborators plan to measure the levels of a few select proteins that will indicate the degree of trauma and may also quantify the degree of natural and post-operative healing and repair that is taking place following a head injury. From a diagnostic perspective this holds great potential because many proteins can be measured from a single small sample, which eliminates the need for repeated, extremely painful extractions of cerebrospinal fluid. Novel discovery is also possible by augmenting the cerebrospinal fluid studies with highly sensitive blood serum measurements to see if leakage from the central nervous system to the plasma can be detected, and whether this correlates with the degree of trauma.

The diagnostic power of biochips is certainly not limited to diseases of the western and developed world. Herr is just beginning to become involved in infectious disease diagnosis through affiliations with organizations like the UC Berkeley Center for Emerging and Neglected Diseases and an international group, Program for Appropriate Technologies for Healthcare (PATH), that seeks to bring healthcare solutions to international rural communities.

With a similar mission, and eye towards solving international problems cost-efficiently, Bernhard Boser of the electrical engineering department has been working for some time on chip-based measurements of Dengue fever infection. Boser has developed a small silicon chip that can directly measure blood samples for the presence of Dengue fever antigens as a result of a viral infection. Inside his chip, the patient's blood is mixed with tiny magnetic beads attached to antibodies that bind the Dengue fever antigens. There is also an immobile plate coated with Dengue antibodies that is anchored to the chip. When the virus is present, an antigen sandwich is formed that tethers the magnetic beads to the chip's antibody coated plate via the viral antigen. Any unbound magnetic beads are washed out of the chip and then a device is activated within the chip to temporarily magnetize the bound beads. This magnetic signal strength is recorded by the chip, which corresponds to the number of bound beads and thus the patient's viral load. Because his chips are cheap (less than $1 each) thanks to potential economies of scale and the use of older (but still very reliable) chip technology, he has long envisioned modify-

Direct cell characterization can be useful for a number of clinical and research applications, but Swomitra Mohanty, a post-doc in the Sohn Lab, is interested in a different use for the pores: antibody detection. The body's immune system creates specific antibodies in response to different infections, so identifying antibodies can be a means for diagnosis. The assay uses glass beads that only bind a given antibody of interest. The beads are exposed to a patient's blood serum and then passed though the pores. If the antibodies of interest are in the serum, they will coat the beads, effectively increasing their size and leading to a greater drop in conductivity when traveling through the pore. Dr. Mohanty hopes use this system to study neglected diseases, especially because the pores' portability and low price make them ideal for use in the developing world. Currently, he is investigating the capability of the pores to distinguish between leptospirosis and dengue fever, two tropical diseases with similar symptoms but very different treatments. With any luck, the pores will be out in the field making diagnoses within a few years.

In addition to directly saving lives, the pores can aid researchers working to better understand diseases. Bioengineering professor Irina Conboy studies stem cell aging, a process strongly tied to conditions such as Parkinson's and Alzheimer's. She needs to separate specific stem cells from mixed populations but finds existing sorting techniques such as fluorescent-activated cell sorting (FACS) to be too difficult and destructive. FACS requires special preparation to label the cells before use, and during this time, cell function can be affected. By contrast, cells can be put through the pores without any modification. In addition, while FACS requires many thousands of cells, the pores are effective with just a few hundred. Professor Conboy is finding the pores to be a useful addition to her toolkit, and many more researchers could similarly benefit from this new technology.

—Mike Brown *is a graduate student in molecular and cell biology.*

A mock crime scene that was established to test the real-world applicability of the DNA forensics chip. Mock blood samples were taken from paper towels and clothing and within 8 hours the three samples were read and genotyped at the site of the mock crime scene.

Image courtesy of Peng Liu

ing the chips to measure a whole host of disease antigens to assess infection rates among isolated, at-risk populations. This type of on-the-ground rapid testing also interests international health organizations who wish to track disease epidemics as they spread by making population wide comparisons of strain variation and environmental response to the propagating epidemic.

Taking chips far and wide

It is easy to recognize how biochips are immediately applicable to health care and disease diagnostics, yet this is a narrow subset of the practical applications for microchip technology. Lab-on-a-chip groups like Mathies' have repeatedly shown that chip-based chemical detection systems that measure a plethora of compounds have immense commercial and industrial utility for analysis and discovery projects. Although the launch timeline has recently been delayed to 2016, his lab has already manufactured a chip and reader that will travel aboard the next Mars Rover to look for biochemical traces of life on the Red Planet. This chip uses small samples collected from the planet's surface to measure the levels and compositions of molecules that can provide strong evidence as to the past or current existence of biological life on Mars. The group took great pains to demonstrate that the instrumentation was sufficiently sensitive to make accurate measurements from a variety of samples found on the planets surface. "We really feel that we developed the most sensitive measure of its kind that is currently available, all because of the technological advances that can be housed within our chips," Mathies says.

Mathies and his group have also been shaking up detection system development with more earthbound innovations by combining their DNA analysis technology with their chip manufacturing expertise. A group of his scientists recently designed, tested, and validated a fully contained human DNA forensics chip. The chip intakes a miniscule amount of human blood from a crime scene and outputs a signature DNA profile that can be compared to a known national databank of previously sequenced genomes. Within the chip, the extracted blood-born DNA is subjected to a PCR reaction to copy certain regions of human chromosomes that are so highly variable from person to person that they are considered a unique DNA fingerprint for every individual, even members of an immediate family. This is the same technology that is routinely used as evidence in criminal court, but the Mathies lab has developed a chip that can analyze blood samples at the site of the crime in only a few hours by a single technician. With the advent of this chip, the multiple days of work by several forensic scientists are reduced to a chip, a chip-reading instrument, a laptop, and a few man-hours of work.

Positioned on the brink of upward expansion, the lab-on-a-chip researchers at UC Berkeley all envision powerful ways that biological microchips can expand opportunity both inside and outside the lab. If chip-technologies successfully reach the marketplace, they will be able to provide up-to-date information to help individuals and organizations to monitor and improve personal and public health, food and drug safety, and environmental metrics. In what has commonly been called our current "age of information", these biological microchips are poised to be a key instrument for furthering our comprehension of the biological information that will be ubiquitously desired for its diagnostic and instructive power in the coming century.

Paul Hauser *is a graduate student in nutrition science.*

Peering Into the Past

How archaeology informs our modern lives

by Hanadie Yusef

Image courtesy of Nemea Center for Classical Archaeology

For the majority of us, Hawaii and Greece are spring break paradises filled with beautiful beaches and lavish parties. But for UC Berkeley archaeologists, these places are rich with artifacts waiting to be excavated and analyzed. Archaeology, however, is not limited to ancient bits of pottery. In actuality it covers a range of disciplines and hundreds of thousands of years of history.

While in some cases archeologists study the evolution of ancient civilizations, archeology is also used to better understand more recent societies. Whether it is the study of ancient Greece or Hawaiian agriculture, Berkeley archaeologists are traveling the globe to dig up the mysteries of our predecessors.

Unearthing history

In a single day in modern Athens, an ambitious tourist can see the Acropolis, the Parthenon, the Temple of Zeus, and a number of other ancient ruins. Archaeologists have been uncovering ancient artifacts in Greece for over 100 years, and in some ways the history of

the country seems completely exposed. But when UC Berkeley's Classics Department started its own archeological excavation in 1973, there was still an important question to be resolved. Written records suggested that athletic competitions similar to today's Olympics were held in Ancient Nemea, located near Athens (see sidebar) but there was no known physical evidence, and the historical events surrounding these games were also obscure.

The search for evidence of the Nemean Games, carried out by professor of classical archaeology Stephen Miller and his team of archaeologists, required a number of phases. First, they had to study the surface debris of stone or ceramics at various sites to choose an interesting place to begin their search. Next, they began excavating the site, digging deeper and deeper to move backwards through time. Each layer of soil was searched for broken pieces of pottery, coins, and other artifacts to determine the time period of that soil deposit. All the materials were collected, labeled, and taken to the site's museum for cleaning, conservation, and cataloguing.

carefully and by more workers—less was also known about the historical and chronological context of the finds than we know now."

Over the course of their time in Nemea, Miller and his cohort of graduate students discovered the stadium where the Nemean Games were held, as well as many new historical and cultural facts about the ancient Greeks. For example, the excavation of the stadium proved that the ancient Greeks accomplished far more in terms of architectural complexity than previously thought. "The single biggest, chilling, goose bump-raising thrill was the discovery of the entrance tunnel to the stadium," says Miller. "We proved that the Greeks, at least by the age of Alexander the Great, knew how to build the arch and the vault, a discovery that actually made it

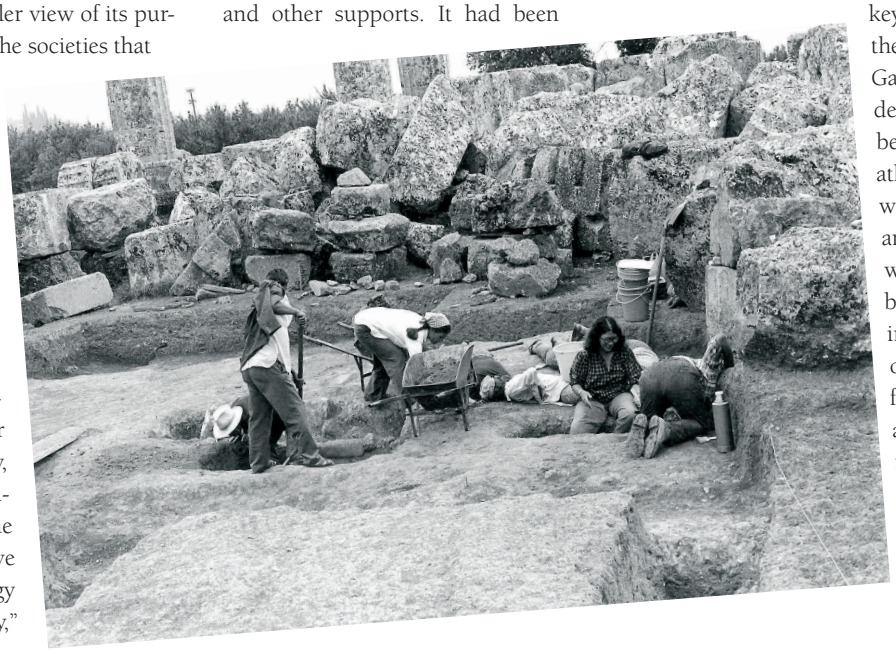
"The single biggest, chilling, goose bump-raising thrill was the discovery of the entrance tunnel to the stadium."

previously assumed the Greeks used a simpler system that only supported flat roofs.

Miller also discovered an ancient locker room where the Greeks could undress before competing in the nude – the first ever identified locker room from Ancient Greece. When Miller began his excavation, locker rooms were the furthest thing from his mind. In fact, when a student in an undergraduate course he was teaching in 1975 asked him about it, he all but dismissed the question. "At some point in the third week or so, a student put up her hand and said, 'Professor Miller, you have told us all about the athletic competitions and various athletic facilities and athletic practices, but you haven't mentioned any locker rooms.' 'Well,' I responded, 'you have learned that the ancient Greeks competed in the nude so you should understand they didn't need locker rooms to put on their uniforms.' Her hand shot back up. 'But Professor Miller, where did they leave the clothes they took off?' No scholar, to the best of my knowledge, had ever asked that question, and it came back to me 15 years later when the Nemea locker room began to emerge from the earth."

Bits of pottery, or sherds, can provide valuable information through chemical analysis of their composition and residue found on their surface, but piecing together an entire vessel provides a much fuller view of its purpose and implications for the societies that used it. "This process is much like putting together a jigsaw puzzle," says graduate student John Lanier, who has worked in Nemea studying ancient Greek pottery under the guidance of Kim Shelton, Assistant Professor in the Department of Classics and director of the Nemea Center for Classical Archaeology, founded in 2004 upon Miller's retirement. "These same techniques generally have been used in archaeology since the early 20th century," says Shelton. "But work was conducted more quickly, less

into the Encyclopedia Britannica Yearbook." The arch and the vault are a fundamental construction system used to create roofs or ceilings and span the space between walls and other supports. It had been



Digging into the foundation of the Nemean Olympic site.

Besides discovering the physical remnants of the ancient Greek athletics, Miller and his graduate students also uncovered key events that shaped the history of the Nemean Games. They found evidence that Nemea, which began to function as an athletic center in 573 B.C., was destroyed in 415 B.C. and that the destruction was accompanied by fire, bronze arrowheads, and iron spear points. "In other words, a battle was fought in this neutral, apolitical sanctuary, almost certainly with the Spartans," says Miller. "The excavations have also shown that the games did not take place at Nemea for a couple of generations thereafter, even though we know

Images courtesy of Nemea Center for Classical Archaeology

from written sources that they were held during this period."

When the stadium was destroyed, the Nemean Games were relocated to Argos until around 330 B.C. The athletic competitions returned to Nemea, together with a major building program including the stadium and its accoutrements that Miller discovered. From this time period, the team unearthed, among other findings, a new Temple of Zeus, a hotel, and a bathing house. Despite this vast construction, within two generations (by 271 B.C.), the games had left again for Argos and never returned. In the end, according to Miller, the Nemean Games were held in Nemea for only about 25% of their history.

Berkeley archeologists sift through soil to uncover ancient artifacts at Nemea.

One of Miller's proudest achievements thus far in the study of Ancient Nemea has been the resurrection of the Nemean Games, beginning in 1996. Today's Nemean Games are organized and run by a local group, The Society for the Revival of the Nemean Games, in collaboration with UC Berkeley. "Although the Nemean Games were known previous to Berkeley's arrival at the site, it was Professor Miller who found the location and excavated the stadium, and who was instrumental in creating the society for the revival of the games," says Shelton.

Digging deeper into time

As the current director of the Nemea Center for Classical Archaeology, Shelton plans to take research into a new direction. In particular, she is interested in why Ancient Nemea was chosen for a site to honor Zeus in the first place. According to myth, the Nemean Games were founded after Opheltes, the baby son of a Nemean king, was tragically slain by a serpent (see sidebar). Apart from a shrine for Opheltes that was excavated by Miller's group and probably built many hundreds of years after Opheltes lived, there is no evidence that Opheltes was ever in Nemea. The history that has been passed through the ages by word of mouth and writings such as poetry and folk tales indicates that the events the

History of the Nemean Games

Ancient Nemea, like Olympia, was not a city, but a festival center that hosted athletic competitions under the flag of truce. "The Nemean Games represent the first, and perhaps the only, time in the history of mankind that wars were stopped on a regularly recurring and predictable calendric basis," says Miller. "This was not an ad hoc truce – we need to stop fighting next Saturday so we can bury our dead – but a real force for bringing all Greeks together in trading the battle field for the playing field." Many have argued that these athletic and peaceful festivals are the ancestors of today's United Nations and Olympic games.

The Nemean Games were religious festivals to honor the God Zeus and consisted of specific religious rituals. The festival were initiated at an altar in front of Temple of Zeus, where there would be sacrifices and prayers to the god for good performances, followed by a procession to the stadium. The competitions would last for one to two weeks, with a big sacrifice and feast at the end to thank Zeus for victories. The victors would then dedicate part of their winnings to Zeus in a final show of honor.

The origin of the Nemean games is believed to lie in the myth of Opheltes. When Opheltes was born, his father Lykourgos consulted the Oracle at Delphi to find out how he might ensure his son's health. The priestess replied that the baby must not touch the ground until he had learned to walk. Lykourgos assigned a slave woman the task of caring for the child, but one day when men known as the Seven Heroes passed through Nemea on their way to a battle in Thebes the slave woman placed Opheltes on a bed of wild celery to get the men something to drink. Opheltes was killed by a snake bite, fulfilling the prophecy. The funeral games that were put on by the Seven Heroes in his honor were said to be the beginning of the Nemean games.

"The athletic competitions consisted primarily of stadium races of various lengths, chariot races in the hippodrome, and there would have been some field events, like a discus throw and javelin throw, as well as some wrestling and boxing," says Shelton. The modern and modified Nemean Games are held once every 4 years, the fourth Nemead having taken place this past summer with record attendance. In ancient times, only men were allowed to participate and watch the competitions, which took place in the nude. Nowadays, men and women of all ages can participate, and competitors wear small chitons (tunics) and run barefoot like the ancient period. The games consist of 100 meter dashes and 7.5 kilometer races. The longer race starts at the Temple of Hercules in Kleonai and ends in the Nemean stadium.

myths are based on took place in the Bronze Age, at which point Nemea was a kingdom of some sort. By the time the Nemean Games were held, Nemea was not a town with inhabitants, but just a sanctuary for Zeus and site for the games.

Shelton is making plans for new excavations, beginning in 2010, to find evidence of human settlement in Ancient Nemea before the founding of the games. She wants to know who was in Ancient Nemea during the time of the myths and what their lives were like. She also wants to learn more about the religious history of the site. During the times of the Nemean Games, Nemea contained not only a stadium for the games, but also held temples, gardens, and cyrpus groves that made up an entire sanctuary to Zeus. Was there also a sanctuary in the time of the myths, during the Bronze Age? In other words, do religious practices such as sacrifices and rituals go back to prehistoric times? Shelton's expertise is in ceramics and pottery, and she hopes to study these types of artifacts, along with small metal fragments and any architectural evidence, to separate myth from fact.

Ancient sustainability in Hawaii

Shelton's and Miller's work fits the traditional view of archeologists as researchers uncovering the history of civilizations that existed thousands of years ago, but some archaeologists are studying civilizations that existed more recently. On a different set of islands, these in the Pacific Ocean, Berkeley archaeologists are actively studying native Hawaiian society and its relationship to agriculture. The Oceanic Archaeology Laboratory (OAL), established by UC Berkeley in 1989, carries out research into the archaeology, prehistory, and historical anthropology of the Pacific Islands and their indigenous peoples and cultures in the hope of applying what they learn to modern agriculture.

Since 2001, archaeologists, ecologists, demographers and soil scientists from several universities, including UC Berkeley, have been collaborating on archaeology projects in Hawaii. They are using Hawaii as a model system to understand the link between changing social and political structures of human civilizations and their non-industrialized agricultural production systems. Patrick Kirch, Director of the OAL and professor in the Departments of Anthropology and Integrative Biology, is heading the project on the Berkeley end, while his principle collaborator from Stanford is biology professor Peter Vitousek.

Kirch's team is trying to understand how the agricultural systems of pre-European Hawaiians related to the environmental aspects of the landscape, such as soil nutrient distri-

Pre-European Hawaiians tended scenic fields like this one in the Kahikinui agricultural zone for several hundred years.

Images courtesy of James Flexner

bution and the long term effects on soil properties, and its sustainability. "We are looking at the linkages between agriculture, soils, and human population, through the perspective of archaeology. We are linking natural science with social science to determine the real long term processes associated with changing societies," said Kirch.

Kirch and his colleagues have studied the effect of long term agriculture and the impact of several hundred years of cultivation on soil nutrients on the Hawaiian island of Maui by combining a geochemical method of dating with an archaeological approach. Kirch's team mapped out the landscape of the Kahikinui agricultural zone, locating all temples that operated as centers for control over production. Based on this analysis, they chose to study layers of soil in various locations once used by native Hawaiians for cultivation, as well as the layers of soil from uncultivated areas as a comparison. They then measured physical characteristics of the soil such as pH, density, color, texture, and the amount of key chemical nutrients. "We were able to get quantitative measurements of key nutrient loss in soil over 300 years of intensive cultivation," said Kirch. The team has found that the soil used by Hawaiian farmers for growing crops has significantly lost its nutrient value, which affects crop yields. In a research project published in Science, they showed that centuries of cultivation resulted in significant loss (28 to 75%) of calcium, magnesium, sodium, potassium, and phosphorous content.

Kirch and collaborators are also studying the relationship between climate, soil fertility and the kinds of agricultural systems developed on the Hawaiian archipelago by the native Hawaiians before European contact. In another Science paper, Kirch and collaborators analyzed climate and soil fertility on the young and old islands in the Hawaiian archipelago to determine the methods of farming used by native Hawaiians in the past. They distinguished between two kinds of agriculture, one suitable for drylands that depends on rainfall to feed crops, and an agricultural system based on wetland irrigation. They reported that irrigated wetland agricultural systems are found primarily on the older islands due to their well-developed natural drainage networks. In contrast, archeological evidence has shown that dryland agricultural systems are constrained to younger islands.

To determine the factors that confined large dryland agricultural systems to the younger islands, Kirch's team studied the rainfall and soil fertility in the Kohala Mountain area. They found that on the younger islands, the amount of rainfall and soil fertility fell in the boundaries necessary to allow high crop yield from intensive dryland agriculture, while on the older islands, greater rainfall resulted in less fertile soil, as measured by the amount of phosphorous and base nutrients in the soil. Nevertheless, wetland irrigation agricultural systems allow greater crop yield and are more predictable and controllable.

Alex Bare and students lay out an excavation grid in Kaupo, Maui.

The differences between rain-fed dryland and irrigated wetland agricultural systems on the younger and older islands of the Hawaiian archipelago give insight into the social and political structures of the native Hawaiian societies that developed on these islands. Dryland agricultural systems are more labor-intensive, have lower crop yields and are more vulnerable to climate perturbations in comparison to wetland irrigation systems. Therefore, Kirch and his colleagues inferred that this may explain why aggressive and ex-

pansive chiefdoms developed on the younger islands, while societies on the older islands were more peaceful.

The timing of societal evolution

Berkeley researchers in Hawaii are also studying the sociopolitical and religious changes that took place in Hawaii before European contact. In particular, they are looking at the types of rituals conducted to honor the god of agriculture at the temples constructed at agricultural sites. Coral branches were thought to be sacred to the god and were taken out of the sea and placed on temples to honor him. Based on a precise dating method that measures the decay of the element uranium to the element thorium, known as 230Thorium dating, Kirch's group and his colleagues dated the coral offerings were made and determined the exact construction period of temples to honor the gods of agriculture at the Kahikinui district on the island of Maui.

The usual method used to date archaeological remains, radiocarbon dating, measures the relative amounts of two isotopes of carbon, one common and one relatively rare, and assigns a date to the objects based on those amounts. While the use of 230Thorium to date objects has been available for some time, this was the first time it was applied to archaeological research. "This technique isn't new," Kirch says, "but its application to dating cultural remains is new. The really neat thing about this is typically when you use radiocarbon dating, you get a high error rate, like plus or minus 50 years. With this coral dating technique, you get plus or minus three to four years! It has really aided in being able to resolve the chronology of these sites."

A more accurate prediction of the time period in which the temples in Maui were built was needed to make inferences about the sociopolitical and religious changes that occurred in pre-contact Hawaii. They used this dating information to determine when the temples were constructed and when the rituals associated with them – such as the collection of surplus food and goods as tribute and the imposition of ritualized controls of production – occurred. They are discovering that the temples in Maui were constructed within a very narrow time span of about 60 years, from 1580 to 1640 a.d. The timing of intensive temple construction reflects a fundamental change in the sociopolitical structure of the inhabitants of the Kahikinui district. Kirch concluded that Hawaiian agricultural societies were transformed rapidly from small chiefdoms to larger states that used a religious ideology based on a temple ritual system to control agricultural societies.

Studying the agricultural societies of Hawaii and how they relate to the ecology of the archipelago, as well as studying the sociopolitical and religious aspects of these societies, required the integration of many fields. Alex Baer, a graduate student working on the projects in Hawaii, explains the significance of this interdisciplinary research. "I'm trained as a Hawaiian archaeologist, but to be effective in that pursuit you need to gain a substantial understanding of biology, botany, geology, even astronomy. All of these disciplines answer different questions and ultimately allow us to better understand how past people, Hawaiians in this case, lived and thought about their world."

"This research is significant because it is relevant not only to Hawaii but anywhere in the world with non-industrialized agriculture, such as Africa and Southeast Asia," says Kirch.

Archaeology and the modern world

Whether they are studying sports from ancient Greece or the more modern native Hawaiian agriculture, archaeologists are unearthing the evolution of human civilization and culture, from the era of hunters and gatherers to advanced societies with complex architectural and cultural foundations. Not only do discoveries about past societies have implications for our current way of life, but sometimes the influence is even more tangible, like when ancient races to praise Zeus are brought into the modern world.

Hanadie Yusef *is a graduate student in molecular and cell biology.*

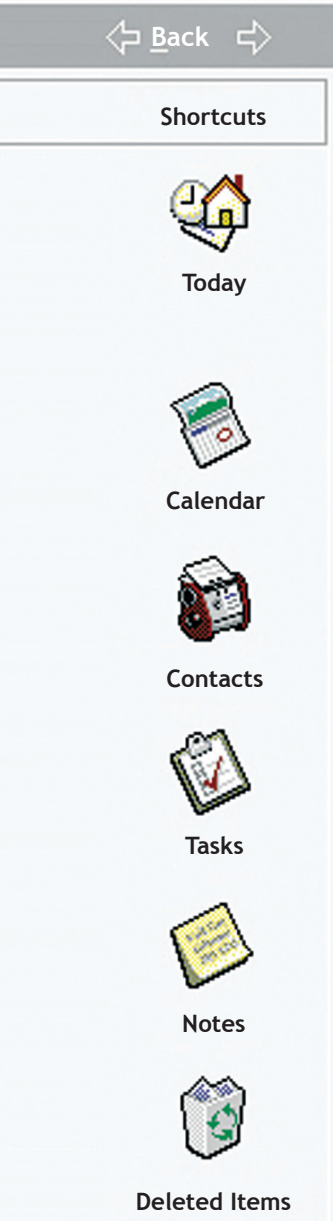
Leprosy Settlements in Hawaii

James Flexner, one of Kirch's graduate students, is conducting an archaeological study of the inmates of the leprosy settlement at Kalawao, which was active from 1866-1900. Leprosy is caused by the bacteria Mycobacterium leprae,which stimulate a severe inflammatory reaction by the body that damages the peripheral nerves and upper respiratory tract. The primary external symptoms of leprosy are skin lesions that, when left untreated, eventually lead to permanent damage of the skin, nerves, limbs and eyes. Historically, patients around the world have been quarantined, or forced to live in leper colonies. Kalawao in Hawaii is one such place.

Flexner is studying the historical archaeology of the leprosy settlement at Kalawao. "The goal of my project is to explore the ways that spatial organization and material culture structure the day-to-day practices of social life in situations of lifelong incarceration, as mediated through the stigma attached to leprosy in this case," explained Flexner.

To accomplish his goals, Flexner has conducted surface mapping and excavations at different kinds of house sites from the Kalawao settlement. He's also been analyzing numerous artifacts he has collected from the old inmates of the leprosy settlement and is also looking into numerous archives, researching the relevant 19th century documents to try to understand what people in the past thought about leprosy.

"What's really interesting is the fact that many of the people exiled to Kalawao really worked hard to create a working community, even though many of them were torn away from their homes and families," said Flexner. "The landscape, and the things they left behind, help tell that story in a way that the written documents typically don't. Leprosy is a powerful symbol for stigma and isolation, and it's fascinating to see how people coped with the disease, which causes a number of physical complications in day-to-day life, and with being exiled from the support of their families and communities."



Spam Grows Up

The increasing threat of internet abuse

by Dan Gillick

Consider the email that found its way into my Gmail inbox this morning: "Any women will jump into the abyss for a man that wears a Submariner SS watch. At any place of the world, you will know the right time. Hurry to Click." Though this sounds like a parody—mock-heroic advertising—the numbers convey a more serious narrative. In 2007, worldwide email spam increased by 100% to over 120 billion messages daily, accounting for 85-95% of all email. Some estimates say this number doubled again in 2008. That means, on average, more than 150 unwanted emails delivered to each internet user every day (though Bill Gates is rumored to receive upwards of 10,000).

The scale of this absurdity appears to justify an existentialist philosophy on the part of Internet users, who tend to treat spam like Estragon his boot in Waiting for Godot: he struggles to remove it, gives up, and mutters "nothing to be done…" In the end, though, the tragicomedy—"killer softwares for the price of nuts"—has an economic interpretation: while most men have little interest in abyss jumpers, it just takes a few curious souls who think nut-priced software sounds good to keep such spam campaigns profitable. As long as average revenue per email is more than the cost to send the email, the spammer's logic—send as much as possible—makes good sense.

Until recently, the dollars and cents details of spam's economic proposition were mostly a matter of rampant speculation. IBM Internet Security Systems expert Joshua Corman is widely quoted as claiming that spam sent from the notorious Storm botnet—an army of hacked personal computers controlled by spammers—is generating "millions and millions of dollars every day." Last year, a team of researchers at UC Berkeley and UC San Diego set out to test this claim.

Spamalytics

Christian Kreibich, a staff member at the International Computer Science Institute's Networking group in Berkeley and co-author of the research paper "Spamalytics: an empirical analysis of spam marketing conversion," presented at the Association for Computing Machinery Conference on Computer and Communications Security last year, begins with a plea: "A lot of people misinterpret what we're doing. We're not sending spam!" And already, the kinds of disadvantages the researchers face in the escalating struggle to secure the Internet are apparent. "The best way to measure spam is to be a spammer"—the paper's most quotable line, taken out of context, has provoked some misguided outrage.

The research, better understood as slipping tracking devices into outgoing spam emails, documents the lifespan of half a billion such messages sent by the Storm botnet. A botnet is a network of "bots", computers in offices, homes, coffee shops and atop laps around the world that have been compromised by the latest incarnation of computer virus. Storm propagates in many ways, often through spam that tricks users into downloading

and running it themselves. Once installed, the software broadcasts its availability to the Storm network. A master server organizes tasks and "proxy" bots distribute specific instructions to "worker" bots, which return status reports and request more work. Some estimate that Storm, at its peak in late 2007, controlled over 1 million computers.

Kreibich and his colleagues intentionally installed the software that runs Storm on their own servers, which began communicating with the vast network of compromised computers. Within Storm's command and control hierarchy, their machines served as renegade proxies, receiving instructions from the botnet operator which they relayed en masse to workers requesting tasks, though altered slightly to direct curious email readers to a mock pharmaceutical web site built by the researchers. The site allowed visitors to fill a shopping cart, but the checkout link returned an error message so neither personal information nor money was exchanged.

Over 26 days, they tracked some 350 million pharmaceutical emails. 76% of them were never delivered (blacklists block all email from a list of addresses which are known to be operated by spammers, for example), and 99% of what remained was probably blocked by inbox spam filters. In the end, 10 thousand users visited the pharmacy page, and just 28 tried to make purchases, averaging $100 each. All but one involved male enhancement products. Estimating that they surveyed 1.5% of the Storm network gives an approximate viagra-inspired revenue of $3.5 million in a year[1]. "A bit less than 'millions of dollars every day', but certainly a healthy enterprise," the paper explains.

In 2003 Slammer infected 75,000 computers in under ten minutes. Airline flights were cancelled, election proceedings faltered, and ATMs failed.

But what about the cost of sending email—the other half of the equation? Are Storm's operators selling Viagra or are they selling the means to sell Viagra? The possibility of the latter is frightening because it suggests a maturing underground economy as opposed to a few isolated programmers causing problems. Anecdotal reports suggest that the retail price of spam delivery, the going rate on the black market, is nearly $80 per million emails. At this rate, however, Storm's "clients" would be losing money quickly: only $1 in revenue for every $10 spent, assuming they keep all the profit from the purchases. And yet, the spam keeps coming.

Abuse arrives

The world's first email spam (the term itself derives from a Monty Python skit involving singing Vikings at a spam-heavy restaurant—repetition ad nauseum) was sent on May 3, 1978 by Gary Thuerk, an aggressive marketer of DEC "minicomputers", who had an employee enter the electronic addresses of 600 west coast customers—mostly computer scientists—by hand. The message, written in all capital letters, advertised product demonstrations in Los Angeles and San Mateo. Delivered via Internet predecessor Arpanet, it was greeted with widespread hostility and a notable promise from Arpanet Management Branch Chief, Major Raymond Czahor: "appropriate action is being taken to preclude its occurrence again".

In September of 1990, Vern Paxson, now Professor of Computer Science at UC Berkeley and senior scientist at the International Computer Science Institute, enrolled in a "special topics" course on networking as a graduate student at Berkeley. He began measuring network traffic, the amount of information flowing over the Internet. At the time, there were some 313,000 Internet hosts, or connected computers, passing 9.5 megabytes of data—the textual equivalent of the six longest works of Charles Dickens—through USENET bulletin boards (a newsgroup precursor to the World Wide Web) in a day. By the time his first paper on network measurement was published in May of 1994, the Internet had grown at least ten times larger, including 3 million hosts shuttling considerably more bulletin board data each day than Dickens wrote in his lifetime.

Looking back, the only thing more striking than the rate of growth is the consistency of the expansion. Between 1986 and 1994, the total volume of USENET traffic grew by 75% each year with startlingly little deviation. And then, everything changed. Between late 1994 and 1996, the average size of USENET postings, which had remained virtually constant since the mid 1980s, increased nearly 10-fold. People were no longer just exchanging small written messages; they were uploading pornography and stolen software. "Abuse had arrived," Paxson declares.

If each outgoing email after the first 1000 in a day were charged one cent, spam would likely disappear at no cost to the vast majority of email users. Or, outgoing emails could incur a small fee, optionally refunded by the recipient. A variety of similarly clever economic measures have been proposed, but with little in the way of results. This is largely because the problem is universal, so any economic solution will require universal cooperation. Instead, spam filters, a technical solution, have become the subject of considerable research.

Most spam filters are based on a statistical model called Naïve Bayes, named after the 18th century British mathematician Thomas Bayes. The idea is that each word in an email is evidence for or against applying the spam label. "Viagra" for example, is strong evidence for spam, but it is not conclusive. Some fraction of legitimate emails contain this word. The classifiers learn probabilities for each word, estimated from huge numbers of manually labeled emails (note the "Report spam" button in Gmail), which are combined as if each word represented independent information. This assumption is faulty (occurrences of "Viagra" and "disfunction" are not independent) but workable, the naïve part of the model—to give a final probability.

Spam filters have grown a bit more sophisticated. How to deal with images of text? What about emails with a few paragraphs of Jane Austen at the bottom that look legitimate to the classifiers? What about emails exchanged by employees of pharmaceutical companies? Modern spam filters incorporate image processing and personalization. But statistical methods have remained standard despite, or perhaps due to, their simplicity.

[1]The tracked campaign was not fully active all 26 days. The $3.5 million estimate is based on revenue for the active days: $9500 per day times 365 days.

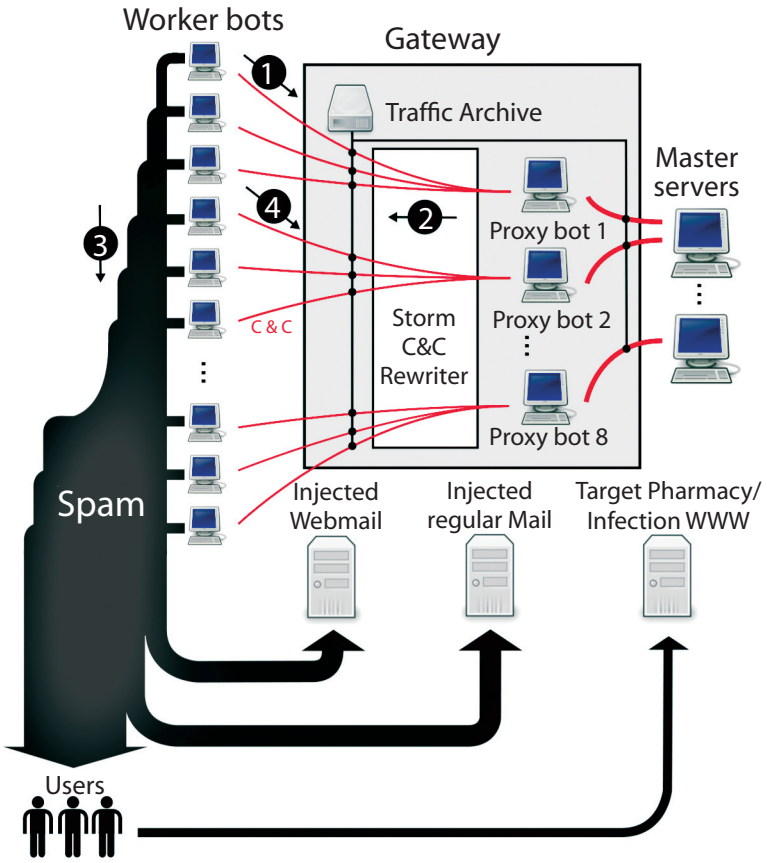


Image courtesy of Christian Kreibich

The Storm spam campaign layout and the Spamalytics infiltration. (1) Worker bots request spam (email text and addresses) through proxy bots, (2) proxies forward work orders from master servers, (3) workers send the spam and (4) return delivery reports. The researchers infiltrated the command and control channels between workers and proxies

Amateurs

"Mid- to late-90s network abuse was characterized by vandals and braggarts," says Paxson. "Hackers were energetic but imitative," their motivations petty rather than financial, often tagging, graffiti-style, the software tools they wrote for exploitation. He estimates that nearly 75% of junk postings involved stolen software during this period.

Meanwhile, as the number of connected computers continued to grow steadily into the new millennium, a far more nefarious trend was developing. Paxson shows a graph of automatic scan activity observed at Lawrence Berkeley Lab (LBL)—programs looking purposefully or at random for computers to connect to easily—that shows a sharp increase in late 1999. The era of automated attacks was dawning.

The conceptual breakthrough that gave birth to the modern state of affairs is the self-replicating program. Abstractly, a computer program takes some input, does some computation, and returns some output (much software combines several of these units to produce an interactive effect). While the theory of a program that could output itself was developed before computers were a reality, practical implementations appeared in the 1980s. The term virus was coined in 1983—a program that infects other programs, modifying them to email everyone in your address book, for example, often with copies of itself. While a virus typically requires some action on the part of the user, like opening a misleading email attachment, a worm, by contrast, works independently, exploiting a flaw in the design of some common software like Microsoft Windows.

"When an attacker compromises a host, they can instruct it to do whatever they want," Paxson says. In particular, "automatically instructing it to find more vulnerable hosts to repeat the process creates a worm—a program that self-replicates across a network." Since each new copy works on copying itself too, a worm can grow exponentially fast. The Code Red worm of July, 2001 infected 360,000 computers in 10 hours. On January 25, 2003, Slammer infected 75,000 computers in under ten minutes. Airline flights were cancelled, election proceedings faltered, and ATMs failed. Paxson estimated that a well-written worm could cause upwards of $100 billion of damage in a day.

The invisible hand

While worms continue to plague the Internet—Conficker infected nearly 15 million Windows-based personal computers in January—the worm era, characterized by an intrepid anarchist playfulness, gave way to something with real staying power: Markets. "A sophisticated underground economy has emerged to profit from Internet subversion," Paxson explains. Bots are herded together into botnets, computational armies with enormous collective bandwidth, and "dirt-cheap access to bots fuels monetization via relentless torrents of spam."

For the average emailer, this monetization has manifested itself mostly in email volume. But behind the scenes, all sorts of new markets are flourishing. ProAgent2.1—"records all keystrokes… usernames, passwords… completely hidden!"—is sold by Spy Instructors Software, which advertises its own customer support department. AllBots, Inc. offers "account creators" for MySpace ($140-$320), Youtube ($95), and Friendster ($95), and advertises "GOOD News!!! We have just integrated CAPTCHA Bypasser"—software for automatically reading the squiggly-lined characters intended to confirm humanness.

Opportunities for monetization lead to specialization, competition, and increasing ingenuity. As Paxson points out, these trends are making technical security research much more difficult than "fending off ardent amateurs." Furthermore, the emergent economic ecosystem, often built on affiliate programs, makes litigation tricky. "Selling software to efficiently subvert a machine is probably not illegal," he notes.

Botnets like Storm seem to be growing, fooling naïve users into installing the program in a variety of ways. In an expansion campaign tracked by Kreibich, Paxson, and their colleagues, Storm computers emailed huge numbers of "AwesomePostcards"—complete with dancing banana—for users to download the malicious software themselves, infecting machines Trojan-horse style. Kreibich reports that this campaign was alarmingly successful: "One in ten people visiting an infection website downloaded the executable and ran it."

Once Storm is installed, it's virtually undetectable. It uses very little processing power and does its work quietly and discretely

when nobody is likely to mind. Orders come in gradually, perhaps a few thousand email addresses at a time, to email regarding Viagra, knock-off watches, stolen software, awesome postcards. Modern spam filters are clever, Kreibich explains, so "no two emails that Storm sends are exactly the same." The bots are instructed to create random permutations of the essential words and letters, specifically designed to slip past the defenses of Gmail, Hotmail, and Spamassassin.

What are we up against?

While a few extra emails about sexual enhancement products are mostly an annoyance, the possibilities for an attacker who controls hundreds of thousands of computers are alarming. Shortly before the 2008 South Ossetia war, a Distributed Denial of Service (DDoS) attack took down the web sites of Georgian President Mikhail Saakashvili and the National Bank of Georgia. This was the work of a botnet, its bots instructed to connect to these sites simultaneously, overloading the servers that process incoming requests for data (it remains unclear whether this was coordinated by the Russian government).

DDoS attacks, described in a Wired article as "the digital equivalent of filling a fishtank with a firehose," have recently targeted the BBC, CNN, AlertPay (online payment), and GoDaddy (domain name registration), for example. Some of these, like a current attack on KidsInMind.com, a movie rating site for parents, appear to be acts of "hacktivism", but the monetary incentive—demanding ransom from companies unprepared to parry such attacks—is feeding a post-cause generation.

Unfortunately, Spam and DDoS are just the tip of a formidable iceberg. Identity theft, by logging keystrokes on compromised computers, or by coordinated password guessing, for example, appears to be on the rise, though it seems that this is not yet the focus of most botnet operators. More generally, any kind of private information with value, from internal business statistics to government secrets, creates incentives for theft.

Bitblazing

Opportunities for attackers create research projects for graduate students like those working with Dawn Song, a professor of computer science at Berkeley. A deep understanding of what makes software exploitable and the ability to infer the logical structure of a program before running it are the keys to buttressing the user side against even the most novel attacks. Broadly speaking, these are Song's research goals in her group's BitBlaze project, which aims to screen software for potential danger and defend against malicious code—exploits that cede control to an attacker.

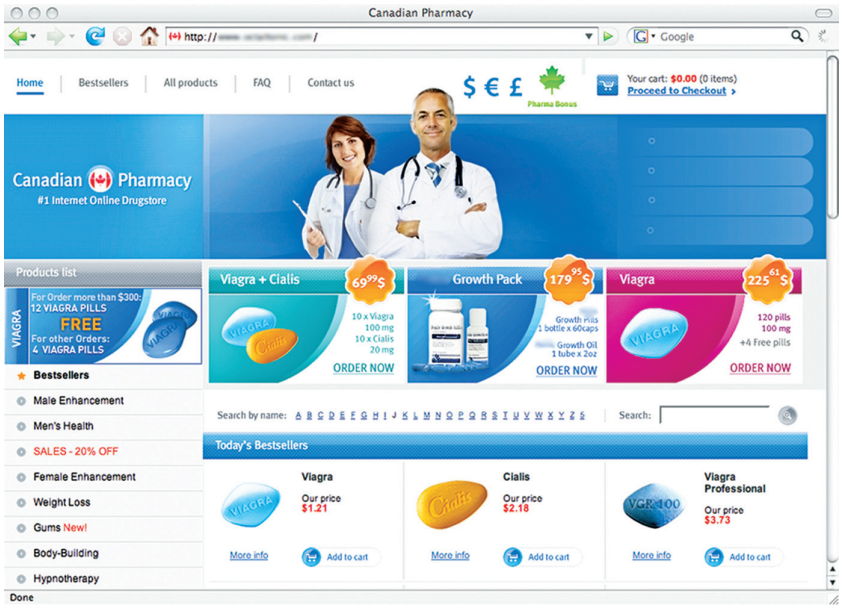
Prateek Saxena, a graduate student working with Song, outlines the most common exploit around, involving a "stack buffer overflow". By studying a piece of software, an attacker can often find a specialized input that causes the program to crash, and in the process, return control to the attacker rather than the user. While it is good programming practice to include checks for buffer overflows, Saxena says "missing a few is all but inevitable." Programmers, after all, are human. Microsoft's updates or "patches" often add an overflow check for some buffer buried deep in the Windows operating system. Unfortunately, according to Saxena less than 5% of users update in a timely fashion. In addition, Song's group has shown that exploits can be generated automatically by using a Microsoft patch to find flawed code—a serious concern given how quickly worms can spread.

More generally, the group is interested in program analysis, a subfield of computer science concerned with inferring the behavior of a program from its source code. This is important for security because it is "a step up from antivirus signatures," Saxena explains (traditional antivirus software looks for distinctive sequences of characters in files—like a fingerprint), "which fails because malware encodes itself."

Consider the problem Kreibich and his colleagues faced in reverse engineering Storm. Following an AwesomePostcards link intentionally, they downloaded a 140 kilobyte executable file. That's around 300 pages filled with 0s and 1s. From this binary novel, they sought first to distill the command and control structure of Storm, and second, to create a subtly modified version of the file for their research purposes. Song's group would like to scan such binary files automatically, looking for suspicious instructions.

Their approach is two-pronged. The first, static analysis, is more theoretically appealing and more challenging. Each computer program, at heart, enacts some underlying flow chart. A student in an introductory computer science course might be asked to produce such a chart from a few lines of code—often a tricky exercise. The task of static analysis is to create this flow chart automatically, from arbitrary code. There is one other complicating factor: modern programming languages provide a layer of abstraction between the commands the machine can actually process and the way human programmers think. "Compiling" a program translates it from a human-readable language into a machine-readable language, written and stored in binary.

The second prong involves dynamic analysis—taking a functional or behavioral



A screenshot of the mock pharmaceutical web site created by the Spamalytics researchers to measure user click-through and conversion.

Image courtesy of Christian Kreibich

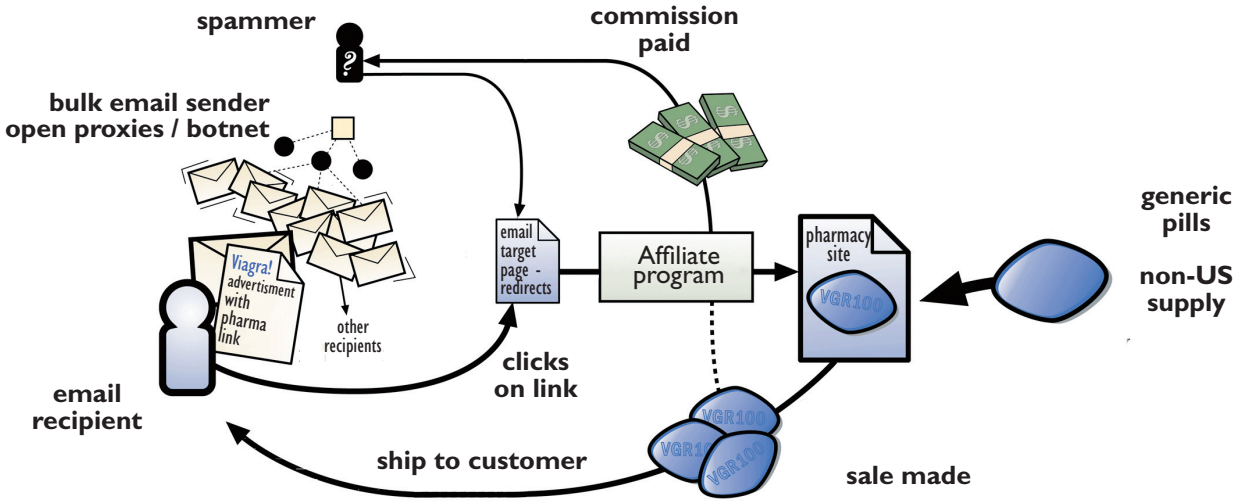


Image courtesy of Stuart Brown

The general structure of an economically mature Viagra spam campaign: The spammer provides addresses and a means to distribute email via a botnet while the pharmacy procures and ships cheap pills. Then, any entrepreneuring individual can rent the spammer's services, making a profit by sending traffic to the pharmacy.

approach to understanding a mysterious binary file. Saxena calls this strategy "taint tracking". The researchers create a "virtual machine", an operating system running inside the normal operating system, and run programs in this controlled environment, collecting information. What data is read from memory and written to memory? What files are accessed? Is any connection established with remote computers? What kind? By assembling such statistics for known safe programs and known malware, they can compute the probability that some unknown program may be dangerous based on its behavior.

One goal of the BitBlaze project is to revolutionize antivirus software by combining elements of both static and dynamic analysis. By testing unknown software in a controlled analysis environment, Song hopes to dramatically improve protection for Internet users. "People download random programs all the time, like curious children will chew on just about anything," Song says. Internet users need something like watchful parents to keep them out of trouble.

Carrots and sticks

Professor John Chuang, at Berkeley's School of Information, shares Song's feelings about required supervision, but takes more of an economist's perspective. "How did botnets come about?" he asks rhetorically, referring not just to the technical achievement but to their centrality in the developing black-market economy. "The fundamental insight is that there is a misalignment of incentives at work." While the botnet operators profit, the perceived cost to each user is effectively zero. Individuals almost never know if they are infected and don't care. Even if the result is some kind of identity theft, the connection between a dodgy website visited six months ago and some mysterious credit card charges is tenuous at best, and practically, the credit card companies and banks almost always assume the financial burden in such cases.

Chuang likens the botnet phenomenon to a kind of "reverse free-riding". Whereas file sharing or public television benefit everyone regardless of their support, botnets are "a peer-to-peer network contributing to network insecurity—a public bad as opposed to a public good." To free-ride the Internet is to contribute to a public bad. "Botnet operators have stumbled upon or engineered technology based on this misalignment and exploited it to the fullest," says Chuang.

If the basic problem is a misalignment, then the solution may involve re-aligning. Chuang and his students are just beginning to explore what this might involve. The "stick" scenario makes users economically liable for security breaches originating at their computers; the "carrot" option—"typically more successful," says Chuang—rewards users who invest in security. Good behavior—keeping antivirus software up to date, installing operating system patches, avoiding suspicious websites and downloads—could result in a

The Russian Business Network

The notorious Russian Business Network (RBN), referred to as "the baddest of the bad" in a report written by security company VeriSign, is "a for-hire service catering to large-scale criminal operations." Originally organized by computer science graduate students as a legal Internet service provider, illegal activity proved financially irresistible. Little is known about the network, but rumors abound: it has been blamed as the perpetrator of the Georgia cyber-attacks; its leader, known as "Flyman" is supposedly related to a powerful Russian politician; it is the alleged operator of Storm.

Many Internet providers host illegal material—online gambling sites, for example—but according to Verisign, "the difference is that RBN is solely criminal." They also seem emboldened by immunity from Western law enforcement. When, in late 2006, the National Bank of Australia tried to fight the "Rock Phish" scheme that tricked users into revealing account numbers and passwords, the RBN took down their website for three days.

"RBN feel they are strongly politically protected. They pay a huge amount of people. They know they are being watched. They cover their tracks," says Verisign. According to the report, only strong political pressure on Russia will keep the RBN in check.

Geographic locations of spam "conversions": 541 users (yellow flags) clicked on emulated greeting cards and 28 users (red flags) tried to pay for products at the mock pharmacy site.

Image courtesy of Christian Kreibich

rebate from an Internet Service Provider like Comcast or Verizon. Otherwise, Chuang suggests, they could raise premiums, like car insurance rates increase after an accident.

The car insurance analogy is not perfect, but it reveals something about how new and unregulated the Internet industry is. "I've heard this line about how we call it the 'Information Superhighway'," says Chuang, "and yet there's no license to drive or driver's education." A reckless driver is dangerous for everyone on the road, so it's good for society to insist on training drivers and penalizing them when they go too fast. Perhaps Internet users should be treated similarly.

Missing data

Back at the International Computer Science Institute, Dr. Paxson produces a few photocopied pages from a precarious stack. They are transcripts of legal proceedings—a credit card fraud case. He flips through and points to a table indicating the stolen amounts, a few million dollars in total. "This guy's not a punk," he says, "but he's probably not a kingpin either." Such fragmented evidence is Paxson's response to a question about the size of the industry. "I wouldn't feel comfortable quoting a number. Not even an order of magnitude," he says.

To understand the discrepancy between the retail price of spam (how much a botnet operator charges to send junk email) and the conversion rate observed in the Spamalytics study requires much more information about the industry. The statistics suggest that Storm is not particularly decentralized—perhaps a few disgruntled expert programmers making a good living selling Viagra. Or maybe the one campaign the researchers tracked was just a side-project, an experiment much less fruitful than their primary activities.

Kreibich admits he knows little about economics, but his sense is that the market is far from mature. To study this question, the group, which recently hired a new postdoc with an economics background, is trying to measure diversification. Spam emails have links, and each link is associated with a domain, which somebody had to register. Unfortunately, databases with this information are neither centralized nor standardized, so automating these lookups is difficult. Worse, registrars offer "domain testing", allowing a potential client to see what kind of traffic a new domain name receives before finalizing their purchase. Spammers capitalize on this service, using a temporary domain for a few days and then moving on.

In 2008 a botnet took down the web sites of Georgian President Saakashvili and the National Bank of Georgia.

Another way to study diversification is through the appearance of the destination sites. While spam emails show impressive variety, the pharmacy sites they link to, for example, are quite consistent, allowing the researchers to make some inference about the major players in the field. At this point, Kreibich says they have a reasonable idea of "which botnets are sending which spam."

One interesting proposal, Paxson's idea, which has not yet developed into a research project, involves studying the unusual "mule" market. Some spam emails offer the opportunity to "make money from home"—receiving and re-shipping packages or transferring funds to international bank accounts. What differentiates these mule requests from typical spam is that there is often a person at the other end. "We responded to one of these emails," says Kreibich, "and sure enough, we were able to see from the reply—this guy in Moscow was using a Macbook, running a particular version of Microsoft Outlook." By automatically generating responses, spamming the spammers, the researchers could try to assemble a map of mule requests. Such data would be invaluable, Kreibich suggests, because "the economy may be bottlenecking on mule supply"—a crucial method for distributing the money-laundering task.

As with each project, "we have no idea what we'll find," Kreibich says, since so much about the market and its operators is still unknown. In November, two Internet service providers decided to stop routing traffic from McColo, a web host suspected of housing computers involved in criminal activity. In one day, worldwide spam dropped by over 60%. The demise of Intercage, another host known to have operated a number of Storm's control servers, led to a similar but less dramatic reduction in September. Both McColo and Intercage are based in California. "We always suspected Storm was operated out of another country, likely Russia," Kreibich says, "and here it turns out that some of their most crucial infrastructure was located just down the street."

Dan Gillick is a graduate student in computer science.

Wired For Good

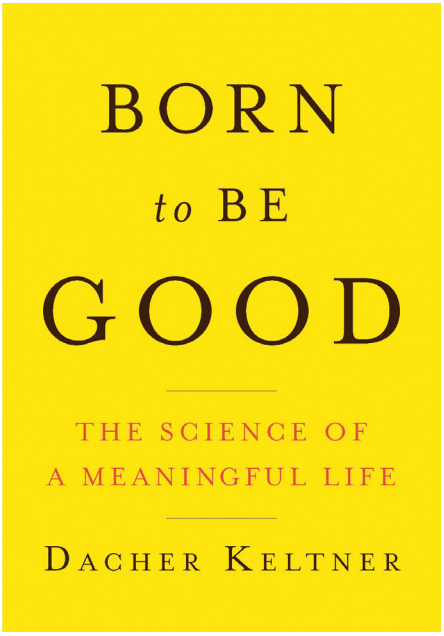
Born to Be Good
by Dacher Keltner
WW Norton & Co.
352 Pages, $25.95

How can we be good? How can we be happy? Dacher Keltner, a UC Berkeley professor of psychology, offers a fresh take on these old questions in his recent book, ***Born to Be Good: the Science of a Meaningful Life***. His effort centers around the Confucian concept of jen, the act of bringing out the good in others. We can be good, and become happy, by maximizing what might be thought of as positive, social emotions (compassion, mirth, awe) and minimizing the negative (anger, resentment, loneliness).

Keltner contends that Western philosophers, who tend to view human nature as fundamentally negative, have marginalized positive emotions. On the contrary, he claims that caring for our resource-hungry, helpless offspring in the hostile environment of early hominid life selected for pro-social emotions through the need to cooperate to survive. Actions of high jen, like touching and smiling, reinforce positive interactions with others. *Born to Be Good* explores the subtle expressions of these positive emotions and tells their evolutionary tale. In so doing, Keltner purports to light the path to a meaningful life.

Pro-social emotions are often communicated by subtle, difficult-to-fake facial movements and vocalizations, so others are sure when our intentions are good. Much of Keltner's research on emotion employs the Facial Action Coding System, or FACS, which Keltner's advisor, Paul Ekman, pioneered. Ekman indexed how the individual activation of each muscle changes the appearance of the face. Any facial expression can be described as a combination of these "facial action units." A smile, for instance, consists of the movement of muscles that pull the lips back and is recognized by the new wrinkle and dimples formed. Different smiles can be distinguished from one another and mean different things; for instance, a smile that reaches the eyes is more sincerity than a smile that doesn't.

Though uncomfortable, embarrassment



is a key high-jen emotion according to Keltner. He asks test subjects to make a funny face and hold it for ten seconds. A participant's eyes shooting downward is a typical response, followed by a turn of the head to the side and down. A nearly restrained two-second smile combined with furtive glances up and a hand touch to the face fills out the rest of the embarrassment reaction. In other species, these are signs of appeasement, aimed at avoiding violent confrontation. In humans, Keltner surmises that embarrassment following a social gaffe is a way of reaffirming our commitment to the moral order.

Corroborating this hypothesis, Keltner describes patients with damage to the orbitofrontal cortex, an area in the frontal lobes of the brain. These patients retain full reasoning and language skills but become immodest and offensive: they lose the ability to feel embarrassment. Some of the muscle movements involved in embarrassment, as in other emotions, are involuntary and difficult to willfully reproduce. The involuntariness makes the emotion a more reliable signal, easily recognized by others. Tellingly, orbitofrontal patients can recognize emotions such as happiness or surprise in photographs, but are incapable of recognizing embarrassment.

Keltner embraces embarrassment as a high jen emotion because it allows us to avoid costly conflict pregnant in social slights and instead engage in reconciliation. When we see embarassment, after all, our first impulse is to playfully downplay the significance of the slip-up and join in laughing it off.

In addition to jen emotions, there are jen actions, like teasing and touching. Teasing may be much maligned in middle school, but Keltner says it is an important, non-violent way to manage social hierarchies and explore romantic interest. With touch, Keltner delves into the physiology of jen. Touch activates the orbitofrontal cortex (it's not just for embarrassment), reduces stress, and increases the concentration of oxytocin in the bloodstream, a chemical associated with trust. By facilitating trust, touch exemplifies the jen concept of "bringing the good things in others to completion": it has a viral quality, spreading jen to others. It's no accident that greetings across cultures tend to involve touch, like a handshake or a kiss on the cheek.

Speaking of cultures, however, one wonders while reading this book why there is such friction within and between groups of people. Keltner allows that group cooperation can be sabotaged by individuals, but fails to mention the characteristics that have evolved in opposition to cooperation. The easy recognition of in-groups and out-groups often leads to violent, decidedly low-jen behavior. Yet Keltner gives no discussion of more anti-social emotions. That's disappointing, since the same process of evolution that gave us high jen emotions also gave us anger and fear. Should they always be suppressed? Is anger at injustice appropriate?

Nevertheless, Keltner presents a fascinating study of frequently neglected emotions. Ultimately, he succeeds with his case that evolution has given us the tools to be good, as well as happy. Fittingly, his tone throughout is playful and engaging, high jen all the way. His warmth for people, such as his former advisor, Paul Ekman, and his young daughters—whose future suitors will no doubt squirm under his FACS abilities—radiates from the pages, quite likely bringing the good in his readers at least part way to completion.

Paul Crider *is a graduate student in chemistry.*

Image courtesy of WW Norton & Co.

So Smart After All

This issue's "Who Knew?" will be my last for the *Berkeley Science Review*, so I thought I would end my run with a bang. I will make all of you 10 times smarter by the end of this article. It's a bold statement, but trust me. You see, you've been consistently lied to for many years, especially in popular entertainment and advertising, forging an impressively resilient myth. The culprit? The belief that we use only 10% of our brains.

The origins of this myth are somewhat hazy. Some argue that it began in the 1700-1800's with the development of phrenology, a pseudo-science that associates certain behavioral traits with the size, shape, and details of the skull. Others attribute the origins to a misunderstood or misinterpreted quote from Einstein. The modern, quasi-scientific version of the myth likely has its roots in a particular experiment conducted in the 1930s by Karl Spencer Lashley, an influential American psychologist and behaviorist. He removed portions of rats' brains and found that they performed normally in a battery of tests, including running through a maze. This key result was seen by some as evidence that mammals only use a small fraction of their brains in the first place, given the heavy brain losses they can sustain.

Image courtesy of Gaetan Lee

We have since learned, however, that this interpretation of Lashley's result is an incomplete one. Kirstie Whitaker, a neuroscience graduate working on childhood brain development in the Cognitive Control and Development Lab at UC Berkeley, explains that Lashley only removed certain sections of the brain, and only administered certain types of tests; by chance, the primary regions needed for those tests were unaffected. For instance, the hippocampus, a region of the brain responsible for spatial navigation and memory, was left intact. It is therefore not surprising that the rats could run through a maze, even remembering their trajectories over the course of multiple trials.

Another remarkable feature of the brain that could help to propagate this myth is its powerful compensatory ability. The left and right hemispheres can adjust for deficiencies in the other half, and many specialized regions are bilateral, meaning copies are found in both hemispheres. "You can easily compensate with large brain loses obtained through injury," and lead a productive life, says Whitaker, who knows from her own research experience the power of the brain to adapt to injury, especially in children. The brain's remarkable mechanisms used to recover from severe trauma can make it appear that we didn't really use much of it in the first place. So how do scientists know that we do, in fact, use 100% of our brain?

Functional magnetic resonance imaging (fMRI) is a widely available form of noninvasive neuroimaging. Oxygenated and deoxygenated blood responds differently in the presence of a magnetic field; this allows neuroscientists to track blood flow changes in the brain, which are then interpreted as neural responses accompanying cognitive activity. By comparing images of a human performing certain tasks with a baseline image, researchers are able to locate where neural activity occurs for such functions as high-level reasoning, processing of auditory and visual stimuli, memory recall, language recognition, and so on. For instance, if you are asked a series of easy math problems (2+2=?), this establishes your baseline image for basic reasoning. A complex follow-up math question will activate the neurons responsible for higher-level quantitative reasoning, and the difference in the images highlights this region. The important result from fMRI studies is that every region of the brain has an associated function. These images are by far the most definitive proof that we use 100% of our brain-- the catch is that we do not use all of it at a single given moment.

This specificity for a given conscious task may be another reason why the myth endures so relentlessly. Coupled with plenty of anecdotal evidence of people leading normal lives in spite of brain injuries, it may seem like most of our head is filled with expendable fluff. But as fMRI images clearly show, neural activity occurs in all regions of the brain, each of which has an associated function. We are also learning just how powerfully adaptive the brain can be. It's time to end the popularization of this myth. So there you have it: you use your whole brain. Don't you feel smarter already?

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