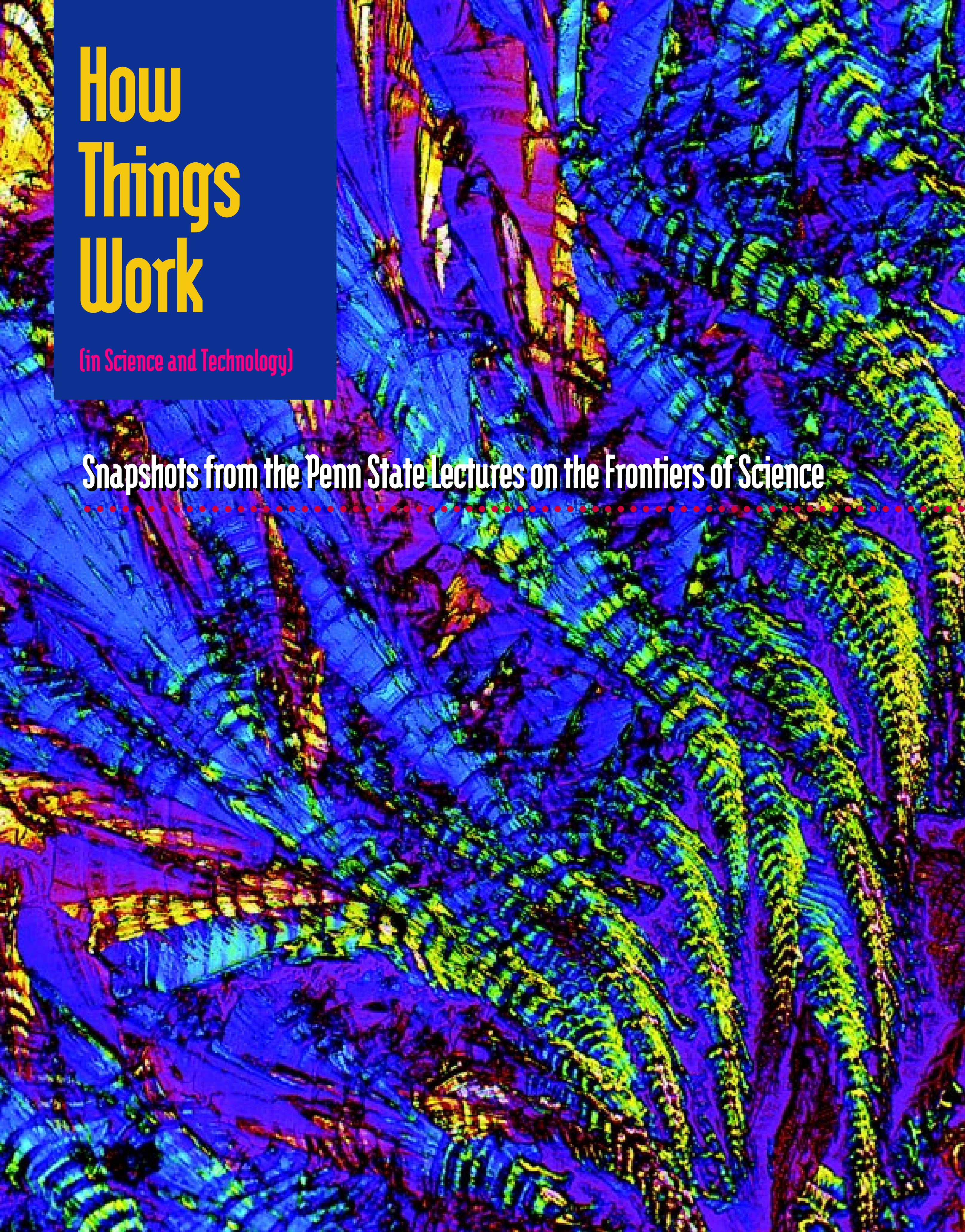
How Things Work

(in Science and Technology)

Snapshots from the Penn State Lectures on the Frontiers of Science



Which Things?

Some things you take for granted. You expect your physician to know what's making you itch or twitch and to prescribe a pill or a shot or some other miracle drug to stop it. Other things seem like happy accidents. Not only is your brand-new laptop smaller than your Mom's (or your boss's) desk-hog of a PC, it runs all the latest games and stores half an ocean worth of data. And when you click on your modem and call into the Internet, it's a cinch finding out what the weather was like in Iceland last Wednesday or sending that singing birthday card to Uncle Thorpe in Minnesota. Then there are things that needle at you, that make you worry or wonder when you see them in the news. Is the Earth heating up and if so, why? Is there another planet, somewhere in the universe, that's habitable — just in case our

> "Like all explorers, we have two questions: What have I found that is new, and where am I?"
> – Robert Simpson

Robert Simpson, who teaches molecular biology at Penn State, described how DNA analysis works. As a medical doctor, Simpson is excited by the Human Genome Project, hurrying toward its goal of sequencing all human DNA by 2003. Yet he himself works on the humble yeast. "The whole genome sequence of Baker's yeast, which is my specialty, has been known for the last three years," he noted. "Yeast is just so tractable. It's the simplest cell with a nucleus." At only 6,000 genes — compared to a human's 100,000 or so —it's a good model system for the new science Simpson calls "functional genomics": "All right, you've got the sequence, now what?" How do we go from knowledge of the alphabet to finding and fixing the typos in the book of life? "What's going on in yeast research today," he said, "is going to define what's going to go on in other organisms."

> "If you understand genetic differences, you can screen patients. It won't be 'one drug fits all' anymore."
> – James Gardner

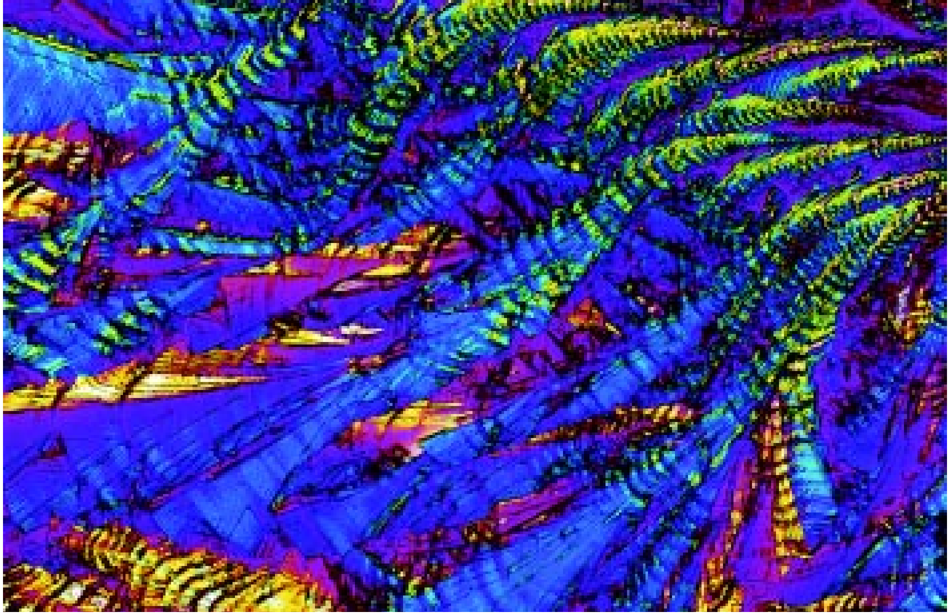
James Gardner, a vice president at Pfizer, the pharmaceutical company that sponsored the Penn State lecture series, told his audience how new drugs are made. "It's sort of like the old game 'Chutes and Ladders,'" he joked. "You roll the dice and land on that big chute and you're back to the beginning." Even Pfizer's "little blue pill," the blockbuster Viagra, was due to chance. (It was originally developed to treat high blood pressure.) But chance is giving way — slowly — to science: as we learn more about our genes, we're learning more about illness and disease. "Genomics research — that's were the insights will come from," Gardner said. "When we better understand where disease comes from, we'll be able to create better tests, identify more drug targets, and customize treatment."

> "At that scale, the physical laws we're used to break down. It allows you to think of new ways of doing computing altogether."
> – Nitin Samarth

Physicist Nitin Samarth teaches introductory courses on electricity and magnetism. In his lab, he works on such exotica as quantum dots and compact blue lasers. At the nano scales he studies, trying to control the spin of a single electron, "the physical laws we're used to dealing with when we connect batteries and bulbs break down," he said. So far, computers have been getting smaller and faster due to good engineering, he explained in his lecture. Eventually, though, the electronics will be so mini that classical physics can no longer apply. Only a "quantum computer" will be any smaller — one that "describes the world using probability and wave functions." It won't happen in Samarth's lifetime, but we're already on our way.

children's children's children need to find a new homebase?

These sorts of things in science and technology were the target of this year's Penn State Lectures on the Frontiers of Science, held on six Saturdays in January and February. The six lecturers were Robert Simpson, James Gardner, Nitin Samarth, Gerry Santoro, Eric Barron, and Larry Ramsey.



> **"The real limiting factor will be the ability of users to deal with all the information that's going to be coming their way."**
> **– Gerry Santoro**

Gerry Santoro, a computer programmer who teaches speech communications, discussed the past and future of the Internet. He's well-versed in its practical aspects, too. Although he keeps a tiny cubicle in the computer building on campus, he mostly telecommutes from his house in the woods at the foot of Tussey Mountain. In the classroom, he teaches from a computer console wired to his students' desks and puts the bulk of his course material up on the World Wide Web. At home, Santoro estimates he spends four to five hours a day reading and answering the 400 e-mail messages he gets each day.

> **"You might say, 'That's unacceptable. I can't live without beech trees.' Or you might say, 'Humans can adapt.'"**
> **– Eric Barron**

Eric Barron, who spoke about climate change, hobnobs at the highest levels. He's a member of the National Research Council's Board on Climate Change and chair of its Climate Research Committee. He is also a member of the Science Executive Committee for NASA's Earth Orbiting Satellite. In 1994, he chaired a forum on climate modeling convened by request of the White House Office of Science and Technology Policy and the General Accounting Office. But the picture on the door of his office is a poster-sized photo of Barron on the deck of a ship, part of a program taking high-school teachers to sea. He is stiff-limbed and smiling in a huge orange immersion suit, a sort of per-sonalized emergency raft. "I look like a giant Gumby," he said — an accurate characterization.

> **"The name of the game for detecting planets is measuring those wobbles very, very precisely."**
> **– Larry Ramsey**

Astronomer Larry Ramsey thought up the Hobby-Eberly Telescope (HET) back in 1983. The thing finally saw first light almost 15 years later. "Ten years is nothing for an astronomer," he said. Then an exhausted sigh. "But 1983 sure seems like a long time ago." In Texas during HET's construction, Ramsey couldn't resist climbing all over the telescope and its dome to take pictures. He was really kid-like in this — distracted half-grin, gleam in his eye. He climbed to heights others wanted no part of (and that project team was one macho bunch, too). His resulting photo record is worthy of a book in itself. He has the precise eye not of an artist, but of a physicist and an engineer. And it's an eye — translated into the HET — that's now focused on other worlds around other suns.

Deciphering DNA

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Looks like harmless gibberish, until you learn it's the DNA signature of Huntington's disease.

"Many persons executed at the Salem witch trials may have had Huntington's," Robert Simpson said. A molecular biologist and medical doctor, Simpson gave the first in this year's Frontiers of Science lectures at Penn State on "How DNA Research Works in Medicine, Law, and Science."

Folksinger Woody Guthrie's mother had the disease: *Her face would twitch and her lips would snarl and her teeth would show,* Guthrie wrote. *She would start out in a low grumbling voice and gradually get to talking as loud as her throat could stand it; and her arms would draw up at her sides, then behind her back and swing in all kinds of curves.* "The description of Woody's mother would certainly fit with an early New Englander's idea of someone possessed by spirits," Simpson said.

DNA research has erased the stigma of such inherited diseases. Understanding the mutations involved could lead to better treatments, even to therapy to correct genetic defects. Tests devised to study genes are changing history, and the law. DNA testing has convicted criminals on the evidence of a hair. It has found black descendants for Thomas Jefferson. And linked a certain president with a stained blue dress.

"A major revolution is in the offing," said Simpson, "comparable to when the microscope was introduced."

How DNA Works

"A surprising statistic about the human genome," he said, "is the length of a unique sequence. It turns out to be about 16 to 20 base pairs, or about half an inch of a string stretched from New York to the West Coast."

If you turn that string into a cross-country zipper, the base pairs are the teeth. A zipper the size of the human genome would need some 3 billion teeth. Coil it into a ball 50 feet in diameter and you'll have an idea of how your genes — all 100,000 of them — are crammed into the 23 pairs of chromosomes in the nucleus of each of your cells.

These analogies, the long string and the coiled zipper, give an idea of how huge and delicate and difficult to get at the human genome is. But to understand how to decipher the information it contains, you need to think of it as a book.

"Measured as Manhattan telephone books, each containing about 1,000 pages of 10-point type," said Simpson, "the genome of the bacterium *E. coli* is about a third of a book. Baker's yeast, which is my specialty, is a full book. The human genome will occupy two hundred books."

These 200,000 pages of genetic information, encoding everything from the color of your eyes to your likelihood of colon cancer, are written in the language of DNA. In structure it's a double helix: two strands of sugars and phosphates linked by pairs of the four bases, A, T, C, or G. The four bases create the alphabet. Every word in this language is three letters long, and stands for one amino acid. Each sentence, which can be many hundreds of words long, is a gene. But to read the human genome like a book, scientists still have to figure out the grammar: where the genetic sentences stop, what's a noun and what's a verb, and what exactly do they mean?

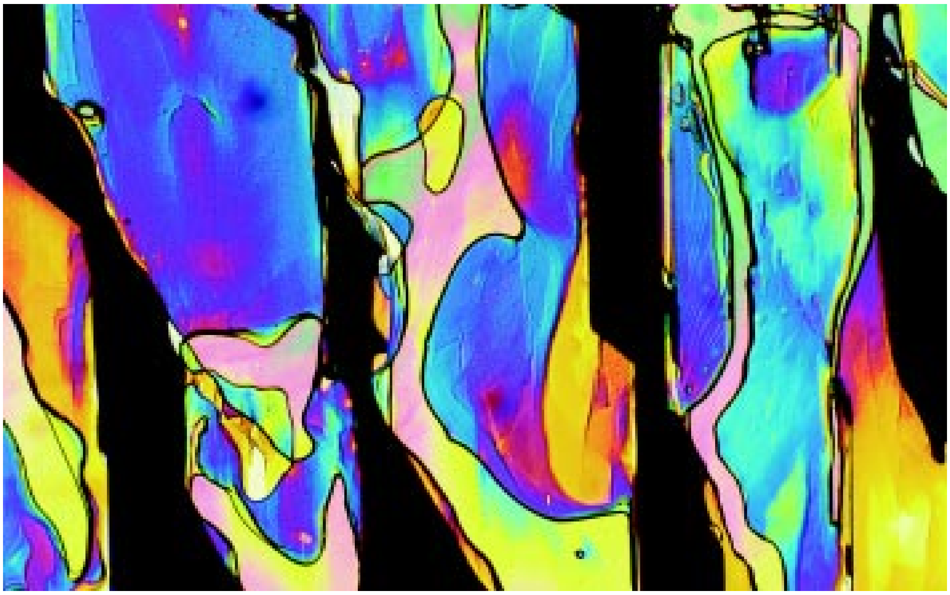
Two things make this task possible:

The first is base pairing. DNA's bases pair up in a very specific fashion. A joins only with T, while C joins only with G. If you know the sequence of bases on one strand of an unzipped snippet of DNA, you can easily guess the sequence on the other strand. Furthermore, single strands of DNA are sticky. Like magnets, they'll find their complement and click back together if they possibly can.

Second, as Simpson pointed out, each set of 16 to 20 bases (more than a word, but less than a sentence) is unique. It's as if in all the works of Shakespeare, the bard only once said *to be, or not to be.*

But just as Shakespeare's works differ from Steven King's, the exact A-T-C-G sequence of one person's genome won't be the same as another person's. These *polymorphisms* can lead to physical differences (blue eyes vs. brown). They can cause disease, or increase the risks of it. But many are as subtle as a difference in blood type. Ten variations, or alleles, can be found at the same spot on ten people's DNA, and all of them are normal.

This fact makes possible the DNA fingerprinting used by forensics experts to solve criminal cases. It also lets DNA researchers find a gene without knowing exactly what it does. To find the Huntington's gene, researchers took DNA samples



Crystals of the DNA building blocks G (previous page), C (above), and A (top of next page) can be beautiful under a microscope. Unraveling DNA's secrets could revolutionize medicine as much as inventing the microscope did. Opposite, a spiral of DNA undergoes a phase transition from liquid to crystal.

All DNA micrographs courtesy Michael W. Davidson/Florida State University

from a large Venezuelan family with many Huntington's patients. Using enzymes that cut DNA whenever they find a certain short sequence, the researchers chopped the DNA up until it looked like a plate of spaghetti. They sorted the noodles by length and saw that the pattern of DNA fragments was different for people with the disease than for those without it. Linking the patterns to the patients' family tree, the researchers saw that people with the disease all had one very long fragment. This fragment, on chromosome 4, must hold a mutation — all those CAG repeats.

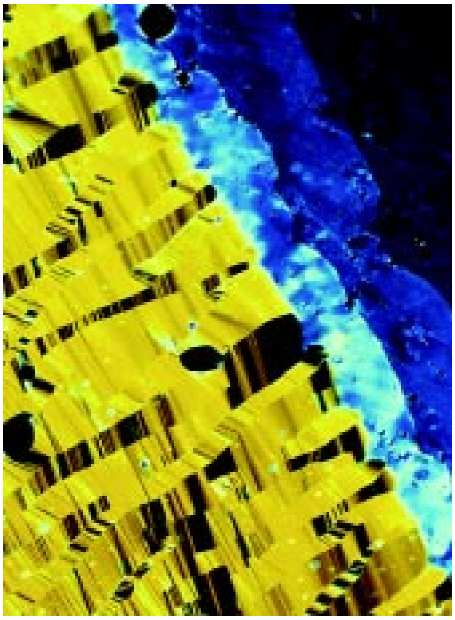
The Gutenberg of Genetics

Sequencing the gene for Huntington's took 10 years. Now deciphering DNA is quicker, due to a technique called PCR, or Polymerase Chain Reaction.

PCR is to genes what Gutenberg's press was to the written word. All it takes is heat, a patented enzyme (originally found in a hotspring at Yellowstone National Park), and two primers, 16- to 20-base-long bits of DNA that flank the gene you want to copy. Mix the primers with your DNA sample. Add free nucleotides — each one a base with its sugar-and-phosphate scaffold — and the hotspring enzyme, known as *taq* polymerase. Heat almost to boiling: the DNA will unzip into its two separate strands. As it cools, the primers, being small and quick, stick on before the two strands can zip back up. Then the *taq* polymerase goes to work.

A polymerase is an ordinary enzyme, part of a cell's repair kit. The *taq* polymerase, from the hotspring-dwelling bacterium *Thermus aquaticus*, is best for PCR because it works in hot water, where most proteins seize up. The job of a polymerase is to make a polymer—to link molecules into a chain. Beginning at one primer, it runs down the strand of DNA, identifies each base, finds its partner among the free nucleotides, and links them together. When it gets to the second primer, it stops. Now instead of one double-stranded piece of DNA we have two. "Each time we repeat this process," said Simpson, "the new product joins with the original molecule to be copied." It's a chain reaction. "The numbers are striking: 25 cycles can generate over 30 million copies."

Before PCR, to get enough copies of a gene to sequence it, you had to clone it. First you spliced the gene into a plasmid vector (a small ring of DNA from a bacterium). You slipped the plasmid back into a bacteria cell and let it grow into a colony, then extracted the human DNA.



Cloning was always the slow step in DNA research. It also took up a lot of lab space: To cover the whole human genome would have required a million colonies of bacteria, each growing in its own Petri dish. "With PCR," said Simpson, "you can store a gene as a code in a computer. Anybody can access the information and synthesize the DNA."

Using PCR, researchers have organized everything that's known about the sequence of the normal human genome. This "physical map" currently has 25,000 landmarks, or "sequence-tagged sites" for which an exact A-T-C-G sequence is known. To make this map took 15 million PCR reactions — a task made somewhat less Herculean by a robotic machine that can do 150,000 reactions at a time.

PCR also takes the human error away from forensic DNA identification. Commercial sets need only 28 PCR reactions to identify an individual — with an error rate of 1 in 50 billion. "Basically, it's a Universal Product Code — a barcode — for a person," said Simpson.

The DNA Chip

After PCR, the next big step is the DNA chip. Using tricks from the semiconductor trade, scientists grow 65,000 different oligonucleotides (short bits of single-stranded DNA) on a chip a half-inch square. (The next-generation chips will fit 400,000.) Among others, you can now get the human tumor suppressor gene p53 and the breast cancer genes BRCA1 or BRCA2 and two genes often mutated in drug-resistant strains of the AIDS virus, each on its own chip. You can make a chip to match any gene, as long as you know the gene's sequence.

Since the bits on the chip are single strands of DNA, they're sticky. They're looking for their match. You can take a blood sample from an AIDS patient, extract the DNA, squirt it onto a chip and see, by the pattern of which pieces stick, if the patient has a drug-resistant strain. "The whole analysis takes five minutes."

"With these chips," Simpson added, "we can start looking at polygenic diseases, at diseases that are influenced by multiple genes. Hypertension, diabetes, some forms of cancer. Things that 'run in the family,' but no one knows why."

Robert Simpson, M.D., Ph.D., holds the Verne M. Willaman Chair of Molecular Biology at Penn State, 308 Althouse Lab, University Park, PA 16802; 814-863-0276; rts4@psu.edu. He is an expert on the structure of chromatin, a protein-DNA complex found in the nucleus of cells.

Discovering New Drugs

Two billion times this year you (and your fellow Americans) will go to the doctor and the doctor will write up a prescription. You'll take that illegible slip to a store. There, a pharmacist will funnel pills from a big jar into a little vial, slap on a label, and hand you a bill. You might not even wait till you get home before taking a dose. And soon your sinus headache or sore shoulder or hacking cough or black mood will quit bothering you and you can get on with the business of living.

Who made those excellent pills, and how?

Thirty years ago, *who* was a scientist sitting at a lab bench pouring liquids from one beaker into another. "You know," said James Gardner, "distillation. Bunsen burners." Gardner, a vice president at Pfizer Inc, gave the second in this year's Frontiers of Science lectures at Penn State (which Pfizer sponsors) on "How Drug Development Works."

How, he explained, was then like negotiating a maze: "You went down a corridor, making progress, until you hit a wall. Then you bounced off and started down another corridor. Sometimes you got somewhere, sometimes not." Since the 1960s, as the pharmaceutical industry and its federal watchdog, the FDA, have grown, that maze has become more like a high-money brand of the boardgame "Chutes and Ladders".

"Based on an insight," Gardner said, "a chemist will come up with a compound that could have an effect on a disease. It could block some reaction, or act as a decoy."

Roll the dice and start the game: Test it on tissue samples or bacteria to see if it really works. Then come trials in animals, in healthy people, in patients. There are lots of chutes to failure and not many ladders to success: Is it safe? What's the proper dose? Does it have side effects? How long does it linger? Can we scale it up — make lots of it economically? Has someone beat us to it? Will the FDA approve it?

Most of those chutes send you right back to *Start.*

"The norm is to fail," said Gardner. "Of 5,000 compounds evaluated, only six will enter human trials. Only one comes out at the bottom as a drug. It could take 12 to 24 years. It could cost $500 million."

The rules are about to change. With the Human Genome Project and new computerized automation, drug development will be less chancy in the 21st century — and more likely to cure a disease instead of just masking its symptoms.

Luck and the Little Blue Pill

From penicillin to Viagra, luck's had a lot to do with drug discovery.

Alexander Fleming was studying *staphylococcus* bacteria in 1928 when *penicillium* mold (then used only to ripen Roquefort and other cheeses) got into his Petri dishes and ruined his experiment.

In the late 1990s, researchers at Pfizer were doing clinical tests in V.A. hospitals on a drug effective against the chest pain of angina. "And we found we couldn't get the pills back from the vets," Gardner said. "Then doctors started finding pills missing from the hospital cabinets. Very quickly we learned the reason." The drug is now known as Viagra, or "the little blue pill," and is prescribed for impotence. "Impotence affects older men, men with spinal cord injuries, coronary artery disease, hypertension, diabetes, depression, prostate cancer . . . It was a surprisingly unpublicized, untalked about, and untreated disease until Viagra was introduced a year ago. Since then, doctors have written millions of prescriptions."

Pfizer's scientists hadn't meant to start a sexual revolution. "We were looking for a drug that would dilate coronary arteries," Gardner explained. "More blood, more oxygen, less angina — better lifestyle." They'd found a substance in the blood, cGMP, that caused arteries to dilate. "Investigating this molecule," Gardner said, "we discovered an enzyme, PDE5, that broke it down." With PDE5 around, cGMP was destroyed and arteries shrank thin and blood-poor; without it they opened up. "So we thought, let's see what we can do to stop the action of this enzyme." PDE5 was, they found, "an amoeba of an enzyme. It wraps itself around the molecule, locks on at several binding sites, then destroys it." They decided to design a decoy, a molecule PDE5 could snugly lock onto — and then find itself caught.

"We worked with the idea on the computer," Gardner said. "It took about four years before we found a molecule that allowed PDE5 to lock on, but that the enzyme couldn't destroy. We tried well over 1,000 compounds before we found Viagra."

Then, after the clinical tests showed its usefulness for something sexier than angina, "we had more work to do to make it very specific, so dilation occurs only in that one part of the anatomy."

So far, Viagra looks to be one of the 3 out of 10 drugs that, on average, will actually pay back its own R&D costs.

Pills made the old-fashioned way -- with lots of luck involved -- are making way for new pharmaceuticals based on the science of genomics. Such pills will be different for different patients, based on the variations in our genes.

Photo by James Collins; pills courtesy Pfizer Inc.

Robot Chemists

Luck may always be needed. But in other ways, how drugs are discovered is changing fast.

In the mid-'40s, following the success of penicillin, which Pfizer manufactured, the company wanted another antibiotic. "For over four years, we asked people — our salesmen, our friends — to send us plastic bags of dirt," Gardner said. Pounds of dirt, over 135,000 samples from all parts of the world, arrived parcel post. "We isolated the compound that had the most effect on the contents of a Petri dish. Terramycin came from dirt."

The technology's a little different now. Although they may still look for active compounds in dirt (or rainforest plants or deep-sea creatures), scientists now use silicon chips instead of Petri dishes to look for an effect: "We lay down strata of bioreactive materials to create 144 'wells' on a chip. Each responds in a different way. We customize the chip to tell us what we want to know, and read the response with a scanner."

Synthesizing new compounds to attack a known target like PDE5 is even more high-tech. "Instead of a chemist creating them one at a time, we have machines that break down chemicals into their components and randomly shuffle the deck to make a bunch of things we never knew about. These new compounds are made in dark, unlighted factories by robots, 24 hours a day. Then we run them through another machine, and in one pass we know what the compound is and whether it has the characteristics we're screening for."

One Drug Fits All?

Bigger changes will come from the Human Genome Project and its offshoots. "Genomics research — that's where the insights will come from," Gardner said. Which genes code for which proteins? Which genes are active in a normal cell that aren't working when the cell is diseased (or vice versa). Which mutations to a gene contribute to disease, and how? These are the sorts of questions genomics researchers are asking. With the answers, said Gardner, "We'll be able to create tests, identify new drug targets, and customize treatment. Before, we got to the proteins and the enzymes often by happenstance. It was relatively crude. Genomics will give us a better understanding of where a disease comes from."

Simple tests for certain single-gene diseases are already in use. Other tests might tell which version of a virus a patient has, or what proteins a patient's cells are producing. Knowing the genetic code, the instructions for how these proteins are made, gives drug developers more clues to how to block — or enhance — their action. "Today we have about 500 targets that we're creating drugs to impact," said Gardner. "The promise of genomics is an exponential jump in the number of targets, and thus in the number of insights.

And best, genomics will help even old drugs work better. "There are genetic polymorphisms, genetic differences from one person to another, that can have an effect on how an individual responds to a certain drug," Gardner said. "If you understand those polymorphisms, you can tailor the drug to cause fewer side effects and to work better. You can screen potential patients and say who should use the drug and who should not.

"It won't be 'one drug fits all' anymore."

James R. Gardner, Ph.D., is vice president of investor relations for Pfizer Inc. He graduated from West Point with a B.S. degree in engineering. His early career includes eleven years of military and government service in such positions as staff assistant with the attorney general of the United States and assistant professor at the U.S. Military Academy. He holds both M.P.A. and Ph.D. degrees from Princeton University.

The Incredible Shrinking Computer

Your name takes up a kilobyte of space. With the latest $300 16-gigabyte hard drive in your computer, you have 15,999,999,000 bytes left for Starcraft, Hover, and Myst, not to mention all those e-mails you absolutely must keep, or the 700 bookmarks on your Netscape browser, and the programs for greeting cards and spreadsheets and slide shows that you hardly ever use, even, if you work for this magazine, the 20,000 names and addresses of your subscribers and eight complete back issues, in case you can't remember what you wrote. And it all fits on your desk.

Fifty years ago, a computer filled a room (with another room next door dedicated to its air conditioners). "It was a monster," said Nitin Samarth, associate professor of physics, of the famous ENIAC. Samarth gave the third in this year's Frontiers of Science lectures at Penn State on "How Computers Keep Getting Smaller, Faster, Cheaper."

"If you want to know why they've gotten cheaper, you'll have to ask somebody else," he joked. "I don't have the foggiest. It probably has to do with marketing and stuff that I don't understand."

But smaller and faster are the result of advances in basic physics and some very inventive engineering. "Open up your computer and look at the number of different advanced technologies that go into something costing less than $2,000. You'll be amazed."

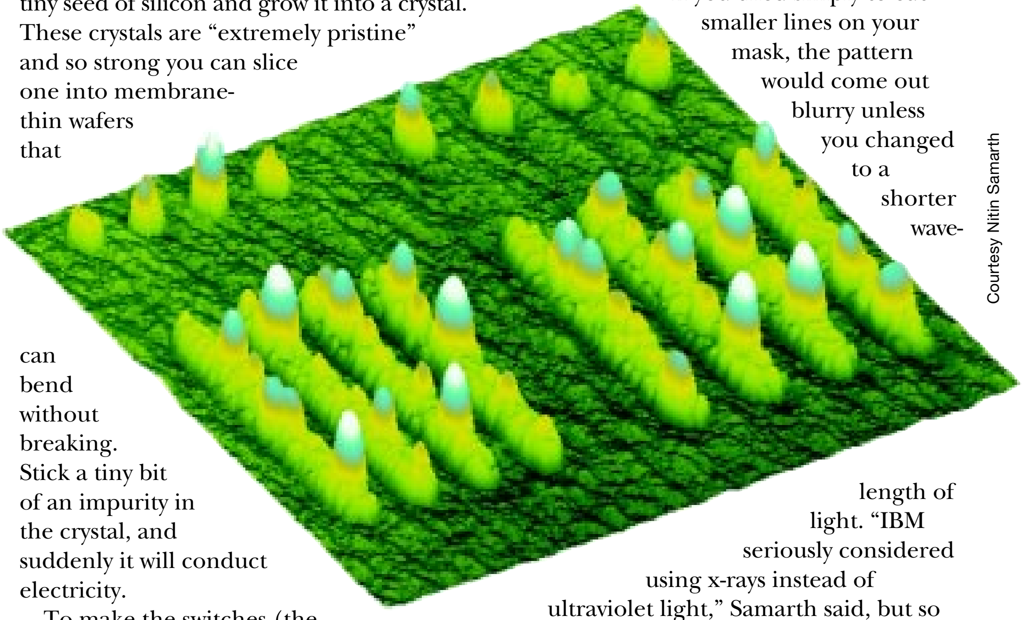
Just Switches

Whether in chips or the old ENIAC's vacuum tubes, the guts of a computer are its on-off switches. "What does your laptop do? It represents data as bits, or binary numbers, strings of ones or zeros," Samarth said. "There are devices in this machine that are either on or off, one or zero, and on those you perform the software functions."

Until semiconductor transistors came along, these binary switches were simply "way too big" to make a practical PC. "I wonder how many people have seen a vacuum tube? They're huge, clunky things." ENIAC had 18,000 of them; it could carry out about 5,000 arithmetic operations every second. A modern semiconductor chip the size of a dime does the same kind of things, but at speeds up to 10,000 times faster.

A semiconductor is a material between a conductor and an insulator. "We all know what a conductor is, a metal wire that you run electrons through to light up a lightbulb. An insulator — that's wood. It doesn't conduct electricity at all. A semiconductor doesn't *want* to conduct electricity, but you can make it."

To make a microchip, you start with a tiny seed of silicon and grow it into a crystal. These crystals are "extremely pristine" and so strong you can slice one into membrane-thin wafers that can bend without breaking. Stick a tiny bit of an impurity in the crystal, and suddenly it will conduct electricity.



Courtesy Nitin Samarth

To make the switches (the transistors) and the rest of the circuitry on a chip can take another 250 steps. First you oxidize the surface of the silicon wafer. Then you coat it with a material called a photo-resist. On top of that you put a mask, which has a pattern cut in it. When you shine ultraviolet light onto the wafer, the places not hidden under the mask change in chemical structure. Expose the chip to certain chemicals, and these weakened places etch away. The surface of the wafer now has a pattern of ridges and valleys. Repeat the masking and etching steps until the wafer's surface is highly textured, and the electrons can flow through it only in a precise and controllable way. Finally, dice the wafer into 200 chips.

The etched pattern, said Samarth, "is the basis of everything that goes on in your computer. Imagine that instead of electrons, you had water. It flows from here to there. Now imagine you had a sluice-gate that could stop the flow of the water. That's what these semiconductor transistors — or Si-MOSFETs — do. They control the flow of electrons."

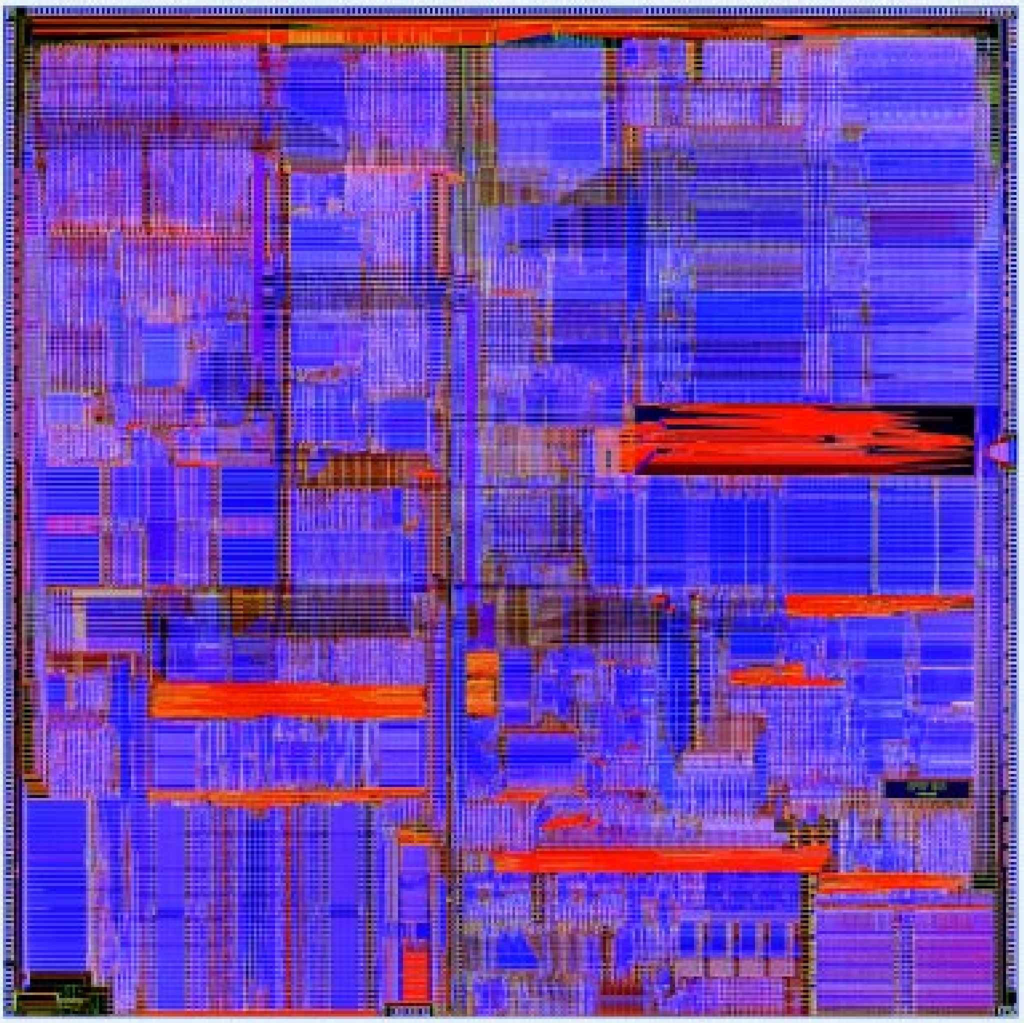
In 1971, the Intel 4004 chip had a "whopping" 2,300 transistors, Samarth said. "The lines on it, defined by this really scientific measure called a 'hair,' were one-tenth of a hair wide."

The Pentium 2 chip, released in 1997, holds 7.5 million transistors, with lines 1/300th of a hair.

In 1999, IBM expects to market a chip with lines as narrow as 1/500th of a hair.

"It's very hard to go much lower than that," Samarth said, without finding a new way to carve the pattern into the chip. If you tried simply to cut smaller lines on your mask, the pattern would come out blurry unless you changed to a shorter wavelength of light. "IBM seriously considered using x-rays instead of ultraviolet light," Samarth said, but so far it hasn't worked as a manufacturing process. "Electron beams are another possibility, but they're also very difficult to use in large-scale production."

Other problems are caused by "the humble wire" that connects the switches. "Think of a very small water hose. You start pushing more and more water through it and eventually it'll burst. In technical terms, this is called 'electromigration.'"



Courtesy Michael W. Davidson/Florida State University

The intricacy of a Pentium chip (above), greatly magnified. To get the wires much smaller will take a new technology. Quantum wires, like these (at left) from Nitin Samarth's lab, are made by moving atoms into place one by one. It's like "atomic Legos," Samarth says.

Leakage is also a problem. When transistors and other devices are packed too close, they start influencing each other.

"Those are not fundamental problems of physics," said Samarth, "but of engineering — and device engineers keep coming up with clever solutions.

"But there is a limit," he added. "When you get to very small scales — roughly below 50 nanometers — you start getting into a different regime of physics." Throw a ball at a wall, it bounces back. Throw it at an open window, it goes through. "That's classical physics. But when you throw an electron at a wall, it has a ghost-like probability of going through the wall. If you throw it at a window, it has a possibility of not going through. When you get to very small scales, you enter the strange world of quantum mechanics, and the usual device schemes we've been using don't work."

The Quantum Computer

Quantum mechanics hasn't affected microprocessors *so far*, Samarth noted. But it has helped hard disks and CD-ROM drives.

"In a hard disk, data is essentially stored in the form of little magnets called 'domains.' These magnets can point in either of two directions. That's all you need to make ones and zeros. The smaller the magnets, the more memory.

"Now, you can construct very dense memory by making materials with very small domains, but there was no way to read their information using the older read heads. You needed a new sensor technology."

In 1988, physicists doing basic research — they were studying the quantum mechanical behavior of thin magnetic films — found that a sandwich made of certain materials was very sensitive to a magnetic field. "This invention was taken advantage of by an excellent materials physicist at IBM," said Samarth, "who learned how to make these sandwiches using a cheap, scalable process called sputtering. That led to the 16-gigabyte hard disk."

Quantum mechanics research has also led to CD players, laser pointers, cell phones, and telecommunications satellites. Components in these technologies draw on the idea of the "electron in a box." Put a marble in a box. "Can you make it move at the rate of one meter per second? Yes, shake it. But if the marble is an electron, there are restrictions. An electron is more like a violin string than a marble. It can vibrate only at certain resonances — and these depend on the size of the box and the mass of the electron. You can change the size of the box to 'tune' the resonance of the electron."

Making these electron boxes, Samarth said, is "like playing with atomic Legos. It's a real thrill to take atoms and arrange them in the order you want." Because of quantum mechanics, "this electron, just like a ghost, can tunnel through the walls of the box and hop onto a wire." In a CD player, for example, "a small laser translates the result of electrons hopping into and out of boxes into a stable light beam of precise color and focus. That light beam can then read music encoded as tiny bumps on the surface of a disk.

"Now imagine you could make a box like that, and a switch that could hop a single electron in and out of the box as memory. It sounds like a crazy idea, but it's being done." Except that it's being done at temperatures close to absolute zero using liquid helium. "People are trying hard to make it work reliably at reasonable temperatures."

An even more tempting idea to a physicist like Samarth is to make a fully "quantum computer." "In a quantum computer, the bits are not definite states like zero and one, but combinations of the two." Instead of just "on" and "off," these switches could be "sort of on" and "partly off." Theorists creating the mathematical framework for these strange computers say that some kinds of mathematical operations would be speeded up "immensely." But you won't be buying one for your desktop tomorrow. "I'd be really surprised if I saw a working quantum computer in my lifetime," said Samarth.

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Networkings

Ask Gerry Santoro how the Internet works and he'll reel off a string of analogies. First of all, he stresses, it works like any other system for communicating between human beings. “We tend to be amazed by the flash of technology, but the whole purpose is in the information communicated to a user by it — or by a user to it. That information flows between people.”

Santoro, who is both lead research programmer for Penn State’s Center for Academic Computing and an affiliate assistant professor of speech communication, gave the fourth of this year’s Penn State Lectures on the Frontiers of Science.

Historically, he noted, the global computer network now known as the Internet grew out of Defense Department experiments conducted in the late 1960s, when researchers at the RAND Corporation were asked to build a communications system that could survive a nuclear war. “The challenge was to create a network where all the nodes were independent,” he explained, “so that even if a large part of the system were destroyed, messages would still reach their destinations.”

Packets of Info

The solution was a concept called “packet switching,” in which streams of digital data are broken into small “packets,” each containing about 200 “bytes” of information. (A *byte* is a set of eight *bits*; a *bit* is a single digit, a ‘1’ or a ‘0.’) Each packet is addressed and sent through the system on its own, traveling node to node, forwarded by successive computers along the best route depending on traffic conditions.

“It’s like mailing a series of postcards, each containing part of a message,” Santoro said. At the end of their separate journeys, the cards are reassembled into a coherent whole.

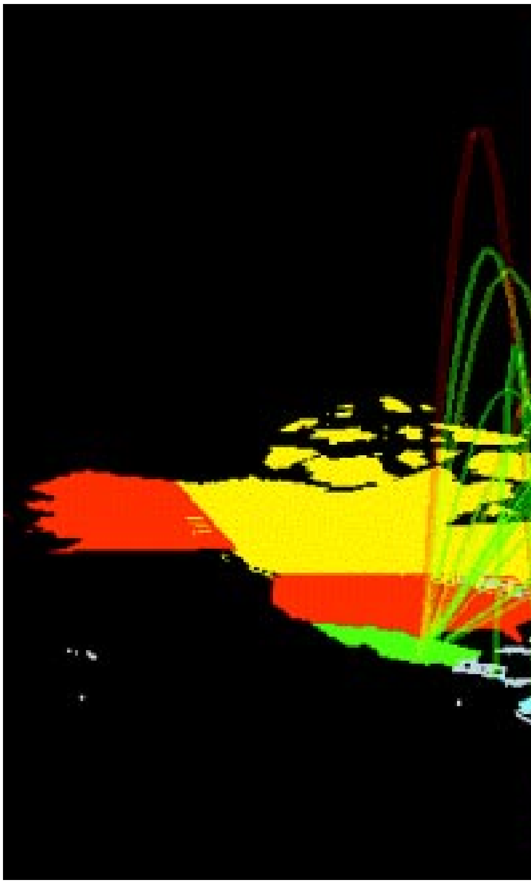
The beauty of packet-switching, Santoro noted, is that, “It doesn’t matter how the cards move through the system. They can arrive successfully by many different routes. “If one post office happens to be closed, the cards can be re-routed through another.” Packet-switching is cheap, too, since communicating doesn’t require an exclusive, closed channel between two parties. Packets can be placed into the system by many users at once, and are simply ferried along in the order received.

The first generation of this new concept was ARPANET, a network joining employees of the Defense Department’s Advanced Research Projects Agency. By the early ’70s, ARPANET offered these cyberpioneers three nifty tools that today are taken for granted. By following a set of programming rules dubbed Simple Mail Transfer Protocol, or SMTP, they could send each other mail electronically. A second set of rules, File Transfer Protocol (FTP), allowed them to exchange files of data. Finally, a program known as Telnet permitted them, with passwords, to log on to their own computers from any other computer on the system.

Following Protocol

Before long, Santoro said, the Army, Navy, and Air Force all had their own networks — each developed by a different computer company. “The question became, How do you interconnect all these different types of equipment?” The answer lay in developing yet another set of standards, an overarching protocol “suite” called TCP/IP. TCP, for Transmission Control Protocol, would standardize the conversion into packets, and their reassembly into messages. IP, for Internet Protocol, would provide an identifying number for every machine on the system and route packets where they needed to go. Together, TCP/IP would function as a sort of common language, laying the groundwork for a world-wide system. Strictly defined, Santoro said, today’s Internet is “the interconnected set of all networks running TCP/IP, supported by packet switching.”

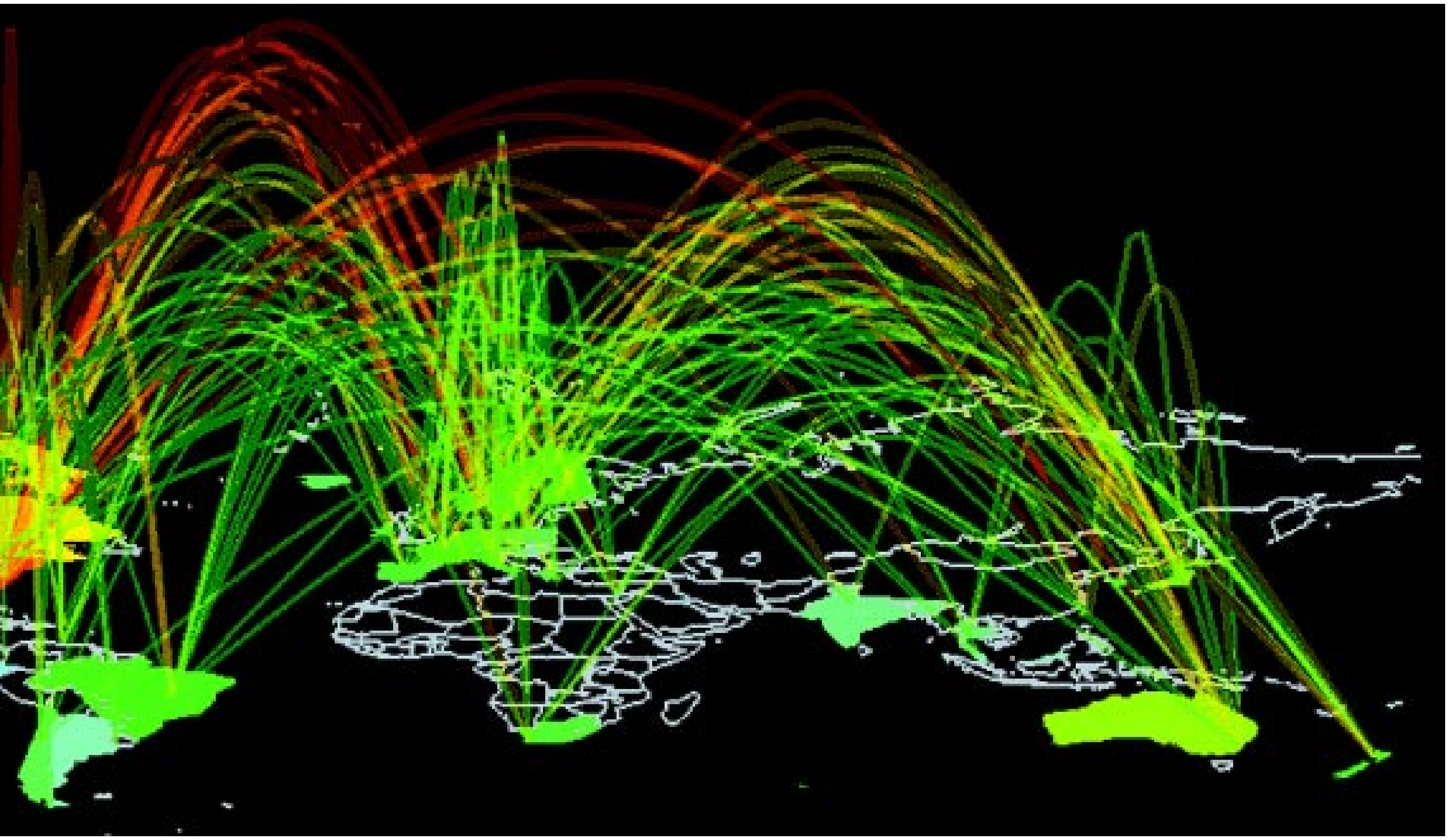
From a technical perspective, he went on, “the Internet works exactly like a telephone network. A phone system requires only two things,” he explained. “Every telephone has to be electrically connected to every other telephone, and each telephone has to have a unique identification number. The Internet follows the same strategy — in fact, a lot of times they share the same wires. And every computer has its own identifier — the IP number. When you run a program like a Web browser, and you select a link, what’s happening is your computer is going out and making contact with some other computer, and the two computers are exchanging packets of information.”



Say you want to see the Web version of Santoro’s talk, for instance. Within your browser, you type in the file locator he assigned it: **http://cac.psu.edu/~santoro/internet/**. When you hit “Enter,” the first thing your browser does is to seize on the part of that locator called the domain name, which corresponds to the IP number of the computer on which the lecture resides. (“Human beings remember names better than numbers,” Santoro explained.)

Your browser passes the domain name, **cac.psu.edu**, to the TCP/IP software on your computer. Your TCP/IP software contacts a domain-name server, a computer that acts like a phone book, containing a long list of domain names and corresponding IPs. Once your computer gets the correct number, it places the "call."

When the remote computer — in this case a machine in Penn State's Academic Computing building — answers, your browser sends it a request for the specific file: **~santoro/internet/**. Through its own TCP/IP software, the remote computer then begins sending the necessary packets, and when all have been received and reassembled, your web browser displays the file on your screen. *Presto!* There's the welcome page, complete with photo image of a smiling Santoro in flannel shirt and shades.



Courtesy Stephen G. Eick/Lucent Technologies

The world, as mapped by the Internet. World-side traffic continues to double every 100 days, the only limit being our ability to deal with all the information heading our way.

Hooking Up

Your actual physical connection to the Internet can be any of several types: a modem connected to your home telephone line, a fiberoptic cable linking several computers in your school or office, even a satellite hook-up. For now, Santoro said, the most popular type remains the modem, a device which converts outgoing digital data into an analog signal — that shrill duo-tone you hear when you mistakenly pick up the telephone receiver in mid-transmission. The analog signal travels the telephone line to another modem at the computer of your Internet service provider, where it is reconverted to packets of 1s and 0s. (Switching from digital to analog is called modulation: "modem" is short for modulator/demodulator.)

Your local provider then merges your packets with those arriving from other users (a step known as "multiplexing") and sends them along to a larger, centralized provider, from where they can be shoved out onto a "backbone" — a high-speed transmission line — to zip across the country, or the world. When they reach a local provider near their intended destination, the initial process is reversed. Finally your packets arrive, all in a heap, at the server — that distant computer serving up the text file or video clip you desire.

On the Road

A trip round the world in cyberspace takes but a couple of blinks. When things go right, that is —and here's where Santoro pulled out the most well-worn Internet analogy of them all. "From a behavioral perspective," he said, "the Internet does work very much like a highway system. It has its rush hours, its traffic jams, its weather and construction delays. To be an effective user, you've got to take these realities into account.

"No one anticipated the traffic levels we have today," Santoro said. And traffic *doubles* every 100 days, he added, as more and more people flock to the World Wide Web.

A group of academic, industry, and government partners, including Penn State, is hard at work developing the infrastructure for Internet 2, a new, superfast network that will relieve some of this space crunch, Santoro noted. But he doesn't see bandwidth as the biggest restricter of the Internet's huge potential.

"The real limiting factor, I think, will be the ability of individual users to deal with all the information that's going to be coming their way," he concluded. "Learning how to make sense out of it."

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Tipping the Scales

From a distance, Earth's climate is a simple matter of equilibrium. Eric Barron made this point with a single vivid image, of Earth from space. There was the mottled orb in high relief: sunlight and shadow, bright reflective cloud-cover and deep absorbing ocean, bone-pale desert and dark tropical forest. Balanced precisely between incoming solar warmth and cold, receiving dark. Yin and yang. It's when you zoom in a little that things start to get complicated.

"The first thing you notice," Barron said, "is that the energy received at the Earth's surface is not evenly distributed. The poles get a lot less than the equator. The poles are actually giving up net energy, while the equator is running a surplus."

The resulting temperature gradient drives the great wind belts, and moves the seas. These giant heat transporters, atmospheric and ocean circulation, are the primary shapers of global climate. But many, many other factors play their parts. Plants, for example, are sponges for heat. Snow and ice cover tend to perpetuate cold — not by their coldness, but by efficiently turning sunlight away. Even the texture of the soil is important, helping to define its moisture content, and so how much moisture the air can draw by evaporation. "You can begin to see the level of complexity we're talking about," said Barron, director of Penn State's Earth System Science Center.

Barron, a professor of geosciences, gave the fifth of this year's Penn State Lectures on the Frontiers of Science. When considering "How Climate Change Works," he said, "It's a good thing we have that underlying rule: Energy coming in must equal energy going out."

Do the Math

There are, it follows, only three basic ways to alter the climatic equation: Change the amount of energy that reaches us from the Sun; change the percent of energy reflected back into space; or change the composition of Earth's atmosphere, so that more (or less) energy is trapped by that life-sustaining insulated blanket we know as the greenhouse effect. (Another heat source, Earth's molten core, has only miniscule climatic impact, Barron said.)

Our climate has always been changing. The sun's power waxes and wanes along cycles of orbit, and we get seasons. On much different time scales, the continents have shifted their positions; there has been more or less ice cover, more or less forest. Volcanic eruptions, spewing their dust, have played havoc — for brief periods — with the composition of the atmosphere.

These "disturbances" are known to climatologists as forcing factors. Alone, Barron said, their effects are relatively minor. Yet, "The fossil record shows us periods when there were alligators off the coast of Greenland. There was a time when over 400 species of plants flourished on the north slope of Alaska. There have been times when palm trees grew in Chicago, and others when all of Pennsylvania was covered in ice." For this kind of change to occur, Barron said, there have to be positive feedbacks: systematic responses that loop back around, spurring more change, and still more, until the original effect is many times amplified.

Feedbacks

Water vapor, for example, is a greenhouse gas. It acts as an insulator, absorbing heat radiated up from the planet's surface and redirecting some of it back toward Earth. A small drop in temperature, however, causes water vapor to condense — and then it falls as rain or snow. That leaves less insulation in the atmosphere, which reduces the greenhouse effect, which in turn causes surface temperature to drop even more — and on and on, until some other limiting factor intervenes. Conversely, if air temperature rises even slightly, more water vapor will be evaporated from the oceans. A moister atmosphere means tighter insulation, and in turn more warming. In both cases, the continued action of the loop ends up being far more important than the original disturbance.

Some of the important feedbacks that affect climate, Barron said, have only recently been observed. "As a student, for example, I was taught that the distribution and character of vegetation were passive responses to climate. Now we know that's not true. Life on Earth is part of the feedback system."

Over the last century and a half, in fact, life on Earth — of the human variety — has become an increasingly potent factor in climate change. Gas samples retrieved from bubbles in prehistoric ice cores and measurements taken at Hawaii's Mauna Loa volcano document a thirty-percent increase, since the beginning of the Industrial Revolution, in the atmospheric con-

Jet Propulsion Laboratory and UCLA

Above, a computer simulation of the topography of the West. Even soil texture shapes climate. Top right, the Mississippi delta from space. Sea levels will "very probably" rise over the next 50 years, but how much?

centration of CO_2. “There is no question,” Barron said, “that this increase is due to the burning of fossil fuels — and, to a smaller extent, to deforestation.”

There is some question about just what effect this massive jump in CO_2, a greenhouse gas, has had on global climate. From the available data, Barron said, it appears that Earth is getting warmer. But taking surface temperature readings on a global scale is a tricky business. “There are plenty of ways for errors to creep into those measurements. Still, after factoring out as many errors as possible,” it appears that the Earth’s temperature has crept up 0.5°C, (about 0.9°F) during this century.

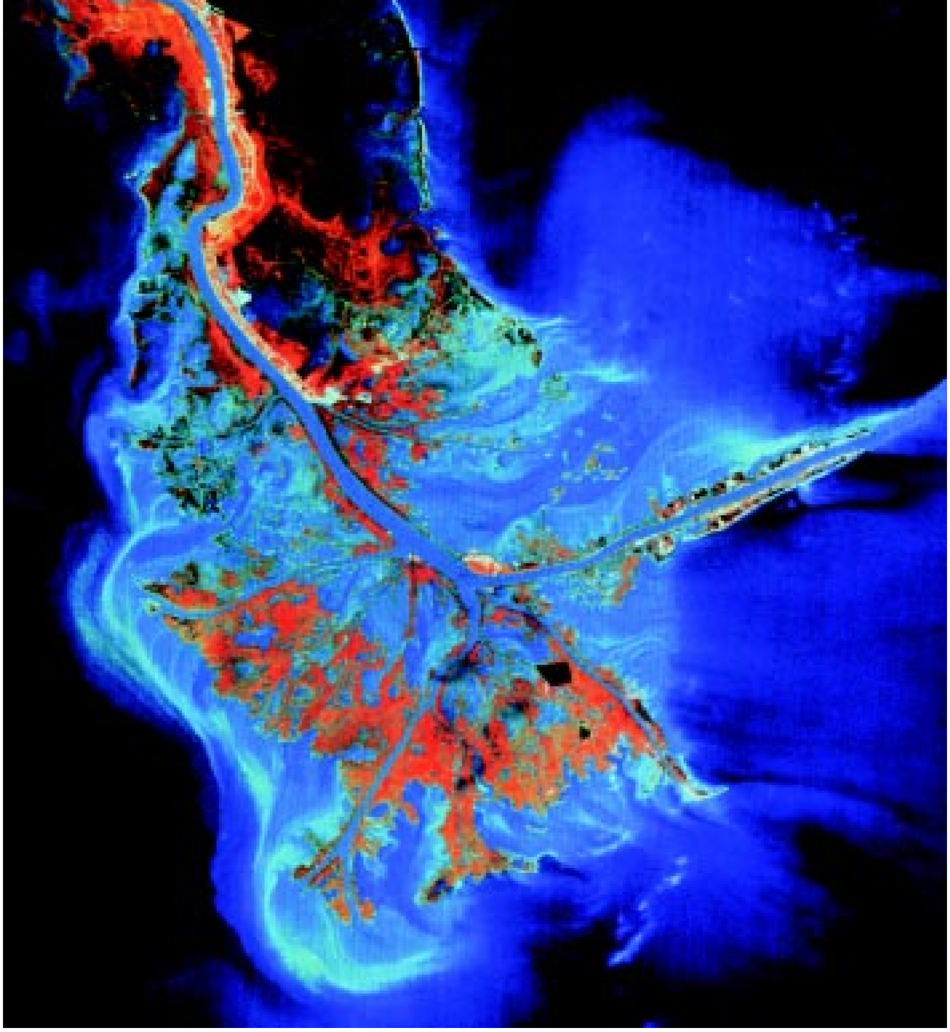
Model Planet

An even bigger debate looms over the effects of rising CO_2 levels on *future* climate. Here’s where Barron and other atmospheric scientists have to turn to computer simulations of the atmosphere and the oceans. These General Circulation Models, or GCMs, can’t settle the question of what sort of warming is going on right now, Barron explained. “What they can do is tell us what *should* happen, given what we know, in response to a wide variety of changes.”

Because modeling is extremely computer-intensive, climate processes and feedbacks, in even the best GCMs, must be highly simplified. Important details are left out. “Cloud response, for example, is huge,” Barron said, but clouds are a relatively small-scale physical process. “At our present level of resolution, anything smaller than the state of Pennsylvania is too small to get right.”

What current models have produced is a range of possibilities, and taken together, these results provide a consensus: At current rates of increase of atmospheric CO_2, global surface temperature will increase from 0.5 to 2.0°C over the next 50 years. If CO_2 doubles, as it will during the 21st century unless fossil-fuel burning is seriously curbed, that warming will be between 1.5°C and 4.5°C. These may not sound like big numbers, but they are. At the high end of possibility, a change of four degrees C would match — although in the opposite direction — the global temperature difference between 1999 and the last Ice Age.

“So what do you do? What do you do when your best science says look out, the change will be enormous, but there’s all this room for error?”



LANDSAT

Warm Response

One thing you do is work on improving your models. “Here at Penn State we’re developing a high-resolution regional-scale model,” Barron said. During the next decade, such models will increasingly be deployed in combination with GCMs to fine-tune predictions and lower the possibility for error. In the meantime, however, “we have to talk in terms of probabilities.”

It is very probable, he continued, that over the next 50 years, at a global level, surface temperature will increase, precipitation levels will increase, sea ice will shrink toward the poles, and sea levels will rise. “No one really questions these things. What we can’t predict with confidence is how much, and what the local-scale effects will be.”

Does that mean there’s nothing to worry about?

“Here’s where it gets personal,” Barron said. “Let’s say, as some models predict, the range for beech trees shifts a couple hundred miles north. There’s a range of possible responses. You might say, ‘That’s unacceptable. I can’t live without beech trees.’ Or you might say, ‘Humans can adapt.’

“The potential human-level impacts of climate change are myriad — and they’re not just aesthetic. Climate is intimately connected to human health, for one. Milder winters would mean more deer in Pennsylvania. More deer mean more deer ticks. More ticks mean more Lyme disease.

“Or you could look at something like dengue-hemorrhagic fever. It’s delivered by a mosquito, which can’t live in cold winter areas. That means right now it’s limited to the southern hemisphere — Africa and South America, mostly. But if the Earth gets warmer, will dengue fever come to, say, Tennessee?

“In the end,” Barron concluded, “how you respond to this information becomes a very personal decision. You have to decide how vulnerable you are to climate change. You have to weigh the probabilities. You have to decide how much risk you are willing to tolerate.”

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Somewhere Out There

Speculators on the night sky, astronomical and other, have long suspected that we were not alone. Putting aside the question of extraterrestrial *life* for the moment, weren't there any other *planets* out there, beyond our cozy family of nine? Other ordinary planets circling other ordinary stars?

It always seemed a good bet. Yet no "extrasolar" planet was actually discovered until 1991, when Alexander Wolszczan, now at Penn State and then working on the giant Arecibo radio telescope in Puerto Rico, picked up some quirky signals from a tiny star in the constellation Virgo. What Wolszczan heard, a semi-regular pulse from space, turned out to be three planets orbiting a pulsar, or dead star, some 7,000 trillion miles away. "Alex was so careful to confirm what he had observed that he didn't actually announce it until 1994," said Larry Ramsey, Wolszczan's Penn State colleague.

The following year, Ramsey went on, two Swiss astronomers detected a planet circling the star known as 51 Pegasi, in the constellation Pegasus. "This was the first planet found around a solar-type star."

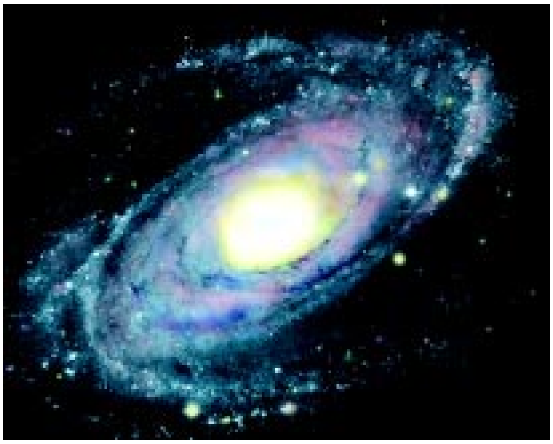
Since then, Ramsey said, new planets have been cropping up like daisies. The grand total, as of mid-February, was 18. It is hardly a coin-cidence, he suggested, that over roughly the same period, "A whole new generation of very large tele-scopes has come on line."

Things Are Looking Up

Ramsey, a telescope designer himself, gave the sixth of this year's Penn State Lectures on the Frontiers of Science, "How Huge Telescopes Work in the Search for Other Planets."

To start things off, he ran down the list: In the northern hemisphere, there are the Keck twins, Subaru, and Gemini North, all on Mauna Kea in Hawaii; the Magnum Mirror, or MMT, near Tuscon, Arizona; and the Hobby-Eberly, in west Texas. Down south, in Chile, you have the European Very Large Telescope, the Magellan pair, and Gemini South. The smallest of these telescopes boasts a primary mirror that measures 6 meters across. The biggest mirror, at 11 meters, belongs to the Hobby-Eberly, conceived by Ramsey and Penn State colleague Daniel Weedman.

Sheer size is one of the keys to finding new planets. In terms of basic optics, both light-gathering power and resolution — the ability to make out fine detail — increase with the diameter of the mirror. Both are crucial for picking out distant, smallish objects like planets, which throw off no light of their own.



The real problem, Ramsey said, is blocking out the light from a planet's parent star. As Andrew Fraknoi of the Astronomical Society of the Pacific puts it, seeing a planet in the glare of its "sun" is like trying, from the far end of a long, dark hall, to see a grain of rice suspended an inch or two away from a 100-watt lightbulb. In the realm of visible light, Ramsey estimated, the planet is a million times fainter than the star.

Shift over to infrared light, however, and you've got a different story. In the infrared wavelengths, a star throws less energy, relatively speaking, and a planet reflects more. As a result, Ramsey said, the planet is only a thousand times fainter. "Sensitive instruments can pick it up." The infrared camera on the Hubble Space Telescope, which has the added advantage of operating above the muddle of Earth's atmosphere, has recently sent back amazing images of dust disks clustered around central stars — important information for the study of how stars form. But Hubble's mirror, at 2.4 meters, is too small to search for new planets, Ramsey said. For now, that job is left to the giants on the ground.

Larry Ramsey

The Hobby-Eberly telescope near Fort Davis, Texas (left) is one of the new generation of giants crucial to finding planets outside our solar system. Above, Galaxy M-31 in the constellation Andromeda.

Fine Optics

A couple of recent technological advances have cleared the way. First, Ramsey said, "You have to have active optics." A piece of glass this big, he explained, changes shape with the slightest change in its environment. It sags under its own weight from simple gravity. Its metal support structure expands and contracts with temperature. A shift as small as 1/100th the thickness of a human hair can skew the clarity of an image from deep space. With active optics, Ramsey said, computer-controlled sensors are mounted all over the mirror's back, and tiny motors can adjust to the slightest change in its shape, moving it precisely to keep it aligned.

The second necessary feature, he continued, is *adaptive* optics. Incoming light, he explained, is distorted by turbulence in our atmosphere. ("You can see this turbulence by looking across a field with binoculars on a hot summer day.") The light waves are actually bent; a telescope only magnifies the distortion, making stars appear fuzzy and shimmery. With adaptive optics, a flexible secondary mirror is placed within the telescope to counteract this effect: The incoming light is bounced off the secondary mirror, which has been "deformed" to cancel out the distortion. By the time the light reaches the primary mirror, it's all straightened out again.

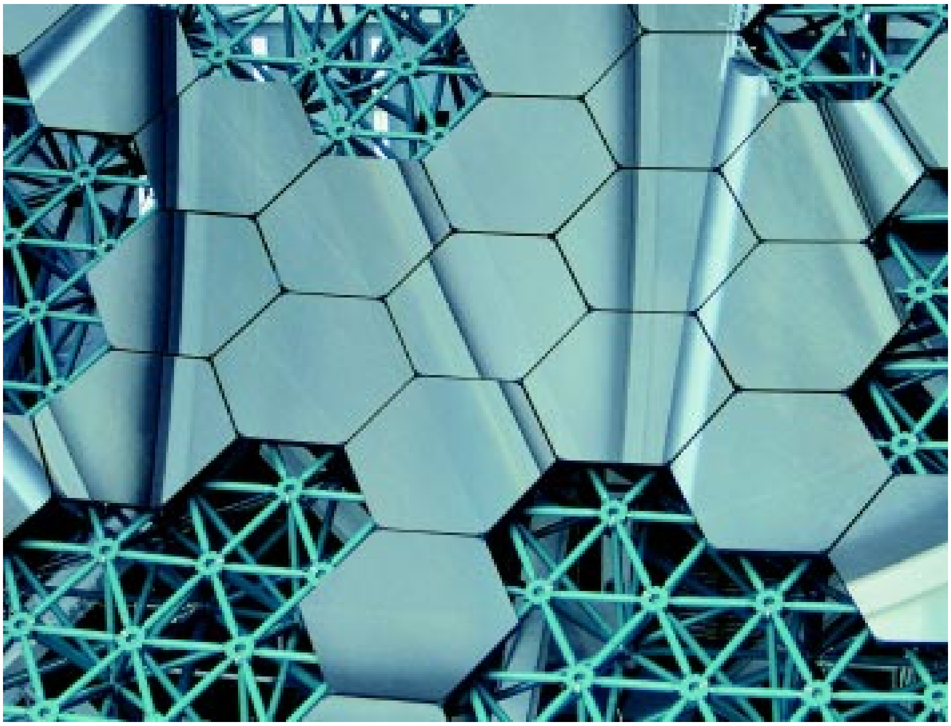
"It's very sophisticated stuff, and it's just in its infancy," Ramsey said, "but it promises to make ground-based imaging as good as that from space."

Watching the Wobbles

Thus far, though, the most productive approach to finding new planets has not been through direct imaging at all, but through spectroscopy.

"We all know how incoming light, dispersed by a prism, splits into different colors. Spectroscopy is just splitting it into more colors."

A high-resolution spectrograph, he explained, splits a star's light through a grating, a super-sensitive "prism" which looks like a long, fine-toothed comb. The spectrum produced is then spread out on a charge-coupled device, or CCD, a light-sensitive receptor. What you see are stacked-up bands of light, broken into subtly colored segments by narrow black lines. These spectral lines, caused by the absorption of certain wavelengths as light passes through the atmosphere, are the key to finding planets.



Larry Ramsey

A close-up of the Hobby-Eberly telescope's primary mirror, taken during construction. In HET's unique design, 91 glass hexagons make a single reflector 11 meters across.

A planet orbiting a star, Ramsey explained, exerts a gravitational pull, which causes the star to wobble. From our perspective here on Earth, the star moves slightly toward us, and then slightly away, as the planet circles around it.

Very slightly, since the planet is relatively tiny, the star huge, and the whole system light years away. In fact, the wobble is too slight (and too slow, at once per orbit) for anyone to actually see it. But this movement, and its speed, can be determined because of the Doppler effect.

The Doppler effect, Ramsey explained, causes the light waves streaming from a star that is moving away from the Earth to lengthen slightly, so that they appear to us more red in color. Those coming from an object that's getting closer to us are shortened, and so they appear more blue.

On a CCD, the Doppler effect causes those black spectral lines to shift — ever so slightly — as the star's light leans toward either the red or the blue end of the spectrum. Those infinitessimal shifts indicate the presence of a wobble, and if they occur periodically — first red, then blue, then red, then blue — that wobble suggests an orbit, which probably means a planet. "The name of the game for detecting planets is measuring those wobbles very, very precisely," Ramsey said.

None of the new-found extrasolar planets has actually been *seen*. But careful spectral analysis can yield an estimate of each planet's mass, as well as the size and frequency of its orbit. "So far," Ramsey said, "the planets discovered have been huge, Jupiter-like in size, and fairly close to their suns." Not surprising, he added, since the largest objects with the shortest orbital periods are the easiest to detect.

Other Earths?

Are there other, smaller planets out there? Planets more like Earth? The search is in full-swing. Around the globe, Doppler surveys are currently keeping watch on over a hundred stellar candidates; when the Hobby-Eberly Telescope becomes fully operational in a year or two, Ramsey said, it will begin to track several hundred more.

Still more help is on the way. Ramsey's final image was a conceptual drawing for the aptly named Extremely Large Telescope, or ELT, to be built some time early in the coming century. The futuristic dome around the massive instrument, drawn to scale, looked as big as the Roman Colosseum. The primary mirror, Ramsey said, will be 35 meters across.

Lawrence W. Ramsey, Ph.D., is professor of astronomy and astrophysics, 517 Davey Laboratory, University Park, PA 16802; 814-865-0333. He is project scientist for the Hobby-Eberly Telescope, a collaboration between Penn State and the University of Texas at Austin.

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