Guiding the Design of Microanalytical Devices

Also in this issue:
- Science at the Nanoscale
- Transport and Fate of Chemical and Biological Agents
- Glucose Sensor for Diabetics
Microchip technology is revolutionizing laboratory instrumentation. These days, researchers are developing microfluidic devices that hold the promise of becoming complete analytical laboratories, even though they are tiny enough to be held in one hand. The devices will be used to perform tasks such as identifying, separating, and purifying cells and other materials. Engineering these miniature instruments is tricky, but designers are turning to computer simulations for help. The article beginning on p. 4 discusses how a team of scientists is collaborating on a complex, three-dimensional simulation tool to guide the design of microfluidic devices.
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In the aftermath of terrorism

A number of capabilities at the Laboratory, developed as part of Livermore’s national security mission, have come to public attention since September 11, 2001.

Livermore scientist Graham Bench led a team from the University of California at Davis to analyze air quality at the disaster site. The team used a device called a Davis Rotating Unit for Monitoring, or DRUM, to collect information about the size and type of particles in the air. The information revealed whether the particulate matter was organic, inorganic, or toxic, and helped officials to determine the best safety measures for the site.

Harry Martz, director of the Center for Nondestructive Characterization in the Engineering Directorate, is on a National Academy of Sciences committee that reviews the Federal Aviation Administration’s safety regulations. Martz’s expertise is in x-ray and industrial computed tomographic scanning technologies, and he has been called on by news media to discuss scanning technologies for passenger and baggage screening.

The Laboratory is researching several technologies for combating terrorism. Among them are the Handheld Advanced Nucleic Acid Analyzer, or HANAA, which can quickly analyze sample DNA in the field to detect the presence of pathogens such as anthrax or plague. In a related effort, biologists are identifying the DNA signatures of a number of pathogens for use in HANAA and other biodetection instruments. Another technology is the Autonomous Pathogen Detection System, or APDS, which also searches for the presence of pathogens in the environment by continuously monitoring the air inside buildings or public venues where the system has been installed. Livermore researchers also are developing gene chips that store genetic information about unique regions of various pathogen strains. Yet other researchers are developing monitoring networks to “sniff” the air over a geographic area for biological agents. And the Laboratory has developed L-Gel, a silica-based oxidizer material that can be sprayed onto any surface to kill biological agents or to neutralize chemical warfare agents.

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Teller symposium educates science teachers

More than 100 high school and community college science teachers from throughout California arrived at the Laboratory on September 21 for the second annual Edward Teller Science & Technology Education Symposium.

The teachers spent two days talking with scientists and engineers about their latest research; attending hands-on workshops in physics, chemistry, biology, and environmental science; and touring state-of-the-art research laboratories.

John Gage, chief researcher and director of the Science Office of Sun Microsystems, was the event’s keynote speaker. He talked about the future of the Internet in education. Director Emeritus Edward Teller also addressed the participants.

The symposium was cosponsored by the Laboratory and the University of California at Davis’s Department of Applied Science as well as other educational, professional, and corporate organizations.

Livermore’s Richard Farnsworth, who coordinated the symposium for the Laboratory’s Science & Technology Education Program, summarized the relevance of the symposium to science education. “It often takes 8 to 10 years to get the information that comes out of research laboratories into the classroom. With this symposium, the Lab and the symposium’s cosponsors are building a bridge so teachers see how today’s science research can affect their science education teaching. . . . We’re giving the teachers materials that come out of our laboratories to take back to their classrooms immediately.”

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THIS issue of Science & Technology Review looks at several exciting Laboratory projects that got their start with Laboratory Directed Research and Development (LDRD) Program funding. Many of the research thrusts that began several years ago under LDRD sponsorship are the foundation of Laboratory programs today. Over the years, LDRD has become the Laboratory’s primary means for pursuing innovative, long-term, high-risk, and potentially high-payoff research in support of our evolving national security mission.

Recent events underscore the importance to national security of LDRD investments in research to counter bioterrorism. For example, one LDRD-sponsored project seeks to develop a model of the actual disease-causing mechanisms within a bacteria pathogen. Such a model represents a strategic first step in understanding, anticipating, and countering threats from rapidly evolving or engineered microbes such as those used in the anthrax attacks. Another LDRD-sponsored project is developing a portable, high-throughput biological threat detection system that can accurately analyze a broad suite of pathogens simultaneously from a single sample. One ongoing project, highlighted in this issue (see pp. 20–22), models the behavior of drops of liquid at extreme conditions to determine what would happen to liquid-borne toxins or pathogens when a missile carrying chemical or biological agents is intercepted at high altitude.

The development of such scientific and technological innovations draws on the very core of the Laboratory’s unique capabilities and stimulates its intellectual vitality. As a mark of its effectiveness in fostering research and development at the Laboratory, the LDRD Program is well represented by projects that have received prestigious national awards and by patents granted to Laboratory scientists and engineers. With its reputation for sponsoring innovative research and development (R&D) projects, the LDRD Program is a major vehicle for attracting and retaining the best and the brightest technical staff as well as for establishing collaborations with industry, universities, and other scientific and research institutions. The articles presented in this issue demonstrate the value of such collaborations.

Authorized by Congress in 1991 to invigorate R&D at the Department of Energy’s multiprogram laboratories, the LDRD Program enables the Laboratory to directly fund a research portfolio in areas aligned with DOE’s missions and helps develop new capabilities to meet current and future national challenges. Funding for the LDRD Program is set at a maximum of 6 percent of the Laboratory’s annual budget. The LDRD budget of $55 million for fiscal year 2001 sponsors over 195 projects. The projects focus on advancing capabilities in areas vital to our national security mission, including high-performance computing, fundamental materials science, advanced sensors and instrumentation, and energy and environmental sciences.

Each year, projects compete for LDRD funding through an extensive process in which committees composed of senior managers, program leaders, scientists, and outside experts review hundreds of innovative proposals submitted by researchers from across the Laboratory. Selection criteria include innovation, scientific quality, impact, risk, and programmatic and strategic relevance. Every year, the number of deserving proposals far exceeds the funding available, making the selection a tough one indeed. The LDRD Office ultimately forwards its recommendations to the Laboratory director and his deputies, who make the final decision on the LDRD awards.

The projects described in this issue are examples of the broad spectrum of award-winning, cutting-edge research and development funded by the LDRD Program. By keeping the Laboratory at the forefront of science and technology, these projects enable us to meet the challenges of an ever-evolving national security mission.

Rokaya Al-Ayat is director of the Laboratory Science and Technology Office.
The microchip revolution made possible today’s miniaturized electronics industry. In like manner, the microchip is changing laboratory instruments that analyze fluids. Large and costly instruments are being replaced by microchip-based systems known as microfluidic devices. These miniature systems move fluids through a maze of microscopic channels and chambers that have been fabricated with the same lithographic techniques used for microelectronics.

Microfluidic devices are fashioned from silicon, glass, plastics, and ceramics into 2- or 3-square-centimeter slices with cover plates. In them, red blood cells, bacteria, biological macromolecules (such as proteins and DNA), polystyrene beads (that bond to targeted macromolecules), and other materials can be manipulated in channels with characteristic length scales on the order of 100 micrometers. The devices integrate sensors, actuators, and other electromechanical components to dispense with myriad moving parts and the people required to operate and service them.

Microscale instruments and processing are the future of medical research and the chemical and pharmaceutical industries. Microfluidic devices hold the promise of a small analytical laboratory on a chip to identify, separate, and purify cells, biomolecules, toxins, and other materials. They would perform these tasks with greater speed, sensitivity, efficiency, and affordability than standard instruments.

They might also be used in the future for detecting chemical and biological warfare agents, delivering precise amounts of prescription drugs, keeping tabs on blood parameters for hospital patients, and monitoring air and water quality.

For more than a decade, Lawrence Livermore researchers have been working on several aspects of microfluidic devices. The Laboratory’s Center for Microtechnology has more than 30 experts in electronics, biology, optics, and engineering who are developing microfluidic components.
for transporting, sensing, separating, mixing, and storing fluids and their constituents. (See S&TR, July/August 1997, pp. 11–17.) Current Livermore projects include the design and prototyping of devices for the human genome program, chemical and biological warfare agent detection, and medical analysis.

**First Complete Model Designed**

To help guide the design of microfluidic devices at the Center for Microtechnology and elsewhere, a team of Livermore researchers is developing a complex, three-dimensional simulation tool. The team consists of chemical engineers David Clague and Elizabeth Wheeler, postdoctoral mechanical engineer Todd Weisgraber, and University of California (UC) at Berkeley student Gary Hon. In this work, they collaborate with other Livermore researchers from several disciplines as well as colleagues at universities. The team has been funded for the past three years by the Laboratory Directed Research and Development (LDRD) Program through Livermore’s Center for Computational Engineering and, more recently, by the Defense Advanced Research Projects Agency (DARPA) of the Department of Defense.

The team’s computer code has drawn increasing interest because it provides an accurate representation of the behavior of suspended particles, especially polystyrene beads and biological macromolecules, as they travel inside a microfluidic device. The simulation capability incorporates into a single numerical code complex channel geometries and such parameters as fluid flow rates, particle interactions, and external forces. “We want to predict the complex interplay of the forces involved in microfluids to give designers a way to accurately predict how beads, cells, and macromolecules will behave,” says team leader Clague.

Clague notes that suspended particles traveling within microscopic channels are subject to a number of physical forces that influence their transport and separation from each other and the channel walls. The forces, such as subtle electrical attractions and repulsions, can be used to achieve the movement and manipulation of suspended particles in ways that would not work in traditional bench-scale laboratory instruments.
The Livermore simulation capability provides a new tool to assist microfluidic device designers who want to engineer systems that will reliably move, separate, concentrate, and identify suspended particles of interest. With effective simulation, the designers can see the effects of design decisions before they build a prototype. For example, a designer may want to position selected biological macromolecules in the central region of a microchannel for capture by an electric field and therefore must determine what field strength will be required. Or a designer may want to see how restricting a channel with a tiny post might affect the fluid flow rate and the mixing behavior of particles as they are forced to “slalom” around it.

The program uses a form of the Boltzmann transport equation called the lattice Boltzmann equation (LBE) to represent the behavior of fluids and suspended particles within microfluidic devices. (Ludwig Boltzmann was an Austrian physicist whose greatest achievement was the development of statistical mechanics, which explains how the microscopic constituents of matter—atoms and their properties—determine macroscopic properties such as thermal conductivity or viscosity.) In recent years, the LBE method has gained popularity and usefulness in simulating the flow of complex gases and liquids. It is based on a statistical description of the fluid on a cubic lattice in which each lattice site represents up to several thousand individual fluid molecules.

In the team’s numerical model, spheres represent polystyrene beads and biological macromolecules within the lattice. The spheres can be assigned different sizes, densities, and electrical properties. Because of their size, the spheres can occupy several lattice sites. The code tracks the spheres as they move on the lattice and calculates the extent to which the spheres interact with each other, the channel walls, the fluid, and external forces that may be applied to manipulate them. The simulation tracks the time evolution of both the fluid and suspended spheres. The algorithms (mathematical routines) used by the program tend to be readily applied, allowing calculations in a straightforward manner and making it easy to incorporate new forces.

A Natural for Parallel Computing

Because the LBE method is naturally suited for parallel computing, the simulation capability is designed for large computers, preferably supercomputers that use tens to hundreds of microprocessors together. Simulations representing time scales on the order of tens of seconds of continuous suspension require a few days of computer time. The team uses several Livermore machines for their simulations, including the Compass Cluster and two massively parallel supercomputers: Blue, the 740-gigaops unclassified portion of Blue Pacific, one of the Department of Energy’s Accelerated Strategic Computing Initiative supercomputers, and the 680-gigaops TeraCluster2000. (See S&TR, October 2001, pp. 4–10.) The TeraCluster2000 is the preferred computing platform; simulations on it use up to 50 microprocessors working simultaneously.

One important advantage of the code is its flexibility. The simulated suspended particles can be assigned different physical and electrical attributes, including electrostatic forces that cause fluids containing biological macromolecules to act far less predictably than ideal species, which would consist of hard, inert spheres.

Simulations can accurately reflect a host of physical forces that act on suspended particles flowing in a microfluidic device that typically measures 100 micrometers long, wide, and high. These forces, such as subtle electrical attractions and repulsions, are typically of much less importance in traditional bench-scale laboratory instruments.
External forces such as gravity, alternating current, or direct current can be simulated. These forces can be turned on and off to isolate their specific effects on particle behavior. Livermore engineer Peter Krulevitch, a microfluidic device project leader, says that until now, no program was capable of simulating all the forces acting on fluids containing particles. “The problem has just been too complex,” he says.

The LBE method contrasts with traditional fluid modeling based on finite-element analysis and boundary-element methods, which typically deal with pure fluids. Results from the Livermore code, however, can be handed off to larger-scale computer-aided design simulation tools that use standard finite-element analysis.

Mike Pocha, a Center for Microtechnology section leader, notes that device designers can build prototype devices—a long and painstaking process—and determine their capabilities or, preferably, simulate them first and then build a prototype guided by the simulation results. Going from concept to manufacturing a prototype is increasingly more time-consuming and expensive as microfluidic devices get more complex, says Clague. “With a more comprehensive simulation tool, researchers will be better able to predict what will happen to the suspended species in these complex microenvironments. Ultimately, such a capability will speed the design effort and reduce costs.”

The physics involved with the operation of microfluidic devices is complex and varies, depending on the fluid, the molecules suspended in the fluid, and the extent, if any, of external fields. In building the code, the team has steadily added capabilities that more completely represent the physical forces at work in microfluidic devices. After every addition of a new feature, the team makes sure the results are in excellent agreement with existing theory and, where possible, with published alternative numerical methods.

LDRD Laid the Groundwork

One of the team’s first accomplishments under LDRD funding was simulating hydrodynamic forces acting on a stationary sphere. These forces are dependent on the velocity of the suspending fluid and the proximity of the suspended particles to channel walls. The LBE method naturally takes into account the entire spectrum of fluid and particle behavior, including inertial effects and hydrodynamic interactions between suspended particles. In other words, the simulations account for the minute disturbances propagated within a fluid by the particles that “feel” each other’s presence and, as a result, change their trajectories and the properties of the fluid.

The hydrodynamic forces, including inertial effects, are particularly well captured. The first is the drag force, which is a result of the fluid exerting a force on a suspended particle because of differences in fluid and particle velocities. The second force is a lift force, which is caused by small inertial effects and gradients in fluid velocity. The lift force is exerted perpendicular to the flow, causing the species to migrate to the center of the channel. Also coming into play is a particle’s density, which affects its buoyancy within a fluid and the extent to which it can be lifted.

Simulations using the lattice Boltzmann equation method are based on a cubic lattice, here with dimensions of 40 by 100 by 100 micrometers. Spheres (in this example, measuring 5 micrometers in diameter) represent polystyrene beads and biological macromolecules within the lattice. The simulations track the spheres as they move on the lattice and calculate the extent to which they interact with each other, the channel walls, the fluid, and the external forces that are used to manipulate them.
Fluids normally flow through microfluidic channels without turbulence so that suspended particles typically mix only by diffusion. One of the key parameters used to characterize fluid flow is the Reynolds number, which defines flow conditions and measures the relative importance of inertial effects to viscous effects. Most fluid flow in small channels occurs at a low (but finite) Reynolds number. However, even at small Reynolds numbers, researchers have found that there are small lift effects. The Livermore simulation capability takes into account these inertial effects for predicting the extent of lift as a function of Reynolds numbers.

The code also simulates the effects on particles that are near channel walls. Much like the effect of a boat’s wake, the motions of molecules cause disturbances in the fluid that bounce off the channel walls and reflect back on the particles. Close to the walls, particles experience forces retarding their motion, and even closer to the walls, they experience large resistive forces known as lubricating forces.

**Adding Real Effects**

If the simulation is to be accurate, it must also account for non-Newtonian characteristics that are exhibited by biofluids containing human cells, bacteria, and biological macromolecules such as proteins and DNA. These materials do not behave like electrically neutral and perfectly round spheres. Instead, they have widely varying shapes, densities, and often electrical charges that are asymmetrically distributed.

More importantly, these materials tend to have elastic character, which gives rise to unexpected effects. Strands of DNA, for example, can be long and gangly with a preferred, three-dimensional shape that orients itself in a particular manner to its neighbors. If forced to travel through a narrow channel, the strands deform but then exert a small force in an attempt to recover their favored configuration, much like a compressed spring reverts to its normal shape. If there is a sufficient concentration of such strands, this restoring force can have a profound effect on fluid behavior.

Depending on their concentration, particles interact with each other and...
with the channel walls. Under certain conditions, they can coagulate with each other or stick to walls because of van der Waals and electrostatic forces (electrical attraction and repulsion forces between species). The simulation team is incorporating these and other forces associated with biological macromolecules into the models, including hydrophobic (water hating) and hydrophilic (water loving) interactions. Clague explains that some proteins have hydrophobic regions that cause the proteins to aggregate when they are in close proximity to other proteins; therefore, these unique forces must be taken into account.

Last August, the team began work for DARPA, the advanced research arm of the Department of Defense and a major backer of microfluidic technology. One of DARPA’s goals is to develop devices called BioFluidic Chips (BioFlips) that will identify biological macromolecules and microbes based on certain electrical or chemical properties. Soldiers would use BioFlips devices both to detect chemical and biological agents and to monitor their own general health. (See the box on p. 10.) As part of the microfluidic development effort, a program called Simulation of Biomolecular Microsystems (Simbiosys) is funding the development of advanced computational tools for the BioFlips design effort. The Livermore team’s simulation work is part of the Simbiosys program.

**Focus on Dielectrophoresis**

The team’s work for DARPA builds upon LDRD research, particularly with regard to simulating the coupling of hydrodynamic and dielectrophoretic forces. Dielectrophoresis (DEP) is an efficient and increasingly popular method for separating molecules in microflows. DEP electrodes generate nonuniform, alternating current electric fields that induce electrical polarization in target species. On an absolute scale, the force is quite small, but in microfluids, the force can be quite effective in manipulating and positioning biological macromolecules with electrodes using less than 10 volts. The degree of induced polarization is dependent on the electrical properties of the molecule, the surrounding fluid, and the magnitude and frequency of the applied electric field.

“Different species typically have their own unique dielectric response fingerprint that can be exploited by DEP,” says Clague. As a result, DEP can be used to select from among a number of different particles suspended in the same fluid. The selected particle will either be drawn toward or repelled from the region of high field intensity (toward or away from the DEP electrode located within a channel wall). The first instance is referred to as positive DEP, and the second is referred to as negative DEP.

DEP forces can be switched on and off to selectively capture cells, bacteria, spores, polystyrene beads, DNA, proteins, and other matter. Once captured, the molecules can be held in place or, with the removal of the force, sent on their way to a different location for analysis.
For example, DEP can be used to selectively capture a suspected pathogen. The pathogen would then be shuttled to a different area where its DNA would be extracted and analyzed.

The DEP simulation work involves close collaboration with pathologist Peter Gascoyne at the University of Texas M.D. Anderson Cancer Center in Houston, Texas. Gascoyne and his colleagues, in a project sponsored by DARPA, are developing an instrument that uses DEP to separate cells and identify them based on their dielectric properties. A prototype has been used on whole blood samples to separate malignant cells from normal cells.

An important group of simulations is focused on examining the interplay of suspended particle concentration, flow rates (and inertial lift effects), and DEP forces with the effects from different kinds of suspended particles. Preliminary simulations show that the hydrodynamic interactions between particles can screen and thwart DEP forces; therefore, concentration effects become very important. The suspended particles that are not screened encounter a positive DEP force and are pulled to the electrode surface, where they are held motionless.

The team is continuing to enhance the numerical model to investigate the forces influencing DEP manipulation of molecules suspended in flowing fluids.

The BioFluidic Chips (BioFlips) program of the Defense Advanced Research Projects Agency (DARPA) is developing a clinical lab on a chip. BioFlips would offer all the advantages of microfluidic devices: miniaturized channels and reservoirs for increased speed of reaction, increased sensitivity, reduced cost of reagents, and reduced power consumption. The devices would be capable of rapid detection of infections and chemical and biological warfare agents, making possible potentially rapid treatment.

BioFlips would be worn directly on the skin, perhaps on the earlobe for continuous blood monitoring through microneedles. BioFlips would provide real-time, unobtrusive monitoring to directly assess the health of defense personnel. A commander could continuously monitor the status of troops—whether they are fatigued or have been exposed to biological threats, including bacteria, viruses, and toxins. The devices could monitor such entities as white blood cells, antibodies, blood pH, and blood glucose.

BioFlips promise fast health assessment, from seconds to minutes, in contrast to laboratory blood cultures using traditional methods that take hours or even days to process. If successful, the technology could perhaps be extended to improve national health care by unobtrusive and continuous monitoring of high-risk patients.

BioFlips designers need powerful computational tools to guide and speed their efforts. Hence, DARPA is sponsoring an allied DARPA program called Simulation of Biomolecular Microsystems (Simbiosys). The Simbiosys program recognizes that engineers have limited understanding of biological molecules and biochemical reactions and, furthermore, that biologists do not generally have knowledge about key biochemical reaction rates and little knowledge about the behavior of biological molecules in microscopic channels. The goal is the creation of what DARPA managers are terming the “first interface between biology and engineering.” Effective simulation models will enable greater understanding of the transport of biological materials at the micrometer scale to enable better control and efficiency of the devices.
One research avenue they are taking is to give biological macromolecules more realistic characteristics. For example, the team has explored replacing the simulated spheres with more accurate bead-and-spring representations of long-chain polymers such as DNA fragments. Also under development are representations of cell properties unique to organelles and membranes, that can significantly influence the response. Finally, the team is working on the inclusion of electrostatic and van der Waals forces as well as hydrophobic and hydrophilic interactions.

The team has collaborated with UC Berkeley researchers on developing arrays of 50-micrometer-diameter needles. The goal is to deliver drugs more efficiently, but interactions between particles cause the microneedles to become clogged. The Livermore team’s simulation work is targeted at obtaining a better understanding of the problem. This work complements a DARPA-funded project at UC Davis, where researchers are developing microneedle arrays for drawing body fluids painlessly to monitor soldiers’ health on the battlefield.

Clague expects the simulation program to become increasingly useful as applications for microfluidic devices expand. By providing a tool that allows microfluidic device designers to turn the variety of physical forces at play on and off, the team hopes to make possible the discovery of new ways to manipulate suspended particles. Such detailed and accurate simulations speed the design and development of novel microfluidic devices. As a result, the simulation effort may well have an important role in saving soldiers’ lives and in developing new medical devices that could help drive down national health care costs.

—Arnie Heller

Key Words: BioFluidic Chips (BioFlips), Center for Microtechnology, Defense Advanced Research Projects Agency (DARPA), dielectrophoresis (DEP), lattice Boltzmann equation (LBE), microfluidic devices, Reynolds number, Simulation of Biomolecular Microsystems (Simbiosys).

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About the Scientist

DAVID CLAGUE is a staff engineer in the Electronics Engineering Technologies Division of the Engineering Directorate. He joined the Laboratory in 1998, after a year as a postdoctoral researcher at the Los Alamos National Laboratory Center for Nonlinear Studies. Clague received a B.S. in chemical engineering from the University of California at Santa Barbara in 1987, an M.S. in engineering in 1993, and a Ph.D. in chemical engineering in 1997, both from the University of California at Davis. His research specialties are in transport phenomena, complex fluids, microfluidics, and numerical methods. At Livermore and previously at Los Alamos, he has developed three-dimensional simulation methods for modeling particulate behavior. This work has been published in a number of refereed journals. Additionally, Clague has experience in industry, working for four years as a research and development engineer at Space Systems Loral to provide engineering and technical support related to polymeric composite materials and adhesives.
Scientists are discovering that big results come from starting small.
Finding the best ways to detect biological warfare agents is one of Lawrence Livermore’s missions today. Detecting large quantities of a biological pathogen is not difficult. The challenge is in detecting a few molecules of a toxin or a few bacteria or viruses to provide the early warnings of a biological attack.

Physicist Christine Orme and colleagues in the Chemistry and Materials Science Directorate are helping to understand some of the fundamental issues that underlie biodetection as well as fulfilling other Laboratory goals. They are performing research at minute scales in a field known as nanoscience, which takes its name from nanometer, a billionth of a meter. The team is examining, on an atom-by-atom and molecule-by-molecule basis, the organization of materials on surfaces and learning how that organization affects material properties. “One of the keys to working in nanoscience is controlling the surface and then being able to detect what is there,” says Orme.

At the nanoscale, experimental results can be viewed only with the most powerful imaging tools. The atomic force microscope (AFM) has been used since the mid 1980s to produce topographic maps of nanostructures. Today, Orme’s colleagues are developing new microscopic techniques based on use of the AFM that give even higher resolution and supply more than just topographic data. They are also refining the spectroscopic techniques that identify chemical bonds and supply fingerprints of molecules.

The current research builds on pioneering Livermore work in crystal growth and thin multilayers, both of which depend on a keen understanding of material behavior at the atomic level. Livermore has a long-standing effort in crystal growth and characterization, born out of the need for large, ultrapure crystals in Livermore’s lasers. Multilayers—exceedingly thin alternating layers of materials—were first demonstrated more than 50 years ago. But improved fabrication technologies developed by Livermore’s Troy Barbee have prompted their use as highly reflective mirrors for telescopes as well as in a variety of optical applications, including electron microprobes, scanning electron microscopes, and particle beamlines in accelerators. (See S&TR, December 1999, pp. 11–13.)

Seeing is Believing

In atomic force microscopy, an extremely sharp tip senses the atomic shape of a sample while a computer records the path of the tip and slowly builds up a three-dimensional image. The AFM tip is positioned at the end of an extremely thin cantilever beam and touches the sample with a force of only 1/10-millionth of a gram, too weak to budge even one atom. As the tip is repelled by or attracted to the sample surface, the cantilever beam deflects. By imaging a larger or smaller area, researchers can vary the level of magnification of an AFM image. The
AFM can also be adapted to sense a range of forces including attractive or repulsive interatomic forces, electrostatic forces, and magnetic forces.

But even the sharp tip of the AFM is sometimes not tiny enough for the small scale at which the research team is working. Physical chemist Aleksandr Noy is growing carbon nanotubes that can be used to replace the standard AFM tip. The figure above compares a typical AFM tip and a carbon nanotube tip. Carbon nanotubes are built of carbon hexagons that are arrayed in a configuration resembling chicken wire. They are 1/50,000th of the width of a human hair but a hundred times stronger than steel at one-sixth the weight. Noy can make many kinds of nanotubes—single wall, multiwall, thick, thin, single isolated, or large arrays. The smaller, lighter nanotube tip tracks the shape of an object more accurately to provide more detailed information about its surface.

Noy used the nanotube-tipped AFM to image the cucumber mosaic virus and reveal its structure fairly clearly. AFM images contain less information than structures revealed through x-ray diffraction techniques, but Noy’s image was captured in minutes, whereas the same structure took over a year to resolve from diffraction data. “In principle, this technology could be used to image a single virus,” says Noy. “Emergency workers could compare its image with a...
computerized database of known virus structures to identify it very quickly."

With the nanotube tip on the AFM, a team led by Noy also obtained the first unambiguous visualization of a DNA repair protein bound to DNA. By incorporating a synthetic mutagenic molecule into DNA and tagging a repair protein with a fluorochrome, they will be able to study the repair process in situ.

Another imaging technique being used by physicist Thomas Huser and others is confocal microscopy. It is based on a fluorescence microscope augmented with a pinhole that limits the volume being probed to get rid of extraneous background "noise." Its beam can be focused to 500 nanometers. The confocal microscope efficiently collects fluorescence emitted from fluorochromes that have been excited by laser light. With this spectroscopic technique, Huser has been able to detect single molecules.

The confocal microscope is ideal for studying conjugated polymers, a new material that may be used to fabricate the next generation of light-emitting diodes (LEDs). Known as 2-methoxy, 5-(2'-ethyl-hexyloxy)-p-phenylene-vinylene, or MEH-PPV, the polymers are composed of a chain of benzene rings that emit light when linked by electrodes to which voltage is applied. The advantages of these polymers over the inorganic semiconducting materials of today’s LEDs are many: They are easier to process on a large scale, they can be used to create ultrathin and flexible devices, and their power consumption is lower. Last year’s Nobel Prize in Chemistry was awarded for the development of conjugated polymers.

Huser has learned that the physical configuration of the MEH-PPV molecules affects their fluorescence. "The photoluminescence of conjugated polymers depends strongly on how they are shaped," says Huser. When they fold up into a well-organized pattern in toluene, their shape enhances efficient energy transfer within the molecule. As conjugated polymers begin to be used as LEDs in electronics, some LED applications will take advantage of the high-energy-transfer configuration while others will benefit from the less ordered pattern for low-energy transfer.

In experiments, Huser exposed MEH-PPV to two solvents, toluene and chloroform. In toluene, the MEH-PPV molecules curl up tightly because, says Huser, “They don’t like toluene. They try to avoid it.” Spectrographic data collected every 5 seconds show a slight flicker as the molecules die off with exposure to oxygen and the light they emit shifts from red to blue. In chloroform, the polymer spreads out. There is no blue shift, the light spectrum is broader, and the light intensity simply decays slowly with time.

Huser recently began experiments with the confocal microscope to examine the dynamics of single molecules of DNA. Fluorescent labeling of DNA, RNA, enzymes, and proteins is common laboratory practice to illuminate the interactions and functions of these important biomolecules.

At the same time, Noy has built a whole new microscope system that combines the topographic capabilities of the AFM and the spectroscopy of the confocal microscope. He will be using this system to obtain even better information about DNA repair as well as DNA repair processes.
as new information on how DNA is packaged.

**Identifying a Single Molecule**

Another tool for identifying molecular species is Raman spectroscopy, a form of light scattering similar to fluorescence. Although Raman-scattered light is much less intense than fluorescence, the technique is a powerful analytical tool because the changes in wavelength of the weakly scattered light are characteristic of the scattering material. Raman spectroscopy can identify chemical bonds and obtain the unique fingerprint of a molecule. Every molecule has a unique Raman spectrum, but not every molecule fluoresces. Raman spectroscopy is one of the few optical techniques that can identify a molecular species and determine its chemical bonding by observing its distinct molecular vibrational frequencies.

To increase the brightness and thus the resolution of Raman-scattered light, Huser has introduced nanometer-size gold crystals to the tip of a scanning probe microscope in a technique known as surface-enhanced Raman spectroscopy. The gold is negatively charged and attracts positively charged materials such as amino acids to adhere to kinks in the crystals. Electron density waves radiate from the corners of the gold crystals and increase the Raman signal by a factor of a quadrillion. At the same time, the scanning probe produces an image of the physical structure of the sample. The combined data allow for identification of single molecules. Unlike fluorescence, which fades with exposure to oxygen, the increased energy from the gold particles persists.

“Being able to characterize materials and chemical bonds at the level of a single molecule is a whole new capability for Livermore,” says Huser. It is possible to perform Raman spectroscopy on single DNA molecules or proteins and to look for differences between individual cells. Using this technique, scientists also can detect and identify the byproducts or precursors of chemical agents such as the nerve gas sarin. This capability is important in the development of sensors for chemical warfare agents.

**Controlling Biomolecules**

Some nanoscience projects require the careful design of surfaces to collect and organize atoms, molecules, nanocrystals, colloids, cells, and spores. These surfaces are known as templates or, as Noy describes them, “landing pads” for toxins, proteins, and other biomolecules.

Livermore is exploring several techniques for creating templates. Physicist Jim De Yoreo is developing one method based on dip-pen nanolithography, which dips the tip of the AFM into an “inkwell” of organic molecules to “write” on an inorganic surface. As the tip moves across the surface, it makes a pattern that has almost no topographic relief but exhibits chemical contrast with the surrounding region. It is even possible to create multiple ink patterns with this method. The feature size is controlled by such factors as tip coverage, humidity, and contact time with the substrate, or, in the case of lines, tip

![An example of the benefit of surface-enhanced Raman spectroscopy. (a) Confocal optical micrograph of 60-nanometer-diameter gold nanocrystals loaded with just a few molecules of the laser dye rhodamine 6G. (b) Surface-enhanced Raman spectrum of one of the gold particles in (a) easily identifies the adsorbed rhodamine by its characteristic Raman signature.](image-url)
speed across the substrate. Examples of patterns created using a gold-coated mica surface for the substrate and 16-mercaptotetradecanoic acid for the ink are shown in the figure at right. This method has been used to deposit patterns of antibodies that would attract toxins and viruses, a first step in the development of nanostructured biosensors.

Another major area of research at Livermore’s Biology and Biotechnology Research Program (BBRP) and elsewhere is in proteomics, the study of proteins. Cells produce particular proteins either all the time or as needed to prompt gene expression, that is, to turn a specific part of the genetic code on or off. Without proteins, our DNA could not operate properly. One of the best ways to examine the structure of a protein is to crystallize it and then subject it to x rays to obtain its unique diffraction pattern. During the crystallization process, molecules come together and separate (in a process known as nucleation) until a critical size is reached. Reaching that critical size can take a long time, and sometimes it does not happen at all. One goal of current proteomics work is to speed up the nucleation process and make it more likely that proteins will crystallize.

Dip-pen lithography, using a chemical that would prompt protein nucleation, is an option. “But,” says Orme, “the size scale is a challenge. Proteins are extremely small, typically from 1 to 10 nanometers.”

“If we make the pen’s lines smaller, they won’t be visible,” adds Noy. So he and researchers in BBRP are developing a fluorescent ink for drawing lines with the density of a single molecule. In initial tests, a single-molecule line of the human chorionic gonadotropin (HCG) antibody has been successfully drawn. The next step will be to attract the HCG protein.

Nanolaminates, the next generation of multilayers, are also being explored as a way to accelerate the nucleation and growth of ordered proteins. Nanolaminate structures have been synthesized with layers that are the same small size as typical proteins. The alternating layers have different surface charges, which prompt the proteins to adsorb in ordered rows. In the example shown in the top figure on p. 18, a nanolaminate was dipped into a solution of the protein ATCase. The nanolaminate was then removed, rinsed, air-dried, and imaged with AFM using a carbon nanotube tip. The resulting extremely high resolution of the image makes nonspherical proteins individually distinguishable on silica stripes. An image of the same deposition onto a homogeneous silica surface is very different, lacking any linear order. This set of experiments was the first step in accelerating nucleation and growing protein crystals that are suitable for x-ray diffraction.

Mimicking Natural Growth

Nanoscience is finding another application in the hands of Orme, De Yoreo, and colleagues whose research on the growth of calcite crystals sheds new light on the formation of bones, eggshells, and seashells.

The natural growth of organic crystals is known as biomineralization. Biomimetics is the term for mimicking nature’s building methods to make a synthetic material. “We can only learn to make better bones and teeth if we first understand how the materials grow and interact with biological molecules,” says Orme. “While there is a big step between this fundamental research and synthesizing materials that are truly similar to the real thing, we are part of the process to create better materials that affect health.”

Pure calcium carbonate in the mineral form called calcite grows only in a symmetrical, six-sided rhombohedral-shape crystal. But that does not explain the intricate shapes found in nature, such as that of seashells. Researchers have known for a long time that organic
molecules can influence the shape of a growing mineral crystal by attaching themselves to it. But it took experiments at Livermore to demonstrate the process in detail, showing how amino acids work at the molecular level to change a growing crystal.

In the experiments, the team added aspartate, one of the more abundant amino acids found in the proteins of shellfish, to calcite crystals growing in solution. Aspartate is typical of many amino acids in that it exhibits handedness, or chirality. As the researchers monitored crystal development, they found that the left-handed and right-handed form of the molecule attached more strongly to opposite atomic steps. The results were crystals that were mirror images of one another. The figure below illustrates how a chiral amino acid influences a growing calcite crystal. By knowing which steps the amino acid interacted with and using the symmetry relations of the crystal and the amino acids, the team was able to predict the binding position of the amino acid to the calcium carbonate step.

Comparable experiments are just beginning on calcium phosphate, the material used by animals to grow bones. Ultimately, experimental results may be put to myriad uses, from potential laboratory growth of human and animal bones to prevention of scale formation in pipes to the manufacture of toothpaste—any situation in which calcium-based crystals grow naturally or are used.

**Fundamental Science at Work**

A nanostructured device is also finding its way into tests for the Yucca Mountain project, the nation’s candidate...
for a repository for long-term storage of nuclear wastes. Tests of corrosion-resistant materials are being developed that use patterns formed by “writing” with voltage rather than with chemical inks. A voltage is applied between the AFM tip and a metal or semiconductor substrate to grow oxide patterns under the tip. In the figure below, an oxide greeting is written into a titanium film. The dot on the “i” is made larger and broader by applying a higher voltage. If the nanopatterns blur or dissolve during testing, the change provides a very sensitive indicator that the protective oxide film is changing.

This project is typical of so much fundamental research performed at Livermore. Using funding from the Laboratory Directed Research and Development (LDRD) Program, the oxide templates were originally developed to nucleate calcium phosphate minerals and to control protein deposition onto medical implants. Now, the Yucca Mountain project is putting the template to practical use. Much of the other work at Livermore to grow and image nanostructures also started as basic research, funded either by LDRD or by the Department of Energy’s Office of Basic Energy Sciences, before finding a range of applications—including sensors that may someday be a lifesaver.

—Katie Walter

Key Words: atomic force microscope (AFM), biological sensors, biomineralization, carbon nanotubes, chemical sensors, confocal microscope, genomics, nanolaminates, proteomics, surface-enhanced Raman spectroscopy.

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About the Scientist

CHRISTINE ORME, a physicist in the Materials Science and Technology Division of the Chemistry and Materials Science Directorate, received a B.S. in physics from the University of California at Berkeley. She joined the Laboratory as a postdoctoral fellow after receiving her Ph.D. in physics from the University of Michigan in 1995. Her background is in experimental physics in the area of surface evolution and pattern formation during the growth of thin films. In her thesis work, she combined imaging with kinetic Monte Carlo simulations and continuum modeling to deduce diffusional processes during vapor growth. At Livermore, she uses this background to study crystal growth from solution (rather than from vapor). She is particularly interested in the area of biomineralization where organic molecules substantially change the shape of inorganic crystals; she wants to understand the formation of materials such as shells, bones, and teeth. Recently, she has become interested in the use of electrochemical driving forces to control electrodeposition and corrosive processes, particularly in their application to biomedical implants and corrosion-resistant industrial materials.
The extreme conditions experienced by a single liquid drop during its reentry into the atmosphere lie in a regime for which no experimental data exist. To better understand the physics of what happens at these altitudes, physicist Glen Nakafuji, analyst Roxana Greenman, professor Theo Theafanous of the University of California (UC) at Santa Barbara, and research colleagues are studying how liquid breaks up and evolves in rarefied (thin) atmospheres.

To do so, they are using unique hydrodynamic and shock-physics experiments coupled with advanced chemical–kinetic and hydrodynamics computer codes. The experiments and codes simulate the supersonic, rarefied flow environments that reentering droplets of a chemical agent would experience. Nakafuji is the principal investigator for the project, which is funded by the Laboratory Directed Research and Development (LDRD) Program.

Thin Atmospheres, High Velocities, Surface Tension

A number of complicated factors determine how a body of liquid breaks up and how the individual drops or streamers break...
apart and shape and reshape themselves. The factors include the pressure of the surrounding atmosphere, the velocity at which the liquid is traveling, and the physical properties of the liquid. “At altitudes of tens of kilometers,” explains Nakafuji, “the agent disperses and expands in an atmospheric pressure that can be ten thousand times less than that at sea level. Pieces of liquid float out, stretch, and tear in milliseconds, then fall in an expanding cloud into the atmosphere.” From there, the mass of drops falls through the air, moving at supersonic velocities through increasing atmospheric pressure. “Originally,” notes Nakafuji, “people in the field theorized that the liquid would aerosolize into droplets on the order of 10 micrometers in diameter and disperse. Initial experiments indicate that this may not be true.” So the question remains open: Would a given liquid break up into these small-size droplets or not?

“There’s a huge gap in experimental data for the behavior of liquids in this sort of environment,” notes Nakafuji. “We know how various liquids break up at sea level, where the atmosphere is dense, and the air molecules—which can be represented as individual particles—are constantly bouncing off each other, pressing together, and acting more like a fluid than individual particles.” However, higher up in the atmosphere, the molecules are fewer and more widely dispersed, acting more like individual particles at altitudes above 30 kilometers. “You add to this the fact that the liquid agent is not in free fall but is experiencing atmospheric drag, and the problem becomes very complex,” notes Nakafuji. “Yet this is the situation we’re faced with in examining the physics of droplet breakup.”

**Of Weber Numbers and Bag Breakups**

The physics of a liquid drop breaking up has much to do with the nature of the fluid (its density and viscosity, for instance) and the forces acting upon it. The ratio of external aerodynamic force—which tends to pull the drop apart—to the liquid’s surface tension—which tends to hold the drop together—is a dimensionless quantity called the Weber number. Drops with different Weber numbers break up in different ways. Drops with higher Weber numbers (above 100) tend to have more catastrophic breakup and result in smaller drops. At very high altitudes, where external aerodynamic forces are small, the Weber number remains relatively low, below 100. When the team conducted experiments on drops with a range of Weber numbers characteristic of high altitudes, interesting findings emerged. For instance, drops 3 to 4 millimeters in diameter tended to oscillate before breakup. For drops with Weber numbers between 12 and 100, the experimenters observed a phenomenon called “bag breakup,” in which a round drop deforms into a shape resembling a bowler hat, with a flat rim and curved crown. As the drop falls, the bag portion, which corresponds to the crown of the hat, oscillates in and out. When the original drop disintegrates, large drops form from the rim, and smaller ones form from the bag. “This happens in tens of milliseconds—much slower than anyone expected,” says Nakafuji. “Previously, it was observed that such bag breakup would occur in hundreds of microseconds to 1 millisecond, tops.”

**ALPHA Goes with the Flow**

These experiments were conducted in the ALPHA facility, a one-of-a-kind experimental system designed and built by the Livermore–UC Santa Barbara collaboration to examine liquid dynamics at high altitudes. The ALPHA facility is a one-of-a-kind experimental system to examine liquid fragmentation. (a) The vertical wind tunnel used to recreate a drop falling through the upper layers of the atmosphere.

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**Diagram:**

- **Drop injector**
- **Simulant droplet**
- **High-speed camera**
- **Accelerating nozzle**
- **Pump chamber**
- **10-centimeter-diameter variable length glass test section**
- **Flow stream**

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**Lawrence Livermore National Laboratory**
fragmentation. The facility is essentially a large, vertical wind tunnel, consisting of a cylinder about 3 meters long and 10 centimeters in diameter, that can be pumped down to pressures of 10 to 30,000 pascals. The methodology for re-creating a drop falling through the upper layers of the atmosphere is as follows. An injector releases liquid through a laser beam. The drop breaks the beam, which makes it act like an optical trigger and causes a diaphragm to burst. Air rushes up the cylinder past the drop, in effect simulating the fall of the drop through the atmosphere, and a high-speed camera records the behavior of the drop. “We have the capability to get air moving at velocities of Mach 5—about 1.5 kilometers per second,” says Nakafuji. The air flows past the drop at a nearly constant velocity for about 200 milliseconds before its speed begins to ebb, long enough to watch a drop fall, reverse direction, rise, and then burst. This past spring, the group tested a drop 1.5 centimeters in diameter—the largest drop yet tested anywhere. “We don’t test actual agents,” Nakafuji emphasized. “We use glycerin and other kinds of fluid, and extrapolate to agents from there.”

Besides examining whether assumptions made at sea level about the breakup of liquid hold true in rarefied environments, the team is also exploring the different break-up modes and whether the dynamics of these modes differ from the dynamics seen for bag breakup. The researchers’ efforts have been rewarded. They have documented dynamics that have never before been seen or predicted. “For instance, before the bag breaks, it oscillates at some frequency,” explains Nakafuji. “What we saw for the first time—and which no one had expected—is that after the drop turns and begins to move upward, the oscillation frequency doubles. We are now trying to understand this.”

**Getting Details, Drop by Drop**

Ultimately, the team would like to understand and be able to predict the dynamics of specific liquid drops in any rarefied environment. “We’d like to be able to calculate the onset of breakup—when a drop will break up, the configuration the liquid will take, which drops are stable, and which are not,” says Nakafuji, adding, “We’ve definitely made strides in that direction, to the point where we can now accurately predict whether a drop will break up under certain conditions.”

The present goal is to obtain critical hydrodynamics and chemical data to validate computer models of these simulations. Working toward this end, the researchers have successfully used the Laboratory’s ALE3D code to predict the drag on rigid spheres in subsonic and supersonic rarefied flows, validate a surface-tension model, and test a deformable drop simulation.

“Using experiments and simulations, we are pinpointing the ranges of drop stability and getting a better handle on the physics of liquid breakup,” explains Nakafuji. “In the final analysis, we want to be able to predict the rarefied atmospheric conditions under which a given chemical agent will break up into lethal-sized stable droplets. This is a critical question, one whose answer could affect us all.”

—Ann Parker

**Key Words:** ALE3D, ALPH facility, biological agent, chemical agent, lethality, liquid breakup, nerve agent, rarefied atmosphere.

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When the 7-year-old daughter of a Livermore physicist was diagnosed with diabetes in 1994, her doctor at Stanford Children’s Hospital, Dr. Darrell Wilson, happened to be familiar with the Laboratory. Wilson’s father-in-law was Carl Haussmann, one of the Laboratory’s founders (see S&T, January/February 2000), so over the years, he had heard about the unique technological capabilities of the Laboratory. He suggested that Livermore might be able to do something for the sufferers of diabetes.

It was a chance remark, one that might have gone nowhere. But the physicist, Tom Peyser of the Defense and Nuclear Technologies Directorate, saw that he could tap into Livermore’s growing capability in medical technologies, a field that combines expertise in chemistry, physics, optics, electronics, and microfabrication. He and fellow physicist Steve Lane took up Dr. Wilson’s challenge and began a systematic examination of the technology necessary for continuous monitoring of blood sugar in diabetics. Many private companies already were working on this problem, but Peyser and Lane thought that the Laboratory was uniquely situated to tackle the problem using optical technologies. They also realized that spinoffs from their work on glucose sensors might benefit other Laboratory missions, such as programs for detecting hostile chemical and biological agents.

Diabetic Jenny Peyser, now 14 years old, and her father, Livermore physicist Tom Peyser. (Photo taken by freelance photographer Margaret Kaye.)
Work on the glucose sensor began in 1995 when the Livermore project team linked up with MiniMed, Inc., of Northridge, California, to develop an optochemical glucose sensor. The project has received grants from the Laboratory Directed Research and Development Program and subsequently been funded by the National Institutes of Health and the Department of Commerce’s Advanced Technology Program.

MiniMed is the largest supplier of insulin pumps, small pager-size programmable medical devices that administer insulin to diabetics in place of multiple daily injections. Someday, the Livermore–MiniMed sensor may be combined with a MiniMed insulin pump to create an artificial pancreas, which could change the lives of millions of diabetics.

Diabetes is a metabolic disease in which the body does not produce or use insulin properly. Insulin is a hormone secreted by the pancreas that allows glucose, the energy source for the cells in our body, to enter the cells. Careful stabilization of glucose levels is crucial for diabetics to avoid a host of complications. Long-term high glucose levels, or hyperglycemia, may lead to heart disease, hypertension, blindness, stroke, kidney failure, and amputations. In fact, complications from diabetes are the leading cause of blindness, kidney failure, and amputations in the U.S. Hypoglycemia, or low glucose levels, can lead to unconsciousness and death. The direct and indirect costs of diabetes to the U.S. health care system exceed $100 billion annually.

Diabetic patients must test their blood sugar daily. Some patients have to test themselves up to eight or more times a day. They prick a finger to draw blood for reading by a handheld blood glucose meter, and then they inject the necessary amount of insulin determined by the meter reading. Because of the pain and inconvenience of the testing, many patients do not monitor their glucose as often as they should. What’s more, even if they do test themselves regularly, current technologies make it virtually impossible to test often enough to maintain reasonably stable glucose levels. The new sensor that Livermore and MiniMed are developing can be implanted under the skin without surgery and is expected to last for a year before replacement. “We’re still in the early developmental stages with the sensor,” says Lane, associate program leader for Livermore’s Medical Technology Program. “It will probably be several years before it hits the market.”

Livermore’s work on this project has not gone unnoticed. At a White House ceremony in January, the Department of Energy awarded one of five Bright Light Awards to the Livermore team for consumer-oriented innovation. In May, the Federal Laboratory Consortium honored Livermore with an Excellence in Technology Transfer Award for transferring the glucose monitoring technology to a private-sector company.

**Fluorescence Tells the Story**

The new device is a small disk with a fluorescent chemical sensor that consists of engineered molecules embedded within a polymer. In the absence of glucose, the sensor’s molecules have a low level of fluorescence. The presence of glucose alters the molecules’ electron configuration so they become much more fluorescent and emit light of a specific color. If developmental work on the device goes as planned, a small handheld instrument will shine light on the skin, and a small detector will measure the resulting fluorescence. The intensity, or brightness, of this emitted fluorescence will allow the body’s glucose level to be determined. A more intense light emission corresponds to a higher glucose level.

An alternative approach is also being developed in which the fluorescent lifetimes of the molecules are measured by the instrument. Sensor molecules bound to glucose have longer fluorescent lifetimes than molecules that are not bound. The average lifetime can therefore be used to determine the
tested at Livermore and MiniMed that absorb red light at 620 nanometers and emit at 670 nanometers. “If these molecules can be made to mimic the other properties of AB, our job will be nearly complete,” adds Lane.

The team has also developed an alternate method that has been tested on rats. In this version, a sensor membrane was fixed onto the end of an optical fiber and then inserted under the skin of the animal where it remained for many hours. Light at one wavelength was sent down the optical fiber from outside the animal’s body. The sensor gave off fluorescence of an intensity duration that depended on the concentration of glucose in the surrounding tissue. The fluorescent light

The Right Fluorescence Molecules

Following earlier work by a Japanese group, several Livermore chemists led by Joe Satcher, working with researchers from MiniMed, designed switchable anthracene boronate (AB) molecules, or fluorophores. The AB molecules are weak fluorescers when not bound to glucose but become bright when they are. Next, Livermore developed “linkers” that could be synthetically attached to the AB molecules so that the molecules could, in turn, be attached to a biocompatible polymer substrate. Finally, the team screened a large number of candidate polymers to hold the AB fluorophores. They found a pHEMA (polyhydroxyethyl methacrylate) blend, a material similar to that used for contact lenses. This material is strong and sufficiently permeable to allow glucose to enter, does not irritate the skin, and allows the AB molecules to function properly even when they are covalently bonded to the polymer.

At the West Los Angeles Veterans Administration Hospital, Livermore and MiniMed first demonstrated the glucose-sensitive fluorescent implant in the ear of an anesthetized rat. The fluorescence signal closely tracked a separate independent measurement of the rat’s glucose levels as the animal’s blood sugar was raised and lowered over a 2- to 3-hour period. In these tests, the implant remained operational for two weeks, the duration of the experiment.

Challenges remain to fully developing the sensor. “The biggest hurdle right now,” says Lane, “is engineering a fluorophor with a wavelength that is long enough to be reliably detected through the skin.”

The AB molecule absorbs light at 380 nanometers and emits fluorescent light at 420 nanometers. Recently, new glucose-sensitive fluorescent compounds have been synthesized and tested at Livermore and MiniMed that absorb red light at 620 nanometers and emit at 670 nanometers. “If these molecules can be made to mimic the other properties of AB, our job will be nearly complete,” adds Lane.
emitted by the sensor was at a different wavelength than the incoming light; it traveled back up the optical fiber where it was measured by a detector outside the body. The glucose levels in the tissue could then be read via the fiber-optic cable rather than via light transmitted directly through the skin. In this case, long-wavelength fluorescence is not necessary.

As they continue to pursue the transdermal sensor, Livermore and MiniMed are also furthering the development of the fiber-optic version, which would be implanted under the skin using a needle. A similar electrochemical glucose sensor already marketed by MiniMed is implanted the same way.

Livermore may be able to exploit the research on fluorescent molecules in its effort to develop sensors to detect biological agents of terrorism as well as for a range of other biomedical applications. Knowledge gained in the process of developing the glucose sensor may lead to methods for detecting small amounts of a deadly toxin or pathogen.

The Search for a Solution
Livermore and MiniMed are not the only ones trying to achieve a reliable glucose sensor for diabetes patients. For 30 years, researchers have been trying to solve the puzzle of long-term glucose sensing. Lane estimates that work is under way in at least 100 public- and private-sector laboratories worldwide to produce a continuously operating glucose sensor. With millions of sufferers and billions of dollars spent annually to treat the disease, a solution to this problem is urgently needed.

Peyser says, “We have a long way to go before making a product, but we have taken the first steps and have measured glucose in animals using this fluorescent technique. We’re at a point similar to that of the Wright brothers flying their first airplane a few hundred feet. We’ve established that fluorescent glucose sensors are feasible.” The Livermore team is hoping that progress on the long-wavelength compound and on the polymer work will allow resumption of animal tests in the near future. When those tests are completed, MiniMed will likely begin the next phase of research and development, namely, rigorously conducted clinical trials supervised by the Food and Drug Administration. It is a lengthy and costly process, but if Livermore and MiniMed succeed in combining their glucose sensor with an insulin pump, diabetes patients everywhere will applaud.

—Katie Walter

Key Words: diabetes, glucose sensor.

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(continued from p. 2)

**Lab astrophysicists on grant-winning team**

Scientists from Lawrence Livermore and Los Alamos national laboratories, the University of California at Santa Cruz, and the University of Arizona have received a $2-million, 3-year grant from the Department of Energy’s Office of Science to research the physics of supernovas, one of nature’s most fantastic events.

A supernova is literally the explosion of a star. Such explosions are observed in nearby galaxies at the rate of more than once a week. They release great bursts of energy, in amounts that can temporarily rival that of the host galaxy.

Although the temporary “new stars” have been witnessed for centuries, no one knows in detail exactly how they work. The scientists who received the grant will be trying to find out what causes supernovas and what happens when a star explodes.

The team will be attempting to produce accurate two- and three-dimensional models of supernova explosions. Each of the institutions will be applying its specialties to the research. “With this grant, we are trying to understand some of the most challenging issues in theoretical and computational physics,” says Rob Hoffman, one of two principal scientists from Livermore on the project. He and Frank Dietrich, the other Livermore scientist, will be studying such processes as hydrodynamics, neutrino and radiation transport, the nuclear equation of state, convection, thermonuclear fusion, and flame propagation. All are subjects at the forefront of research at the national laboratories and are of importance to both national security and basic science.

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**Bomber convicted with help from Lab scientist**

Rodney Blach was arrested in October 1999 for planting six bombs, four of which exploded. They were such powerful bombs that it was a wonder no one was killed, although two of the exploded ones did cause extensive property damage.

Blach thought he could outsmart authorities in their attempts to convict him for the attempted murder of governmental officials in Fremont, California. To do so, they had to link him and his bomb-making supplies to the pipe bombs. Blach, a former forensic investigator, hadn’t counted on the district attorney of Alameda County to bring in expertise from Livermore in the form of Brian Andresen of the Laboratory’s Forensic Science Center. Andresen, trained in chemistry, electronics, and forensics, was able to demonstrate how Blach had been able to adapt a sparkplug for use as a detonator and how Blach’s lack of experience in electronics engineering showed up in inexpertly soldered bomb circuit boards.

Blach was found guilty of 11 felony counts, including attempted murder, after an 11-week trial. Andresen said that the case is similar to the kind of terrorist activity the Laboratory is dedicated to thwarting as part of its national security mission.

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**Livermore wins eight Lab–University proposals**

The Laboratory’s scientists will join forces with University of California (UC) researchers on eight collaborative projects or exchanges being funded by the Department of Energy. The collaborations are among 11 projects proposed by universities and the Livermore and Los Alamos national laboratories. UC officials selected the winning proposals and announced the awards in late August.

The selected projects and exchanges that involve Livermore scientists are: (1) a study of how low levels of unwanted radiation exposure that occur near a tumor during radiation therapy affect the genes and proteins in nearby healthy tissue; (2) development of techniques to measure the carbon-14 content of individual amino acids isolated from oceanic organic matter, which will provide insight into marine ecology, ocean upwelling, and global climate processes; (3) development of noninvasive techniques for the diagnosis of breast cancer with optical lasers; (4) development of new capabilities in medical imaging using gamma-ray detectors originally developed for astronomy; (5) a study of the pathogenic characteristics of the bacteria Chlamydia, which has been implicated in a range of illnesses, so a vaccine against it may be developed; (6) development of catalytic flow technology for small, long-lasting fuels to provide power for telemetry and other remote applications; (7) a study using accelerator mass spectrometry to determine the means by which carbon can be stored in or released by the soil and the implications for climate change and global warming; and (8) development of targeting agents to make cancer cells more susceptible to damage by radiation and thereby improve the effectiveness of therapy using injected radiopharmaceuticals.

The University of California takes some of the management fees paid to it by DOE to fund the collaborations, explained Laura Gilliom, director of the Laboratory’s University Relations Program. She added, “Programs like this really show UC’s commitment to the scientific vitality of the Laboratory. The University being our manager is a great benefit to us.”

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Vacuum Fusion Bonding of Glass Plates
Steve P. Swierkowski, James C. Davidson, Joseph W. Balch
U.S. Patent 6,289,695 B1
September 18, 2001
An improved apparatus and method for vacuum fusion bonding of large, patterned glass plates. One or both glass plates are patterned with etched features such as microstructure capillaries and a vacuum pump-out moat, with one plate having at least one hole through it for communication with a vacuum pump-out fixture. The plates are accurately aligned with a temporary clamping fixture until the start of the fusion-bonding heat cycle. A complete, void-free fusion bond of seamless, full-strength quality is obtained through the plates because the glass is heated well into its softening point and because a large, distributed force is developed that presses the two plates together. This pressure is caused by the vacuum drawn from the difference in pressure between the furnace ambient (high pressure) and the channeling and microstructures in the plates (low pressure). The apparatus and method may be used to fabricate microcapillary arrays for chemical electrophoresis; for example, any apparatus using a network of microfluidic channels embedded between plates of glass or similar moderate melting point substrates with a gradual softening point curve, or for assembly of glass-based substrates onto larger substrates, such as in flat-panel display systems.

Highly Charged Secondary Ion Mass Spectroscopy
Alex V. Hamza, Thomas Schenkel, Alan V. Barnes, Dieter H. Schneider
U.S. Patent 6,291,820 B1
September 18, 2001
A secondary ion mass spectrometer using slow, highly charged ions produced in an electron-beam ion trap permits ultrasensitive surface analysis and high spatial resolution simultaneously. The spectrometer comprises an ion source producing a primary ion beam of highly charged ions that are directed at a target surface, a mass analyzer, and a microchannel plate detector of secondary ions that are sputtered from the target surface after interaction with the primary beam. The unusually high secondary ion yield permits the use of coincidence counting, in which the secondary ion stops are detected in coincidence with a particular secondary ion. The association of specific molecular species can be correlated. The unique multiple secondary nature of the highly charged ion interaction enables this new analytical technique.

System and Method for Chromatography and Electrophoresis Using Circular Optical Scanning
Joseph W. Balch, Laurence R. Brewer, James C. Davidson, Joseph R. Kimbrough
U.S. Patent 6,296,749 B1
October 2, 2001
A system and method for chromatography and electrophoresis using circular optical scanning. One or more rectangular microchannel plates or radial microchannel plates have a set of analysis channels for insertion of molecular samples. One or more scanning devices repeatedly pass over the analysis channels in one direction at a predetermined rotational velocity and with a predetermined rotational radius. The rotational radius may be dynamically varied to monitor the molecular sample at various positions along an analysis channel. Sample-loading robots may also be used to deliver molecular samples into the analysis channels. As a third step, the scanning device is passed over the analysis channels at dynamically varying distances from a center point of the scanning device. As a fourth step, molecular samples are loaded into the analysis channels with a robot.

Enhanced Modified Faraday Cup for Determination of Power Density Distribution of Electron Beams
John W. Elmer, Alan T. Teruya
U.S. Patent 6,300,755 B1
October 9, 2001
An improved tomographic technique for determining the power distribution of an electron or ion beam. It uses electron-beam profile data acquired by an enhanced, modified Faraday cup to create an image of the current density in high- and low-power ion or electron beams. A refractory metal disk with a number of radially extending slits, with one slit being about twice the width of the other slits, is placed above a Faraday cup. The electron or ion beam is swept in a circular pattern so that its path crosses each slit in a perpendicular manner. By this means, all the data needed for a reconstruction are acquired in one circular sweep. The enlarged slit enables the beam profile to be oriented with respect to the coordinates of a welding chamber. A second disk, also having slits, is positioned below the first slit disk and inside the Faraday cup. This second disk provides a shield to prevent the majority of secondary electrons and ions from leaving the Faraday cup. A ring is located below the second slit disk to help minimize the amount of secondary electrons and ions produced. In addition, a beam trap is located in the Faraday cup to provide even more containment of the electron or ion beam when full beam current is being examined through the center hole of the modified Faraday cup.

Vacuum Fusion Bonded Glass Plates Having Microstructures Thereon
Steve P. Swierkowski, James C. Davidson, Joseph W. Balch
U.S. Patent 6,301,931 B1
October 16, 2001
An improved apparatus and method for vacuum-fusion bonding of large, patterned glass plates. One or both glass plates are patterned with etched features, such as microstructure capillaries and a vacuum pump-out moat. One of the plates has at least one hole through it for communicating with a vacuum pump-out fixture. The plates are accurately aligned and temporarily clamped together until the start of the fusion-bonding heat cycle. A complete, void-free fusion bond of seamless, full-strength quality is obtained through the plates. This fusion bond occurs because the glass has been heated well into its softening point and a large, distributed force has developed from the drawn vacuum—caused by the difference in pressure between the furnace ambient (high pressure) and the channeling and microstructures in the plates (low pressure)—which presses the two plates together. The apparatus and method may be used to fabricate microcapillary arrays for chemical electrophoresis. Examples include any apparatus.
using a network of microfluidic channels embedded between plates of glass or similar moderate-melting-point substrates with a gradual softening point curve, or systems in which glass-based substrates are assembled onto larger substrates, such as in flat-panel display systems.

Method of Making Self-Aligned Lightly-Doped-Drain Structure for MOS Transistors
Kurt H. Weiner, Paul G. Carey
U.S. Patent 6,303,446 B1
October 16, 2001
A process for fabricating lightly doped drains (LDDs) for short-channel metal-oxide semiconductor (MOS) transistors. The process uses a pulsed laser to incorporate the dopants, which eliminates the need for oxide deposition and etching beforehand. During the process, the silicon in the source-drain region is melted by laser energy. Impurities from the gas phase diffuse into the molten silicon to appropriately dope the source-drain regions. By controlling the energy of the laser, an LDD can be formed in one processing step. First, a single high-energy laser pulse melts the silicon to a significant depth. The amount of dopant incorporated into the silicon is small, and furthermore, the dopants diffuse to the edge of the MOS transistor gate structure. Next, many lower-energy laser pulses are used to heavily dope only the source-drain silicon in a very shallow region. Because of two-dimensional heat transfer at the MOS transistor gate edge, the low-energy pulses are inset from the region initially doped by the high-energy pulse. By controlling the laser energy from a computer, the single high-energy laser pulse and the subsequent low-energy laser pulses are carried out in a single operational step to produce a self-aligned LDD structure.

Method to Reduce Damage to Backing Plate
Michael D. Perry, Paul S. Banks, Brent C. Stuart
U.S. Patent 6,303,901 B1
October 16, 2001
The present invention is a method for penetrating a workpiece using an ultrashort-pulse laser beam without causing damage to subsequent surfaces facing the laser. Several embodiments are shown that place holes in fuel injectors without damaging the back surface of the sack in which the fuel is ejected. In one embodiment, pulses from an ultrashort-pulse laser remove about 10 to 1,000 nanometers of material per pulse. In another embodiment, a plasma source is attached to the fuel injector and initiated by common methods such as microwave energy. In a third embodiment of the invention, the sack void is filled with a solid. In a fourth embodiment, a high-viscosity liquid is placed within the sack. In general, high-viscosity liquids preferably used in this invention should have a high damage threshold and a diffusing property.

Blue Diode-Pumped Solid-State Laser Based on Ytterbium Doped Laser Crystals Operating on the Resonance Zero-Phonon Transition
William F. Krupke, Stephen A. Payne, Christopher D. Marshall
U.S. Patent 6,304,584 B1
October 16, 2001
The invention provides an efficient, compact means of generating blue laser light at a wavelength near approximately 493 ± 3 nanometers, based on the use of a laser diode–pumped, ytterbium-doped laser crystal emitting on its zero-phonon line (ZPL) resonance transition at a wavelength near approximately 986 ± 6 nanometers, whose fundamental infrared output radiation is harmonically doubled into the blue spectral region. The invention is applied to the excitation of biofluorescent dyes (in the approximately 490- to 496-nanometer spectral region) used in flow cytometry, immunoassay, DNA sequencing, and other biofluorescence instruments. The preferred host crystals have strong ZPL fluorescence (laser) transitions lying in the spectral range from approximately 980 to 992 nanometers (so that when frequency-doubled, they produce output radiation in the spectral range from 490 to 496 nanometers). Alternate preferred ytterbium-doped tungstate crystals, such as Yb:KY(WO4)2, may be configured to lase on the resonant ZPL transition near 981 nanometers (in lieu of the normal 1,025-nanometer transition). The laser light is then doubled in the blue at 490.5 nanometers.
Awards

Lawrence Livermore National Laboratory received a Technology Innovation Award from the Hydrogen Technical Advisory Panel (HTAP) for developing a hydrogen fuel tank for next-generation automobiles. HTAP is a federal committee established by Congress to review Department of Energy programs.

In a collaborative effort with QUANTUM Technologies, Inc., and ATK Thiokol Propulsion, scientists from Livermore achieved a breakthrough in advanced hydrogen storage technology. They successfully tested a lightweight hydrogen fuel tank that extends the range of fuel-cell vehicles to the equivalent of gasoline vehicles. The HTAP singled out the work of the team for advancing the development of high-cycle-life storage systems, including zero emission vehicles; advancing lightweight compressed hydrogen storage tanks; and developing products for commercial use.

In August, delegates from Hungary honored Livermore cofounder Edward Teller by bestowing on him the Hungarian Corvin Medal, which recognizes exceptional achievement in arts and sciences. The medal was last awarded in 1930.

The award was presented in a private ceremony at Teller’s home on the campus of Stanford University. Delegates representing Hungarian Prime Minister Viktor Orban spoke of Teller’s accomplishments not only as a scientist but also as a poet and pianist. Furthermore, said delegate Attila Varhegyi, “I am standing face to face with history. The name of Edward Teller is more than just a person, it is a symbol for Hungary. Edward Teller is the most distinguished Hungarian living in the world today.”

In early November, the American Society for Metals recognized the achievements of members of the materials science and engineering community in its 2001 International Awards Program.

Among the honorees was Christopher Schuh, postdoctoral fellow in the Chemistry and Materials Science Directorate, who received the Henry Marion Howe Medal, an award established in 1923 to recognize authors whose papers have been selected as the best in a particular volume of the society’s professional publication. Schuh’s paper is titled “Modeling Gas Diffusion into Metals with a Moving-Boundary Phase Transformation” and was published in the October 2000 issue of Metallurgical and Materials Transactions A.
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Simulation-Aided Design of Microfluidic Devices

Microfluidic devices are chip-based systems used for processing and analyzing fluids and their constituents. Fabricated with the same lithographic techniques used for microelectronics, the devices integrate sensors, actuators, and other electromechanical components to move fluids through a maze of microscopic channels and chambers. A Lawrence Livermore team is developing a complex, three-dimensional simulation capability to help guide the design of microfluidic devices. The team’s computer code provides, for the first time, an accurate representation of the behavior of suspended particles, especially polystyrene beads and biological macromolecules, as they travel inside a microfluidic device. The simulation capability incorporates channel complexities and such parameters as fluid flow rates, particle interactions, and external forces. The team is working for the Defense Advanced Research Projects Agency (DARPA), the advanced research arm of the Department of Defense. DARPA is developing microfluidic devices called BioFlips (for BioFluidic Chips) for detecting biological macromolecules and microbes if used in biowarfare.

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Small Science Gets to the Heart of Matter

Working on almost the smallest possible scale, Livermore scientists are examining how materials are organized on surfaces and are conducting their examinations on an atom-by-atom and molecule-by-molecule basis. They are learning how the organization affects the materials’ properties. At this nanometer scale, the scientists need to use only the most powerful imaging tools. Thus, they are making the atomic force microscope more sensitive and developing new imaging methods, including the confocal microscope and surface-enhanced Raman spectroscopy. The goal for these imaging tools is to identify single molecules. The scientists are also working with molecular templates that can be used to develop sensors to detect biological and chemical warfare agents, to enhance protein crystallography, and to test corrosion resistance. Other projects are mimicking the natural growth of calcium-based structures.

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Lawrence Livermore turns 50 in 2002. In each issue of the coming year, S&TR will publish an article about the development of the Laboratory’s science and technology programs. The series of 50th anniversary highlights kicks off with an account of the Laboratory’s origins and early successes in developing nuclear weapon designs that are the basis for the present-day stockpile.

Also in January/February

• Simulations of the turbulence in extremely hot plasma are observed in magnetic fusion experiments.

• The new elements 114 and 116, more stable and more long-lived than anticipated, were created in the laboratory by a collaboration of Russian and Livermore scientists.

• Two biodetection systems developed at Livermore respond to bioterrorism by providing early warning of an attack and quick identification of the agent.
Guiding the Design of Microanalytical Devices

Also in this issue:
- Science at the Nanoscale
- Transport and Fate of Chemical and Biological Agents
- Glucose Sensor for Diabetics