LOS ALAMOS SCIENCE AND TECHNOLOGY MAGAZINE AUGUST 2008

1663

The Smartest Living Nanomachine

Silent Sentries

Retrovision

The Legacy of GenBank

Los Alamos
NATIONAL LABORATORY
EST.1943

1663

About Our Name: During World War II, all that the outside world knew of Los Alamos and its top-secret laboratory was the mailing address—P. O. Box 1663, Santa Fe, New Mexico. That box number, still part of our address, symbolizes our historic role in the nation's service.

Located on the high mesas of northern New Mexico, Los Alamos National Laboratory was founded in 1943 to build the first atomic bomb. It remains a premier scientific laboratory dedicated to national security in its broadest sense. The Laboratory is operated by Los Alamos National Security, LLC, for the Department of Energy's National Nuclear Security Administration.

About the Cover: Kevin Sanbonmatsu (left) and Scott Hennelly (right) work at the National Stable Isotope Resource to understand how RNA (ribonucleic acid) molecules act as genetic switches that regulate protein synthesis. Sanbonmatsu also uses powerful biomolecular simulations to reveal how the ribosome (nature's protein factory) maintains quality control.

LOS ALAMOS ARCHIVE

Keeping up with laundry chores in Los Alamos, 1943.

From Terry Wallace

The Mission-Science Tapestry

The stated mission of Los Alamos National Laboratory is national-security science, which means the Laboratory must provide science-based solutions to difficult national problems. That mission is inherently driven by applied science, so questions inevitably arise about how basic and discovery science (fundamental science) fit in at the Lab.

The fact is that the Laboratory must excel in many areas of fundamental science if it is to continue to fuel the applied-science engine. Mission and fundamental science are intricately woven together at the Laboratory and always have been.

Examples of that complex interweaving abound; they can be found in every article in this issue of 1663. *One of the best examples, however, stems from the Laboratory's long-standing mission to help monitor and assess other nations' nuclear weapons programs.*

In the late 1950s the United States launched Project Vela to monitor nuclear testing. The project initially had three parts: Vela Uniform for monitoring underground testing, Vela Sierra for detecting atmospheric tests, and Vela Hotel for detecting nuclear tests from space.

Between 1960 and 1963, Vela Uniform received funding of $110.7 million, 30 percent of which was earmarked for basic research. Much of the remaining 70 percent went into developing a worldwide system of standardized seismic stations that could detect all but the smallest underground nuclear tests. Within a few short years, tremendous quantities of data were flowing from those stations to the seismology community, and in classic discovery-science fashion, this body of data led to the development of the modern theory of plate tectonics. The theory revolutionized our understanding of how the Earth works, and between 1965 and 1980, scientists learned the vast majority of what is currently known about the Earth's internal nature. In turn, this knowledge benefited the Laboratory's mission by allowing the United States to develop methods for detecting and identifying—anywhere on the globe—small nuclear explosions, with yields as low as one kiloton. Mission drove science, which led to discovery, which fed back into mission—a perfect weave.

The key to managing science at Los Alamos lies in anticipating the mission's needs and ensuring the development of strategic capabilities. Today the nation faces an evolving set of threats to its environment and to its energy and information systems, threats that endanger national security. By investing in basic and discovery science and managing them properly, we can address those evolving threats and continue to fulfill

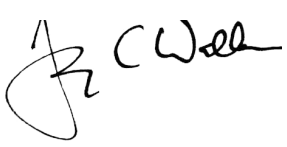
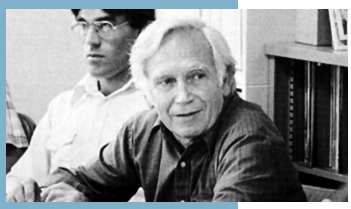


TABLE OF CONTENTS




TYR
PRO
LEU
TYR
VAL
tRNA
tRNA
tRNA
GAG
AUA
CAU
UAU CCG CUC UAG GUA JAC GGU CGU UCG
AA
REJECT

The Smartest Living Nanomachine!

In the largest biological simulation ever done, Los Alamos scientists uncovered in atomic detail how the ribosome, the protein factory in all living cells, decodes genetic information. The methodology behind this discovery—a painstaking integration of experimental results with basic physics calculations—has paved the way for developing new antibiotics and for modeling the entire process of protein synthesis from start to finish.

From childhood on, we take for granted that the human body is a chemical factory that breaks down food and converts it into the molecues needed for life.

But the body is also a container for a mind-blurring number of nanofactories called ribosomes, all working at full capacity around the clock to keep us alive.

In each of the trillions of cells in the human body, a million ribosomes continuously churn out proteins: the tangled, ribbonlike chains of amino acids that run the chemistry of all living things. That's a quintillion protein factories rebuilding our entire bodies every 7 years.

Ribosomes are found in practically identical form in every living cell on Earth, whether it be the single-celled archaea in the thermal vents of the ocean floor, the bacteria on the surface of the planet, or the cells in the human body. Because they have retained the same form throughout most of evolution, ribosomes are believed to be among the most-ancient molecular machines of life.

Says Los Alamos theoretical biologist Kevin Sanbonmatsu, "The ribosome has been studied for almost half a century. But only now can we use supercomputers to investigate, in atomic detail, how this very-complex machine really works. It has been a holy grail for people who do biomolecular simulations, and now our team at Los Alamos is making it happen."

Already Sanbonmatsu and Chang-Shung Tung, Theoretical Biology and Biophysics group leader, have created the first atomic-level computer model of a single ribosome. They used it to simulate the initial steps in protein synthesis, in which the correct amino acids are brought into the ribosome. Sanbonmatsu and his team, which includes Andrea Vaiana, Yanan Yu, and Scott Hennelly, are now ready to simulate the entire process. Their simulations require close collaboration with experimentalists Scott Blanchard of Cornell and Simpson Joseph of the University of California, San Diego.

Two goals are driving their intensive work.

One is a matter of basic science. Sanbonmatsu and his team are hoping their 3-D simulations, based on the fundamental forces among the ribosome's 250,000 atoms, can break through the conflicting interpretations of ribosome experiments by integrating the results into a coherent picture. Their simulations have already revealed the active molecular players that keep the ribosome's error rate down to no more than 1 amino acid in a sequence of 5,000.

The second goal is a health matter. Bacterial ribosomes are the target of about 50 percent of the antibiotics used in U.S. hospitals. But bacteria such as the deadly MRSA superbug (methicillin-resistant *Staphylococcus aureus*) are developing resistance to these antibiotics and now infect nearly 5 percent of all U.S. hospital patients. By simulating the ribosome at the molecular level, researchers can gain information needed for designing new combinations of drugs that will interfere with MRSA's ribosome function.

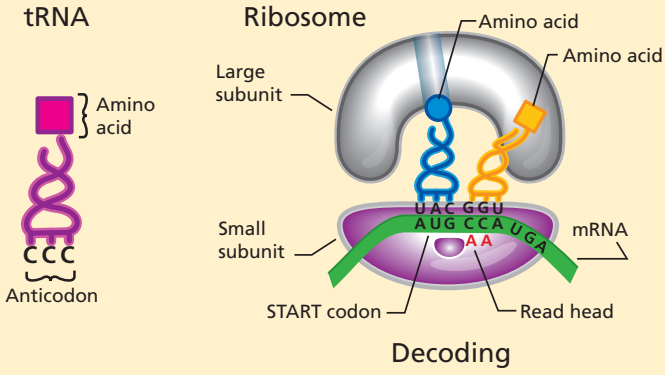
Left: Quality control in the ribosome factory. A chemical middleman, a tRNA with a three-letter "anticodon" for its feet and an amino acid atop its head, attaches to the next-available codon on the mRNA conveyor. Down below, the security forces use the ribosomal "read head" (AA) to check that the anticodon fits and properly matches the codon. If it does, the protein assembly crew in the ribosome's upper level is told to detatch the amino acid and hook it up to the growing protein chain. How that message is communicated is reported in this article.
ILLUSTRATION BY DAVID R. DELANO

From DNA to Protein

DNA. *The DNA of an organism is a sequence of four chemical units called nucleotide bases and designated by A, G, C, and T. Because the base C is complementary (binds strongly) to G, and A is complementary to T, a single strand of DNA will bind to another strand that has the complementary bases, forming the famous double helix.*

From DNA to RNA. *When a protein is to be made, the double helix unwinds, and the DNA sequence (the gene) for that protein is copied into a strand of RNA, a close molecular cousin of DNA. (In RNA, the base U takes the place of T. Thus, A is complementary to U, while C remains complementary to G.) The RNA copy of the gene is called messenger RNA, mRNA, and is shown in green in the figures.*

From RNA to Protein. *To start protein synthesis, the mRNA wraps around the neck of the small subunit of the ribosome, and the (blue) transfer RNA (tRNA) binds its anticodon to the START codon, AUG, which marks the beginning of the mRNA's protein-coding sequence. Simultaneously, the large subunit of the ribosome descends on top of the small subunit.*



When a second (orange) tRNA arrives, its anticodon binds to the next mRNA codon. The ribosome's RNA "read head" checks whether he anticodon and codon are fully complementary, that is, every A is binding to U, and every C is binding to G.

Meet the Ribosome

Only 25 nanometers (billionths of a meter) in diameter, the ribosome performs the most-complex information-processing task of any molecular machine. It reads protein recipes, which are written in the four-letter language of nucleic acids, and produces finished proteins, which are constructed from amino acids (see "From DNA to Protein" above).

The tool it uses in its work is RNA (ribonucleic acid), a molecular cousin to DNA. Two types of RNA are involved.

The first is messenger RNA (mRNA), which carries a copy of the recipe for making a specific protein. (The original information is stored in the cell's DNA.) The information is encoded in the sequence of bases (nucleotide bases, named for their nucleic acids) that hang like charms from the chainlike RNA.

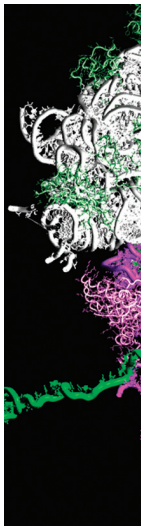
All RNA molecules are composed of four different nucleotide bases, designated by the letters A, C, G, and U. In the mRNA strand, any group of three consecutive bases, for example, AUG or CCA, is called a codon. Each codon codes for an amino acid—AUG codes for methionine, and CCA codes for proline. The mRNA strand is therefore a chain of codons specifying the order in which amino acids are to be linked to form a specific protein.

The ribosome is itself an assemblage of RNA and protein. It has large and small subunits that cooperate during construction of a protein. The mRNA moves through the small subunit like a molecular conveyor belt, presenting each codon in turn. The small subunit decodes each codon, and the large subunit responds by adding the prescribed amino acid to the protein chain. The process ends when a STOP codon at the end of the mRNA strand causes the ribosome to release the completed chain, which then folds into the tangled shape of a finished protein.

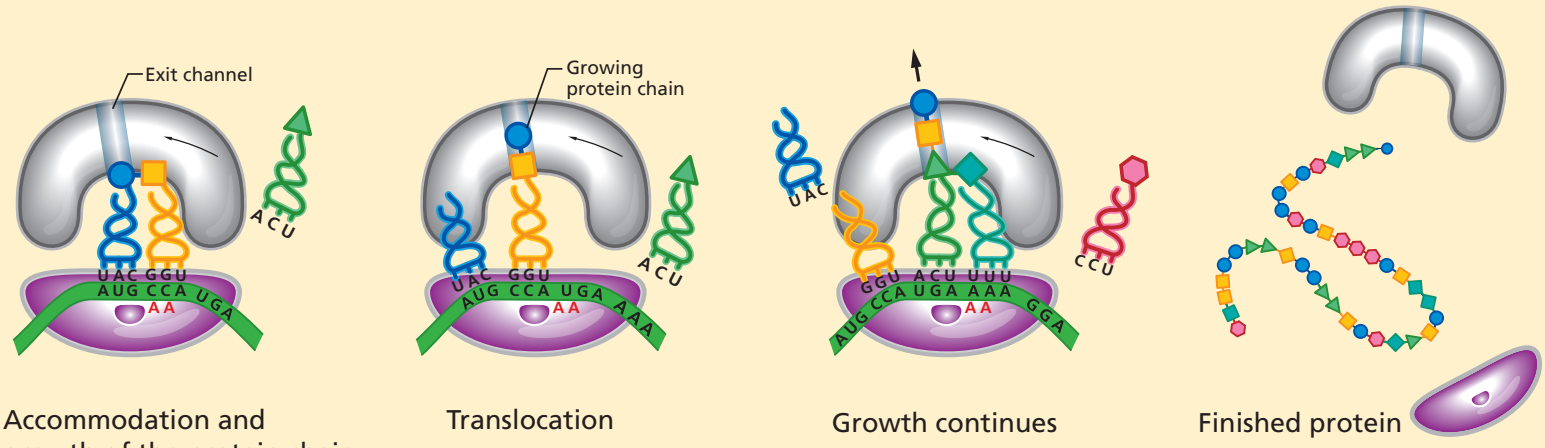
The amino acids for this construction project are delivered by the second type of RNA, transfer RNA (tRNA). Molecules of tRNA float to the ribosome's small subunit through the cellular fluid, each carrying an amino acid on one end. At its other end, each tRNA has an "anticodon"—a triplet of bases that will bond strongly to only the mRNA codon that specifies the amino acid carried by the tRNA.

When a tRNA arrives at the small subunit, its anticodon tries to bond to the next-available codon on the mRNA strand. If the fit is strong, the tRNA is accepted into the ribosome through a process called accommodation. A weak fit indicates that the tRNA is carrying the wrong amino acid, in which case the tRNA is rejected to float back into the cellular fluid.

That the ribosome accommodates only the right tRNAs and rejects the wrong ones has been known for quite a while. But the selection mechanism—the "how"—was unknown until Sanbonmatsu figured it out.



A simulation of tRNA accommodation, the step by which amino acids are brought into the ribosome. Left: The blue tRNA is inside the ribosome, and the yellow tRNA, with a tiny green amino acid on one end, is partially inside the ribosome, with its body in a bent (spring-loaded) position. (In order to clearly display the tRNA positions, the top half of the ribosome is not shown in this figure.) Both tRNAs have their anticodon ends bound to the long mRNA strand (green) that winds through the ribosome's small subunit (purple). Center:The yellow tRNA begins to straighten out as its amino acid end starts entering the ribosome's large subunit (white). Right: The amino acid end of the yellow tRNA has moved past the ribosomal gate (red) and has disappeared inside the large subunit.



Accommodation and growth of the protein chain

The tRNA is accepted (accommodated) inside the ribosome's large subunit. Its amino acid binds chemically to the first amino acid, and the growth of the protein begins.

Translocation

The small subunit pivots (not shown) over the large subunit, and the tRNA and mRNA move to the left by exactly one codon to reset the machine. The growing protein is pushed along the exit channel.

Growth continues

The cycle repeats until the STOP codon (not shown) is reached. The protein is then complete.

Finished protein

The ribosome disassembles itself, and the finished protein is ready for its work in the body.

Building a 3-D Model

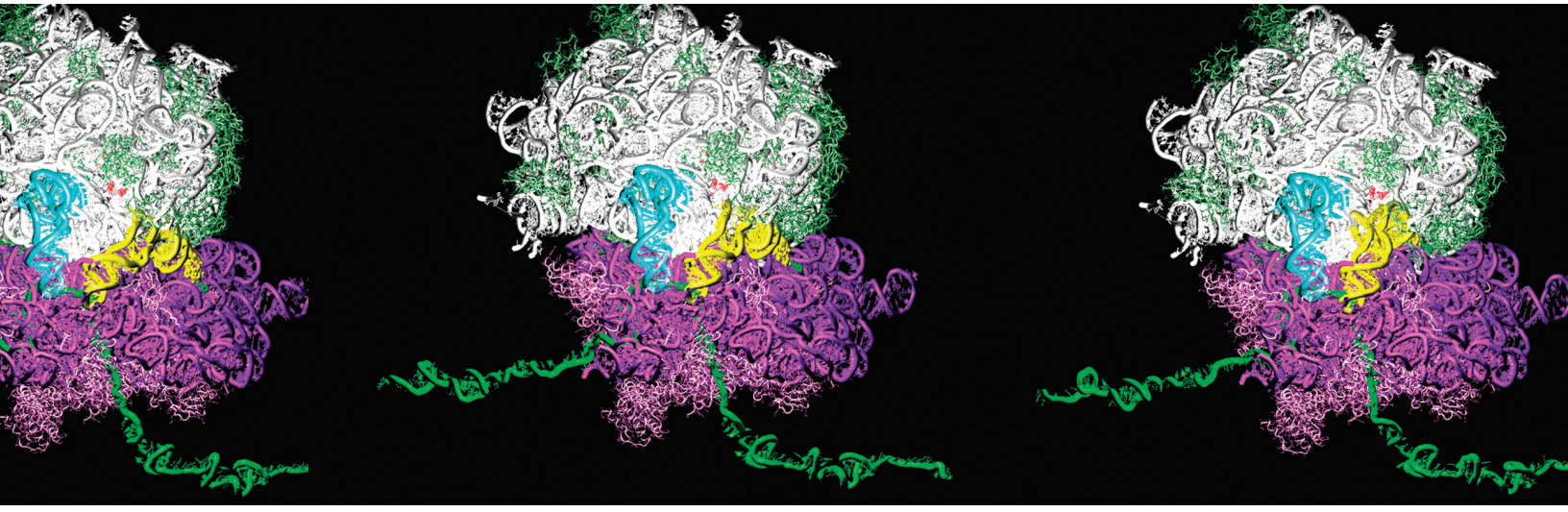
Sanbonmatsu came to his ribosome studies indirectly. Originally a theoretical plasma physicist, he left that field of study in 2000 to pursue an interest in the origin of life, an interest that became more urgent the more he read. "Popular science books," he says, "would begin with explanations of the building blocks of life—DNA and proteins—but when they came to the ribosome, they would punt and say either God made the ribosome or aliens must have brought it to Earth." The ribosome was a mystery. Researchers knew it was composed of RNA and protein and that it used mRNA and tRNA to translate the genetic code into proteins. But nothing was known about the details. What were the forces at work inside the ribosome?

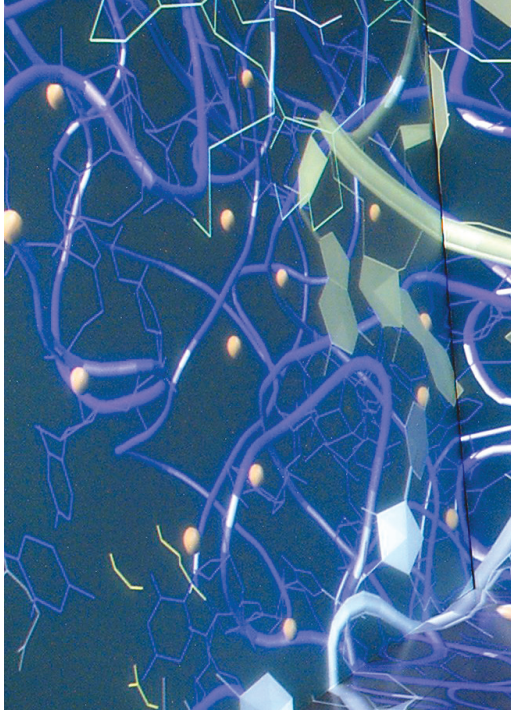
The route to an answer opened up in 2000 when researchers around the world solved the 3-D atomic-level structure of each of the ribosome's two subunits. Sanbonmatsu and Tung then fit the two very asymmetrical subunits into a single mathematical representation and built a computer code to represent how all the constituent atoms and molecules could interact and move over time: a molecular-dynamics code.

Combined, the two subunits formed a very challenging structure, dominated by a rat's nest of RNA loops. Sanbonmatsu and Tung could see no obvious way for a tRNA to be accommodated into the interior.

"Our simulation work was to find the tRNA's entry route and to explore how the right tRNAs are accepted into the ribosome and the wrong ones rejected," explains Sanbonmatsu.

The first simulation was the largest biomolecular-dynamics simulation ever done, encompassing more than 2.5 million atoms. (About 10 percent of the atoms





were in the ribosome, the tRNAs, and the mRNA strand. The rest were in the water and ions permeating the whole molecular complex.)

Sanbonmatsu was warned that the simulation was too ambitious for a newcomer to the field, but it was successful and won him the PECASE Award (the Presidential Early Career Award for Scientists and Engineers).

The Path to Accommodation

During accommodation, the tRNA moves between two positions that are known from experiments. In the initial partially bound position, the tRNA's anticodon is bonded strongly to the correct mRNA codon in the small subunit. The tRNA is bent, as if it were spring-loaded, and the end with the amino acid is entirely outside the ribosome. In the final fully bound position, the tRNA has straightened, and the entire molecule, including the amino acid, has been accepted inside the ribosome.

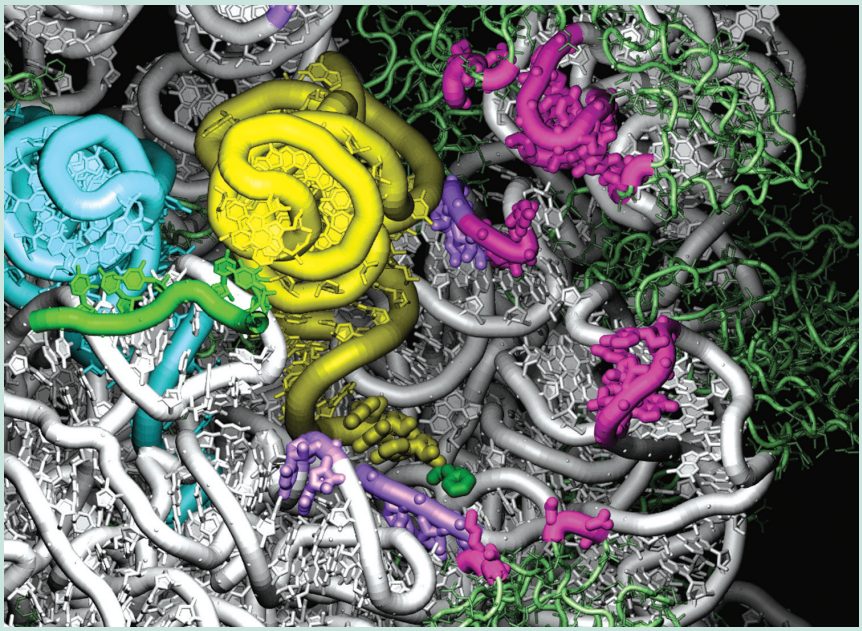
Sanbonmatsu's simulation computed the forces among the atoms to determine the path of least resistance—the minimum-energy path—from the initial, partially bound position to the final. fully bound one (see figure, p. 5, bottom).

Viewing the results was the hardest part. Sanbonmatsu had to sift through many terabytes of data to make a 3-D movie of the tRNA traversing the entrance path. He then inspected the movie from every angle, zooming in on the active regions. After months of staring at each frame, literally getting to know every atom near the path of the tRNA, he found the heretofore-invisible entry channel.

It was a pathway where only 68 of the ribosome's 5,000 nucleotide bases interacted with the tRNA as it entered the ribosome. The only real resistance along the accommodation pathway came from a kind of gate made of ribosomal RNA that seemed to block the way. In the simulation, the end of the tRNA with the amino acid was deflected backwards to get around that barrier (shown in red in the simulation) and reach the final position inside the ribosome's large subunit.

Like a master sleuth, Sanbonmatsu saw the gate's presence as a major clue to how the ribosome rejects the wrong tRNAs.

Ribosomal Sites for New Antibiotics



Sanbonmatsu and his team are using their simulations to discover potential sites for new antibiotics that will interfere with the ribosomes of disease-causing bacteria. This frame from the simulation looks into the tRNA entry channel in the ribosome's large subunit. The amino-acid ends of the yellow and blue tRNAs have fully entered the ribosome. The pink and purple regions indicate 68 ribosomal bases that interact with the tRNAs during entry. Eighteen of those are identical in every organism ever sequenced, making them promising binding sites for new antibiotics that would block tRNA passage and thereby halt a bacterium's protein synthesis.

The Mechanics of Rejection

Sanbonmatsu conjectured that a tRNA that carries the complementary anticodon for the mRNA codon must somehow be securely bound at the decoding position in the small subunit. He conjectured further that once bound, the tRNA would use its mechanical strength, or rigidity, to get past the gate. In other words, if the tRNA is held fixed at its anticodon end, then as its body unflexes, it will be able to swing rigidly into the ribosome, bringing its amino acid with it.

Conversely, if the tRNA is incorrectly matched, Sanbonmatsu thought the binding of the anticodon must be much less secure. As a result, the release from its spring-loaded position would dislodge the tRNA from its footing, and no entry would be made. This conjecture implied that the tRNA is an active player, transmitting between the ribosomal subunits the information that the correct amino acid is being delivered. Previously, people thought that information was sent through an elaborate ribosomal mechanism, not through the tRNA.

Sanbonmatsu then ran another simulation, showing in great detail how the anticodon end of the tRNA interacts with the small subunit's molecular "read head," a small RNA loop that chemically "proofreads" the attempted anticodon-codon match. If the match is good, nine chemical interactions anchor the tRNA to the mRNA read-head complex. If the match is poor, only seven chemical interactions take place, so the connection is weaker, drastically reducing the tRNA's footing and its chances of getting through the gate.

Thus, tRNA is revealed as playing an active role in ensuring correct translation of the genetic message, which suggests that it may well have existed long before the ribosome in evolutionary time and facilitated protein synthesis in prelife systems.

Theory Attracts a Following

Sanbonmatsu's simulations have set a precedent in ribosomal research. Not only are his findings gaining traction, but other theorists and experimentalists are also choosing simulation to both interpret and plan experiments.

Meanwhile, Sanbonmatsu and his small team are readying a new simulation code for Roadrunner, the new supercomputer at Los Alamos that has taken the lead as the most-powerful supercomputer in the world.

Roadrunner will enable Sanbonmatsu's team to mimic the ribosome's massive coordination of its moving parts in a step called translocation (see top box on previous spread). This amazing process resets the ribosomal machinery after the addition of each new amino acid to the protein chain. The ribosome's two subunits somehow swivel relative to each other in a ratchet-like motion that moves the mRNA conveyor belt forward by exactly one codon.

According to Sanbonmatsu, the motion may be powered in part by spring-loaded tRNAs. To check out such speculation and guide the simulations, the team will work with its Laboratory colleagues to experimentally track these complicated movements.

Sanbonmatsu announces his plans with a cool matter-of-factness, but beneath the calm is the unmistakable air of intense excitement. Many mysteries are waiting to be solved. ❖

— Necia Grant Cooper

Above: Sanbonmatsu stands inside his ribosome simulation, the largest biomolecular-dynamics simulation to date.

SILENT SENTRIES

For 45 years, Los Alamos space-based sensors have monitored the Earth and its environs for any above-ground nuclear explosions. But a shifting nuclear landscape makes monitoring in today's world particularly challenging, a challenge that the Laboratory meets by designing intelligent detectors.

The Limited Test Ban Treaty came into being during the summer of 1963, just 18 years after a mushroom cloud swept the radioactive remains of the first atomic bomb miles into the sky. With a stated desire to put an end to both "the contamination of man's environment by radioactive substances" and "the armaments race," the treaty prohibited nuclear explosions on Earth's surface, in its atmosphere or oceans, or in space.

Six days after the treaty went into effect, the United States launched a pair of satellites, the Velas, to verify compliance. The Velas were followed over the years by other satellites, dozens of them, each carrying various packages of gamma-ray and neutron detectors, x-ray telescopes, or radio and optical sensors—instruments that could detect the telltale radiations of a nuclear blast.

Those Cold War–era instruments, all built by Los Alamos (save the optical sensors, which were built by Sandia National Laboratories) were robust, highly reliable, and well suited for monitoring a world with six declared nuclear-weapons states: the United States, the Soviet Union, the United Kingdom, France, China, and India

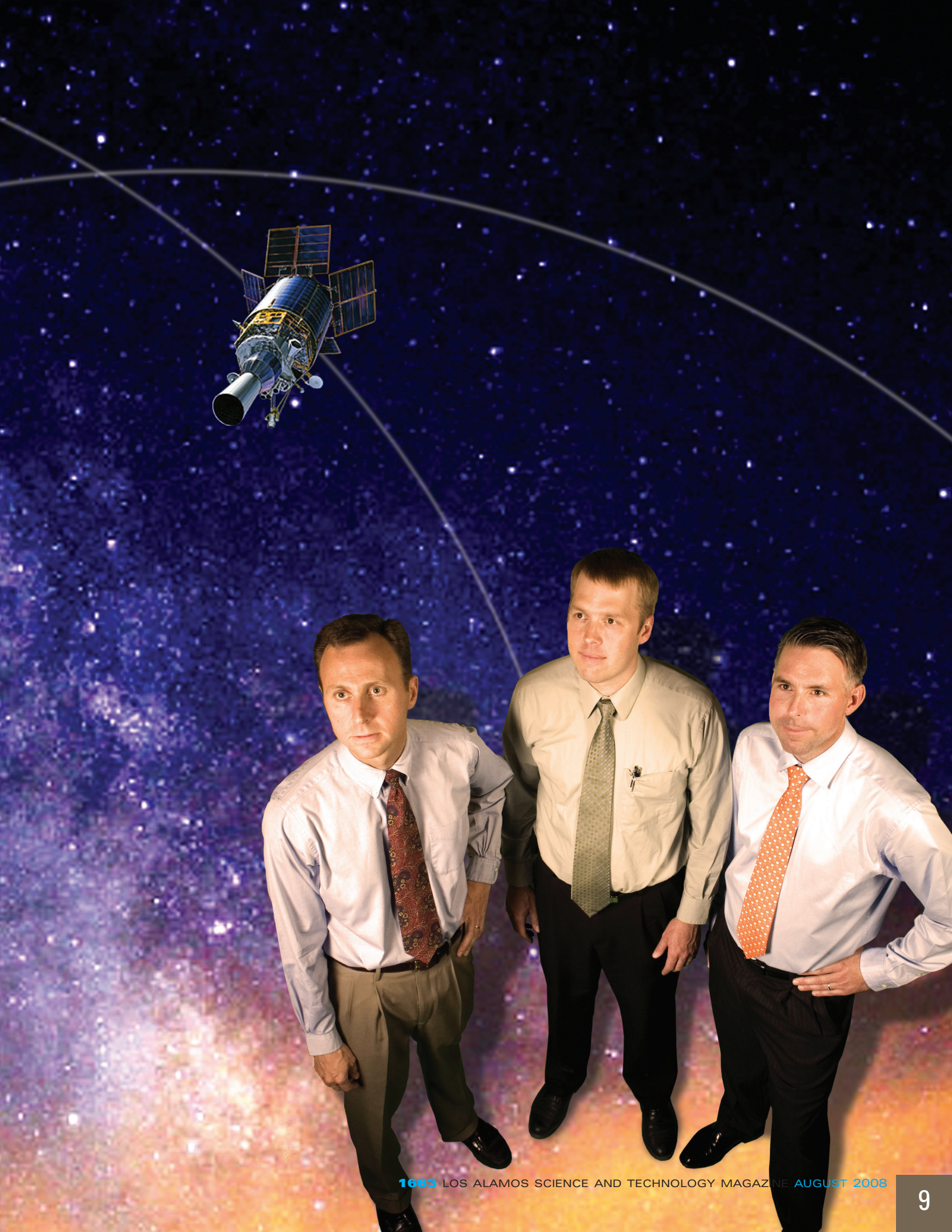
But then the world changed.

"The Berlin Wall came down in '89, the Cold War ended, and the nuclear threat just seemed to metastasize," recalls Mark Hodgson, a senior program manager and unofficial historian for the Satellite Nuclear Detonation Detection (SNDD) program at Los Alamos. "The world was suddenly full of nuclear-weapons information and strategic materials and, to a lesser extent, the engineering and economic capability to make a weapon."

The nuclear landscape began to change rapidly. The Soviet superpower broke into four nuclear weapons states—Russia, Kazakhstan, Belarus, and Ukraine—then four became one when the latter three returned their weapons to Russia. Iraq was rumored to be developing weapons, and Pakistan detonated a device. In addition, there was the specter of terrorist bombs. To keep pace, monitoring in the 21st century would have to run a different race.

Instruments would have to be savvier, sensors more able to detect a much-broader spectrum of signals, in greater detail and with higher sensitivity. But the enhanced sensors would also see countless

Facing page: Marc Kippen, Eric Dors, and Dave Smith head teams responsible for building instruments that detect nuclear explosions anywhere on or above Earth's surface.



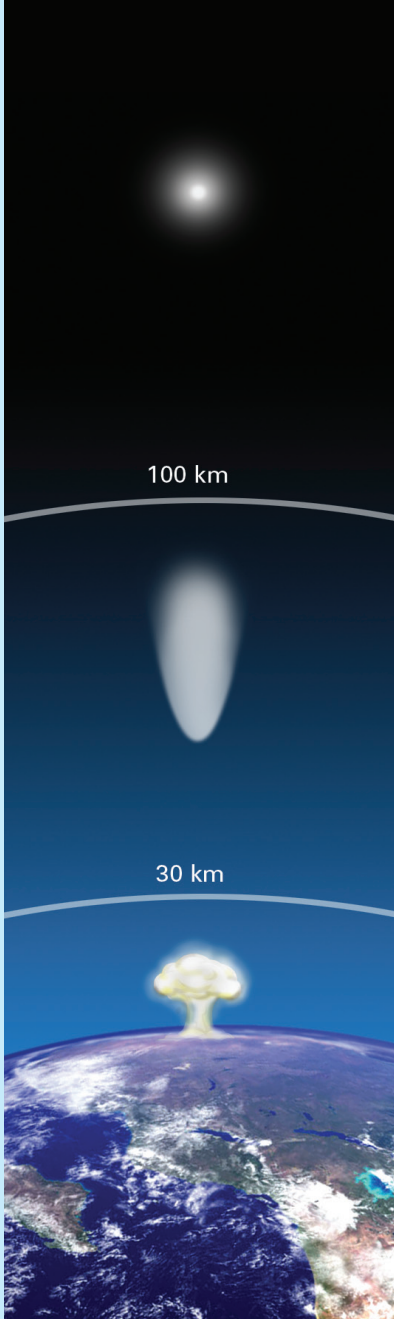
Nuclear Detection 101

A nuclear explosion releases gamma rays, neutrons, x-rays, and radioactive debris and leads to the production of visible light and radio waves. One or more of these radiations can be seen by satellite-borne SNDD detectors thousands of kilometers above Earth.

For a detonation within 30 kilometers (km) of Earth's surface (bottom image), visible light is the primary detectable signal; the atmosphere prevents the gamma rays, neutrons, and debris from traveling into space. The gamma rays, however, collide with atmospheric atoms and dislodge electrons, which then emit radio waves when accelerated by the Earth's magnetic field. These large-amplitude, short-duration radio signals, known as nuclear electromagnetic pulses (EMPs), are also detected.

For a detonation 30 to 100 kilometers above the Earth (middle), the atmosphere is thick enough to prevent particles from reaching space-based detectors. EMPs, although present, are not used in this altitude range for detection. Instead, visible light, x-rays, and gamma rays are the primary signals of interest.

For a detonation above 100 kilometers (top), gamma rays, x-rays, neutrons, and other particles can be detected directly.



natural background events, such as lightning flashes or cosmic-ray collisions.

Distinguishing a true nuclear signal from false background signals is *the* critical task of monitoring, a task performed primarily by ground-based supercomputers and human analysts. But the current SNDD group of some 200 scientists, engineers, and technicians is changing how the job gets done. It is building intelligent instruments that can rapidly assess the data while in space and look for probable events. Team members are also using advanced technologies to make the instruments smaller and lighter and to make them adaptable to different host satellites. And yes, they have made these marvelous instruments cost effective, too.

Hostile Space

"Simply put," says Eric Dors, the confident project leader in charge of fielding neutron and gamma-ray detectors, "our job is to detect a nuclear explosion, find out where it occurred, and estimate its yield."

Dors' job description downplays what in reality is an exceedingly difficult task. The surface area of the Earth is more than half a billion square kilometers. (One kilometer is just over a half mile.) With a 100-kilometer-thick band of atmosphere tacked on, there are about 50 billion cubic kilometers to monitor.

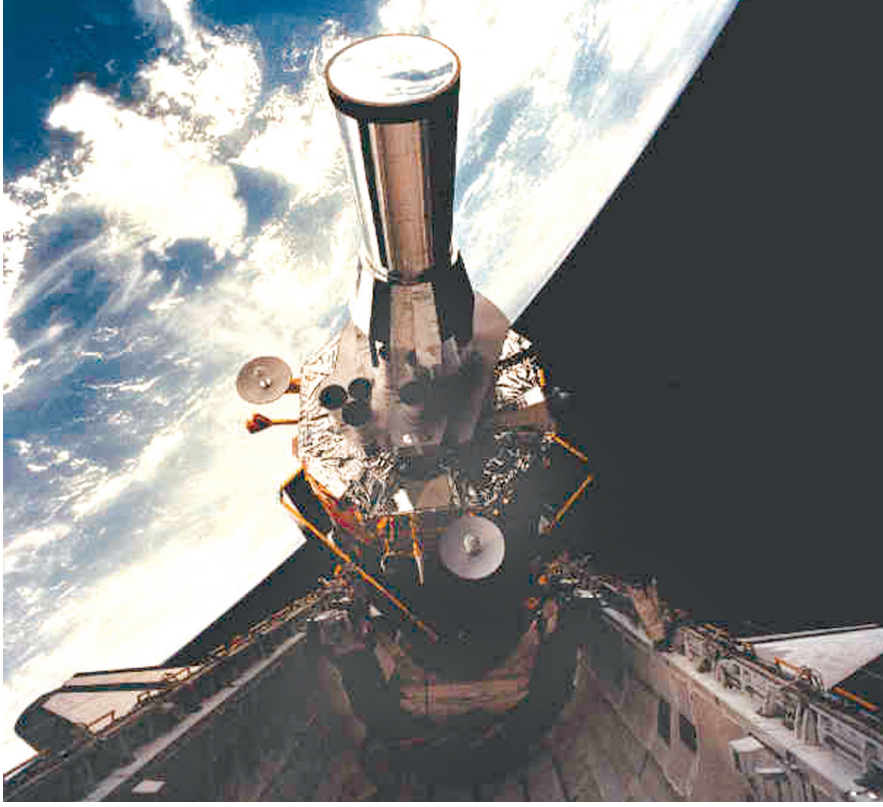
Actually . . . more. There's near-Earth space to monitor as well, a seemingly endless black "void" that happens to be as harsh as the Sahara for sensitive electronics.

In reality, the void is filled with energetic charged particles that have become trapped by Earth's magnetic field. These particles collide with and blast away at a satellite's materials and also deposit charges (both positive and negative) on exposed surfaces. Charge imbalances can grow large enough to create electrical discharges, inducing currents inside the satellite that can interfere with and sometimes damage electronics.

The particles also hit the sensors and are a major source of background signals. *How* major depends on the particle density, which depends in a complex way on the intensity of the solar wind—electrons and ions that race away from the sun at about 400 kilometers per second. On windy days some sensors will fire every few minutes. Occasionally, the sun will eject a large mass of material from its corona and precipitate a "storm" in near-Earth space, during which both the background signals and the potential for satellite damage get blown sky high.

When the first treaty-verification satellites, the Vela Hotels, were launched back in 1963, little was known about "space weather." Each of the two inaugural satellites (the Velas were launched in pairs, six pairs in all) carried 30 x-ray, gamma-ray, and neutron sensors that had never before operated in space. Skeptics gave them

two weeks to live.
The sensors survived much longer, however, in part because the Velas orbited in a part of space where the charged-particle radiation wasn't severe. Those first-generation sensors worked like gangbusters and detected many nuclear events. (France and China delayed signing the Nuclear Test Ban Treaty and continued atmospheric testing until 1974 and 1980, respectively.) The Velas also detected plenty of background signals, unique data that researchers mined to investigate numerous natural phenomena. Vela's sensors were even the first to detect bursts of gamma rays originating from across the universe.



CREDIT: NASA JOHNSON SPACE CENTER (NASA-JSC)

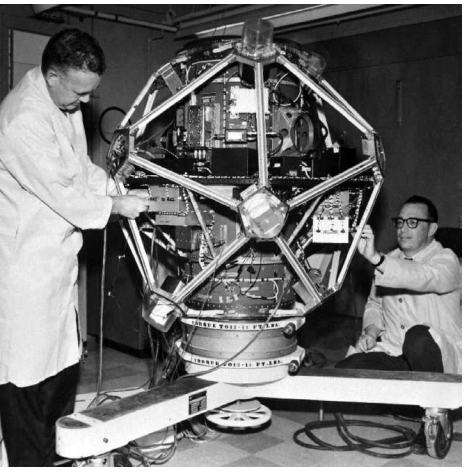
A Model Program

The SNDD program's need to distinguish nuclear signals from backgrounds strengthened what had been a shotgun wedding between science and monitoring, making it an enduring marriage. Early on, the program realized that better knowledge of space weather, Earth's atmosphere, x-ray sources, gamma-ray bursts, and planetary science would help scientists discriminate detonation events from backgrounds. Conversely, scientists realized the program offered new opportunities for research.

Strong ties developed with NASA, the University of New Mexico, and dozens of other institutions. For example, neutron-detection guru and Laboratory Fellow Bill Feldman began his career designing neutron detectors for the monitoring program, then went on to develop the NASA neutron detectors that helped discover water on the moon and Mars.

Similarly, Los Alamos Fellow Ed Fenimore designed the gamma-ray trigger for nuclear-event detection, then used his expertise to design the sensor that alerts NASA's SWIFT satellite of a gamma-ray burst.

Although scientific collaborations kept the mental juices flowing, the program endured because it attracted bright, exceptionally talented scientists and engineers, then passed the torch to them.



Dors is a prime example. As a NASA graduate research fellow, before joining Los Alamos, he built plasma sensors for ionospheric sounding-rocket experiments. Marc Kippen, the project leader in charge of fielding x-ray instrumentation, is another example, as is Dave Smith, a project leader responsible for electromagnetic pulse (EMP) detection. (See "Nuclear Detection 101.") Kippen began working on the detection of gamma-ray bursts as a graduate student and continued that work as a postdoctoral student and research scientist with several universities and NASA. Smith, a confessed radio-hardware junkie, has worked in the satellite EMP group since completing his first year of college in 1989.

Proud of "their" instruments, the three project leaders are equally proud of the teams that make those instruments work.

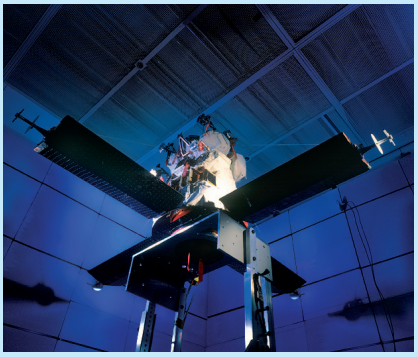
"Some of our technicians have been with the program for decades," explains Kippen. "They're the ones that carry the mission memory. They know, for example, that if you anchor the circuit board 'this way,' instead of 'that way,' it will survive the launch *and* the severe temperature changes that occur every time the instrument rotates in and out of the sunlight."

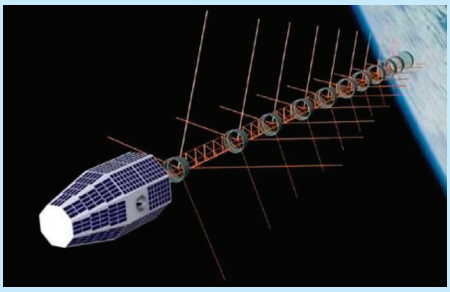
Success is also due to the program's sponsors, an interagency group that is part Department of Energy and part Department of Defense. Anything but timid, the sponsors have aggressively funded technology that provides capabilities way ahead of the present-day requirements.

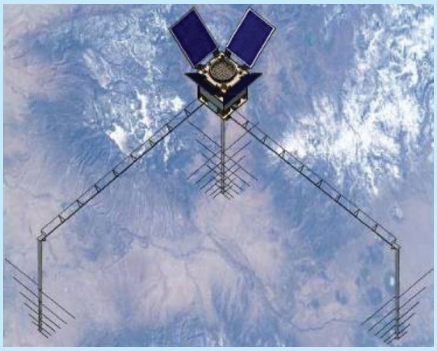
Changing of the Guard

The last of the man-sized Velas was sent skyward in 1969. It was followed into space by the enormous,

Left: A Vela satellite under construction. Above: A Defense Support Program (DSP) satellite deploys from the Space Shuttle Atlantis, carrying instruments that detect nuclear events in space and monitor space weather. The photo is unique; all other DSPs were deployed from rockets.







Validation Experiments

The instrumentation required for monitoring in the post–Cold War era was challenging to develop, so as soon as new technologies became available, they were incorporated into instruments. Los Alamos then had to validate these "higher risk" technologies for space use. To do so without impacting existing programs, the Laboratory built its own small satellites and had them launched into space with the prototype instruments on board. It was the ultimate "trial-by-fire."

ALEXIS (Array of Low-Energy X-Ray Imaging Sensors, launched in 1993) was the first—a small satellite that tested sensors sensitive to the lower-energy x-rays that might come from a nuclear device. It was followed by FORTE (Fast On-orbit Recording of Transient Events, launched in 1997), often described as an antenna with a satellite attached. FORTE addressed how one might better detect an EMP but also had two Sandia-built optical packages for investigating terrestrial optical emissions.

The Cibola Flight Experiment (CFE) was launched in 2007 to test several revolutionary concepts for space-borne computing. Cibola's supercomputer was built from field-programmable gate arrays, chips that can be rewired at the touch of a software button. Errors induced in the non–radiation-tolerant chips by charged-particle bombardment could be corrected either in software or by rewiring the arrays.

All of the validation experiments are dual purpose, with pure science goals co-mingled with mission-oriented ones. ALEXIS, for example, carried a broadband radio-frequency (RF) receiver—dubbed Blackbeard—that mapped the RF coming from Earth. (This background sets a lower detection limit for EMPs.) Scientists using Blackbeard discovered a class of cloud-to-cloud lightning discharges that emit light and very high frequency (VHF) radio waves. The discharges proved to be the most-powerful type of lightning in the VHF band.

The mission response module is the latest validation experiment. Not a satellite, but a radio receiver, the module advances CFE technology and capability 100-fold in terms of processing speed. It will launch sometime in the future.

Left to right: ALEXIS, FORTE, and Cibola satellites.

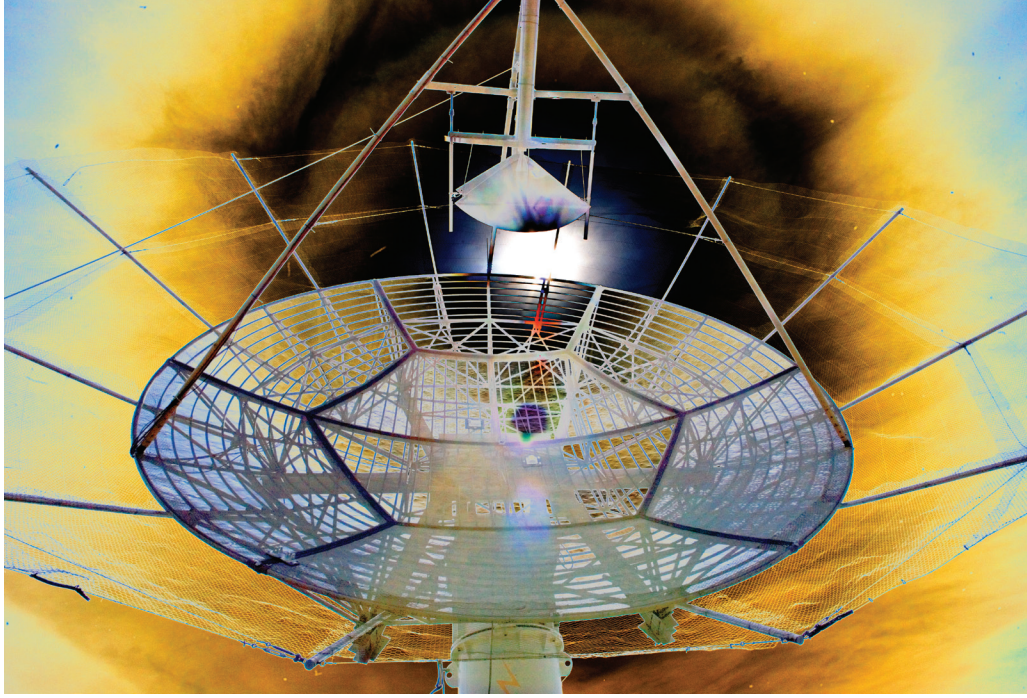
schoolbus-sized Defense Support Program (DSP) satellites, orbiting observatories that were optimized for detecting explosions in space and the upper atmosphere. First launched in 1970, the satellites carry 10 separate instruments that were developed, built, and tested by Los Alamos.

Monitoring the Earth's surface and lower atmosphere, originally done by the Vela satellites, eventually became the job of Global Positioning System (GPS) satellites—the same ones that made global navigation an easily accessible commodity.

"Few remember this, but nuclear-event detection was used as one of the original justifications for the entire GPS program," says Smith, whose EMP sensors (along with optical sensors built by Sandia) fly on the dual military- and commercial-use satellites.

The current system of 24 GPS satellites was declared fully operational in 1995—17 years after the first experimental one settled into its orbit. At least four satellites view any point on the surface of the Earth all the time. The downside to such complete coverage is that, for the EMP sensor, it increases a troublesome background: lightning, whose flash of light is accompanied by a burst of radio waves that can look very much like a nuclear EMP.

"A true nuclear explosion would obviously warrant the attention of the highest levels of our government," says Smith. "Lightning strikes the Earth approximately 100 times a second, and needless to say, we can't go tapping the President on the shoulder every time



The Los Alamos Portable Pulser produces an RF signal that mimics what would come from a weapon. The signal, broadcast into space through this dish antenna located near the Lab's Physics Building, is used to calibrate EMP sensors on orbiting satellites.

there's a lightning flash."

Sensing the New Nuclear World

A sensor triggered by some event outputs a signal that is then evaluated to determine what kind of event it was (nuclear or other). Ground-based computers do most of the evaluating—very little is done by the instrument's relatively simple computer. (It takes so long to design and validate radiation-tolerant computer chips that a space computer, at liftoff, is significantly less powerful than what's available commercially.)

The next-generation instruments are different. Kippen's team, for example, developed the combined x-ray spectrometer and particle dosimeter (CXD) by using advanced technology to integrate the two instruments into a single, more-capable x-ray sensor system. The particle detectors monitor the space environment, and the system uses that information to help assess whether events seen by the spectrometer are nuclear. In-depth testing ensured that the new technologies would work in space. (See "Validation Experiments.")

CXDs are already in orbit. First launched on a GPS satellite in 2001, they now enter space at the rate of two or three per year.

Smith's team has engineered a next-generation EMP sensor—the burst detector-verification (BDV) sensor—that will carry out a huge amount of computation and data storage compared with its predecessors. The sensor makes use of software algorithms and a relatively sophisticated pair of computers (think 10-year-old desktops) to do on-board processing of events. The first BDV will be launched in the spring of 2009.

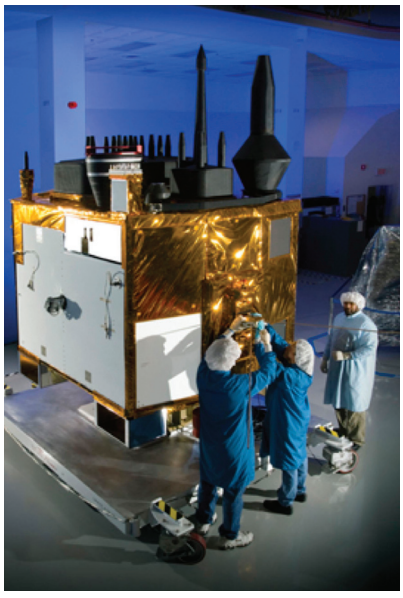
The group's newest instrument, built by Dors' team, is the space and atmospheric burst reporting system (SABRS), a highly modular package for detecting neutrons and gamma rays. It combines the 10 instruments on the DSP satellite into one compact package that is smaller, consumes less power, and weighs half as much as the old suite of instruments. Employing advanced on-board signal processing, SABRS autonomously evaluates a signal to determine what data must be sent to the ground for further processing.

SABRS' compact design heightened the importance of understanding how the radiation sensors respond to and are affected by natural backgrounds. To test the new sensor technologies, the team developed SAVE, or the SABRS Validation Experiment. ("We like acronyms so much that we double up on them," notes Dors wryly.) SAVE was launched in November 2007 on the 23rd (and final) DSP satellite.

These new instruments will help the satellite nuclear detonation detection program continue its monitoring mission. To the extent that monitoring inhibits treaty violations, that mission has been staggeringly successful—the last above-ground detonation occurred more than a quarter of a century ago. That's led some to question a program that essentially finds nothing—the so-called "silent sensor quandary."

Mark Hodgson acknowledges the criticism but raises a counterpoint. "The probability of a nuclear explosion occurring is probably pretty low, but the consequences would be extremely high. We think the scales are tipped such that monitoring is worthy of continued support from the President. And the President always backs us up." ❖

—Jay Schecker



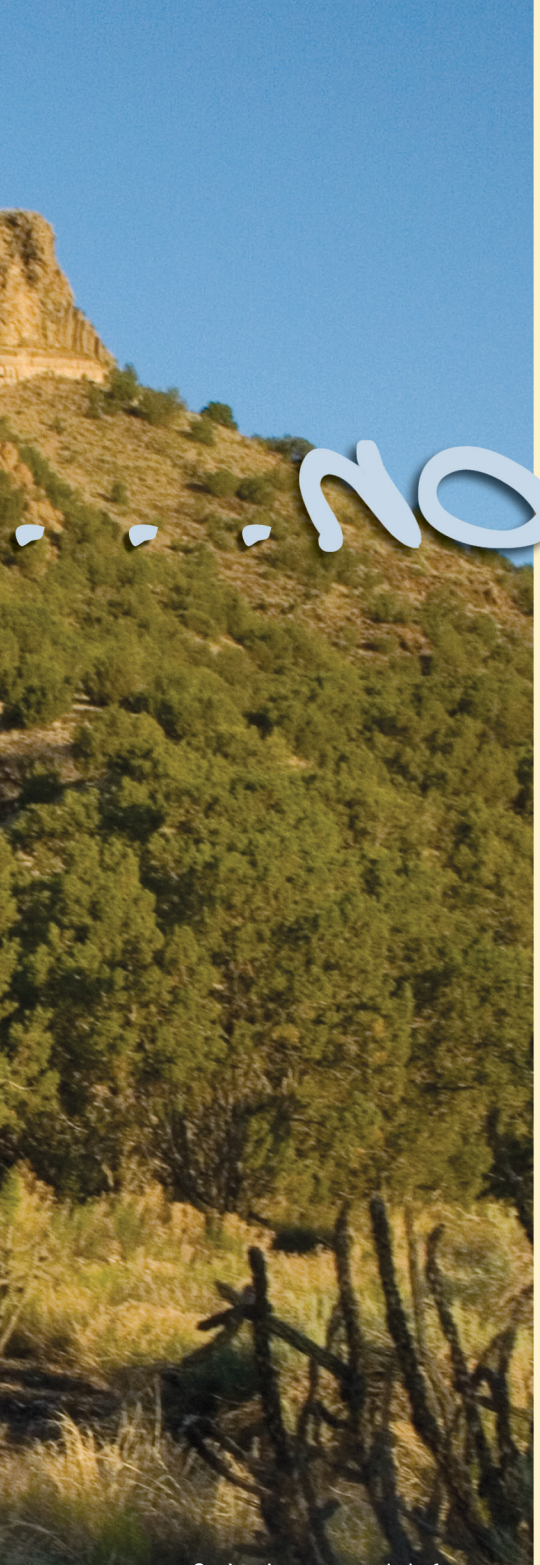
The antenna for the next-generation EMP sensor, BDV, is installed on a GPS satellite.

Retrovision . . .

Reversing Time to Find Wave Sources

Retrovision . . .

Members of a Los Alamos team are reversing time to find invisible cracks in mechanical parts or watch the source of an earthquake develop. They may even be able to locate the sources of faint subterranean vibrations called tremors, which could be used to predict large earthquakes.



Carène Larmat stands before a "Toreva block" located near the Rio Grande river, several miles east of Los Alamos. A long time ago, the block broke off from the peak seen behind it in the photo. Its impact with the ground produced a very small earthquake. Larmat uses time reversal and computer modeling to form images of the sources of earthquakes and other seismic events.

Retrace your steps. It's a good way to find lost items: your glasses, your keys . . . the TV remote. It can also be a good scientific way to find things. Just ask Paul Johnson.

The Los Alamos geophysicist heads a team that uses time reversal—a technique that relies on the ability of waves to retrace their steps to their source—to find defects inside mechanical parts or to locate the sources of earthquakes deep underground.

Time reversal is quite different from most techniques that use waves as locators. Consider radar, for example, which uses radio waves to track planes. A radar unit emits a brief pulse of radio waves in a beam that travels through the air, bounces off a plane, and returns to the unit's receiver. The speed of the waves is known, so one can use the round-trip time to calculate the distance to the plane. Moreover, the beam's position when it bounces off the plane can be used to calculate the plane's angular coordinates. Clearly, radar tracking involves a lot of calculating.

By comparison, time reversal is a no-brainer, as Johnson points out. In time reversal, one first records the waves that travel from a source through a medium and are recorded at any number of sensors during a specified time interval. A set of time-reversed signals is then created by "flipping" the recorded signals: the last wave recorded becomes the first wave in the time-reversed signal. These new signals are then "broadcast" back into the medium from the same positions where they were recorded. Some time after the broadcast starts, major portions of the time-reversed waves converge back at the source—as if one had filmed the circular waves produced when a pebble is dropped into a pond and then had run the film backwards.

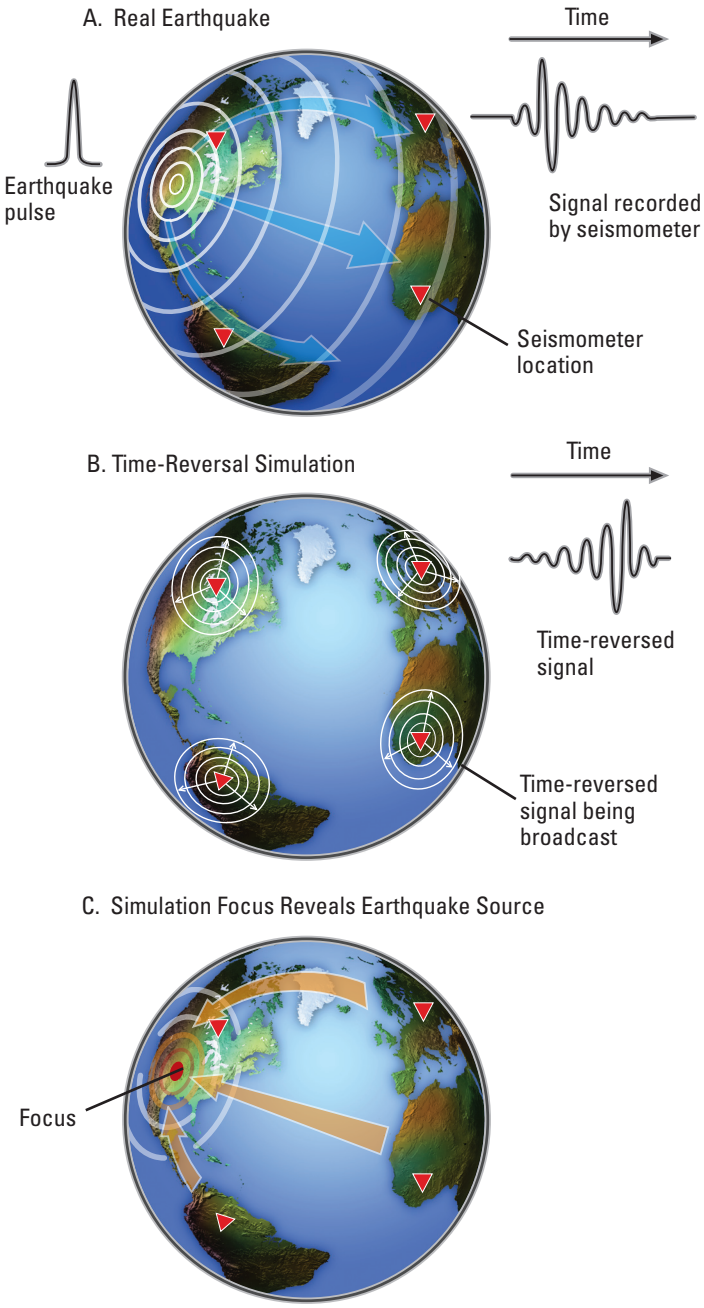
If the source location is unknown, time reversal can usually find it. Moreover, if the recording captures the higher-frequency waves—those with short-enough wavelengths—time reversal can often reconstruct the source's physical extent and evolution in time with remarkable detail.

Using Time Reversal to Find the Source of an Earthquake

A. An earthquake creates a relatively brief pulse of seismic waves. The waves fan out in all directions and can be recorded by faraway seismometers. Because they take different paths through the Earth's various layers, some waves arrive at a seismic station later than others, and the recording produced by the seismometer is much longer than the original pulse.

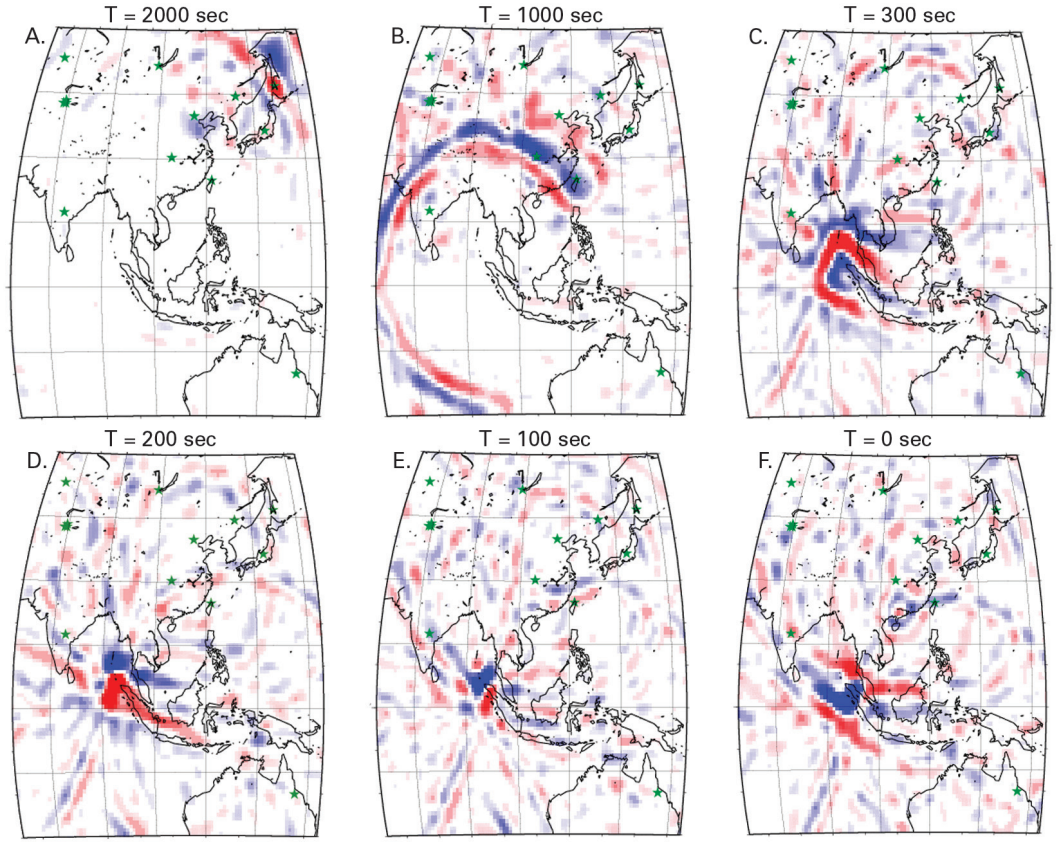
B. A time interval containing the earthquake data is chosen from each seismometer recording. The signals are loaded into a computer and flipped around in time so that waves that took the longest to arrive at the station become the first waves of the time-reversed signal. A computer simulation is then run, wherein the appropriate time-reversed signal is "broadcast" from each seismic station into a simulated Earth. Once again, waves fan out in all directions.

C. As waves propagate out from each seismic station, portions retrace (in reverse) the original paths between that station and the earthquake source. These portions all arrive at the source simultaneously and combine to produce a large enhancement of the wave amplitude—a focus.



Time reversal achieves this great advantage over other wave-locator methods by using the information contained in all of the waves that reach a sensor during the recording interval, including waves of different types, waves that come directly from the source, and waves reflected from boundaries. Each recording therefore contains wave information also present in recordings from other sensors, as well as information that complements the information from other sensors. As the time-reversed waves converge on the source, the duplicated information adds up to form a high-amplitude wave, or "focus," at the source, while the complementary information fills in other details about the wave's shape. As a result, time reversal reconstructs the behavior of a source clearly and completely.

Carène Larmat, a postdoctoral researcher who works with Johnson and Lianjie Huang, has used time-reversal simulations to find the sources of several major earthquakes (see box above). Her work aligns with Los Alamos National Laboratory's national-security mission, which includes distinguishing natural seismic events from underground nuclear explosions. Time reversal



Simulation showing time-reversed motion of the seismic waves produced by the 2004 Sumatra earthquake. Panels A–C show seismic waves beginning to converge, while D–E show the waves forming a strong focus (as indicated by the single pair of thick blue and red lines) at the earthquake's source. At T = 0 seconds (Panel F), the fault began to rupture. Most of the seismic energy was released about 100 seconds later, which is why Panel E shows the most-intense focus of waves. Panels D and E also reveal that the source moved north. Other researchers observed the same source motion using existing source-location techniques.

may also allow scientists to measure the depth at which a nuclear explosion occurs, information that is usually hard to obtain.

Johnson's team, however, is finding lots more applications. The technique can be used to find and image cracks and/or material separations (delaminations) in mechanical parts. The method is currently being developed as one of the many diagnostic techniques used to inspect weapons and could easily transfer to industry for examining machine parts.

Paul Johnson, artist and time-reversal project lead, in his studio in Nambé, not far from Los Alamos.

But the most-exciting application of time reversal may be to locate the weakly vibrating subterranean sources known as tremors—because tremors may be key to predicting large earthquakes.

Earthquakes and Tremors

For more than a century, scientists have searched for a reliable way to predict large earthquakes. Strange clouds, radio emissions, water level in wells, unusual animal behavior, and more have been tried—but none have proved useful. However, a short article that appeared in the journal *Science* last January indicates that tremors—faint, low-frequency vibrations in the Earth that can last for weeks—could be the long-sought predictive signal.

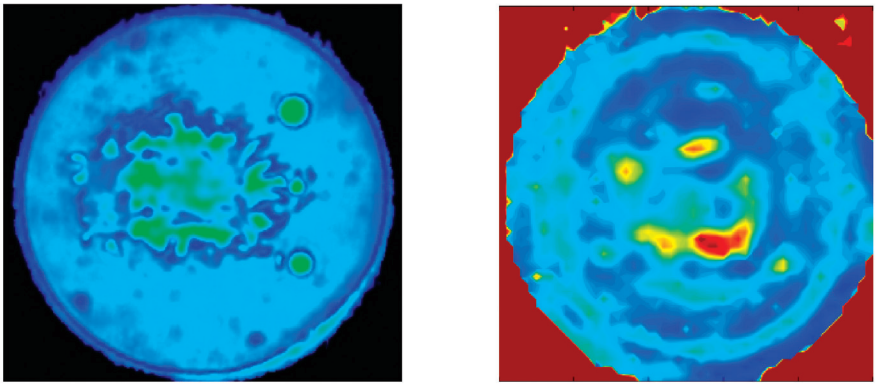
"I never thought earthquake prediction would happen in my lifetime," says Johnson. "But the idea that tremors could be used to predict large earthquakes is being tested today, and we're in the thick of it."

Tremors create waves that are often detected at the same time as low-frequency earthquakes, which are too small to do any damage themselves but sometimes appear just before a large earthquake. Thus, an increase in tremor activity could mean a "big one" is coming.

However, finding tremor sources is difficult because the method now used on earthquakes doesn't work with tremors.

Most earthquakes are associated with boundaries

between tectonic plates, for example, in "subduction zones," where one tectonic plate, moving perhaps a couple of inches per year, serenely passes beneath another. The area where the two plates overlap is called a "subduction fault."



The linear-elastic (left) and nonlinear-elastic (right) responses of a laminated disk. The bright spots at right are where delamination has occurred.

At some point, parts of the plates stop moving because of increased friction over a region of the fault covering hundreds of square miles. Eventually, the mounting stresses overcome the friction, and the plates abruptly start moving again, releasing a huge pulse of energy and generating seismic waves that travel through the Earth and over its surface. Seismic waves can be detected thousands of miles from their source by a seismometer. In the seismometer's otherwise mostly flat output, an earthquake looks like a succession of "blips," each one signaling the direct arrival of a wave produced by the fault "rupture" or the delayed arrival of a wave reflected from one or more boundaries between layers in the Earth.

To locate an earthquake's source, one first uses the blips to determine the difference between the direct arrival times of two types of wave: "shear" and "pressure" waves. Using that difference and a "velocity model," which describes how the speeds of the two types of waves change in the various media composing the Earth, one can then find the distance from the source to each station. Usually the distances from three or more stations are used to locate a source.

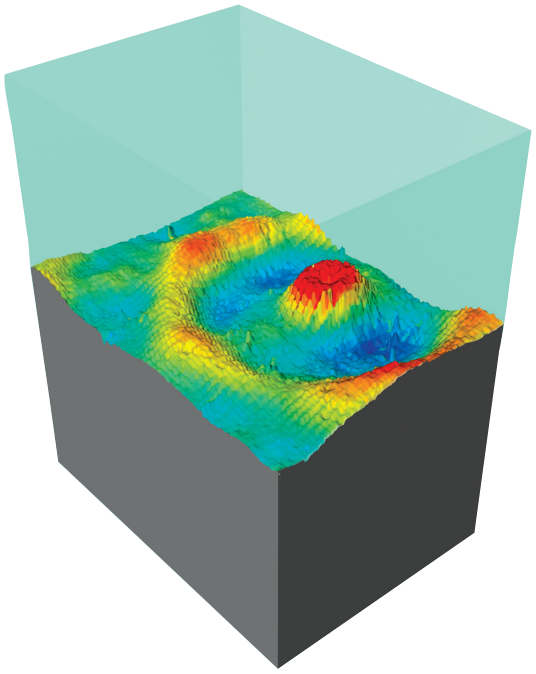
The problem with trying to locate the source of a tremor is that a tremor signal has no blips. Instead, the signal is a nearly continuous, low-frequency tone or simple combination of tones lasting from minutes to days. With no clearly defined events in the seismic signal, it is impossible to find the source of a tremor in the usual way.

Moreover, the signal can be almost too faint to be distinguished from "noise"—unwanted signals produced in a seismometer by such things as a passing truck or the wind. "In fact," Johnson says, "scientists first thought tremor signals *were* noise." Later, however, sophisticated techniques discerned subtle correlations between signals recorded at the same time but at different locations. The correlations indicated a common source—that of the tremors. Scientists have since determined that tremor signals often slowly emerge from the noise, then sink back into it.

Larmat is optimistic that time reversal can locate the sources of tremor. While a postdoctoral researcher at the California Institute of Technology, Larmat used the technique to study glacial earthquakes that had recently been discovered in Greenland. Their signals, like tremor signals, are nearly buried in noise, but time reversal was able to locate their sources.

Recently, Larmat ran a simulation and was able to find the source of a computer-generated tremor signal. She is about to try again, this time using real tremor data.

Johnson is not surprised the method works so well. "Time reversal is incredibly robust," he says. "It's almost impossible for it not to work."

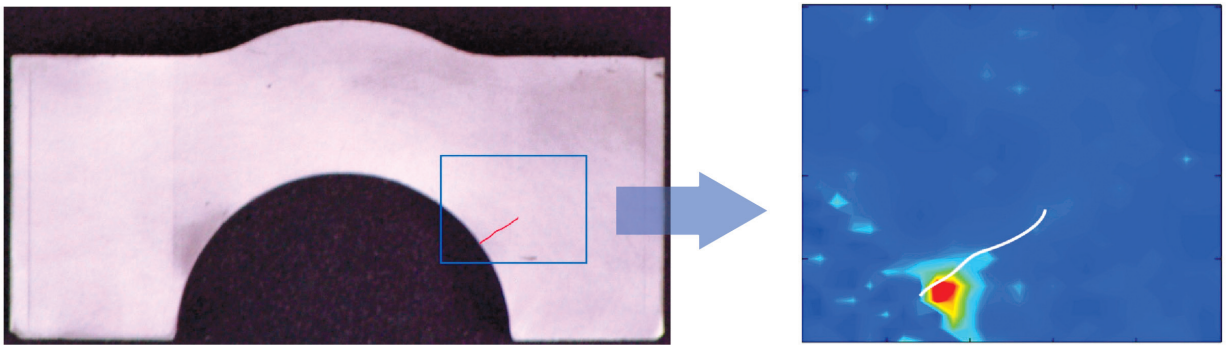


Seeing Cracks and Delaminations

Another member of Johnson's team, T. J. Ulrich, uses time-reversed sound waves to image cracks and delaminations in solid parts. The technique can detect damage invisible to existing sonic techniques or x-rays.

The method evolved from Johnson's pioneering work in "nonlinear elasticity" and uses the fact that a part's response to sound energy is dramatically changed by cracks or other damage.

Left: Laser vibrometer recording of time-reversed sound waves converging to form a focus at a defect in a glass (top)/metal (bottom) interface in an experiment—proof that time-reversed sound waves can be used to find buried structures.



Time-reversed nonlinear-elastic analysis of a bearing cap reveals a crack (red spot at right) that is invisible to conventional acoustic techniques or x-rays.

To detect this change, Ulrich bathes an object in sound waves at two frequencies. This action makes the object "ring" like a bell. An intact object will ring at only the original two frequencies (a "linear-elastic" response).

However, a damaged object will ring at many new frequencies as well because each damaged region responds in a nonlinear-elastic fashion. The two original waves become mixed at the damage sites and produce lots of new waves at many frequencies. Ulrich detects damage by seeing if any new frequencies show up.

Of course, knowing that there's a crack or delamination somewhere in an object is not enough. It's best to actually see the damage. To do so, Ulrich has adapted a technique that Mathias Fink, the father of time reversal with sound waves, originally developed to find and destroy kidney stones.

Ulrich simultaneously sends two wave pulses, each at a different frequency, into an object to make it ring. He then records the response with an array of sensors and filters the signal from each sensor to remove all but one of the new waves produced by damage in the object. For each sensor, he now has a signal whose sources are only the damaged regions. Time reversing and sending all the signals back into the object focuses acoustic energy on those sources.

At the same time, Ulrich scans a laser vibrometer over the object's surface to measure how the surface moves, ever so slightly, up and down at each point. Since the damaged regions are now the focus of the sound energy, they vibrate more vigorously than the surrounding regions, bringing the location of cracks and delaminations to light.

The Future

Johnson's team has also used sound pulses to measure the nonlinear-elastic response of bone. In this case, the "damage" providing the nonlinear-elastic response consists of microcracks. Microcracking makes bone fragile, a condition associated with osteoporosis, in which bones become more porous than normal.

Initial experiments have shown the method to be far more sensitive to such damage than were existing measurement techniques. Moreover, the new technique does not use x-rays, which are currently used to detect bone density and indirectly infer bone integrity.

Johnson tries not to get heady over the potential uses of time reversal. He notes that many aspects of the technique are not well understood, such as how the presence of the sensor affects the focus of the time-reversed signal. But aside from such subtleties, time reversal may, in the future, be used to find all sorts of things, including ways to prevent the disastrous outcomes of large earthquakes. ❖

—Brian Fishbine

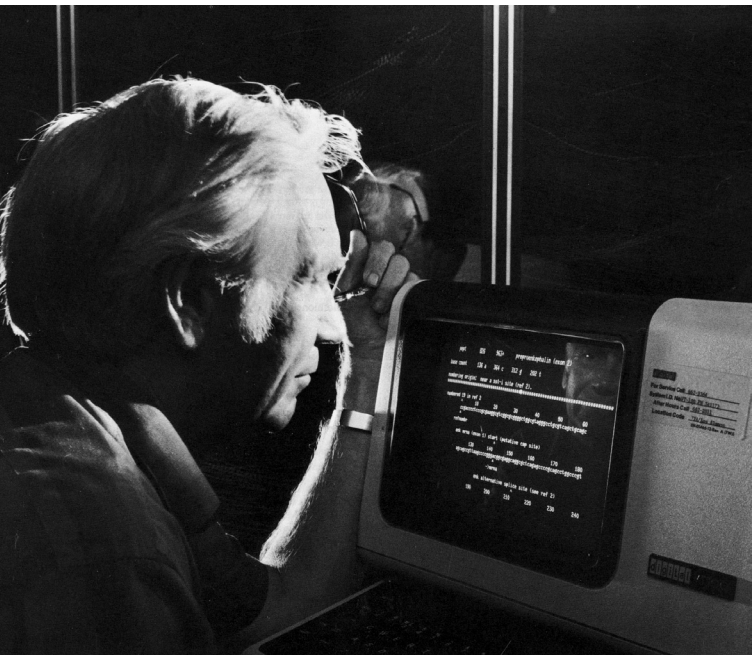
Members of the time-reversal team meet for morning espresso. Left to right: T. J. Ulrich, Carène Larmat, Michele Griffa, Paul Johnson, Pierre-Yves Le Bas, and Brian Anderson. Not shown are Los Alamos scientists Lianjie Huang and Jim TenCate and university collaborator Robert Guyer.

The Legacy of GenBank

The DNA Sequence Database That Set a Precedent

DIALOGUE

This year the life sciences research community celebrated the 25th anniversary of GenBank, the computerized database originally founded at Los Alamos to contain the information encoded in the genes of all life on Earth. Here, GenBank's legacy is discussed by early members of the GenBank team: Gerald Myers, eventual founder of the genetic database for the AIDS virus, a GenBank offshoot; Christian Burks, now president of the Ontario Genomics Institute; and Chang-Shung Tung, current leader of the Los Alamos Theoretical Biology and Biophysics group.



Walter Goad, founder of GenBank, studies a DNA sequence.

1663: Los Alamos is primarily a physics lab, so how did GenBank, come to be established here?

Tung: In the 1960s leading Los Alamos theoreticians, including the mathematician Stan Ulam and physicists Jim Tuck, George Bell, and Walter Goad, became fascinated by the revolution in biology—the ability to manipulate DNA and to understand how it controls an organism's development and replication. Goad, who later founded GenBank, liked to point out that biology was unlike anything known in physics because a single molecular change in DNA, a mutation, could be faithfully cloned millions of times in an organism, and then one could actually examine the mutation's consequences with the tools of physics and chemistry.

These scientists met weekly for over a decade, and when DNA-manipulation tools made it possible to determine the sequence of building blocks in a DNA molecule, they became interested in using mathematical analysis to study the patterns of information contained in those sequences.

1663: So how do you decipher that information?

Tung: The information is determined by the order in which the basic building blocks—the four nucleotide bases known as adenine (A), thymine (T), cytosine (C), and guanine (G)—are strung along a strand of DNA. Based on mathematics and the rule of parsimony, theoretical physicist George Gamow proposed that every three consecutive bases in a protein-coding gene was a three-letter word specifying one of the 20 possible amino acids that make up a protein. Gamow's basic concept was correct, but scientists took 10 years to crack the genetic code—the code that tells you which triplet of bases (called a codon) stands for which amino acid. It was done through test tube experiments using synthetic pieces of DNA.

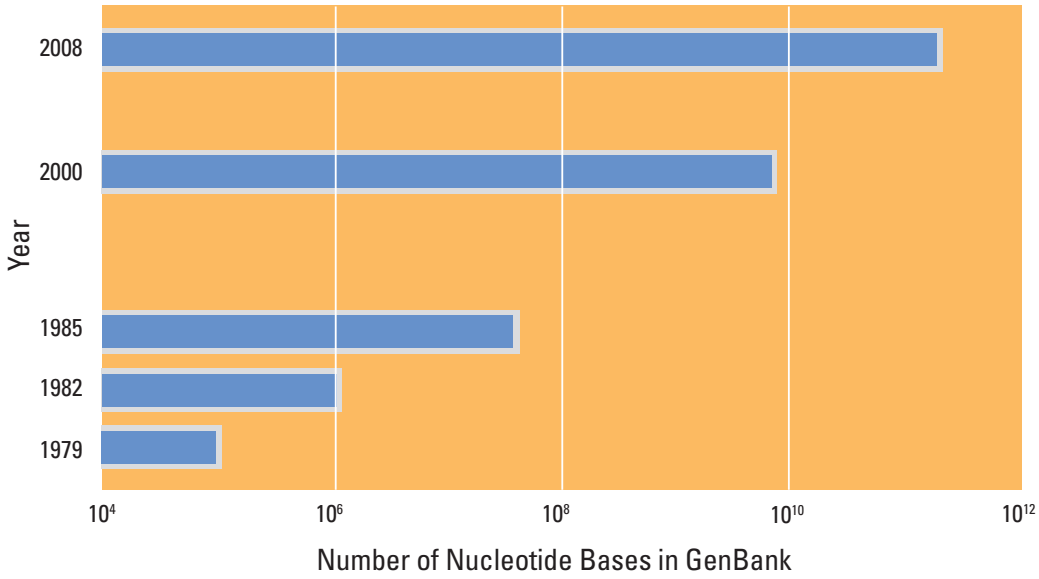
Myers: The first really interesting published sequence was not for DNA but for an RNA molecule known as transfer RNA (tRNA), which carries a single amino acid and takes part in protein synthesis. It took a year to determine the exact sequence of the tRNA's 75 bases, but the result led to an understanding of the role tRNA plays in the creation of proteins.

The completed sequence revealed an exposed loop of three bases identical to a codon of a protein-coding gene. It was then clear that tRNA was the adaptor molecule that Francis Crick, a decade earlier, had predicted must exist to serve as a chemical bridge between a codon in a gene and the corresponding amino acid. Discovering that triplet of bases on the tRNA molecule, the carrier of amino acids, showed how the genetic code was implemented in the cell.

Burks: That first sequence was published in March 1965, and it took almost a year to crank it out. A decade or so later, sequencing really took off when Fred Sanger in England and Allan Maxam and Walter Gilbert at Harvard published much more rapid sequencing methods for DNA. Academic groups began producing sequences hundreds and thousands of bases long, and computers became essential for sequence storage and analysis.

Tung: People from throughout biology immediately saw how DNA sequences could be used to pinpoint and track genetic

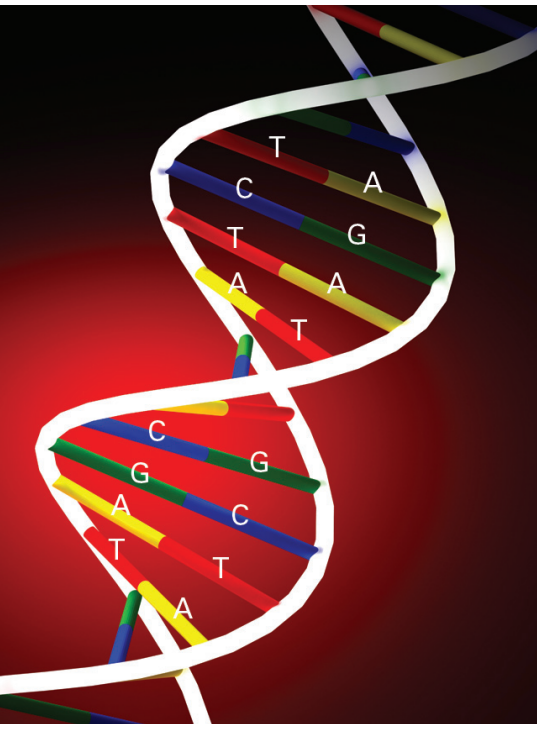
Right: The growth of sequence data in GenBank.



changes. Data began to accumulate very rapidly. In 1979, a meeting was organized at Rockefeller University to discuss how these sequence data could be collected and managed for public dissemination. Mike Waterman and Temple Smith, who attended that meeting, reported on it and convinced several Los Alamos people, including Walter Goad, to think about developing a data bank for DNA sequence information.

Burks: By then, George Bell and Walter Goad had started the Theoretical Division's new Theoretical Biology and Biophysics group. They, along with Charles DeLisi, who later helped start the Human Genome Project, were dedicated to bringing the mathematical and computational prowess of theoretical physics to bear on molecular biology. Walter wrote the proposal for "The Los Alamos Sequence Library," which got funding from Laboratory-Directed Research and Development, the discretionary research program at Los Alamos.

Other groups around the country were also interested in starting a database, but Los Alamos moved quickly and in 1982, in partnership with BBN Laboratories, a Cambridge, Massachusetts, engineering company, won a competitive bid for a public sequence database to be sponsored by the National Institutes of Health (NIH). That's when the name changed to GenBank.



Francis Crick, James Watson, Maurice Wilkins, and Rosalind Franklin's double-helix DNA structure.

1663: Was there something special about the Los Alamos proposal?

Burks: On one hand, some thought the NIH should never trust such a database to "those weapons mongers" in Los Alamos. On the other hand, Los Alamos had people with very bright, very agile minds who didn't care about disciplinary boundaries and were quick to get things going. None of those people came from molecular biology and DNA sequencing, but they all came with an incredible endowment of intelligence and experience.

In addition, Goad proposed a remarkably community-focused strategy for providing access to the sequence data. His model was wide open: talk to anyone, take suggestions from anyone, share data with anyone. This strategy is still reflected in GenBank's ongoing productive collaborations with two other such databases—the EMBL Data Library in Europe and the DDBJ in Japan.

1663: Were Los Alamos computers a factor in the NIH choice?

Burks: Goad certainly pitched our computational resources, but building the database was primarily a word-processing task, so over the first two years, the project migrated off the big mainframe computers and onto a single personal computer in Walter's office. The project later became one of the first at Los Alamos to adopt Sun Microsystems workstations and the Unix operating system. We were probably the first group worldwide to adopt Sybase's relational database management system for molecular biological data.

Myers: In those early days, all the sequences appeared in published papers first, so GenBank hired typists to enter them into the database manually. When a new sequence of special interest to one of us was published, we'd elbow a typist to put it at the front of the line because we were so eager to get it into GenBank and start the analysis.

Christian Burks, president of the Ontario Genomics Insitute

Burks: Very soon after GenBank began, personal computers and portable electronic media were taking hold, and it became possible for authors to submit their sequence data electronically, eliminating retyping. We knew that using electronic media would be essential to GenBank's keeping up with the ever-increasing rate of new published sequences, so we lobbied the NIH for increased resources to build up the infrastructure. GenBank's second 5-year contract quintupled the project budget. This allowed us to implement the electronic publishing paradigm, including developing the computing infrastructure to monitor the flow of electronic data.

In addition, we lobbied the journals to require authors to electronically submit their data directly to Los Alamos before publication. It was a radical proposal that stirred up a heated debate about everything from the autonomy of journalists to the civil liberties of scientists. But the interest in making the data quickly available carried the day, and in a couple of years, most journals went from saying "never in our lifetime" to making electronic submission a requirement. That set a precedent for the Human Genome Project as it was getting off the ground in the late 1980s.

Myers: Data accuracy was a key issue, however, and people began to worry about totally fallacious sequences getting into GenBank. Once in there, they'd be very, very difficult to get out.

We actually had such a case. A viral sequence that turned out to be from a monkey was thought to be a new form of the human AIDS virus. It stayed that way in GenBank's human category for a decade before being corrected. Taking in the influx of new sequence data was like drinking from a fire hose all the time; once stuff got into GenBank, we had no time to go back and review it. Also, sequence analysis was not part of the charter for GenBank, which was focused first on being a complete, current archive. That fact ultimately led to specialized databases that could curate the data in a more leisurely manner.

1663: GenBank started a specialized database for the AIDS virus. Did that include sequence analysis?

Myers: Yes. In 1986, soon after an isolate of the AIDS virus was first sequenced, GenBank was funded by NIH to start a combined sequence database and analysis center for HIV. We thought the project would run about a year, but the virus mutated very rapidly within a single individual, so we soon learned we could expect a flood of widely varying viral sequences from around the world. NIH tripled our funding, and the project is still ongoing.

1663: What have you learned?

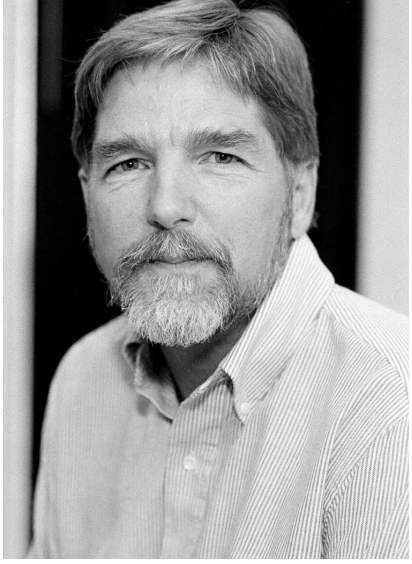
Myers: Our initial focus was on molecular epidemiology, tracking AIDS outbreaks through the sequenced viruses rather than through people. We helped assess the virus's average rate of mutation. We got involved in the France-United States dispute about who discovered the AIDS virus, and we helped the Centers for Disease Control track unexpected transmission pathways, like a dentist's transmission of HIV to his patients. The viral genes were rapidly identified from the sequences, the biology of the virus became apparent very quickly, and sequence analysis helped with the development of a drug cocktail. But the virus mutates so rapidly that vaccine development has been all but impossible.

Tung: There might be new hope on the horizon. Bette Korber, a scientist in the Theoretical Biology group and the present leader of the HIV database, together with her team, is using the entire set of sequence information to derive three new vaccines: the "consensus," the "best natural," and the "mosaics." All three were developed to target viral strains across the globe. Extensive animal tests are underway, and the results look quite promising. Small-scale human trials are in the initial stages of planning. These vaccines might finally deal a lethal blow to the AIDS virus. Bette won the 2004 E. O. Lawrence Award in life sciences for her work on this front.

1663: Are there other exciting developments on the horizon?

Tung: AIDS researchers are planning to use new machines that in one run—only hours—can sequence the DNA from 100,000 different viral particles found in a single human being. The result will reveal the diversity of the virus within an individual. Continued sampling and sequencing can then be used to track how that diversity changes under medical treatments.

Burks: A related development is metagenomics, an approach started by Craig Venter to sequence, en masse, the DNA from a broad spectrum of organisms in an environmental sample—say, a liter of seawater or a few tablespoons of

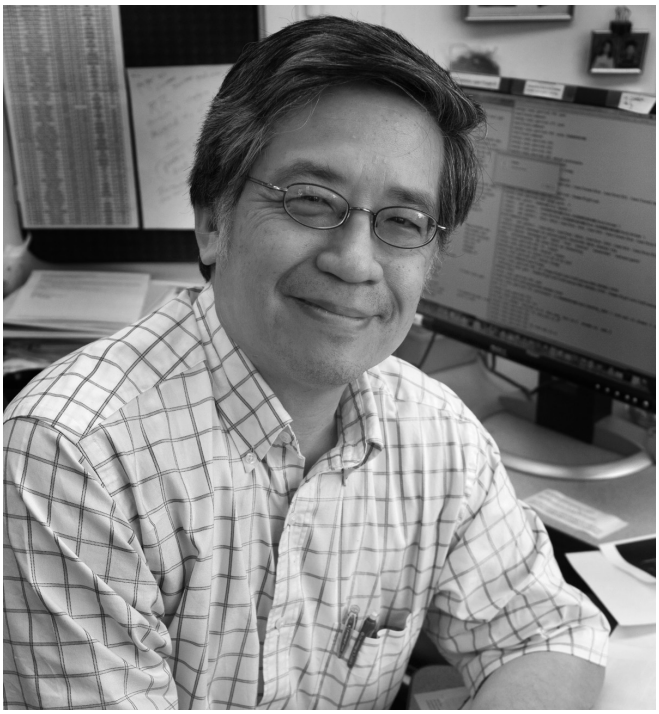


Gerald Myers, founder of the HIV database

soil—and use computational analysis to tie sequences to separate genes and species. It's nearly impossible to isolate and cultivate the species individually before sequencing. Information from such work can eventually be applied to developing new industrial enzymes or harnessing bacteria for environmental cleanup.

The Ontario Genomics Institute is funding the development of DNA barcodes, a short stretch of DNA that is 700 nucleotides long and that is found in a mitochondrial gene in every animal on Earth. By sequencing 10 examples of that stretch from each of a half-million species, we can build up a database of barcodes that would enable nearly automatic species identification for most animals. This will have a tremendous impact on regulatory or forensic proceedings in which exact knowledge of the species involved can make a difference in the outcome.

Myers: If we consider that the human body contains about 10 bacterial cells for every "human" cell and that the entire human genome contains an overwhelming number of sequences from viruses, we start to see a human being as a community of microbes. DNA barcoding might begin to show human diversity not just at the genomic level but also at the level of the microbes that a body contains. Both our metabolism and our mental state may depend on the organisms we're carrying around in addition to the genes we've inherited.



Chang-Shung Tung, leader of the Theoretical Biology and Biophysics group at Los Alamos

Burks: We're also finding surprising variations in the structure of the human genome. For example, the number of copies of a given gene can vary widely from individual to individual. If those regions code for a particular protein, they may lead to different amounts of that protein in different individuals, and the "extra" copies could be a signal that the protein is evolving new functional capabilities in that individual.

Myers: Those protein differences could have an impact on human behavior. There are multiple copies of regulatory elements, the promoter genes that are involved with controlling serotonin production. As that copy number increases, the chances for depression increase. That's an excellent example of how multiple copies of regulatory elements affect particular traits.

1663: How fast have sequence data been accumulating?

Burks: The sequence database has been doubling every 18 months since 1979. I remember the official memorandum announcing that tea and cookies would be served to celebrate entry of the first 100,000 nucleotides into the Los Alamos Sequence Library. We hit a million bases in March 1982 and had a wild celebration. Now the number is about 200 billion bases.

1663: Are databases prepared to handle and support analysis of metagenomic data?

Burks: GenBank, which has been run by the NIH since 1992, now has a section called Whole Genome Sampling that is specifically designed to archive the information from metagenomic sequencing. With metagenomics data, you don't necessarily know right away what organism the individual sequences came from or even what gene an individual sequence is associated with. It's a challenge to organize and annotate metagenomic versus traditional sequence data.

1663: Any last words?

Burks: In looking back I would say that Los Alamos has had a tremendous impact on the world through GenBank. Los Alamos got this endeavor off the ground through scientific freedom within the Lab, interdisciplinary freedom, and a strong, competitive student and postdoctoral program that attracted bright new minds to Los Alamos to explore new frontiers. It's been incredibly enabling for the whole world.

Tung: Los Alamos is holding a colloquium on August 5 to honor this proud legacy, and Mike Waterman, Bette Korber, and Gerry will be speaking. ❖

—Necia Grant Cooper and Eileen Patterson

SPOTLIGHT

by Eileen Patterson

Pavlov's Bees

Take a little behavioral psychology, add sugar water, and what have you got? Trained bees. Bomb-sniffing bees.

In Pavlovian tradition, members of the Laboratory's Stealthy Insect Sensor project have used sweet treats to condition honeybees to respond to the chemical scent of explosives.

The bees extend their proboscis (tongue) when exposed to explosives. Team members have trained the bees to do this by rewarding them with a dose of sugar each time they react to the smell of explosive chemicals such as TNT and C-4. Proboscis extension is a reflex normally triggered by the presence of nectar.

Yum! A bee extends its proboscis in response to a delicious whiff of chemicals.

Like dogs, which usually get the scent-detection assignments, not all bees respond well to training, but the team has improved the odds by adding a memory enhancer to the sugary reward.

"I can't tell you the exact mix of this 'cocktail,'" project member Kirsten McCabe apologizes. "We're hoping to patent it." What she's willing to say is that it's made of enzymes that play an essential role in memory formation and that it includes that universal waker-upper, caffeine.

The trained bees ride five at a time in a toaster-size box, the Proboscis Extension Reflex Platform (PERP), which can be hand carried or mounted on a robot. The PERP concentrates scents and contains a camera that watches the insects.

"A software imaging program captures what the camera sees," says McCabe, "and signals a hit through an image on a monitor or an auditory tone." The tone can be turned off in situations requiring stealth.

Why use bees instead of dogs? They train faster, are less conspicuous, are cheaper to maintain, can work longer hours, and once inside their carrier, require no special handler. And they pick up scents at parts-per-trillion concentrations.

The bee system will be validated this summer in field trials with the Laboratory's protection force subcontractor, SOC LA. And it'll be featured on the Discovery channel series, "Next World," in an episode titled "Security in the Future," tentatively scheduled for September 5.

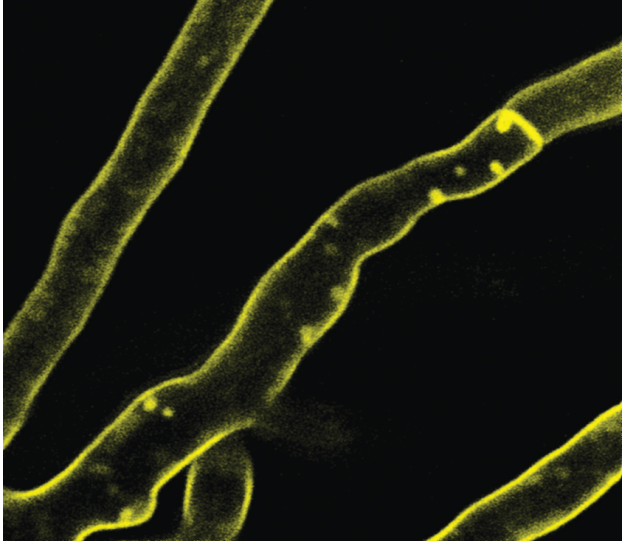
Besides McCabe, members of the bee team are Robert Wingo, Rhonda Robinson, and Sherri Sherwood, all drawn from the Laboratory's Bioscience, Computer, and Environmental Protection Divisions. Tim Haarmann, a Bioscience researcher, is a consultant.

From Fungus Food to Biofuel

The fungus *Trichoderma reesei* is exceptionally talented at getting the sugary food it needs, and the Laboratory's Diego Martinez thinks that skill could be put to good use making biofuel.

T. reesei makes enzymes, such as cellulases, that turn plant fibers into simple sugars. "It's actually the world's record holder for enzyme production," says Martinez.

Those enzymes might be the economical mechanism for turning plant material (biomass) into the sugars that are fermented into burnable fuel. Current conversion methods are too costly for potential biofuel sources such as switchgrass, wood from fast-growing trees, and agricultural crop residues.



It's not a squid. It's a fluorescence microscopy image of *T. reesei*, stretching out its growth filaments. IMAGE CREDIT: MARI VALKONEN, VTT TECHNICAL RESEARCH CENTRE, FINLAND

Martinez, a bioscience graduate student who splits his time between Los Alamos and the University of New Mexico, is part of a research team led by the Department of Energy's Joint Genome Institute and Los Alamos National Laboratory. The team has decoded *T. reesei*'s genetic sequence, looking for ways to enlist the fungus in the production of biofuels.

What team members learned about *T. reesei* was unexpected.

For such a prolific enzyme producer, the fungus makes only a surprisingly limited variety of cellulases. But it still outstrips other fungi in overall production.

How can that be?

"*T. reesei*'s enzyme-encoding genes are organized for efficiency," says Martinez, who led the analysis of the genome data. "They're in clusters instead of being scattered through the genome. An entire cluster is activated when the fungus encounters food, so all the genes go to work at the same time."

Martinez thinks scientists may now be able to supplement *T. reesei*'s limited-but-voluminous enzyme supply to create an improved enzyme "brew" for breaking down plant cells. They can either put additional enzymes into the mix or add genes to *T. reesei*'s genome so the fungus can produce more enzyme types.

Other Laboratory researchers involved in the work are Thomas Brettin, David Bruce, Chris Detter, Cheryl Kuske, Olga Chertkov, Melissa Jackson, Cliff Han, Monica Misra, Nina Thayer, Ravi Barbote, and Gary Xie.

A Cure for the Brittle Diamond

A diamond is a paradox. It's the hardest naturally occurring substance; you can't scratch it except with another diamond. But it's also brittle and prone to fracture. It can break if struck sharply enough or exposed to thermal extremes.

The diamonds we wear typically escape that fate, but industrial diamonds aren't so lucky. As essential components of drill bits and other cutting tools, they undergo serious punishment in the form of friction, impact, and high heat. As a result, they wear out, and so do the tools made with them.

U.S. Synthetic, a leading producer of diamond-enhanced cutting tools, has found an answer for the problem in a technology just licensed from Los Alamos National Laboratory: a composite of diamond (a crystalline form of carbon) and silicon carbide.

This superhard material was developed at the Laboratory by Yusheng Zhao, a staff member at the Los Alamos Neutron Science Center, and his former postdoctoral associate, Jiang Qian.

"The thermal stability, high thermal conductivity, overall toughness, and extreme durability of this material make it a perfect solution for extending the functional life of any tool," says Zhao, who won the Laboratory's 2007 Distinguished Licensing Award for his work transferring this technology.

A roller-cone drill bit equipped with teeth made of the Laboratory's newly licensed diamond composite.

Diamonds are breakable because intrinsic atomic-level misalignments in the stones can initiate cracks that, under stress, become fractures. In the new product, individual diamond crystals are caught in a silicon carbide matrix composed of ultra-tiny crystals (nanocrystals) thousands of times smaller than the diamonds they surround. The matrix stops cracks from growing beyond single diamond crystals, thereby preserving the integrity of the overall composite.

Says Zhao, "We developed a two-step synthesis process to ensure that silicon carbide completely surrounds each diamond and that the silicon carbide crystals remain extremely small to exploit the high fracture toughness of nanocrystalline materials."

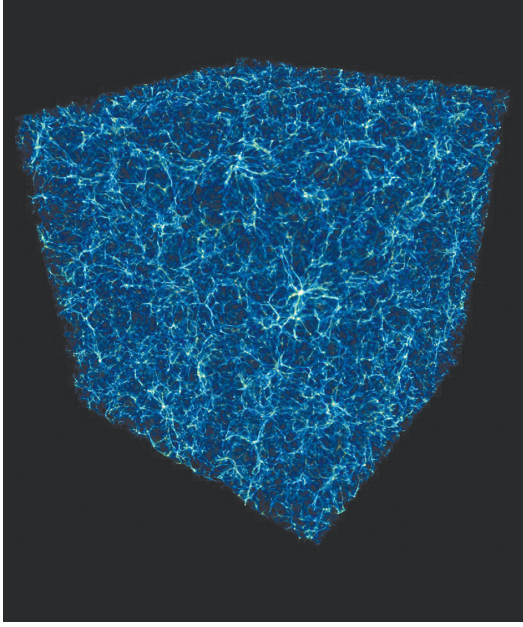
U.S. Synthetic will use the new material for mining and oil- and gas-exploration tools as well as for industrial bearings, wire-drawing dies, heat-sink devices for electronic devices, and other industry applications.

Out on a WHIM

In the universe, galaxies are only the tip of the iceberg. Or the tip of the mountain.

Brian O'Shea of the Laboratory's Theoretical Division says, "They're like the Pacific islands, which are just the tips of underwater mountains. Galaxies are only the tips of what's really there in the universe."

Normal matter, made of baryons (mostly neutrons and protons), accounts for only 4 to 5 percent of the universe. (The rest of the universe is dark energy and nonbaryonic dark matter, which neither emits nor absorbs light.) Only a small fraction of the baryonic matter is in the galaxies; the rest is in the intergalactic medium, a web of gas, varied in temperature, that stretches between the galaxies. Much of the intergalactic medium has never been detected, so exactly *how much* baryonic matter exists *where* is elusive information.



A portion of a supercomputer simulation of the universe, showing the filamentary intergalactic medium.

To find out, O'Shea and a team of university collaborators (led by the University of Colorado at Boulder) conducted the first supercomputer simulation that included both dark matter and baryonic gas in a model of the universe. The simulation incorporated virtually all of the known physical conditions of the universe and modeled a region more than 1.5 billion light-years across (one light-year equals about six trillion miles of space).

The results, reported last December in the *Astrophysical Journal*, suggested that about 40 percent of the intergalactic medium is in a heretofore-invisible portion called the *warm-hot* intergalactic medium—the WHIM. Further, the team predicted that about half of the WHIM (20 percent of the intergalactic medium) may eventually be seen, by virtue of its temperature and the wavelength of the radiation it emits.

And now someone has actually seen it.

While analyzing images from the Hubble Space Telescope and the Far Ultraviolet Spectroscopic Explorer, University of Boulder astronomers Mike Shull and Charles Danforth detected bits of the WHIM dimly superimposed on the backlight of distant quasars. Apparently, the WHIM is able to absorb some of the quasar light, leaving a faint, detectable shadow of itself. Shull and Danforth estimated they were looking at about 25 percent of the intergalactic medium.

Is that confirmation of the model?

"They said 25 percent; we predicted 20 percent," says O'Shea. "Close enough."

ISSN: 1942-6631

Los Alamos
NATIONAL LABORATORY
EST.1943

Los Alamos National Laboratory, an affirmative action/equal opportunity employer, is operated by Los Alamos National Security, LLC, for the National Nuclear Security Administration of the U.S. Department of Energy under contract DE-AC52-06NA25396.

A U.S. Department of Energy Laboratory LALP-08-026

Printed on recycled paper

Address mail to
1663
Mail Stop M711
Los Alamos National Laboratory
Los Alamos, NM 87545

email: 1663magazine@lanl.gov
Tel: 505-667-1447
Fax: 505-665-4408
www.lanl.gov/science/1663/

The Rio Grande, late summer, with Black Mesa in the background.