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Lawrence
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Science & Technology

REVIEW

The Biomedical Frontiers of Accelerator Mass Spectrometry

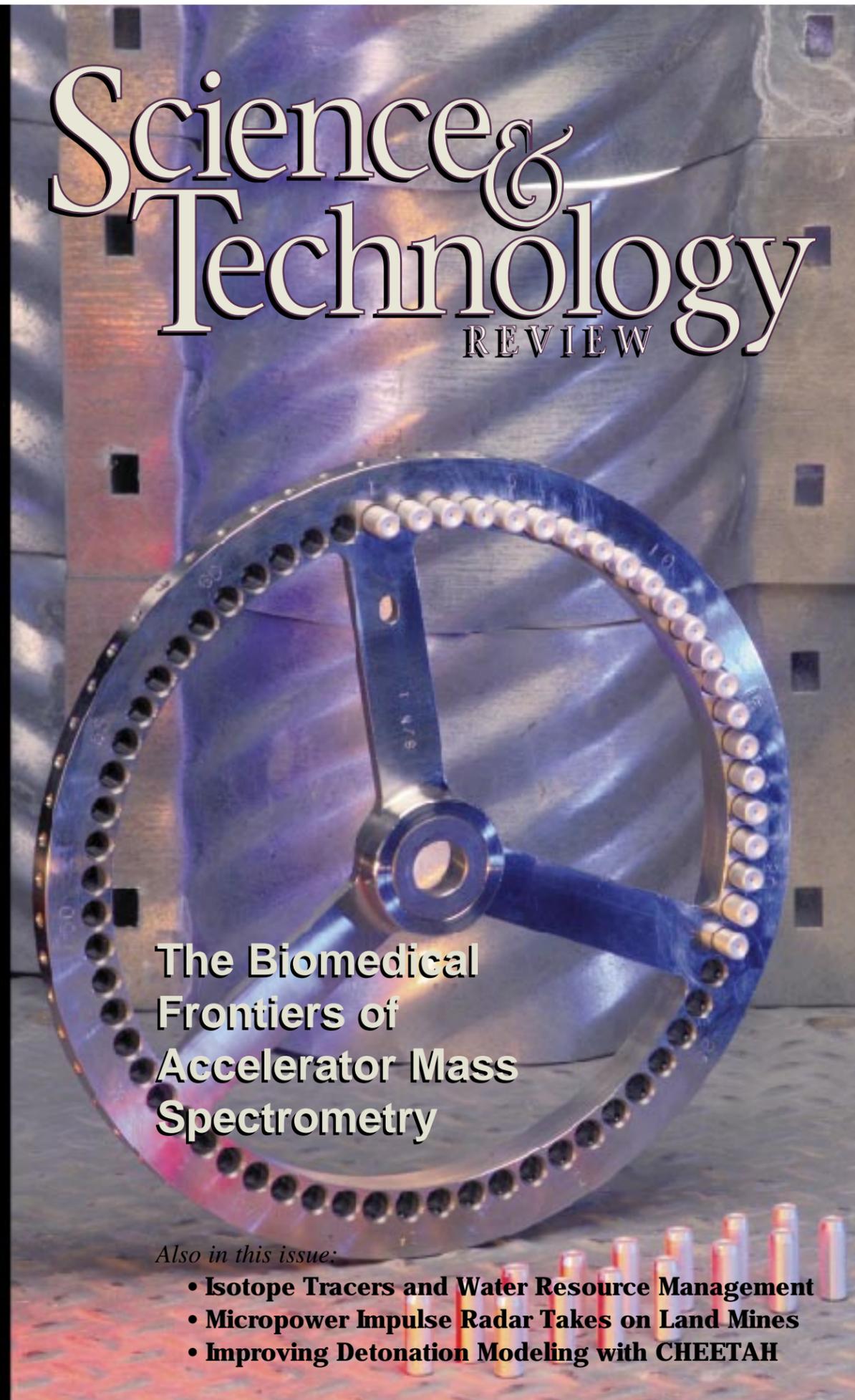
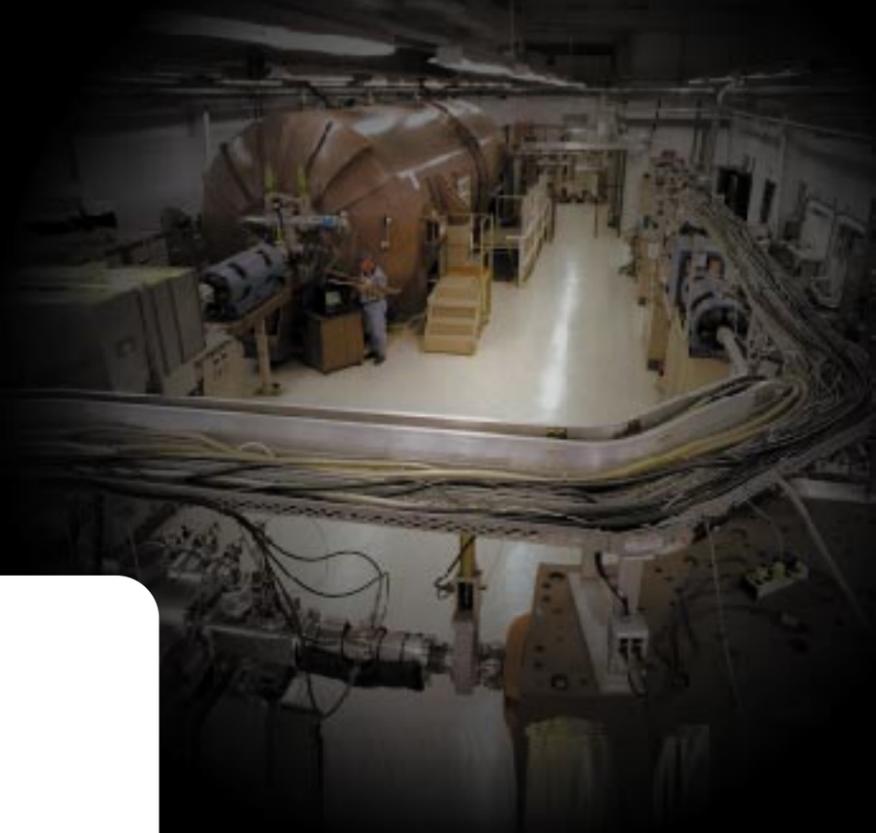
Also in this issue:

- **Isotope Tracers and Water Resource Management**
- **Micropower Impulse Radar Takes on Land Mines**
- **Improving Detonation Modeling with CHEETAH**



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About the Cover

Lawrence Livermore's Center for Accelerator Mass Spectrometry is a leader in the application of accelerator mass spectrometry to biomedicine. Currently, the center performs some 95% of all biomedical AMS research under way worldwide. Key to all of the center's work is the enormous accelerator itself (pictured on the back cover), which can measure with remarkable sensitivity the exact trace amounts of specific radioactive isotopes in the tiny, specially prepared samples pictured in their holder on the front cover. A report on the center and its work, particularly in biomedical research, begins on p. 4.



Cover photo: Michael Anthony

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About the Review

Lawrence Livermore National Laboratory is operated by the University of California for the Department of Energy. At Livermore, we focus science and technology on assuring our nation's security. We also apply that expertise to solve other important national problems in energy, bioscience, and the environment. *Science & Technology Review* is published ten times a year to communicate, to a broad audience, the Laboratory's scientific and technological accomplishments in fulfilling its primary missions. The publication's goal is to help readers understand these accomplishments and appreciate their value to the individual citizen, the nation, and the world.

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Five universities bolster computer simulation effort

Secretary of Energy Federico Peña has announced the selection of five major American universities to participate in a \$250-million initiative in collaboration with three DOE national laboratories—Lawrence Livermore, Los Alamos, and Sandia—to help advance high-performance computer simulation capabilities needed to make an historic leap in large-scale computer modeling and simulation. Stanford University, California Institute of Technology, the University of Chicago, the University of Utah at Salt Lake, and the University of Illinois at Urbana/Champaign were selected as Academic Strategic Alliance Program (ASAP) centers.

Each of the chosen universities has proposed very-large-scale applications that collectively drive the development of modeling and computing capabilities. Their endeavors will assist the three national laboratories in developing and validating the technologies needed to certify the reliability of the nation's nuclear weapons stockpile without underground testing. This stockpile stewardship work is being done in support of the Clinton administration's nuclear test ban objectives.

"President Clinton has challenged us to find a way to keep our nuclear stockpile safe, reliable, and secure without nuclear testing," Peña said. "We're going to meet his challenge through computer simulations that verify the safety, reliability, and performance of our nuclear weapons stockpile. I believe these alliances will produce a flood of new technologies and ideas that will improve the quality of our lives and boost our economy. In fact, with the Academic Strategic Alliance Program in place, Americans will begin to see the results—as the acronym suggests—ASAP."

ASAP will accelerate the emergence of high-performance computer-based modeling and simulation as a "third research methodology" in many scientific and engineering areas, along with theoretical and experimental studies.

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Livermore technology may improve bridge safety

Lawrence Livermore scientists have found a way to "see" beneath the asphalt without disturbing the surface of bridges. The technology that allows them to do this is called micropower impulse radar, which has been licensed to more than 20 companies for everything from measuring heartbeats to checking fluid levels in automobiles to locating studs in walls.

This technology has caught the attention of the California Department of Transportation (Caltrans), the agency responsible for upkeep of some 16,000 bridges in northern California. For more than a generation, Caltrans engineers have been dragging chains across old bridges, listening for

"a kind of punky, hollow sound" that means a bridge is deteriorating from the inside out, according to Caltrans Branch Manager Tom Harrington.

For the bridge work, the Lab assembled 64 of the radar devices, each capable of making fine measurements that, in concert, describe a three-dimensional image. Caltrans is sending core samples of a bridge that its crews are dismantling to Lawrence Livermore, where scientists are correlating bridge damage with their radar data.

Harrington is hopeful that the new technology will save considerable time and money for the Department.

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Celebrating a cleanup success

Scientists at Lawrence Livermore recently celebrated what they say is a successful effort to clean up groundwater contaminated by harmful practices of the past.

During the five years since it was listed as a Superfund site, the Laboratory has stopped the westward migration of a toxic plume of groundwater and is ahead of schedule to clean up the water underneath the mile-square site itself, officials said.

Representative Ellen Tauscher praised the Laboratory for making a "nice glass of lemonade" out of a "nasty bag of lemons," while Livermore Mayor Cathie Brown credited the Laboratory for being a good neighbor to residents. "The Lab has demonstrated once again . . . its commitment to the environment," Brown said.

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Russians visit Superblock at Livermore

In ongoing efforts between Russia and the U.S. to dispose of surplus plutonium, a team of Russian scientists ventured into what has previously been considered forbidden ground—the Superblock, Lawrence Livermore's plutonium facility.

The Russians toured the building to learn more about immobilization techniques for surplus plutonium. Livermore is the U.S. lead laboratory for DOE in immobilizing plutonium in glass or ceramics. These encapsulated forms can then be disposed at a suitable geologic repository site.

The Russians spent five days meeting with Livermore and U.S. experts, as well as studying the Laboratory's facilities to incorporate plutonium into glass or ceramics. Proposals for each option were presented to a steering committee formed by MINATOM (the Russian equivalent of the Department of Energy), DOE, and the White House Office of Science and Technology Policy.

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The Evolution of a Technology

BEFORE an accelerator mass spectrometry measurement was ever performed at Livermore, Laboratory scientists began the process of pushing this physics-based technology across the disciplinary boundary into the biosciences. In July 1987, Ivan Proctor and I briefed bioscientists Mort Mendelsohn, Bart Gledhill, Jim Felton, and Ken Turteltaub on our "not yet real" AMS capability with a simple premise: "We are building a tool that can detect an isotope commonly used in your field with a millionfold increase in sensitivity. You can throw us out after an hour, but give us the hour." From that briefing, we created together an exciting collaboration and became the first group to realize the promise that had lain fallow for a decade since the invention of AMS—application of this exquisitely sensitive technology to biosciences. Academic collaborators continue to reaffirm that this disciplinary fence-hopping could only happen at Livermore.

A decade later, we are well along the path that will eventually make AMS a biomedical and clinical commonplace, just as so many other physics-derived technologies have previously. (See the article on Livermore's Center for Accelerator Mass Spectrometry beginning on p. 4.) The potential of this tool has continued to grow and be recognized, so that even as we realize the promises made a decade ago, Livermore's practitioners of AMS can have their pick of collaborators worldwide for new projects. Academic and industrial researchers come here in a steady stream to learn the components of this technology and how to apply it to their needs.

Progress has required a combination of both science pull and technology push—plus a continuous education of collaborators and potential funders. The application to toxicology in support of the Laboratory's ongoing program to study food mutagens was an early and successful use of this immense gain in sensitivity. The subsequent spread of applications to clinical studies and screening of candidate pharmaceuticals could be anticipated, but not so the possibility of studying the expression of proteins by the human genome—at least not by the physicists and geochemists who first sought to apply AMS technology to the biosciences. As we find more examples of the differences between human and animal response to potentially genotoxic materials, the need to use this tool in assessing human health risks will become more important.

Technology push has an obvious and familiar direction: smaller, faster, cheaper, and friendlier. To make AMS viable

in clinical and commercial settings, the spectrometer and its supporting molecular speciation and sample preparation hardware must make the transition from physicist-friendly to biologist-friendly. The need to reduce all costs by an order of magnitude or more means that the new device must be not only smaller and more cost-effective, but also physicist-free, a condition that startles and sometimes offends many of our friends in the traditional AMS fields. Additionally, the spectrometer must be able to be ordered to specification from an equipment supplier and maintained on contract as is other biomedical equipment—not assembled and operated as an experiment. We have program elements that address all of these needs and are working to create the industrial partnerships and relationships that will make the transition real.

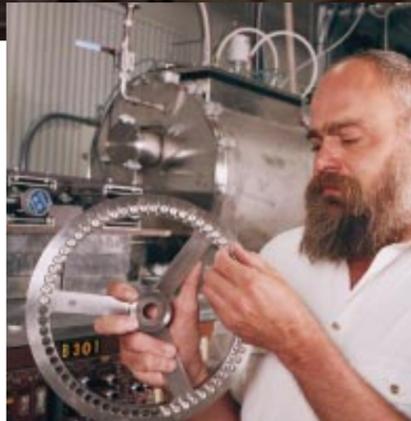
Our interest in the biological area does not mean that we will abandon or disregard the other components of Livermore's AMS activities. The recent successful support of the U.S. Geological Survey's investigation of the seismic record of the Hayward fault (made possible by our participation in acquiring of samples from trenches on the fault and by 24-hour data analysis turnarounds) is one example of our continuing use of this tool in geoscience and environmental cleanup areas. Another is the use of AMS to measure unambiguously the destruction of subsurface creosote contamination at a commercial site. The article on isotope tracers beginning on p. 12 provides examples of AMS's use in groundwater remediation and water management. Exciting projects that will tell us more about the historical record of the ocean's ability to absorb carbon dioxide are in progress, providing important information for the international dialogue on climate change.

We are a decade into the effort to create a new and valuable tool for the biosciences. The scientific and technological accomplishments are impressive, as are the social ones. A lipid biochemist has replaced a neutron physicist as the director of a significant accelerator facility—ours at Livermore. The next decade should see us well along toward a central goal for this activity—the replacement of scintillation counting with accelerator mass spectrometry in much of the biosciences.

■ Jay Davis is Associate Director, Earth and Environmental Sciences.

A New World of Biomedical Research

The Center for Accelerator Mass Spectrometry



Approximately 95% of all biomedical accelerator mass spectrometry currently under way in the world is being performed at Livermore's Center for Accelerator Mass Spectrometry.

YOU are scheduled for major surgery and have been asked to come to the doctor's office a few days prior to surgery to have some preparatory tests done. One such test that is currently under development may revolutionize surgery and followup treatment. It will determine your metabolism, allowing doctors to personalize your treatment. If your body metabolizes substances quickly, you will need more anesthesia during surgery and higher dosages of medications afterward. A person who metabolizes more slowly will need less anesthesia and smaller doses of medication perhaps at less frequent intervals.

For the test, you will first inhale a small dose of the anesthesia or take a bit of the proposed medication. Then you will breathe into a bag that contains antibody molecules that have been "tagged" with carbon-14 (^{14}C), making them mildly radioactive. The antigens in your breath will react with the antibodies in the bag. A highly sensitive process called accelerator mass spectrometry (AMS) will analyze the contents of the bag, searching for the enzymes that govern metabolism. Those few radioactive molecules will have attached themselves to the enzymes, and the AMS process will count them. AMS (described in the box on p. 6) is so sensitive that it can detect

just one ^{14}C nucleus among a quadrillion stable ones. The presence of more enzymes indicates that you are a fast metabolizer, while the numbers are different for a person with a slower metabolism.

With these highly sensitive breath tests, therapies of all kinds—from dosages for individual prescription drugs to complex chemotherapy treatments—can be tailored to fit the needs of a particular individual.

Breath tests are already being used by some doctors to test for hepatitis B and for the bacteria that cause certain ulcers, but AMS is not being used. AMS will make these and similar tests much more effective, allowing doctors and patients to know even earlier whether an infection is present.

The remarkable sensitivity of AMS opens the way to a host of other new diagnostic tests as well: assays for early detection of various disorders, tests that determine the efficacy of therapeutic regimens, studies of how the body handles various nutrients and vitamins, and assessment of the effects of environmental substances and toxins. When combined with such imaging technologies as magnetic resonance imaging, accelerator mass spectrometry will be able to assess changes in tissues, hormone levels, and metabolites in real time.

One of the Few

Lawrence Livermore's Center for Accelerator Mass Spectrometry is one of the few AMS facilities in the world working on biomedical and pharmaceutical applications. Since 1990, Livermore has been developing tests that can measure the effects of extremely small amounts of chemical substances, from suspected toxins to new drugs to dietary nutrients. Early testing with AMS used laboratory animals and this work continues. But the goal is to use AMS to study the effects of these substances on humans.

For example, to study a new drug using AMS, scientists modify just a few molecules of the drug to include a detectable atom such as ^{14}C . The amount of radioactivity in the drug dose is less than a person absorbs during a day on Earth from natural sources of radiation such as cosmic rays. Using a radioactive isotope such as ^{14}C as a "tracer" is not new. What is new is the high sensitivity of AMS, which allows the use of much smaller drug doses and consequently less ^{14}C —from a thousand to a million times less than is used in studies that do not use accelerator mass spectrometry.

Using AMS to count ^{14}C nuclei, researchers can follow the movement of the ^{14}C -tagged drug through the

body, identifying how long it remains there, how much and when it is excreted, how much is absorbed, and what organs it affects. How does this work? Carbon-14 is a naturally occurring radioactive isotope that can easily be incorporated into a drug or nutrient before a human ingests it. Counting ^{14}C atoms in urine samples will tell researchers how much of the chemical was digested and how long the ^{14}C -tagged drug was in the body before being excreted. Similar studies may be done with samples of blood or saliva. Studies over time can determine drug absorption and excretion and what the drug's effects are.

The tiny drug dose in this kind of study contrasts with the large quantities typically given to laboratory animals to determine dose-response relationships. Data from tests of potential carcinogens, toxins, and other compounds will serve as the basis for potency calculations and risk assessments relevant to humans, few of which exist today.

Accelerator mass spectrometry was developed in the mid-1970s and was first applied to ^{14}C counting for archaeological radiocarbon dating. In 1989, Lawrence Livermore researchers pioneered the use of AMS in ^{14}C measurements for biomedical

applications. Today, Livermore holds three patents for AMS applications to bioresearch.

The center at Livermore was originally designed to diagnose the fission products of atomic tests, to monitor the spread of nuclear weapons to other countries by detecting telltale radioisotopes in air, water, and soil samples, and to use isotopic tracers to study climate and geologic records. Work recently began on assessing the effects of low-level exposure to chemical weapons.

The center's scope also includes archeology, biodosimetry, atmospheric studies, paleoclimatology, combustion processes, and material science as well as biomedical research.¹ Today it is among the largest of about 40 AMS facilities in the world. It processes more samples (about 20,000 per year) and, perhaps more importantly, measures more different kinds of isotopes than any other AMS facility. Operating 24 hours a day, the center performs about 25% of all AMS analyses in the world.

Studies of the effects of chemical substances on human subjects are few and far between, but several now under way at Livermore are looking at the metabolism and effects of various chemicals, including vitamins, calcium,

Accelerator Mass Spectrometry

Mass spectrometry has been used since early in this century to study the chemical makeup of substances. A sample of a substance is put into a mass spectrometer, which ionizes it and looks at the motion of the ions in an electromagnetic field to sort them by their mass-to-charge ratios. The basic principle is that isotopes of different masses move differently in a given electromagnetic field.

An accelerator was first used as a mass spectrometer in 1939 by Luis Alvarez and Robert Cornog of the University of California at Berkeley. To answer what at the time was a knotty nuclear physics question, they used a cyclotron to demonstrate that helium-3 was stable and was not hydrogen-3 (tritium), which is not stable. Accelerators continued to be used for nuclear physics, but it was not until the mid-1970s that they began to be used for mass spectrometry. The impetus then was to improve and expand radiocarbon dating. Van de Graaff accelerators were used to count carbon-14 (¹⁴C) for archaeological and geologic dating studies.

Accelerator mass spectrometry (AMS) quickly became the preferred method for radiocarbon dating because it was so much quicker than the traditional method of scintillation counting, which counts the number of ¹⁴C atoms that decay over time. The half-life of ¹⁴C is short enough (5,730 years) that counting

decayed atoms is feasible, but it is time-consuming and requires a relatively large sample. Other radioactive isotopes have half-lives as long as 16 million years and thus have such slow decay rates that huge samples and impossibly long counting times are required. The high sensitivity of AMS meant that these rare isotopes could be measured for the first time.

Before a sample ever reaches the AMS unit, it must be reduced to a solid form that is thermally and electrically conductive. All samples are carefully prepared to avoid contamination. They are reduced to a homogeneous state from which the final sample material is prepared. Carbon samples, for instance, are reduced to graphite. Usually just a milligram of material is needed for analysis. If the sample is too small, bulking agents are carefully measured and added to the sample.

As shown in the figure below, the AMS unit comprises several parts, all of which are controlled by computer. At the ion source, the sample is bombarded by cesium ions that add an extra electron, forming negative elemental or molecular ions. The ions then pass through a low-energy mass spectrometer that selects for the desired atomic mass. In the tandem Van de Graaff accelerator, a second acceleration of millions of volts is applied, and the atoms and molecules smash through a thin

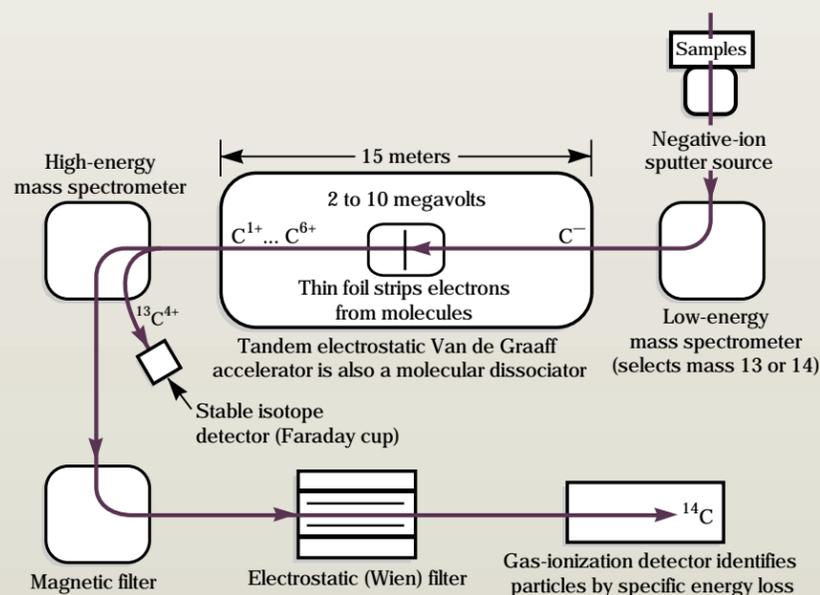
carbon foil or gas, which strips them of at least four electrons. Here, all molecular species are destroyed. Without the high energies in the accelerator, the very tight carbon-hydrogen bonds could not be undone. The ions continue their acceleration toward a magnetic quadrupole lens that focuses the desired isotope and charge state to a high-energy mass spectrometer.

The rare isotope being examined is always measured as a ratio of a stable, more abundant (but not too abundant) isotope, e.g., ¹⁴C as a ratio of ¹³C, which acts as an internal standard and provides a clear signature to differentiate the rare isotope from the background. Their ratio is shown as ¹⁴C/¹³C. In the high-energy mass spectrometer, the abundant isotope is removed from the ion beam and counted in the Faraday cup. Additional interfering ions are removed by the magnetic filter before the remaining ions finally slow to a stop in the gas ionization detector. The charge of individual ions can be determined from how the ions slow down. For example, carbon-14 slows down more slowly than nitrogen-14, so those ions of the same mass can be distinguished from one another. Once the charges are determined, the detector can tell to which element each ion belongs and counts the desired isotope as a ratio of the more abundant isotope.

The two “tricks” that make AMS work are the molecular dissociation process that occurs in the accelerator and the charge detection at the end. The resulting sensitivity is typically a million times greater than that of conventional mass spectrometry. AMS can detect one ¹⁴C ion in a quadrillion (10¹⁵) other ions.

For ¹⁴C dating, precision with accelerator mass spectrometry is typically within 0.5 to 1%, which corresponds to an uncertainty of plus or minus 40 years in a radiocarbon date. For other isotopes, precision generally ranges from 1 to 5% depending on the application.

In biological studies, AMS is used today primarily for counting ¹⁴C because carbon is present in most molecules of biological interest and also because ¹⁴C is relatively rare in the biosphere. Increasingly, however, other isotopes are being studied. The periodic table below presents the range of long-lived isotopes that are being used or have potential to be used in AMS studies.

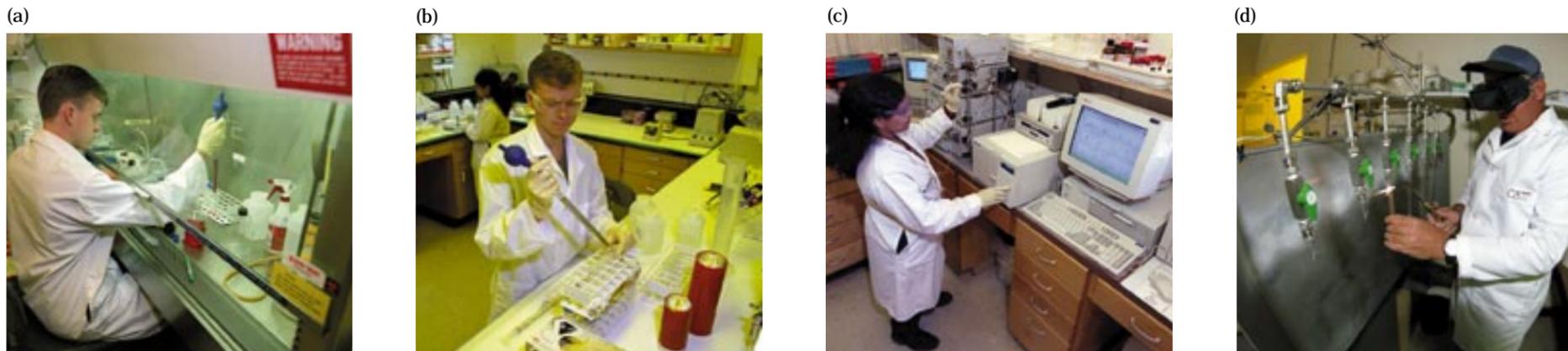


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Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr																																	

The periodic table of accelerator mass spectrometry. Elements with isotopes whose half-lives are between 10 years and 100 million years are not easily detected by decay counting and are rare in nature.

Atomic mass spectrometry units can be arranged in many ways, but all incorporate bends with magnets that help separate ion masses in space. Ions of different masses travel around corners differently. The symmetry of Livermore’s U shape makes the unit more accurate than units in other configurations, tightly focusing the beam of the desired ion mass.

Figure 1. Preparing biomedical samples for accelerator mass spectrometry (AMS) requires many steps in an ultraclean environment to prevent contamination and maximize sensitivity. Many of the sample preparation techniques for biomedical applications of AMS were developed at Livermore. (a) Chad Risner prepares cell cultures for use in biomedical AMS experiments and then (b) uses columns to purify DNA from those cultures prior to AMS analysis. (c) For another application, Chitra Mani uses high-performance liquid chromatography (HPLC) to separate metabolites from the urine of animals to which carbon-14 benzene has been administered. Finally, (d) Kurt Haack seals the AMS samples collected from the DNA isolation procedure or HPLC analysis in quartz tubes as part of the process that turns the samples into graphite. Once the graphitization process is complete, the samples are ready to be loaded in a sample holder for their spin through the AMS system.



and several suspected human carcinogens. This kind of research represents a world of new biological research possibilities that will lead to major improvements in our everyday lives. According to Jay Davis, Associate Director of Earth and Environmental Sciences and the first director of the Center for Accelerator Mass Spectrometry, “AMS in archeology and the geosciences is a mature field. But applying AMS to bioresearch is relatively new. Ninety-five percent of all biomedical work with AMS is being done at Livermore. With our expertise, we can provide the technology that will enable these applications to find more widespread use. We hope to see these processes commercialized so that pharmaceutical and chemical companies can use AMS on a routine basis. They will be able to test—using realistic, low-level doses—drugs, pesticides, and other chemicals to learn how they affect our health.”

A New Direction

The bulk of the center’s work is radiocarbon dating for archeology and the geosciences, but a growing fraction of its sample analysis is related to biomedical research.

The arrival in late March 1997 of Caroline Holloway as the center’s director signified the new direction that the center is taking. Holloway is a biochemist who had worked for many years in advanced technology development at the National Institutes of Health in Bethesda, Maryland. Why did she leave NIH to “hang out with a bunch of physicists”? As an NIH representative, she had visited Livermore in 1994 and was impressed with the evolution of AMS into biology being led by Livermore. When the directorship became available, Holloway says, “I jumped at the opportunity. Without question, the future of AMS in biology is now, and the future is happening at Livermore.”

The center’s emerging emphasis on biomedical applications has been preceded by years of experiments, many of which were performed primarily to prove the significance of AMS for biomedical research.

In 1990, the first biomedical experiment using AMS was performed at Livermore. It measured the effects on rat DNA of a suspected carcinogen, 2-amino-3,8-dimethyl-imidazo[4,5-f]-quinoxaline, known as MeIQx. MeIQx results from cooking meat and may be partly responsible for the observed

frequency of gastrointestinal-tract cancer in the U.S.² Adducts, which are the defects formed by the covalent binding of certain chemicals to DNA, are routinely monitored as biomarkers of carcinogen exposure. These DNA adducts can result in chromosomal rearrangements, mutations, cell death, cancer, and birth defects.

Livermore gave low doses of synthesized MeIQx with a single ¹⁴C atom in each molecule to rats. With AMS, they achieved a detection limit of one adduct in a trillion (10¹²) nucleotides, a tenfold improvement over assays using other methods of detection.

Another early experiment looked at the effects of the highly toxic chemical dioxin, which was shown not to bind directly to DNA. The significance of this experiment and the one with MeIQx was not merely that AMS can be used to study genotoxicity at low levels but that accelerator mass spectrometry had potential value as a screening tool for genotoxicity of drugs or other industrial chemicals. Similar preliminary studies were performed to develop a methodology for conducting experiments on pharmacokinetics (how drugs move through an organism after being swallowed or injected) using relevant human exposure levels.

With all of this early work, Livermore scientists were defining not only how AMS could be used for biomedical research but also how best to do it. Process development continues today as Livermore “pushes the envelope” for accelerator mass spectrometry in biology. Every new experiment requires the development of new procedures and protocols and sometimes new instruments for such important work as sample preparation. A spin through the AMS machine takes just a few minutes, but preparing the sample beforehand takes much longer (Figure 1). Maximizing sensitivity requires new, ultraclean lab techniques to prevent sample contamination. Thus, the technology of biomedical AMS research is being developed along with new experimental applications.

Studies in Humans

A team of scientists that included collaborators from Livermore is using AMS to study the effects of MeIQx in humans. The purpose of this work is to quantitatively compare humans and animal models for human risk assessment. Experiments with animals typically use doses designed to induce tumors, and extrapolating from those

numbers to the kind of doses that humans might encounter is not easy, in part because of the differences in physiology and metabolism between humans and animals.

At York University in England, five volunteers previously diagnosed with operable colon cancer and scheduled for colon surgery were administered ¹⁴C-tagged MeIQx 4 to 6 hours before surgery. Tissue removed during surgery and not needed for pathology was analyzed for ¹⁴C content by AMS. Urine samples were collected for 24 hours after administration of the dose and were analyzed for metabolism of MeIQx.

Test results suggest that the concentration of MeIQx in the human colon was highly variable among the five subjects. There also appear to be differences between normal and tumor tissues of the same volunteers. Among the volunteers, there seemed to be individual variations in MeIQx absorption and processing, which suggests differences in DNA adduct levels.

Even with all these variations, DNA adduct levels in humans appears three to four times higher than adduct levels in mice and rats. This study suggests strongly that MeIQx affects

humans more than it does mice and rats and supports using AMS to pursue additional human biomedical risk assessments.

Calcium and Bone Health

AMS is also changing the study of the effects of vitamins and minerals in our daily diet. We know that they are needed for healthy living, but their effects are virtually unknown, other than that illnesses may result from their absence in our diet. AMS is finally allowing researchers to trace such nutrients in the human body.

A study of the dietary nutrient calcium is, for example, under way at Livermore. Studies of the skeleton and osteoporosis are a high priority, given the one million osteoporotic fractures that occur in the U.S. every year and their attendant \$10-billion annual cost. Calcium is the key nutrient for bone health, so understanding calcium metabolism is critical (Figure 2). But until the advent of accelerator mass spectrometry, measuring calcium kinetics in bone directly was difficult. With decay-counting methods, only the short-lived radioisotopes of calcium can be used to trace the movement of calcium through the body. Very large amounts of the tracer

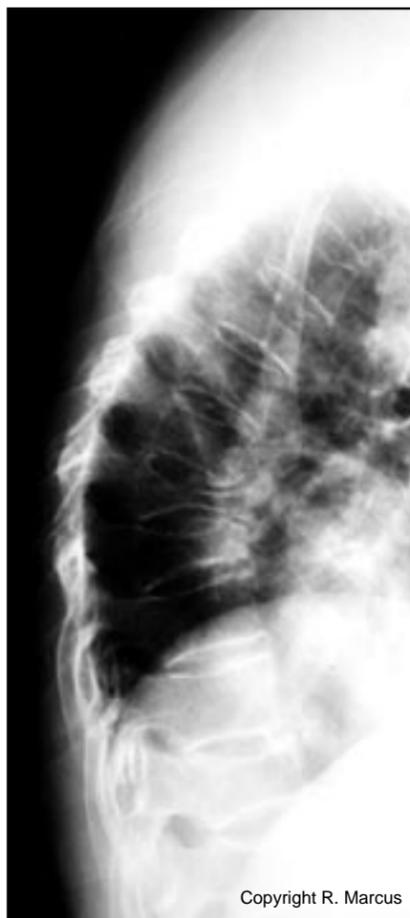


Figure 2. Sideview x ray of severely osteoporotic spine showing effects of prolonged calcium depletion.

must be used because ingested and absorbed calcium is only slowly resorbed by the skeleton. For any of the tracers to show up in urine, which is where calcium appears that has been lost from bone, the patient must ingest a dangerously high radiation dose. An alternative testing method is the use of stable isotopes as tracers, but they are extremely expensive.

What scientists do know about calcium metabolism comes from assays of blood and urine samples that look at byproducts related to calcium. These indirect data are useful for indicating trends in large populations. But they cannot be used for information on an individual because of the indirect nature of the tests.

With AMS, longer-lived isotopes can easily be studied. Because of AMS's sensitivity, only minute quantities are needed, so the patient receives a radiologically benign dose. Calcium-41 (^{41}Ca), with a 100,000-year half-life, fills the bill neatly for bone studies.

If calcium with a ^{41}Ca tracer is given to a patient, the skeleton will become "tagged" with ^{41}Ca . The ^{41}Ca in subsequent urine samples will indicate how much ^{41}Ca is being lost from the skeleton. Scientists from Livermore, the University of California at Berkeley and Davis, Stanford University, Creighton University, and the National Institutes of Health are currently testing data from initial ^{41}Ca experiments against the results of conventional calcium studies.

Calcium-41 shows promise as an effective tool in testing drugs that may prevent osteoporosis. Some drugs are designed to "seal" the bone to reduce calcium resorption. When treatment with such drugs begins, calcium loss will slow, and the amount of ^{41}Ca in urine samples will be reduced (Figure 3). Various therapeutic dosages and formulations can easily be studied and compared.

With ^{41}Ca and AMS, the kinetics of calcium in the human skeleton can for

the first time be studied directly, enabling studies of fundamental bone processes and providing indicators of an individual's bone health.

The Future of AMS

Elemental trace nutrients are also yielding to the new developments in accelerator mass spectrometry at Livermore. Among those under investigation at the center are nickel, selenium, and iodine. The very long-lived isotopes of these elements that are detected through AMS will eventually be traced in humans at levels that present no discernible chemical or radiological danger.

More tests of drugs using human subjects and the tiny doses that AMS can measure will expand the base of information on metabolism, efficacy, and toxicity. The time period for testing drugs can be shorter, which will decrease the cost of bringing new drugs to market. Definitive human data will give users a larger margin of safety than they have today. As the database on human metabolism grows, scientists will come ever closer to being able to tailor and individualize therapeutic treatments.

According to Holloway, "Perhaps even more exciting is the relationship of accelerator mass spectrometry to the human genome. When the Human Genome Project is completed, some scientists envision a 'periodic table' for biology that comprises not 100-plus elements but 100,000 genes. Armed with knowledge of the complete human genome, scientists will begin to understand each protein that a cell makes as a result of instructions from a single gene."

Proteins are the life substances of the cell, carrying out the energy functions, synthesizing life components, and serving as the regulatory agents that control the traffic of molecules in the cell. AMS can contribute to understanding those cellular proteins that are made in only small amounts or that are present for only short periods of time because they are cell-signaling agents. For such studies, AMS scientists will collaborate across scientific disciplines and technologies with scientists using genomic tools, protein separation techniques, and other molecular speciation and separation methodologies.

Says Holloway, "Work on the human genome is just one of several new opportunities for the future growth of accelerator mass spectrometry in basic biomedical research."

—Katie Walter

Key Words: accelerator mass spectroscopy, biomedical research, calcium, Human Genome Project, human subjects, MeIQx, osteoporosis, radiocarbon dating, tandem Van de Graaff accelerator, toxicology.

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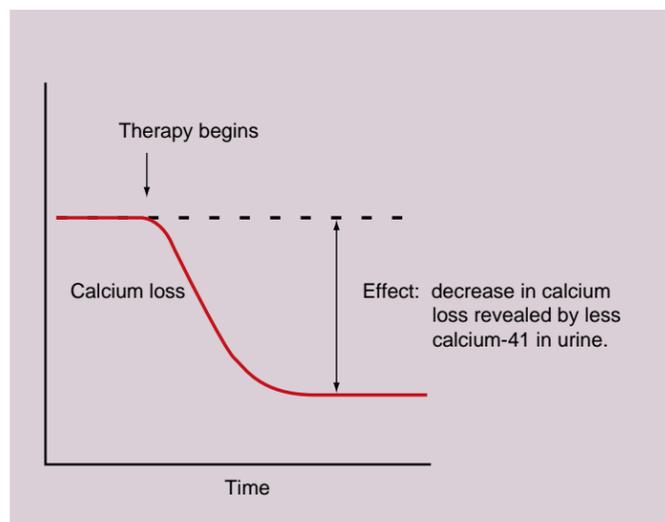


Figure 3. Graph showing drop in calcium resorption after drug treatment for osteoporosis begins.

About the Scientist



CAROLINE HOLLOWAY has been director of the Center for Accelerator Mass Spectrometry since March 1997. She was previously with the National Institutes of Health, most recently as acting director of Biomedical Technology at NIH's National Center for Research Resources in Bethesda, Maryland. Holloway is a biochemist interested in lipids and biomembranes. She has conducted biomedical research at E. I. Du Pont de Nemours, the University of Virginia School of Medicine, and the

Duke University School of Medicine. Holloway received her B.S. in 1959 from City College of New York and her Ph.D. in biochemistry in 1964 from Duke University, after which she completed postdoctoral research at Shell Agricultural Chemicals in England. She has published more than 25 scholarly articles and papers.

Isotope Tracers Help Manage Water Resources

Livermore is using isotope tracer techniques to investigate groundwater movement beneath the Nevada Test Site and the Livermore site and to provide public water managers with tools to manage valuable groundwater resources.

HAVE you ever thought about how old your drinking water is or where it came from? How would you figure out the answers to those questions if you wanted to know? If you had access to Lawrence Livermore's isotope tracing techniques, those questions might not be too difficult to answer.

Since the inception of the Laboratory, Livermore scientists have been studying both radioactive and stable isotopes. Support to the nuclear test program has given Livermore unparalleled nuclear chemistry expertise. This experience found an unexpected application when, after a decade of underground testing at the Nevada Test Site (NTS), the Laboratory began studying the movement of radioactive elements from those tests in groundwater.

Initially, conventional hydrogeologic characterization

methods were used to learn about the aquifer beneath NTS. These studies look at data from well pumping tests to learn about the porosity, permeability, and other properties of the aquifer. The drawback to these conventional methods is that the natural heterogeneities in an aquifer are difficult to characterize without detailed geologic information. Additional data can be gathered only by drilling more wells. Drilling costs are particularly high in an arid region such as NTS where the water table is sometimes more than 600 meters (2,000 feet) below the surface. Moreover, the test site is enormous, encompassing over 3,600 square kilometers, which could necessitate hundreds of drilling sites.

Livermore scientists knew that determining the nature and extent of

radionuclide contamination in groundwater at NTS was a complex project. To augment conventional hydrogeologic techniques for their groundwater studies, Livermore began using isotope tracers, which look directly at the groundwater itself rather than at the rock through which the water flows. These methods are described in the [box on p. 15](#).

Today, Dave Smith manages Livermore's work on radionuclide migration at NTS. (See [Figure 1](#).) To better predict the possible transport of contaminants in groundwater, his team measures both stable isotopes (ratios of deuterium to hydrogen, oxygen-18 to oxygen-16, carbon-13 to carbon-12, strontium-87 to strontium-86, and noble gases) and radioactive isotopes (tritium, carbon-14, chlorine-36, and uranium isotopes) at more than a hundred springs and wells throughout southern Nevada. Recently obtained oxygen and hydrogen isotope data suggest that the regional aquifer underlying the test site is recharged from north of NTS rather than from the east as originally concluded from conventional hydrogeologic evidence alone. Carbon-14 age measurements indicate that the flow system is very heterogeneous, with highly variable flow rates. Exact flow rates are currently under investigation.

Some of the contaminants in the NTS groundwater, such as tritium and

many products of nuclear fission, have short half-lives and may decay long before they leave the test site. But a few contaminants have longer half-lives, posing a potential threat as the groundwater migrates far from its source. Knowing the future location of contaminated groundwater is important information for water managers. When they can accurately predict where this groundwater will be, they can avoid using it.

A Water Management Tool

Having proved their mettle at the Nevada Test Site, isotope tracer methodologies have since been applied to a number of other water resource projects, which are under the direction of Laboratory scientists Bryant Hudson and Lee Davisson.

Orange County Water District

For the Orange County Water District in southern California, Hudson and Davisson's team is investigating the flow of artificially recharged water, which is recharged to the subsurface from spreading ponds. (See [Figure 2](#).) Orange County wants to supplement its water supplies with treated wastewater



Figure 1. Groundwater sampling at the Nevada Test Site.



Figure 2. Orange County Water District uses abandoned gravel pits as spreading ponds to artificially recharge water to its aquifer.



Figure 3. A look down an Orange County Water District monitoring well.

and must respond to regulations requiring that such waters remain in the aquifer for a year before being withdrawn for drinking. Using the tritium–helium-3 (^3H – ^3He) dating method and isotopically labeled water, Livermore has shown how recharged water moves from Orange County's main spreading pond facility. A plume of very young water extends several miles to the west of the spreading ponds, suggesting very rapid groundwater flow in that direction.

Orange County also brings in water from the Santa Ana River and sometimes from the Colorado River and recharges it to the subsurface. Santa Ana River water shows significant seasonal variations in the ratio of oxygen-18 to oxygen-16 ($^{18}\text{O}/^{16}\text{O}$), and Colorado River water has a different stable isotope signature altogether. In the fall of 1996, a batch of Colorado River water was spiked with a xenon tracer when it was introduced into the spreading ponds. From water samples taken at monitor wells down-gradient of the ponds (Figure 3), the distinctive $^{18}\text{O}/^{16}\text{O}$ signature and the noble gas tracer have allowed Livermore scientists to follow the migration of this water in the subsurface, with a time resolution of just a few days. These isotope data also provide a means of delineating groundwater mixing with an accuracy of $\pm 10\%$ for oxygen-18 and $\pm 1\%$ for xenon-124.

In another project, the Orange County Water District is injecting reclaimed wastewater into an array of wells that parallel the Pacific coastline. This "wall" forms a barrier to seawater that had begun to intrude into groundwater supplies and provides a significant source of drinking water as well. Livermore used ^3H – ^3He ages of the injected water to demonstrate compliance with required regulations.

Isotope Hydrology at Livermore

Lawrence Livermore scientists use both stable and radioactive isotopes to learn about groundwater sources, ages, travel times, and flow paths and to determine the path and extent of contaminant movement in the water. The combination of Livermore's unique nuclear chemistry experience, multidisciplinary staff, and highly sensitive mass spectrometry equipment, including use of the Center for Accelerator Mass Spectrometry, means that Livermore can take the measurements and interpret the results effectively. Livermore is unique among isotope hydrology centers in having all of the various tracing methods in one place. Researchers routinely use a variety of isotopes to evaluate a groundwater system and create the most accurate picture possible.

The Water's Origin

All waters have "fingerprints" of naturally occurring isotopes that provide information about their origin. Among the most powerful and cost-effective fingerprinting tools are the ratios of stable isotopes of hydrogen—deuterium to hydrogen (D/H)—and of oxygen-18 to oxygen-16 ($^{18}\text{O}/^{16}\text{O}$). For example, the D/H and $^{18}\text{O}/^{16}\text{O}$ ratios in precipitation vary according to elevation and distance from the ocean. An altitude difference of 250 meters (820 feet) produces a clear and measurable change in the two ratios, which is preserved once the precipitation infiltrates to the aquifer. While some mixing of waters in the aquifer is inevitable, an aquifer is typically not homogeneous. Layers of heavy clay retard the movement of groundwater within the aquifer and often serve to keep waters from different sources distinct from one another. Thus, scientists can use D/H and $^{18}\text{O}/^{16}\text{O}$ ratios to determine the recharge location for a groundwater and to discriminate among multiple water sources within an aquifer.

The concentrations of atmospherically derived noble gases (neon, argon, krypton, and xenon) in groundwater provide another excellent fingerprinting tracer because the noble gases do not react with surrounding materials and because their concentrations are preserved as they are recharged into the aquifer. The relative abundances of the noble gases provide information about the temperature and altitude at the time of recharge. Isotopically enriched noble gases, which are commercially available at low cost, can also be used as nonhazardous artificial tracers. They are detectable at very low concentrations, rendering them highly effective for delineating groundwater flow systems.

The Water's Age

Naturally occurring radioactive isotopes provide information about a groundwater's age, which refers to the last time the water

was in contact with the atmosphere. Once the recharge area has been established using isotope fingerprinting methods, radioisotopes may be used to estimate how long it took for a parcel of groundwater to travel from its recharge area to the measurement point. For young groundwaters, the best dating method is one that measures the relative abundance of tritium (^3H) and helium-3 (^3He). Tritium is a radioactive isotope of hydrogen that decays to ^3He with a half-life of 12.4 years. The amount of ^3He from the decay of tritium is measured along with the amount of tritium remaining in the water. That sum is equal to the amount of tritium that was present at the time of recharge. The ^3H – ^3He dating method is remarkably accurate for groundwaters up to 40 years old with an age resolution of plus or minus one year.

The ages of older groundwaters can be measured in several ways. One is by measuring the carbon-14 (^{14}C) dissolved in the water. Carbon-14 decays at a known rate with a half-life of 5,730 years, providing a useful dating method for groundwaters less than 40,000 years old. Another method uses the isotope helium-4 (^4He), which is produced continuously deep within the earth by the radioactive decay of uranium and thorium. Relative age relationships determined from the amount of ^4He in a groundwater are a valuable supplement to ^{14}C age determinations. The long-lived radionuclides chlorine-36 and iodine-129 are also being used to study very old regional groundwater flow systems.

Rock and Contaminants

Other isotopic and elemental measurements provide useful information about the interaction of water and its host rock or sediment or about the migration of contaminants in the water. For example, the isotopic composition of strontium (Sr) in groundwater depends on the $^{87}\text{Sr}/^{86}\text{Sr}$ ratios of the rocks with which it interacted. (Different rock types can have significantly different $^{87}\text{Sr}/^{86}\text{Sr}$ ratios.) In basins containing several aquifers with differing rock characteristics, the dissolved $^{87}\text{Sr}/^{86}\text{Sr}$ of a water sample may help distinguish where a particular groundwater resides.

Pollutants in groundwater can be studied in several ways. Measurements of nitrogen and oxygen isotope ratios ($^{15}\text{N}/^{14}\text{N}$ and $^{18}\text{O}/^{16}\text{O}$) can supply information about the source of nitrates, which are prevalent in agricultural fertilizers and may contaminate groundwater. Similar information about manmade pollutants can be gathered by measuring lead isotopes and heavy metal concentrations.

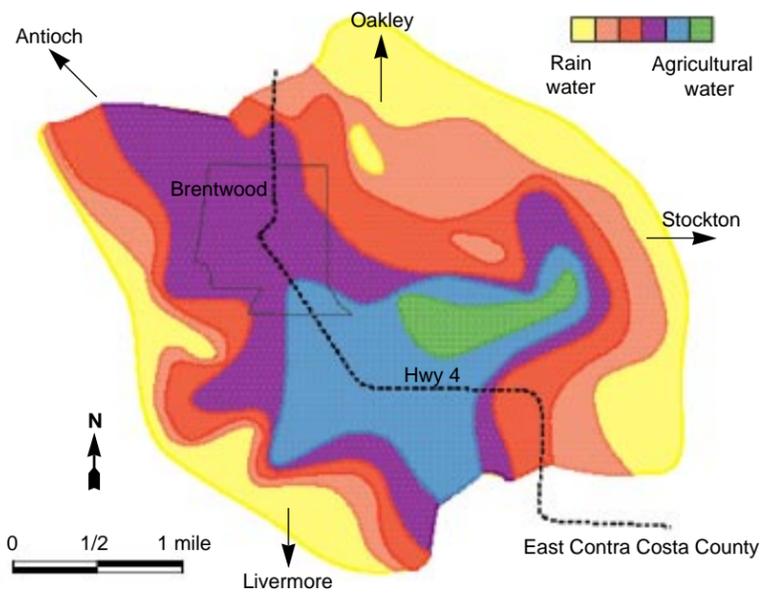
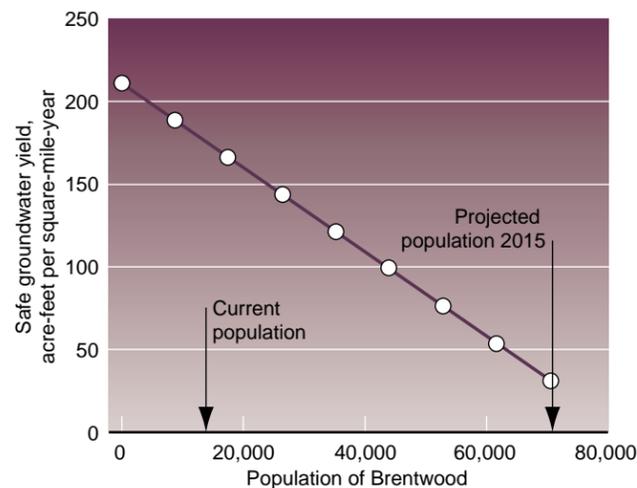


Figure 4. A contour map of groundwater in the Brentwood area of Contra Costa County, California, based on measurement of the ratio of oxygen-18 to oxygen-16. Two distinctive types of groundwater are evident from this map: local rainfall and irrigation water. Precipitation accounts for only 6% of total annual recharge in the area.

Figure 5. The safe yield is the amount of water that can be withdrawn from an aquifer without exceeding recharge. The relationship between the safe yield and population growth in the Brentwood, California, region shown here indicates that the future water demands of Brentwood will be difficult to meet using only local groundwater resources.



Contra Costa County

Livermore was also asked to study groundwater resources in the Brentwood region of Contra Costa County, California, which is undergoing rapid urbanization after decades of agricultural use. Declining water quality, particularly that caused by high nitrate concentrations, is the result of fertilizer application and extensive agricultural irrigation. Water samples from 80 different wells in the area were used to construct a contour map of groundwater ¹⁸O/¹⁶O ratios, shown in Figure 4. Two distinctive types of groundwater were observed, one corresponding to local rainfall and the other to irrigation water imported from the San Joaquin River. Most of the local groundwater recharge is from irrigation. In fact, Livermore’s study revealed that only 6% of total annual recharge is from precipitation.

As urbanization in the Brentwood area increases, agricultural recharge will decrease, reducing total recharge to the aquifer. Figure 5 shows the relationship between population growth and the amount of groundwater that can be pumped out without exceeding recharge. It is clear from the graph that it will be difficult to meet future water demands in Brentwood using only local groundwater resources.

Groundwater Remediation

Isotope tracers are also playing a role in a groundwater remediation project at the Lawrence Livermore site. Hudson and Davisson’s team is working with the Environmental Restoration Division and the Earth and Environmental Sciences Directorate, which are cleaning up fuel hydrocarbons that several decades ago had leaked from fuel storage tanks into the subsurface.

Recently, steam was injected into the subsurface to stimulate recovery of the hydrocarbons.

Groundwater samples collected from monitoring wells farthest from the spill show relatively high carbon-14 (¹⁴C) and carbon-13 to carbon-12 (¹³C/¹²C) values, which are consistent with normal dissolved inorganic carbon levels in Livermore Valley groundwaters. In contrast, samples taken from within the spill have low ¹⁴C and ¹³C/¹²C values, as would be expected from the breakdown of petroleum products. These results indicate that fuel hydrocarbons are breaking down and provide a measure of how much breakdown has taken place.

Meeting the Demand

Isotope scientists use isotope tracing methods to determine the origin, age, and flow paths of groundwater in hydrogeologic systems. At the same time, geologists input data from conventional hydrogeologic studies to computerized groundwater models to predict where and how fast groundwater is flowing. Until recently, the two technologies had not been combined to solve groundwater resource issues. But steps are being taken at Livermore to “marry” them because each has much to offer the other. For example, isotope tracer data are proving valuable for verifying and validating the predictions of the numerical models for the Nevada Test Site. Together these technologies can give water resource managers a powerful forecasting tool.

As the demand for fresh water grows with increasing population, so will the demand for creative ways to predict the availability and sustainability of our underground and surface water resources. Some isotope tracing methods are beginning to be applied to surface

water, which is a source of water for millions of people. These techniques offer solutions, on both a local and regional scale, to such critical problems as water resource management, water quality, and contaminant transport.

—Katie Walter

Key Words: groundwater, groundwater contamination, groundwater remediation, hydrology, Nevada Test Site, nuclear chemistry, radioisotopes, stable isotopes, water resource management.

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About the Team



Members of the Isotope Sciences Division whose work is reported in this article are (left to right): LEE DAVISSON, JACKIE KENNEALLY, BRYANT HUDSON, DAVID SMITH, JEAN MORAN, TIMOTHY ROSE, WAYNE CULHAM, SIDNEY NIEMEYER, ANNIE KERSTING, and JOAN BEIRIGER.

The Isotope Sciences Division is a multidisciplinary organization responsible for isotopic sciences programs in nuclear safeguards, nonproliferation, stockpile stewardship, environmental monitoring and technologies, waste repositories, and hydrology. Isotope hydrology is currently a principal area of scientific interest in the division. The division’s isotope hydrology program applies the broadest range of isotopic techniques to characterize groundwater systems. The program seeks to develop isotope hydrology as a new tool for water resource management.

Niemeyer is the division leader, and Hudson, Davisson, and Smith are principal investigators for the various isotope hydrology projects being done by the division. Rose, Kersting, and Moran are research staff for the program; Kenneally, Beiriger, and Culham provide research support.

LANDMARC

Making Land-Mine Detection and Removal Practical

WHILE diplomats work to restrict the manufacture, sale, and use of land mines worldwide, a massive cleanup effort is needed to find and destroy the estimated 100 million land mines still buried in 65 countries. Land mines left behind from wars worldwide are one of the century's main unsolved problems of war and remain the focus of humanitarian mine detection and removal primarily in Europe, Africa, Asia, and Central and South America.

A combination of technologies from Lawrence Livermore National Laboratory is being directed toward the most daunting challenge presented by land mines—quickly determining the location of each individual land mine in an area so all of them can be removed. The Laboratory's patented micropower impulse radar and advanced imaging technologies are being combined in a practical system called the Land-Mine Detection Advanced Radar Concept, or LANDMARC, that is making pivotal advances in meeting the challenge of land-mine detection.

The Detection Dilemma

Effective solution of the problem posed by land mines means that close to 100% of the mines in any area must be detected at the fastest rate possible and with few false alarms (i.e., mistaking a buried object, such as a rock, for a mine). The United Nations, for example, has set the detection goal at 99.6%, and the U.S. Army's allowable false-alarm rate is one false alarm in every 1.25 square meters. No existing land-mine detection system meets these criteria. And the reasons for this failure have as much to do with the mines themselves and the variety of environments in which they are buried as with the limits or flaws in the current technology.

Land mines are of two basic types—antitank and antipersonnel. Antitank mines are larger and more powerful than antipersonnel mines. However, antipersonnel mines are the most common type of mine, yet the most difficult to find because they are small and often made of plastic. Antitank mines generally contain more metal than do antipersonnel mines and are thus more easily detectable by simple metal detectors. Both types are buried as close to the surface as possible and are found in a variety of soils and terrain—rocky or sandy soil, open fields, forested areas, steep terrain, jungle. For both types of mines, detonation is typically caused by pressure, although some are activated by a trip-wire or other mechanisms. Thus, a land-mine detector must do its job without having direct contact with a

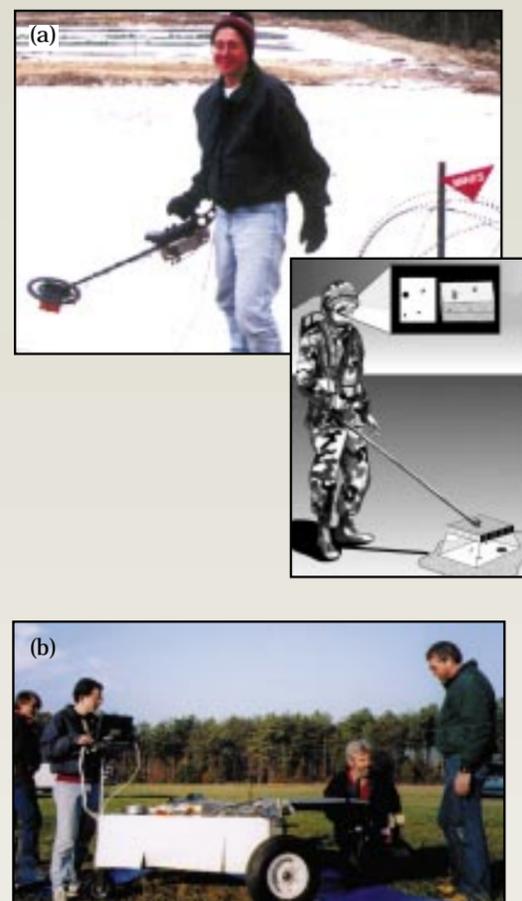


Figure 1. (a) Hand-held and (b) vehicle-mounted LANDMARC systems.

mine. It also must be able to locate all types of mines individually in a variety of environments.

Other Detection Technologies

Various detection technologies are currently used, each with limits or flaws. Dogs and other “sniffers” have high ongoing expenses, are subject to fatigue, and can be fooled by masked scents. Metal detectors are sensitive to metal mines and firing pins but cannot reliably find plastic mines. Infrared detectors effectively detect recently placed mines, but they are expensive and limited to certain temperature conditions. Thermal neutron activation detectors are accurate but are large for field use, slow, and expensive.

In early attempts, ground-penetrating radar was sensitive to large mines, had good coverage rate at a distance, and with signal processing, could discriminate antitank mines from clutter such as rocks beneath the ground surface. This type of radar, however, remains expensive, cannot detect antipersonnel mines because its resolution is too low, and frequently records false alarms from clutter sources.

Livermore's ongoing LANDMARC project addresses all of these problems and stands a good chance of solving them,

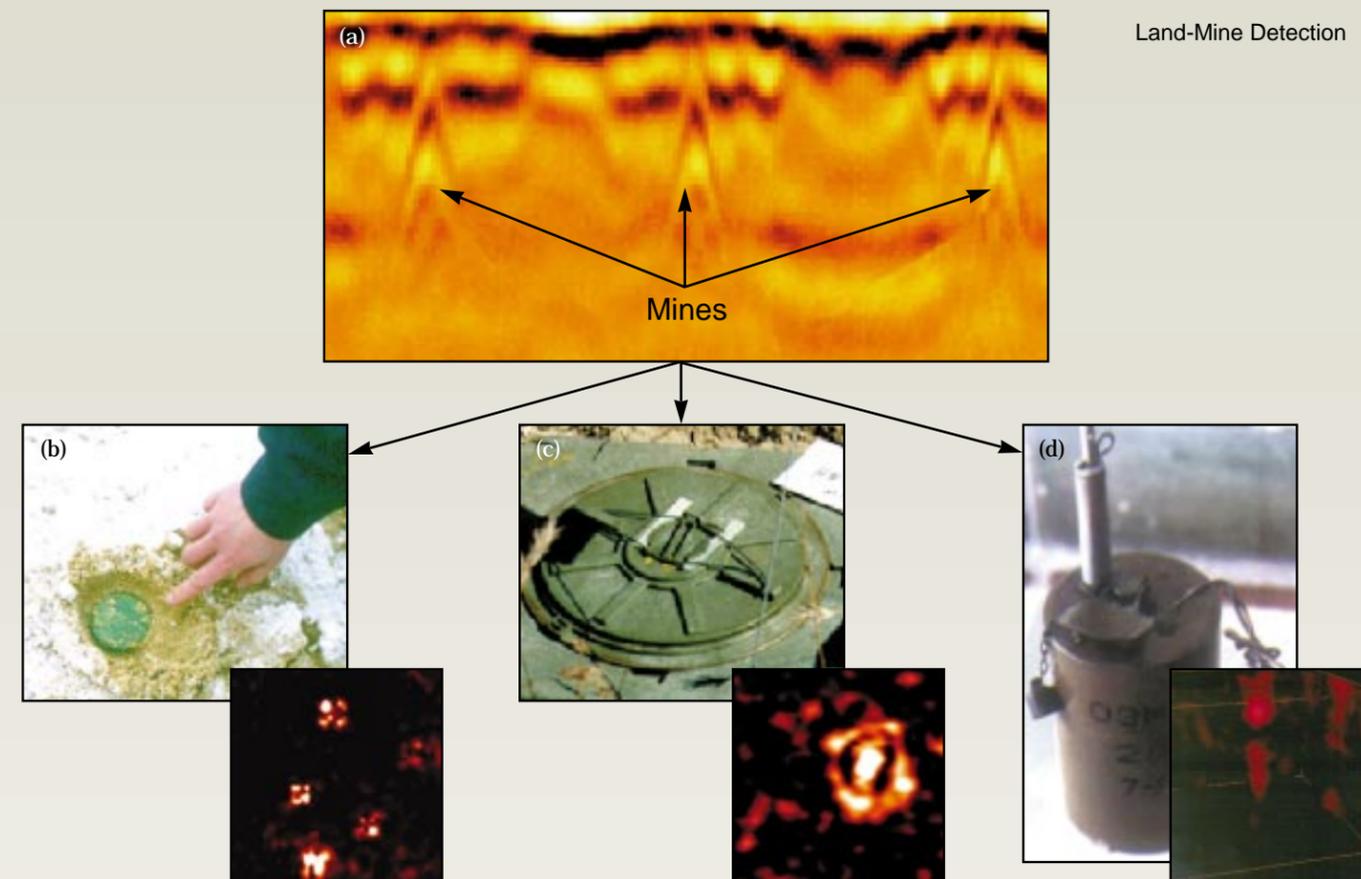


Figure 2. The LANDMARC system has the power to process (a) raw radar data into two-dimensional tomographic images of (b) antipersonnel and (c) antitank mines in a few seconds. In the same time frame, it can also process (d) three-dimensional renderings of, in this case, a buried antitank mine.

especially the problems of detecting small plastic antipersonnel mines and reducing the false-alarm rate.

Livermore's Systems Approach

The LANDMARC system's enabling technology is micropower impulse radar (MIR), which was invented at Livermore in 1993 as an outgrowth of the Nova laser program.¹ The invention, which won an R&D 100 Award in 1993 and an Excellence in Technology Transfer award from the Federal Laboratory Consortium in 1996, led directly to a battery-operated pulsed radar that is remarkably small and inexpensive, has a wide frequency band, and works well at short ranges²—all necessary attributes of land-mine detection systems.

MIR's small size, light weight, and low power requirements make it superior to any previous attempts to use ground-penetrating radar to detect land mines. MIR's ultrawide bandwidth is the source of the high-resolution imaging capabilities that differentiate LANDMARC from similar land-mine-detection technologies. Furthermore, the ability to group individual MIR units in arrays increases the speed and coverage area of LANDMARC's detection work.

Livermore's LANDMARC team has combined MIR units with a high-performance imaging system that uses sophisticated computer algorithms to convert large amounts of raw waveform data from the MIR units to high-resolution two- and three-dimensional images of the subsurface. The prototype systems enable users to visualize both antitank and antipersonnel mines and to differentiate them from rocks and other clutter of similar size and shape by the reflected MIR signal. Once the mines can be “seen” and identified, they can be recovered and destroyed.

LANDMARC prototypes have multiple MIR units that are either configured in a hand-held wand, much like that used for simple metal detectors, or mounted on a small robotic cart (Figure 1). In either configuration, the MIR array is passed over the ground with the antennas of the units about 10 centimeters above the surface. The units rapidly emit microwave impulses with very short risetimes (100 trillionths of a second) that radiate from transmitting antennas and penetrate the ground. These impulses strike and penetrate buried objects, bounce back to a receiving antenna, and are sampled and processed by an onboard computer to measure changes in the dielectric and conductivity properties of the

subsurface. In a few seconds, the data reconstruction algorithms convert the raw radar data into high-resolution two- and three-dimensional tomographic images of the subsurface (Figure 2). On the system currently under development, the images will appear on either a laptop computer or the operator's headset screen.

LANDMARC Innovations

One of LANDMARC's chief contributions to land-mine detection technology is combining MIR units with a high-performance imaging system.³ LANDMARC's MIR-based imaging software, which was originally developed for radar inspection of steel-reinforced concrete bridge decks, provides a great improvement over previous land-mine detection technology in sorting out clutter—the most difficult of the imaging tasks—and lowering the false-alarm rate.

Central to perfecting LANDMARC's imaging capabilities are the comprehensive signal and noise models being developed by the Livermore team. These models are based on the contributions from temperature differences, inhomogeneity in the soil, increased noise resulting from multiple reflections in MIR arrays, surface reflections, and subsurface clutter such as rocks, roots, and voids. They identify terrain and soil conditions where radar is likely to work well and other situations where different types of sensors would be more appropriate. More important, the models are used to design algorithms to help reduce the false-alarm rate and increase the positive identification rate in laboratory and field tests, both of which, in turn, improve LANDMARC's ability to discriminate between mines and clutter.

Results from Field Testing

Preliminary experiments identified the operational requirements of the prototype systems. The LANDMARC team developed the reconstruction algorithms that generate a three-dimensional image and is using them to investigate design trade-offs such as array size, sampling rate, and overall speed. In laboratory tests, the prototype clearly distinguished plastic antipersonnel mines from surrounding soils. In field tests at Fort Carson in Colorado and Fort A. P. Hill in Virginia, funded by the U.S. Defense Advanced Research Projects Agency (DARPA), the system performed well, though at a slow pace. The images it produced indicated that much progress has been made in removing the strong ground-surface reflection and other noise sources—that is, improving the signal-to-clutter ratio.

Field tests also indicated areas for additional refinement, among them using higher frequencies (that is, wider bandwidth) to improve resolution and better distinguish mines from clutter, and providing the system with a means of communicating a more accurate field position of the imaged mines.

Future Plans

When field tests with the prototypes are complete, the LANDMARC team plans to conduct blind tests at U.S. Army mine fields to measure detection probabilities under realistic conditions. In addition, plans to speed up the scan rate with advanced arrays are under way. Already experienced in industrial licensing of the MIR technology, the team will then direct LANDMARC toward external sponsorship for deployment in actual mine fields. The Department of Defense, U.S. industries, nongovernmental organizations such as Operation USA and the World Bank, and foreign governments have all shown interest in using Livermore's land-mine detection technology.

—Sue Stull

Key Words: antipersonnel mines, antitank mines, humanitarian land-mine detection, ground-penetrating radar, LANDMARC (Land-Mine Detection Advanced Radar Concept), micropower impulse radar (MIR), subsurface imaging, ultrawide bandwidth.

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Also see the MIR home page (<http://www-lasers.llnl.gov/lasers/idp/mir/mir.html>).

Improved Detonation Modeling with CHEETAH

A Livermore software program called CHEETAH, an important, even indispensable tool for energetic materials researchers worldwide, was made more powerful in the summer of 1997 with the release of CHEETAH 2.0, an advanced version that simulates a wider variety of detonations.

Derived from more than 40 years of experiments on high explosives at Lawrence Livermore and Los Alamos national laboratories, CHEETAH predicts the results from detonating a mixture of specified reactants. It operates by solving thermodynamic equations to predict detonation products and such properties as temperature, pressure, volume, and total energy released. The code is prized by synthesis chemists and other researchers because it allows them to vary the starting molecules and conditions to optimize the desired performance properties.

One of the Laboratory's most popular computer codes, CHEETAH is used at more than 200 sites worldwide, including ones in England, Canada, Sweden, Switzerland, and France. Most sites are defense-related, although a few users, such as Japanese fireworks researchers, are in the civilian sector. In the U.S., the software has become the Department of Defense's preferred code for designing new explosives (Figure 1) and, to a lesser extent, propellants. (The Livermore work is supported under a Memorandum of Understanding between the Departments of Defense and Energy and is administered through the Office of the Secretary of Defense, Office of Munitions.) CHEETAH is also used by many defense contractors, such as Lockheed Martin and Thiokol, and by small detonation companies.

CHEETAH was developed in 1993 by Livermore chemist Larry Fried and his colleagues at the Laboratory's High Explosives Applications Facility (HEAF) in an effort to update the long-standing TIGER thermochemical code. TIGER, in turn, was a derivative of the Laboratory's original RUBY code from the 1960s. The goal in creating CHEETAH, says Fried, was to make the use of thermochemical codes more attractive to high-explosive formulators through fast, yet scientifically rigorous codes, convenient user interface, and time-saving features such as a library of 200 starting reactants and 6,000 possible products.

Using CHEETAH

CHEETAH's graphical user interface is designed for both Macintosh and Microsoft Windows or Windows NT operating systems. The interface sports three "views." The first view is the input window, from which most commands are entered. The second view is the main output file, in which text is displayed in black when CHEETAH is inactive and red when a calculation is being performed. The third view provides a concise summary of the calculations. Advanced Windows and Macintosh users can also access CHEETAH's command line interface. This command interface is the only form of input possible on systems running the UNIX operating system.

The user first chooses the starting reactants by clicking on the reactant button represented by an Erlenmeyer flask icon. CHEETAH's database of starting reactants, which includes the most frequently used explosives and binders, saves the user the inconvenience of looking up thermodynamic constants for each reactant.

Next, the user chooses one of three different kinds of calculations corresponding to a high-explosive detonation or to the firing of an artillery gun or a rocket. Runs are accomplished by clicking on the green-light icon.

Alternatively, the user could employ the automatic formulator that adjusts the relative proportions of starting materials to match desired performance. For example, a shaped charge designed to penetrate armor needs to deliver its energy as quickly as possible, say, in 10 microseconds. By contrast, high explosives used in rock blasting must deliver energy more slowly, over tens of milliseconds. In this way, researchers can use CHEETAH to "test" new high-explosive formulations without resorting to actual small-scale tests.

The States menu allows the user to specify the thermodynamic states that CHEETAH will calculate. For example, the user can determine the total energy of detonation or the energy of explosion at constant volume.

Updates Expand Capabilities

In 1996, the Livermore team released CHEETAH 1.40, which had extensive improvements to stability and user-friendliness and included advanced features to make its

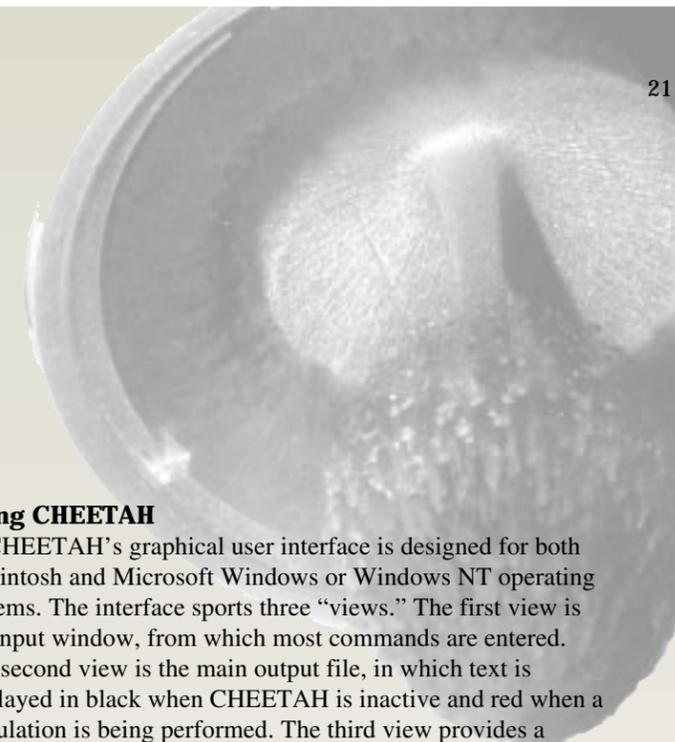
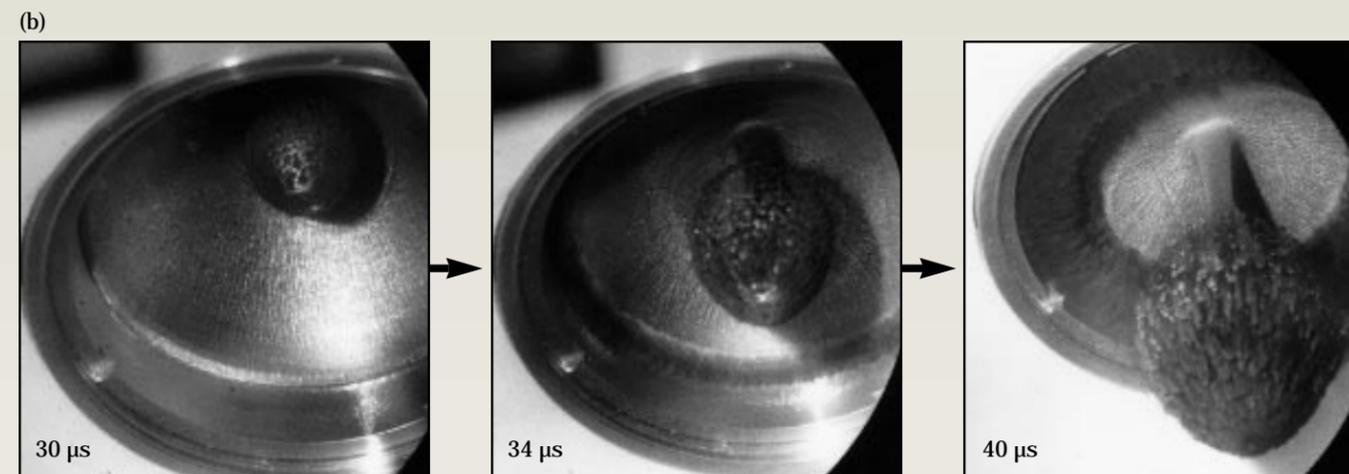


Figure 1. (a) This new explosive paste material was designed using CHEETAH to deliver high energy very quickly for use against armored tanks. (b) After formulation, it was used in an experimental shaped charge, which launches a copper metal jet in only 10 microseconds.



calculations more reliable over a wider range of material types and applications.

Fried says that the most significant improvement in CHEETAH 2.0 is the addition of chemical kinetics, which should help greatly in treating nonideal (slow) detonation processes. The addition of a chemical kinetic framework, based upon modern Wood-Kirkwood detonation theory, allows for modeling of time-dependent phenomena such as partial detonation.

Such nonideal phenomena are often poorly modeled by traditional Chapman-Jouguet thermodynamic theory, the basis for most of CHEETAH's calculations. Chapman-Jouguet theory assumes that thermodynamic equilibrium of the detonation products is reached instantaneously and that all products are consumed completely. In truth, actual situations may give different results because some components of the explosive react too late to drive the detonation front and because heat flows too slowly to bring all components into thermal equilibrium.

Fried has found that with chemical kinetics, CHEETAH can predict the detonation velocity of slowly reacting materials such as PBXN-11 (a mixture of the explosive RDX and aluminum, ammonium perchlorate, and rubber binder, with a detonation velocity of 8 millimeters per microsecond) to within 0.2 millimeters per microsecond. A calculation

ignoring kinetics is only accurate to within 2 millimeters, and thus, CHEETAH improves prediction of detonation velocity tenfold.

CHEETAH and Weapons Stewardship

The new chemical kinetics capability is very important for simulating the insensitive high explosives used in nuclear weapons. Simulating these materials has traditionally been difficult because they are much slower to react than classical high explosives. Yet, realistically modeling insensitive high explosives has acquired much greater importance in the current era of no nuclear testing and with the advent of the Department of Energy's Stockpile Stewardship and Management Program.

"As the Laboratory's mission changes to nuclear weapon stewardship, we need to change our tools from those focusing on design to those looking at aging," says Fried. "High explosives change over time, and we need to know more about how those changes could affect their performance."

Toward that end, a major effort was launched last year, in collaboration with Livermore computer scientists Steve Anderson and Shawn Dawson, to link CHEETAH to the extensive hydrodynamic codes of DOE's Accelerated Strategic Computing Initiative. The goal is to create more complete models of high-explosive detonations.

User Satisfaction

At Livermore, CHEETAH is being used to help guide the work of both synthesis and formulating chemists in a molecular design process similar to that found in pharmaceutical research (see *June 1997 Science & Technology Review*, pp. 4-13). It is part of the Laboratory's effort to provide more rigorous scientific structure for a field long dominated by intuition and trial and error.

Fried reports high satisfaction among CHEETAH users. He notes that in the current era of constrained funding, the software can take the place of many actual experiments, thereby saving money by permitting the user to see the result of different formulations. And when cost savings are combined with safer and faster operation of experiments, there is even greater cause for user satisfaction. What's more, the program, now supplied on a CD-ROM, is free of charge to researchers in nonsensitive nations.

There is also no charge for customer support in the form of e-mail dialogues with Fried. User problems and their resolutions are posted electronically in the hope of alerting users to commonly encountered problems.

Fried and fellow researchers Clark Souers and Michael Howard continue to update and strengthen CHEETAH's capabilities. Fried is considering establishing a World Wide Web site so that a researcher lacking good computer resources

could log onto one of Lawrence Livermore's smaller computer systems. A Web site could also provide a forum for discussions with users as well as provide ready electronic access to the 300-page manual.

—Arnie Heller

Key Words: Accelerated Strategic Computing Initiative (ASCI), Chapman-Jouguet thermodynamic theory, CHEETAH, High Explosives Applications Facility (HEAF).

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Each month in this space we report on the patents issued to and/or the awards received by Laboratory employees. Our goal is to showcase the distinguished scientific and technical achievements of our employees as well as to indicate the scale and scope of the work done at the Laboratory.

Patents

Patent issued to	Patent title, number, and date of issue	Summary of disclosure
Layton C. Hale	Adjustable Link for Kinematic Mounting Systems U.S. Patent 5,642,956 July 1, 1997	A device that provides backlash-free adjustment along its single-constraint direction and flexural freedom in all other directions. The adjustable link comprises two spheres, two sockets in which the spheres are adjustable-retained, and a connection link having threads connected at each end to the spheres. The adjustable link provides a single direction of restraint and adjusts the length or distance between the sockets. Six such adjustable links provide for six degrees of freedom for mounting an instrument on a support. The adjustable link has applications in any machine or instrument requiring precision adjustment in six degrees of freedom, isolation from deformations of the supporting platform, and/or additional structural damping.
James A. Folta	Miniaturized Flow Injection Analysis System U.S. Patent 5,644,395 July 1, 1997	Microflow channels and capillaries formed by etching microchannels in a substrate or wafer, such as silicon or glass, followed by bonding to another substrate or wafer. Microvalves, available commercially, are bonded directly to the microflow channels. An optical absorption detection cell is formed near the capillary outlet, and light is both delivered and collected with fiber optics. The microflow system is designed mainly for analysis of liquids and currently measures 38 by 25 by 3 millimeters, but can be designed for gas analysis and be substantially smaller in construction. The system can be used when analysis involves small samples mixed with small quantities of reagents, the reaction is within a capillary flow system, and the reaction products are detected.
Milton A. Northrup Dino R. Ciarlo Abraham P. Lee Peter A. Krulevitch	Microfabricated Therapeutic Actuator Mechanisms U.S. Patent 5,645,564 July 8, 1997	An electromechanical microgripper that has a large gripping force (40 millinewtons), where actuation is generated by shape-memory alloy thin-films. The stress induced can deflect each side of a microgripper up to about 55 micrometers for a total gripping motion of about 110 micrometers. The microgripper has a relatively rigid structural body and flexibility in function design such that it can be used as a biopsy tissue sampler, a tip designed for handling microparts, or a release-retrieval mechanism for items such as platinum coils or other materials in bulging portions of the blood vessels, known as aneurysms. The micromechanism can be mounted at one end of a catheter and manipulated from the other end, thereby extending and improving the application of catheter-based intervention therapies.
Richard M. Christensen	Fabrication Method for Cores of Structural Sandwich Materials Including Star Shaped Core Cells U.S. Patent 5,647,933 July 15, 1997	A simple and cost-effective method that involves bonding folded or unfolded sheets of lowdensity material in both vertical and horizontal directions to form a block, which, when mechanically pulled normal to the plane of the sheets, expands to form interconnected star-shaped cells. The fabrication method produces a cellular core material that is much more flexible than any previously known core materials and can be conformed easily to curved shapes, thereby providing for the fabrication of curved sandwich panels. This method can be used to fabricate geometric cell arrangements other than the star/non-star-shaped cells. Four sheets of material (either a pair of bonded sheets or a single folded sheet) are bonded to define an area between them, which forms the star-shaped cell when expanded.
Randall L. Simpson Cesar O. Pruneda	Non-Detonable and Non-Explosive Explosive Simulators U.S. Patent 5,648,636 July 15, 1997	A material that contains small amounts of the actual energetic material to be simulated, but only as a minor component overall in a nonreactive matrix or on a nonreactive substrate. The fabrication of explosive simulants, which are chemically equivalent to explosives but cannot chemically react violently (nondetonable, as well as nonexplosive), involves formulating materials with large surface areas of explosives, but with volumes too small to sustain detonation. These methods are carried out either by standard slurry-coating techniques to produce a material with a very high binder-to-explosive ratio or by coating inert beads with thin layers of explosive molecules.

(continued on inside back cover)

A New World of Biomedical Research: The Center for Accelerator Mass Spectrometry

Lawrence Livermore's Center for Accelerator Mass Spectrometry (AMS) is one of the leading AMS facilities in the world, performing about 25% of all AMS analyses. It is also at the forefront of the emerging field of AMS as applied to biomedical research. AMS is so sensitive that it can identify just a few molecules of a substance among trillions of molecules. This sensitivity makes possible for the first time the study of toxins, dietary nutrients, drugs, and other substances in dosages that are relevant to humans. Work with volunteer subjects indicates that a chemical that is produced when meat is cooked adversely affects human DNA more than it does the DNA of laboratory animals. This research supports the need to pursue additional human biological risk assessment using AMS. Livermore is also performing studies of the human metabolism of calcium, which are difficult without AMS.

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Isotope Tracers Help Manage Water Resources

Livermore isotope scientists are using stable and radioactive isotopes to learn about groundwater sources, ages, travel times, and flow paths and to determine the path and extent of contaminant movement in the water. These studies started at the Nevada Test Site because of concern about the transport in groundwater of contaminants from underground nuclear testing. When water managers can accurately predict where contaminated groundwater will be, they can avoid using it. Groundwater studies have also been performed for the Orange County Water District, Contra Costa County, and other public agencies, as well as at the Livermore site. Livermore scientists are some of the first to marry isotope tracing techniques and numerical groundwater models, using data from the former to verify and validate the predictions of the latter and thus provide a powerful forecasting tool for water managers.

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(continued from p. 24)

Awards

Jack Dini, former leader of the Laboratory's Manufacturing and Materials Engineering Division, has been named a **fellow of the American Electroplaters and Surface Finishers Society (AESF)**. Dini was recognized for "his contributions to the advancement of the science and technology of surface finishing, and for leadership in the dissemination of this knowledge. . . ." He was president of the AESF (1984-85), chaired and served on many of the society's committees,

and has published over 200 technical articles on metal finishing as well as a book, *Electrodeposition: The Materials Science of Coatings and Substrates* (Noyes Publications, 1993). Dini is also a fellow of the only other electroplating technical society in the world, the Institute of Metal Finishing, London, England. He recently retired after an 18-year career at the Laboratory and continues to work here as a participating guest.

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