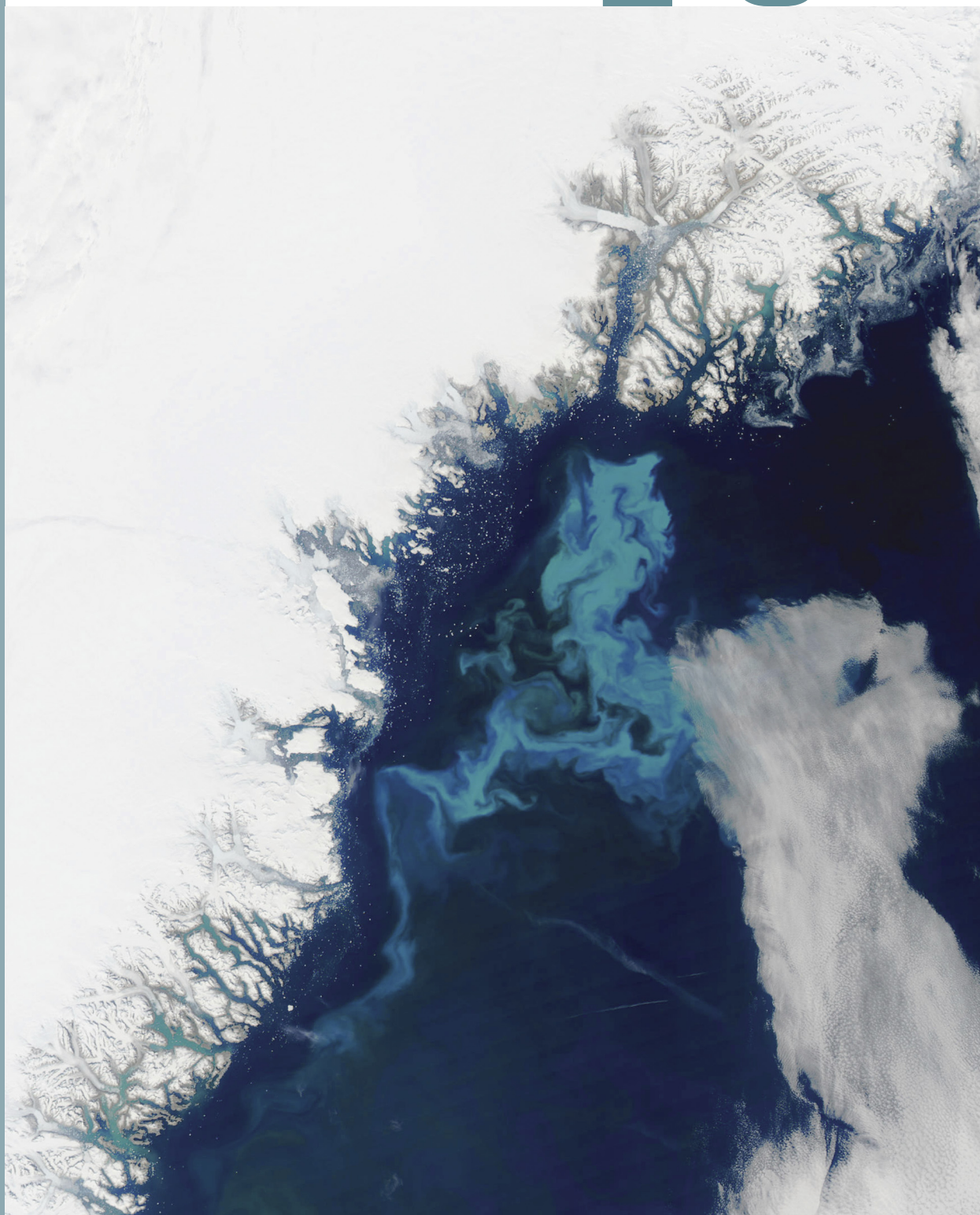
California Institute of Technology

E&S

ENGINEERING AND SCIENCE



Volume LXVIII,
Number 4,
2005

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Blue-Green Bacteria

"Greener" Chemistry

Fluorescent Green Cells

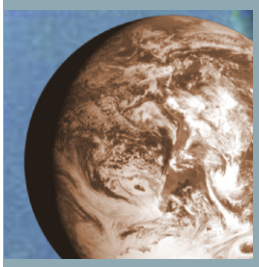
No, Dabney Lounge isn't haunted . . . as far as we know. Here members of the Caltech Ballroom Dance Team exchange partners in homage to Robert Grubbs, the Atkins Professor of Chemistry, who shared this year's Nobel Prize for developing catalysts for metathesis reactions. An invaluable synthetic tool, metathesis allows a chemist to mix and match portions of different molecules as easily as dancers trade partners. **For more, see the story beginning on page 21.**

California Institute of Technology

ENGINEERING AND SCIENCE

Volume LXVIII, Number 4, 2005

On the cover: In July 2003, NASA's Aqua satellite captured a blue phytoplankton bloom off the east coast of Greenland. These blooms occur each summer when nutrient-rich meltwater from the glaciers boosts the numbers of photosynthetic algae and cyanobacteria in the ocean. In the article starting on page 10 of this issue, you can read about a Precambrian cyanobacterial bloom that may have almost permanently destroyed Earth's ability to sustain life. (Image from the Visible Earth catalog of NASA images.)



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PICTURE CREDITS: 3, 4, 6 — Doug Smith; 5 — Kathy Svitil, Will Heltsley; 8, 9 — NASA/JPL/STScI

Performance artist, author, and public-radio personality Sandra Tsing Loh, BS '83 in physics, has come to terms with her inner geek.

The Loh Down on Science

Can "funny" and "science" be used in the same sentence? Caltech and public radio think so. On December 5, KPCC—located just blocks from Caltech on the campus of Pasadena City College, and at 89.3 on your FM dial—began giving its listeners their recommended daily allowance of science along with a healthy dose of humor. *The Loh Down on Science* is hosted by Sandra Tsing Loh (BS '83) and marries her hard-earned physics degree with her wry on-air persona. It airs daily at 9:19 a.m. and 7:04 p.m., and is available as a download or podcast at http://KPCC.org.

Produced by Caltech's public relations office, the *Loh Down* aims to bring science to people who don't consciously encounter it on a daily basis—including those who don't know the difference between a quark and a quasar or who flunked trigonometry. Says Loh, "We believe even the intellectually nervous deserve to explore the wonders of science and technology in all their infinite variety. But not too infinite. Like some strange new franken-vitamin, *The Loh Down on Science* is a convenient, easily digestible one minute a day."

Loh feels her listeners' angst. "I have a Caltech diploma entirely made of partial credit. Yes—my degree was glued together, faintly pulsing with radioactivity, graded less on a curve than on a kind of wild hyperbola asymptotically approaching some imaginary actual answer." But seriously, folks, she received Caltech's Distinguished Alumni Award in 2001, and last spring became the first alumna to speak at commencement.

National public radio audiences have been hearing Loh monthly on the business program *Marketplace*. She has also been a regular on *Morning Edition* and *This American Life* with Ira Glass. Her weekly commentary on life in Southern California, *The Loh Life*, has been airing locally since 1998.

In other media, Loh's latest one-woman show, *Mother on Fire*, is running at the 24th Street Theatre in Los Angeles. She is a contributing editor to the *Atlantic Monthly* and the author of the books *A Year in Van Nuys*, *Depth Takes a Holiday: Essays from Lesser Los Angeles*, *Aliens in America*, and *If You Lived Here, You'd*

Caltech's robot van Alice, side doors open, sits in the starting chute at the second running of the DARPA Grand Challenge. To her right, wearing number 38, is Virginia Tech's Cliff; to her left is the Gray Team's KAT-5, a crowd favorite. Originally dubbed Gray-Bot, KAT-5 (for Category 5) was begun in Metairie and finished in Hammond, Louisiana, despite fully three-quarters of its team having been rendered homeless by Hurricane Katrina. Waiting for its turn is number 08, Team Cimar's NaviGATOR, from the University of Florida.

Be Home By Now. The last was chosen by the *Los Angeles Times* as one of the 100 best fiction books of 1998. She won a Pushcart Prize for her short story "My Father's Chinese Wives," which has also been featured in the *Norton Anthology of Short Fiction*.

The *Loh Down*'s writers have previously written for *Nature*, *Science*, and *Discover* magazines, and even for Bob Hope. (If anyone out there has the itch to write short, snappy scripts about science—for pay!—contact Kathy Svitil, ksvitil@caltech.edu.)

For more details about the program, visit http://pr.caltech.edu/public_relations/lohdown/.

KPCC is the flagship station of Southern California Public Radio, and the fastest-growing public radio station in the country. The program is being sponsored in its first year by TIAA-CREF, a national financial services organization and the leading provider of retirement services in the academic, research, medical, and cultural fields. □—*JP*

Alice's Adventures in Primm

Fame, prestige, and a hefty check were riding on the outcome of the Defense Advanced Research Projects Agency (DARPA) Grand Challenge, the off-road race of robotic vehicles held on October 8 in Primm, Nevada. The machine that drove itself, without human intervention, over a 132-mile course—a route not divulged until 4:30 a.m. on race day, in order to prevent vehicles from being programmed to drive it from memory rather than figuring it out as they went—in the fastest time under 10 hours would net its builders a $2 million prize. But for some members of Team Caltech, more was at stake: fish tacos.

"I have two bets of ten fish tacos apiece with [Caltech senior] Jeremy Gillula—one on whether we finish the race, and one on whether we win," said senior Jeremy Leibs, who was sitting with other team members in the spectator grandstands in the parking lot behind Buffalo Bill's Resort & Casino as Team Caltech's

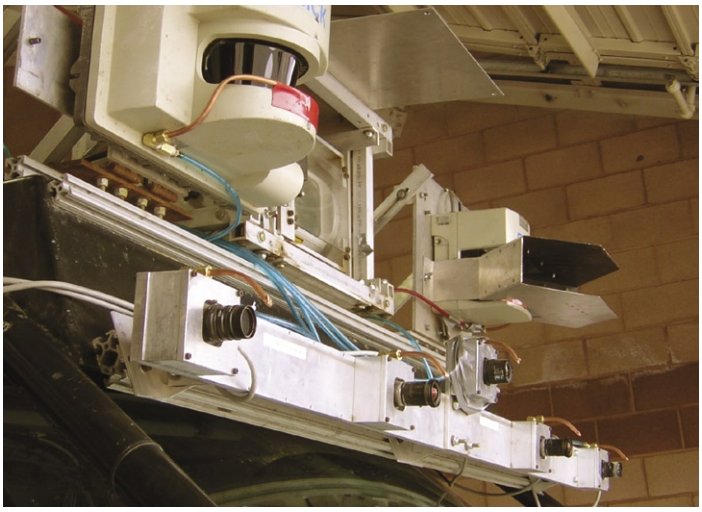
Terra Engineering's TerraHawk had the most unusual design, consisting of three articulated segments not unlike a toddler's pull toy. Seen here at the qualifying course at the California Speedway in Fontana, it failed to navigate the track and advance to the finals.

entrant, a heavily modified Ford E-350 van named Alice, rolled up to the starting chute. "If we don't finish, Jeremy owes me 10 fish tacos. If we win, I owe him 10. I don't even like fish tacos," Leibs admitted, "but I can use them as currency with other team members."

"That's true. They are legal tender around here," agreed Richard Murray (BS '85), professor of control and dynamical systems and leader of Team Caltech, a disparate group of undergraduate and graduate students, faculty advisors, volunteers, and professional engineers from the Jet Propulsion Laboratory, Northrop Grumman, and elsewhere.

Fueled by fish tacos, Team Caltech members had been working toward this day for a year and a half—ever since the finals of the first Grand Challenge, held on March 13, 2004. That race, which began at the Slash X Ranch Cafe just outside Barstow, California, and was supposed to run 142 miles through the mountains and dry washes of the Mojave Desert to Primm, saw no winner. In fact, the best effort was the mere 7.4 miles logged by Carnegie Mellon's Red Team. (See *E&S* 2004, No. 1.) The unclaimed $1 million purse was doubled for this year's event.

During the first Grand Challenge, Team Caltech's Bob, a '96 Chevy Tahoe 4x4, plowed into a barbed wire fence at mile 1.3 to end his race. This year, the team was determined to build upon, and better, Bob's performance. Alice contains the next generation of hardware and software from Bob, and her license plate reads, "I8BOB." ("Alice" and "Bob" are famous monikers from communications and encryption theory, where they represent two people sending messages to each other. Bob had gotten *his* name from his license plate, 5BOB235.)



Attention to detail: Alice's LADAR units (the things resembling coffee makers) and her cameras each had a compressed-air line to blow dust off their lenses.

A big, tough gal, Alice was outfitted for off-roading as a donation to Caltech by Sportsmobile West Inc., of Fresno, California. She's got heavy-duty shocks, a Dynatrac high-performance front axle, skid plates, and four-wheel drive. And she has more bells and whistles than did Bob: seven computer servers, a Global Positioning System (GPS) receiver to measure her absolute position, and an inertial measurement unit (IMU) consisting of accelerometers and gyroscopes. GPS and IMU data are processed to produce an estimate of Alice's "state"—her exact position and orientation in space. To plot terrain and detect obstacles, Alice's front bumper and roof bristle with a pair of short-range and a pair of long-range stereo cameras, a road-finding camera, and five laser "radars," called LADARs, that scan the road ahead at various ranges.

The stereo camera and LADAR readings are fed into a program the undergrads developed that creates a 3-D map of Alice's world. The planning software uses that map, the state data, and the route information provided by DARPA to plot Alice's best path. A trajectory-following program and an executive program translate that path into commands to the actuators that control Alice's throttle, brakes, and steering. The data transfer between the various servers and modules is overseen by SkyNet, a communications system named for the artificial intelligence–based neural network that controlled the machines in the *Terminator* movies.

Bob didn't run autono-

Got LADARs? The Indy Robot Racing Team, which included students and faculty from Indiana and Purdue Universities, may have bought up the Midwest's entire supply. Alas, IRV also failed to qualify.

mously until a little over a week before the first Grand Challenge. Alice was far more precocious; her first self-guided runs began at the beginning of the summer. By summer's end, she'd driven a few hundred miles on her own across increasingly more arduous terrain in the desert near Stoddard Wells, just a couple of hours from Pasadena. The team did encounter a few roadblocks; in late August, for example, Alice began blowing fuses, causing her to occasionally (and unpredictably) stop dead in her tracks. For a while Murray and others thought she might have to be scrapped, and her computers, sensors, and other equipment moved into Bob.

A week before the start of the qualifiers in late September—during which 43 teams (out of a starting pack of 195) would be narrowed to 23 finalists—team members discovered why Alice was stalling. "A wire that fed power to the rear winch had come loose and dropped down against the exhaust pipe," explained team member Tony Fender, lecturer in engineering. "The heat burned through the insulation, so as we drove, every now and then it shorted out."

With the wire repaired, Alice was set for her stab at the finals. During her first run, she got hung up on a hay bale, which she dragged a few hundred feet as it turned into shredded wheat, and then lost her way after leaving a tunnel designed to block out signals from the GPS satellites overhead. She went into reverse, and began turning, haltingly, off the course. DARPA officials eventually stopped the trial. Team members tinkered with her planning software, and over the next five days she sailed through three more test runs.

Alice's adventure in Primm began at 9:02 a.m., as she pulled cautiously out of the starting chute, headed west past the grandstands, and hung a right to trek north across a dry lake bed. Team members watched from the stands through binoculars as she disappeared into the dust. "I'll feel better when I can't see her anymore," said one student.

Half an hour and a little over seven miles later, Alice headed back toward Buffalo Bill's. The course passed along the eastern edge of the casino's parking lot, paralleling a berm before turning east again into the desert. The berm's northern half was reserved for media; team members and visitors waited for Alice to streak by from the southern end. Alice's software was set for a maximum speed of 35 mph, and the flat expanse around Primm was a piece of cake compared to the rough-and-tumble terrain Alice was used to, so she should have been running flat out. But when she appeared, she seemed slow and hesitant. She made the turn to parallel the berm, then stopped, cogitated a bit, started, stopped, cogitated a bit more, turned left, and then straightened out. Finally, she cocked her wheel hard right, toward the berm, and began driving at about 10 mph toward it—and the media. From the perspective of those in her path, it seemed much faster.

A line of K-rails, those concrete barriers you see in freeway construction zones, prevented carnage. Alice climbed one and knocked it flat—a tribute to her off-roading prowess—before being paused part way up the berm, and eventually disabled, by the DARPA chase team's wireless kill switch. Her day was over.

"I'm frustrated. I didn't spent two and a half years of my life to have it end at mile eight," said mechanical engineering student Tully Foote, a member of the embedded systems team, who helped get Alice off the K-rail so she could be removed from the course. "We all worked on this thing for so long. We want to know what went wrong, why it went wrong, and how to fix it."

Leibs, of fish taco fame, was not terribly surprised. "I've been kind of pessimistic the whole time. Our architecture has too many interfaces, and too many things that weren't sufficiently tested. This was a clear, wide-open straightaway that should have been trivial to drive. It was just a random screwup."

In fact, a number of system failures—and a power line—contributed to Alice's attempt to take out the media. Postrace analyses showed that while her long- and short-range LADARs, which detect obstacles at around 3 meters and 35 meters, were fine, the two medium-range LADARs quit just four minutes into the race. (They now work perfectly, so the team has no idea why they malfunctioned.)

This shouldn't have been a death blow, but Alice had other issues. Just before making the turn to get onto the dirt road paralleling the berm,

Above: The media's-eye view of an onrushing Alice.

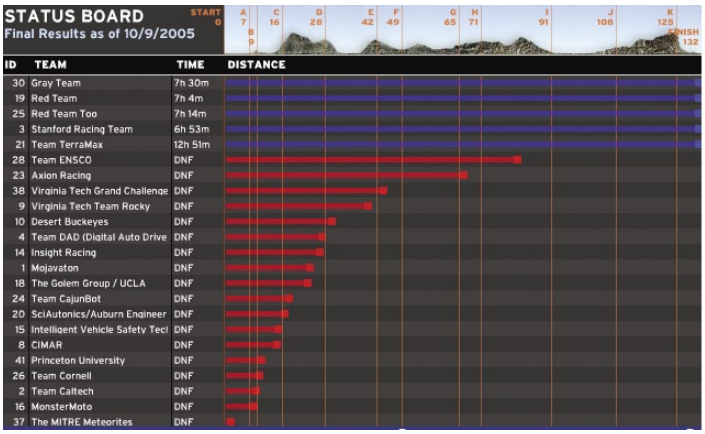
Below: Alice grinds the K-rail, taking some steering-system damage in the process.

she passed under a power line that temporarily knocked out the GPS signal. When the GPS came back, the state estimator realized that its dead-reckoning position and the GPS readings had drifted about five meters apart. This meant that all the obstacles in Alice's field of vision suddenly appeared on her map as new obstacles, offset by five meters from the original set, which remained on the map. As part of the correction process, Alice stopped while the software erased all the obstacles and waited for the real ones to reappear. But, says grad student Lars Cremean (MS '00), manager of the planning team, "The state estimator corrected itself, but not completely; when the GPS measurements resumed, the unit reported an unusually low confidence in these measurements. And because of its incomplete correction, the state estimator continued to accumulate drift."

When Alice turned right to get back onto what she thought was the course, her assorted sensors should have put the looming K-rails back on the map. The long-range LADARs did just that, says Cremean, but by now "the state estimator had accumulated a pointing error of several degrees. This put the K-rails in the wrong location. Alice thought she was heading south, paralleling the rails, but she was really heading toward them at a shallow angle." Even so, she still could have recovered, had not both pairs of stereo cameras chosen that exact moment to join the medium-range LADARs on the disabled list. "Our current hypothesis is that stereo didn't detect the obstacles because of the orientation of the sun," says Murray. Put bluntly: Alice was blinded. The short-range LADAR units did eventually spot the barriers, but not in time. It was a perfect convergence of failures.

"We were designing a vehicle that could complete the course, and we didn't do that, so in that sense it was a failure," says Murray. "But if you look back two and a half years ago when this project began, we didn't think we would do as much research as we did, we didn't think we would be as innovative. We accomplished far more than we thought would come out of an undergraduate class."

"We've done things with Alice that I didn't think we were going to achieve in five years," says Fender. More importantly, he adds, the endeavor provided Team Caltech's student members with an unprecedented educational experience. "Caltech has taken a different approach to the whole of the Grand Challenge. Teams like Carnegie Mellon were in there to win at all costs. Richard is in this to teach these students. It is for education—and the education that these students have gotten is something I've never seen available to any student, anywhere. In a year of taking



STATUS BOARD
Final Results as of 10/9/2005

ID	TEAM	TIME	DISTANCE
30	Gray Team	7h 30m	
19	Red Team	7h 4m	
25	Red Team Too	7h 14m	
3	Stanford Racing Team	6h 53m	
21	Team TerraMax	12h 51m	
28	Team ENSCO	DNF	
23	Axion Racing	DNF	
38	Virginia Tech Grand Challenge	DNF	
9	Virginia Tech Team Rocky	DNF	
10	Desert Buckeyes	DNF	
4	Team DAD (Digital Auto Drive	DNF	
14	Insight Racing	DNF	
1	Mojavaton	DNF	
18	The Golem Group / UCLA	DNF	
24	Team CajunBot	DNF	
20	SciAutonics/Auburn Engineer	DNF	
15	Intelligent Vehicle Safety Teci	DNF	
8	CIMAR	DNF	
41	Princeton University	DNF	
26	Team Cornell	DNF	
2	Team Caltech	DNF	
16	MonsterMoto	DNF	
37	The MITRE Meteorites	DNF	

The standings as posted on the Grand Challenge website. (Note that the five finishers are not listed in the order of their elapsed times.) "DNF" stands for "Did Not Finish."

Left: Entrants were seeded based on their performance at the qualifying rounds, with the first three 'bots taking the line just at sunrise. Stanford University's Stanley, the second seed, is flanked by the two Hummers from Carnegie Mellon (the Red Teams) whose clocks he cleaned.

these classes, they've gotten about the same experience as I got in my first ten years as a professional engineer."

The Grand Challenge did have a winner—Stanley, a robotic Volkswagen Touareg from Stanford University—and won't be rerun. Alice is officially retired from professional competition, but will continue to be used as a platform for research and education. Meanwhile, Richard Murray and his colleagues are dreaming up new challenges for CS/EE/ME 75, the class in multidisciplinary design taken by Team Caltech's students. "I don't know what project we'll choose," he says. "Maybe it will be autonomous driving in urban environments. I'm open to anything that seems like a challenge and that will allow the students to push the envelope of what we know how to do." □—*KS*

Non-Incoming Tax

In 1789, Benjamin Franklin wrote, "In this world nothing can be said to be certain, except death and taxes." He may have been mistaken. With the possible exception of Elvis, who continues to be seen in supermarkets, death is still inevitable; but taxes are becoming easier to avoid.

This year, over $250 billion in income tax will not be collected—a sum larger than the entire amount spent on the Iraq war through November 2005. Amazingly, most cheats will probably never be caught. Says Jeffery Dubin, Caltech professor of economics, "For tax evaders, money launderers, and those involved in fraudulent tax schemes these are heady times indeed."

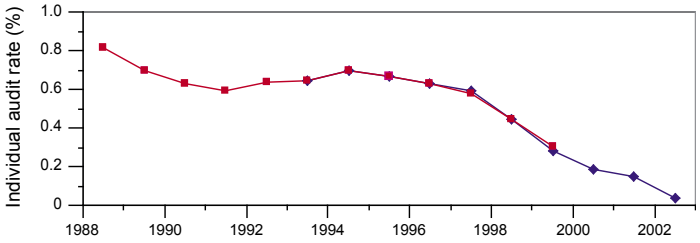
Americans have never liked paying taxes—after all, the birth of this country involved a tax revolt. But the carrot of fairness with the stick of audits and penalties makes the average Joe pay taxes honestly. Today, this system is breaking down, because the number of agents enforcing the tax code has not kept up with the increase in taxpayers. Statistics from Syracuse University's Transactional Records Access Clearinghouse (http://trac.syr.edu) reveals a plummeting face-to-face audit rate—from 0.72 percent in 1994 to 0.15 percent in 2004—and a decline in the number of tax prosecutions—from 1,176 to 546 over those same years. With this drop, many people figure they can get away with underreporting income, which accounts for about 80 percent of the tax gap.

For over a decade and a half, Dubin has been trying to understand this gap. But controlled experiments are nearly impossible. Ideally, you would like to change one variable—say increase tax penalties in Ohio—while keeping things constant elsewhere, and see what happens. Besides infuriating the citizens of Cincinnati, that is. So in reality, economists take what data they can find and work backward, like a gastronome tasting a soup and trying to figure out its ingredients.

In a recent study, Dubin used publicly available data to create a model that predicts taxes due; subtracting the taxes actually collected gives the tax gap. Previous work on this topic gave a static picture, one only relevant to the particular year analyzed. In contrast, Dubin's study can forecast the tax gap for *any year*. Using his model and statistical methods to tease out one relation from another, Dubin was able to predict how factors like audit rate or media coverage affect the tax gap—crucially obtaining, not just the direct consequences of change in a variable, but also the "spillover," or indirect effects. For instance, if the IRS increased audits, it would catch more fraud and make more money in penalties. It would also scare some people—who would have cheated otherwise—into complying with the tax code. This is the "spillover."

The study disproves an IRS claim that automated corrections, known as correspondence audits, are as effective as the old-fashioned kind. "There is no evidence that correspondence audits have made up for the decline in face-to face audits," Dubin says. A computer-generated form letter simply doesn't have the same "spillover" deterrence as summoning you and your sorry shoebox of receipts to a windowless room with an IRS agent.

Predictably, the strongest motivator for compliance was found to be fear of jail time, not fines. This suggests an emphasis on both prison sentences and higher audit rates to reduce cheating. But surprisingly, the study shows that extra media attention to celebrity criminal investigations has little additional impact in making people more honest. "The key is not



Above: This plot of audit rates of individual taxpayers (as opposed to corporations) shows that the overall audit rate as a percentage of returns filed has been steadily decreasing. The two colored lines represent a change in reporting methods caused when the IRS began consolidating its operations in individual states into regional offices.

to get more publicity of those currently prosecuted, but to prosecute more," Dubin says. In other words, sending a high-profile Leona Helmsley to jail has less of an impact than a tax investigation of your neighbor.

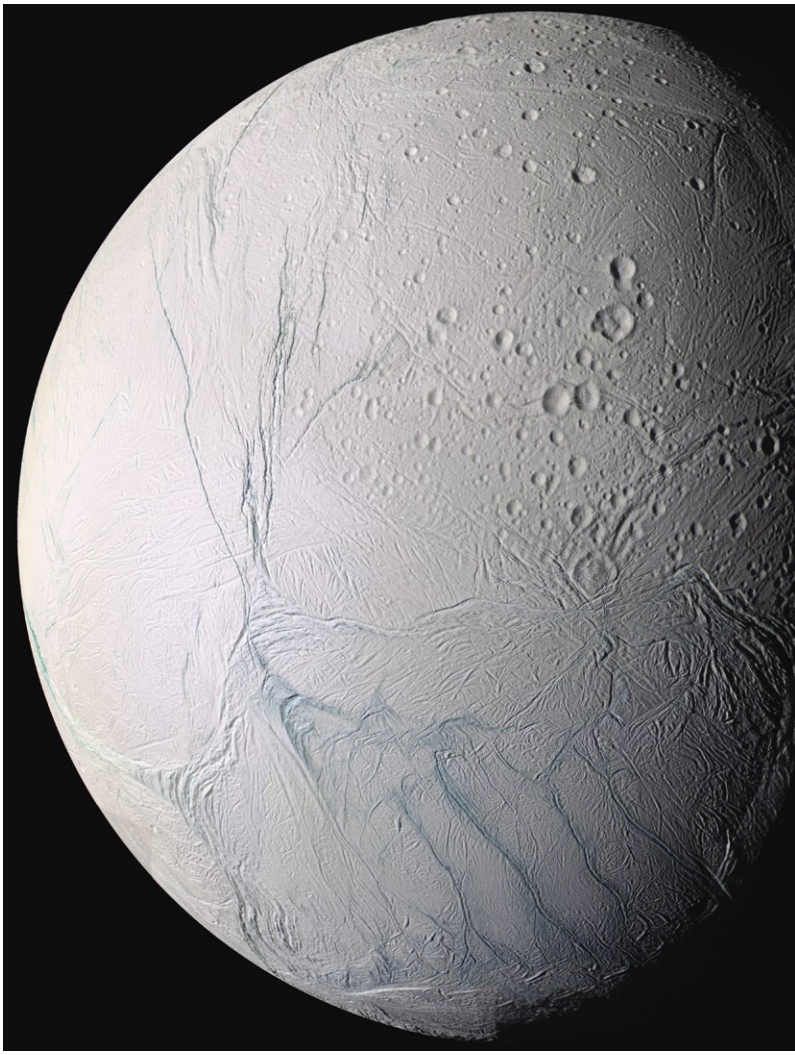
However, audits cost money. Does increasing their number really benefit the honest taxpayer, overall? The answer from the study is overwhelmingly yes. One extra dollar spent on audits leads to a reduction of $58 in the tax gap. Similarly, an extra dollar spent by the Criminal Investigation (CI) arm of the IRS provides a return of $66 in taxes and penalties.

According to Dubin, no one is suggesting that the tax gap can be eliminated. However, he says, "Historically we do know that the tax gap has been smaller, even accounting for inflation and growth." He suggests modest increases in CI's budget as a way to start curbing cheating—his simulations show that a budget increase of $25 million should result in a $1 billion reduction in tax evasion.

Unfortunately, this advice seems to be lost on politicians. Recently, California governor Arnold Schwarzenegger vetoed a bill that would have increased prosecution for tax evasion. The danger in lax enforcement of tax codes is that it leads to a runaway effect—if honest taxpayers think the system is unfair, more and more of them will be tempted to cheat.

"There is no kind of dishonesty into which otherwise good people more easily and frequently fall, than that of defrauding the government," wrote Benjamin Franklin. Today, with so many incentives, that is no surprise at all. □—*SV*

Dubin's complete paper is available on the IRS's website at http://www.irs.gov/pub/irs-soi/04dubin.pdf. This is his farewell appearance in E&S*, as he will be retiring from Caltech in 2007 after 25 years at the Institute. The author, Saurabh Vyawahare, is a graduate student in applied physics. He works with Axel Scherer, the Neches Professor of Electrical Engineering, Applied Physics, and Physics.*



President Baltimore to Step Down

David Baltimore, president of the California Institute of Technology, will retire on June 30, 2006, after nearly nine years in the post. He will remain at the Institute, where he intends to focus on his scientific work and teaching, and has agreed to continue serving as president until a successor is named.

A search committee, chaired by Henry Lester, the Bren Professor of Biology and chair of the faculty, is now hard at work and hopes to present a short list of candidates to the Board of Trustees in March. Anyone who wishes to nominate a candidate, or who would like to suggest qualities that Caltech's next president should have, is encouraged to visit http://presidentialsearch.caltech.edu/.

Baltimore is the seventh person to lead "modern day" Caltech, his predecessors being James A. B. Scherer, Robert A. Millikan, Lee A. DuBridge, Harold Brown, Marvin L. Goldberger, and Thomas E. Everhart. □

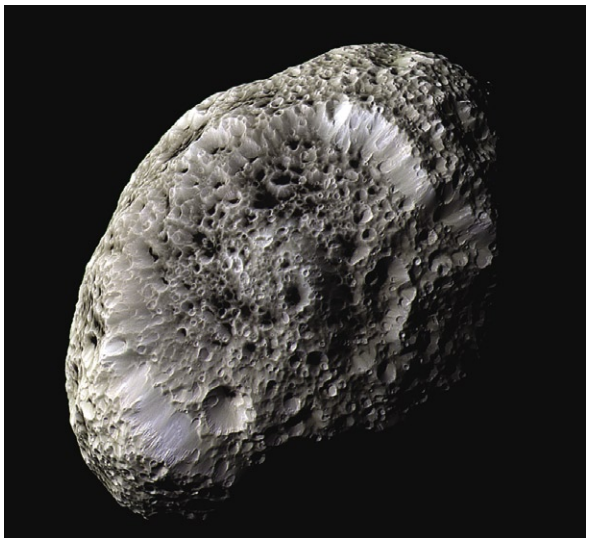
Cassini's Finds: Enceladus Leaks; Hyperion Is a Sponge

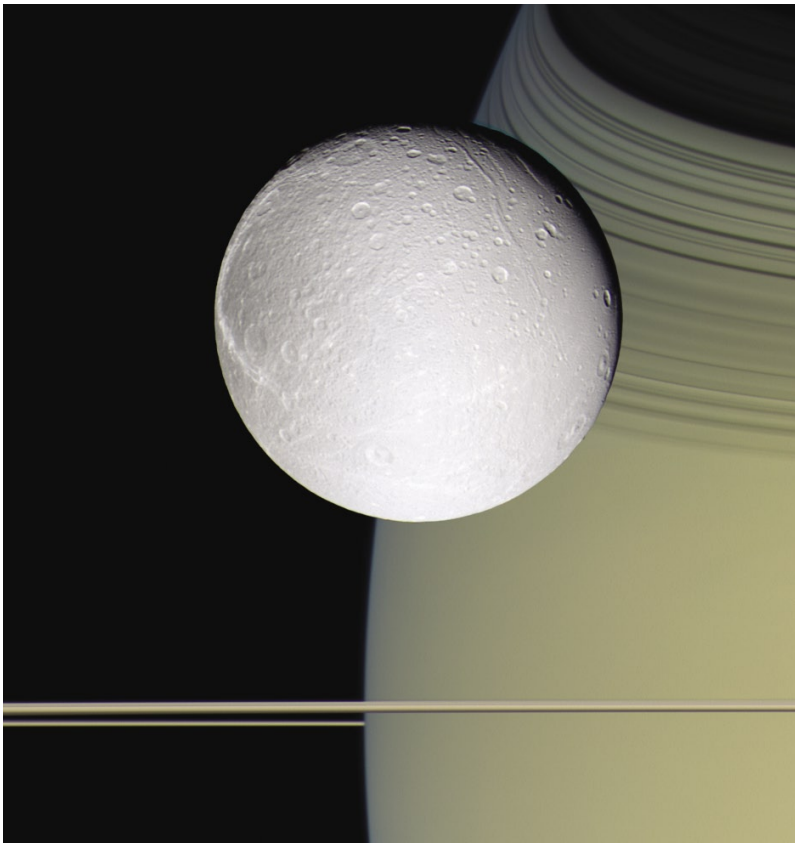
The Jet Propulsion Laboratory's Cassini mission to Saturn is discovering that the ringed planet's moons are just as weird as Jupiter's. A close flyby of the ice moon Enceladus on July 14 discovered a region of prominent, bluish fractures dubbed "tiger stripes" in the south polar region. (See the image at left, taken in ultraviolet through infrared wavelengths.) These fractures are one to two kilometers wide and more than 100 kilometers long, and appear to be bluer than their surroundings because the fresher, coarser-grained ice exposed in the fractures has a bluish cast as do icebergs on Earth. Cassini's infrared spectrometer found that the tiger stripes are significantly warmer than their surroundings—around 90 Kelvin, with "hot spots" of over 100 Kelvin, versus the 74 to 81 Kelvin of the rest of the region. Enceladus's feeble ration of sunlight—about 80 percent of which is reflected by the icy surface—cannot account for this, so it appears that heat is leaking out of the interior. Add this to the detection back in January of a fine spray of ice particles over the south pole that may extend as high as 400 kilometers, and Enceladus joins a very exclusive club of worlds known to exhibit some form of internal activity.

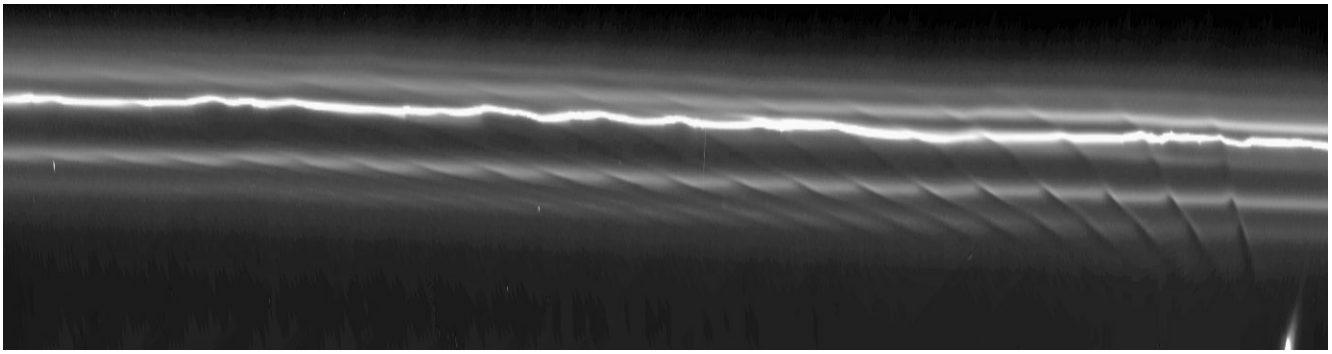
Cassini buzzed Hyperion, whose beaten-up body is shown at right, on September 26. At 280 kilometers across, it is the largest known irregularly shaped moon in the solar system. Its surprising spongy appearance may be the result of thermal erosion, in which dark material accumulating on the crater floors absorbs sunlight and melts the ice beneath it, which then evaporates and deepens the craters. Viewed in natural color, Hyperion has a decided reddish tint that has been toned down in this false-color image to highlight the other subtle color variations that may indicate compositional differences.

And finally, on October 11 Cassini zoomed by Dione, catching this true-color shot of it against its mother planet. The rings, seen edge-on, cast shadows on Saturn's cloud tops, with the B ring at the top and the thinner C ring making the series of stripes.

Speaking of rings, the mosaic below shows how Prometheus's gravity opens channels in the F ring. The channels shear over time, causing the older ones to the left to have a shallower slope. □—*DS*







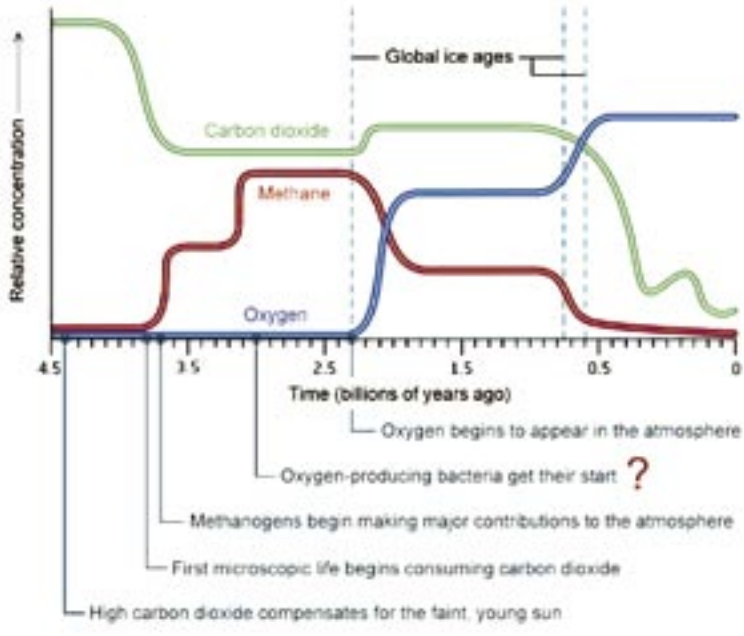
Red Earth, White Earth,

by Joseph L. Kirschvink

Oxygen drives the biosphere—we can't live without it. But most scientists now agree that there was no free oxygen in the air during the earliest portion of Earth's history. The first oxygen came from a group of bacteria—the cyanobacteria—that had developed a new method of photosynthesis. Their method was so efficient that they spread rapidly throughout the oceans of the world and overtook their less-efficient predecessors. But their success may have created a catastrophic climate disaster that plunged Earth into a global deep freeze for tens of millions of years and almost wiped out life on the planet forever. That, at least, is a scenario I have developed in collaboration with geobiology grad student Bob Kopp.

Our planet formed about 4.6 billion years ago, at a time when the young sun was only 70 percent as bright as it is today. With such a weak sun, Earth should have been very cold, but that doesn't seem to have been the case; no evidence of glaciers has (so far) been found for the first 1.5 billion years of the planet's history. It's possible that the greenhouse effect of carbon dioxide produced by volcanic eruptions kept the young planet warm, but it would have required enormous amounts of this gas to stop Earth's surface from freezing—amounts that the geologic record suggests could not have been present for much of the planet's first 2.3 billion years. Unless, that is, it was aided by methane, which is a much more powerful greenhouse gas than carbon dioxide. Methane is produced as a metabolic by-product by a group of primitive bacteria that feed on hydrogen and carbon dioxide—gases emitted in abundance by volcanoes. These bacteria could easily have produced the levels of atmospheric methane needed to make an effective insulating layer.

The cyanobacteria were the first organisms on Earth to produce oxygen, and their evolution led to a rise in atmospheric oxygen levels and a drop in methane levels. Kirschvink's team thinks the cyanobacteria evolved shortly before the first global ice age rather than at the earlier time shown here—hence the question mark.



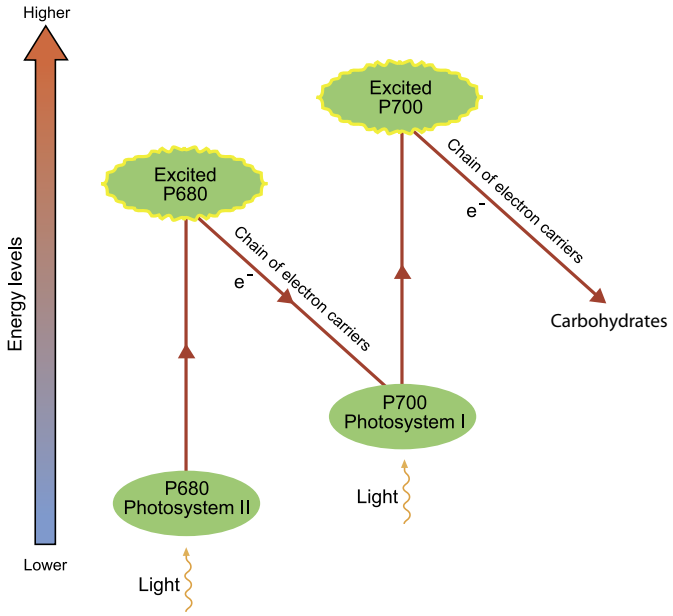
J. Johansen (John Carroll Univ.), M. Schneegurt (Wichita State Univ.) & Cyanosite (www-cyanosite.bio.purdue.edu).

Green Earth, Black Earth

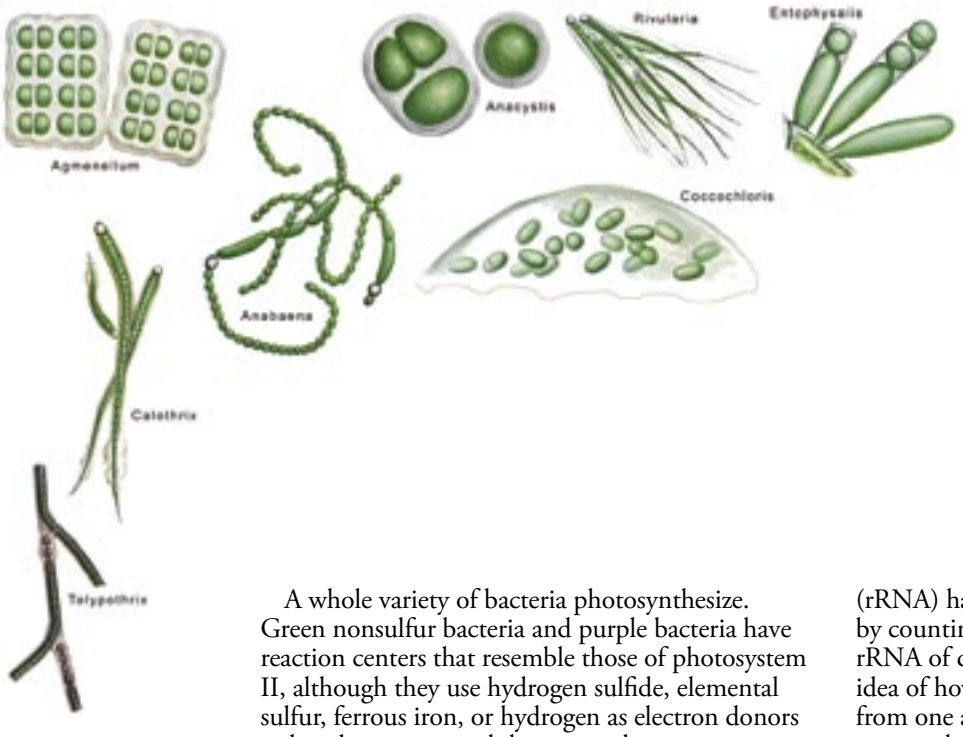
Then along came oxygen. Jim Kasting at Pennsylvania State University, and many other earth scientists, including Bob and myself, think that oxygen arose on our world about 2.3 billion years ago. But other scientists think there was prolific oxygen production much earlier than that, so it's a subject of hot debate. We do agree, however, that copious quantities of this gas were first produced by the cyanobacteria, which evolved a more efficient method of photosynthesis that released energy from a ubiquitous source—water—and produced oxygen as a waste gas. The cyanobacteria used to be called blue-green algae, until they turned out not to be algae at all and were found to come in yellow, brown, and red as well as blue-green.

In photosynthesis, the energy from sunlight starts a chain of events that eventually splits hydrogen atoms off from water molecules and combines them with carbon dioxide molecules to make sugars. These sugars, often converted to insoluble carbohydrates, store energy for the organism, while the remaining oxygen from the water molecules is given off as a waste product. The sequence of events begins when a green pigment, chlorophyll P680, absorbs energy from sunlight and releases an electron. This electron is passed along a chain of electron carriers (which store energy by pumping protons across a membrane) until it reaches a second type of chlorophyll, P700, which can also be excited by sunlight. When that happens, the P700 is able to transfer an electron into a pathway that ultimately results in the transformation of carbon dioxide into organic carbon. To replace the electron that left chlorophyll P680, an enzyme splits water into protons (H^+), oxygen, and electrons.

The diagram above right shows the changes in energy levels that occur during the process. Its Z shape reflects the fact that oxygenic photosynthesis is a two-stage process in which the two chlorophylls work together to raise energy levels higher than either could manage separately. The stage involving chlorophyll P680 is known as photosystem II, and the one using chlorophyll P700 is photosystem I. This dual photosystem evolved in the cyanobacteria. Incidentally, the reason it is also used by all green plants is that the photosynthetic organelles of green plants, the chloroplasts, are descended from cyanobacteria that once lived in a symbiotic relationship with an early ancestor of plants—chloroplasts still contain a residual loop of DNA inherited from their cyanobacterial ancestors.



The chain of events in the light-dependent stage of photosynthesis used by the cyanobacteria and all green plants begins when sunlight hits a molecule of chlorophyll P680, bottom left.



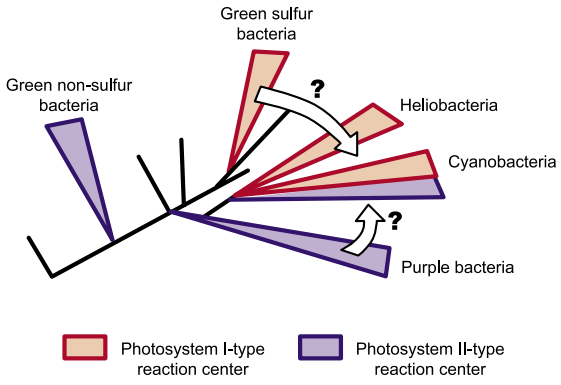
Cyanobacteria are both the heroes and villains of life on Earth. When they evolved, they—or rather, their oxygen—killed off most of the existing organisms and almost made Earth permanently uninhabitable. But without them, we would not be here today. Mistakenly classified as blue-green algae until it was realized that they were bacteria, they're a large and varied group. The paintings of cyanobacteria above were done by C. Mervin Palmer for a 1952 Public Health Service publication.

A whole variety of bacteria photosynthesize. Green nonsulfur bacteria and purple bacteria have reaction centers that resemble those of photosystem II, although they use hydrogen sulfide, elemental sulfur, ferrous iron, or hydrogen as electron donors rather than water, and do not produce oxygen. The reaction centers of green sulfur bacteria and heliobacteria resemble those of photosystem I and use a similar array of electron donors. Although many genes appear to have moved around among photosynthetic bacteria, the simplest interpretation of their genetic architecture suggests that the ancestor of the first oxygen-producing cyanobacterium arose from a chance fusion between a green sulfur bacterium and a purple bacterium (see below right).

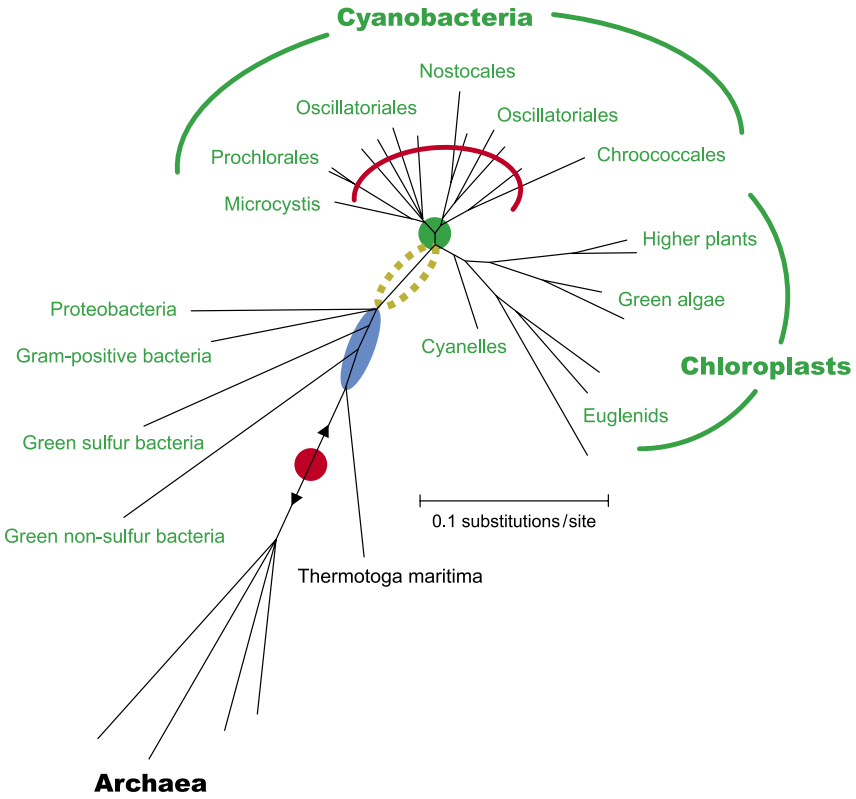
Why do we think it was a whole-cell fusion and not a mutation? The shift in energy levels of chlorophyll P680 when it captures a photon is among the largest of any known organic molecule, yet it is still not enough to couple directly into the electron transport chain following chlorophyll P700. This is presumably why a two-stage process is needed, and why such a process is unlikely to have arisen via a chance mutation in a bacterium with only one of these photosynthetic machines.

Furthermore, in an organism sustained by two photosystems, evolution would have had more flexibility to experiment until, ultimately, natural selection modified the ancestral photosystem II so that it could use water rather than other, less abundant molecules, as an electron donor. It's a very standard way for evolution to work—bits and pieces that have evolved separately combine and make a new system that does something novel. But whole-cell fusion events like this are *extraordinarily rare*, and wouldn't necessarily happen on any given planet.

Are there any clues as to when this fusion happened? We can get some idea by looking at the genomes of bacterial species and drawing up a phylogenetic tree. Mutations in ribosomal RNA (rRNA) happen at a fairly steady but slow rate, so by counting the number of differences between the rRNA of different bacterial species, we can get an idea of how long ago the two species diverged away from one another. The red dot in the phylogenetic tree on the facing page indicates the position of the last common ancestor of all living things. The blue ellipse highlights a radiative burst for the bacteria—a time when many different types evolved. And the branch surrounded by the dashed line leads to the cyanobacteria. It's a fairly long branch, indicating that the cyanobacteria had evolved away from the other bacterial groups for some time before a starburst of different groups suddenly appeared. The green dot, we believe, represents the point when photosystems I and II combined—the



This phylogenetic tree of the photosynthetic bacteria based on rRNA differences also shows the type of reaction center possessed by each group. It's likely that the cyanobacteria, with both reaction centers, are the result of the chance whole-body fusion of a green sulfur bacterium and a purple bacterium. Diagram courtesy of Bob Blankenship, Arizona State University.



This rRNA phylogenetic tree shows the relationships between the Archaea (a group that includes the methane-producing organisms), the bacteria, and chloroplasts. Groups that photosynthesize are labeled in green. The red dot indicates the last common ancestor of all living things (the higher organisms also branch off here but haven't been included to save space); the blue ellipse highlights a radiative burst of bacterial groups; and the green dot is the point at which oxygenic photosynthesis most likely evolved. No clearly identifiable fossils of cyanobacteria have been found earlier than the red line, 1.9 billion years ago.

start of the cyanobacterial success story. While bacteria that used hydrogen, ferrous iron, sulfur, or hydrogen sulfide could only live close to the sources of their electron donors, there was no longer any such constraint on the cyanobacteria. Their electron source, water, was everywhere. They could now radiate all over the world and diversify into many groups. The starburst occurs well after the main bacterial radiation, which places the start of oxygenic photosynthesis quite a long time after the evolution of the first bacteria.

So the evolution of oxygenic photosynthesis was, in fact, not very close to the origin of life, but about halfway through the evolution of the biosphere. Many scientists argue that it happened 2.7 billion years ago, based on the evidence from organic biomarkers—molecules such as fatty acids and lipids that only living organisms make. They fossilize as petroleum. But petroleum moves around through the geological strata, so it's hard to pin down the age at which it formed.

In 1999, Jochen Brocks and Roger Summons at MIT found derivatives of methylhopanol, a type of lipid, in Australian sediments that were 2.7 billion years old. These compounds are predominantly produced today by a number of cyanobacteria, but their function is not understood and their biosynthesis does not appear to require oxygen. Even if these compounds were produced by early cyanobacteria, we don't know if these organisms had yet evolved the ability to split water and make oxygen.

Brocks also found derivatives of sterols—molecules used in the cellular membranes of all known higher organisms—in the same sediments. Sterol synthesis, it is argued, requires oxygen. But these sterols may have formed more recently and moved down into the ancient sediments. Among the molecules present were ones produced today only by dinoflagellates, a type of algae with no fossil record until around 400 million years ago. Large parts of Australia were covered by limestone with reef complexes (a good source rock for petroleum) at about this time, so there are many possible sources of contamination in the present and past environments.

In addition, the assumption that oxygen has always been needed to produce sterols may be wrong. Bob Blankenship of Arizona State University and Jason Raymond of Lawrence Livermore National Laboratory checked out the BioCyc database, a collection of metabolic pathways for hundreds of organisms, for instances where completely oxygen-free reactions, using anaerobic enzymes, could perform the same work as oxygen-dependent enzymes. They found a real beaut: The synthesis of chlorophyll requires oxygen. But to make oxygen, you need chlorophyll. Where did the oxygen to make chlorophyll come from if oxygen wasn't there before chlorophyll evolved? Blankenship and Raymond found that anaerobic photosynthetic organisms had a different enzyme that catalyzed exactly the same chlorophyll-making step—closing a small ring in the carbon backbone—without needing oxygen. *Two completely unrelated enzymes were doing exactly the same chemical conversion.*

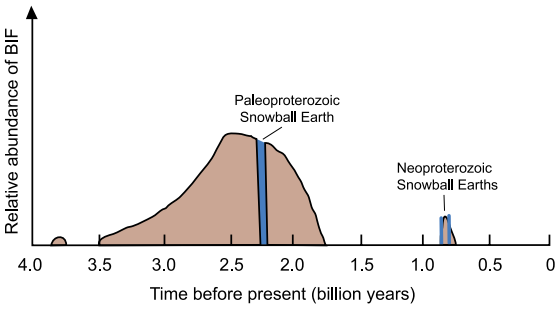
Of over 400 known oxygen-dependent reactions, there were more than 80, in at least 20 metabolic pathways, for which there was a direct anaerobic-to-aerobic substitution. It seems that once oxygen came in, many of the old enzymes were replaced with more efficient oxygen-dependant versions. The extrapolation of modern biochemistry to the early Earth must therefore always be handled with extreme caution.

Let's see if we're on firmer ground when we look at the geological record. The presence of sedimen-

tary banded iron formations (BIFs for short) has often been claimed as evidence that locally oxygen-rich environments were present as long as 3.8 billion years ago. With their beautiful banding, BIFs are stars of the Precambrian rock world. The oldest BIFs formed about 3.8 billion years ago, peak formation time was about 2.5 billion years ago, and they stopped forming 1.75 billion years ago, apart for a small blip at 700 million years ago that I'll tell you about later.

BIFs form when something happens to change highly soluble ferrous iron, Fe^{2+}, to insoluble ferric iron, Fe^{3+}, which then drops to the ocean floor as a rain of rust. For a long time, many argued that this "something" was the interaction of dissolved iron—carried through oxygen-free bottom waters—with oxygen produced by small communities of cyanobacteria living in surface waters.

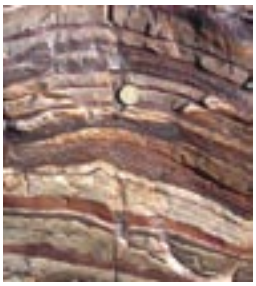
But does the deposition of BIFs actually demand oxygen? Both UV light and iron-oxidizing photosynthetic bacteria could also be responsible. Some strains of green sulfur, purple nonsulfur, and purple sulfur bacteria can use ferrous iron, rather than water, as the electron donor in photosynthesis. Strong support for this has come from my colleague Dianne Newman, associate professor of geobiology and environmental science and engineering. Newman and former postdoc Andreas Kappler simulated water of the chemistry that we think was present in the Precambrian, and put some iron-oxidizing photosynthetic bacteria into it. Even at a light level equivalent to that found at a depth of 100 meters, the bacteria received enough light for photosynthesis, and oxidized ferrous iron to ferric iron so rapidly that they used it all up (facing page). So it seems quite likely that the BIFs were formed by these bacteria, which makes sense; their lineage is much more ancient than that of the cyanobacteria. BIFs are not good indicators of free oxygen.



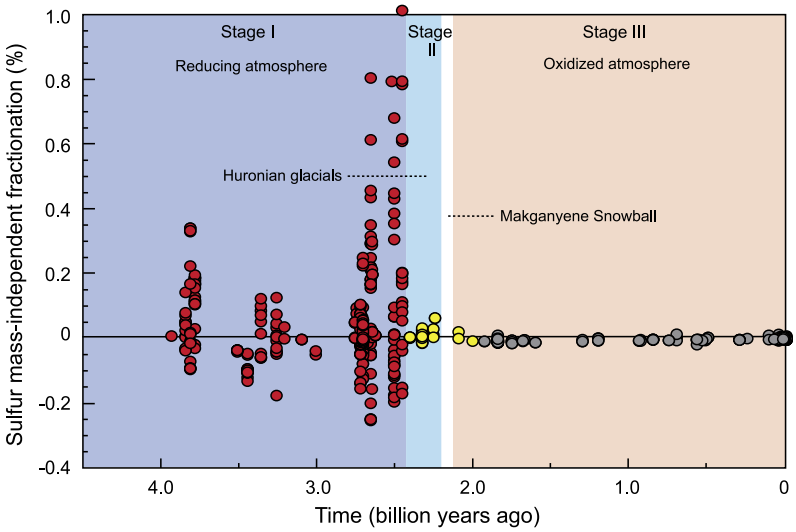
Aside from a few more recent deposits, banded iron formations (BIFs) are confined to the period of Earth's history ending around 1.8 billion years ago. Periods when Earth was in a global ice age, or "snowball" state, are also shown.

Evidence for the *absence* of oxygen in Earth's early atmosphere comes from pyrite, FeS_2. Pyrite is unstable in an oxygen-rich environment**,** but river deposits almost anywhere in the world that are older than 2.3 billion years contain pyrite grains. They show signs of having been carried for long distances by water—something that would be impossible in today's oxygenated world, because the sulfide would quickly oxidize to sulfate, and the iron would rust.

Another reliable line of geological evidence is the study of sulfur isotopes, of which there are four: ^{32}S, ^{33}S, ^{34}S, and ^{36}S. Most chemical reactions involving sulfur produce what's called mass-dependent fractionation—the reaction separates ^{34}S from ^{32}S twice as strongly as it separates ^{33}S from ^{32}S, and separates ^{36}S from ^{32}S twice as strongly again, proportional to the difference in masses. But this isn't true when gaseous sulfur species, particularly sulfur dioxide, are struck by photons of UV light. James Farquhar at the University of Maryland has shown that this produces something called mass-*independent* fractionation. It doesn't happen much today, both because the ozone layer blocks high-energy UV light from most of the atmosphere, and because sulfur dioxide tends to be oxidized



Western Australia has extensive banded iron formations; in some areas, individual layers of deposition can be traced for more than 300 kilometers. The dark bands in the close-up above are iron oxides, and the red bands are chert stained with fine-grained iron oxides. The coin is for scale. These photos were taken in Karijini National Park.



Plotting the ratio of different sulfur isotopes in rock samples against the age of the planet gives a good insight into the evolution of the atmosphere. A phenomenon known as mass-independent fractionation (MIF) only happens in an oxygen-free atmosphere, which indicates that the Earth was oxygen-free during the early years. Much less MIF is found in Stage II, perhaps due to the rise of oxygen, or maybe because glacial conditions enhanced the mixing of sulfur isotopes. No MIF is found after 2.2 billion years ago, a good indication that the atmosphere was fully oxygenated from that time on. Diagram courtesy of J. Farquhar.

The purple nonsulfur bacterium *Rhodopseudomonas* produces rust in the absence of oxygen.

pretty quickly to sulfate aerosols, which is why we don't see it in recent deposits of pyrite and other sulfides. But mass-independent fractionation *is* found in rocks older than 2.2 billion years. As the effect can only happen in a reducing ("reduction" being the chemical opposite of "oxidation") atmosphere, it's a good indication that the change from an oxygen-free to an oxygenated atmosphere happened at about this time. Our research is now focused on the period between 2.45 and 2 billion years ago (Stage II in the diagram above), when there appears to have been a transition between the two types of atmosphere.

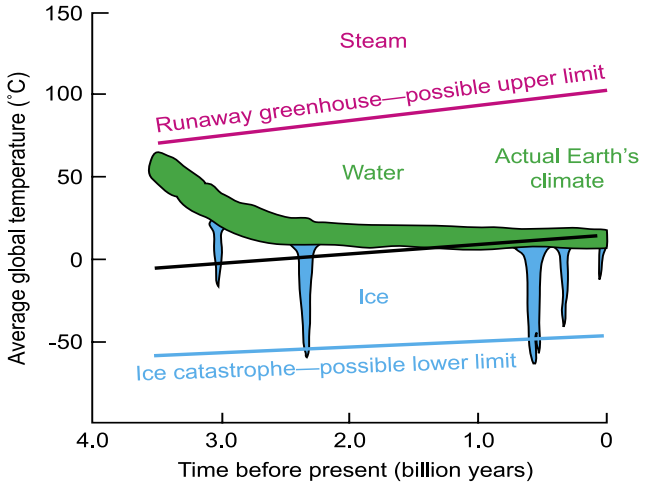
Every now and again in Earth's history, there's a geological event that happens once and is never repeated. The Kalahari manganese field in South Africa is one of those. It's the world's largest manganese deposit by far. Mostly buried beneath the sands of the Kalahari Desert, it's 11 kilometers wide, 50 kilometers long, and about 50 meters thick—and that's just what's left after erosion. The deposit formed about 2.2 billion years ago when insoluble manganese precipitated out of ocean water in vast quantities. It's a unique deposit, and a very valuable one. Without manganese, skyscrapers would fall down, because you need about a tenth of a percent manganese to be alloyed with iron to make steel. But there's no need to worry about that; there's so much here, it will be a long, long time before it ever runs out.

Manganese is a powerful indicator of the presence of oxygen because, electrochemically, it's as close as you can get to oxygen with a metal—much closer than iron. The only way you can oxidize soluble Mn^{2+} to insoluble Mn^{4+} is with nitrate (NO_3^-) or oxygen. Since nitrate itself requires oxygen to form, it's pretty clear that when sedimentary manganese starts to come out of solution in copious quantities, molecular oxygen has to be present. Anoxygenic photosynthetic bacteria couldn't be responsible for the manganese

A vast deposit of manganese lies below the sands of the Kalahari desert in South Africa.

deposit, the way they were for the BIFs, because Mn^{2+} is not a good electron donor for the one-part photosystems used in anoxygenic photosynthesis. So this is the earliest time for which we are certain that copious quantities of free oxygen were available, most likely from oxygenic photosynthesis. What caused this dramatic precipitation of manganese, and when did it happen?

Before I outline a possible scenario to explain this manganese deposit, I'd like to make a small detour into "snowballology." Back in the 1980s, it was known that over time the sun has been getting



The green band shows Earth's climate range over the past 4 billion years, and icicles indicate the major ice ages. Earth has managed to avoid getting so hot that a runaway greenhouse effect occurs, but there were periods—the icicles that extend below the ice catastrophe line—when it got cold enough for the entire planet to freeze over and become a snowball. The ice ages are, from left to right, the Pongola, the Huronian plus Makganyene, the Neoproterozoic, the Gondwana, and the Pleistocene. Adapted from a diagram by James Lovelock.

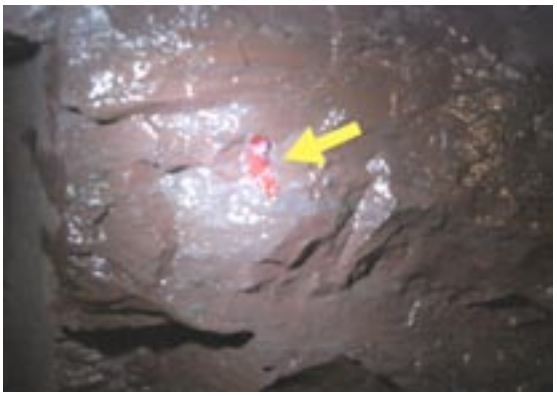
warmer, that the planet had had liquid water for most of its geological history, and that there had been four or five major ice ages. But all the global climate models that people were using had a persistent problem: the runaway ice-albedo effect. "Albedo" is a fancy word for brightness or, in this case, reflectivity. The landmasses and oceans of a planet absorb sunlight, but ice reflects it back into space. When the ice sheets only cover the north and south caps of the planet, this isn't a problem, but if everything above 30 degrees latitude—that's about the position of Houston or Perth—was frozen, the planet would reflect more heat than it could absorb. Earth would cool rapidly and unstoppably, floating pack ice would reach the equator in about 10 years, and sea ice at the equator would eventually be about a mile thick. Earth would become a snowball.

In all of these early climate models, there was no way Earth could escape from this ice catastrophe once the globe had frozen over. For this reason all of the climate modelers and most of the scientific community assumed that this had never happened. Then, in the late 1980s, our lab was dealing with some puzzling paleomagnetic data that showed there had been widespread ice on the equator about 700 million years ago. I must have been chewing on this in my sleep, because I woke up one night and realized that if it *had* happened, it would explain a lot of things, including that small blip of BIFs at 700 million years ago in the diagram on p. 14. If the oceans had indeed completely frozen over, hydrothermal vent fluids pumping reduced metals like ferrous iron into the ocean would have stripped the water beneath the ice sheets of oxygen (by converting it to rust) after a few million years. Once all the oxygen was gone, these reduced metals, still pumping out of the vents, would build up in the water. Then, once the ice melted and oxygen levels increased again, all that ferrous iron in the water would be oxidized again. Vast amounts of rust would precipitate out and form the BIFs.

But what could possibly stop the ice-albedo effect once it had started? Volcanoes. The climate modelers had forgotten to put them into the models. Volcanoes wouldn't become inactive when all the land and oceans were covered in ice—they would still erupt and emit carbon dioxide, which would slowly build up in the atmosphere. And once the insulating greenhouse effect of this carbon dioxide kicked in, it would reverse the cooling. Carbon dioxide levels would have had to build up to four or five hundred times the present levels before there was enough warming to melt the ice, but our calculations showed that this could have happened in as short a time as 10 million years.

Today, the idea that Earth was a snowball at least twice between 800 and 600 million years ago, in the Neoproterozoic period, is gaining widespread acceptance. Most of the debate now is about how complete the snowballs were, and whether there were bits of open ocean around the equator. Was it a snowball or more of a slushball?

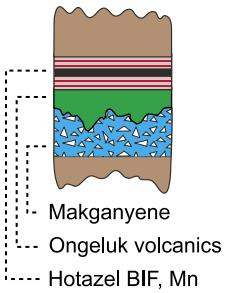
These snowballs happened well after the period that may have seen the rise of the cyanobacteria, but there's good evidence that Earth was also encased in a snowball between 2.3 and 2.2 billion years ago, in the Paleoproterozoic. And this snowball was directly related to their evolution. The evidence comes from the Makganyene glaciation in the Kalahari area of South Africa. When you walk in the field there, you find stones scratched in multiple parallel directions on both sides, a sign that they've been dragged across the bottom of a glacier. We've been able to estimate the latitude these rocks were at during the glaciation because a huge series of eruptions, the Ongeluk volcanics, flooded the area with basalt 2.22 billion years ago, and the lava intermingled with rocks carried along by the glaciers. When lava cools, tiny magnets made of iron oxide crystals within it get frozen in alignment with Earth's magnetic field, and we can tell the latitude of the eruption by the dip of their preserved magnetism to the horizontal. The Ongeluk eruptions were just 11 degrees from the



Dropstones like this one were embedded in the bottom half-meter of the Nchwaning manganese mine.

equator, the present-day level of Costa Rica. The runaway ice-albedo effect that causes a snowball kicks in when ice sheets get below about 33 degrees latitude, so finding signs of glaciers much closer to the equator, at 11 degrees latitude, is good evidence that Earth was entirely frozen over.

The Precambrian geology of the Kalahari (left) is very interesting. We start with rocks that are 2.415 billion years old, above which lie the glacial deposits of Makganyene, intermingling with and covered by the 2.22-billion-year-old Ongeluk flood basalts. Above that is a BIF that includes the enormous manganese deposit, named the Hotazel formation after a local mining town (which, I can vouch, lives up to its name). It occurred to me that the Hotazel formation could be related to the Makganyene snowball, but to pursue my theory, I had to know when the glaciation ended.



A section through the Precambrian strata of the Kalahari area.

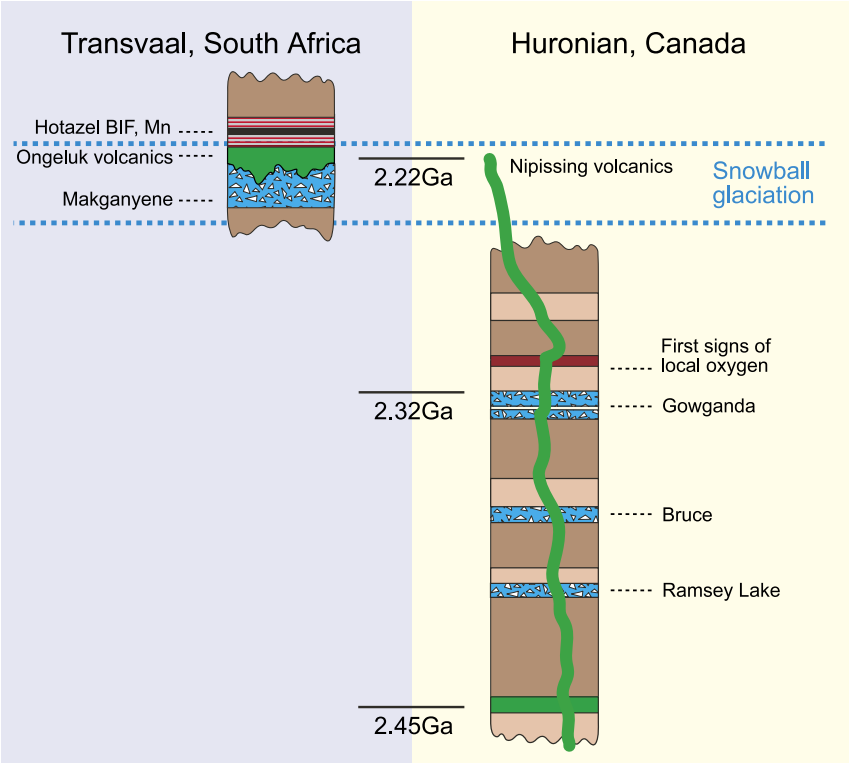
The prevailing view is that the Ongeluk eruptions marked the end of the ice age. But we know from other places where flood basalts have occurred, such as the Deccan Traps in India, that lava comes out of Earth's interior in enormous quantities over no more than one or two million years. That's much shorter than the time required to build up enough carbon dioxide to melt a snowball. In this early Earth, with its much weaker sun, it would take 70–100 million years to build up enough carbon dioxide to reverse the ice-albedo effect. So let's step back and look—could it be that the Hotazel BIFs, like the 700-million-year-old BIF blip in the Neoproterozoic, are related to the snowball?

Geologists use dropstones as evidence of melting glaciers. These are stones carried along in the ice as the glacier travels, and by icebergs after they calve off into the sea. When the ice melts, the stones drop down one by one and become embedded in the sedimentary layers. To see if the Hotazel BIF contained any dropstones, we looked at some drill cores. There were stones in the bottom meter or so of the BIF, on top of the volcanic layer, that might have been dropstones, but we couldn't be sure. They could equally well have been ejecta—rocks thrown up into the air by little explosions from a volcanic vent. But there is a way to tell the difference: ejecta are all in the same geological layer, while dropstones are arranged randomly, wherever they drop when the glacier melts. The drill cores couldn't tell us that, so we just had to go look at them *in situ*.

The best place to examine this contact between the Ongeluk lavas and the Hotazel formation is in the Nchwaning mine on the Kalahari manganese field, where the base of the ironstone and manganese deposits just happens to be exposed along an access tunnel, about 200 meters below ground. It wasn't easy working in the dark looking at rocks covered with many years' worth of diesel soot. We had to spray the rocks with soapy water to see what we were looking for, but there, in the bottom half-meter or so of the Hotazel formation, were dropstones. Not in discrete layers, as ejecta would have been, but dropped randomly here and there, as from a melting glacier. This, to me, shows that the snowball glaciation ended here, after the Ongeluk eruptions. And this melting is somehow tied up with the massive deposition of BIFs and manganese that came immediately after.

We know there were a number of earlier ice ages, including three known as the Huronian glacials (named after rock exposed around Lake Huron). There's no evidence from magnetization data that the Huronian glaciations occurred at low latitude. As far as we can tell, they may well have occurred at midlatitudes, further than 33 degrees from the equator. So they might not have been snowballs. Nevertheless, the Huronian strata have been very helpful in our attempts to discover the reason for the Makganyene snowball. By a lucky chance, the whole Huronian formation is overlaid and cut through by a volcanic dike stemming from an

Knowing they wouldn't look this clean afterward, the dropstone-detection team posed for a photo before descending into the manganese mine. Kirschvink (second from right) and geobiology grad student Cody Nash (third from right) were accompanied by a driver (next to Cody), and mine manager A. Pretorius's son and daughters.



A possible chronological correlation between the Kalahari (left) and Huronian (right) strata is shown above. The blue and white areas are glacial deposits from ice ages. Lava (green) from the Ongeluk volcanoes erupted during the Makganyene glaciation 2.22 billion years (Ga) ago, while lava from the Huronian Nipissing volcanics that occurred at about the same time erupted through the lower strata.

eruption that happened at the same time as the Ongeluk eruptions**.** This gave Bob and me a way to correlate the South African rock strata with the Huronian ones. When we put the two areas in chronological order, as in the diagram above, we could see that the final Huronian glaciation, the Gowganda, predated the Makganyene snowball. Before Gowganda, there is little evidence for oxygen. After Gowganda, there is; sulfates (from the oxidation of sulfides like pyrite) and ferric iron appear in the strata. And then the Makganyene snowball happens.

Is this just a temporal coincidence, or did planetary oxidation start just after the last Huronian glaciation and before the snowball? Did the mutant cyanobacterium, the one that combined photosystems I and II, do something bad? It's a possibility: an exponentially growing bacterium that releases oxygen into an anaerobic world could quite rapidly create a very unstable situation, eventually leading to a snowball.

When did the critical mutation happen? Was it during the Huronian glaciations? As I said earlier, cyanobacterial growth isn't limited by the availability of electron donors, only by the availability of nutrients like phosphorus and iron. This is true today—it's why you get cyanobacterial blooms from phosphorus- and nitrogen-rich agricultural runoff—and it would also have been true in Huronian times.

Bob constructed a simple cyanobacterial growth model using the sort of carbon, phosphorus, and iron fluxes that might have been present during a partial glaciation in an anoxic world. Phosphorus, which originates in the rocks of the continents and is carried into the oceans by rivers and glaciers, is the main nutrient limiting their growth, and the

F. Emiliani (Universidad National Litoral), M. Schneegurt (Wichita State University) & Cyanosite (www-cyanosite.bio.purdue.edu).

A bloom of *Anabaenopsis* on Bodetti Lake, Argentina; the bubbles are likely oxygen.

cyanobacterial bloom would increase rapidly until it was all used up. The oxygen the cyanobacteria released during photosynthesis would initially be taken out of solution by the ferrous iron, and other reductants, from the hydrothermal vents, or locked up in organic matter in sediments on the ocean floor. But eventually, there would be so many cyanobacteria that excess oxygen would build up in the atmosphere and affect the methane greenhouse.

According to Bob's model, this could happen in around a million years if the phosphorus input was pumped up enough. And guess what? Enhanced weathering during a glaciation is just the thing to pump up the flux of phosphorus into the ocean and spur the proliferation of the cyanobacteria. So if there *were* cyanobacteria around during the Huronian ice ages, these glaciations might well have been the trigger that pushed the system over the edge.

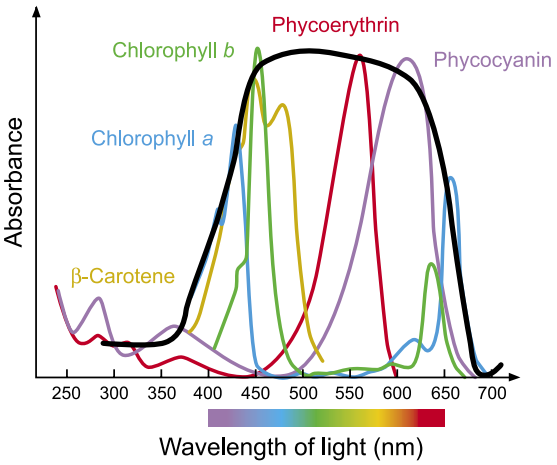
The cyanobacteria changed the planet forever . . . . But it all so nearly went wrong, and it's a sobering thought that a single mutant cell—the first oxygen-releasing cyanobacterium—could have destroyed the entire ecosystem of planet Earth.

But we don't see any evidence of cyanobacterial oxygen production affecting sediments until *after* the three Huronian glaciations, and before the Makganyene. If Earth was experiencing glacial cycles in Huronian times the way it does today, the Makganyene ice age may have been just the fourth ice age in the series. If the cyanobacteria evolved just before it started, the extra phosphorus pumped into the ocean by the glaciers would have caused the huge bloom that oxygenated the oceans and the atmosphere. Even today there are mini-blooms in the wake of melting icebergs.

In attempting to cope with the influx of oxygen, many species died, others evolved the ability to breathe it, and some, like the methane-generating bacteria, survived in deeper parts of the ocean that were still anoxic. The methane from these bacteria no longer reached the atmosphere, but oxygen from the cyanobacteria, who live near the surface, did. Aided by sunlight, the oxygen would have reacted with the methane, changing it to water and carbon dioxide—a much less effective greenhouse gas, as I said earlier. With the destruction of the methane greenhouse, the planet would have lost heat rapidly. Global temperatures would have plummeted to -50 degrees C, Earth would have become a snowball, and most living things would have died.

It was a close call. If Earth had been a bit farther from the sun, temperatures at the poles could have dropped enough to freeze the carbon dioxide into dry ice, robbing us of the greenhouse escape route. The planet would never again have been able to support life. (Did something like this happen to Mars?) As it was, it likely took at least 70 million years for the planet to warm up again. But when the swing from freezing to warming came, it would have been rapid. Once enough carbon dioxide had built up in the atmosphere to start melting the glaciers, the extra water vapor released would have compounded the greenhouse warming, and temperatures would have jumped rapidly up to perhaps +50 degrees C.

While the oceans were frozen over, the hydrothermal vents continued to release large amounts of trace elements and minerals, including ferrous iron and soluble manganese, so by the time the ice melted, the waters were again rich in nutrients. Particularly in upwelling zones on continental margins, the cyanobacteria would have given off an abundance of oxygen, and this would have reacted with all that dissolved iron and manganese, and precipitated it out. That is the unique event that created the Kalahari manganese field.



The pigments that plants and photosynthetic bacteria use to absorb sunlight during photosynthesis respond to all the wavelengths of visible light except green, which is reflected. That's why plants appear green. Photosynthesis would be more efficient if the green photons were harnessed as well (black line), but then the green parts of our planet would look black.

The cyanobacteria changed the planet forever. Living things were able to increase in size and become multicellular, as respiration using oxygen produces more energy than respiration with other electron acceptors. A few methane-excreting bacteria survived, but only in places well away from oxygen, such as the mud under rice paddies, and the stomachs of cows. But it all so nearly went wrong, and it's a sobering thought that a single mutant cell—the first oxygen-releasing cyanobacterium—could have destroyed the entire ecosystem of planet Earth.

Could it happen again? I remember attending a Chem 1 lecture back in a 1971 freshman class given by Harry Gray, now the Beckman Professor of Chemistry, in which he showed us a slide of the absorption spectrum of the various photosynthetic pigments. Gray, a chemist trying to find better ways of harnessing solar power, complained how inefficient the system was, because all those green photons in the middle of the spectrum were going to waste.

Which leads me to think, what if some clever genetic engineer made a bacterium that could photosynthesize those green photons as well? And what if it got out and spread? If all the green photons were captured, our green planet would look black. Imagine the albedo effect of a black planet—every living thing would fry. If one cyanobacterium 2.3 billion years ago could destroy most of life on Earth, it could happen again. We've got to watch those chemists. □

Bob Kopp is holding some of the oldest evidence for life on this planet, a stromatolite that formed 3.5 billion years ago.

Joe Kirschvink is the Van Wingen Professor of Geobiology. His research focuses on the way in which major events on the surface of Earth, and possibly Mars, have influenced biological evolution, and how biological evolution has affected the climate and geology. As a high-school student in Phoenix, Arizona, a talk by a visiting professor—Kip Thorne—so impressed him that he decided he wanted to study at the speaker's university. Working with the late paleoecologist Heinz Lowenstam, the discoverer of biomagnetism, he earned his Caltech BS in biology and MS in geology in 1975, followed by a PhD in geology/geobiology from Princeton in 1979. Returning to Caltech in 1981 as an assistant professor, he became an associate professor in 1987, a full professor in 1992, and the Van Wingen Professor in 2004.

Kirschvink has a knack for proposing controversial hypotheses that subsequently gain acceptance and lead to new ways of thinking. They include the Snowball Earth hypothesis; the proposal that polar wander led to the Cambrian evolutionary explosion; and the idea that bacteria could have traveled to Earth from Mars in meteorites. He discovered that some magnetized sedimentary rocks contain the fossilized remains of magnetotactic bacteria, and his idea that the higher animals can sense magnetic fields by using biogenic magnetite led to the discovery of these sensory organelles and provided a biophysical basis for the understanding of magnetic effects on animal behavior.

A fellow of the American Association for the Advancement of Science, the American Geophysical Union, and the American Academy of Arts and Sciences, Kirschvink is an enthusiastic and popular teacher who was awarded the Richard P. Feynman Prize for Excellence in Teaching in 2002. There is even an asteroid 27711 Kirschvink, which orbits between Mars and Jupiter with an unusually high eccentricity.

This article is adapted from a talk given in May at the 68th Annual Seminar Day. Bob Kopp is the lead author of a paper on this subject that appeared in the August 2005 issue of PNAS, *vol. 102, p.11131.*

The Metathesis Waltz

by Douglas L. Smith

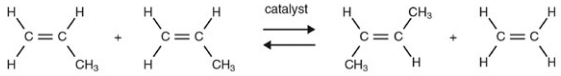
Robert Grubbs, the Atkins Professor of Chemistry, got a phone call from Stockholm in the late evening of October 5 in Christchurch, New Zealand, where he was on a fellowship at the University of Canterbury. The 2005 Nobel Prize in Chemistry had been split equally between him, Richard Schrock of MIT, and Yves Chauvin, retired from France's Centre National de la Recherche Scientifique, for what the Royal Swedish Academy of Sciences called "one of organic chemistry's most important reactions." The Academy's advanced supplementary material added, "Considering the short time during which Grubbs' and Schrock's catalysts have been available, the breadth of applications is truly remarkable. We have witnessed the synthesis of polymers with special properties, additives for polymers and fuels, and biologically active compounds such as insect pheromones, herbicides, and drugs." Small wonder, perhaps, that the normally impassive Swedes were moved to write, returning to the press release, "Imagination will soon be the only limit to what molecules can be built!" (Exclamation mark theirs.)

Grubbs is also an accomplished canyoneer and mountain climber. Here he descends a waterfall in the upper reaches of Eaton Canyon in the San Gabriel Mountains just north of Pasadena, heading for a refreshing dip in the pool below.

The metathesis waltz, as performed by the Caltech Ballroom Dance Team. A molecule containing a carbon-carbon double bond (grad student Kate Campbell, MS '03, and Robert Nissen) approaches a molecule with a metal-carbon double bond (grad students Megan Ferguson and Michael Cohen, whose back is to the camera). Silver-sashed (and shod!) Megan, dancing the catalyst, leads the joining of hands in a four-membered ring, and when the couples part, she is now dancing with Robert. A second carbon-carbon double bond (grad student Candy Tong, MS '04, and Kenneth Kuo) approaches, and the figure repeats. At the end, Robert and Candy are paired up as the product molecule, and Megan is ready to begin the catalytic cycle again.

This marvelous reaction, called metathesis from the Greek word for transposition, may be visualized as a stately Viennese waltz. Picture a man and a woman dancing the roles of carbon atoms, holding both of each other's hands to form a carbon-carbon double bond. Another couple, similarly holding hands, approaches—but the second lady, in a shimmering silver sash, represents a metal atom. (A carbon atom double-bound to a metal atom is called a carbene—in general, the suffix "ene" in the name of an organic, i.e., carbon-based, compound signifies the presence of a double bond. Make a note of this, as it will save you a lot of flipping back to this page later.) The two couples join hands to form a square, then pair off again, changing partners as they do so. The silvery lady—our catalyst—dances her new partner over to another hand-holding couple—two more carbon atoms—to form a new square, and when this breaks up, all six dancers will have changed partners but all of them remain part of a double bond. To the outside observer, looking only at the final pairings, no bonds have been broken or new ones formed, yet somehow the atoms have traded places.

Recalls Grubbs, "In 1968 I was a postdoc working with Jim Collman at Stanford, and he came



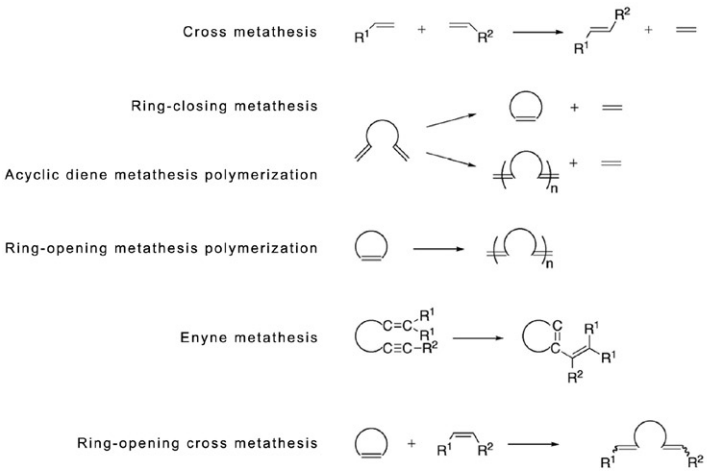
In a metathesis reaction discovered in the 1950s, two molecules of propylene (left), each with three carbon atoms, become a molecule of 2-butene, with four carbon atoms, and a molecule of ethylene with two carbon atoms. (Or vice versa—the reaction is reversible.)

Special thanks to Caltech Ballroom Dance Club president Kate Campbell for the choreography, and to Grubbs graduate student Michelle Robbins for technical assistance.

back from a consulting trip talking about this crazy reaction he had just heard about. You passed propylene over a catalyst, and it turned it into ethylene and 2-butene." (See above right.) "There was absolutely no clue about how it happened, and I was really interested in mechanisms, so it struck me as being a perfect place to start." Of course, people knew how to make carbon-carbon double bonds, how to break them, and how to transform them into bonds with other atoms. But what was weird here was the *rearrangement*. The carbon atoms usually danced with the ones that brung them, but here they traded partners with abandon. Everyone was excited by this reaction because, if the process could be generalized and controlled, it would be the means to a whole lot of different ends. Metathesis had actually been employed industrially on a limited scale since the 1950s, and several patents had been issued on various processes that exploited it, but nobody knew how or why it worked.

Grubbs left Stanford for an assistant professorship at Michigan State in 1969. He continued thinking about metathesis, doing model studies to try to figure out how the carbon atoms could leap around like that, and even published a plausible mechanism that turned out to be completely wrong. Then, in 1971, Yves Chauvin, at that time with the Institut Français du Pétrole, and his student Jean-Louis Hérisson wrote a paper describing what turned out to be the correct mechanism. So Grubbs "designed some studies that helped convince people that the Chauvin mechanism was the best description of how the reaction proceeded. And that was probably the work that got me tenure." (Grubbs became an associate professor at Michigan State in 1973.) These "labeling" studies involved replacing the two atoms of hydrogen attached to one of the carbon atoms in the dance with two atoms of deuterium, or "heavy hydrogen," and noting where the deuterium wound up when the dance was over.

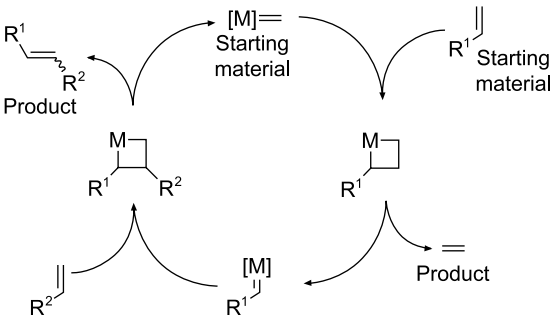
Understanding *how* the reaction worked was one thing; figuring out *what* made it work proved to be quite another. The catalysts were "heterogeneous," which is to say that they were ill-defined mixtures of organic chemicals in dubious association with metal atoms in unknown oxidation states. "They were cobalt and molybdenum on alumina that you prepared in a sort of hocus-pocus way," Grubbs remembers. "These were recipes, true recipes. Like tungsten hexachloride mixed with the right amount of alcohol and then some alkyl aluminum reagent and something magic happened. And sometimes the soluble part was the catalyst, and sometimes the insoluble part was the catalyst. You never knew." And if you counted the active catalytic sites in this witches' brew, it became apparent



These examples of the types of rearrangements that metathesis can do give some hint of its versatility. In this drawing and those that follow, hydrogen atoms are not shown for clarity, and every vertex and every end of a line segment represents a carbon atom. R is shorthand for the rest of the molecule.

that all the catalysis was being done by a small percentage of the metal atoms. Consequently, no one had any idea what the arrangement of atoms was that was actually doing the job, and like any other poorly understood piece of magic, it was hard to work with. (Just ask Harry Potter about his Potions classes.) For metathesis to live up to its potential, a molecule whose structure was well-known and whose behavior could be predicted—nay, designed—would be required. That wouldn't happen for some time, however.

Meanwhile, Caltech wooed Grubbs away from Michigan with a full professorship in 1978, and when he arrived he and graduate student Thomas Howard (MS '81) started doing model studies on a titanium-based catalyst that *was* well-defined, but painfully slow to react. This was actually a plus, as it allowed them to capture and identify the intermediate chemicals in the reaction for the first time. By then the Chauvin mechanism was pretty much accepted, says Grubbs. "We'd done most of the labeling stuff before I came to Caltech. Isolating the intermediates just nailed down the details. The labeling studies had basically ruled out all the other mechanisms—Schrock was doing stuff, we were doing stuff, and the consensus became that Chauvin's mechanism was the best explanation. So we knew to start looking for catalysts that



Chauvin's catalytic cycle. R^2's squiggly bond in its product molecule indicates that R^2 might also lie on the upper side of the double bond, the way R^1 does. In its simplest form, the reaction produces both products; part of the art of using metathesis is in engineering the reaction system to get the product you want.

contained metal-carbon double bonds. And we knew that this titanium system contained such a bond, so we were able to isolate the first example of that kind of system that would do metathesis." The titanium catalyst proved to be really useful for making polymers, and Grubbs's lab spent the next decade doing just that. (See *E&S*, Summer 1988.)

Metathesis's turning point came in 1980 at MIT, when Schrock made a well-defined catalyst with a tantalum-carbon double bond that worked at a reasonably zippy rate. A brace of more active tungsten-carbene catalysts followed, and then in 1987 a very active molybdenum carbene. (The most efficient molybdenum version, commercially available as "the Schrock catalyst," appeared in 1990.) But while these catalysts briskly and efficiently rearranged molecules containing just carbon and hydrogen, they tended to react irreversibly with oxygen atoms. This meant that they were sensitive to water—and air—which was a pain in the neck; worse, from an organic chemist's point of view (Schrock is an inorganic guy), it meant that you couldn't have any oxygenated "functional groups" in the molecules being catalyzed—no alcohols, no aldehydes, no amides, no esters, no carboxylic acids. "The functional groups killed the catalyst," says Grubbs. "And we were trying to make functionalized polymers, so none of the Schrock catalysts would work."

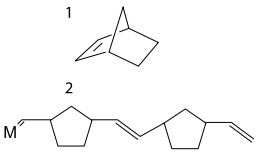
Molybdenum, tungsten, tantalum, and titanium are all early transition metals. That is, they lie near the left edge of the periodic table, a little to the right of the alkaline earths such as magnesium and calcium. If you think of a metal atom as tract housing for electrons, the early transition metals are fresh-built subdivisions with lots of vacancies—unoccupied *d* orbitals—in their outer precincts. Thus they eagerly recruit the two rich, nonbonding electron pairs on an oxygen atom, passing over the less upwardly mobile single electron pair available at a carbon-carbon double bond. But as you travel to the right across the periodic table, the *d* orbitals gradually fill up. This makes the metals choosier about the electron pairs they pick to fill their remaining orbitals, and so they are able to reject an oxygen atom in favor of a carbon-carbon double bond. In fact, some even prefer the latter, as an unoccupied antibonding orbital on the double bond can soak up some of their greater electron density—as the neighborhood gets crowded, the metal's electrons like a little elbow room. So grad student Bruce Novak (PhD '89) began looking at the late transition metals.

Other chemists had used solutions of ruthenium trichloride to do metathesis with some success, but, says Grubbs, "if you did site counting, the number of metal centers that became active was incredibly low. Less than a percent. They seemed to be extremely active but very short-lived." Novak discovered that the ruthenium atom had to be in the right oxidation state—Ru^{+2} instead of Ru^{+3}—and came up with a catalyst that, while it didn't set any

speed records, was unaffected by all the functional groups that Schrock's catalysts fell prey to. It still wasn't well-defined, but, says Grubbs, "we realized that there had to be a ruthenium-carbon double bond there. Some people had made ruthenium carbenes before, but none of them worked for metathesis because, as we now know, they were in the wrong oxidation state. And this catalyst was clearly a very special one, because it survived water and air."

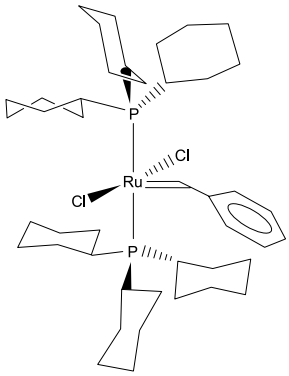
You can let Novak's concoction sit in a beaker by the sink overnight, whereas Schrock's catalysts need to be kept under an inert atmosphere in a drybox—an airtight chamber with an air lock for getting things in and out, and rubber gloves sealed to the walls to allow manipulation of the materials within—and reactions using Schrock's catalysts have to be run in elaborate vacuum systems using all kinds of special techniques.

The ruthenium catalyst had one serious drawback—it needed a little extra oomph to get it going. It only worked when the carbon-carbon double bond was under strain, bowed like a stick ready to snap. Practically speaking, this meant that the carbon-carbon double bond had to be part of a ring containing five or fewer atoms. The ability to open rings is a useful thing, but Schrock's catalysts worked happily on unstrained, linear molecules.



A molecule of norbornene (1) looks like the business end of an eggbeater, and its double bond is highly strained. When it polymerizes (2), it becomes a flatter, much happier molecule. (The M represents the catalyst metal atom.)

Now that the Grubbs group had found the magic metal and its all-important oxidation state, it fell to Sonbinh Nguyen (PhD '95) to build a working ruthenium carbene from scratch. "Sonbinh was just an amazing kid," beams Grubbs, "and he's the graduate student I invited to go to Stockholm. He did the breakthrough reaction." The lab had been experimenting with different ways to make Schrock catalysts, including using cyclopropene—a highly reactive molecule containing three carbon atoms in a triangle, one of whose sides is a double bond—to make tungsten carbenes. "It was some intelligent

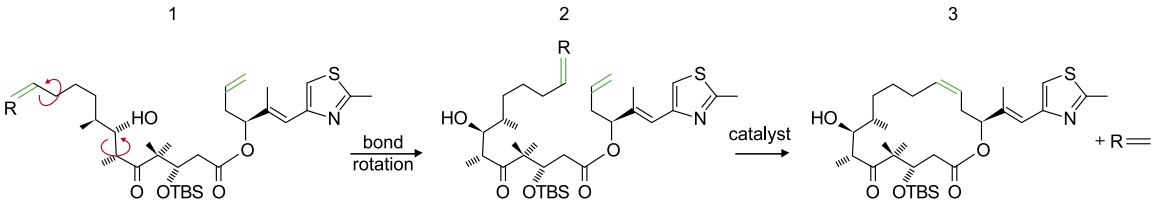


The first-generation Grubbs catalyst. Solid triangles indicate bonds that stick out of the plane of the page toward the viewer. Shaded triangles show bonds that recede behind the page.

design and some evolution," says Grubbs. "He applied the cyclopropene route to ruthenium, and it sort of all worked. I'd proposed this approach to a few other people, and it hadn't quite worked. It all happened pretty fast, and I still remember the group meeting where Sonbinh got up and talked about this, and afterward one of the guys who had been working on this area for a long time went up to him and said, 'You lucky son of a bitch!' And Sonbinh just smiled. It wasn't luck. He'd got it all put together right." Nguyen's first catalyst, developed in late 1991, also only opened strained rings. But he kept at it, and by 1993 he had an improved version that worked on straight-chain molecules, just like Schrock's did. "And it was tolerant of water, fairly tolerant of air, and tolerant of almost all functional groups," says Grubbs. "So that really was the break that started all the applications."

Nguyen's molecule had several parts. There was the ruthenium-carbon double bond, of course, plus a couple of chlorine atoms bound to the ruthenium to maintain the correct oxidation state—a leftover from the original ruthenium chloride system that Novak had started with. And there was some inconsequential stuff attached to the carbene that was basically debris from the molecule's synthesis. The carbene and the chlorines lay in a plane around the ruthenium's equator, as it were, and Nguyen's critical innovation—the introduction of two phosphorus atoms attached to some other organic groups—were affixed to the north and south poles. The phosphorus atoms supported, in the second version, a parasol made of three cyclohexyl groups—big, bulky, six-carbon rings. The northern cyclohexyl phosphine, as it's called, guards the approaches to the catalytic center, directing potential dance partners to the carbene below, and it also lends some of its electron density to help stabilize that critical step in the waltz where the ruthenium and three carbon atoms all hold hands. But the southern cyclohexyl phosphine is the key to the whole shebang—it activates the catalyst by detaching itself from the molecule, taking two electrons with it. Ruthenium^{+2} with five atoms bound to it has 16 electrons to play with, and metathesis only occurs when it has 14 electrons. "We obviously didn't know that at the time," Grubbs admits. "We found that out in the studies that came later. The way things work in this area is you make a guess and then you make something. And part of the time it works. Or it works better, but for a different reason than you thought it was going to. Or it does something you didn't intend really, really well. As I reassured one of my students recently, 'If you plan something and it works, then you're a scholar. If you plan something and it does something else even better, then you're creative!'"

Nguyen's preparation methods were very labor-intensive, and it proved impossible to make his molecules in bulk. So Marcia France (PhD '95) and postdoc Peter Schwab came up with an easier



A critical step in the synthesis of epothilone A, a potential anticancer drug, involves creating a 16-membered ring. This is complicated by the fact that the unclosed ring is a long, floppy chain (1). Solvent molecules banging into the chain cause it to writhe around, and eventually its various links will rotate in just the right way to bring the two green double bonds close together (2). The waiting catalyst then does its magic (3).

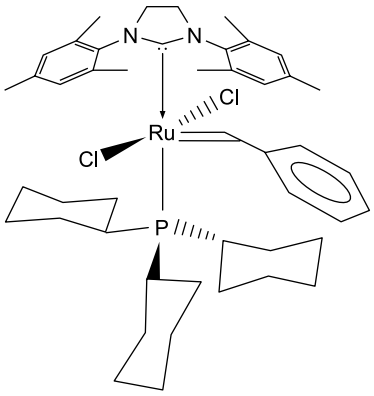
synthetic route, which postdoc Michael Giardello was able to scale up. This catalyst, published in 1995, is commercially available as the "first-generation Grubbs catalyst."

Meanwhile, postdoc Gregory Fu used Nguyen's catalyst to demonstrate ring-closing metathesis—a critical step in many pharmaceutical syntheses. These drug rings, like their criminal counterparts, are large, multifunctional, and flexible. They often contain a dozen or more members—epothilone A has 16—and before the ring is closed the free ends can lie quite some distance apart along a loose, floppy backbone. There are innumerable ways that things can go wrong when you attempt to round up your suspects, but planting double bonds at the right spots and using metathesis to handcuff the end atoms together greatly raises the odds of making a successful collar. Just this past June, Boehringer-Ingelheim, a German pharmaceutical company, reported the manufacture of some 400 kilograms of a hepatitis C protease inhibitor for use in possible Phase II clinical trials. The process uses ring-closing metathesis in the 20th step of a 25-step synthesis. No metathesis-based pharmaceutical has yet reached Phase III, the final hurdle before a drug goes to the FDA for approval, but several are in Phases I and II.

A "second-generation" catalyst came out in 1999. Developed by grad students Matthias Scholl (PhD '00), Tina Trnka and John Morgan (both PhD '03), and undergrad Sheng Ding (BS '99), it is even more reactive, is stable at higher temperatures, and is now the catalyst of choice for splicing dissimilar molecules together in what's called cross metathesis.

There wouldn't be all this fanfare if none of these wonderful products ever made it out of the lab. The chemical industry is embracing metathesis because, besides being easy to use, it's more efficient. Products can be made in fewer steps, using fewer reagents, and generating less waste. And, if you're using Grubbs's catalysts, you can do a lot of reactions in water that you would otherwise have to do in a toxic solvent such as benzene. The Nobel press release calls metathesis "a great step forward for 'green chemistry'" because it allows us to make stuff we can't (or don't want to) live without, in the most environmentally friendly way possible.

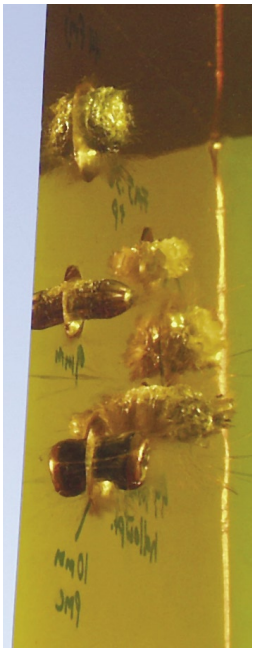
Not surprisingly, a company has been formed around these catalysts. Materia Incorporated, headquartered in Pasadena, has Grubbs and Schrock on its scientific advisory board. Materia manufactures and sells all of their catalysts as well as those developed by Boston College's Amir Hoveyda, a frequent collaborator of Schrock's, and licenses their use. Materia also uses these catalysts to make products, including polydicyclopentadiene resin, which, in the words of Grubbs's former postdoc Giardello, now Materia's CEO, is "tough, durable, corrosion-resistant, and amenable to large-part fabrication." A 1½-inch-thick layer will stop a 9-millimeter copper-jacketed bullet within its own length, and it can be molded into things as diverse as hulls for personal watercraft or body panels for farm equipment. It is also used for valves and pipes to handle chlorine, concentrated alkalis, and strong acids—some of the nastiest substances in the chemical industry. Easton Sports even injected it into low-grade, porous wood, turning out baseball bats—approved for use in every league but the majors—until the Chinese construction boom soaked up all the cheap timber.



The second-generation Grubbs catalyst has an even better donor of those dance-promoting electrons at its north pole.

PICTURE CREDITS: 21 — Luca Chiarabini; 22–23 — Herb Shoebridge; 25, 26 — Doug Cummings; 27 — Materia, Inc.

Some of the catalysts available from Materia. The dark purple one at bottom right is the first-generation Grubbs catalyst, and the reddish-brown one at center left is the second-generation Grubbs catalyst.



A rear view of a sheet of polydicyclopentadiene resin into which several bullets of various calibers have been fired, including a 9-millimeter copper-jacketed one (left center) and a .44 Magnum hollow-point (lower right).

Materia also makes pheromones, chemical signals secreted by an animal to communicate with other members of its own species. One favorite message, roughly translated, is "Hello, sailor—come here often?" Since insect mating is induced by chemical cues rather than sexy lingerie or whispered nothings, organic farmers use pheromones instead of pesticides, wafting scents that lure amorous males into death traps and leave the females high and dry. It takes a fair amount of patience to go completely green, but a reasonable middle ground can be achieved by setting a few pheromone-baited traps and then applying pesticides judiciously when the fleet comes in.

The use of pheromones for pest control is still in its infancy, generating perhaps only several millions of dollars in annual sales worldwide versus the more than one billion dollars spent on pesticides by U.S. farmers alone. But the market share grows each year. Says Giardello, "We target only the pests our chemistry is best suited for. This is mainly the *Lepidoptera*—moths and butterflies—whose larvae do tremendous damage to stone fruits such as peaches." Materia's peach twig borer pheromone did several hundred thousand dollars in sales last year, its first year on the market. And a spruce budworm pheromone, now in development with the Canadian government, could be a multimillion-dollar seller in a few years.

But the faux pheromone of the future may be the one for the omnivorous leafroller, which is very fond of grape leaves but also likes those of apple, pear, peach, and nectarine trees. The compound is produced from jojoba oil and 3-hexene in a six-step process with a 50 percent overall yield. (The jojoba, from whose edible seeds the oil is extracted, is a shrub native to the American southwest and Mexico.) By contrast, the traditional synthetic method takes 14 steps, starts entirely with petroleum-based compounds, and gives a 15 percent overall yield at three times the production cost.

What's neat is that Materia's process requires no solvent of any kind whatsoever—you just process the jojoba oil to extract its main component, and add the 3-hexene and the catalyst to the extract. "It's its own solvent," says Grubbs. "And essentially all the products you make are useful. So it provides a way of making bonds without wasting solvents, and without generating by-products and streams of pollutants." Caltech, Materia, agribusiness giant Cargill, and the Department of Energy are working on a joint project to expand this whole notion of solventless processes to seed oils in general—corn oil, soybean oil, and what have you. As any viewer of margarine commercials knows, these oils consist mostly of unsaturated fatty acids, which is just a fancy way of saying molecules with double bonds in them. Cargill's goal, says Grubbs, is "a process where, as they describe it, they take a barrel of vegetable oil and sprinkle a little magic dust to make it a new product. And the less magic dust you have to add, the happier they are."

And that's the greenest thing of all—seed oils are renewable resources. If we could cheaply and efficiently convert seed oils into products that are normally made from petroleum, we'd be one step closer toward kicking our oil habit. Giardello says that Cargill has already come up with a process that "converts a renewable feedstock into a proprietary industrial product with household applications that's going to be really big," but he's cagey about saying more before the patents go public next summer.

Grubbs's research group is now working to extend catalyst lifetimes. Obviously, the more stuff you can crank out per molecule before something goes wrong, the cheaper the process becomes, and the more opportunities arise to use it. "We've got some reactions where the catalyst does a few hundred-thousand turnovers, that's the high end, and then for some really hard reactions, it's as low as four or five turnovers." This means that, "in terms of stuff you're selling, very few things are worth it. But in terms of academic applications, I've had people say, 'Look, I don't care if it only turns over once. I just want to make this compound.'" So the lab is exploring all the side reactions that can kill the catalyst or tear it apart. "If we can find all the mechanisms for decomposition and termination, maybe we can design strategies for preventing them from taking place. And we've already come a pretty long way in that.

"Right now we're still in the nitty-gritty of getting the first round of products out, and developing the next round of catalysts. What's been amazing to me about this research is that when I first started, I didn't think we would ever be able to make catalysts that tolerated functionality. And then we did that, and we didn't think that we'd be able to make catalysts that would tolerate air and water. And we did that. I didn't think that we'd be able to do metathesis on double bonds that contained functional groups directly on the double bonds. And we can do that, now. So I keep getting surprised. And every surprise leads to a new direction to go in." □


ALTECH

Molecular Switches for Cellular Sensors

by Christina Smolke

Left: Undergrad Jack Lee, Smolke, and grad student Travis Bayer enjoy decaf, regular, and espresso laced with caffeine-sensing cells.

Right: Stem cells make many life choices en route to their eventual careers. After deciding to become a hematopoietic, or blood-forming, cell, various forks in the road lead to immune-system cells including natural killer (NK) cells, red blood cells (erythrocytes), platelet factories (megakaryocytes), and various types of white blood cells. (Graphic adapted from Eckfeldt, et al, *Nature Reviews Molecular Cell Biology*, Vol. 6, pp. 726-736, 2005.)

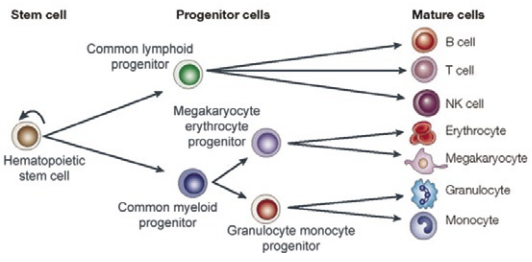
I work in a new field called synthetic biology, which is an amalgam of molecular biology, biochemistry, and control theory. And I'm actually a chemical engineer. Synthetic biologists try to design systems—cells—that will perform some sort of complex task. Now cells do complex things all the time, of course, but what makes synthetic biology different is that it emphasizes robust, predictable design—tiny cellular machines that, like mechanical ones, will reliably do what we want them to do. A vacuum cleaner always sucks up dirt, for example, but without adequate controls, the cellular equivalent might decide to in effect ingest dust bunnies one day and reheat frozen burritos the next.

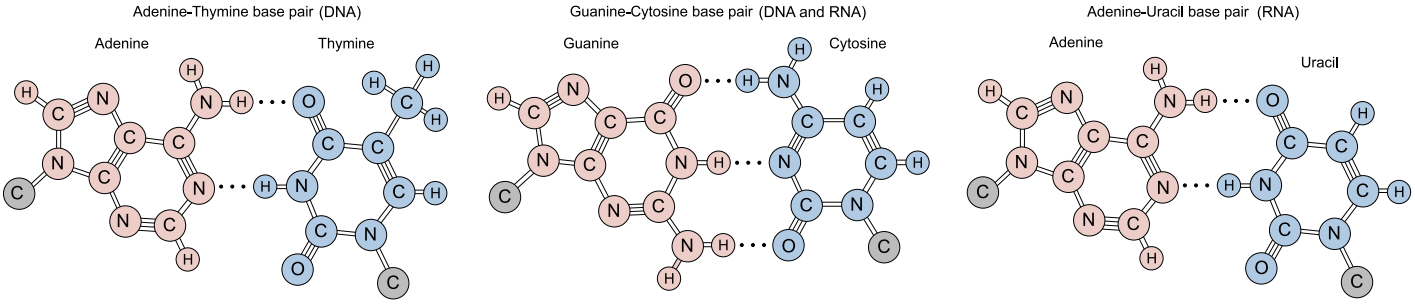
There are several kinds of tasks that we're interested in. In metabolic engineering, we reprogram a cell to produce a valuable compound, such as a pharmaceutical. Nature produces a wonderful array of medically useful molecules, but not always the ones we want in the quantity we'd like. It can also be very expensive and time-consuming to grow, harvest, and extract the natural product, but the molecules are frequently so complex that it is even more expensive and time-consuming to try to make them in factories. For example, the opium poppy produces morphine and codeine through a metabolic process that proceeds by way of several intermediate products, including (*S*)-reticuline, which is a molecule from which many potential anticancer and antimalarial drugs can easily be synthesized. But (*S*)-reticuline doesn't normally accumulate in the poppy, and shutting down a metabolic pathway partway through its course is a tricky proposition. For example, knocking out the gene for codeinone reductase, the final step in the path, actually shuts it down seven enzymatic steps upstream. Several intermediates accumulate, including (*S*)-reticuline, which then needs to be separated from the other intermediates and purified. This is in contrast to some simpler organisms, such as bacteria and yeast, where you can knock out a gene anywhere along a pathway and—assuming this action doesn't kill the cell—accumulate whatever substance was produced in the previous step. So if we could reconstruct the pathway of interest in some tractable microorganism, we might be able to make it produce bulk quantities of anything we want. With the sophisticated genetic-engineering tools at our disposal and an artificially constructed pathway, we'd be better able to control the production process and isolate our chosen substance.

We could also reprogram a diseased or problematic cell through "intelligent molecular therapeutics." That is, we'd design molecules that could identify the cell that they're in and then do something based on that identification. So, for example, if the molecule determines that it is in a cancer cell, it would rewire that cell's aberrant metabolism to make it behave like a normal cell.

Alternatively, we could design cellular biosensors, where the molecule would make the cell produce a detectable signal, such as fluorescence or luminescence, which would then be read by a machine. Such biosensor molecules could be used for enhancing our understanding of the key pathways that regulate important cellular functions (or make codeine!), or in the early detection and diagnosis of diseases.

And finally, we could reprogram a cell's entire life choice, not just some facet of its metabolism. There's been a lot of discussion about stem cells recently in the media. Stem cells are undifferentiated—that is, they have the potential to become any of many types of cells. So a completely undifferentiated stem cell first chooses to become one of several general types





Above: The bases in DNA and RNA recognize one another by forming hydrogen bonds (dotted lines). The gray carbon atoms are part of the backbone chain on which the bases are strung.

of cell—nerve cells, blood cells, liver cells, and so on—and then once it decides to be, say, a blood cell, it makes choices from progressively narrower sets of options until it reaches a particular sub-classification such as a T-lymphocyte, which is a specific type of white blood cell. Cells have natural preferences for certain choices at various forks in these pathways, so if we can figure out which molecules actually make those decisions, we could try to influence the choices. We could even make a cell decide to kill itself—programmed cell death, or apoptosis, is a choice that a surprising number of cells make in every developing embryo. If we found a cancer cell, for instance, that was too far gone to reprogram, we could simply shut it down altogether.

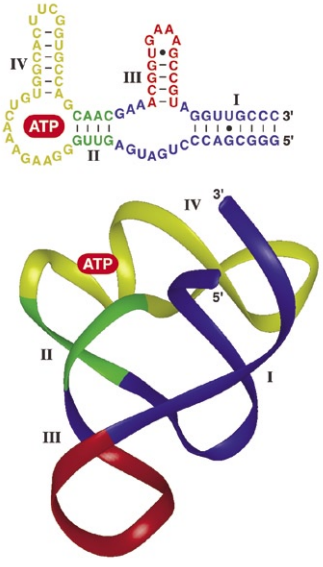
The cell's behavior is a property of the molecules that are within it at that moment, so the first thing to do is take inventory—what is the global set of proteins (and other biomolecules) that results in this particular behavior? And once we've identified all those proteins, what are the interactions, or the links, between them? One set of proteins will interact with another set of proteins that interacts with the next set of proteins which goes on to interact with other proteins, and eventually the cell winds up doing something. These interactions are the moving parts of the machine—the cogs, cams, and flywheels—and if we want to rebuild the machine to do something else, we need to trace their motions to determine what each part does.

But what controls the machine? For each protein, there is a gene, and when the gene is turned ON, the protein is produced. The gene is made up of DNA, which encodes the blueprint for that protein as well as instructions for when it should be produced, and in what quantity, depending on the cell's environment. These instructions are the buttons on the control panel, if you will, and their interplay is the wiring diagram. Once the gene is turned ON, the cell reads the blueprint through the medium of an intermediate molecule, called messenger RNA, via a process called transcription. And the messenger RNA instructs the cell's machinery to make the protein.

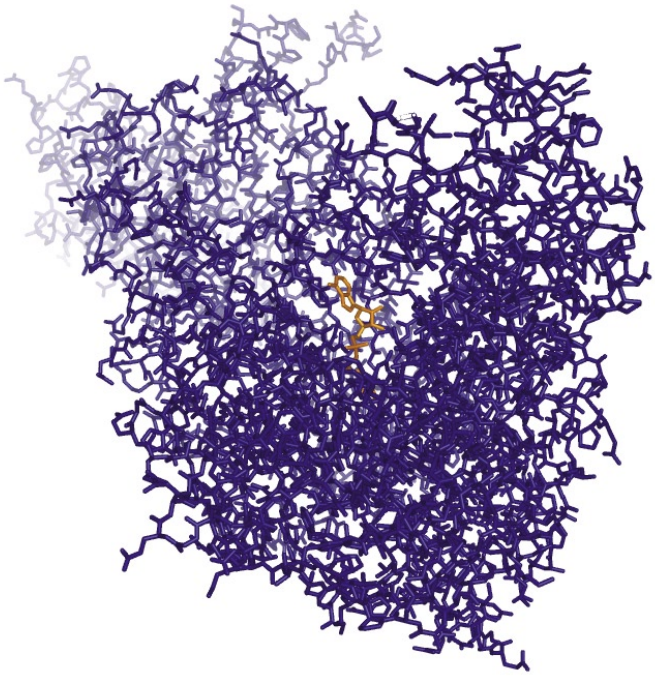
DNA and RNA are nucleic acids—a completely different type of molecule from proteins. They're made up of four different building blocks, called bases—adenine (A), guanine (G), thymine (T), and cytosine (C), with uracil (U) instead of thymine in RNA—strung together like pearls on a necklace. Inside cells, DNA normally exists as two strands that are bound to each other by interactions between the bases, like the meshing of teeth in a zipper. The bases recognize one another, so that T always bind to A, and G always pairs up with C. So, for instance, if I tell you that one strand of DNA has the sequence AGTC, you know immediately the complementary sequence—TCAG—that's going to bind to that strand. RNA is generally a single-stranded molecule, but its bases interact in the same way, with U being complementary to A. RNA molecules can bind to themselves, with parts of the molecule forming railroad-track structures called stems, often capped with little protruding knobs called loops. Ultimately, the whole molecule coils up, twisting and knotting like an unruly telephone cord, as does DNA. The sequence of bases in RNA or DNA is called the primary structure. The way the bases associate with one another forms the secondary structure, and the wadded-up tangle that results is called the tertiary structure.

Nucleic acids have traditionally been viewed as passive molecules within the cell. They stored genetic information, or they acted as intermediaries that transported it, but they didn't really *do* anything by themselves. But this turns out to be a very limited view. In the past couple of decades, nucleic

Far right: An RNA molecule's primary structure is its sequence of letters (top); some of the letters bind to one another to form its secondary structure of stems and loops. (The dots represent "wobble pairs"—slight mismatches that distort the molecular backbone.) The secondary structure kinks and twists to form the tertiary structure (bottom), shown as a ribbon. The colors and roman numerals mark various "domains" that actually do things—domain IV recognizes and binds to the adenosine triphosphate or ATP molecule, for example.



Adapted from Soukup and Breaker, *Trends in Biotechnology*, Vol. 17, No. 12, pp. 469-476, 1999.



There are about 300 amino acids in this protein, a tRNA synthetase, which recognizes and binds to phenylalanine, shown in orange.

acids have been found to have a number of very interesting functions. They really *do* do things, and we are exploiting these functions to design molecules to perform functions of our own choosing.

First, nucleic acids can exhibit catalytic activity: they can perform reactions, which is traditionally the province of proteins. RNA turns out to be very good at cutting apart other pieces of RNA. The reverse of a cleavage reaction is a ligation reaction, in which the RNA joins nucleic acids together, and RNA is very good at that as well. RNA has, in fact, been found to catalyze a large number of different types of reactions, leading some scientists to propose the existence of an "RNA world" on the early Earth, before the advent of DNA and proteins, in which RNA alone carried out all the business of life. So catalytic activity is a very powerful property with many uses.

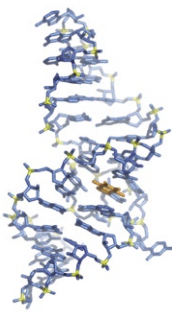
Second, nucleic acids can also act as regulatory elements. Remember, DNA encodes genetic information that is transcribed to messenger RNA, which is read, or "translated," by the cell. Meanwhile, scavenger proteins are destroying the RNA, preventing the cell's machinery from getting stuck in overdrive. So the amount of protein being produced at any given time is a balance between the competing rates of transcription, translation, and decay, and the cell modulates the fluxes between these different pathways to control the amount of protein that's produced.

Recently, it's been discovered that "trans-acting RNA" molecules—small RNA molecules that do not code for any protein—actually regulate protein production. They carry a complementary sequence of bases that allows them to bind to the messenger RNA. Because the messenger RNA makes sense to the cell's machinery, these strands of RNA are called "antisense" strands. Some antisense RNAs simply impede the translation of the messenger RNA—like trying to feed too many sheets of paper into a printer at once, they jam up the machinery. Others actually increase the messenger RNA's decay rate by flagging the molecule for destruction. Either way, less protein is produced.

There's another class of RNA regulatory elements called "cis-acting" molecules. These are actually parts of the messenger RNA molecule itself. They don't contain any of the code for the protein molecule, but they have a well-defined secondary structure—oftentimes some variety of stem-loop structure. This stem-loop structure forms a tertiary structure that interacts with other biomolecules in the cell to modulate the relative rates of transcription, decay, and translation of the messenger RNA to which it belongs. Each RNA molecule usually has several cis-acting regions that respond to different stimuli.

But the final type of activity is the most exciting, and is the basis for a lot of the engineering work in my laboratory. Nucleic acids can actually act as sensors to detect and identify other molecules, which is another property that was typically only associated with proteins. An RNA (or DNA) molecule can fold back onto itself to form a tertiary structure that creates a binding site for a protein molecule in a very specific manner—in other words, it will recognize and bind to the latter. Such pockets can also recognize small molecules, like caffeine and other drugs, and medium-sized molecules, such as the lipids in the cell membrane. Thus nucleic acids have enormous potential as molecular sensors, with specificities and affinities rivaling that of protein-based sensors.

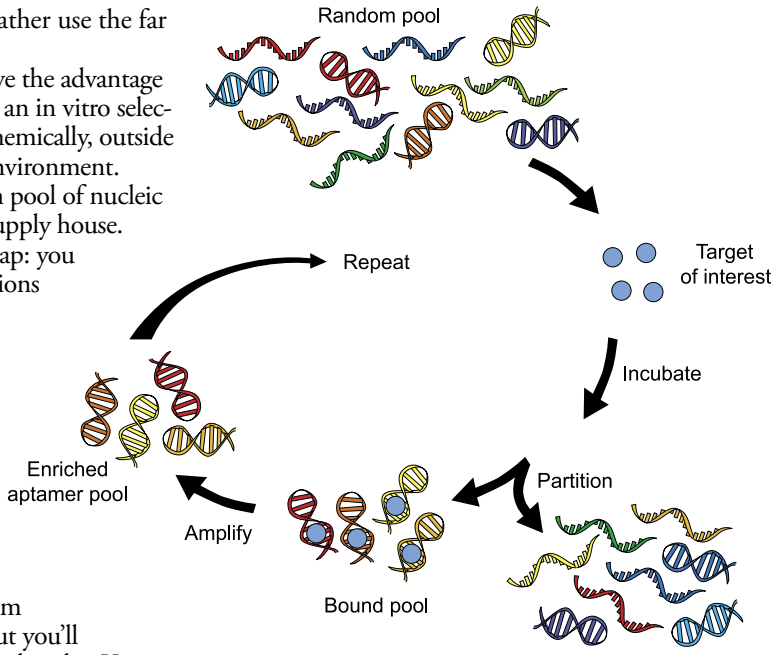
And nucleic acids have one huge advantage. Above left is the complete structure of a protein molecule, shown in blue, and a small biomolecule, shown in orange, to which it is binding. (The molecule being bound is called a ligand.) And below is a single-stranded RNA molecule that has twisted up to form a pocket that binds a ligand of similar size. The RNA likes to stack its base pairs in that famous double helix, and the ligand slips in between the pairs like a spatula sliding between flapjacks in a short stack. I don't know about you, but if I had to try to design one of these two



This much smaller strand of RNA contains about 30 nucleic acids, yet it recognizes and binds to theophylline, which is a molecule about the same size as phenylalanine.

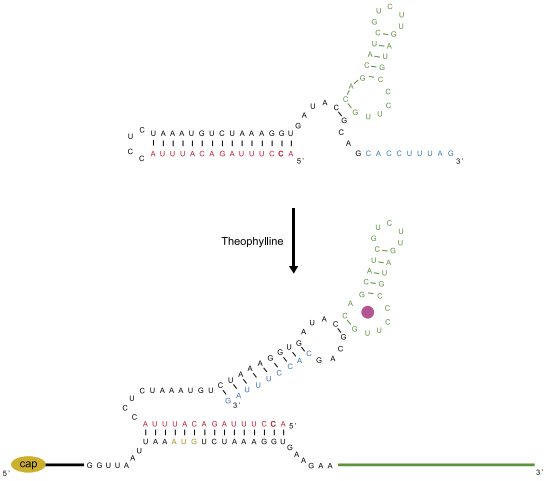
molecules from scratch, I'd much rather use the far simpler nucleic acid structure.

These nucleic acid sensors also have the advantage that you can generate them through an in vitro selection process. You can make them chemically, outside of cells, in a reasonably controlled environment. You basically start off with a random pool of nucleic acids, which you can order from a supply house. DNA synthesis is fairly easy and cheap: you just ask for all the possible permutations of, say, a sequence 40 base pairs in length. Using standard methods, you transform this random pool of DNA into the corresponding RNAs in your lab. Then you take whatever molecule you want the sensor to recognize—say, a viral protein that you want to use to detect infected cells—and you incubate it with this pool of random RNAs. Most of them won't bind to the target molecule, but you'll get a very small population of RNAs that do. You then fish those out, again by standard methods, and use them as the starting pool for the next cycle. Each cycle can take as long as a day—or at least several hours—to complete, and it usually takes eight to 15 cycles to get a good result. (My lab is working to get this down to one to three cycles of a couple of hours each.) In any case, you eventually wind up with a very selective, high-affinity pool of aptamers—nucleic acid structures that bind to the target. Then you decide which is the best one for your purposes and incorporate it into your molecule.



Far right: How to find the perfect aptamer: Lather. Rinse. Repeat.

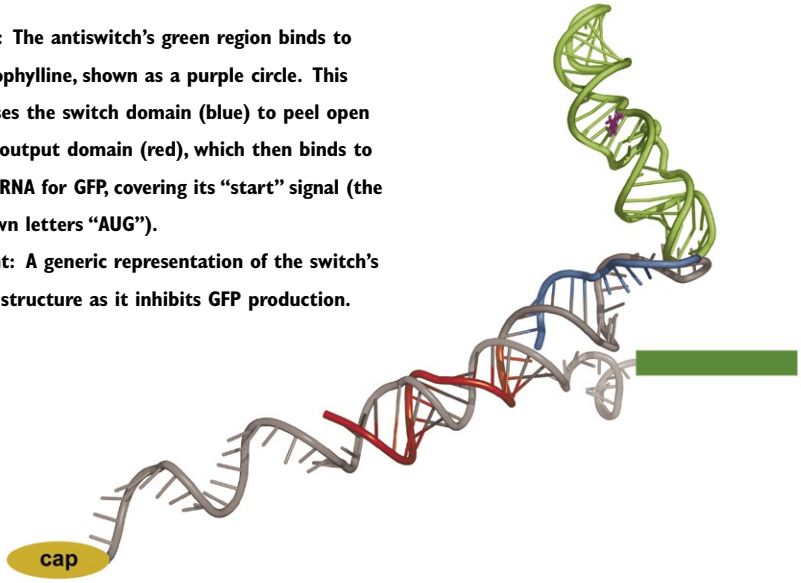
But a sensor is no good if you can't read its output. So we engineer RNAs that contain several different domains in each molecule, as you can see in the color-coded structures below. The sensor domain (green) is the winning aptamer from the talent search I described in the previous paragraph. This is linked through a switching domain (blue) to an output domain (red) that controls the production of some protein by the cell. This protein could generate a detectable signal—for instance, green fluorescent protein (GFP), which makes the cell emit green light when you excite it with a laser, is commonly used. GFP is popular because you don't have to disturb the cells in any way to sense its presence. You just hook up a video camera to your microscope, zap the cells, and watch them glow. Or the protein might direct the cell to change its behavior in some way—to stop dividing if it's a cancer cell, for example. Or the protein might stimulate the production of something we're interested in, like a pharmaceutical. The output can be digital—a very sharp response, basically ON/OFF or ONE/ZERO, meaning we've either detected the ligand or we haven't—or it can be analog, a graded response that increases



Adapted from Bayer and Smolke, *Nature Biotechnology*, Volume 23, Number 3, pp. 337-343, 2005.

Left: The antiswitch's green region binds to theophylline, shown as a purple circle. This causes the switch domain (blue) to peel open the output domain (red), which then binds to the RNA for GFP, covering its "start" signal (the brown letters "AUG").

Right: A generic representation of the switch's 3-D structure as it inhibits GFP production.



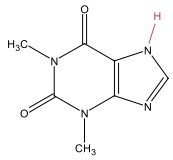
in proportion to the concentration of the molecule being sensed. We're working on both, but the one I'll describe here is the digital version.

We call it the antiswitch, because the output domain is an antisense, trans-acting RNA domain. But we could also call it the antiswitch because it works backward, in a way. The antisense domain is designed to bind to a messenger RNA and keep it from being read by the protein-producing machinery. But when there is no ligand present, the RNA loops back upon itself like a bobby pin and the antisense domain is actually bound to another part of the molecule containing the complementary sequence. So the antisense domain is all tied up, and can't bind to the messenger RNA and shut it down. The target messenger RNA I've shown here produces GFP, so that when the cell fluoresces, the detection value is ZERO. (In order for this to happen, of course, the cell must have been reprogrammed to produce GFP by default, but fortunately that's a well-known procedure.)

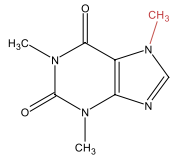
When the ligand slips into its binding pocket between the neatly stacked base pairs, something really interesting happens. The RNA molecule changes its tertiary structure, which actually forces a change in its secondary structure. The switching domain (blue) pivots inward and displaces the antisense domain (red), peeling it free from the other side of the hairpin. The liberated antisense domain then binds to the messenger RNA and shuts it down. The cell no longer fluoresces, and the detection value is ONE—the ligand is present. In digital terms, ONE is OFF and ZERO is ON—the opposite of computers.

So then, of course, we put this antiswitch in cells to see if it would actually work. Graduate student Travis Bayer created an antiswitch with an aptamer that recognizes theophylline, which is found in tea and is chemically very similar to caffeine. He then inserted instructions for making the theophylline antiswitch into the DNA of yeast, specifically *Saccharomyces cerevisiae*, using standard molecular-biology techniques, and grew a batch of yeast cells, which took several hours. At right is a plot of the cells' behavior. The blue line is the switch response. You can see that as the theophylline concentration increased, the GFP response was not affected until a threshold concentration was reached. Then the switch suddenly shifted its conformation as it bound the theophylline, letting the antisense domain bind to the GFP messenger RNA, and GFP production ceased. So these molecules really work, and they exhibit a sharp, binary, response. I also want to point out their specificity—when Travis grew the yeast in the presence of caffeine (the orange line), there was no switch effect. So these sensor domains really can differentiate between very similar molecules.

RNA aptamers can recognize both small molecules and big proteins, which is a really powerful property. To demonstrate this, Travis has developed switches that respond to such things as the



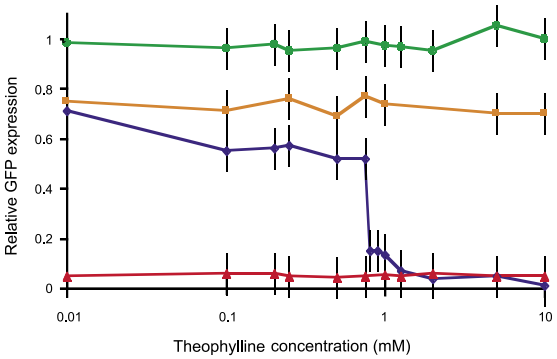
Theophylline



Caffeine

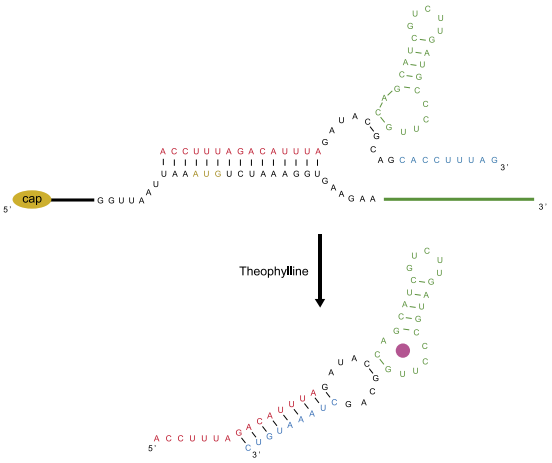
Theophylline and caffeine are very similar.

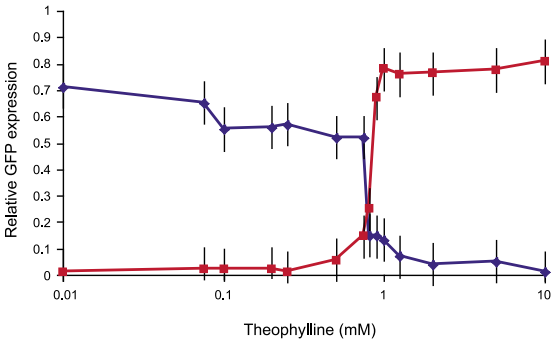
Adapted from Bayer and Smolke, *Nature Biotechnology*, Volume 23, Number 3, pp. 337-343, 2005.



Above: The blue line is the theophylline switch response. The green and red lines are control experiments. The green line represents a molecule with just the aptamer, so it never binds to the GFP messenger RNA to suppress production. The red line has the antisense domain but no aptamer, so it always suppresses GFP. And the orange line shows what happens when caffeine is added to the brew instead of theophylline, demonstrating that the response is specific to the latter. (The orange line is slightly lower than the green one because a few RNA molecules open their hairpins even with no ligand present, so GFP production is slightly inhibited.) The vertical black lines represent the error ranges in the measurements.

Right: This inverse switch turns GFP production ON when theophylline is present.





Above: In this plot, the blue line shows the response of the switch we saw before. The red line shows the behavior of the inverse design.

Both figures adapted from Bayer and Smolke, *Nature Biotechnology*, Volume 23, Number 3, pp. 337-343, 2005.

phosphorylated form of ERK2, which is a protein 250 amino acids in length that is involved in intracellular communication networks in human cells.

And we can adjust the threshold concentration by altering the relative binding energies of the antisense domain and the switching domain. Travis put some mutations in the antisense stem so that the nucleic acid sequences weren't a 100-percent match any more, and showed that this lowered the concentration at which the stem opened up. The two sides of the hairpin didn't stick together as tightly, so it didn't take as much effort—or, effectively, as many ligand molecules—to force them to let go of each other. On the other hand, when he elongated the stem (and kept all the matches perfect), it increased the stability of the closed state because it took additional energy to pry the longer sequences apart. This moved the switching response to a higher concentration of the ligand. So this is a really powerful platform, because not only can we sense a specific ligand by our choice of aptamer, but we can also program the concentration at which the switch senses that molecule.

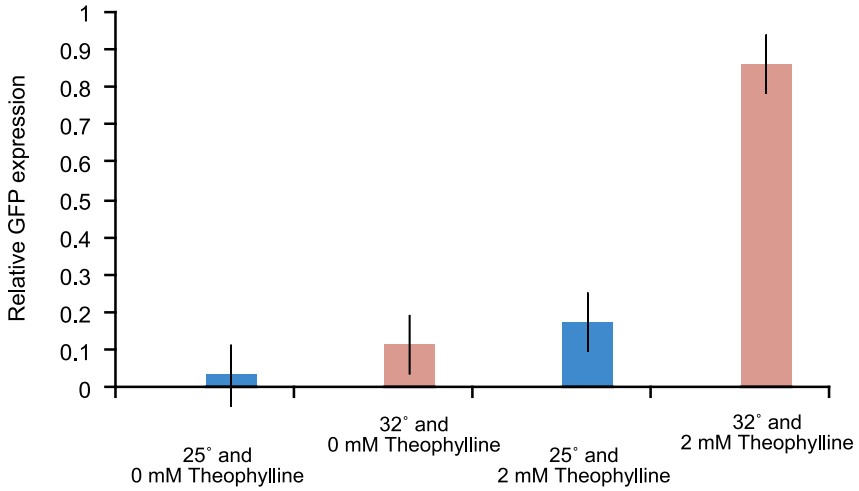
Jack went to the Red Door Café in Winnett Student Center and picked up decaf, regular, and espresso, and grew the gradient-filter yeast cells in them. Yeast cells do just fine in coffee as long as you add the standard culture medium, which is a broth of the sugars, amino acids, and other nutrients that they need to grow.

In real life, of course, you'd want to look at more than one ligand at a time. So Travis made a switch for tetracycline, an important antibiotic, which controlled the production of Yellow Fluorescent Protein, or YFP. When he put it and the theophylline GFP switch into the cell at the same time, the two switches retained their specificity. In the absence of the ligands, both were ON. In the presence of only one ligand, the respective messenger RNA got shut down as it should, and the other was unaffected. And in the presence of both ligands, both RNAs were shut down.

Travis also engineered the inverse design, where the antisense domain is bound to its messenger RNA in the absence of the ligand, and lets go when the ligand is present. He kept the same base-pairing energetics in the red and blue stems so that the switch would be triggered at the same concentration of theophylline, but in reverse.

We next asked whether we could make the molecular equivalent of electronic components within a cell, and we decided to start with a gradient filter. A concentration gradient is analog, varying smoothly from low to high, and a filter would translate it into, say, three discrete cellular states—LOW, MEDIUM, and HIGH—that you could then represent digitally. So in the summer of 2004, Jack Lee (BS '07) took our ON and OFF switches, altered their sensor domains to detect caffeine, and tuned their set points apart from each other. The ON switch, which controlled YFP, was tuned for a low concentration of caffeine (but higher than that found in decaf), and the OFF switch, which shuts down GFP, was tuned for a high concentration—higher than in regular coffee. Then Jack went to the Red Door Café in Winnett Student Center and picked up decaf, regular, and espresso, and grew the gradient-filter yeast cells in them. Yeast cells do just fine in coffee as long as you add the standard culture medium, which is a broth of the sugars, amino acids, and other nutrients that they need to grow. And behold, several hours later, GFP was found in the decaf. In the regular brew, he got GFP and YFP together, and the yeast in the espresso produced only YFP. So our caffeine sensor really works under field conditions, and we were very pleased by that.

Now we're looking at producing actual logic gates, which is the first step toward biocomputation. In practical terms, this means that the cell assays different biomarkers simultaneously—bio-

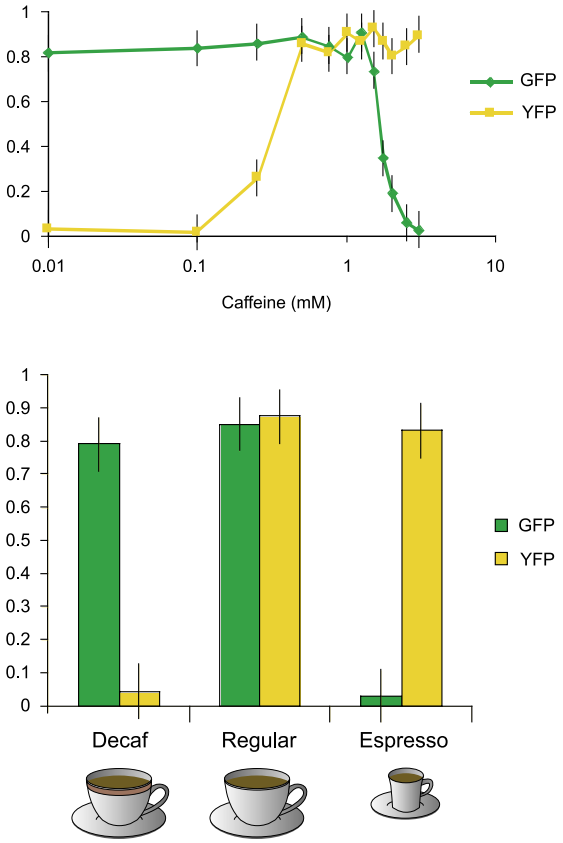


Right: The behavior of an AND gate sensitive to both high heat and theophylline.

markers being molecules that are indicative of certain conditions, such as a protein that is produced in cells only when they are dividing—and then, depending on the precise combination of biomarkers it finds, the cell performs a specific output. But the inputs to a biocomputer do not all necessarily have to be chemical in nature. For instance, Travis engineered a temperature sensor comprised of nucleic acids. I won't describe it in detail, but it's a cis-acting regulator inserted into the messenger RNA for GFP. The stem changes conformation with temperature, so that at low temperature, the protein is not produced, and as you increase the temperature, GFP production begins. So he put both the temperature-sensing GFP RNA and the inverse theophylline switch in the cell to create an AND gate that only fluoresces in the presence of high temperature and high concentrations of theophylline. Graduate student Maung Nyan Win (MS '05) is also working on the design of AND and OR gates that take two different biochemical inputs, but these are rather complex, and I won't go into them here. But in any case, these are our first steps toward performing logical functions within cells.

This logical capability will probably be really important in the design of intelligent molecular therapies. A properly chosen set of biomarkers would differentiate between normal cells and diseased or cancerous cells. That is, if and only if all the biomarkers are present, the cell performs some output, which might be metabolic reprogramming to make the diseased cells act like healthy cells, or targeted cell death, in which case we would *really* want to be sure that the cell is a diseased cell. Travis and grad student Chase Beisel are adapting our switches to function in mammalian cells. We are just getting started on this, but we are already seeing some very exciting results.

It's great to be able to identify all these biomarkers inside a cell, and maybe you wouldn't mind being injected with our switches as part of a cancer treatment, but if you're just going to the doctor's office for a checkup, you don't want to have all this stuff put in your body on the off chance that you might be coming down with something that it could detect. And you probably don't want to light up green, either. So the next logical step is to build some sort of chip-based diagnostic device that you could put a droplet of blood or urine or saliva into and get a rapid readout. Such a device would detect the presence of various critical proteins while also measuring the levels of important small molecules such as sugars, reliably pulling



Top: The set points for the caffeine-sensing GFP and YFP switches. Bottom: Their behavior in actual beverages.

Ultimately you'd be able to take, say, a blood sample, lyse the cells—split them open—and add their contents to a solution containing the switches and the templates . . . If testing several people revealed specific differences between normal, healthy subjects and people with a particular cancer, we could then use this as a diagnostic device for early detection.

all these diverse molecules out of a very complex mixture. So we're working toward a nanosensor based on our programmable switches and DNA amplification technology, the latter of which is the workhorse of biotech.

The polymerase chain reaction, or PCR, which won Kary Mullis one-half of the chemistry Nobel in 1993, allows you to start with one copy of a piece of DNA and turn it into millions of copies. The process basically takes the DNA-duplicating machinery out of the cell and puts it in a test tube. First you "denature" the DNA, pulling its two strands apart to reveal the bases. Then you add two short pieces of single-stranded DNA called primers that tell the polymerase enzyme where to start work. One primer binds to the strand of DNA that you want to copy, and the other one binds to the antisense strand of DNA that was pulled loose in the denaturing step. The PCR reaction uses both strands as templates, so that you wind up with two faithful copies of the original double helix. You denature those two and get four copies in the next cycle, then eight, and so on, increasing exponentially.

So Travis made an assortment of DNA templates some 100 to 200 base pairs long, and he made a unique switch for each of them, whose antisense domain acts as one of the primers. The other primer comes from the PCR kit. It's sort of like on a submarine, where it takes two officers, each with a different key, to launch a nuclear missile. When the ligand is present, the PCR reaction gets turned ON, and lots of copies of that particular DNA are cranked out. The switches recognize a substance called PDGF, for Platelet-Derived Growth Factor, which is one of many proteins that regulate cell growth and division, and he tuned the switches to respond to various concentrations of the factor. Then he put all the templates and all the switches and all the other primers into PCR reaction mixtures that contained varying amounts of PDGF, plus a complex stew of molecules that you get when you rupture cells—the sort of thing you'd find in a real medical specimen—which he added for background noise. And the switch-amplification combo not only successfully identified the PDGF, but it gave a digital readout of its concentration.

Other people in my lab are expanding on this work. We're moving toward a device that can detect multiple analytes, both proteins and small molecules, in a sample all at once. As a start, graduate students Arwen Brown and Maung Nyan Win are working on high-throughput technologies for generating and characterizing large numbers of switches and sensors. It would be nice, eventually, to be able to say, "I want a switch sensitive to growth factor X that stimulates the amplification of DNA template Y," and be able to make it more or less automatically. And the idea, of course, is that ultimately you'd be able to take, say, a blood sample, lyse the cells—split them open—and add their contents to a solution containing the switches and the templates and all that other PCR stuff. Then, once you've done the amplification reaction you'd pass the solution over a chip where the antisense DNA strands would be bound. The chip would be set up as a matrix, with each row being a different analyte, and the columns being various concentration thresholds. So we might be assaying for a whole set of growth factors, for example, and by reading the dots get easy, positive identification and quantification. And if testing several people revealed specific differences between normal, healthy subjects and people with a particular cancer, we could then use this as a diagnostic device for early detection.

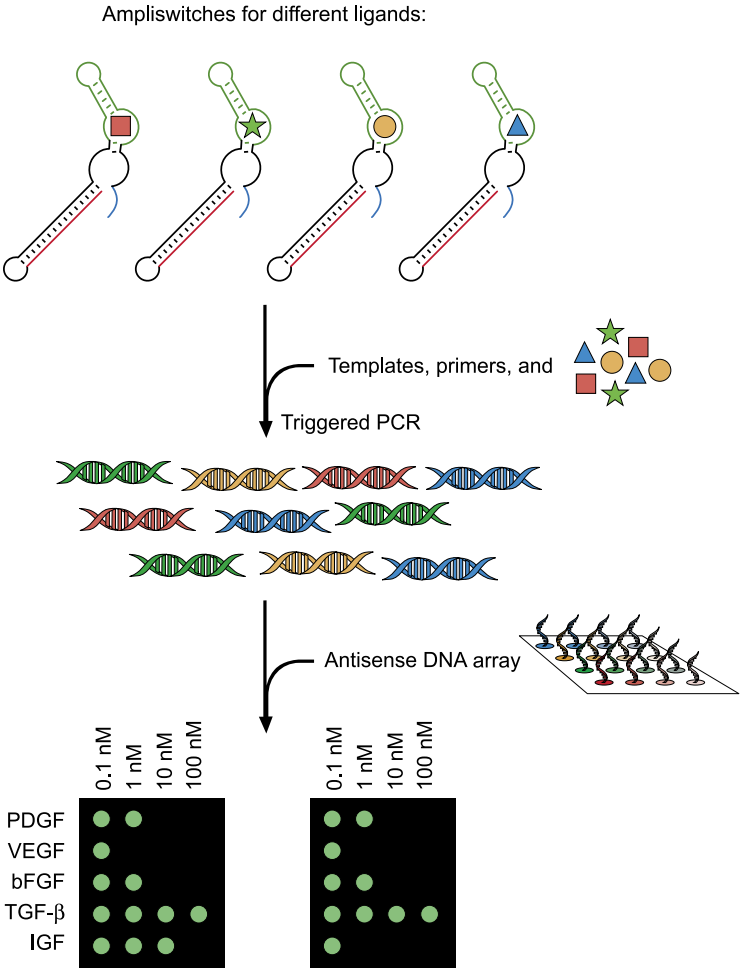
We've been using a similar scheme to pull out biomarkers for various diseases. We perform the reaction in a special way so that it outputs only the differences between, say, a regular cell and a diseased cell. We then identify those molecules with something like mass spectroscopy, which gives us biomarkers for different cellular states. And once we identify these biomarkers, we can use

PICTURE CREDITS: 28, 30, 32, 37 — Doug Cummings

Below: A schematic of a possible blood-test chip. This one is measuring the levels of various growth factors (Platelet-Derived Growth Factor, Vascular Endothelial Growth Factor, basic Fibroblast Growth Factor, Transforming Growth Factor-β, and Insulin-like Growth Factor). In general, growth factors direct the cell to change some aspect of its behavior in response to other cells or the environment. Altered levels relative to a healthy person could indicate, for example, the possibility of cancer.

them as targets for molecular engineering in their own right. But more importantly, we can use them to find other targets—by using each biomarker to find the next one, we can map the entire web of interactions that programs the cell to do whatever it's doing. This gets us back to the challenge I started with, of taking a global inventory of the cell's proteins and tracing the wiring diagram that connects them.

In summary, it's a very exciting time to be in this field. Nucleic acids present an inexpensive and robust platform for biomolecular science. These molecules exhibit impressive specificity and a staggering diversity of function. And because we understand so much about how their sequences of bases translate into structure and function, they are really a very powerful design paradigm. They're amenable to techniques that enable us to rapidly pull out functional molecules from randomized pools, and they're easily amplifiable, which is important for detection and diagnostic devices based on very small sample volumes. I've also been very fortunate, starting here at Caltech only a year and a half ago, to get great graduate students and undergraduate researchers. They come in with a lot of excitement, a lot of energy, and a lot of creativity, and that's really helped us make so much progress in this area so quickly. □



Assistant Professor of Chemical Engineering Christina Smolke earned her BS in chemical engineering, with an emphasis in biology, from the University of Southern California in 1997, and received her PhD in chemical engineering at Berkeley in 2001. After a postdoctoral fellowship in cell biology there, working on RNA decay pathways in S. cerevisiae*, she came to Caltech in 2003, returning to her southern California roots.*

PICTURE CREDITS:
Doug Cummings

Several readers pointed out the error in the caption accompanying the picture of the plasma ball in last issue's excerpted chapter of *Copies in Seconds* by David Owen. (The error was not Owen's nor Simon and Schuster's, but *E&S*'s own.) The following, taken from an exchange of e-mails, is perhaps the definitive word on the subject.

Hello Douglas,

I've long enjoyed *E&S*, and would like to commend you and your staff on a great publication.

I'm confident that what I'm writing about is simply a typo, but am compelled to comment none the less.

On page 26 in the subject issue, there is a photo of a plasma ball discharging to a finger, with the accompanying caption, "The creative spark: Static electricity allows you to play with very high voltage but very small currents—this plasma ball has a couple of thousand volts running through it, but only about ONE AMP." I'm reasonably sure the correct statement should say ONE MICRO-AMP, because I can assure you that 2,000 volts at 1 amp could easily be lethal.

I haven't actually measured the current flowing to my finger from my plasma ball, but will do so sometime soon, just to verify my claim, but I can tell you that I regularly measure currents from a Van de Graaff generator at 7 microamps, and the source voltage is somewhat higher—approaching 200,000 volts.

Best regards,
Chuck Newcombe

And later that evening:

Hi Doug—thanks for the quick response. Rest assured the article was informative and interesting in any case.

Ok, let me see if I can sort this out.

First, the plasma ball isn't exactly purely electrostatic in nature, as is a Van de Graaff generator and the Xerox copier—the ball is based on a Tesla coil, which uses a high frequency AC voltage to ionize the gas in the ball, and capacitance to conduct current through the surface of the ball to your hand.

With my Fluke meter I measured about 30 volts at 23 kilohertz at the surface by placing my probe against the ball and grounding the other lead.

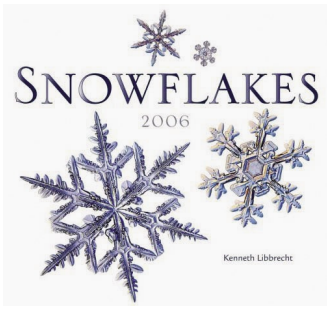
Now, 100 picofarads (the estimated capacitance in parallel with the meter's 10 megaohm input resistor) equates to a reactance of about 70 kiloohms at 23 kilohertz, becoming the effective input impedance of the meter. And, using Ohm's law with that reactance, I compute a current of 430 microamps.

Curiously, I did note that the power supply for my plasma ball is rated 12 volts at 1 amp. But that 1 amp supplies the oscillator that produces the high voltage. It does not flow through the hand of the person touching the ball.

As a point of reference, the ground fault circuit interrupter in the receptacle in your bathroom (now required by the national electrical code) allows about 6 milliamps of current to flow before it trips—about 15 times the current I measured on the plasma ball.

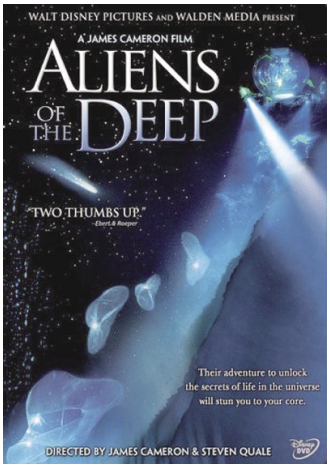
This is way more than I ever intended when I wrote you, but I must admit, it sure is fun to go through such an exercise from time to time :-)

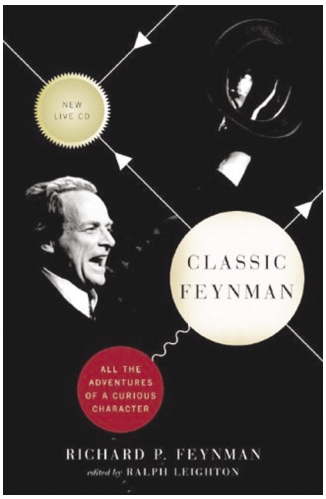
Chuck



It's not every day that the work of a Caltech faculty member is found in a "lifestyle" store like Restoration Hardware, but Professor of Physics Kenneth Libbrecht's *Snowflakes* wall calendar is there with the Christmas ornaments. With stunning photos and well-chosen quotes, this is one cool calendar. Voyageur Press, $11.99.

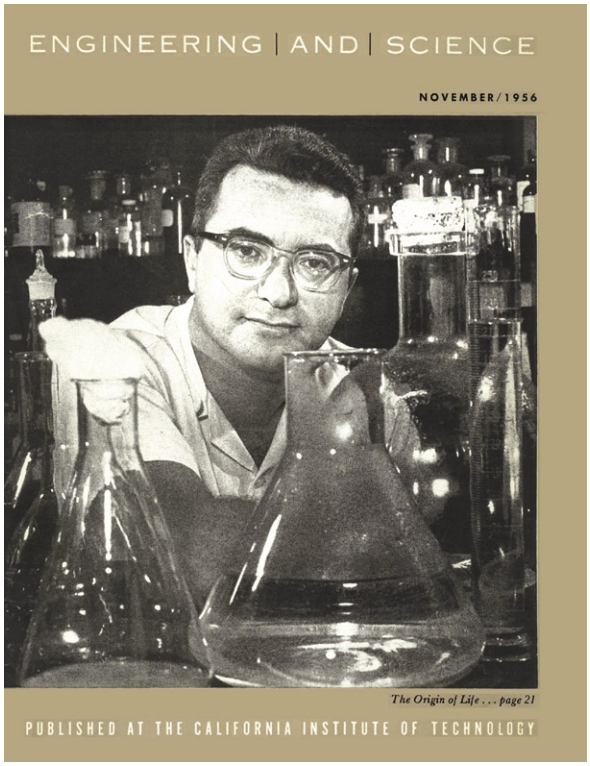
You read the article in *E&S* (number 4, 2004), but you didn't get to see the 3-D IMAX movie? Bummer! Well, here's your chance to see it—in two dimensions only, alas—at home. The DVD contains the original 47-minute movie plus a 99-minute version with lots of bonus footage. Walt Disney Video, $29.99.





***Surely You're Joking, Mr. Feynman!* and *What Do You Care What Other People Think?* have been reissued in one hardbound volume titled *Classic Feynman: All the Adventures of a Curious Character*. Noteworthy this time around is the inclusion of an hour-long audio CD of the great raconteur telling the story of his part in building the atomic bomb, "Los Alamos from Below," to a rapt audience at UC Santa Barbara in 1975. W. W. Norton, 608 pages, $29.95.**

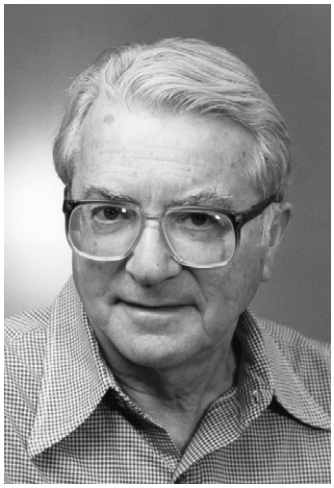
Horowitz made the cover of E&S in November 1956 when we published *The Origin of Life*, his historical account of man's attempts to discover the fundamental characteristics of living matter.



Norman H. Horowitz
1915 — 2005

Norman Harold Horowitz, professor of biology, emeritus, died on June 1. He was 90. "Horowitz was one of the pioneers of biochemical genetics," said Caltech president David Baltimore at a memorial service held on September 12. "He helped put in place our understanding of the role of genes in the overall economy of the cell, which enabled people to go on and think about how genes can exert their action and be controlled in their action. His investigations established a paradigm on which all other work on genetic regulation was based."

Born 1915 in Pittsburgh, Horowitz attended the University of Pittsburgh and graduated in 1936 with a bachelor's degree in zoology, before coming to Caltech for his graduate studies. He wanted to do genetics research, but T. H. Morgan assigned him to work with embryologist Albert Tyler on the development of sea urchins and the marine worm *Urechis*. The trio spent their summers at Woods Hole, which is where Horowitz met his wife, Pearl Shykin, who was then at Radcliffe. They married soon after Horowitz received his PhD in 1939.



A one-year fellowship took him to Stanford to work on marine worm respiratory pigments with Douglas Whitaker, after which he returned to Caltech to work with Henry Borsook on tooth calcification.

In early 1941, George Beadle came down from Stanford to give a seminar about the genetics research he had begun with fellow biochemist Ed Tatum using the red bread mold, *Neurospora crassa*. Beadle had attended Tatum's microbiology lectures at Stanford and learned that bacteria and fungi have the same biochemistry, but different nutritional requirements, recounted Horowitz in his 1984 Caltech Archives oral history. Fungi need growth factors, the fungal equivalent of vitamins. Beadle realized that if he could find mutants that couldn't make a particular growth factor—because a biochemical pathway had been blocked—he could get an insight into the way the genes worked. He chose to use *Neurospora*, which could make all its own growth factors bar one (which was added to the growth medium). If, as he believed, one gene made one enzyme, the loss of a gene could be shown by the loss of a growth factor.

Beadle and Tatum agreed to induce mutations with X-rays in a normal culture of the mold, "mate" it with an unirradiated culture, raise 5,000 progeny, and see which biochemical abilities they had lost; and if they didn't find any mutants among these 5,000, they would give up. Fortunately, their first nutritional mutant was no. 299. It lacked the ability to make pantothenic acid, vitamin B_6.

Beadle's seminar stunned the audience. And when he asked for a couple of postdocs to help him, Horowitz immediately signed up. "I've always felt that was the single most important decision of my life," he said, "because working for Beadle was just marvelous." Horowitz spent the rest of the war years at Stanford gathering evidence in support of Beadle's one gene–one enzyme hypothesis.

Speaking at the memorial service, Elliot Meyerowitz (Caltech's Beadle Professor of Biology and chair of the biology division) reminded the audience that, in the mid-'40s, the hypothesis that one gene made one enzyme was viewed with great skepticism. It was generally thought that every gene contributed to a very large number of different biochemical processes: some genes made small peptides, and other genes made products that stitched these peptides together to make enzymes. As many as 100 genes might be involved in the production of one enzyme and, conversely, each gene might contribute peptides to the synthesis of many different enzymes. The results found by the Beadle team, however, supported the one gene–one enzyme hypothesis. They eventually identified mutations for all the growth factors, amino acids, and nucleic acids.

Beadle's team now had a simple method of determining biochemical pathways. In a biochemical pathway,

explained Meyerowitz, one chemical is changed into another via a series of intermediates, and each change is catalyzed by an enzyme. For example, in the pathway A – B – C – D – E, chemical A becomes B as a result of enzyme W, then enzyme X converts B to C, enzyme Y converts C to D, and enzyme Z converts D to E. Beadle and Horowitz showed that if they mutated the gene coding for enzyme Y, for example, they would get two effects. First, the substances coming after this stage in the biochemical pathway would be absent, so there would be no D or E. Second, there would be an accumulation of C as its conversion to D was blocked. By looking at the amount of chemical precursors in the biochemical pathway, and knowing the final product from normal *N. crassa*, they could eventually block every step in the conversion process.

Not only did their research show that each gene was responsible for a protein that implemented a single enzymatic step in a biochemical pathway, but successive mutations could also be used to determine the order of the steps. As Horowitz later wrote, this work was revolutionary. It bridged the gap between genetics and biochemistry and ushered in the age of molecular biology.

When Beadle left Stanford in 1946 to chair Caltech's biology division, Horowitz came with him as a research assistant, becoming an associate professor in 1947.

The one gene–one enzyme hypothesis was regarded as a vast over-simplification, said Werner Maas at the memorial service. Now professor of microbiology, emeritus, at the New York University School of Medicine, Maas was a colleague of Horowitz who also joined Caltech in 1946. He recalled how Max Delbrück had raised a very serious objection to the conclusions: perhaps their method had only found a small subset of genes that coded for one enzyme, and missed the much larger set that coded for many enzymes. In response, Horowitz came up with the ingenious solution of using temperature-sensitive mutants; these act like normal fungi (or bacteria) at one temperature, but are mutants at another. With Urs Leupold, he isolated and tested temperature-sensitive mutants of both *N. crassa* and *Escherichia coli,* and found, to his immense relief, that the majority of mutants of both species was indeed the one gene–one enzyme type. Leupold and Horowitz presented the results at the 1951 Cold Spring Harbor symposium, after which the hypothesis was widely accepted. (Delbrück had by that time lost interest and was not at the symposium.) Horowitz later admitted to Maas that before he found a way to answer Delbrück's objection, he had felt quite desperate.

"It was a brilliant experiment," said Meyerowitz. "The history of conditional mutants—the condition in this case being temperature—after 1951 is enormous, and it's all due to a seed planted by Horowitz."

Beadle and Tatum were awarded the 1958 Nobel Prize in Physiology or Medicine for their work on how genes regulate chemical events (they shared it with Joshua Lederberg, who worked on bacterial genetics). In his Nobel speech at the award ceremony, Beadle gave much of the credit to Horowitz and his coworkers.

He also told the Stockholm audience about an important application of the one gene–one enzyme hypothesis that Horowitz had published in 1945, while still a postdoc. In this paper, he speculated on how biochemical pathways could have evolved from a succession of mutations. Horowitz suggested that, initially, the organism would have got the end product of the pathway, a chemical it needed, directly from its environment. At some point, a mutation in a gene produced an organism able to manufacture this end product itself from another chemical found in the environment. A subsequent mutation could then allow it to biosynthesize that chemical as well, and so on until the whole pathway had evolved. Each successive mutation would produce a generation of organisms that were less dependant for survival on the availability of chemicals in their environment, conferring a big evolutionary advantage.

With this thought experiment, Horowitz inaugurated the study of evolution at the molecular level. "If the present-day proponents of intelligent design would go back 60 years and read this paper," said Meyerowitz, "I'm sure they'd drop the whole thing."

Horowitz was made a full professor in 1953. Despite a tempting offer from Delbrück to join his bacteriophage group, he stayed loyal to *Neurospora*, and when Beadle moved to Chicago in 1961, Horowitz elected to stay at Caltech. He served as executive officer for Caltech's Division of Biology from 1971 to 1976, and as chair from 1977 to 1980, before becoming a professor emeritus in 1982.

In 1965, he moved to JPL for five years to head the lab's bioscience section, which had been set up to plan for the biological exploration of Mars. To see what types of life forms could survive in the harsh Martian environment, he dispatched a team of microbiologists to Antarctica—the nearest analog on Earth. They found only a very small number of soil bacteria there, which didn't bode well for the chances of finding life on the Red Planet.

Between 1965 and 1970, Horowitz worked on the Mariner missions, and, with George Hobby and Jerry Hubbard, designed an experiment for the Viking mission that would test the Martian soil for signs of life. Once on the planet, their instrument would incubate a soil sample in carbon dioxide and carbon monoxide—some of which was radioactively tagged—in simulated Martian

Horowitz was caricatured by Swiss geneticist Hans Gloor when he was a visiting postdoc at Caltech between 1947 and 1948. Image courtesy of the Caltech Archives.

sunshine. After incubation, the soil would be analyzed in a simple pyrolytic gas chromatograph for the presence of organic compounds labeled with carbon-14. If the level of radioactive carbon exceeded a predetermined background level, it would show that there had been organic synthesis during incubation. The Viking craft, finally launched in 1976, landed at two sites, Chryse Planitia and Utopia. Although several samples were tested at both sites, all the results were negative, as were those for the other life-detection instruments on board. "Horowitz's work was important in a negative way," said Baltimore at the service. "He showed that life really couldn't exist on the surface of Mars—but we're still looking beneath the surface and hoping for the best."

Returning to Caltech in 1970, Horowitz started to look for mutations that would enable *Neurospora* to live with less water. None were found, but his research led to the discovery of some interesting growth factors—chelating agents called siderophores that were involved with iron uptake. Out of this work grew the important realization that iron in our bodies has to be kept very closely "locked up" by proteins to stop harmful organisms from getting at it with their chelating agents.

In 1998, the Genetic Society of America awarded Horowitz its highest honor, the Thomas Hunt Morgan Medal. He was a member of the National Academy of Sciences and the American Academy of Arts and Sciences, and the holder of a NASA Public Service Medal.

But Horowitz was not concerned with gaining honors. "My father always felt that he had been incredibly lucky to have landed at the right place at the right time, which for him was Caltech at the dawn of the era of biochemical genetics," said his daughter, Elizabeth, at the memorial service. "He was very modest about his achievements and had absolute integrity in his approach to science, untainted by self interest or the desire for personal gain." Son Joel talked about his father's love of classical music and opera, and how he played the piano every evening and tended his roses. He also enjoyed hiking and camping in the mountains.

His great generosity to Caltech resulted in part in the George Beadle Professorship of Biology (Meyerowitz is the second holder of that chair) and the Norman Horowitz lecture series. After the death of his wife in 1985, he set up the Pearl S. Horowitz book fund in the biology division in her honor. According to Meyerowitz, he also left the Institute a very valuable gift in his will—his house in Altadena. The proceeds of the sale of the house will supplement the Horowitz lecture fund, with the balance used to assist graduate students in the Division of Biology.

In his 1986 book, *To Utopia and Back: The Search for Life in the Solar System*, Horowitz concluded: "The failure to find life on Mars was a disappointment, but it was also a revelation. We are alone, we and the other species, actually our relatives, with whom we share the earth. If the explorations of the solar system in our time bring home to us a realization of the uniqueness of our small planet and thereby increase our resolve to avoid self-destruction, they will have contributed more than just science to the human future."

Horowitz was predeceased by two brothers who were also scientists, one a petroleum engineer, the other a chemist. He is survived by his daughter, Elizabeth; his son, Joel; and two grandchildren. □—*BE*

Tom Apostol and Mamikon Mnatsakanian.

Three Math Papers . . .

Who says mathematicians do their best work before the age of 30? Eighty-two-year-old Tom Apostol, professor of mathematics, emeritus, and director of Project MATHEMATICS!, along with 63-year-old project assistant Mamikon Mnatsakanian, received this year's Lester R. Ford Award of the Mathematical Association of America.

The award is for "an article of expository excellence" published in *The American Mathematical Monthly* or *Mathematics Magazine*, but in 2004, each of the three articles Apostol and Mamikon published was a worthy candidate, and the judges couldn't decide between them. They solved the dilemma by awarding the prize to all three papers—a first in the history of the Association.

The articles, entitled "Isoperimetric and Isoparametric Problems," "A Fresh Look at the Method of Archimedes," and "Figures Circumscribing Circles," give classical geometry a modern twist and modern geometry a classical twist, said the citation, producing new and surprising results in areas that have been mined for centuries.

We featured some of this innovative work in *E&S*, No. 3, 2000. □—*BE*

Michael R. Hoffmann

Michael R. Hoffmann, the Irvine Professor of Environmental Science, has been reappointed dean of graduate studies for a further three years. He has been dean since 2002, prior to which he served for six years as executive officer for environmental engineering science. He was also a multi-year chair of the freshman admissions committee. □

Two AVPs . . .

Caltech has appointed two new assistant vice presidents: Richmond Wolf, for technology transfer; and Denise Nelson Nash, for public events.

. . . And A New Director for IST

Richard Murray, professor of control and dynamical systems, is to be director of Caltech's Information Science and Technology (IST), the first initiative in the country that combines research and teaching, from the fundamental theoretical underpinnings of information to the science and engineering of novel information substrates, biological circuits, and complex social systems (see *E&S*, No. 1/2, 2005).

Conceived as an organization that would support multiple centers, each focused on a particular aspect of information science, the current configuration includes the Center for Mathematics of Information (CMI), the Center for the Physics of Information (CPI), the Social and Information Sciences Laboratory (SISL), the Center for Biological Circuit Design (CBCD), the Lee Center for Advanced Networking, and the Center for Neuromorphic Systems Engineering (CNSE).

Murray succeeds Professor Jehoshua "Shuki" Bruck, the founding director of IST, and will start full time in April 2006. Professor of Computer Science Leonard Schulman, the new associate director of IST and head of CMI, will manage the day-to-day activities until then.

Murray, who retired as chair of the Division of Applied Science and Engineering on September 1, will lead IST as it creates national visibility for Caltech in Information Science and Technology; and will develop and implement a plan for graduate and undergraduate curricula related to IST and oversee the construction of the Walter and Leonore Annenberg Center for Information Science and Technology.

Since its inception, IST has received almost $50 million from the Gordon and Betty Moore Foundation, the Annenberg Foundation, and Howard Oringer. □

Honors and Awards

David Anderson, Sperry Professor of Biology and investigator with the Howard Hughes Medical Institute, has received a Humboldt Research Award from Germany's Alexander von Humboldt Foundation.

Fred Anson, Gilloon Professor of Chemistry, Emeritus, has received the Hans Fischer Career Award in Porphyrin Chemistry from the Society of Porphyrin and Phthalocyanines.

James Beck, professor of applied mechanics and civil engineering, has been awarded the Senior Research Prize in the area of Computational Stochastic Mechanics by the International Association for Structural Safety and Reliability.

Marc Bockrath, assistant professor of applied physics, has been selected by the Office of Naval Research to receive a Young Investigator Award, which provides up to $100,000 per year for three years.

Charles Elachi, Caltech vice president, director of the Jet Propulsion Laboratory, and professor of electrical engineering and planetary science, has been selected by the American Astronautical Society (AAS) to receive its 2005 Space Flight Award, the AAS's highest honor.

David Goodstein, Caltech's vice provost, professor of physics and applied physics, and Gilloon Distinguished Teaching and Service Professor, has had his book *Out of Gas: The End of the Age of Oil* (W. W. Norton & Co., 2004) selected by the National Academies Keck Futures Initiative as one the two finalists for the National Academies Communication Award in the book category.

Tracey Ho, assistant professor of electrical engineering, has been named one of the nation's top 35 innovators under age 35 by MIT's Technology Review magazine.

Hans Hornung, Johnson Professor of Aeronautics, Emeritus, has been elected a fellow of the American Association for the Advancement of Science.

Matthew Jackson, Wasserman Professor of Economics, has been named a Fellow of the John Simon Guggenheim Memorial Foundation.

David MacMillan, Anthony Professor of Chemistry, has been named a corecipient of the 2004 Corday-Morgan Medal and Prize by the Royal Society of Chemistry. He has also been selected to receive the 2005 Elias J. Corey Award for Outstanding Original Contribution in Organic Synthesis by a Young Investigator.

Richard Murray, professor of control and dynamical systems, **Kenneth Pickar**, visiting professor of mechanical engineering, **Yu-Chong Tai**, professor of electrical engineering, **Michael Vicic**, lecturer in chemical engineering, and **Alan Weinstein**, professor of physics, have been named as faculty recipients of 2005 ASCIT (Associated Students of Caltech) Teaching Awards. Graduate Student Council Awards went to **Ali Hajimiri**, associate professor of electrical engineering (Teaching Award) and **Oskar Painter**, assistant professor of applied physics (Mentoring Award).

Mitchio Okumura, professor of chemical physics, has been elected a fellow of the American Association for the Advancement of Science.

John Preskill, MacArthur Professor of Theoretical Physics, has been invited by Harvard University to be a Morris Loeb Lecturer this spring. He will give a series of lectures on quantum information science.

Ares Rosakis, von Kármán Professor of Aeronautics and Mechanical Engineering and director of the Graduate Aeronautical Laboratories, has been selected by the Society for Experimental Mechanics to receive its 2005 W. M. Murray Medal.

Athanassios Siapas, assistant professor of computation and neural systems, has received a McKnight Scholar Award to support his work in cortico-hippocampal interactions and memory formation. The award is granted by the McKnight Endowment Fund for Neuroscience.

Athanassios Siapas

Christina Smolke, assistant professor of chemical engineering, has been named the recipient of a 2005 Beckman Young Investigator Award.

Brian Stoltz, assistant professor of chemistry, has been selected by the American Chemical Society to receive the 2006 Arthur C. Cope Scholar Award.

Keith Taylor, a member of the professional staff, Caltech Optical Observatories, has been awarded the Royal Astronomical Society's Jackson-Gwilt medal for his role in developing world-class instrumental facilities for astronomers.

Eric Van de Velde, director of library information technology, has been named a recipient of a 2005 Meritorious Service Award by the American National Standards Institute (ANSI).

Alexander Varshavsky, Smits Professor of Cell Biology, has been elected to the Academia Europaea.

Yuk Yung, professor of planetary science, has been elected a fellow of the American Association for the Advancement of Science.

Ahmed Zewail, Pauling Professor of Chemical Physics and professor of physics and recipient of the 1999 Nobel Prize in chemistry, has been awarded the Grand Gold Medal by Komensky University in Slovakia. □

PICTURE CREDITS:
42–44 — Bob Paz

Milford H. "Bill" Davis (MS '50, PhD '55, both in physics) came to Caltech after earning his bachelor's degree at Yale. After graduating magna cum laude, he worked for the RAND Corporation, a Southern California "think tank," for 12 years before joining the National Center for Atmospheric Research in Boulder, Colorado. But the majority of his career was spent with the Universities Space Research Association (USRA), a nonprofit liaison between university research and NASA. In fact, he was instrumental in getting Caltech to join the USRA.

Even though Bill had already named Caltech as a contingent beneficiary in his will, he decided that it would be to his greater advantage to make a gift while he is living. Therefore, after careful consideration, he used highly appreciated securities to establish a charitable gift annuity (CGA) to benefit the Summer Undergraduate Research Fellowship (SURF) program.

A CGA is an appealing option for a donor who wants to contribute to the Institute while at the same time secure a consistent, guaranteed payment for life. It can benefit solely the donor, or may benefit up to two other people whom the donor designates. However, there are gift and capital gain tax implications if an annuitant is anyone other than the donor or the donor's spouse.

Gift annuity payments can begin immediately or be deferred until a later date—commonly the annuitant's retirement. Whether payments are immediate or deferred, the donor may claim a current income tax deduction for part of the gift. As the annuitant receives annuity payments quarterly, a portion of each payment will be tax-free for a number of years.

When appreciated securities are contributed, the capital gain on the appreciated portion is spread out over the life of the annuity, allowing the donor to avoid the immediate capital gain taxation that would otherwise occur upon their liquidation. In addition to capital gain tax deferral, a contribution of appreciated securities has the advantage of converting these assets into both an income stream and a current tax deduction. □—*Kerry Etheridge*

SURF students like Hannah Shafaat will be supported by Bill's gift when it matures. For the past three summers, Hannah has SURFed with Visiting Associate in Chemistry Adrian Ponce (PhD '00), a staff scientist at JPL. A Caltech senior, Hannah plans to further her research in microorganisms in graduate school.

Have Your Gift and Give It, Too

Did you know that Caltech currently serves as the trustee of 266 charitable trusts and annuities? Assets under management total an estimated $138,796,549. These assets fall into the following categories:

- 168 trusts
- 98 gift annuities
- 26 pooled income fund shareholders
- 1 foundation

For information contact:

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