September/October 2008

Science & Technology REVIEW

National Nuclear Security Administration's
Lawrence Livermore National Laboratory

Modeling Supernova Explosions

Also in this issue:

- **Counteracting Biothreats and Treating Cancer**
- **Microneedles Revolutionize Biological Fluid Extraction**
- **Planarization Process Removes Microchip Defects**

About the Cover

On the cover, a white dwarf star pulls matter from a companion star onto its surface through an accretion disk. When the white dwarf reaches a particular mass known as the Chandrasekhar limit (named after its discoverer Subrahmanyan Chandrasekhar in the background photo), it explodes with a luminosity about 5 billion times brighter than our Sun, typically outshining its host galaxy. The article beginning on p. 4 describes one of Livermore's 2007 Computing Grand Challenge collaborations, which used supercomputers to simulate the dynamics of this class of exploding stars known as Type Ia supernovae. (Illustration by Justyn R. Maund, University of Cambridge, courtesy of the National Aeronautics and Space Administration.)

Cover design: Amy Henke

About the Review

At Lawrence Livermore National Laboratory, we focus science and technology on ensuring 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 six 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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Lawrence Livermore National Laboratory

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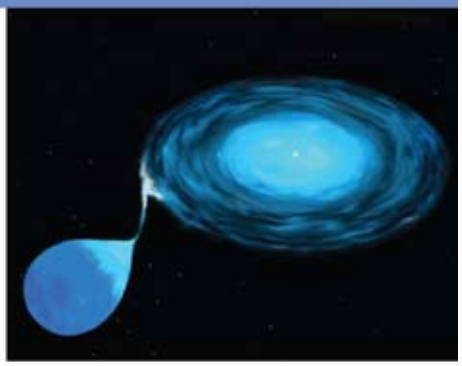
Features



Research Highlights

Departments

Laboratory captures three R&D 100 awards

The Laboratory has garnered three R&D 100 awards this year. Each year, *R&D Magazine* presents these awards, also known as the "Oscars of Invention," to the top 100 industrial, high-technology inventions submitted to its competition.

The three Livermore inventions honored are as follows:

• Dynamic Transmission Electron Microscope—A microscope that provides the highest resolution ever for digital imaging of ultrafast material processes on the nanometer, or billionth-of-a-meter, scale. This technology was developed in conjunction with JEOL USA, Inc., of Peabody, Massachusetts.

• Autonomous Alignment Process for Laser Fusion Systems—A revolutionary "hands-off" technology that directs and aligns multiple high-energy laser beams to enable controlled fusion reactions in a laboratory. The technology was developed for the National Ignition Facility.

• SecureBox—A low-cost, reliable, reusable system designed to improve the security of cargo containers during shipping. This award was won in collaboration with Secure Box Corporation of Santa Clara, California, and the National Infrastructure Institute's Center for Infrastructure Expertise of Portsmouth, New Hampshire.

S&TR will feature detailed reports on these award-winning inventions and the teams that created them in its November/December issue.

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LLNS 2008 Community Gift Program Award recipients

Donations totaling $100,000 were distributed through the 2008 Lawrence Livermore National Security, LLC (LLNS) Community Gift Program. The monetary gifts are a reflection of LLNS's commitment to being a good neighbor and making a positive contribution to its local communities. From the 141 applications received totaling nearly $1.7 million in requests, 20 were selected for awards through a committee review process. The majority of these awards serve children in the Tri-Valley Area (Livermore, Pleasanton, Dublin, San Ramon, and Danville) and San Joaquin County, with a focus on science and math education and cultural arts. The donations come from the fee LLNS receives to manage Lawrence Livermore National Laboratory. More information on LLNS and its Community Gift Program is available at www.llnsllc.com.

The new program expands on LLNS's community giving, which already has benefited the greater Bay Area. In December 2007, LLNS matched $1 million in employee donations to the Laboratory's HOME (Helping Others More Effectively) Campaign. The HOME Campaign benefits nonprofit agencies in the Tri-Valley, San Joaquin Valley, and greater Bay Area. Since 1997, HOME has raised more than $1 million annually through employee donations that go directly to agencies selected by employees. This year, Laboratory employees pledged $1.4 million to the campaign, benefiting 446 agencies. By adding $1 million to the funds, LLNS brought the total contribution to $2.4 million.

"LLNS is committed to being a good neighbor in our local communities and is proud of the generous support of employees to those in need," says George Miller, president of LLNS and director of Lawrence Livermore.

Contact: Ann Willoughby (925) 423-4234 (willoughby1@llnl.gov).

Chemical vapor research makes cover of *The Analyst*

A paper by Lawrence Livermore researchers describing the development of a compact, low-power sensor array to detect chemical vapor analytes was chosen by *The Analyst* for the cover article of the May 2008 issue, which is devoted to "Detection for Security." Researchers from the Chemistry, Materials, Earth, and Life Sciences Directorate and the Physical Sciences Directorate demonstrated the use of the sensor array to detect 11 chemical vapors representing a breadth of chemical properties, in real time and over a wide range of vapor concentrations. The article also describes the detection of chemical warfare agents (CWAs) VX and sulfur mustard, representing the first published report of CWA vapor detection by a polymer-based, cantilever sensor array. Bradley Hart led the research team that included Albert Loui, Tom Wilson, Tim Ratto, Scott McCall, Erik Mukerjee, and Adam Love during the three-year project, which began in 2005.

Slightly larger than a matchbook, the system can fit unobtrusively in small spaces. According to Hart, it could be a candidate for use in a Homeland Security Advanced Research Projects Agency proposal that seeks technology to integrate sensors for chemical, biological, or radiological threats onto a mobile communications platform, such as a cell phone. Such a network would warn, identify, and detect the scope of a potential threat agent.

The eight-cantilever sensor array has shown sensitivities from 4 parts per billion to 16 parts per thousand in 13 chemicals ranging from water to volatile organic compounds, whose industrial emissions are regulated because of their deleterious health effects. Eventual capabilities include onboard data storage and wireless transmission.

Contact: Bradley Hart (925) 423-1970 (hart14@llnl.gov).

Answering Scientists' Most Audacious Questions

EVEN before the Laboratory opened in 1952, Ernest O. Lawrence and Edward Teller placed an order for one of the first commercial supercomputers, a Univac mainframe. The lumbering machine featured vacuum tubes and barely supported primitive one-dimensional simulations; yet it revolutionized scientific calculations. Today, simulations performed on extremely powerful supercomputers have become so essential to scientific discovery that simulation is considered a peer to theory and experiment.

Many investigators first build a computer model to design and guide their physical experiment and then use simulations to better understand experimental results. Some computer simulations take the place of physical experiments because the time period of the physical reality is too short or long, hazardous materials are involved, or they can't be done in a laboratory (as with earthquake simulations or underground nuclear weapons tests). These kinds of virtual experiments are accomplished every day with great fidelity on Livermore supercomputers.

The National Nuclear Security Administration (NNSA) sponsors the Laboratory's pioneering work in computer simulation, which has been driven by the need to support classified weapons research. At the same time, advanced simulations have played a crucial role in unclassified research. Over the past decade, we have made significant investments in Livermore's high-performance computing resources dedicated to unclassified research. The capabilities have grown from performing 72 gigaflops (billion floating-point operations per second) to more than 280 teraflops (trillion floating-point operations per second) today. These unclassified resources leverage the supercomputing expertise and infrastructure we have put in place for classified research. In turn, computing advances made in support of unclassified research initiatives bolster our classified research efforts and strengthen our expertise in computer science, mathematical modeling, computer architecture, software development, and infrastructure support.

Despite the growing proliferation and capability of unclassified supercomputers, demand for access far exceeds capacity. To best use limited resources and spark scientific discoveries in a broad range of scientific fields, Livermore launched the Institutional Unclassified Computing Grand Challenge Awards in 2006.

The annual Grand Challenge award competition seeks proposals that, with significant supercomputer resources, might address compelling, audacious, even grand-scale mission-related problems that promise unprecedented discoveries in science and engineering. These proposals cover a broad range of disciplines in climate change, astrophysics, inertial confinement fusion, seismic and nuclear explosion monitoring, and many other project areas. Internal and external referee panels that include subject-matter and computer-science experts review the proposals. They are judged on the quality of scientific investigation, importance of access to computing resources, ability to effectively use a high-performance supercomputer, quality and extent of external collaborations, and the proposed project's alignment with Department of Energy, NNSA, and Livermore's national security missions.

The article beginning on p. 4 describes one 2007 Grand Challenge effort that used Atlas to simulate in great detail the dynamics of a class of exploding stars known as Type Ia supernovae. Obtaining a better understanding of these enormously energetic explosions improves our knowledge of the physics of nuclear explosions. The simulations also promise to advance our understanding of the expansion of the universe and the phenomenon of dark energy, which some cosmologists call the greatest mystery in the universe. Typical of most winning proposals, the supernova effort involved colleagues at universities and other national laboratories, in this case the University of California at Santa Cruz, State University of New York at Stony Brook, and Lawrence Berkeley National Laboratory.

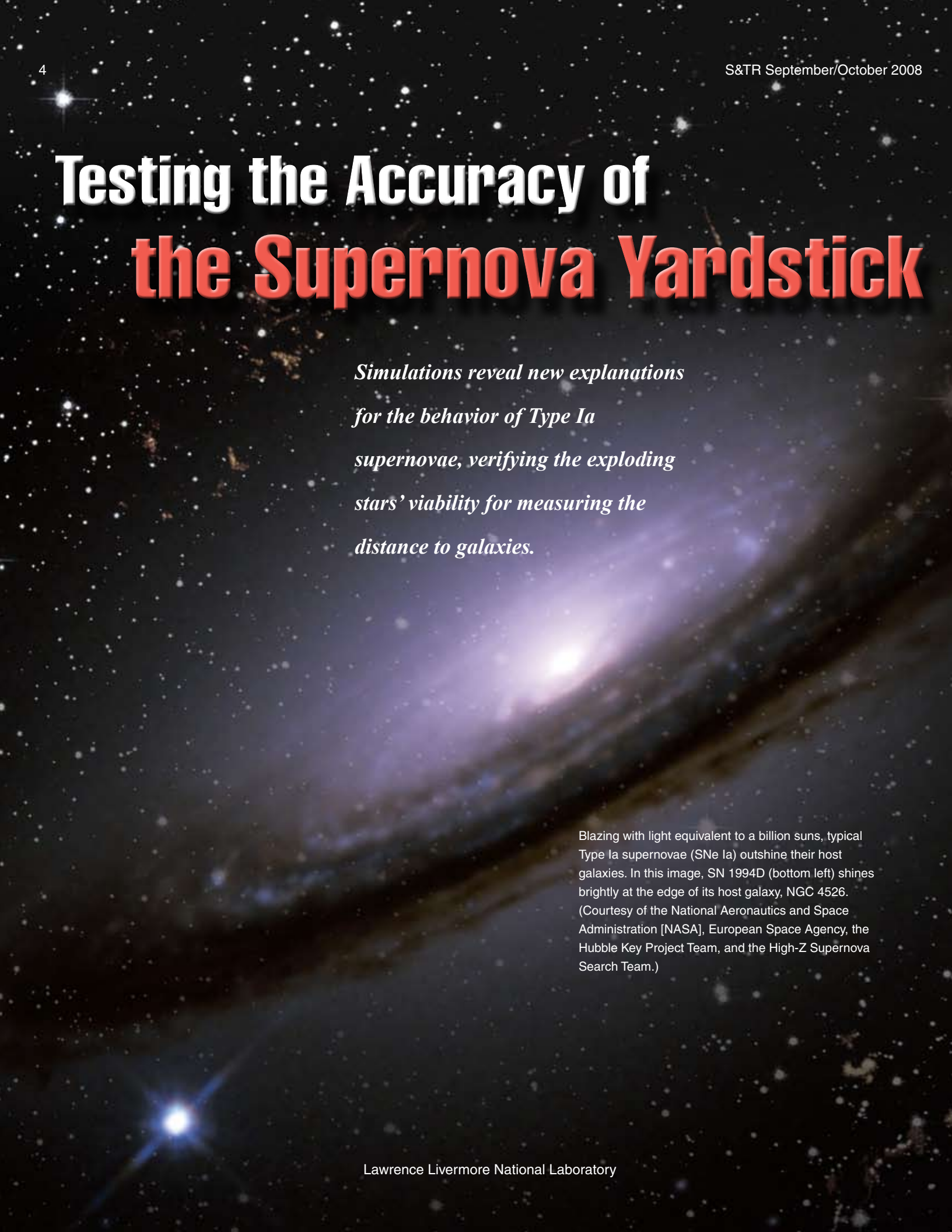
In May, we announced the winning proposals in our third round of Grand Challenge awards. Out of 29 proposals, 18 were granted a combined 84.5 million central-processing-unit (CPU) hours on Atlas, a 44-teraflops machine, or Thunder, a 22-teraflops machine. Additional CPU hours will be granted on the newly unclassified portion of BlueGene/L, an approximate 200-teraflops machine. Last year, we held a public symposium to showcase the accomplishments of the Grand Challenge participants, and we plan to host a similar meeting later this year.

Staying focused on high-end computing problems helps us ensure a breadth of supercomputing technologies. We're working to improve our simulations by enhancing resolution, adding more physics, and making possible greater use of three-dimensional modeling. These applications, in turn, demand the best possible computers and infrastructures. Thanks in part to Grand Challenge projects, Livermore is continuing to redefine what is computationally possible.

■ Dona Crawford is associate director for Computation.

Testing the Accuracy of the Supernova Yardstick

Simulations reveal new explanations for the behavior of Type Ia supernovae, verifying the exploding stars' viability for measuring the distance to galaxies.



Blazing with light equivalent to a billion suns, typical Type Ia supernovae (SNe Ia) outshine their host galaxies. In this image, SN 1994D (bottom left) shines brightly at the edge of its host galaxy, NGC 4526. (Courtesy of the National Aeronautics and Space Administration [NASA], European Space Agency, the Hubble Key Project Team, and the High-Z Supernova Search Team.)

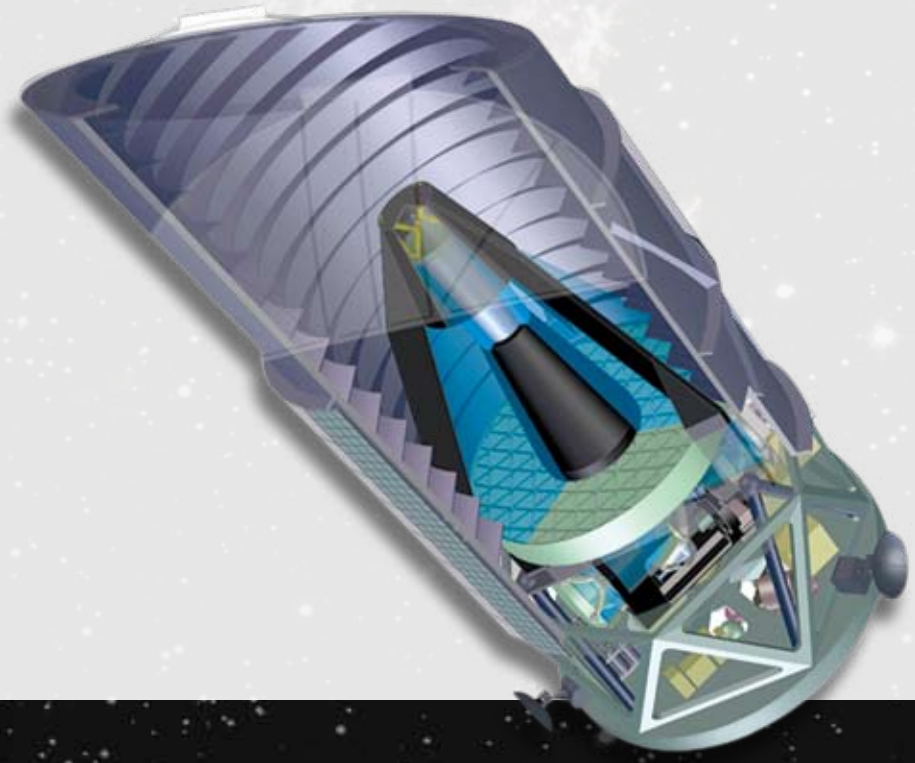
ASTRONOMER Edwin P. Hubble, for whom the Hubble Space Telescope is named, discovered in 1929 that the universe is expanding. Astronomical observations almost 70 years later revealed the startling news that not only is the universe expanding, but also the rate at which it is expanding is accelerating. Theories for the observed acceleration abound, and they differ in many ways. But all theories ascribe the acceleration to dark energy—matter of unknown composition that does not emit or reflect electromagnetic radiation and is therefore difficult to observe directly. Dark energy, which may constitute up to 70 percent of all matter and energy in the universe, is the greatest mystery in astronomy today.

News about the accelerating expansion, reported in 1998, was based on observations of exploding stars known as Type Ia supernovae (SNe Ia). (See the box on p. 9.) These thermonuclear explosions mark the death throes of white dwarf stars. SNe Ia are less common than Type II supernovae, which occur from gravitational collapse. Because most SNe Ia are observed to have quite similar characteristics, astronomers have used them as "standard candles," which serve as "yardsticks" for calculating the distance to their host galaxies from Earth. Using the calculated distances and observed velocity (determined by the red shift of the light), cosmologists gauge the degree of acceleration of these galaxies and, by extension, the influence of dark energy.

The Department of Energy (DOE) Office of Science has identified "dark energy and the search for genesis" as one of its top priorities. Fusion energy, advanced computing, and nuclear matter at the extremes are among others. Solving the mystery of dark energy is a key component of *Quantum Universe: The Revolution in 21st-Century Particle Physics*, a recent report from the Office of Science and the National Science Foundation that identifies the most compelling questions facing contemporary particle physics research. DOE and the National Aeronautics and Space Administration (NASA) plan to launch the SuperNova Acceleration Probe (SNAP) before 2020 to more precisely measure the expansion of the universe and to investigate the nature of the dark energy accelerating this expansion. SNAP is one of several Earth- and space-based missions planned over the next 15 years to quantitatively observe supernovae, examine dark energy, and better understand the beginning and possible future of our universe.

The application of SNe Ia as standard candles for determining distances to galaxies has revolutionized cosmology, giving astronomers an essential tool to extend their knowledge of the universe's expansion and acceleration. However, that

The SuperNova Acceleration Probe (SNAP) is a proposed space-based observatory that would locate and analyze thousands of SNe Ia each year. SNAP is part of the Joint Dark Energy Mission, a cooperative venture between NASA and the Department of Energy. (Image courtesy of Lawrence Berkeley National Laboratory.)



knowledge depends on the assumption that all SNe Ia are truly "standard." Does each explosion provide the same intrinsic brightness? With the planned space missions, the number of observed SNe Ia is expected to increase from a few thousand to hundreds of thousands in the near future. Accurately understanding the behavior of SNe Ia is essential to making the investments in science pay off.

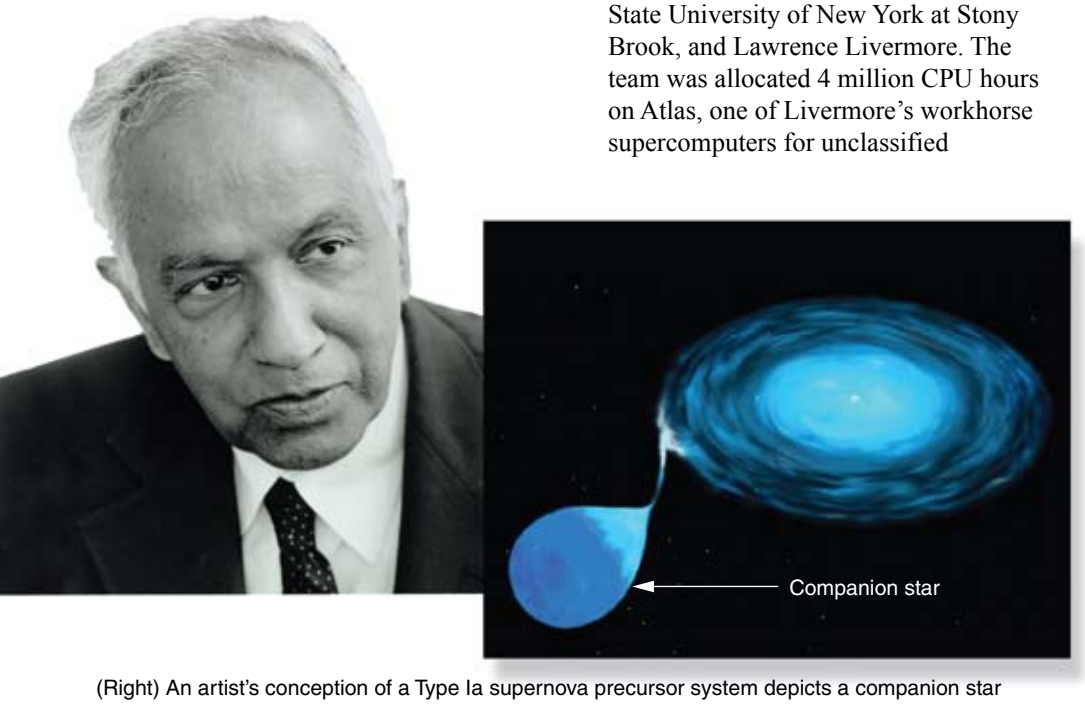
Birth of a Candle

Nearly all of the SNe Ia identified to date have been observed with ground-based telescopes. This sampling thus consists mostly of nearby SNe Ia, which are fairly young. The older, more distant SNe Ia are dimmer and more difficult to observe and may explode differently than nearby SNe Ia. Livermore nuclear physicist Rob Hoffman led a collaboration that used one of the world's largest supercomputers for simulating the physical processes underlying the explosions of SNe Ia to understand their similarities and differences.

The study was a part of Livermore's Computing Grand Challenge Program, which allocates millions of central-processing-unit (CPU) hours on Laboratory supercomputers to unclassified projects that support Livermore's missions. The supernova simulations were performed by the Computational Astrophysical Consortium (CAC), with members from the University of California at Santa Cruz, Lawrence Berkeley National Laboratory, State University of New York at Stony Brook, and Lawrence Livermore. The team was allocated 4 million CPU hours on Atlas, one of Livermore's workhorse supercomputers for unclassified research. Previously, the team had used supercomputers at Oak Ridge National Laboratory, the National Energy Research Scientific Computing Center at Lawrence Berkeley, and NASA Ames. Likening these supercomputer resources to a baseball lineup, Hoffman says, "Atlas is our 'cleanup' hitter, not because it is a particularly heavy hitter—they all are—but because it gets a hit every time."

SNe Ia evolve from a complex of two stars, in which a dead stellar core called a white dwarf accretes material from a companion star. As the white dwarf collects more material, it becomes denser and hotter. Eventually, conditions become so extreme that carbon atoms fuse and ignite one or more miniscule nuclear flames, which erupt near the center of the dwarf. A runaway thermonuclear reaction ensues that disrupts the entire white dwarf, creating an extremely bright optical display that is visible billions of light years away. For a few weeks, SNe Ia are so bright they outshine their host galaxies. "Astrophysicist Subrahmanyan Chandrasekhar, who made enormous contributions to the study of stellar structure and dynamics, showed theoretically in the 1930s that a white dwarf could grow no larger than 1.38 solar masses before it would explode," says Hoffman. "An exploding white dwarf burning a significant fraction of this mass provides the observed luminosity. A strong argument for using SNe Ia as standard candles is their initial identical configurations."

A Type Ia supernova explosion generates a light curve, which is quite similar for nearly all SNe Ia. The brightness of a typical Type Ia supernova peaks about 20 days after the explosion, after which the light curve follows almost exactly the radioactive decay curve for nickel-56, an isotope that decays to iron. Although the light curves of all SNe Ia



(Right) An artist's conception of a Type Ia supernova precursor system depicts a companion star accreting material through an accretion disk onto a dead stellar core composed of carbon and oxygen, called a white dwarf. (Drawing courtesy of Space Telescope Science Institute and NASA.) (Left) In 1931, astrophysicist Subrahmanyan Chandrasekhar showed theoretically that a white dwarf would explode as a supernova when its mass exceeded what is now called the Chandrasekhar limit (1.38 times the mass of our Sun). In 1983, Chandrasekhar, along with William Alfred Fowler, was awarded the Nobel Prize in Physics in part for this work.

exhibit a similar pattern, they do differ in peak brightness and the brighter ones (with higher peaks) are wider.

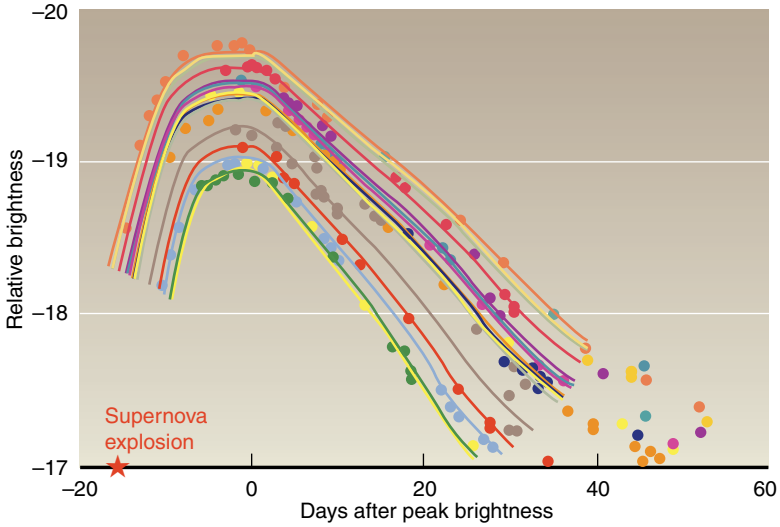
Astronomers use a technique that reduces all SNe Ia light curves to a single width–luminosity relationship. In this way, all SNe Ia can be considered as a single parameter family. The width of a light curve indicates the supernova's intrinsic brightness, according to the rule "broader is brighter." Also similar are the emission spectra sampled at specific times after peak brightness, lending yet more credence for use of SNe Ia as standard candles. The spectra of SNe Ia indicate the presence of silica, sulfur, calcium, and nickel-56. "About one-third of all iron in the universe, and by inference the hemoglobin in our blood, comes from these exploding white dwarfs," says Hoffman.

A major goal of the team's simulations is to better understand the width–luminosity relationship. In particular, scientists want to rule out the possibility that distant SNe Ia, formed in the earliest epochs of the universe, might explode differently from SNe Ia formed more recently. For example, the star-forming environment may have been different in the early universe because far fewer heavy elements were present. "We want to know if variations in initial conditions influence supernova brightness as we go back in time," says Hoffman. "If so, we would like to account for those variations to more accurately determine the distances, which would be required for the dark energy surveys. By accounting for variations, we can better use SNe Ia as standard candles."

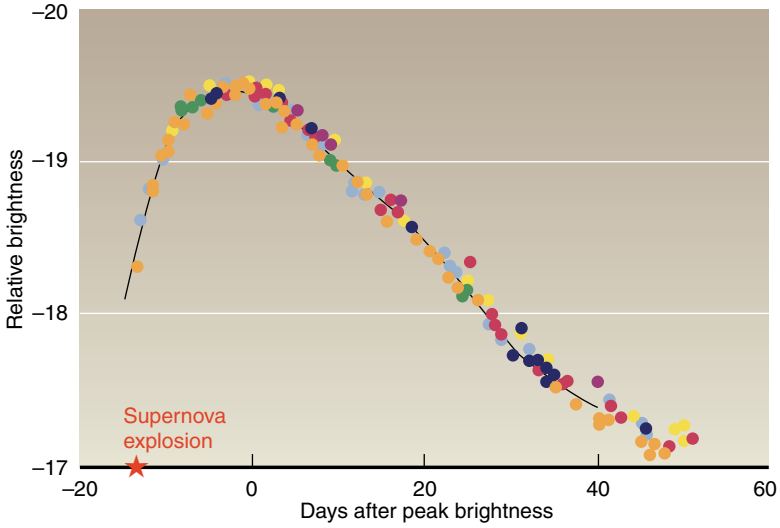
A Library for Observations

The CAC team's Grand Challenge effort, which ended in May, has resulted in a library of one- and two-dimensional models of SNe Ia with light curves and spectra. An astronomer spotting what appears to be a Type Ia supernova can compare its brightness, spectra, and light curve to the library data. Such a library will be particularly important because the planned DOE and NASA Earth- and space-based telescopes promise to discover tens of thousands of SNe Ia every year. Livermore scientists are helping design one of these telescopes, the Large Synoptic Survey Telescope, a ground-based, 8.4-meter device that will image faint astronomical objects. (See *S&TR*, November 2005, pp. 12–20.)

This same library of calculations and simulations also reveals for the first time why the amount of nickel-56 apparently controls the width of the light curve. Scientists have known for some time that the brightness of SNe Ia is determined by the amount of nickel-56 synthesized in the explosion. The decay of this radioactive



SNe Ia explosions exhibit similar light curves. In this graph, brightness is plotted against time before and after peak light (Day 0). Although the light curve patterns are similar, the brighter ones (top) are broader. Data are from the Calan–Tololo supernova survey.

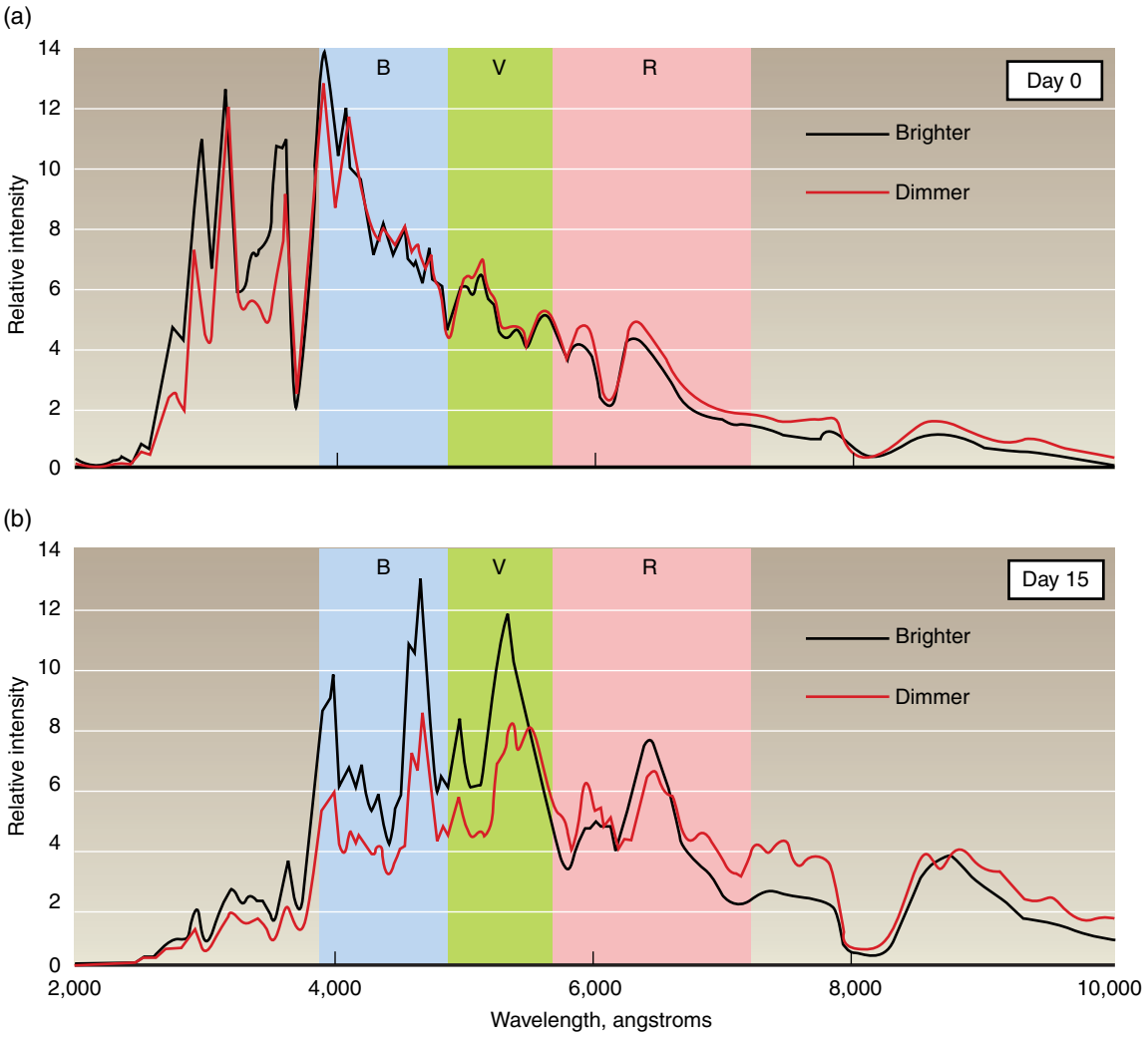


Astronomers use a technique that allows them to collapse SNe Ia light curves to a single curve so that the curves all obey a general width–luminosity relationship. The supernovae can thus be used as standard candles to infer the distance to their host galaxies.

isotope powers the luminous display. However, the problem of the light-curve width is challenging because the physics involves complex details of light transfer through the time-evolving, wavelength-dependent opacity of the supernova gas.

Because most SNe Ia have been observed from Earth, they have traditionally been seen through the electromagnetic spectrum of visual light. One of the team's important discoveries is that the width–luminosity relationship is most apparent in the color blue. Scientists are investigating how the color of supernova light evolves over time. Simulation results show that as supernovae iron-group elements (iron, cobalt, and nickel) cool, they exhibit a strong fluorescent effect, whereby light absorbed at blue wavelengths is reemitted at red and infrared wavelengths. The degree of fluorescence thus largely determines the color of the emergent supernova's spectrum.

Numerical models reveal that the fluorescence process is more efficient in lower temperature gas. Thus, as supernovae expand and cool, their color becomes increasingly red. In the dimmer supernovae, where the gas is initially cooler, this reddening effect evolves more quickly. When observed, the light curves of dim supernovae are found to drop rapidly. These findings are the basis of the width–luminosity relationship. "We are finding that not all SNe Ia are standard



The color of supernova light evolves over time. These graphs compare the evolution of a brighter supernova with more nickel (black line) and a dimmer supernova with less nickel (red line). Astronomers use the blue (B), visual (V), and red (R) filters to view specific ranges of the electromagnetic spectrum. The spectra have been superimposed so that they have the same intensity at about 4,200 angstroms. (a) At Day 0, both simulated supernovae have similar spectra. (b) By Day 15, light has shifted from the blue to red wavelengths as the supernovae expand and cool. In the dimmer supernova, this process happens more quickly and is responsible for the observed rapid decline of its light curve with time and hence the width–luminosity relationship.

candles," says Hoffman, "but most are within reasonable constraints."

Simulating Chaos

The evolution of SNe Ia is long and slow in the beginning, fast and furious in the middle, and then slow again in the end. For about a million years, the white dwarf accretes material from its companion star while its own core of carbon and oxygen becomes increasingly hot and dense. Eventually, convection takes over from conduction as the dominant cooling process, transferring heat from the center of the star outward toward the surface. When the buoyant material rises, shear forces generate turbulence, and nuclear energy from carbon burning increases exponentially as a function of temperature. That is, as the temperature rises, the amount of energy builds faster and faster, and the convection process alone cannot release this immense heat and energy. The temperature rises hundreds of millions of degrees over several hundred years. Suddenly, a nuclear flame ignites. The resulting explosion occurs in 1 second and is followed by a free expansion—an irreversible process in which gas expands without constraint. The expansion's light curve and spectra can be observed for up to 100 days.

Many uncertainties remain regarding the evolution of a white dwarf to its full expansion and the observed variation in brightness. Still not clearly understood are the strong convection currents leading to the formation of hot spots that ignite the flame, the propagation of turbulent nuclear burning through the star, the explosion itself, the accompanying synthesis of new elements, and the light curve and spectra emitted from the explosion.

The Livermore simulations, however, did address several outstanding questions surrounding SNe Ia, each of which has eluded a solution for decades. These questions included whether the flame ignites at one or several points and whether it originates at or near the center of the dwarf. The simulations also showed how the flame propagates through the white dwarf, how it is affected by turbulence as it moves outward toward less dense regions, and how it may transition from subsonic to supersonic speeds.

Tools of the Trade

"No computer today is capable of modeling chaotic, submillimeter-scale phenomena occurring in an object 1,800 kilometers across over the course of 100 days," notes Hoffman. "The space and time scales differ too much." Separate models are needed to simulate each component. Modeling SNe Ia requires computer codes tailored to reveal the multiple aspects of the entire event. The collaborative team used a suite of codes developed for the

Evolution of a Type Ia Supernova

In a galaxy the size of the Milky Way, Type Ia supernovae (SNe Ia) occur about once every 50 years. Astronomers discover new supernovae in other galaxies at a rate of a few per week. New spacecraft and ground-based telescopes currently being planned are expected to increase the number of recorded supernovae seen yearly by many times.

SNe Ia begin as a complex of two stars. The first is a dead star, called a white dwarf, composed mostly of carbon and oxygen, the products of helium burning. This intrinsically faint star has a very small radius and high density. Its mass is about 0.6 that of our Sun, and its average radius is about 8,000 kilometers. The white dwarf's thermonuclear energy sources are extinct, and the star is in its final stage of evolution. Its companion star is either a young (main sequence) star, such as the Sun, or a middle-aged (red giant) star.

The white dwarf and its companion star orbit each other so closely that gravity from the white dwarf pulls material from the younger star onto its surface, a process called accretion. As the white dwarf reaches a mass 1.38 times that of our Sun (known as the Chandrasekhar limit), it can no longer support the bulk of its mass. Its central temperature and density rise to extreme conditions—300 million degrees and a density of 3 billion grams per cubic centimeter. Increasing temperature and density inside the core ignite carbon fusion as the star approaches its mass limit before exploding.

The explosion releases a tremendous shock wave, with star matter expelled at a velocity of up to 20,000 kilometers per second, or up to 10 percent the speed of light. An enormous increase in luminosity occurs. This extremely luminous object, 5 billion times brighter than our Sun, may outshine its entire host galaxy before fading from view over several weeks. During that short period, the supernova releases as much kinetic energy as the Sun will radiate in its entire lifetime.

After the explosion, a Type Ia supernova follows a characteristic light curve, the graph of luminosity as a function of time. This luminosity is generated by the radioactive decay of elements synthesized in the explosion—in particular nickel-56, which decays to cobalt and then to iron. About one-third of all the iron in the Milky Way Galaxy comes from exploding SNe Ia. These explosions can also trigger the formation of new stars and planets.

most part by Lawrence Berkeley and Lawrence Livermore.

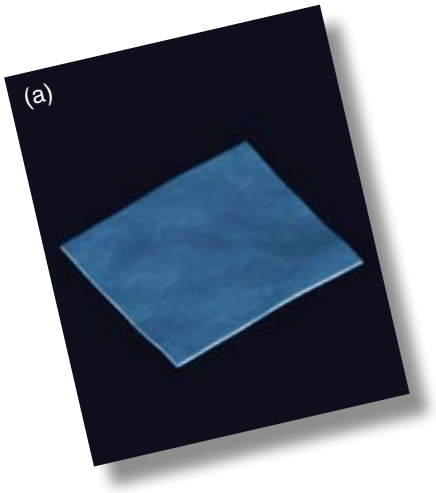
The code SNe is used to study the microphysics of nuclear flames and how these flames interact with turbulence. Another code, MAESTRO, incorporates the changes that occur as the dwarf begins to expand and release heat and as its hot core and less dense outer strata create buoyancy. Simulations from both codes concentrate on early events occurring at subsonic speeds.

When the thermonuclear explosion begins and materials start to move at supersonic speeds, the CASTRO hydrodynamic code takes over. Livermore has a long history of studying hydrodynamic behavior, which plays an important role in exploding nuclear weapons. In addition, the SEDONA code calculates the emergent spectra.

The team successfully combined these codes to model different phases of supernova evolution, ranging from the time when hot spots deep inside a dwarf's core give birth to the tiny nuclear flame to the weeks following the explosion. Various computer runs included modeling a white dwarf both in a stationary position and rotating at different speeds, the dwarf's initial flame igniting at different sites, flames burning at different speeds, and turbulence of varying amounts.

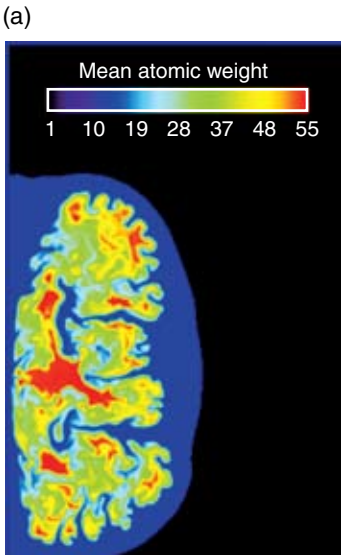
In two-dimensional simulations, a detonation with supersonic burning looks bright, and the spectra match most SNe Ia. If supersonic detonation and burning do not occur, the white dwarf explodes but is dimmer. Simulations showed that these spectra do not match those of most SNe Ia.

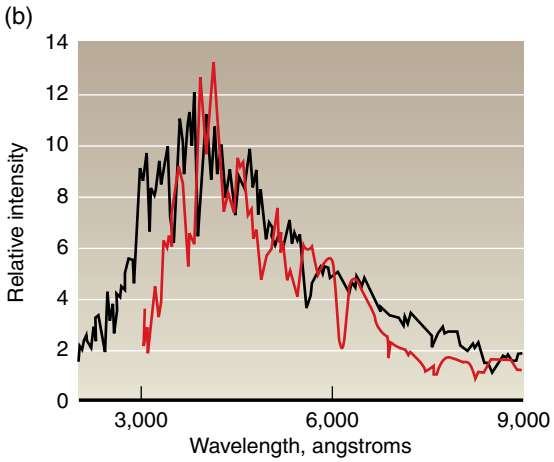
Scientists have debated whether an asymmetric explosion might modify both the luminosity and spectra of the material streaming out. The team's simulations of an asymmetric explosion produced the startling result that the peak brightness can vary with the viewing angle by nearly 40 percent. Therefore, if the spectra indicate an asymmetric explosion, one can mathematically correct for the brightness level.

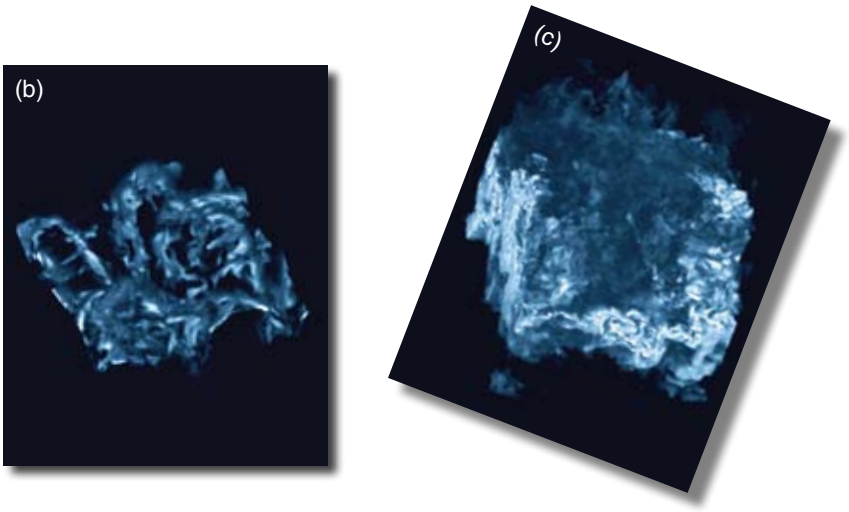


Simulation results show an initially thin nuclear flame—just 0.1 millimeter thick—moving through the dwarf's core, being pushed around by convective currents, and traveling at less than the local speed of sound. At first the flame remains fairly coherent. As it moves into regions of cooler and less dense fuel, turbulent motion deforms the flame, making it appear thicker and more wrinkled. At a critical point, the flame passes into the

(a) In this simulation, flames consuming a white dwarf remain subsonic throughout the explosion, exhibiting a dim supernova light curve. The nuclear burning produces a distribution of elements color-coded here by atomic weight (for example, blue is carbon and oxygen, green is silicon, and red is nickel). (b) The simulated spectrum (black line) reveals atypical features when compared with the spectrum observed in SN 1994D (red line). (c) When the turbulence is adjusted on the same model, the flame transitions to supersonic speeds after an initial subsonic explosion. This supernova produces 2.5 times more nickel, and hence, its brightness is much greater. (d) The spectrum of this simulated delayed detonation (black line) compares well to features observed in SN 1994D (red line).





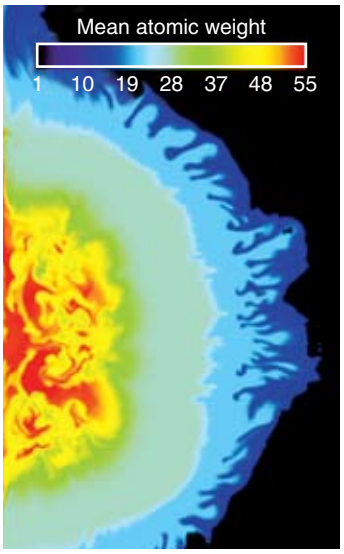


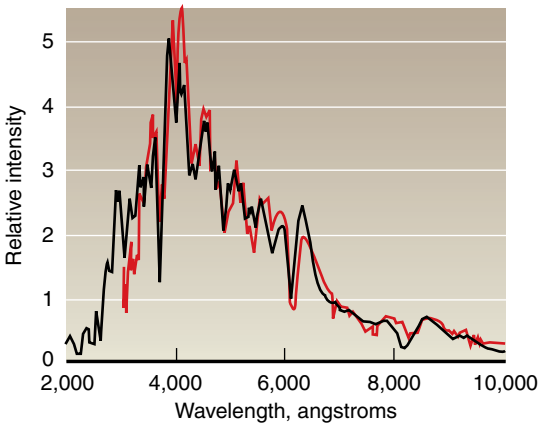
(a) In nuclear flame simulations, an initially thin (micrometer-wide) flame moves subsonically through a white dwarf's carbon fuel, releasing nuclear energy in the process. (b) As density decreases and turbulence increases, the flame enters a transitional stage in which it becomes extremely wrinkled. (c) Eventually, the flame enters the distributed burning regime, where it is shredded, its thickness and burning rate increase manyfold, and its velocity transitions to supersonic. At this stage, the flame is about 1 square meter. (Courtesy of Andrew Aspden of Lawrence Berkeley National Laboratory.)

so-called distributed burning regime, in which its thickness grows dramatically, its burning rate increases by a factor of five, and its speed transitions to supersonic. Hoffman notes that many aspects of the burning process are similar to those that drive the burning of fuel in an internal combustion engine. In fact, the simulation results have been aided by combustion modeling expertise of scientists at Sandia National Laboratories.

Uncovering the Truth

The CAC team plans to perform its first three-dimensional simulations of SNe Ia. The long-term goal is a continuous, end-to-end simulation, from the moments leading up to flame ignition to the weeks following the explosion. Such a comprehensive simulation is probably five years away and will require computational resources much larger than Atlas can currently provide.





Many questions remain, perhaps the most significant being why some SNe Ia are good standard candles while others are not. Livermore and other institutions will be examining additional aspects of SNe Ia, such as metallicity, the ratio of carbon and oxygen at the white dwarf's core, and binary properties that might be the cause of SNe Ia "outliers"—that is, those that do not conform to the width–luminosity relationship.

The findings from current and future observations, together with data from simulations, will also help astronomers and cosmologists determine if dark energy was stronger in the early universe and whether the expansion of the universe will continue to accelerate. "There are many theories and many conflicts but little guidance about the nature of dark energy," says Hoffman. "We're hoping our simulations will help uncover the truth."

—Arnie Heller and Katie Walter

Key Words: CASTRO code, Computational Astrophysical Consortium (CAC), cosmology, dark energy, Grand Challenge computing, hydrodynamics, MAESTRO code, SEDONA code, SNe code, Type Ia supernovae (SNe Ia).

For further information contact Rob Hoffman (925) 424-6411 (hoffman21@llnl.gov).

Developing New Drugs and Personalized Medical Treatment

Livermore research is behind a new technique for precisely measuring how drugs affect people.

Livermore built the first accelerator mass spectrometer specifically designed for biological research. Physicist Ted Ognibene was a key member of the design team.

IMAGINE attaching a bit of carbon-14 to a minute quantity of an antibiotic being developed to treat patients exposed to a biothreat agent or an emerging disease. The extremely small drug dose is nontoxic, and the amount of radiation is nearly negligible. This "microdose" is given to a small group of healthy people to determine whether the drug finds its way to the sites in the body that are thought to harbor infection. Blood and tissue samples taken from the subjects over the following hours, days, or weeks are run through an accelerator mass spectrometer, which can measure the amount of carbon-14 and, therefore, the amount of the drug in the body. These analyses reveal not only how much of the new drug is distributed to targeted sites but also how long it resides in the body. These data allow researchers to determine an optimal dosage that could counteract infection while minimizing side effects. A significant benefit to this so-called microdosing technique is that expensive and time-consuming animal testing would not be required. Microdosing studies on humans would provide a faster, more cost-effective way to deploy new countermeasure drugs. In the next year, Laboratory researchers hope to apply this method to new drugs that counter biological and radiological threats.

In a similar scenario, a microdose of an established drug tagged with carbon-14

is given to a patient sick with a difficult-to-treat infection. Tests taken just a few hours later would measure the amount of the drug in the body and its location. The resulting data could allow the physician to effectively adjust the standard dosage for that individual, minimizing side effects and increasing the patient's chances for a full recovery. Lawrence Livermore is working with oncologists to test this method on cancer patients and volunteer subjects.

The accelerator mass spectrometer is the essential tool that makes these scenarios possible. The amounts of the drugs and carbon-14 being measured are so small that no other instrument can detect the miniscule quantities, much less measure them.

Highly sensitive accelerator mass spectrometry (AMS) has most often been used for carbon-14 dating in research areas such as archaeology, paleoclimatology, and paleobotany. (See the box on p. 18.) Livermore researchers were the first to apply AMS to biological research almost 20 years ago. The earliest biological experiment at the Laboratory's Center for Accelerator Mass Spectrometry (CAMS) examined the effects of low doses of a suspected carcinogen on mouse DNA. Today, AMS studies of new drugs, nutrients, and toxic compounds can use human subjects because the safety of AMS has been demonstrated repeatedly. The amount of radioactive carbon-14 used to tag a biomolecule is less than the naturally occurring cosmic radiation an airline traveler encounters during a routine flight. The carbon-14 moves through the body without disturbing normal metabolic processes, even when it remains for many days or weeks.

Some human subjects for AMS studies are healthy volunteers and others are patients. Doctors and researchers at the University of California (UC) Davis Cancer Center have collaborated with Livermore scientists for more than a decade in such studies. Particular patients volunteer to help researchers learn more

about the effects of commonly used cancer chemotherapy drugs. Doctors know that drugs such as carboplatin are highly effective at destroying cancer cells. Interestingly, researchers found that this drug works well for treating testicular cancer, but the results for other types of cancer have been much less spectacular. Why is this the case?

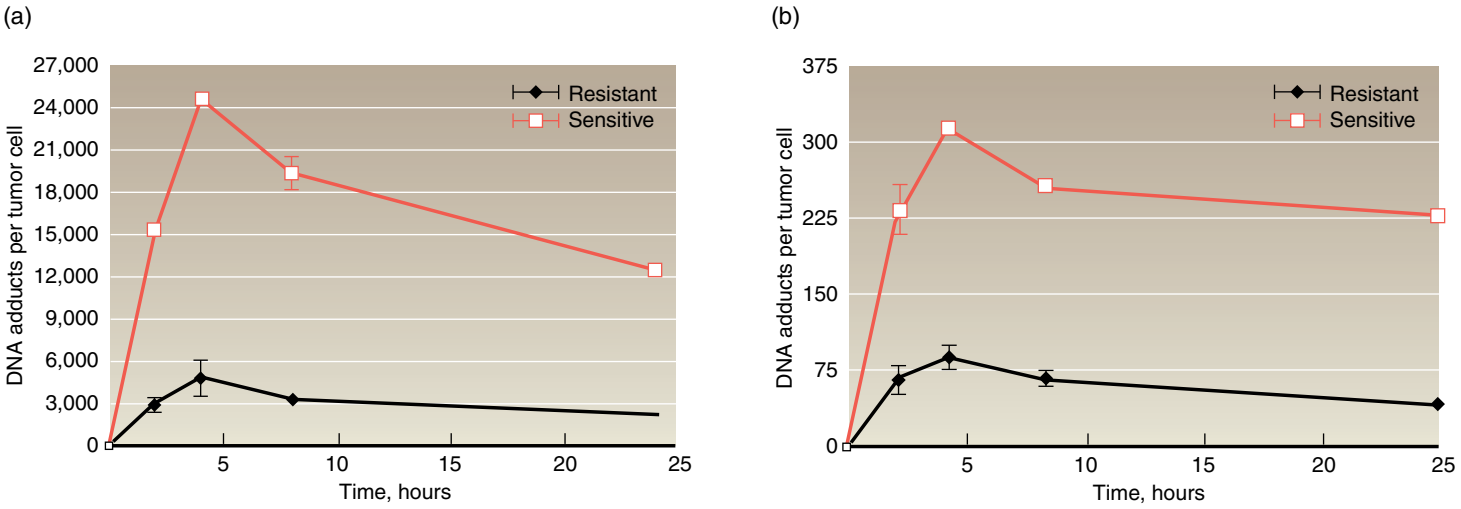
The specifics of a drug's absorption, distribution, metabolism, and excretion (ADME)—its pharmacokinetics—are poorly understood, and better information is needed to provide the answer. AMS, the most effective tool for human pharmacokinetic studies, will be a boon to drug companies for ADME research on new drugs.

Accelerating Drug Development

ADME studies performed early in the development of a new drug could be a deciding factor in whether a pharmaceutical company will continue its pursuit to market the drug. "Ninety percent of the drugs that start on the path to market don't cross the finish line," says biochemist Ken Turteltaub, a codeveloper of AMS for biological research. Developing a new drug typically takes 10 to 12 years and can cost as much as $1.5 billion. Making the "go" or "no-go" decision as early as possible could save pharmaceutical companies—and consumers—billions of dollars.

Drug development often requires 6 to 8 years of laboratory research, which is then followed by injecting laboratory animals with the drug and extrapolating the measured effects to a human-relevant dose. If the animal test results seem promising, Phase I clinical trials follow. Phase I testing typically involves 10 to 20 healthy human subjects who volunteer to participate. They are given the new drug at clinical doses to evaluate its safety, determine a safe dosage range, and help identify its possible side effects. Subsequent Phase II and III trials involve a larger number of human subjects, who are patients diagnosed with the specific illness that scientists hope the drug will help treat or cure.

The process often fails at the point where Phase I clinical trials begin. Research has repeatedly shown that humans and animals metabolize many substances differently. For example, chocolate is poisonous to a dog but can be a delicious treat for a child of similar weight because humans metabolize the theobromine in chocolate much more quickly than dogs. A decade ago, Turteltaub and colleagues compared the effects of PhIP, a substance that forms in meats during cooking, on humans and rodents. PhIP damages DNA and is carcinogenic to rodents at high doses, causing colon, breast, and prostate tumors. The team found that DNA damage in the colon was 5 to 10 times higher in humans than in rats given comparable doses based



Some chemotherapy drugs form damage products, called DNA adducts, that are toxic to rapidly dividing cells. Carboplatin is one such drug. Some patients are "sensitive" to carboplatin, while others are "resistant" to the drug (that is, fewer adducts are created). Laboratory tests show (a) cellular response to a full dose of carboplatin that a patient would receive during chemotherapy and (b) cellular response to a dose 1/100th of that amount, called a microdose. The two responses are similar, indicating that experiments using microdoses of carboplatin could be useful for predicting the pharmacokinetics of this drug in humans. (Courtesy of Chong-xian Pan and Tao Li of the University of California at Davis.)

Some accelerator mass spectrometry measurements require that samples be converted to small cylinders of graphite before they are ionized inside the spectrometer. Michale Kashgarian places the sample holder.

on body weight. The consensus in this case was that humans must also metabolize PhIP differently.

Microdosing can facilitate the leap from animal to human studies. In a microdose study, a person receives just 1/100th of the clinical dose of a drug. This dose contains a small amount of the isotope carbon-14, just enough for the drug's ADME to be measured using AMS. The tiny doses are sufficient to study cellular response but not large enough to produce either therapeutic or toxic effects in the individual. Because of the sensitivity of AMS, only very small samples of blood, urine, biopsy tissue, or cerebrospinal fluid are needed for the tests that follow.

"Tests to date comparing microdoses and clinical doses of particular drugs indicate that the cellular responses are similar," says Turteltaub. "Only a small number of drugs has been tested so far, and much more work needs to be done to validate these findings. Microdosing may not work for all compounds."

If microdosing does prove to be an effective tool, it will help researchers determine if a candidate drug has the properties needed to reach targeted tissues and then remain at sufficient levels for a specified period. Researchers could more quickly determine which compounds have the proper pharmacokinetic properties and eliminate those that do not, allowing more time and money to be focused on the most promising candidates. Drugs could reach the marketplace faster, and their development would be more cost effective. These early tests could also give developers information on which individuals are likely to benefit from the drug—the foundation of personalized medicine.

In addition to moving new drugs more quickly to the marketplace and into the hands of health providers, AMS tests might help researchers better understand the interactive effects when more than one drug is injected. AMS and microdosing could allow for studying the interactions of multiple drugs because the effects of such tests would be so small. Frequent sampling of human subjects could provide highly accurate data about drug behavior and metabolism, resulting in improved models. Three private companies have licensed Livermore's AMS biomedical technology with the goal of managing microdosing studies for pharmaceutical firms developing new drugs.

Less Expensive AMS

Two developments are behind the increased use of AMS: smaller, less expensive accelerators and faster, less labor-intensive sample processing. Livermore's primary AMS system, in place since 1989, is the size of a basketball court. Ten years ago, the Laboratory custom-built the first accelerator mass spectrometer dedicated to carbon-14 biological research. This 1-megavolt machine is just one-tenth the size of the larger spectrometer.

Physicist Ted Ognibene, whose specialty is AMS instrumentation, says, "AMS researchers have since discovered that even 1 megavolt is more energy than necessary. Half that energy, or 500 kilovolts, is plenty. Since 2002, a U.S. firm has been building 500-kilovolt systems at a cost of $1 to $2 million." An even smaller machine is being tested that uses just 200 kilovolts. However, according to Ognibene, the jury is still out on that one. He says, "Most of these small systems are for natural carbon. They would work for biological research, but few scientists are using them in this way."

Livermore's 1-megavolt spectrometer serves as a test bed for new sample preparation and delivery technologies. Now, some samples containing carbon-14 are run through a high-performance liquid chromatograph (HPLC), which

separates the compounds and creates mini-samples called fractions every 15 seconds or so. Carbon is added, and the fractions are converted to small cylinders of graphite. The samples are placed in the ion source, where they are ionized. Then they travel through the accelerator into the spectrometer, where the ionized particles are counted. "It takes about a day to prepare 60 individual samples and 4 hours to run them through the AMS machine," says Ognibene. "Each sample costs about $150 to produce." Multiply that cost and time by the days and weeks of a drug test, and the roadblock that has kept AMS from broader, routine use becomes obvious.

Ognibene and others at Livermore are working to change that daunting arithmetic. They are developing methods whereby carbon-14 can be measured directly from HPLC, avoiding graphite sample preparation. Continuous-flow HPLC AMS, "a name that is admittedly a mouthful," notes Ognibene, "is still a few years away. Several interfaces have to work perfectly."

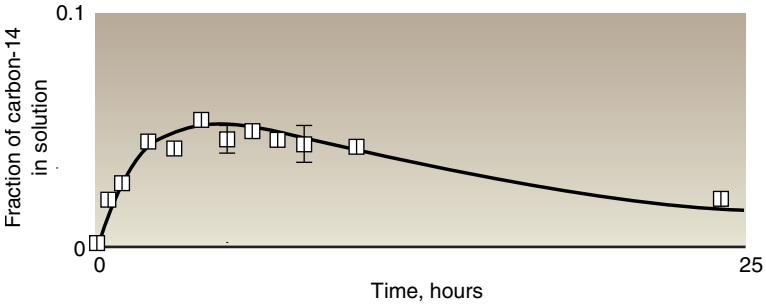
Output from HPLC will connect to a combustion chamber that breaks down the sample material and sends it directly to the AMS ion source. In 2007, the team installed a new ion source that can accept sample material in gaseous form. The next step, which will take another year, is to align the HPLC with the spectrometer.

The current system of collecting fractions every 15 seconds or so generates data at those same intervals. The continuous-flow process will offer better ADME data because the spectrometer can make more frequent measurements, up to once per second. This process will also result in less sample handling and less contamination for better overall test results.

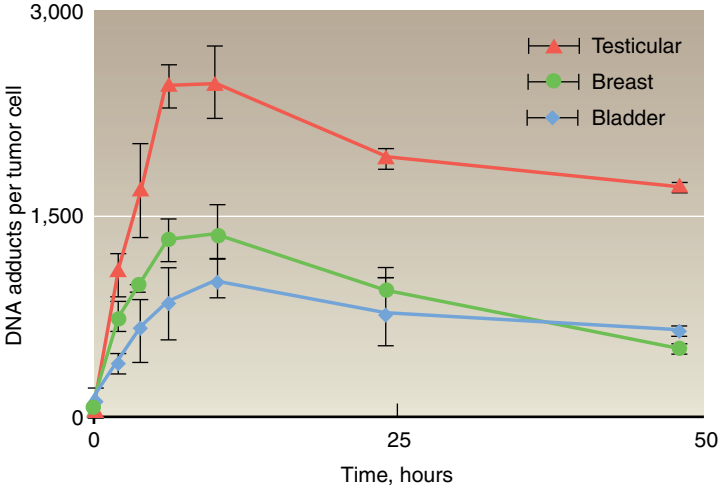
Predicting Patient Response

A collaborative team of Livermore scientists and clinical researchers at the UC Davis Cancer Center is using AMS to test whether DNA damage caused by a single microdose of an anticancer drug will correlate with tumor shrinkage and increased survival times. The ultimate goal is a diagnostic tool that can predict how individual patients will respond to therapy. Says biochemist Paul Henderson, "Genetic screening and microdose testing together would determine the best way to use a particular drug or combination of drugs for a patient."

Chemotherapy agents that damage the DNA of cancer cells are among the most effective compounds for treating cancer. In particular, the platinum-based compounds cisplatin and carboplatin have revolutionized the treatment of many solid tumors. These drugs form damage products, called DNA adducts, that are toxic to rapidly dividing cells. However, a patience's resistance to one of these drugs may cause the drug to produce fewer adducts. Either the patient's tumor may be intrinsically resistant to the drug, or the tumor may shrink for a time and then acquire resistance and stop shrinking. Oxaliplatin, a more recently developed drug, is effective against tumors that are resistant to cisplatin and carboplatin. Both carboplatin and oxaliplatin are compatible with AMS technology because their



Results of a new AMS assay indicate how much carboplatin becomes attached to salmon sperm DNA over 25 hours. These results demonstrated AMS can measure carboplatin–DNA damage, which led to experiments with cancer cells. The next phase is to develop protocols for microdosing experiments with human subjects.



Tests using cultured human cells were performed with oxaliplatin, a chemotherapy drug similar to carboplatin, to determine its effects on the DNA of various types of human cancer cells. Testicular cancer cells (red) are much more responsive to the drug than either breast cancer cells (green) or bladder cancer cells (blue).

carbon-12 atoms can be replaced with carbon-14 atoms.

In an ongoing project funded by Livermore's Laboratory Directed Research and Development Program, the team has developed an AMS-based assay for carboplatin–DNA adducts in cells using purified DNA and several types of cultured human cancer cells. AMS measurements of the kinetics of carboplatin bound to salmon sperm DNA were the first-ever experimental determinations of adduct formation using radioactively labeled carboplatin. Subsequent tests exposed human bladder cancer cells to a microdose of carbon-14-labeled carboplatin. In addition, a variety of human platinum-sensitive and platinum-resistant cancer cells were exposed to oxaliplatin to show that cell-dependent differences in DNA adduct formation and repair are detectable. The highest DNA adduct accumulation was in testicular cancer cells, which may explain why plantinum drugs cure about 95 percent of nonmetastatic testicular cancers. The assay was also tested on mice. This series of tests, undertaken before any experiments with human subjects, indicated that the assay was accurate and safe.

The next step is a clinical study to develop dosing and sample preparation protocols. UC Davis Cancer Center director Ralph deVere White and other UC collaborators will locate five bladder-cancer patients willing to participate as human subjects. The patients will receive a microdose of carbon-14-labeled carboplatin, and the AMS assay will be applied to whole blood, plasma, white blood cells, and biopsy tissue. "We expect to find similar concentrations of DNA adducts in tumor and white blood cells," says Henderson, "which will support the idea that blood cells can be used as a surrogate marker of tumor response." In the future, invasive biopsies could be avoided. Only blood samples would be needed to locate and count carboplatin–DNA adducts.

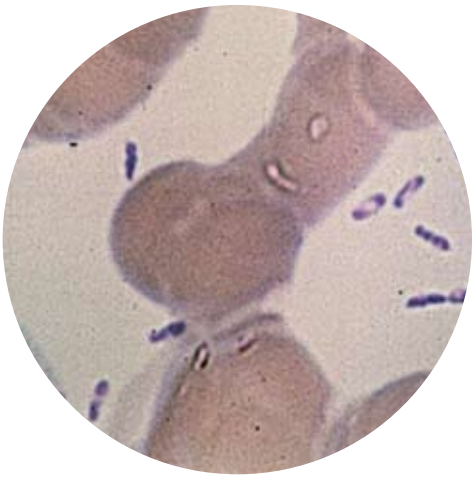
Fifty bladder- and breast-cancer patients will be recruited for a second study to correlate carboplatin–DNA adduct levels with patient response. AMS analyses will measure the quantity of adducts while computed tomography scans will assess whether tumors have shrunk. Individual responses will be added to a future database built to study pharmacokinetic parameters of these important chemotherapeutic drugs.

New Drugs for New Diseases

Livermore also hopes to move its AMS expertise in a new direction, applying AMS to the Laboratory's mission in national security, specifically biosecurity. Livermore has a long history of developing methods and devices to detect biological agents that could be used in a potential terrorist attack, and it leads the national BioWatch program. In the near future, Laboratory scientists hope to explore how AMS can be used to develop treatment methods that deal with the aftereffects of a biological attack.

"The nation needs a flexible biodefense strategy," says Dave Rakestraw, chief technologist for the Chemistry, Materials, Earth, and Life Sciences Directorate. "We could stockpile ciprofloxacin [a synthetic antibiotic] to treat anthrax. But anthrax engineered with resistance to ciprofloxacin might appear. We need medical countermeasures that are broadly applicable." A rapid response is critical: the 1918–1919 influenza epidemic killed approximately 25 million people in its first 25 weeks.

The Laboratory's goal is to find broad-spectrum anti-infective drugs that can target agents, such as plague or Hantavirus, which may be modified or engineered. Equally challenging are naturally occurring diseases, such as AIDS, severe acute respiratory syndrome, and perhaps as-yet-unknown pathogens. Rakestraw notes that the National Institutes of Health has spent more than $30 billion on AIDS/HIV research, yet 6,000 people die every day from AIDS. Finding solutions is clearly a challenge.



Yersinia pestis, or plague (the purple rod-shaped cells), is one of the disease models that will be used if Livermore begins the search for new drugs to fight modified or engineered bioterror agents.

With expertise in physics, biochemistry, bioinformatics, and genomics, the Laboratory is in an excellent position to identify commonalities among pathogens and ways that they adapt to the people who become infected. Scientists could identify both common and unique factors in the immune response—a critical process for fighting infection—based on research on four particular disease models: *Yersinia pestis* (plague), *Francisella tularensis* (tularemia), *Brucella abortus* (brucellosis), and Hantavirus. All are highly infectious diseases that may infect humans or animals.

Most major pharmaceutical companies have stopped developing anti-infective drugs because the market is too small, and the rapid rate of pathogen evolution shortens the effective lifetime of a drug. Many of these companies also no longer

Accelerator Mass Spectrometry at Livermore

Livermore's Center for Accelerator Mass Spectrometry (CAMS) is home to the most versatile and productive AMS facility in the world. AMS is an exceptionally sensitive technique for measuring concentrations of isotopes in small samples, typically less than 1 milligram, and the relative abundance of isotopes at low levels. It can, for example, find one carbon-14 isotope among a quadrillion other carbon atoms.

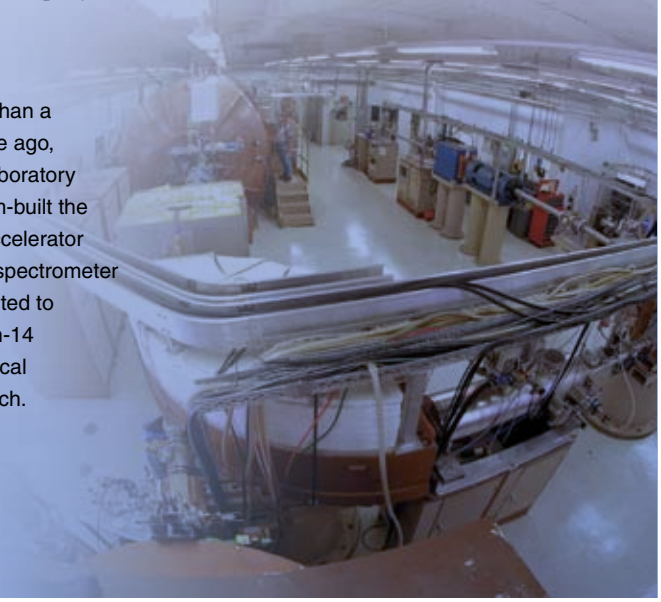
All over the world, AMS is used primarily to count carbon-14 in archaeological and geologic samples for dating purposes. Only at Livermore and a few other sites has AMS been applied to biological research. In 1999, the National Institutes of Health named CAMS as a National Research Resource for AMS. The facility remains the only such research resource for AMS worldwide.

Mass spectrometry has been used since early in the 1900s to study the chemical makeup of substances. The various ions in a sample are sorted by their mass-to-charge ratios in an electric field. The basic principle is that isotopes of different masses move differently in a given electromagnetic field.

In an accelerator mass spectrometer, negative ions made in an ion source are accelerated in a field of hundreds of thousands of volts. The accelerated ions smash through a thin carbon foil or gas that destroys all molecular species. After passing through a high-energy mass spectrometer and various filters, the ions finally slow to a stop in a gas ionization detector. The identity of individual ions can be determined by how the ions slow. For example, carbon-14 slows down more slowly than nitrogen-14, so ions of the same mass can be distinguished from one another.

Once the charges are determined, the detector determines which element each ion belongs to and counts the desired isotope as a ratio of a more abundant isotope. Rare carbon-14 is counted as a ratio of carbon-13, which is quite common. The molecular dissociation process in the accelerator and the ion detection at the end give AMS a sensitivity that is typically a million times greater than that of conventional isotopic detection.

CAMS was established in 1989 to diagnose the fission products of atomic tests and to monitor the spread of nuclear weapons to other countries by detecting telltale radioisotopes in air, water, and soil samples. In addition, plans were to develop isotopic tracers for studying climate and geologic records and to use AMS technology for biomedicine applications. Today, CAMS performs these services, and many others, 24 hours a day, 7 days a week for Livermore researchers and their collaborators as well as for others on a fee-for-service basis. The facility performs more than 25,000 AMS measurement operations per year.



More than a decade ago, the Laboratory custom-built the first accelerator mass spectrometer dedicated to carbon-14 biological research.

develop new anti-infectives because existing chemical libraries have run out of the natural products on which anti-infective drugs are based. Most such drugs come from naturally occurring microbes in soils and plants.

Livermore has proposed a collaborative effort with Trius Therapeutics of San Diego, California, a firm that specializes in developing antibacterial drugs to treat infections caused by antibiotic-resistant bacteria. Says John Finn, chief scientific officer at Trius, "We would first identify a pool of possible drug candidates based on an analysis of molecular structures that fit the disease models. Microdosing experiments with AMS would then give us the metabolic data we need to narrow the field. Highly precise data on pharmacokinetics is critical." Says Rakestraw, "Together, we have the expertise to develop entirely new anti-infective drugs. A new chemical library would be based on natural products from oceans and other water sources."

AMS has repeatedly proved its value in biological research. Applying this expertise to the challenge of countering bioterrorism would give the Laboratory a unique capability in helping to protect our nation. Says Turteltaub, "With AMS, we can address a host of health problems that cannot be solved otherwise."

—Katie Walter

Key Words: accelerator mass spectrometry (AMS), ADME (absorption, distribution, metabolism, excretion), biosecurity, cancer, Center for Accelerator Mass Spectrometry (CAMS), chemotherapy, microdosing, pharmacokinetics, University of California (UC) Davis Cancer Center.

For more information contact Ken Turteltaub (925) 423-8152 (turteltaub2@llnl.gov).

Triage in a Patch

FOLLOWING an explosion at a chemical plant, employees and neighbors may find themselves in a triage facility where a nurse will apply a small, disposable patch to each person's arm. In a few minutes, a simple color change in this colorimetric patch will indicate whether the person was exposed to dangerous levels of a toxic substance.

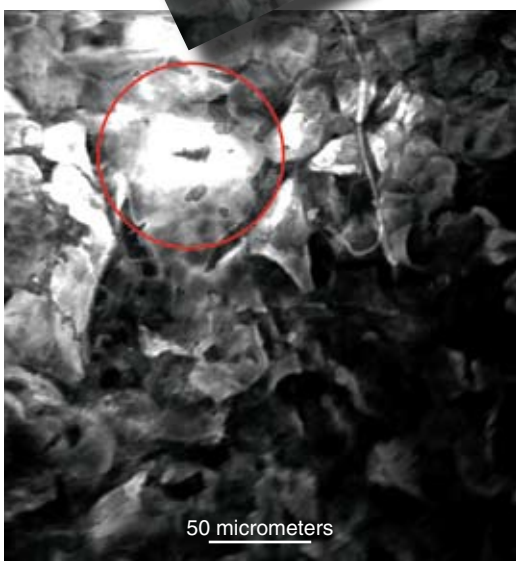
The patch contains hundreds of hollow silicon "microneedles," each of which draws fluid from the outer layer of skin by capillary action. The needles are so short—just a few hundred micrometers—that the patch is painless. Integrated into the Band-Aid®-size patch are various chemical processes for testing biological fluids. Research is under way at Livermore for this scenario to become a reality.

Painless Needles

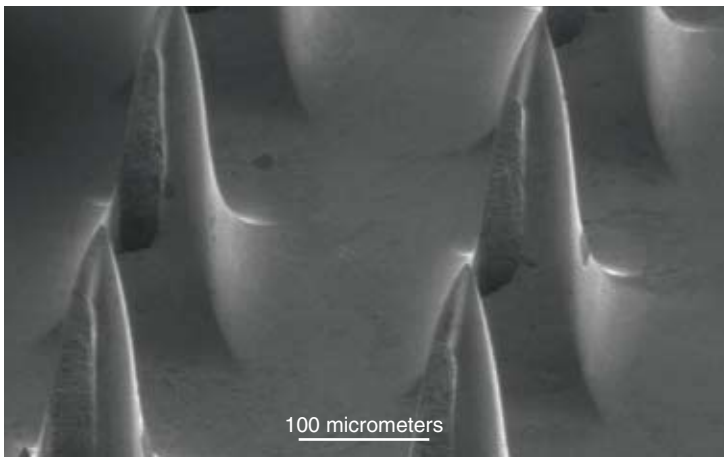
Microneedles have been in development for nearly 20 years to replace painfully invasive hypodermic needles for delivering drugs. Today, a revolutionary needle geometry has been designed that allows for fluid flow both out of the skin and into it. While a graduate student at the University of California (UC) at Davis, Livermore biomedical engineer Erik Mukerjee led a team that expanded the potential uses for microneedles. Mukerjee was inspired while watching a nature television program about poisonous snakes. He noticed that most cobras inject their venom via a tiny channel behind each fang and thus was born the "snake fang" microneedle.

Using this novel microneedle design, the UC Davis team went on to develop a patch that could, for the first time, extract fluid from the body. If the fluid to be withdrawn is blood, the microneedles on the colorimetric patch need be only 350 micrometers long. If the target is interstitial fluid, which lies in the epidermis (the outer, nonvascular, nonsensitive layer of the skin), the microneedles can be even shorter—a mere 250 micrometers long. "We have an amazing amount of freedom during the microfabrication process," say Mukerjee, who now works in Livermore's Engineering Directorate. "We can easily modify the shape and length of the microneedles to suit a specific application."

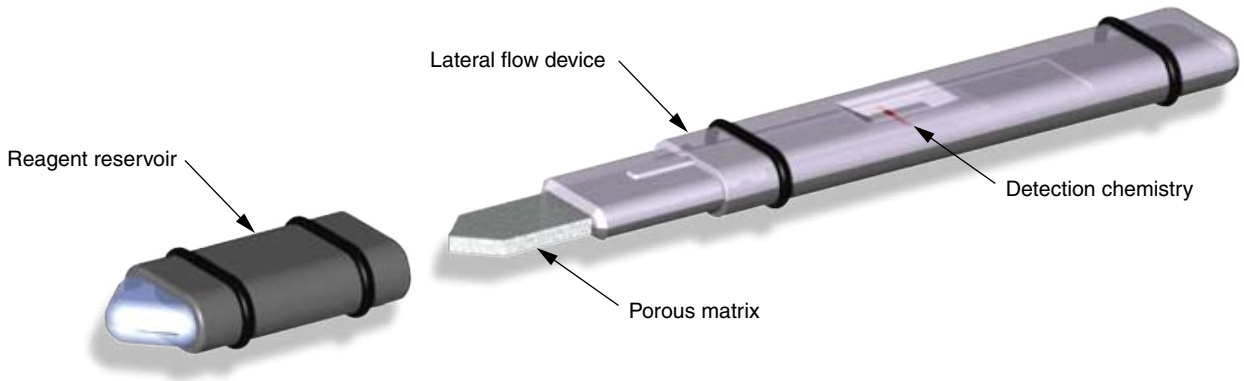
Using a patch made of microneedles and tiny microchannels that lead to a common reservoir, the team tested the application by monitoring blood glucose in interstitial fluid. The needles on the patch were just long enough to enter the epidermis and collect a fluid sample. Says Mukerjee, "Although a 10-minute lag exists between glucose level changes in the blood and in the interstitial fluid, it is still the perfect fluid for glucose monitoring. The epidermis has only a few nerve endings and no blood capillaries. By targeting interstitial fluid, we can painlessly and continuously



These images show the difference in the size of the hole made when human skin is pierced with a hypodermic needle (above) and with a microneedle (left). A microneedle makes a much smaller hole—a fraction of the width of a human hair.



A patch of microneedles modeled after snake fangs can be used to extract bodily fluid through human skin.



In this modified lateral flow device, a blood sample mixed with reagents wicks up into the exposed porous matrix. Capillary action draws the sample into the 7-centimeter-long device and over the embedded chemical detector. If the substance of interest is present, the detector will change color.

monitor a person's glucose levels. This method eliminates the need for testing blood with painful needle sticks."

Following proper protocols, Mukerjee applied the patch—which he could not feel—to his own arm, drank a soda sweetened with high-fructose corn syrup, and watched his interstitial-fluid glucose levels rise as glucose diffused from the blood into the fluid. UC Davis has licensed this painless technology to a private company, which is now developing a commercial product for use by diabetics.

Integrated Real-Time Detection

In everyday life, people are continuously exposed to various chemicals and compounds that penetrate their bodies via the lungs, digestive track, and skin. These chemicals circulate in the blood system either as primary compounds or as secondary metabolic by-products. Most chemicals present in our bodies are merely part of human dynamic equilibrium, or homeostasis. However, the monitoring of specific circulating chemicals and resultant altered biomolecules may provide a signature that indicates whether a person has been exposed to a material of concern.

Currently, medical staff must either draw blood or collect a urine sample to determine whether a person has been exposed to a dangerous substance. Blood samples can at times take days to analyze. Results from a urine sample can be determined quickly, but some agents can take hours to find their way into the body's urine. For on-the-scene triage by first responders and for optimal follow-up care, a faster and easier-to-use system is essential.

Mukerjee has begun working with chemical engineer Elizabeth Wheeler of the Engineering Directorate to integrate the microneedle fluid-extraction technique with an in situ detection system. Biological systems integration is Wheeler's forte. She has experience with both lateral flow immunoassay methods and DNA sampling.

Lateral flow assay devices draw fluid through a wicking substrate into an immobilized chemical detector. Color change in the chemical detector indicates the presence of a targeted chemical. A home pregnancy test is an example of a simple lateral flow device.

Wheeler was also involved in the development of the BioBriefcase, a prototype system for detecting environmental biological contaminants. The unique DNA preparation methods in the BioBriefcase could be used with the microneedle patch. A bed of silica beads traps the DNA, separating it out from the bits of dirt and other environmental particles that are also in the sample. The DNA is then amplified on the silica surface. This process minimizes the loss of DNA prior to detection.

A Colorful Future

The painless microneedles for fluid sampling combined with colorimetric lateral flow assay technologies will give first responders the tool they need to quickly respond in potential cases of exposure to toxic substances. Another Livermore detection device that first responders are already using is E.L.I.T.E.^{TM} (Easy Livermore Inspection Test for Explosives). (See *S&TR,* October 2006, pp. 16–17.) The E.L.I.T.E. card technology uses a swipe with color-changing detection chemistry. The microneedle detector will incorporate similar technology.

In the future, DNA and RNA detection assays may be incorporated in the microneedle detector. The patch may also be made to detect multiple substances at the same time, a process called multiplexing. Mukerjee adds, "This system may not be the fictional Star Trek tricorder, but our research brings us one tantalizing step closer."

—Katie Walter

Key Words: BioBriefcase, DNA sampling, exposure monitoring, lateral flow assay, microneedle.

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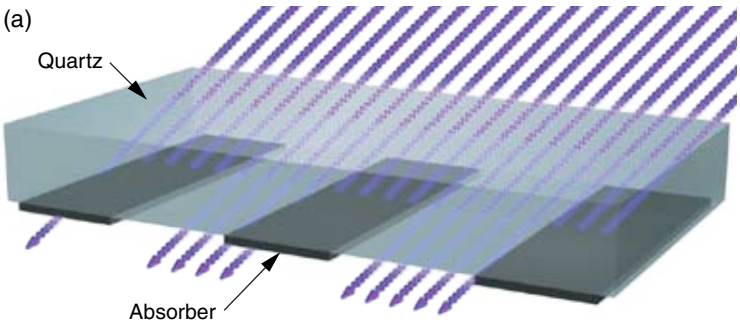
Smoothing Out Defects for Extreme Ultraviolet Lithography

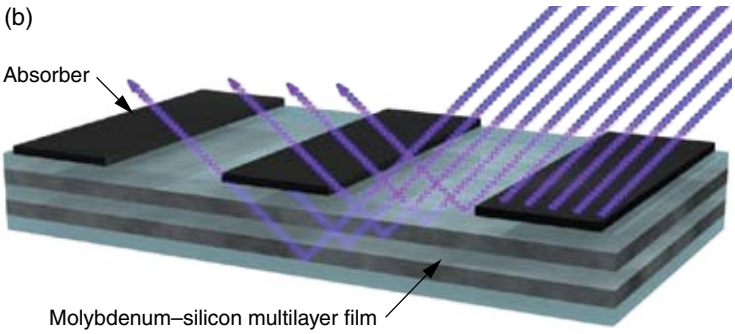
Livermore scientists Paul Mirkarimi (left) and Jeff Robinson examine the mask substrate after it has been smoothed and coated with a molybdenum–silicon reflective multilayer. In the background is the ion-beam deposition and etching system.

SMALLER. Faster. Cheaper. Together, these three words form the mantra of the semiconductor industry as manufacturers search for new methods to increase the computing power of integrated circuits. According to the principle of Moore's Law, the number of transistors on a circuit will double about every two years, and so far, industry has kept up the pace. Photolithography—a process that uses light to "print" a circuit pattern on a semiconductor wafer—has enabled industry to create microchips with nanometer-scale features. Extreme ultraviolet lithography (EUVL) may be the key to continuing Moore's Law into the future, allowing manufacturers to produce even smaller, more powerful microchips.

Current lithographic technologies transmit 193-nanometer-wavelength light through a quartz-based photomask and a series of lenses to create the minute features on microchips. EUVL technology uses light with a much shorter wavelength, 13.5 nanometers. Lenses absorb light at this wavelength rather than transmit it, so EUVL systems include optics to collect and direct light onto a reflective mask. The mask, which contains the pattern for the transistors, reflects the light through another set of optics. These optics reduce the image and direct it onto a silicon wafer coated with photoresist—a light-sensitive material that absorbs the light and retains the projected image. (See *S&TR*, November 1999, pp. 4–9.) The "printed" pattern serves as a guide during the manufacturing process in which portions of the photoresist are chemically removed to create the microchip.

One mask can be used to manufacture tens of thousands of semiconductor wafers, but the pattern on each wafer must be virtually flawless to create a reliable circuit. Tiny imperfections on the mask, such as nanometer-size particles or pits, can transfer defects to the photoresist, causing many chips to fail—a major drawback for an industry that thrives on high-volume production. For EUVL to succeed commercially, the semiconductor industry must reduce these defects to nonprintable sizes. Livermore scientist Paul Mirkarimi, who works in the Chemistry, Materials, Earth, and Life Sciences Directorate, and his colleagues Jeff Robinson and Sherry Baker from the Engineering Directorate along with Eberhard Spiller from the Physical Sciences Directorate have developed such a process. Called ion-beam thin-film planarization,





(a) Masks used in current photolithography systems transmit light through a quartz substrate. (b) In extreme ultraviolet lithography, masks contain a molybdenum–silicon multilayer film that reflects light. In both systems, light exiting the mask travels through a series of lenses that transfer the light onto a semiconductor wafer to create a chip's minute features.

the process planarizes, or smooths, mask defects to create an almost perfectly uniform surface.

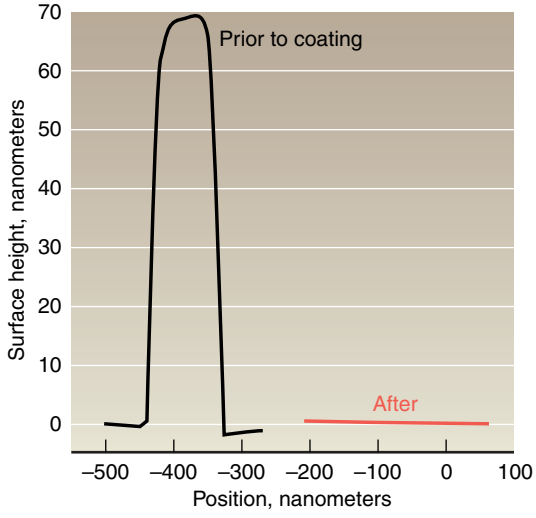
Two Birds with One Stone

An EUVL mask is a substrate coated with a multilayer film of molybdenum and silicon and covered with metal lines that form the pattern for the transistors. Extreme ultraviolet light projected onto the mask is absorbed by the metal and reflected by the multilayer film. The intensity of the reflected light must be uniform to create a usable pattern on the photoresist. Surface perturbations greater than just 1 to 2 nanometers can distort the light enough to create defects in the pattern. The planarization process effectively smooths these defects to less than 1 nanometer.

The smoothing process has two phases. In the first phase, an ion-beam sputtering tool applies a 9-nanometer-thick layer of silicon to the mask substrate. In the second phase, another ion beam etches the silicon, removing about 8 nanometers of the previously deposited layer. These two steps are repeated until the defect is reduced to the required size. Once this smoothing process is complete, multiple layers of molybdenum and silicon are added.

The two-step process earned Mirkarimi and his team an R&D 100 Award in 2003 after the system had successfully planarized substrate particles piled up to 50 nanometers high. (See *S&TR*, October 2003, pp. 10–11.) The researchers have since improved the technique, and it now works effectively on particles up to 80 nanometers.

Over time, manufacturers developed cleaner methods to fabricate masks, significantly reducing the number of substrate particles. Pits, however, were a problem that could not be cleaned away. "Our sponsor, Intel Corporation, encouraged us to work on pits at a time when no one else in the EUVL community was concerned about these defects," says Mirkarimi. "Later, data on mask substrates revealed a significant number of pit defects."



Livermore's ion-beam thin-film planarization process effectively smooths 70-nanometer particles to nonprintable sizes, less than 1 nanometer.

When planarizing particles, the deposition and etching steps are performed at a near-normal angle of incidence. That is, the ion beam is almost perpendicular to the substrate—or approximately 0 degrees to normal incidence. The Livermore researchers found that this method was less effective on pits, at times making the pits larger. However, by adjusting the angle of the substrate during the etching phase, they could eliminate the problem. Placing the ion beam at an off-normal incidence of about 45 degrees produced the required smoothing effects.

Unfortunately, the two approaches were not interchangeable. Each process was effective on only one type of defect: particles or pits. "We then needed to find a method for doing both operations at one time," says Mirkarimi. The team combined the individual processes into a multistep deposition-and-etch system. Deposition still occurs at normal incidence, but etching is performed at two angles, first at off-normal incidence for the pits and then at near-normal incidence for the particles. An etching step follows each deposition step, and defect size determines the total number of deposition-and-etch cycles. In experiments using masks with precise defects, each 70 nanometers in height or depth, the multistep process planarized both particles and pits simultaneously.

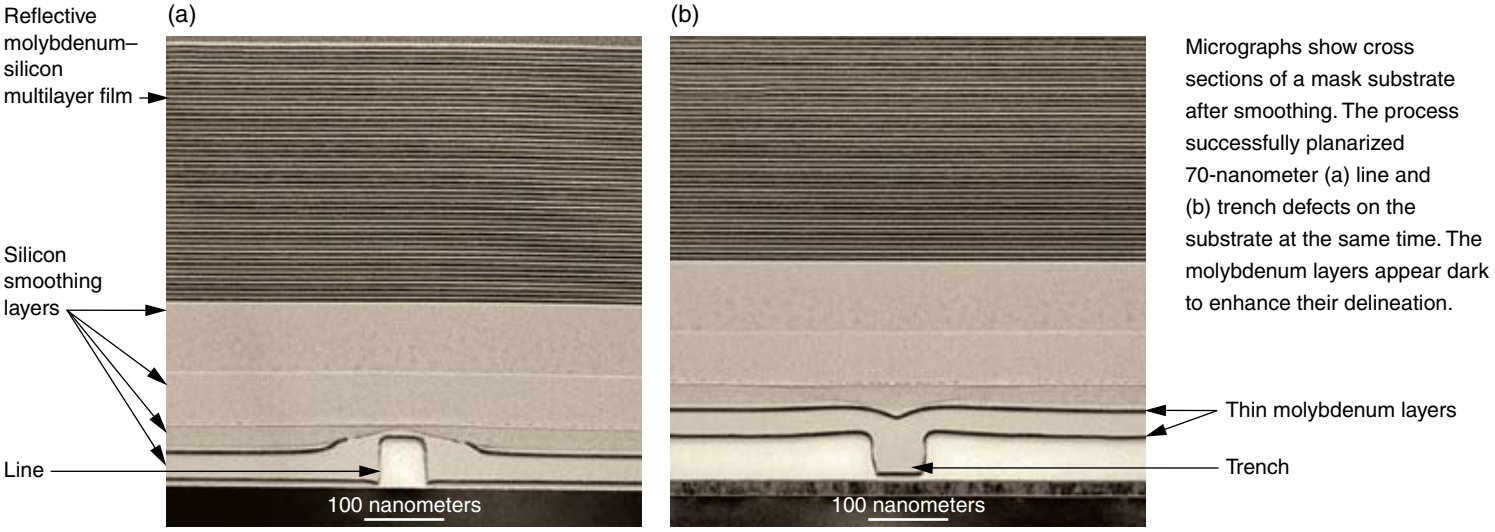
Time Is a Terrible Thing to Waste

In industry, time is money. A smoothing process that takes too long may not be worth the investment to commercialize it. A long processing time is also more likely to introduce additional particles to the mask's surface. When Mirkarimi and his team started their work, the smoothing process took up to 7 hours—too slow for production purposes.

To reduce this time, the team increased the energy of the ion sources by 200 electronvolts for the deposition phase and by 250 electronvolts for etching. These changes increased the deposition rate by 45 percent and the etching rate by 600 percent. The team also adjusted the angles for etching pits from 45 to 52 degrees to compensate for the increased energy from the ion etch source. Together, these modifications reduced the process to about 2 hours.

The team's next challenge was to make the process work on mask defects of varying shapes and sizes. The 70-nanometer particles designed for the Livermore experiments are similar in size to particles found in production environments. Pits, however, can be shallower and wider than the experimental defects. "For this phase of our research, we targeted the largest known pits, which are approximately 18 nanometers deep by 100 nanometers wide," says Mirkarimi. "Once we were successful with the largest pit size, we knew we could smooth the smaller ones."

The team then focused on refining the planarization process to smooth these real-world pits and particles at the same time. Silicon layers are first applied at normal incidence followed by etching at a 70-degree angle for the pits and 0 degrees for the particles.



Micrographs show cross sections of a mask substrate after smoothing. The process successfully planarized 70-nanometer (a) line and (b) trench defects on the substrate at the same time. The molybdenum layers appear dark to enhance their delineation.

This revised method simultaneously planarized the largest pits and particles up to 40 nanometers. The team is confident that the process could be further adjusted to planarize particles with heights up to 50 nanometers.

"We are working on defects that are smaller than anyone has been interested in before," says Mirkarimi. He adds that the semiconductor industry has stringent defect-acceptance specifications. A mask 15 centimeters square can have about 0.0025 defects per square centimeter, which is equivalent to one defect for every two masks. The Livermore planarization process will be needed to produce EUVL masks that meet this specification.

Beyond the 45-nanometer Node

Laboratory researchers have been involved in EUVL research since the mid-1990s. As part of a collaboration known as the Virtual National Laboratory, they worked with colleagues at Lawrence Berkeley and Sandia/California national laboratories to develop EUVL technology. This research was funded through a cooperative research and development agreement with EUV, LLC, a consortium of semiconductor firms, with Intel Corporation as a major contributor.

In 2003, the Virtual National Laboratory began transferring the technology to the semiconductor industry. Intel continued to fund research on the ion-beam thin-film planarization process for another five years in a work-for-others project based out of Livermore's Physical Sciences Directorate. In February 2008, Mirkarimi and his team completed their work, signifying the end of EUVL research at the Laboratory.

Further research and development are needed before the technology will be ready for production. SEMATECH, an organization that helps commercialize semiconductor technology, tested the smoothing process at its Nanotech Center at the University of Albany in New York and obtained results consistent with those achieved at Livermore. Veeco Instruments, Inc., which manufactures mask-coating tools, is helping SEMATECH commercialize the ion-beam thin-film planarization process and has recently developed a multimillion-dollar ion-beam coating and etching tool. This year, Veeco, Inc., and SEMATECH are implementing the faster procedure developed by the Livermore team and making the process cleaner to ensure no new particles are added to the mask during the deposition-and-etch cycles.

The semiconductor industry continues to research other components needed to make EUVL a viable approach for producing computer chips. Livermore's accomplishments have helped move the technology one step closer to production. "If EUVL technology is successful," says Mirkarimi, "it could be the long-term lithography technology the semiconductor industry needs." Because it uses light with an incredibly short wavelength, EUVL has the potential to last for multiple generations of microchips. Manufacturers are currently producing chips with 45-nanometer features, but research is focused on reducing feature size to 32 nanometers and then even smaller. Imagine the technologies that will become available as microchips continue to get smaller, faster, and cheaper.

—Caryn Meissner

Key Words: deposition, etching, extreme ultraviolet lithography (EUVL), integrated circuit, ion-beam thin-film planarization process, mask defect, microchip, reflective multilayer, semiconductor industry, transistor.

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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.

Awards

Laboratory Deputy Director Steve Liedle presented 11 Livermore recipients with the **Department of Energy's** (DOE's) **2007 Outstanding Mentor Award**. Recipients included **Malvin Kalos** and **Patrick Brantley** of the Weapons and Complex Integration Directorate; **Pam Hullinger** of the Physical Sciences Directorate; **Richard Johnson** and **Dan White** of the Engineering Directorate; **Eivind Almaas**, **Ted Laurence**, and **Michael Thelen** of the Chemistry, Materials, Earth, and Life Sciences Directorate; **Dustin Froula** and **Wren Carr** of the National Ignition Facility and Photon Science Directorate; and **Ming Jiang** of the Computation Directorate. The DOE Outstanding Mentor Award program began in 2002 as an effort to establish a culture that values mentorship within the DOE national laboratories. This year a total of 83 awards were presented to recipients from DOE national laboratories.

Judy Kim, a graduate student from the University of California at Davis and a Lawrence Fellow in the Chemistry, Materials, Earth, and Life Sciences Directorate, received the **John Farrant Memorial Award** for her abstract and research entitled, "Nanosecond Imaging in the Dynamic TEM [Transmission Electron Microscope] Reveals Unquenchable Transient Microstructure." The award, which includes $1,000, is presented to a student who has demonstrated a scientifically significant study in the physical sciences.

Ida Shum, a business development executive within the Laboratory's Industrial Partnerships Office, has been elected **Far West Regional Coordinator** for the **Federal Laboratory Consortium for Technology Transfer**. Shum will offer information on best practices for technology transfer, address tech-transfer barriers, assist with training, and help bring the public and private sectors together to commercialize new technologies.

The **XX25 Fuel Cell** developed by UltraCell Corporation and based on Livermore-developed technology captured the **2008 Best Soldier System Innovation and Technology Award**. The micro fuel cell serves as a power source for computing, communications, and sensing devices used in critical mobile and remote operations. These can include military missions, emergency and disaster response, remote surveillance, and field research and exploration. UltraCell has an exclusive license with the Laboratory for micro fuel cell technology.

Two Lawrence Livermore fusion pioneers, **Dick Post** and **John Nuckolls**, will be honored when **Fusion Power Associates** holds its first meeting ever on site at Livermore, December 3–4, 2008. Post came to the Laboratory within months of its founding in 1952 and has conducted magnetic fusion energy and other scientific research for 56 years, still coming into work several days a week now at age 89. Nuckolls came to the Laboratory in 1955. His 53-year career has been devoted to the development of advanced inertial fusion concepts and applications. Today, Nuckolls is focused on the National Ignition Facility Campaign and beyond ignition and gain to the development of laser-fusion power.

Livermore's **Technology Resources Engineering Division** (TRED) received two awards from the **National Safety Council** after surpassing 1 million work hours and 12 months without a lost workday injury or illness. The division's employees routinely work with a wide range of hazardous materials and operations in support of the Laboratory's research programs and infrastructure maintenance. The division received the awards **Million Hours Worked** and **Perfect Record** for working one year without an occupational injury. TRED has continued to extend its safety record to more than 1.1 million hours and 17 months without an occupational injury or illness resulting in days away from work.

Abstracts

Testing the Accuracy of the Supernova Yardstick

Type Ia supernovae (SNe Ia) are thermonuclear explosions marking the death throes of white dwarf stars. Because most SNe Ia have similar characteristics, astronomers have used them for calculating the distance to host galaxies from Earth and, by extension, the influence of dark energy. Nuclear physicist Rob Hoffman is leading a collaboration using Lawrence Livermore's Atlas supercomputer to simulate the behavior of both distant and nearby SNe Ia to understand their similarities and differences. The study is part of Livermore's Computing Grand Challenge Program, which allocates millions of central-processing-unit hours on Laboratory supercomputers to unclassified projects that support the Laboratory's missions. The supernova simulations were performed by the Computational Astrophysical Consortium, with members from the University of California at Santa Cruz, Lawrence Berkeley National Laboratory, State University of New York at Stony Brook, and Lawrence Livermore. The team combined simulation codes to model different phases of SNe Ia evolution, ranging from the time when hot spots deep inside a dwarf's core give birth to a tiny nuclear flame to the weeks following the explosion.

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Developing New Drugs and Personalized Medical Treatment

Thanks to developments by Livermore researchers in the use of accelerator mass spectrometry over the last 20 years, the effects of new drugs, chemotherapy compounds, nutrients, and toxic substances can safely be studied in humans. In a process referred to as microdosing, a group of human subjects receives 1/100th of the therapeutic dose of a new drug, which has been tagged with carbon-14 atoms. Blood and tissue samples taken over hours, days, or weeks are run through the accelerator mass spectrometer to measure the amount of carbon-14 and thereby the amount of the drug remaining in and leaving the body. With enough data on a candidate drug's adsorption, distribution, metabolism, and excretion—called its pharmacokinetics—pharmaceutical researchers can determine the drug's properties for reaching targeted tissues and remaining in place at sufficient levels to be effective. Finding the compounds that have the proper pharmacokinetic properties early and eliminating those that do not allow drug developer to focus their time and money on the most promising candidates. The Laboratory also hopes to apply microdosing techniques to the development of drugs to counter biological threats.

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And the Award Goes to . . .

Three Laboratory research teams were honored in *R&D Magazine*'s annual competition for the 100 top industrial innovations:

- Dynamic Transmission Electron Microscope
- Autonomous Alignment Process for Laser Fusion Systems
- SecureBox: National Security through Secure Cargo

Also in November/December

• Sandwiches of extremely thin layers of materials, called nanolaminates, exhibit remarkable and highly useful properties.

• A supercomputing "grand challenge" team has made precise calculations predicting the behavior of plutonium's most important solid phase.

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