Lawrence Livermore National Laboratory

Science & Technology Review

September 2012

New Platform Speeds Vaccine Delivery

Also in this issue:

About the Cover

The article beginning on p. 6 describes a new platform technology, based on the tiny nanolipoprotein particle (NLP), that can be used to rapidly produce vaccines to counter infectious diseases and biological threat agents. Laboratory scientists have shown that nickel-chelated NLPs can act as a stable platform to bind antigens and adjuvants, delivering measured amounts of each substance to the immune system. NLPs are also being used to develop vaccines for anthrax and for the biological warfare agents *Burkholderia* and *Francisella tularensis*. The cover shows Nicholas Fischer (upper right corner), a Livermore scientist who works on the NLP development team.

Cover design: Amy E. Henke. Rendering: Kwei-Yu Chu.

About *S&TR*

At Lawrence Livermore National Laboratory, we focus on science and technology research to ensure 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 eight 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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NIF Fires a Record 500-Terawatt Laser Shot

On July 5, 2012, the National Ignition Facility (NIF) team at Livermore conducted a record-breaking shot that delivered more than 500 trillion watts (terawatts) of peak power and 1.85 megajoules of ultraviolet laser light to a NIF target. That performance amounts to about 1,000 times more power than the U.S. generates at any one instant and about 100 times the energy routinely produced by other lasers operating today.

The shot validated the challenging performance specifications set for NIF in the late 1990s. Combining extreme levels of energy and peak power on a target is a critical requirement for achieving one of science's grand challenges—igniting hydrogen fusion fuel in a laboratory setting and producing more energy than is supplied to the target.

In the July 5 test, 192 lasers fired within a few trillionths of a second of each other and hit a 2-millimeter-diameter target. (The preamplifiers shown below are the first step in increasing laser-beam energy.) The total energy generated by the beams was within 1 percent of the amount requested by shot managers. The beam-to-beam uniformity also had an accuracy of within 1 percent, making NIF not only the highest energy laser of its kind but also the most precise and reproducible. "NIF is becoming everything scientists planned when it was conceived over two decades ago," says Edward Moses, principal associate director for NIF and Photon Science.

The giant laser routinely operates at unprecedented performance levels. The July 5 shot was the third experiment in which total energy on the target exceeded 1.8 megajoules. On July 3, scientists achieved the highest energy of any laser shot ever fired, with more than 1.89 megajoules delivered to the target at a peak power of 423 terawatts. A shot on March 15 set the stage for the historic experiment by delivering 1.8 megajoules for the first time with a peak power of 411 terawatts.

NIF is the only facility with the potential to duplicate the phenomena that occur in the heart of a modern nuclear device. It is thus a crucial tool for sustaining confidence in the nation's weapons stockpile without a return to underground nuclear testing. NIF is also helping scientists better understand the universe by creating the same extreme states of matter that exist in the centers of planets, stars, and other celestial objects. In addition, it is laying the groundwork for future fusion energy power plants, which would provide an abundant, sustainable source of clean energy.

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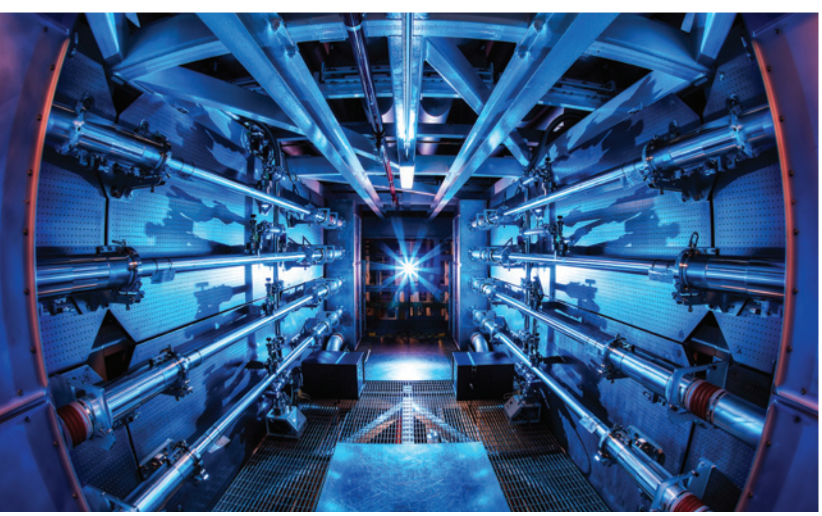

Livermore Researchers Honored with Six R&D 100 Awards

Six technologies developed by teams of Livermore researchers and their collaborators received R&D 100 awards for their efforts in developing breakthrough technologies with important applications. The winning technologies in *R&D Magazine*'s annual competition are as follows:

- A photonic method called HVLAD (high-velocity laser-accelerated deposition) produces protective coatings that prevent corrosion, wear, and other modes of degradation in extreme environments.
- LEOPARD is a laser energy optimization system that precisely adjusts the radiant distribution, or intensity profile, from a laser beam to extract the maximum amount of energy from the amplifiers while preserving a high degree of reliability among the optical components.
- Plastic scintillators for neutron and gamma-ray detection offer efficient pulse-shape discrimination and can distinguish neutrons from gamma rays with equal or better resolution than is available with standard commercial liquid scintillators.
- The Snowflake power divertor, developed in collaboration with Princeton Plasma Physics Laboratory and the Center for Research in Plasma Physics in Switzerland, reduces the hot plasma exhaust generated in doughnut-shaped tokomaks and other magnetic fusion energy sources.
- The multiplexed photonic Doppler velocimeter (MPDV) is a portable optical velocimetry system developed by National Security Technologies, LLC, with assistance from Livermore.
- NanoSHIELD uses a laser-fusing process, developed in a collaboration led by Oak Ridge National Laboratory, to produce superhard coatings that can extend the life of cutting and boring tools by more than 20 percent.

The R&D 100 awards have long been a benchmark of excellence for a diverse range of industries from telecommunications and software development to high-energy physics, manufacturing, and biotechnology. Winning the prestigious award often gives a product the push it needs to succeed in the marketplace and helps industrial leaders, government laboratories, and academic institutions to gauge the potential for commercializing emerging technologies.

Since 1978, Lawrence Livermore has captured 143 R&D 100 awards. The October/November issue of *S&TR* will highlight the six winning inventions and the researchers who developed them.

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Commentary by Penrose (Parney) C. Albright

Honoring the Past with a Look to the Future

THE Laboratory at Livermore opened for business 60 years ago, on September 2, 1952, as a branch of the University of California Radiation Laboratory led by Ernest O. Lawrence. Herbert York, then only 31 years old, was tasked by Lawrence to draw up a mission statement and organizational plans for the new laboratory and to serve as its first director. The founding 75 staff members were in their 20s and 30s except for senior scientist Edward Teller, who was 44.

Establishment of the Laboratory was triggered by the Soviet Union's successful test of an atomic bomb. Its founding was an experiment by the U.S. government at a time when the Cold War was raging and nuclear security was a preeminent concern. Lawrence and Teller urged decision makers in Washington, DC, to create a second design laboratory to augment the ongoing efforts of the Los Alamos laboratory in New Mexico. They believed the nation would benefit from having a second, independent source of nuclear design expertise to spur design innovation. The two renowned physicists had the credibility to convince Washington that, as York later said, "the youngsters could make the Lab work."

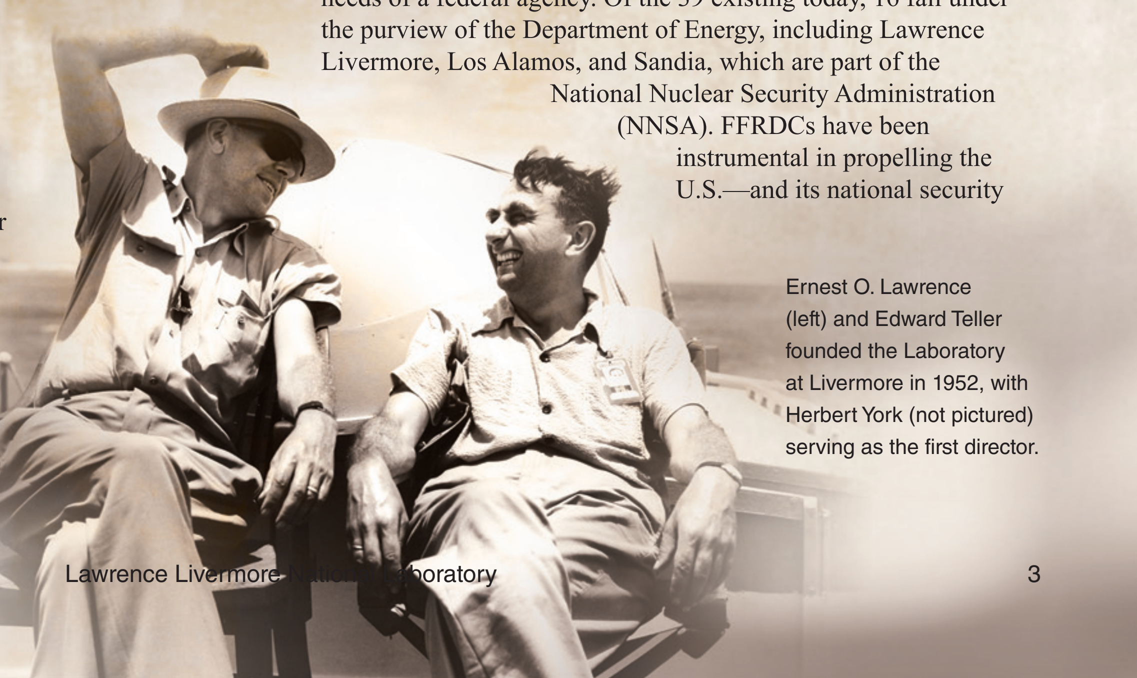
Those youngsters set out to build a "new ideas" laboratory, focusing on novel approaches to nuclear design that were not being pursued at Los Alamos. Success did not come right away. The Laboratory's first test of a fission device failed, as did the second. So did the first test of a hydrogen bomb design. But during the 1950s, critical breakthroughs led to compact strategic warheads, small enough to place inside missiles that could be launched from submarines. The fielding of these Polaris-missile submarines offered the nation a survivable nuclear deterrent at sea. These technological breakthroughs led to the intercontinental ballistic missile portion of the deterrent and to air-carried standoff weapons. Having a broader, more varied suite of nuclear capabilities allowed the nation's leaders to develop a more sophisticated nuclear deterrence strategy and provided them with the richer set of options they desired.

The novel design and rapid development of the Polaris warhead established Livermore's reputation for innovation. And that first group of talented scientists and engineers created the Laboratory's culture, which we share and benefit from today. They pursued multidisciplinary "team science" to solve multiyear, large-scale problems. This approach, pioneered by Lawrence, has been key to the Laboratory's many successes. Our founders set a remarkably high standard for innovative scientific and technical excellence, product delivery, and dedicated service to the nation.

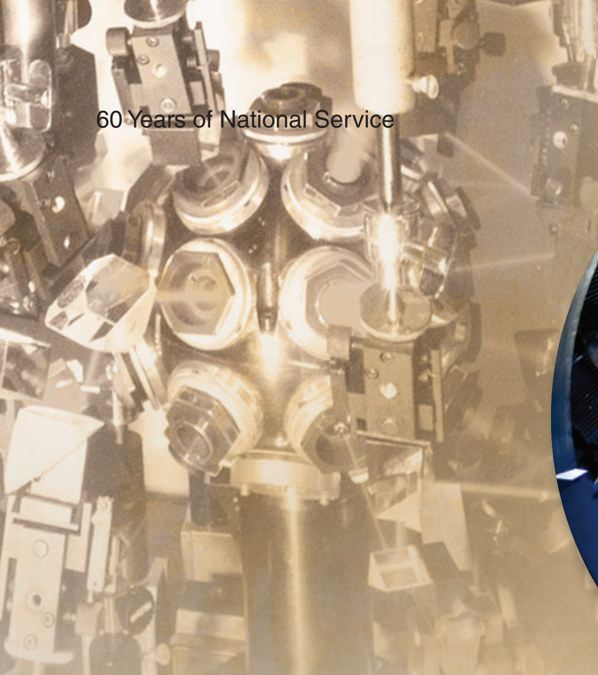
Independent Centers of Expertise

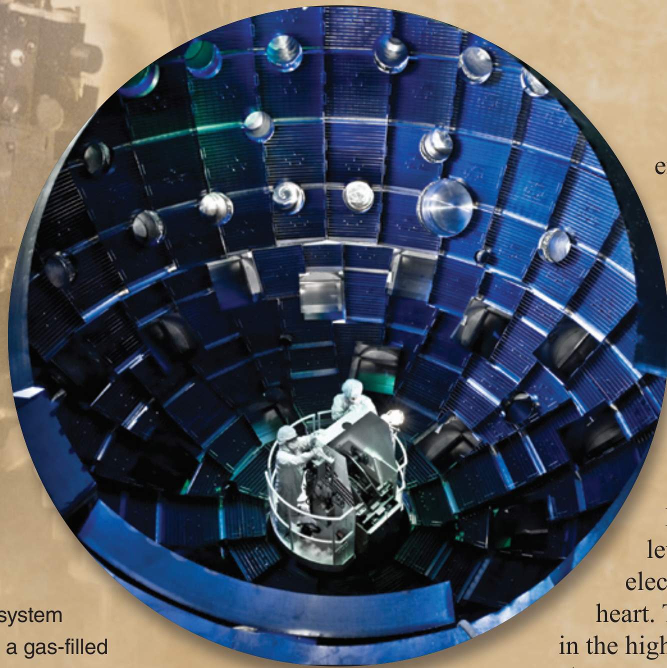
The government's "experiment" in cooperative competition of ideas has paid off. Throughout the Cold War, Livermore and Los Alamos provided key innovations in weapons effectiveness, safety, and security, and working with Sandia National Laboratories, they met the demanding military requirements for the entire weapons package. These independent centers of expertise are proving to be equally essential after the Cold War. In the absence of nuclear testing, peer review between the nuclear design laboratories and their different approaches to problem-solving provide a crucial safeguard in carrying out the U.S. policy to "sustain a safe, secure, and effective nuclear arsenal as long as nuclear weapons exist."

Lawrence Livermore and Los Alamos were also part of a grander national experiment in how best to pursue large-scale, long-term research and development to meet important national needs. After World War II, U.S. decision makers identified a capabilities gap between the basic research conducted at universities and the product-directed work in private industry. To fill that need, they created a system of federally funded research and development centers (FFRDCs). Managed and operated by a private entity, each FFRDC is focused on meeting the special needs of a federal agency. Of the 39 existing today, 16 fall under the purview of the Department of Energy, including Lawrence Livermore, Los Alamos, and Sandia, which are part of the National Nuclear Security Administration (NNSA). FFRDCs have been instrumental in propelling the U.S.—and its national security



Ernest O. Lawrence (left) and Edward Teller founded the Laboratory at Livermore in 1952, with Herbert York (not pictured) serving as the first director.





In the 1960s, Livermore scientists built the 4-pi system (left) with 12 ruby laser beams arranged around a gas-filled target chamber about 20 centimeters in diameter. A concerted Laser Program, started in 1972, has led to the National Ignition Facility, where 192 laser beams are directed toward the center of a 10-meter-diameter target chamber (right).

capabilities—to a position of scientific and technical leadership for more than half a century.

The long-term relationship between an FFRDC and its federal sponsor provides the continuity an institution needs to attract and retain talented personnel, construct and operate large research facilities, and develop capabilities for national use. The bargain between an FFRDC and its government sponsors is a simple one: The center commits to sustained excellence in supporting the sponsors' missions, and the sponsors commit to a sustained relationship with specific centers, investing in infrastructure and new capabilities. An FFRDC embeds itself in the sponsors' mission and culture and serves as a trusted partner to these agencies.

Livermore, for example, not only shares mission goals with NNSA but also offers objective and independent technical advice when needed to inform programmatic and national policy decisions. The three NNSA laboratories have provided technical support to arms-control negotiations from the earliest discussions on nuclear-test bans to the current strategic arms-control agreement, called New START. Our input has helped shape successive nuclear posture reviews and key decisions about nuclear nonproliferation policy.

Innovation and Excellence in Science and Technology

At Livermore, we have greatly benefited from our close ties to the University of California (now a parent organization for our managing contractor, Lawrence Livermore National Security, LLC). Through this working relationship, we have consistently explored new ideas and pushed at the frontiers of science and technology in areas central to the success of NNSA's missions.

For example, Lawrence, Teller, and York recognized that the key to making more rapid progress on nuclear weapons design was high-performance computing and simulations. The most powerful existing computer in 1952—the UNIVAC I—was ordered before the Laboratory even opened. We continue to lead in high-performance computing and are home to Sequoia, which is now the world's most powerful supercomputer. To test the new machine and demonstrate its utility for breakthrough research, we collaborated with IBM researchers to develop cell-level simulations that examine the electrophysiology of a beating human heart. This astonishing effort is described in the highlight beginning on p. 22.

Laboratory engineers needed to make advances to meet stringent requirements for our early weapon designs. Parts had to be manufactured with an accuracy of 25.4 micrometers (0.001 inches)—a much higher precision than was possible at the time. Through this work, a Livermore engineer, Jim Bryan, became widely recognized as being "the founding father of precision engineering." Concurrently, we demonstrated prowess in systems engineering through many successful large-scale projects in weapons and fusion energy research. From the earliest days, our expertise in high-performance computing has been applied to diverse engineering applications. The highlight beginning on p. 26 features our state-of-the-art engineering simulations that address challenging national security issues.

We have made groundbreaking advances in many other areas, perhaps most notably in research on lasers and fusion. In 1960, calculations performed by John Nuckolls and colleagues showed that fusion might be achieved by imploding a small capsule of fuel with intense radiation. Coincidently, a possible source for the required level of radiation was demonstrated elsewhere: the first working laser. With sponsor support, Livermore launched efforts to develop high-energy lasers and explore inertial-confinement fusion because both concepts offered potential benefits for the Laboratory's nuclear weapons research.

Today, researchers at the National Ignition Facility (NIF) are on the verge of creating fusion ignition and burn for the first time in a laboratory setting. NIF offers researchers the unique opportunity to design experiments that explore the energy, pressure, and density regimes occurring within an operating nuclear weapon. Results from those experiments provide the data needed for model development and validation. When combined with our high-performance computing simulations, these data allow us to determine how changes contemplated for stockpiled systems—for example, to improve a weapon's safety and security features or to extend its service lifetime—will affect weapon performance. The article beginning on p. 14 features experimental work at NIF and explains the importance of this research in sustaining the nation's nuclear deterrent.

Serving as a Broad National Security Laboratory

Collectively, the FFRDCs are an invaluable resource for the U.S. They are needed today, now more than ever, to help address the many difficult challenges that so broadly affect national security. A National Academy of Sciences panel studying the three NNSA laboratories recently recommended that these laboratories be recognized more explicitly as broad national security laboratories and their capabilities put in the greater service of multiple sponsors. Such work builds on and strengthens the extensive scientific and technological capabilities applied to the laboratories' core mission in nuclear security.

Readers of *S&TR* appreciate the Laboratory's contributions to national security, broadly defined. Current programs in defense and international security include work on advanced conventional munitions, cybersecurity, space situational awareness, intelligence assessments, directed-energy weapons, enhanced protection for soldiers, and countermeasures against the use of chemical and biological weapons and improvised explosive devices.

Our nation also faces major challenges in energy and environmental security, public health, and economic competitiveness. Livermore has a long history of innovative accomplishments in these areas, as well. For example, expertise in nuclear fallout modeling led to analyses of stratospheric ozone depletion in the 1970s; radioactive material dispersion predictions after nuclear reactor events at Three Mile Island, Chernobyl, and Fukushima; and our current leadership in assessing climate change. Similarly, expertise in geophysical science to ensure containment of nuclear tests now supports field experiments on carbon capture and sequestration as well as computer modeling of induced fracturing to enhance geothermal energy systems and natural gas extraction.

The article beginning on p. 6 provides another remarkable example of our innovative research to address an important national need: an exciting new approach to rapidly develop vaccines that target infectious diseases or biological agents. Our work in biosciences began in the 1960s with efforts to understand the effects of ionizing radiation on human health. The research evolved to focus on DNA analysis and technologies, such as flow cytometry and fluorescent tagging, to study chromosome damage and repair, and the use of our unique high-performance computing resources, to develop advanced capabilities in bioinformatics and molecular modeling. This pioneering work helped lead to the Human Genome Project and current efforts in biosecurity.

Future Filled with Challenges and Opportunities

Our Laboratory continues to look forward, working to meet a broad set of national needs. The challenges are daunting. It is vitally important that we focus our innovative skills on anticipating and then meeting the needs of our sponsors, with a thorough understanding of their requirements and constraints. As the stories in this and other issues of *S&TR* report, the possibilities are endless for creative scientists and engineers who want to make lasting contributions.

Anniversaries are an appropriate time to celebrate the past and cast attention on future challenges. They are also a time to thank Livermore's outstanding staff—past and present—for their new ideas and dedicated hard work. Carrying on traditions established by the Laboratory's founders, we look forward to the next 60 years of excellence in mission-directed science and technology, delivering innovative solutions in service to the nation.

■ Penrose (Parney) C. Albright is director of Lawrence Livermore National Laboratory.

The Laboratory has often been home to the nation's most powerful computers. The Sequoia system (below left), which can perform 20 quintillion floating-point operations per second, is currently ranked number 1 on the Top500 list of supercomputers. The Laboratory's first computer was the UNIVAC I (below right), the most powerful computer available in 1952 with a performance capability of 1,900 operations per second.

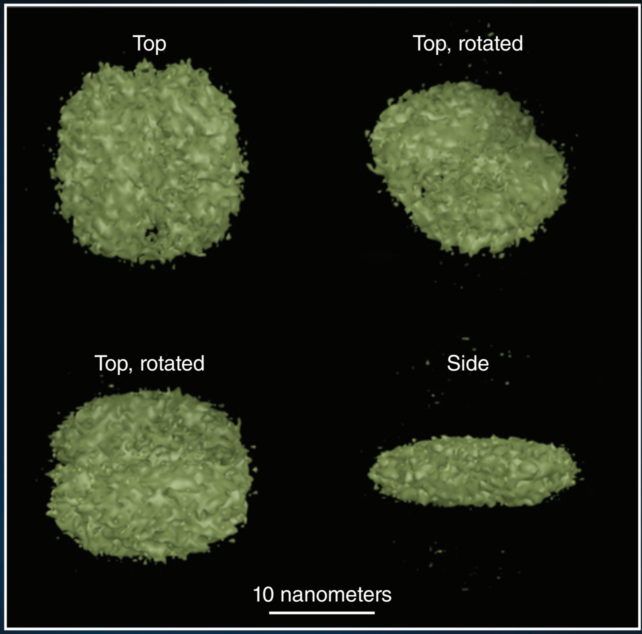
BUILDING NEW VACCINES FOR THE 21ST CENTURY

Tiny nanolipoprotein particles deliver the antigens and adjuvants needed to create vaccines against infectious diseases.

SINCE the invention of vaccines, humankind has had a potent weapon against debilitating diseases such as smallpox, polio, diphtheria, tetanus, pneumonia, and influenza. Vaccination may also provide an effective approach to protect warfighters against biological threat agents and thus is a major research focus supported by the Department of Defense.

Traditional vaccines have drawbacks along with the benefits. Those made from attenuated, or weakened, microorganisms often pose safety concerns that limit their use in special populations, especially in people with compromised immune systems. New preparations can take years to bring to market, and research and development costs can soar into millions of dollars. In addition, most formulations require cold storage and have reduced lifetimes outside the cold chain. Some vaccines, such as the one for anthrax, require repeated injections over several months to elicit the protective immune response, plus an annual booster to maintain that effectiveness. As a result, vaccines have limited utility in protecting naive, or unexposed, populations.

Livermore researchers have developed a technology that reduces or eliminates these drawbacks in vaccine development and could one day lead to treatments that save thousands of lives. The new approach with such huge potential uses the tiny



Nanolipoprotein particles (NLPs) are naturally occurring molecules that serve as the structural components of cell membranes. This reconstructed image reveals the structural details of an NLP from different angles. (Courtesy of Baylor College of Medicine.)

nanolipoprotein particle (NLP) as a platform that can be conjugated, or attached, to protein antigens to quickly produce potent, custom-targeted vaccines.

Many Uses for an Intriguing Particle

NLPs are an amalgam of naturally occurring apolipoproteins and lipids. Discoidal in shape and nanometer in size, they are similar to "good" and "bad" cholesterol—those high- and low-density lipoprotein particles that move fats and lipids through our bloodstream. NLPs self-assemble in a relatively simple manner and, much like a set of interlocking building blocks, can provide a structure or platform for connecting other molecules.

Livermore chemist Paul Hoeprich and his colleagues in the Physical and Life Sciences Directorate began working with NLPs in an effort to better understand the structure and function of membrane-associated proteins in support of the Laboratory's ongoing biodefense research. Membrane proteins are involved in an array of cellular processes required for organisms to survive, including energy production, communication between cells, and drug interactions. "They are the first responders for what passes through every cell in the human body," says Hoeprich. "They connect the outside, or extracellular, world to the inside, or intracellular, world."

Membrane proteins are tricky to study, however, because they are hydrophobic and notoriously insoluble. In addition, when removed from their natural lipid environment, they often become so distorted that they are no longer biologically active.

Thirty years ago, a pioneering study led by Steven Sligar at the University of Illinois at Urbana-Champaign used NLPs to solubilize membrane proteins. Building on this effort, the Livermore researchers decided to adapt the tiny particles for their membrane protein study. NLPs mimic the membrane protein's natural cellular environment, but they are smaller and more stable in aqueous environments than the cell membranes themselves. With funding from the Laboratory Directed Research and Development (LDRD) Program, Hoeprich led a research effort to develop and integrate novel technologies for producing and characterizing membrane proteins. (See *S&TR*, July/August 2008, pp. 20–22.)

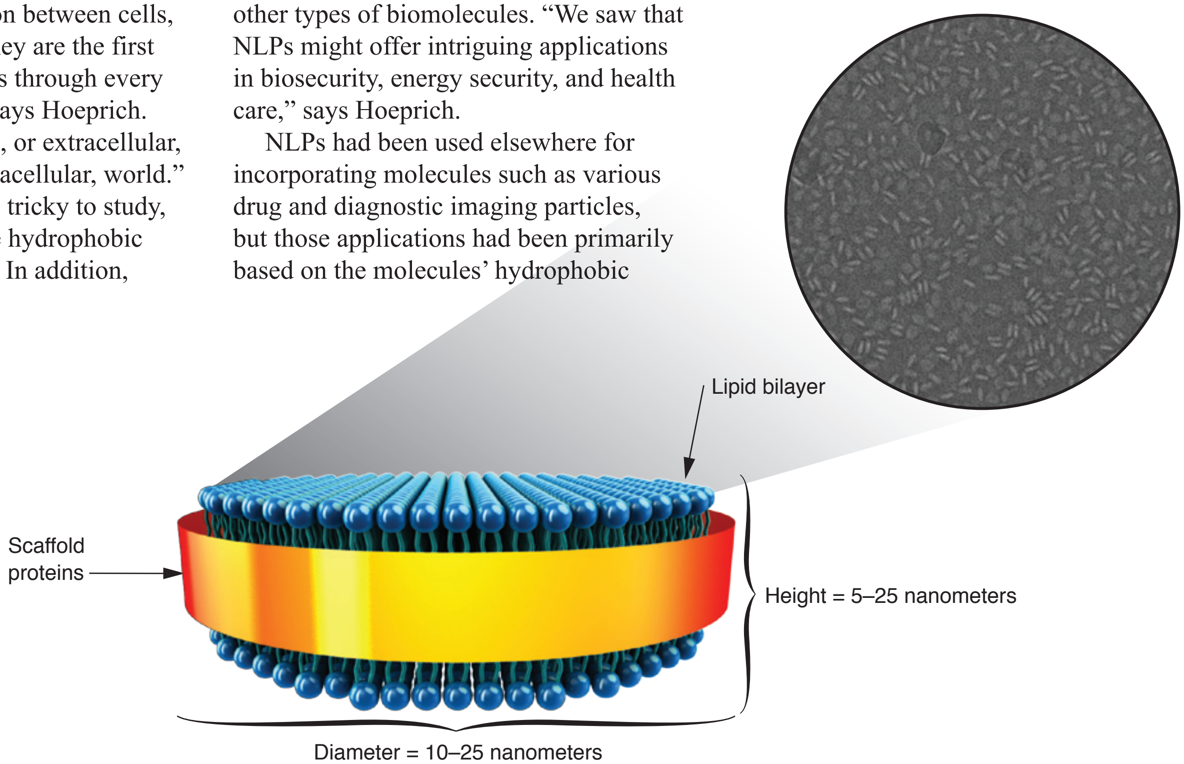
Exploring the "Universal Platform"

Once the researchers demonstrated they could create NLPs that capture and stabilize membrane proteins, they focused on developing the particles as platforms for other types of biomolecules. "We saw that NLPs might offer intriguing applications in biosecurity, energy security, and health care," says Hoeprich.

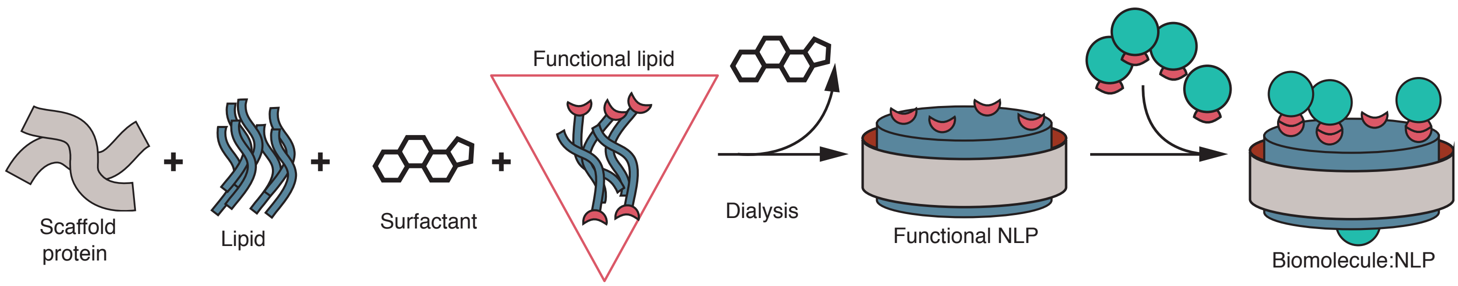
NLPs had been used elsewhere for incorporating molecules such as various drug and diagnostic imaging particles, but those applications had been primarily based on the molecules' hydrophobic nature. "Restricting the interactions to simply hydrophobic molecules limited the range of potential applications," says Hoeprich. "Because NLPs are multifunctional, we realized that, by changing the lipid involved in the process, we could target particles for specific tasks, such as being a platform for vaccines."

An alternative to the more classic vaccine production process, which relies on a neutralized or attenuated infectious agent, involves recombinant DNA technology (genetic engineering). This approach produces specific proteins, also called antigens, that will elicit an immune response. "We refer to these newer vaccines as 'subunit' vaccines because they are made with part of a microbe rather than the whole microorganism," says Hoeprich.

Subunit vaccines can be generated in a decades-old genetic engineering method that results in a protein with a polyhistidine tag (His-tag). Traditionally, this tag facilitates purification of recombinant proteins from a cellular reaction mixture. In the Livermore effort, the His-tag enables



NLPs are made of hydrophobic lipids surrounded by a band of scaffold proteins. The cryogenic electron microscopy image (inset) shows the top side of an empty NLP magnified 60,000 times. (Rendering by Kwei-Yu Chu. Micrograph courtesy of H. Change, University of California at Davis.)



NLPs are produced by mixing scaffold proteins and lipids with a surfactant, such as detergent. Other lipids, such as nickel-chelated lipids, can be added, if desired. The scaffold protein and lipids self-assemble into a disklike structure. When the surfactant is removed via dialysis, the resulting NLP provides a platform on which to attach other molecules at the ends of the functional lipids.

conjugation to the NLP vaccine platform. Thus, coming up with a universal platform to exploit the His-tag on an antigen could help speed vaccine development.

The team explored nickel-chelating NLPs (NiNLPs) as a vehicle to deliver His-tagged protein antigens. "The lipids in these particles have nickel atoms attached to their polar head groups," says Hoeprich. "The nickel binds to His-tagged molecules, turning the particle into the stable platform we needed."

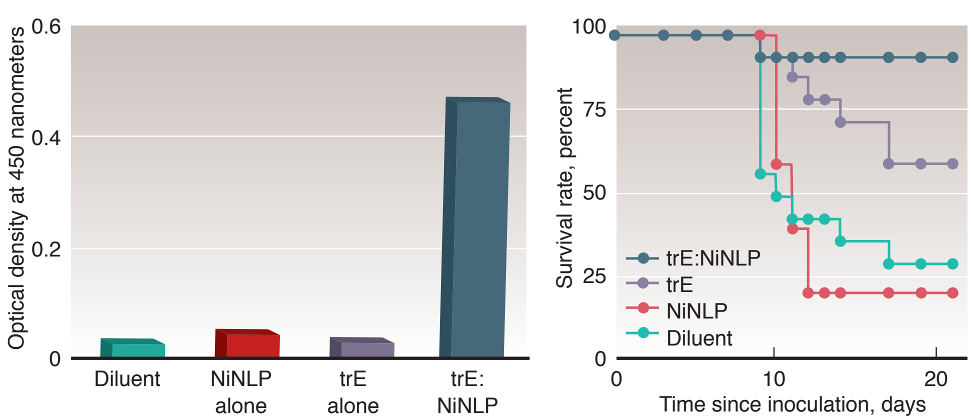
The team's first step was to develop a procedure for producing NiNLPs, attach appropriate His-tagged proteins to them, and examine how well these proteins bound to the particles. Livermore researchers Nicholas Fischer and Craig Blanchette, working with Hoeprich and colleagues from the University of Texas Medical Branch at Galveston, developed a candidate West Nile virus vaccine that used the NiNLP platform. They conjugated a His-tagged protein from the virus to a NiNLP and injected the vaccine into mice. The results were impressive: More than 90 percent of the vaccinated mice survived a viral challenge, compared with 20 percent of the unvaccinated mice. "This project demonstrated that we could indeed use NLPs as a platform to capture and hold antigenic proteins," says Hoeprich.

Creating All-in-One Delivery

In exploring ways to improve the platform technology, the team decided to incorporate adjuvants—molecules that, when paired with antigens, will generate a more rapid and focused immune response. Blanchette led a three-year LDRD project that explored using NiNLPs to bind other pathogenic antigens accompanied by adjuvants. Hoeprich notes that this practice is common in the vaccine industry, although the Food and Drug Administration has yet to approve the use of adjuvant-containing vaccines in the U.S.

"The traditional whole- or killed-cell pathogen approach to vaccine development worked well in the past, but it had many technical difficulties," says Blanchette. "Antigen vaccines were promising, but they lacked the efficacy of more traditional preparations. In particular, there were challenges in efficiently delivering antigens and the required adjuvants in equal measure to the immunogenic cells." Even though the antigen and the adjuvant were "mixed" in solution, they were not bound together. Thus, vaccine developers could not guarantee that a cell would take up both antigen and booster in equal amounts.

Blanchette proposed using NiNLPs as a single delivery vehicle for both adjuvants and antigens. "We wanted to find ways to attach the two substances to an NLP, all in a single package," he says. Having discrete numbers of antigens and adjuvants bound to each NLP would



A Livermore collaboration with the University of Texas at Galveston used a nickel-chelating NLP (NiNLP) platform to increase the protective effects of a West Nile virus antigen. In experiments to test the vaccine, mice were inoculated with NiNLP alone, a West Nile antigen only (trE alone), and the West Nile antigen attached to a NiNLP (trE:NiNLP). The diluent acts as the neutral agent or control for the experiments. Graphs show (left) the amount of specific antibodies generated and (right) the survival rate for each inoculating agent. The trE:NiNLP combination had the highest survival rate by far—well over 90 percent more than 20 days after inoculation. Sample size: NiNLP = 5; diluent, trE, and trE:NiNLP = 15 each.

present each cell with defined amounts of both agents, thus making a vaccine more effective.

Blanchette and the team began by identifying lipid-to-scaffold-protein combinations that yielded stable, uniform NiNLPs. Then using analytical size-exclusion chromatography and surface plasmon resonance, they characterized how the His-tagged protein binds with the optimized NiNLP compositions. Next, they conjugated different antigens, including those from bubonic plague and West Nile virus, to the NiNLPs. They also demonstrated that they could control the number of antigen particles attached to an NLP by varying the initial ratios of antigen to NLP during the conjugation step. "We could actually quantify what attached to an NLP, basically engineering a batch of NLPs such that we could reliably control what goes on each particle: antigens and adjuvants," says Blanchette. "It was a huge breakthrough."

The result was a just-in-time production process for fabricating a vaccine candidate from a specific gene and having it ready for use in a matter of hours. "This method could be a viable option for developing vaccines against hundreds of pathogens," says Blanchette.

The next challenge was to address the cold-storage issue. "If a vaccine could be stored at ambient or room temperature and still work, that would be a great advantage, particularly for supplies shipped to distant clinics in hot climates served by poorly developed transport networks," says Blanchette. "It would be a boon for the military and for developing countries."

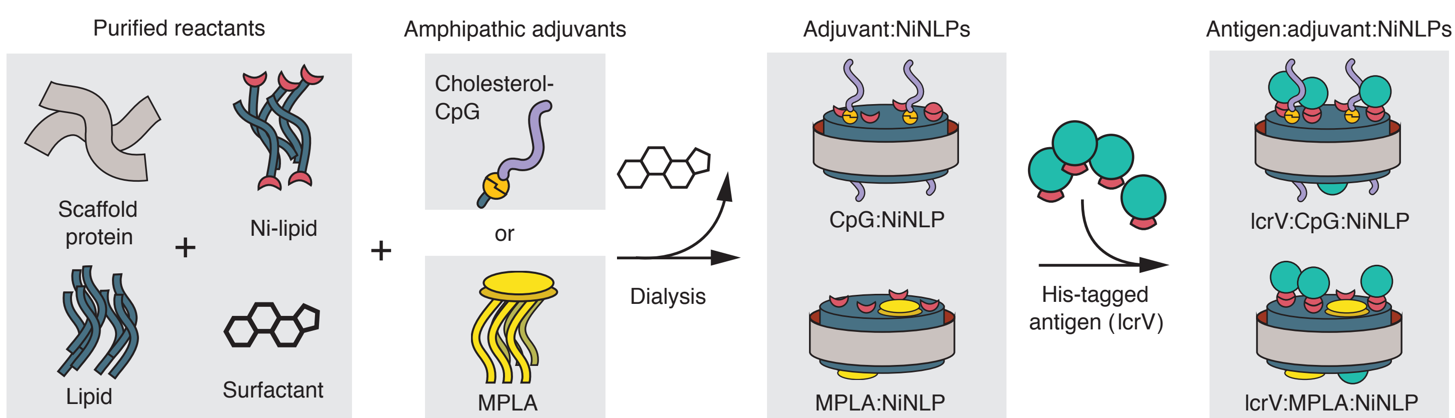
The researchers discovered that NiNLPs could be dehydrated, or freeze-dried, to form a stable powder. The powder could be stored for months at room temperature and easily rehydrated for field inoculation. Moreover, vaccine administration via dry powder inhalation is a possibility with further formulation and milling.

Interest Ramps Up

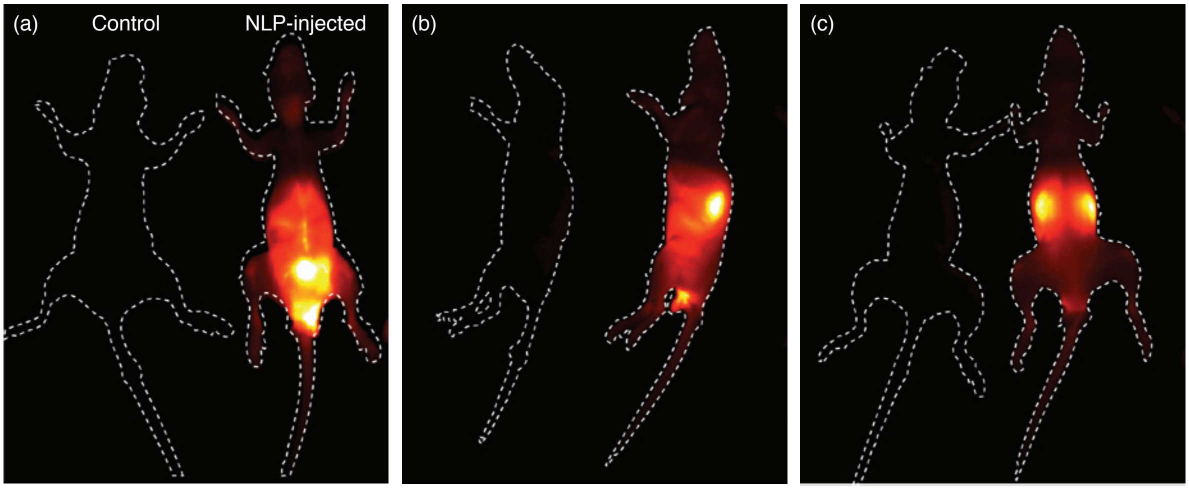
In October 2011, Lawrence Livermore and Loyola University in Chicago, Illinois, received a $3.5-million grant from the National Institutes of Health (NIH) to help develop a new anthrax vaccine. It was the first major NIH-funded biodefense grant focused on the promising NLP technology. Livermore scientist Amy Rasley, a coauthor on the proposal, says, "The current anthrax vaccine requires several injections over an 18-month period before an individual develops a protective immune response. This lengthy inoculation schedule would severely limit the vaccine's ability to protect targeted populations following a deliberate anthrax release."

An even bigger issue is that the current vaccine targets a protein expressed in the late stages of the disease. As such, the immune system is not called into action until the disease has taken hold throughout the body. Rasley is working on a team led by Loyola's Adam Driks to develop an alternative that targets anthrax spore coat proteins. By attacking the bacteria at the spore stage, the researchers hope to stop the disease initiation before spores germinate. They also want to develop a vaccine that can be administered intranasally, similar to FluMist, to induce potent immune responses against anthrax at mucosal surfaces.

The team is now exploring which spore coat proteins to include in vaccine formulations. Five such proteins have already been identified. Once all the proteins are characterized, the team will try different combinations, loading NLPs with one, two, or even three proteins at a time. "We will be looking at what combinations of antigens elicit the most robust immune response," says Rasley.



Adjuvants can be included in an NLP by adding components such as cholesterol-modified CpG or monophosphoryl lipid A (MPLA) to the assembly reaction. When the surfactant is removed via dialysis, the adjuvants are anchored to the NiNLP bilayer. Antigens introduced at this stage attach to the nickel atoms at the ends of the lipids, creating an NLP that delivers both substances.



Fluorescent images taken 4 hours after injection reveal the NLP uptake in a mouse viewed from the (a) underside, (b) side, and (c) top. In each panel, a control mouse (left) injected with saline shows no fluorescence. The NLP-fluorophore solution (right mouse) accumulated most prominently in the liver and kidneys.

Focusing on Adjuvants

Vaccines, long considered the gold standard in countermeasures for disease prevention, do not exist for many biothreat pathogens and are not effective in some individuals, such as those with compromised immune systems. To better protect populations from a broad range of traditional and emerging biothreat agents, researchers are exploring innovative approaches that allow for rapid response to a bioterrorist attack or an acute disease outbreak.

Rasley is leading one such effort, also funded by LDRD, that uses NLPs and adjuvants alone, without antigens. This novel treatment targets the innate immune system to provide an immediate, nonspecific protective response to a broad range of pathogens.

A person's innate immune system begins to function immediately when it encounters a pathogen, whether a known, newly emerging, or unknown infection. "It's the body's surveillance system, the first line of defense," Rasley says. "An infection of any kind triggers an immediate cascade of events. This response is very old and very basic—it appears even in fruit flies." The ultimate goal is to develop a therapeutic approach that does not require a pathogen to be identified or its biology to be completely understood. Because the treatment does not target the pathogen directly, it is less likely to induce antibiotic or antiviral resistance and has the potential for broad-spectrum efficacy.

Adjuvant-laden NLPs could quickly induce a protective immune response. For example, if a microbial threat agent were intentionally released, an inoculated individual, such as a first responder, would most likely not be incapacitated and thus could help facilitate protection of a larger community. "These particles might provide an alternative treatment that could be given alone or in combination with existing therapies," says Rasley. "Plus they might be especially useful for people who cannot tolerate traditional vaccines."

A large part of the study is determining what happens to the NLP–adjuvant structure in vivo, to understand how the particles distribute in the body and how long they remain stable. "We attach a fluorescent tag to the particles, inject them into mice, and track where they go," says Rasley. For the most part, the distribution and half-life of adjuvant-laden NLPs in mice depends on how the particles are administered. "NLPs administered intranasally in mice appear to remain localized in the lung for an extended time compared with those injected into the peritoneal cavity, subcutaneously or intramuscularly, where the particles appear to be cleared from the body much more rapidly," Rasley explains.

When an adjuvant such as CpG is added, the immune response is much more robust and the uptake in the spleen increases dramatically. "We found significant improvement in the immune response to CpG and MPLA [monophosphoryl lipid A] when they are conjugated to NLPs," says Rasley. "We also see enhanced uptake of CpG in the spleen. We're now trying to tease apart why this happens and what mechanism is at work."

DTRA Weighs In on NLPs

A project funded by the Department of Defense's Defense Threat Reduction Agency (DTRA) is focused on optimizing NLP antigen–adjuvant vaccines for two pathogens: *Francisella tularensis* and *Burkholderia*. *F. tularensis*, the bacterium that causes the disease tularemia, is highly virulent and spreads easily by aerosols. *Burkholderia* is probably best known for its species *B. mallei*, a bacterium used in World War I as one of the first biological weapons to infect animals and humans. *B. mallei* and its cousin *B. pseudomallei* are highly infectious and exhibit significant resistance to antibiotics. The Centers for Disease Control and Prevention regard all of these bacteria as viable biological warfare agents.

"No vaccines have been approved to treat these infections, and researchers face

60 Years of National Service

Biosecurity Research Prepares for the Coming Storm

Lawrence Livermore was founded 60 years ago to develop and deliver advanced capabilities for national defense, and many of these technologies have improved the nation's biosecurity. This long history of innovation has also provided the building blocks for future technological advances.

A key area of innovation has been flow cytometry. The Laboratory's remarkable advances began in the 1970s, when researchers developed improved methods to sort cells and used them to process isolated chromosomes. Further breakthroughs in the 1980s, including the idea of attaching fluorescent probes to chromosomes, opened up many new avenues of biological research and ultimately led to the Human Genome Project, an international effort to sequence the 3 billion base pairs that make up human DNA.

In the mid-1990s, Livermore scientists Joe Balch, Anthony Carrano, Allen Northrup, and Ray Mariella developed a miniature flow cytometer that used an immunoassay system to examine proteins and other materials on a cell's surface. They also designed a new approach for polymerase chain reaction (PCR) to dramatically shrink the size of PCR instrumentation and speed up the process for identifying DNA samples.

Both devices were much smaller and more efficient than the laboratory-size instruments then in use for DNA analysis. (See *S&TR*, June 1998, pp. 4–9.) The flow cytometer excelled in international field trials held by the U.S. Army in 1996 and helped launch Livermore's biodefense program. At the Army's field trials two years later, the portable PCR unit proved that DNA could be quickly and accurately identified outside a laboratory setting. It thus shortened the response time for responding to a natural disease outbreak or an intentional release of a biothreat agent.

"At Livermore, we focus on identifying and understanding emerging and future biological threats," says David Rakestraw, a program manager in the Global Security Principal Directorate. One of the great threats facing the nation involves some of the smallest organisms in the world: viruses and bacteria. Today, when a new disease or pathogen comes to light—such as severe acute respiratory syndrome or methicillin-resistant *Staphylococcus aureus*—it can take researchers 10 to 15 years to develop an effective countermeasure, such as a vaccine or antibiotic. And those countermeasures often come with a multimillion-dollar price tag.

In addition, says Rakestraw, biological sciences are advancing at such a fast pace, the technology needed to manipulate viruses and bacteria has far outstripped the capabilities available for developing an antidote. "Groups from two universities in different countries recently demonstrated the ability to modify a virus to allow its transmission to hosts that previously were not susceptible to infection," he says. "Such capabilities could lead to catastrophic outcomes if misused."

He adds that this technology is becoming more available to a broader range of people. "Because access to these tools is spreading so quickly, we want to speed up our ability to develop a response to a biological threat," says Rakestraw. The Laboratory is applying advanced scientific tools and nanoscience techniques to create biological entities, such as nanolipoprotein particles (NLPs), that may provide an effective path for quickly delivering countermeasures to biothreat agents.

The Laboratory's research to develop medical countermeasures takes a three-pronged approach, starting with a foundational understanding in traditional bioscience and biotechnology. "To that, we add sophisticated measurement tools such as high-resolution microscopy to characterize nanometer-scale particles," says Rakestraw.

The third arm of research is using the Laboratory's high-performance computing resources to model biological processes. Simulations allow researchers to examine molecular structures in detail and predict responses to new or revised treatments. "Livermore researchers can simulate particles with a wide range of sizes and properties and view how they form and respond," says Rakestraw. Measurement techniques are used at this stage as well, to confirm the predicted structures and response.

He notes that biosecurity efforts must take a broad multidisciplinary approach to effectively address the evolving biological threats to the nation. "Our goal is to develop the skills needed to rapidly mitigate existing and emerging biothreats," says Rakestraw. "The nation needs a flexible and agile biodefense strategy. At Livermore, we focus on quickly identifying and characterizing any pathogen, whether known or unknown, and on creating the capabilities needed to rapidly develop and deploy medical countermeasures."

The NLP work conducted by a broad group of the Laboratory's research staff is an excellent example of this effort. That work not only builds on the Livermore tradition of multidisciplinary science research but also leads the way for future teams to tackle important national challenges.

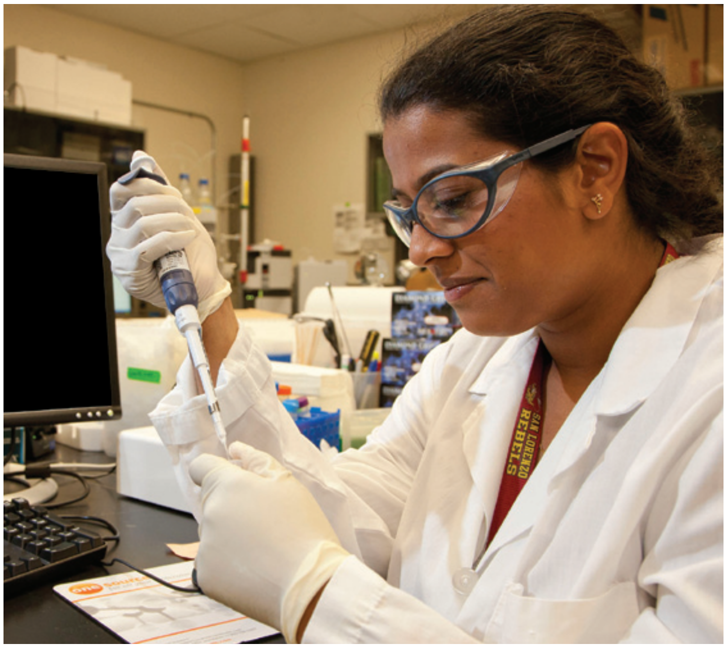
many challenges in developing effective ones," says Fischer, who leads the DTRA project. "In particular, using inherently safe subunit antigens has failed to provide significant protection against pathogen exposure." The team is working to enhance the potency of candidate subunit antigens by optimizing formulations with multiple adjuvants. "We believe we can improve antigen efficacy, especially if all components are contained within a single particle," he says. "One approach we're working on is a cocktail of adjuvants and antigens on the NLP platform."

The researchers face several hurdles to a successful treatment. First, they must optimize NLPs to handle a diverse range of adjuvants—not just MPLA and CpG, but also flagellin and muramyl dipeptide. Next, they must determine how the immune system responds to NLPs loaded with adjuvants and specific subunit antigens from the bacteria of interest. In the final tests, which will take place at the Battelle Memorial Institute, the team will inoculate mice with the loaded NLPs, expose them to aerosols of the targeted bacteria, and assess the protection afforded by the various combinations.

"We're not in the business of developing protein antigens," emphasizes Fischer. "We're developing enabling technologies that will enhance the end product or vaccine. We believe the NLP technology will do just that."

A Road to the Future

The NLP research is just one example of the Laboratory's efforts in the strategic mission area of biosecurity, which remains a pressing national concern. The success achieved to date offers great hope for developing NLP technology as a medical countermeasure to biological threats. (See the box on p. 12.) These novel particles have moved from acting as surrogates for cell membranes to being possible vehicles for vaccines that can be stored at room temperature, rehydrated, and injected or perhaps even inhaled directly when needed. Most importantly, NLPs may provide a suitable approach to quickly fabricate and deliver vaccines to protect against some of the most recalcitrant infectious diseases facing humankind.



Purna Venkataraman, a former summer student at Livermore, prepares laboratory samples to be used in tests on the NLP platform.

"Our work is just beginning," says Hoeprich. "NLPs could prove useful in many other applications." In fact, six Livermore programs are examining innovative uses for the particles. For example, when complexed with a hydrophobic drug such as amphotericin B, they provide a treatment for systemic fungal infections in critically ill patients or those with compromised immune systems. Future NLP systems could deposit cancer-fighting drugs directly into the diseased cells, leaving healthy cells untouched. NLP platforms might also carry imaging agents, such as copper-64, so clinicians can more clearly image cancer lesions. Other platforms could be developed to detoxify chemical entities in the blood or promote bone healing and metabolism.

No doubt, as research continues, even more innovations will become apparent. It's a new day, the horizon is open, and the future is bright for these tiny but promising particles.

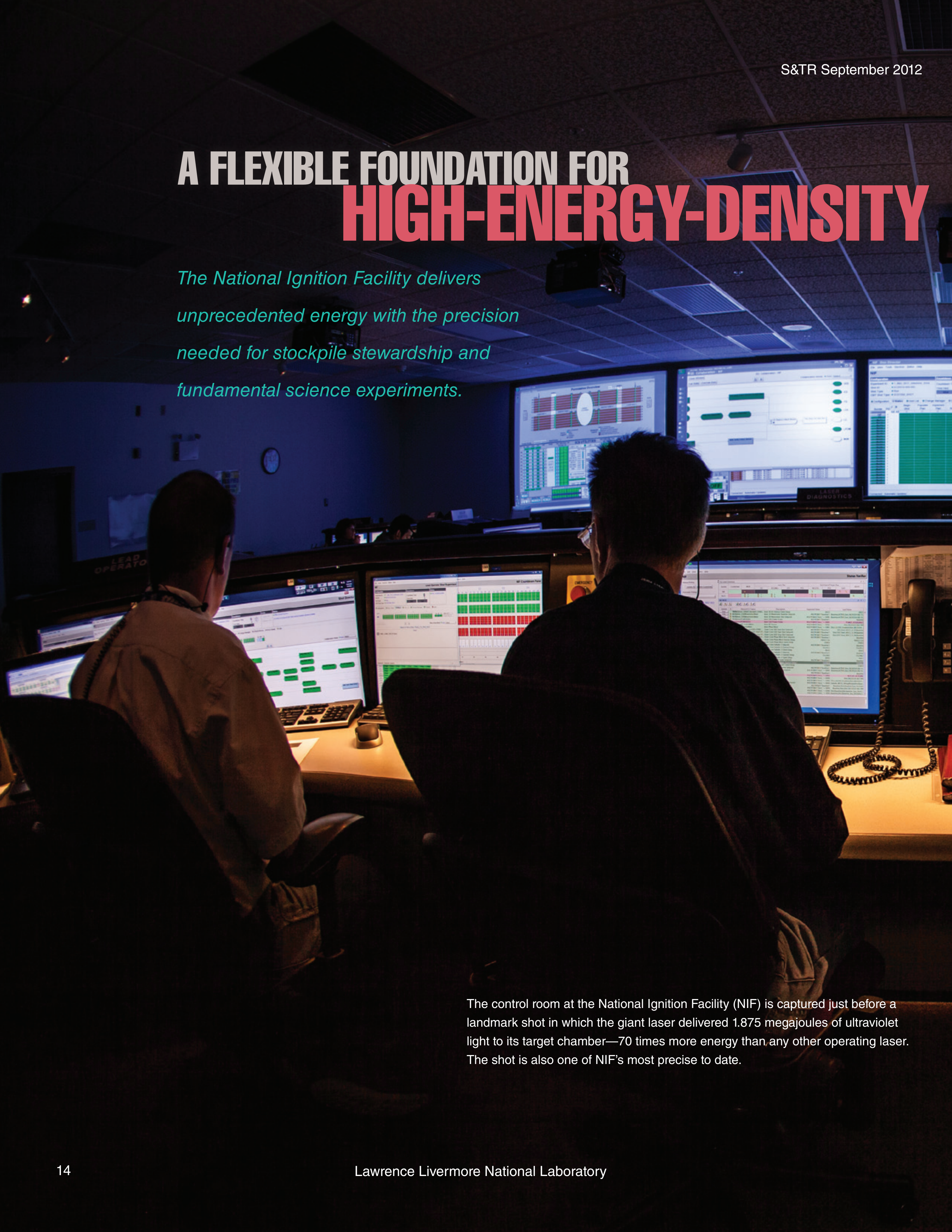
—Ann Parker

Key Words: adjuvant, anthrax, antigen, biodefense, biological threat agent, biosecurity, *Burkholderia*, *Francisella tularensis*, immune system, lipid, membrane protein, nanolipoprotein particle (NLP), nickel-chelated NLP (NiNLP), scaffold protein, vaccine, West Nile virus.

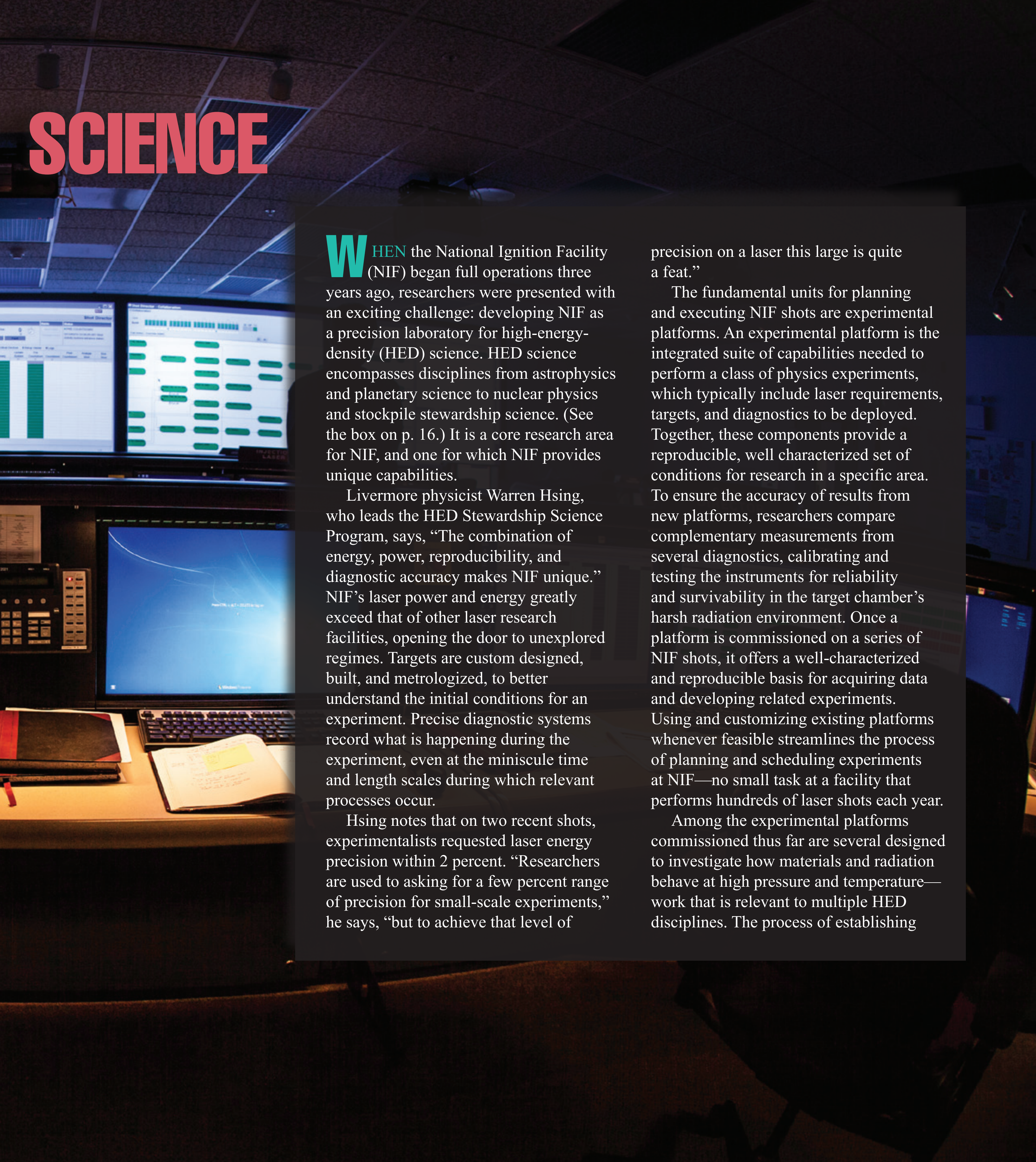
For further information contact Paul Hoeprich (925) 423-9298 (hoeprich2@llnl.gov).

A FLEXIBLE FOUNDATION FOR HIGH-ENERGY-DENSITY

The National Ignition Facility delivers unprecedented energy with the precision needed for stockpile stewardship and fundamental science experiments.



The control room at the National Ignition Facility (NIF) is captured just before a landmark shot in which the giant laser delivered 1.875 megajoules of ultraviolet light to its target chamber—70 times more energy than any other operating laser. The shot is also one of NIF's most precise to date.



SCIENCE

WHEN the National Ignition Facility (NIF) began full operations three years ago, researchers were presented with an exciting challenge: developing NIF as a precision laboratory for high-energy-density (HED) science. HED science encompasses disciplines from astrophysics and planetary science to nuclear physics and stockpile stewardship science. (See the box on p. 16.) It is a core research area for NIF, and one for which NIF provides unique capabilities.

Livermore physicist Warren Hsing, who leads the HED Stewardship Science Program, says, "The combination of energy, power, reproducibility, and diagnostic accuracy makes NIF unique." NIF's laser power and energy greatly exceed that of other laser research facilities, opening the door to unexplored regimes. Targets are custom designed, built, and metrologized, to better understand the initial conditions for an experiment. Precise diagnostic systems record what is happening during the experiment, even at the miniscule time and length scales during which relevant processes occur.

Hsing notes that on two recent shots, experimentalists requested laser energy precision within 2 percent. "Researchers are used to asking for a few percent range of precision for small-scale experiments," he says, "but to achieve that level of precision on a laser this large is quite a feat."

The fundamental units for planning and executing NIF shots are experimental platforms. An experimental platform is the integrated suite of capabilities needed to perform a class of physics experiments, which typically include laser requirements, targets, and diagnostics to be deployed. Together, these components provide a reproducible, well characterized set of conditions for research in a specific area. To ensure the accuracy of results from new platforms, researchers compare complementary measurements from several diagnostics, calibrating and testing the instruments for reliability and survivability in the target chamber's harsh radiation environment. Once a platform is commissioned on a series of NIF shots, it offers a well-characterized and reproducible basis for acquiring data and developing related experiments. Using and customizing existing platforms whenever feasible streamlines the process of planning and scheduling experiments at NIF—no small task at a facility that performs hundreds of laser shots each year.

Among the experimental platforms commissioned thus far are several designed to investigate how materials and radiation behave at high pressure and temperature—work that is relevant to multiple HED disciplines. The process of establishing

60 Years of National Service

Validating Computer Models through NIF Experiments

To maintain and verify the performance of the nation's aging nuclear weapons stockpile without performing underground nuclear experiments, scientists rely heavily on integrated computer modeling and experimental validation of the physical behavior of individual weapons components. The National Ignition Facility (NIF), in only three years of operation, has become a cornerstone of the experimental element of stockpile stewardship.

Bruce Goodwin, the principal associate director for Weapons and Complex Integration and a veteran of many underground tests, began his career as an astrophysicist studying supernovae—rare events that occur in our galaxy about once every 400 years. Even when a supernova does occur, researchers cannot prepare for it or control the experimental conditions. Once they observe a supernova, they attempt to gather what data they can.

Goodwin notes that this approach is quite similar to past weapons experiments. "During an underground test, we could not directly measure the crucial parameters of a nuclear detonation," he says. At best, researchers could infer physical phenomena from the data acquired. An ongoing challenge was finding reliable methods to separate various weapons effects, since researchers could not simply turn off one part of an explosion.

"NIF changes the whole game," says Goodwin. "It allows us to perform experiments in a controlled environment and at a much higher rate than we ever could with underground testing. We can pick a problem apart and study individual physics pieces, which is immensely valuable. No longer do we have to wait and hope for a supernova event or attempt to parse information from an underground test with limited diagnostics. We can actually do experiments at NIF that benefit both stockpile stewardship and astrophysics research, with an array of state-of-the-art diagnostics to measure and record the results."

NIF can generate extreme pressures, temperatures, and densities—the three axes of the equation of state. For example, scientists have squeezed carbon to 100 million times Earth's atmospheric pressure using a special ramp-compression technique. "Ramped compression is truly a tour de force," says Goodwin. "The experiments on carbon helped confirm that we can do all of the pressure experiments we need for stockpile stewardship with NIF." Radiation transport is also central to the operation of nuclear weapons. With NIF, researchers can, for the first time, perform detailed radiation-hydrodynamic experiments.

In the two decades since underground testing ended, stockpile scientists have made great strides in improving computer models to simulate the complex interactions that occur in a nuclear detonation. But, adds Goodwin, "For experimental validation, we needed NIF." Integrating experimental results into these computational models provides confidence that the codes are reflecting nature. "The accuracy of our weapons models could mean the difference between a weapon working as designed and not," says Goodwin. "By eliminating luck and replacing it with rigorous testing and accuracy, NIF is meeting a need that no other research facility can." NIF will allow the Laboratory to maintain a preeminent role in the nation's stockpile stewardship efforts for many years to come.

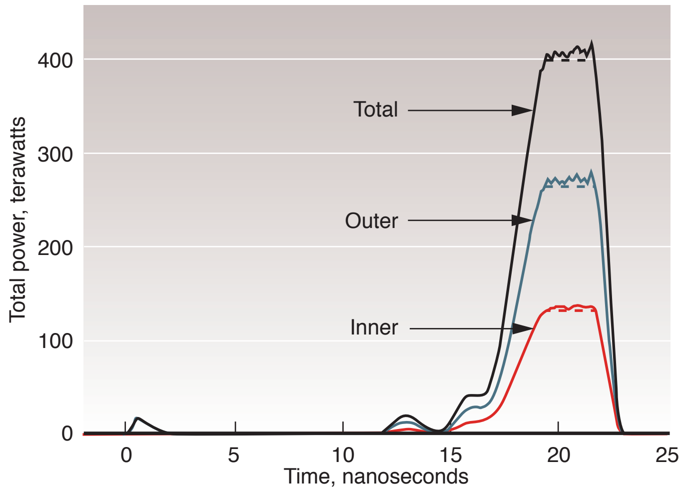
these platforms has laid the groundwork for future experiments and has already produced noteworthy results.

Radiation Transport

Within the dense clouds of gas and dust where stars are born, regions of interstellar gas will vary in density. As a star begins to form, it bathes the nonuniform cloud in radiation, producing shock waves and other radiation-driven hydrodynamic effects. Scientists are developing several NIF platforms for studying the interaction of radiation with matter. These platforms will allow researchers to examine the ionization of molecular clouds, star formation, and radiation transport through lower and higher density materials, phenomena relevant to astrophysics and stockpile science.

The Pleiades campaign is an HED science effort focused on developing a high-temperature NIF platform to study how radiation in the form of x rays interacts with matter. This effort, which is led by Los Alamos National Laboratory in collaboration with the Atomic Weapons Establishment (AWE) in the United Kingdom, is focused on better understanding the physics of stellar environments such as the bright blue star cluster for which the campaign is named. The Pleiades platform will help researchers evaluate how low-density matter behaves when it is driven by radiation at extremely high temperatures.

In the Pleiades experiments, 80 of NIF's 192 laser beams are directed upward at a half-hohlraum target. A half-hohlraum, or halfraum, is a metal cylinder with a laser entrance hole at only one end, whereas a hohlraum has entrance holes at both ends. Inside the halfraum, above and opposite the laser entrance hole is a tube made of substances with extremely low density, such as silicon dioxide or carbon foam. Laser beams hit the inside walls of the halfraum and generate x-ray photons, which illuminate the foam. The photons are absorbed by the foam, reemitted, and reabsorbed, producing a radiation wave that travels the length of the tube. Because the radiation moves faster than the shock wave it produces, the foam is not displaced or heated by the shock.



This graph displays the close agreement between the laser power requested (dashed) and delivered (solid) to the target chamber for inner and outer groups of beams and NIF's full 192 beams.

Photons must reach extremely high temperatures for the radiative wave to exceed the shock speed. Thus, a crucial element in the Pleiades campaign was ensuring that the platform could consistently generate temperatures over 3 million degrees. To confirm this performance, researchers characterized x-ray emissions from the target at different angles using two x-ray power diagnostic devices known as Dante spectrometers.

The Los Alamos–AWE team then tested whether the target generated a supersonic wave. A time-integrated camera, the Dante instruments, and a spectral and time-resolved camera commissioned for Pleiades precisely measured when radiation exits the foam tube. Together, these diagnostics generate data regarding the temperature, velocity, and quantity of radiation transported through the foam.

Pleiades platform development produced at least one surprise. When the researchers noticed a mismatch between simulations and early experimental results, they realized that the experiments required more extensive target characterization. NIF's laser energy precision actually demanded greater accuracy for other experimental inputs, such as foam density, than researchers had anticipated. Says AWE physicist Alastair Moore, "We are now trying to assess all aspects of the foam for future shots so we'll know that the results we're measuring are due to the physics being studied, not to the material properties of the foam."

The new spectrally resolved camera also allowed the team to examine the spectral content of radiation entering and exiting the foam tube. This information helps constrain the foam's material properties, including its opacity and equation of state—how it responds to changes in temperature, density, and pressure. Information on material properties also enhances the fidelity of radiation transport models and codes that use the Pleiades experimental data.

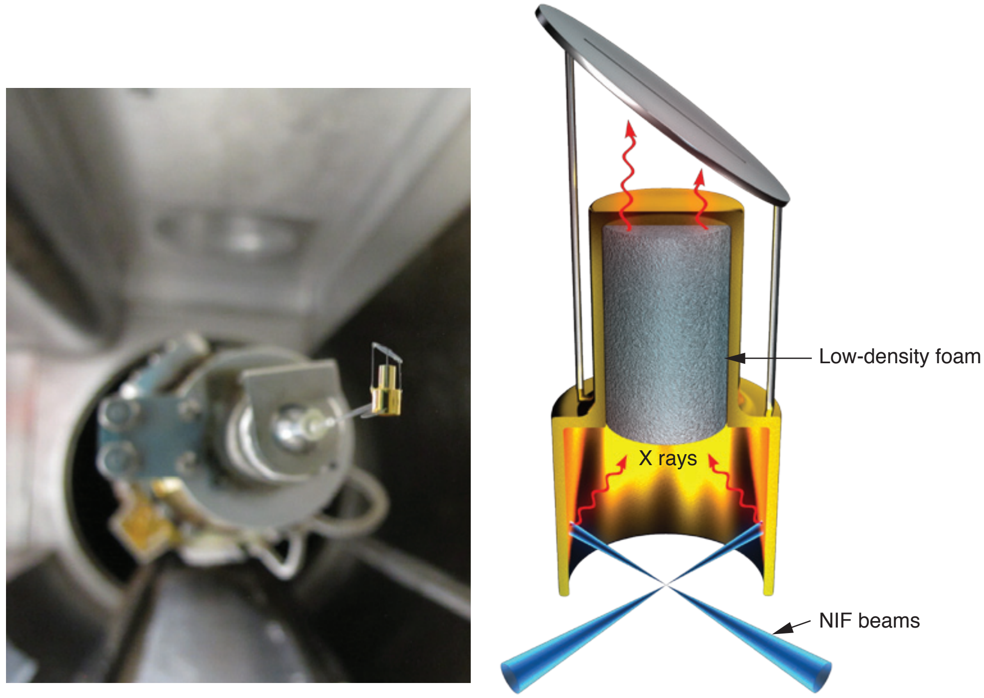
NIF's high energy and precision are key assets for the Pleiades experiments. "Because of the laser energy available, we can heat enough material to have absorption events down the full length of the tube," says Moore. "We can't do that with other lasers." Los Alamos physicist John Kline adds, "NIF allows us to test larger samples with higher densities, resulting in more accurate measurements."

Shaping Plasma Evolution

A second experimental platform is designed to study the interaction of radiation with higher density material. In contrast to the Pleiades experiments, the radiation wave produced with this platform is closely coupled to the shock wave it creates in the medium. The team designing and commissioning the platform includes participants from Lawrence Livermore, Los Alamos, AWE, National Security Technologies, and General Atomics.

To examine how radiation travels through evolving density gradients, the researchers again use a gold halfraum to generate x rays. By precisely changing the shape of the laser pulse in time, they can control the temperature of the halfraum. Eighty laser beams illuminate one end of the halfraum and generate an x-ray temperature of 2.1 million kelvins—hot enough to strip electrons from neutral atoms and form a plasma. Affixed to the upper end of the halfraum is a thin piece of tantalum oxide foam with slots cut into it. Except for the slot openings, the foam is opaque to the x-ray photons. The radiation heats the foam and generates a plasma. As plasma is generated on the inner edges of the slots, it begins to fill in the openings, modifying the material's density profile and thus the radiation transport through the slots. As part of the commissioning work on this platform, a VISAR (Velocity Interferometer System for Any Reflector) diagnostic recorded the speed of a shock generated in an aluminum disk loaded in place of the foam target. The VISAR data provide a measure of the energy delivered to the target package and the angle at which beams hit the package. The shock velocity and angle were within an impressive 2 percent of predictions.

For some of these experiments, a gold calorimeter captures the energy passing through the slots. The two Dante devices measure x-ray emissions from within the hohlraum and the calorimeter. By comparing these measurements, scientists can determine how much radiation has been transported over time.

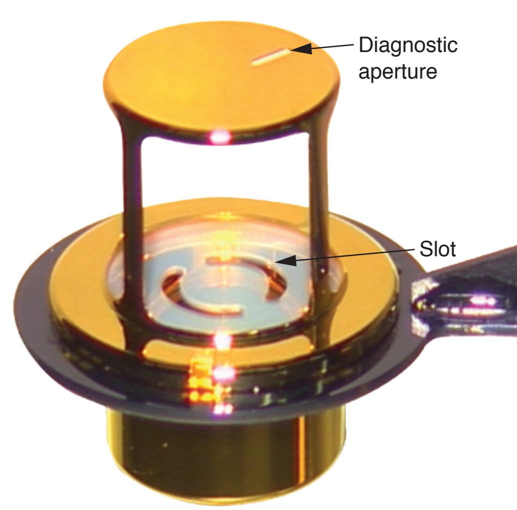


For the Pleiades experiments, 80 laser beams focus through a hole in the bottom of a hollow gold cylinder, causing x rays to illuminate a foam-filled tube. The "lid" positioned above the tube has a small opening for radiation to pass through for diagnostic measurements. (Rendering by Kwei-Yu Chu.)

An alternate platform was developed to record the hydrodynamic evolution of radiation within the slot. Measuring the changes in a material's motion and density as well as the radiation transported provides a more complete data set for validating computer models. An x-ray source for radiography, similar to a dental x ray, is created by illuminating a target with eight NIF laser beams. X rays from the target pass though the plasma in the slot and are recorded with a time-resolved camera. The x-ray radiography source, or backlighter, developed specifically for this platform, enables precise measurements of a material's evolution over time.

A series of calorimetry and radiography experiments collected physics data using the newly commissioned platforms. Scientists fielded a succession of slot patterns to test how radiation transport is affected by variables such as slot width and angle (straight or slanted), proximity of adjacent slots, and the effect of intersecting slots. Again, the experimental measurements aligned well with predictions. "NIF really delivered on shot-after-shot reproducibility," says Livermore physicist Stephan MacLaren, who worked on the experiments. "The laser's reproducibility was even better than expected."

MacLaren notes that the experiments have already provided enough high-quality data for scientists to evaluate and fine-tune relevant radiation-hydrodynamics models. Future endeavors will also benefit from this platform, which can produce the hot, precise stream of x-ray energy needed to



study radiation flow. In fact, an upcoming effort will study the radiatively driven molecular clouds of the Eagle Nebula, a region of active star formation about 6,500 light-years from Earth.

The Pressure Builds

Another important area of HED research is examining solids under extremely high pressures and densities—conditions that exist at Earth's core, inside giant planets such as Jupiter and Saturn, or those relevant to stockpile science. At high pressures and densities, materials can behave in complex and sometimes unpredictable ways. Subjected to sufficient pressure, a material may even form a previously unknown molecular arrangement with new properties.

To accurately map this behavior, researchers perform experiments to find a material's equation of state. Livermore physicist Jon Eggert says, "NIF is the only facility where we can study solids at pressures above a few million times Earth's atmospheric pressure." This information is then incorporated into weapon simulations and astrophysics codes to better understand a material's characteristics under such extreme conditions.

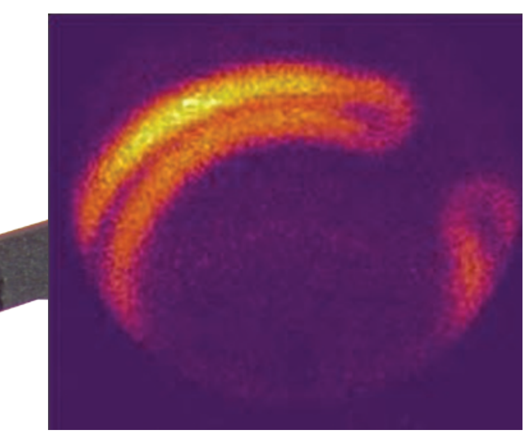
Livermore scientists often use tantalum, a dense and very hard metal, as a substitute for fissile materials in hydrodynamics research. NIF experiments on tantalum are allowing researchers to examine the strength, compressibility, and phase transitions (in this instance, from one solid crystalline state to another) of materials at high pressures. For these experiments, 176 laser beams are directed at a gas-filled hohlraum, which converts the laser power to x-ray power. Mounted on the side of the hohlraum is a target with a high-density carbon layer topped by a stepped sample made from tantalum (or other material). Each layer has a different thickness.

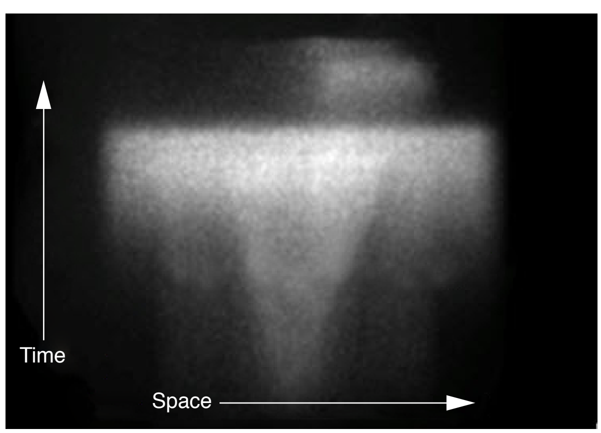
X rays heat and ablate the high-density carbon, driving a pressure pulse into the tantalum. The laser energy directed into the hohlraum is tailored so that the x-ray power on the high-density carbon layer increases in a controlled, ramped fashion, gradually compressing the tantalum samples to high pressure while keeping the tantalum below its melt temperature. Instantaneous shock compression tests cannot detect phase transitions, but ramped compression over a period of about 25 nanoseconds can. (See *S&TR*, June 2009, pp. 22–23; July/August 2007, pp. 20–21.)

Characterizing the high-density carbon properties is important for platform development because the carbon serves as both a pressure-inducing layer and a "window" for the equation-of-state experiments. A window is a layer applied to the exterior of the stepped tantalum sample. It is typically made of a strong yet transparent material that preserves the sample's surface at high pressure yet allows light to pass through to diagnostic detectors. Knowing the window's compressibility and opacity with great accuracy helps scientists interpret diagnostic measurements correctly.

A smooth, shock-free compression produces the most accurate thermodynamic analysis. To prevent the laser pulse from generating a shock and possibly melting the sample, researchers must customize the pulse shape precisely to match the material being compressed. Accurate knowledge of the sample material's compressibility is necessary to optimize the laser pulse shape, which requires several iterations of data gathering and pulse adjustment. Because of the precision and repeatability of NIF and its diagnostics, this process can be performed rapidly and efficiently, sometimes with only one or two shots.

VISAR records the velocity of each layer. By comparing data from the different thicknesses, scientists can deduce the sample's equation of state. The streak cameras are carefully calibrated to acquire data with spatial and temporal accuracies within a few percent. A calibration system built specifically for these experiments generates a series of precisely timed optical impulses at 10 locations across the input slit of the streak camera, right before and immediately after each shot. The resulting calibration information is used in the VISAR data analysis.





Scientists use two primary diagnostic techniques to study radiation as it passes through a feature, such as the slot cut in the lightweight foam (left) mounted on top of a target. Time-integrated x-ray emission (middle) or streaked radiography (right) measurements document the evolution of radiation as it moves through the feature.

NIF experiments using the ramped-compression platform have acquired data on tantalum more than 10 million times Earth's atmospheric pressure and have reached nearly 10 times that amount of pressure on high-density carbon. Although experiments on high-density carbon have achieved spectacular pressures, experiments on the much denser tantalum samples have produced more intriguing results. The first tantalum experiment unexpectedly produced a shock at around 3.5 million atmospheres (roughly the pressure at Earth's core). Even after adjusting the pulse shape and laser drive energy for subsequent experiments, shocks still occurred at around the same pressure.

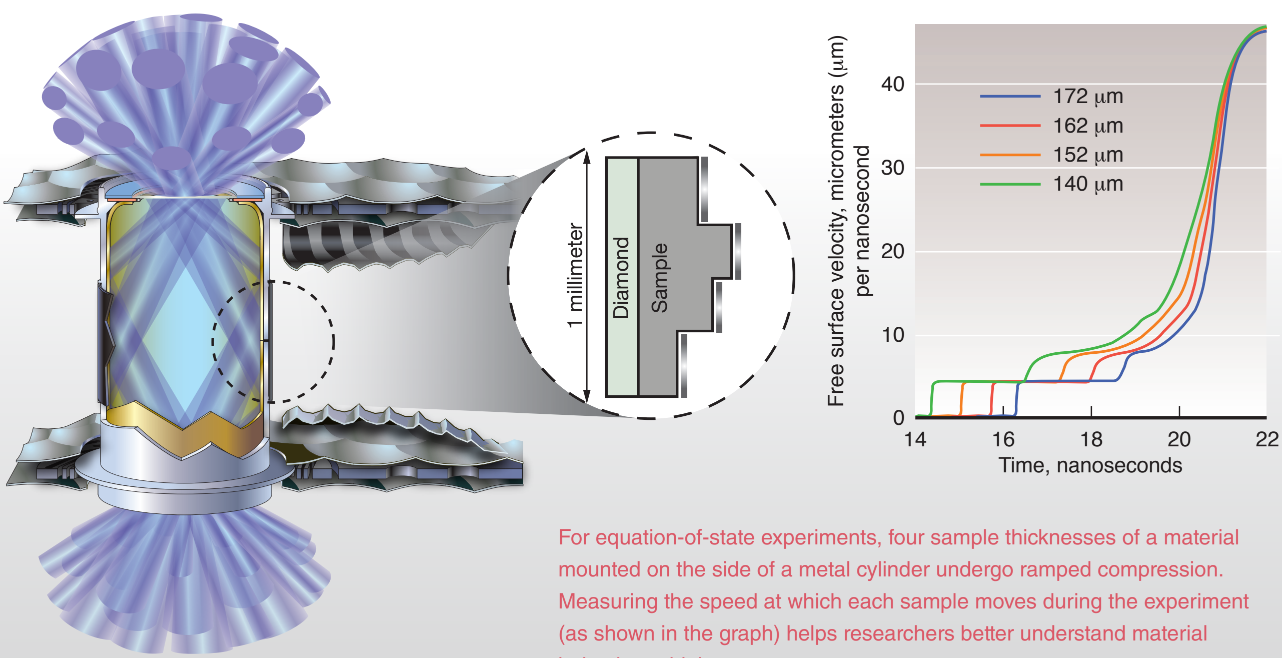
The team suspects that the tantalum behavior is signaling a previously unrecorded phase transition. "Unexpected events such as this are at the heart of scientific discovery," says Edward Moses, principal associate director for NIF and Photon Science. Results from gas-gun and diamond-anvil-cell experiments indicated a possible phase transition in tantalum, but confirming the discovery will require further study. Meanwhile, the researchers have modified the target design and laser pulse shape so they can collect the high-pressure data required for platform development.

Inducing Instability

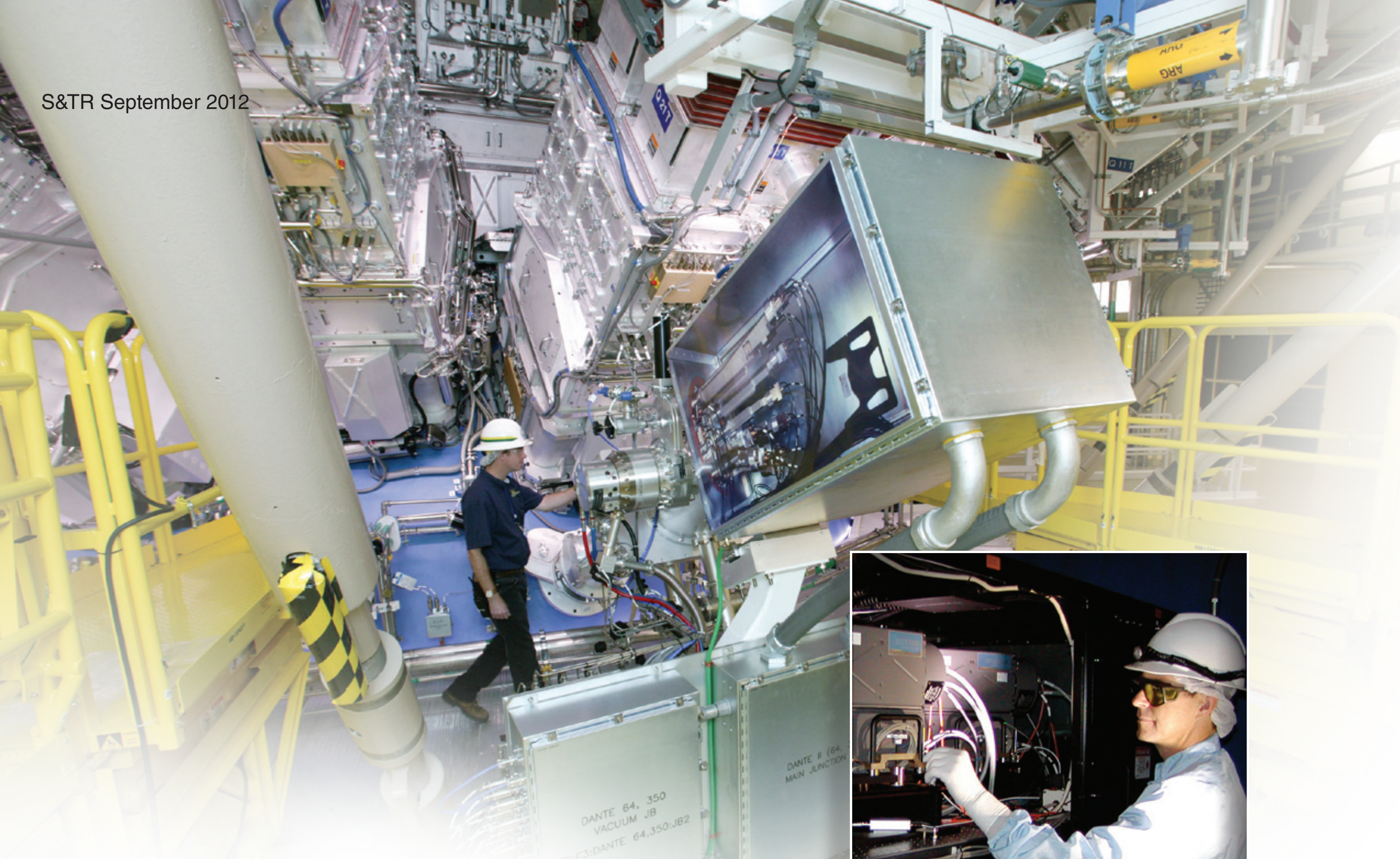
Livermore scientists are commissioning a separate platform to investigate the strength of materials at extreme pressures. This experimental arrangement has been used to demonstrate ramped compression up to 4.5 million atmospheres in molybdenum and nearly 10 million atmospheres in tantalum. As commissioning experiments continue, scientists will increase the laser energy to compress rippled samples and measure the ripple growth over time to understand how the material responds to stress.

These experiments are designed to produce a hydrodynamic phenomenon called Rayleigh–Taylor instability at the interface between two materials, one heavier than the other. The target package consists of a multilayered structure known as a reservoir, a 50-micrometer-thick sample of rippled tantalum, and a layer of carbon foam that is less dense than the tantalum. Laser energy heats the hohlraum and produces x rays. The x-ray energy generates plasma, which heats and expands the reservoir and compresses the tantalum sample. The ripple machined into the front surface of the sample grows via Rayleigh–Taylor instability, and an x-ray backlighter records the changes. "By examining the ripple growth, we can test various strength models," says Livermore physicist Brad Wallin. "A material that resists deformation will inhibit instability growth. In a weaker material, instability increases quickly."

In these experiments, researchers are fielding the largest hohlraums ever fired



For equation-of-state experiments, four sample thicknesses of a material mounted on the side of a metal cylinder undergo ramped compression. Measuring the speed at which each sample moves during the experiment (as shown in the graph) helps researchers better understand material behavior at high pressure.



Diagnostics that excel at precision measurements over short timescales and distances are essential to high-energy-density science experiments. Key diagnostics include (above) Dante, a broadband, time-resolved x-ray spectrometer, and (right) VISAR, a time-resolved Doppler velocity camera, which in this photo is being aligned by Livermore scientist Gene Frieders.

at NIF: 16-millimeter-long gold cylinders large enough to hold a standard NIF ignition hohlraum. (See *S&TR*, June 2012, pp. 16–19.) Experiments tested both gas-filled and vacuum hohlraums, but only the gas-filled ones produced the continuous pressure increase necessary for shock-free compression. The laser pulse, diagnosed using VISAR and corroborated by Dante, was very repeatable and in agreement with simulations in terms of pressure ramp timing and peak pressure.

Scientists are testing other high-density materials for use as reservoir layers to determine how those properties influence the timing of the pressure pulse on the tantalum. Experiments performed in June 2012 characterized tantalum and compared copper and palladium as candidate materials for the reservoir.

Recent enhancements have boosted NIF's power and energy to its full design specifications, which benefits many experimental configurations, including those to push material strength and equation-of-state experiments to even higher pressures. Some new platforms, such as one to study high-temperature material opacity, have become possible for the first time with the boost in capabilities.

Hsing notes that the goal is to develop two to three new HED platforms a year. Each new platform extends the scope of scientific inquiry available at NIF. Those already commissioned have demonstrated the laser's ability to perform precise experiments that are relevant to both stockpile stewardship and basic science research and provide a reliable and flexible foundation for future exploration of HED phenomena. As Wallin says, "Scientifically, NIF is taking us into regimes no one has been to before."

—*Rose Hansen*

Key Words: backlighter, Dante spectrometer, equation of state, halfraum, hohlraum, National Ignition Facility (NIF), Pleiades campaign, ramp compression, Rayleigh–Taylor instability, Velocity Interferometer System for Any Reflector (VISAR) diagnostic.

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Venturing into the Heart of High-Performance Computing Simulations

IN the field of high-performance computing (HPC) and advanced simulations, Lawrence Livermore researchers have gained a worldwide reputation for success, especially in calculations showing how matter responds to extreme pressures and temperatures. Now, researchers have applied their expertise to a new type of simulation that aims to realistically mimic a beating human heart. The results could contribute to advancements in human health in much the same way that Livermore's computational work for stockpile stewardship helps ensure the safety, security, and reliability of U.S. nuclear weapons.

The new simulations are made possible by a highly scalable code, called Cardioid, that replicates the electrophysiology of the human heart. Developed by Laboratory scientists working with colleagues at the IBM T. J. Watson Research Center in New York, the code accurately simulates the activation of each heart muscle cell and the cell-to-cell electric coupling.

On every heartbeat, electric signals normally traverse the entire heart in an orderly manner, resulting in a coordinated contraction that efficiently pumps blood throughout the body. However, these signals can become disorganized and cause an arrhythmia, a dysfunctional mechanical response that disrupts the heart's pumping process and can reduce blood flow throughout the body. Without medical intervention, a serious arrhythmia can lead to sudden death and accounts for about 325,000 deaths every year in the U.S.

The groundbreaking heart simulations were developed and performed on Lawrence Livermore's Sequoia supercomputer, a BlueGene/Q system designed to achieve 20 quintillion floating-point operations per second (20 petaflops). The machine, which was built by IBM, has 98,304 nodes, each with 16 central processing units, or cores. When the full system is in operation, more than 1.5 million cores are available to execute calculations in parallel. Cardioid assigns roughly 3,800 heart cells to a node, for a total of about 370 million cells. The code is highly scalable, meaning it is written so that its performance increases in proportion to the number of cores applied to a problem.

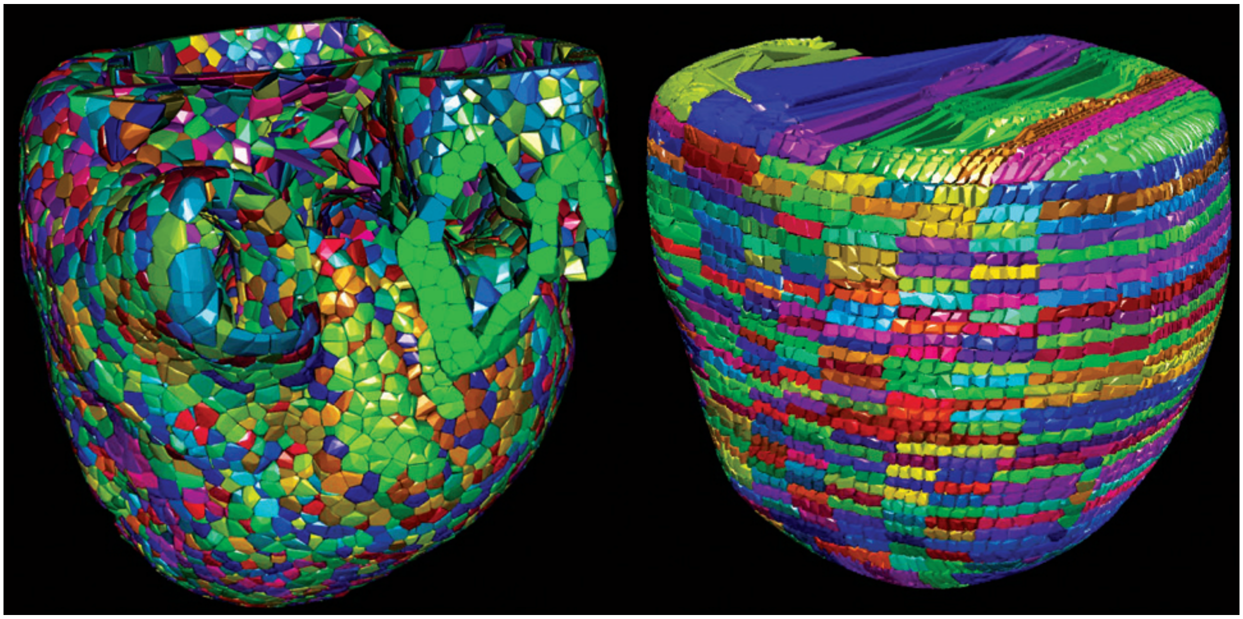
Success through Long-Term Partnership

Sequoia is one of several supercomputing systems developed and deployed through a long-standing partnership involving the National Nuclear Security Administration, Lawrence Livermore, and IBM. In June 2012, Sequoia was named the world's fastest computer on the industry-standard Top500 list. One of its predecessors, Livermore's BlueGene/L, held the No. 1 ranking for nearly four years (2004–2007).

During the months required to "shake down" Sequoia, while IBM and Livermore scientists installed and tested the machine in the process of bringing nodes online, managers in the Laboratory's Computation Directorate made the system available for unclassified science calculations. "Our heart code work has been a great opportunity to demonstrate Sequoia's power with an application that most people consider important to society, in this case, cardiac modeling," says computational scientist Art Mirin. He notes that when the shake-down testing is complete, Sequoia will be dedicated to classified simulations in support of the nation's Stockpile Stewardship Program.

An Extended Look at Cardiac Health

The Livermore–IBM team began developing Cardioid with only a fraction of Sequoia's nodes and took advantage of additional nodes as they became available for research. In addition to Mirin, team members included Livermore scientists David Richards, Jim Glosli, Erik Draeger, Bor Chan, Jean-Luc Fattebert, Liam Krauss, and Tomas Oppelstrup and seven IBM researchers, many of them experts in computational biology.



The Cardioid code developed by a team of Livermore and IBM scientists divides the heart into a large number of manageable pieces, or subdomains. The development team used two approaches, called Voronoi (left) and grid (right), to break the enormous computing challenge into much smaller individual tasks.

Richards, a computational physicist who wrote the largest share of the code, notes that Cardioid is essentially an extensive reworking of a code IBM scientists developed a few years ago for machines with only 2,000 nodes. "Livermore is one of the few places with the expertise to get past a lot of potential barriers that developers would likely encounter in adapting an existing code to run on the world's most powerful supercomputer," he says.

Richards explains that although the Livermore team was not experienced at simulating the human heart, many HPC techniques are "agnostic" to the specific problem at hand. That is, writing different types of codes for parallel supercomputers requires similar development tasks, no matter the phenomena being modeled.

In working on the code, IBM computational biologists contributed their expertise in cardiology, while Laboratory scientists provided support in computational science, especially parallel algorithms. "The Cardioid effort became an interdisciplinary problem involving both computer science and physics," says Richards. "Because I was trained in the physical sciences, I could ask meaningful questions about heart function and understand how to apply the answers in a complex calculation."

Cardioid allows simulation at roughly the spatial resolution of a heart cell, which is about 0.1 millimeters long. It thus provides researchers with a level of detail that was impractical with early codes. High-fidelity simulation at the organ level requires a three-dimensional discrete model of the human heart.

To achieve this resolution, the IBM scientists combined two-dimensional cross-sectional images from the Visible Human Project®, a detailed dataset from the National Library of Medicine. The team also developed software to reconstruct the anatomy of a torso so that an electrocardiogram from a typical body surface could be simulated. When combined with these components, Cardioid offers a multiscale simulation capability that spans from subcellular mechanisms up to clinical signals collected from actual patients.

Simulating Thousands of Heartbeats

Operating on Sequoia, the Cardioid code can simulate hundreds of times as many heartbeats as previous codes. One minute of Sequoia processing time is required to replicate nine human heartbeats at a nearly cellular spatial resolution. Simulating an hour of heart activity, or several thousand heartbeats, can be accomplished in seven hours when using the full Sequoia system. Less sophisticated codes took up to 45 minutes to compute a single heartbeat, making it impossible to model the heart's response to a drug or an electrocardiogram trace for a particular heart problem.

Extended cardiac simulations are critical when investigating how specific medications affect heart rate. Many drugs disrupt heart rhythm. In fact, even those designed to prevent arrhythmias can be harmful to some patients. In most cases, however, researchers do not fully understand the exact mechanisms producing these negative side effects. With Cardioid, scientists can examine heart function as an anti-arrhythmia medication is absorbed into the bloodstream and its concentration changes. "Observing the full range of effects produced by a particular drug takes many hours," says Mirin. "With Cardioid, heart simulations over this timeframe are now possible for the first time."

The Cardioid simulation has been named as a finalist in the 2012 Gordon Bell Prize competition, which annually recognizes the most important advances in HPC applications. The Livermore–IBM team hopes the code will grow into a product that is widely adopted by medical centers, pharmaceutical companies, and medical device firms, helping them better understand the

60 Years of National Service

Expanding Laboratory Collaborations Grows the Regional Economy, as Well

The Laboratory's High Performance Computing Innovation Center (HPCIC) is home to a growing number of collaborations aimed at helping industries deploy simulation and visualization tools to build prototypes and solve difficult technical challenges. In June 2012, Lawrence Livermore and IBM announced one such venture, called Deep Computing Solutions, which will operate out of HPCIC. The agreement will combine IBM computational science expertise with the Laboratory's own, to help U.S. businesses harness the power of high-performance computing (HPC) and boost economic competitiveness.

"The new collaboration between the Lab and IBM is an excellent example of using the technical expertise of both the government and the private sector to spur innovation and investment in the U.S. economy," said California Senator Dianne Feinstein when the agreement was announced.

HPCIC represents the first step in an ambitious strategy to operate an open, unclassified collaboration zone called the Livermore Valley Open Campus (LVOC). The new campus, which debuted in 2011, consists of approximately 110 acres located along the eastern edge of Lawrence Livermore and Sandia national laboratories. (See *S&TR*, March 2011, pp. 22–25.)

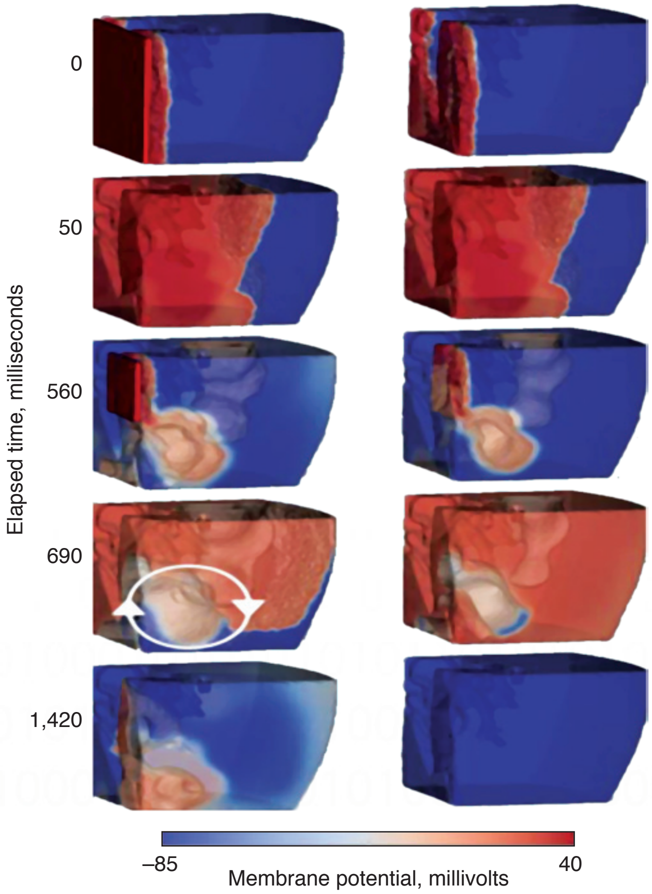
LVOC is modeled after research and development campuses at industrial parks and other Department of Energy laboratories, providing security, business, and operating rules designed to enhance scientific collaboration. The open campus is expected to grow steadily as collaborations increase and U.S. companies look to LVOC resources for help in such areas as cybersecurity, energy, transportation, and health care. As an example, the IBM Deep Research Team, members of which helped write the Cardioid code, are relocating to the campus.

Buck Koonce, director of economic development, notes that Livermore's Industrial Partnerships Office and Office of Strategic Outcomes help connect industrial partners with Laboratory-developed technologies. Collaborations are formalized through various partnering arrangements, such as cooperative research and development agreements, and more than 100 companies have licensed Livermore technologies for commercialization.

In addition, says Koonce, Laboratory managers are working with regional economic development authorities to help create 5,000 high-tech jobs in the Tri-Valley area of northern California. (Located about 35 miles east of San Francisco, the Tri-Valley has a population of about 300,000 and includes the cities of Pleasanton, Livermore, Dublin, San Ramon, and Danville.) The job-creation goal seems eminently reachable; in 2011, the region added 1,800 high-tech jobs. Some of the area's businesses were started by Laboratory employees or use a Livermore-developed product or technology. For example, Compact Particle Acceleration Corporation in Livermore is developing a proton therapy system based on accelerator technology that originated in the Laboratory's stockpile stewardship research. (See *S&TR*, October/November 2011, pp. 4–11.)

"Effective collaborations in fields such as health care strengthen national security in its broadest meaning," says Koonce. In a similar manner, the nation's security is improved by research to advance energy independence, as in Livermore's efforts to help U.S. companies more accurately interpret seismic data for oil and gas exploration, adapt wind power resources for large-scale energy generation, and modernize the nation's electric grid.

Koonce emphasizes that the Laboratory is careful not to compete with any company offering a similar service or technology. "Our goal is to help U.S industry to be more competitive in the global marketplace," he says. "Working with industry and academia also keeps us in the forefront of technology. The expertise we develop in simulation goes back into our national security research. A project such as Cardioid also helps us attract and train talented people, many of whom may well end up working on a variety of national security problems in the future."



Snapshots from a Cardioid simulation show how a drug might affect heart function. Side-by-side images compare a portion of a beating heart with (left column) and without (right column) the administered drug. An electric stimulus applied at 0 milliseconds causes heart cells to depolarize (red). Before repolarization is complete (blue), an unplanned stimulus causes a premature depolarization (at 560 milliseconds). In the simulation with the drug, a reentrant circulation pattern develops (see circle at 690 milliseconds), inhibiting repolarization of the cells and thus preventing the heart from beating normally.

mechanisms that can lead to heart ailments and the potential drug interactions that may occur during treatment. One intriguing idea is to merge a Cardioid simulation with a patient's clinical data—electrocardiograms, magnetic resonance imaging, and computed tomography scans, for example—to better quantify treatment options for each individual.

A Boost to Economic Competitiveness

The Cardioid modeling effort is sponsored by the High Performance Computing Innovation Center (HPCIC). The center opened in June 2011 with the goal of boosting the nation's economic competitiveness by partnering with American industry to develop and deploy HPC solutions. (See the box on p. 24.)

"HPCIC is about industry teaming with some of the world's foremost practitioners of simulation and visualization," says Fred Streitz, the center's director. A computational physicist, Streitz led two of the six Livermore teams awarded the Gordon Bell Prize for groundbreaking simulations. (See *S&TR*, July/August 2006, pp. 17–19; September 2010, pp. 13–15.)

At HPCIC, industrial partners can access Livermore's supercomputing resources and technical expertise in an open collaboration area with office space, classrooms, and networked conference rooms. The center hosts conferences, workshops, and training events to encourage HPC development and innovation in an environment that protects intellectual property and promotes collaboration. The current computing system at HPCIC provides industrial partnerships with 300 trillion (tera) flops of computing power. In the near future, a 5-petaflops "mini-Sequoia" machine, called Vulcan, will be available.

Enhancing the Code

The Livermore–IBM team is now working on a mechanical component that simulates the contraction of the heart and pumping of blood. The new feature will be coupled to the electrophysiological model in Cardioid, allowing the code to be applied to other health problems. For example, congestive heart failure, a condition that reduces the heart's ability to pump an adequate supply of blood, affects roughly 5 million Americans. Despite the best treatments available, the 5-year survival rate remains stubbornly below 50 percent.

"Congestive heart failure is a complex and multifaceted disease," says Jeremy Rice, a biomedical engineer at IBM and a Cardioid collaborator. "An accurate electromechanical heart model could be the key to developing effective new therapies." The team also wants to incorporate physiological systems such as coronary blood vessels that feed heart tissue to create a more comprehensive model with even wider applicability.

"HPC can be used for so many applications beyond national security," says Richards. "Through our collaborations, we want to demonstrate the impact it can have on a broad section of society."

Streitz adds that HPC involves much more than performing the same simulations in a shorter time. "It's about doing something in a new way that otherwise would have been impossible."

—Arnie Heller

Key Words: arrhythmia, Cardioid code, congestive heart failure, Gordon Bell Prize, high-performance computing (HPC), High Performance Computing Innovation Center (HPCIC), Livermore Valley Open Campus (LVOC), Sequoia, Vulcan.

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Engineered Solutions through Simulation Insights

WHEN it comes to finding solutions to tough, national security challenges, scientists and engineers cannot always rely on experiments to ferret out the information they need. Many experiments would simply be too large, dangerous, or expensive to be feasible, leaving technical experts to reconcile knowledge gaps by other means.

Simulations have become an increasingly valuable tool, helping researchers better understand experimental results and bolstering confidence in solutions they develop for various problems. (See the box on p. 28.) Computational engineers at Lawrence Livermore focus most of their efforts on issues related to national security. Bob Ferencz, a group leader in Livermore's Engineering Directorate, says, "We use simulation to evaluate high-consequence scenarios that we cannot easily test because of experimental costs or other concerns."

For example, Laboratory engineers are applying the hydrostructural analysis codes ALE3D and ParaDyn to simulate physical events that last only a few microseconds to several hundred milliseconds and involve large material deformations, high strain rates, and strong shocks. ALE3D and ParaDyn can offer insight into the detonation process of high explosives and material collisions at hypervelocities, in which materials travel 2 kilometers or more per second. By continually developing and improving these computational methods, Laboratory scientists and engineers are providing decision makers with reliable data for evaluating national security efforts.

An Unexpected Twist

ALE3D is a multiphysics-based numerical simulation tool for analyzing the fluid and elastic, or plastic, response of materials under extreme conditions. The finite-element code applies arbitrary Lagrangian–Eulerian (ALE) techniques to simulate material response on an unstructured grid. With funding from the Department of Homeland Security's Science and Technology Directorate, a Livermore team led by computational engineer Lee Glascoe used the code to evaluate techniques that limit damage to underwater structures from destructive blasts.

Underwater structures often suffer more severe damage from a blast than those surrounded by air because water has a higher density and is more incompressible than air. As a result of this tamping effect, the energy released during an explosive detonation couples to the structure more efficiently. "When trying to protect a structure from a blast, creating an appropriate standoff distance is normally the most inexpensive solution," says Glascoe. "However, for this particular scenario, space was limited. The question we had to answer was what to do when the standoff distance is so tightly constrained."

Using ALE3D, Glascoe and his team analyzed methods for diffusing explosive energy coupled to a vertical, partially submerged structure in a restricted space. The researchers simulated several possible tactics, specifically, placing an air gap or a matrix of air-filled media between the explosive source and the structure. In experiments, they used different-sized, water-filled aquariums fitted with aluminum plates to represent the structure and subjected each one to controlled blasts from explosives. When they analyzed the data, the results seemed rather strange. "At first, we thought there might have been an error in the data acquisition," says Glascoe.

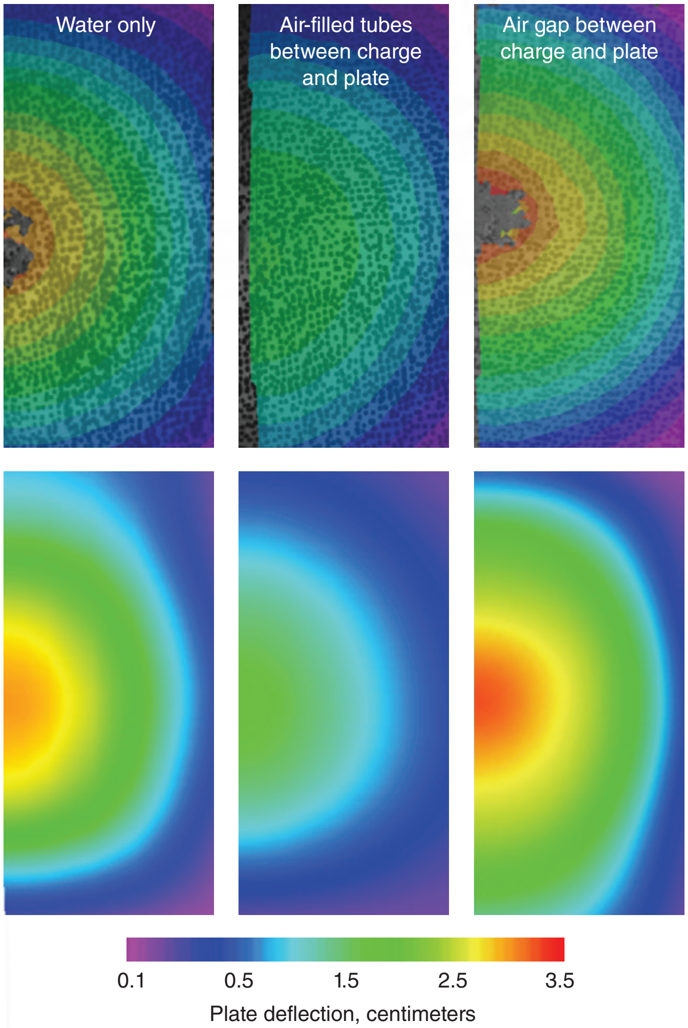
With an air gap in front of the plate, the plate unexpectedly became deformed over one area. The researchers hypothesized that a small, previously unaccounted-for water layer between the charge and air gap could be to blame. "We then ran ALE3D simulations to better understand the results and obtained the same focused deformation." Instead of dispersing the energy from the shock wave, the water-tamped explosive projected the intervening water as a jet toward the plate. Conversely, tests with a matrix of air-filled tubes scattered the shock wave and prevented water jets from forming. Glascoe says, "This relatively heterogeneous material creates an impedance mismatch that disrupts and scatters the blast wave, providing protection across a large threat space."

Glascoe is quick to point out the positives of computational power for understanding complex physics problems and evaluating solutions. "Once we understand the problem well enough to focus on a specific response—plate deformation, for example—we can use advanced sampling techniques to stitch together a comprehensive picture of the anticipated result with fewer simulations," says Glascoe. Carefully analyzing the computational results also helps researchers optimize the design of future experiments. "Smart approaches to simulation save us time and money," he says. The team is now integrating strategies developed in this study into plans for better protecting existing civil structures.

Target Acquired

The Missile Defense Agency (MDA) is responsible for protecting the U.S. and its allies from short- and long-range ballistic missile attacks. Toward this end, MDA's goal is to develop an integrated ballistic missile defense system for neutralizing potential threats. Flight tests of different systems provide valuable data, but they are costly and cannot assess a particular design's effectiveness to all possible threats. MDA is thus working with a team of Livermore engineers to simulate system operations for various threat scenarios. "We bring a comprehensive knowledge of hypervelocity impact physics and of material response in this type of high-rate, high-pressure environment," says Laboratory computational engineer Ed Kokko. "Our physics-based simulation tools coupled with our high-performance computing platforms allow us to provide timely, cost-effective answers to sponsor concerns."

One strategy for neutralizing incoming threats is through a kinetic-kill approach, where an inert projectile, or kill vehicle, engages the incoming threat at a very high speed. MDA system architects are primarily concerned with intercept lethality, that is, whether the intercept event successfully destroys the threat. The ParaDyn code is well suited for examining such events because it allows engineers to analyze the transient dynamic response of three-dimensional solids and structures. It is especially effective at detailing the interaction between independent bodies, such as the incoming threat and the kill vehicle. "ParaDyn and ALE3D provide us with insight into the time sequence of events during an intercept," says Kokko. "They help us determine the effectiveness of the kill vehicle in neutralizing a threat payload for a range of conditions."



Experiments (top row) and hydrodynamics simulations (bottom row) of a structure's response to a water-tamped explosion compare the effects of pure water tamping (left) with mitigation by a matrix of air-filled tubes (middle) or the presence of an air gap (right). Placing the matrix between the blast and an underwater structure improves structural protection over a large threat space.

60 Years of National Service

Accelerating Scientific Discovery

Supercomputing systems continue to grow in size and processing speed. With these more powerful resources, scientists and engineers can examine complex physical processes in greater detail.

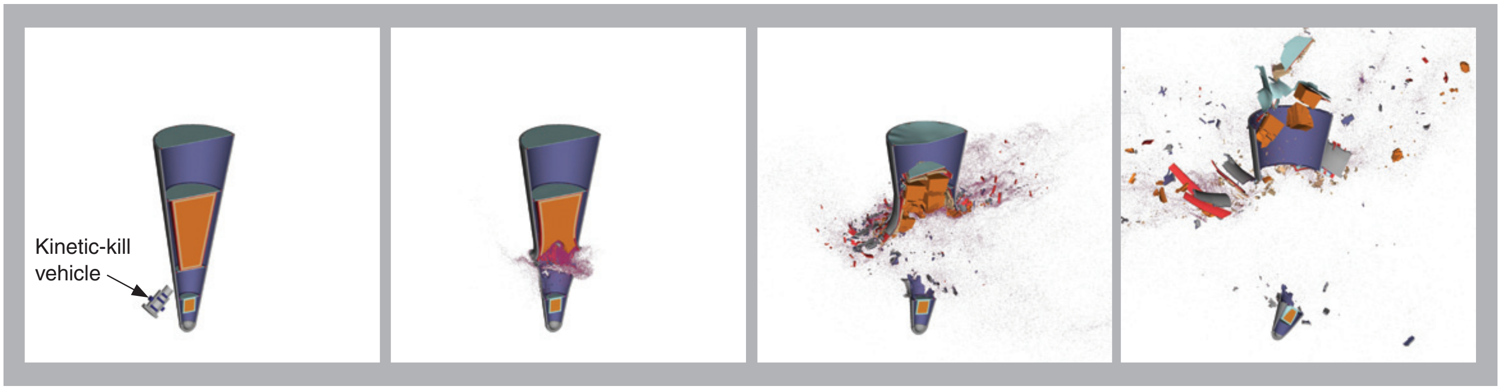
Advanced simulation capabilities have been crucial to the National Nuclear Security Administration's Stockpile Stewardship Program, instituted in 1992 to ensure the safety, security, and reliability of the nation's nuclear weapons stockpile without underground testing. Computational codes such as ParaDyn and ALE3D stemmed from the needs of stockpile stewardship, and code enhancements continue to support the missions of the Departments of Energy and Defense and other government agencies.

"Simulations help us better understand the physics of a particular problem so we can develop a more robust set of solutions," says Rob Sharpe, a division leader in Livermore's Engineering Directorate. "Going forward, advances in computational engineering will offer different methods to optimize and assess system design and to provide solutions in a more systematic manner, which ultimately will accelerate scientific discovery." The natural coupling of ParaDyn and ALE3D into an embedded grid is a prime example of how Livermore computational engineers are using their expertise to further simulation capabilities. "By combining techniques and using more precise variables, we can get closer to seeing the true physics involved in a scenario, which in turn will change the way we design and build systems," says Sharpe.

The Laboratory typically invests in creating simulation tools when no third-party source will suffice or when the tool is considered essential to fulfilling programmatic requirements. Such efforts have already paid off in the design and assessment of complex mechanical and structural systems as well as in high-fidelity modeling of electromagnetic phenomenon. According to Bob Ferencz, an Engineering group leader, development of code capabilities arises from a focus on specific applications but can be extended to meet the needs of sponsors in addressing broader concerns, especially in support of national security.

While simulation cannot exist in the total absence of experimentation, the continued "virtualization" of engineering assessment and design certification is inexorable. Sharpe points out that further enhancements in computational engineering will be extremely valuable for uncertainty quantification assessments, which focus on measuring how accurately simulations predict the outcomes that are most likely to occur. (See *S&TR*, July/August 2010, pp. 12–14.) "Improved computing ensures that we're asking the right questions of the simulations to get the right answers," he says. The models support more focused experiments, the results of which then inform the next set of models, providing higher confidence in the overall data.

The expertise developed by the Livermore staff and the continued investment in computing resources position the Laboratory to further enhance its capabilities in computational engineering. "Our accomplishments in engineering simulation also help the Laboratory expand collaborations with the public and private sectors," says Ferencz. "In addition, these techniques and tools could lead to new avenues of research and experimentation." Sharpe adds that the rapid increases in supercomputing power and improved algorithms, combined with high-fidelity data and an expanded knowledge base, are being applied to solve some of the nation's most challenging problems. Sharpe says, "We're bringing science to bear in a practical way."



ParaDyn helps engineers analyze the mechanical interaction between independent bodies. In this theoretical missile defense scenario, the code simulated a kinetic-kill vehicle as it impacts a reentry threat at hypervelocity and the resulting breakup.

Engineers are also interested in understanding how the interceptor and threat break into pieces on impact. Livermore code developers have enhanced ParaDyn with advanced material models and improved numerical techniques to more accurately simulate an intercept event. Computational engineers, including Kokko, are working with the revised code to provide detailed information about the debris scene.

Simulation codes such as ParaDyn offer a cost-effective approach for system-level analysis at a time when expensive, full-scale experiments are becoming more difficult to stage. "We have been focused on establishing a basis of confidence in our modeling methodology to verify that simulations compare well with experimental results at the fundamental, component level and for scaled and full-scale systems," says Kokko. Confidence in simulation results is essential to sponsors who rely on the data to make critical decisions, and the widespread adoption of physics-based numerical codes for analyzing such events makes this an ever-more important effort.

Two Codes Team Up

The old adage "two heads are better than one" can apply to computer codes as well. In a project initially funded through the Laboratory Directed Research and Development Program and led by Livermore engineer Mike Puso, new algorithms were developed to combine codes such as ALE3D and ParaDyn into a united capability. "This work focused on creating a fundamental numerical technology that allows multiple codes to attack different parts of the same problem," says Ferencz. "In this way, a broader range of problems can be solved with higher fidelity." The result is an embedded-grid numerical code in which two meshes overlap and are processed together by two distinct simulation codes.

Successful demonstration of the technology led to an exciting partnership between the Laboratory and the Blast Protection for Platforms and Personnel HPC [high-performance computing] Software Applications Institute, sponsored by the Department of Defense's High Performance Computing Modernization Program and headed by the Army Research Laboratory. The institute has embarked on a six-year program to develop a suite of tools for analyzing high-explosive blasts and mitigating the effects on military vehicle platforms and personnel. Says Ferencz, "Our primary contribution is to provide a simulation capability that enables efficient, accurate analysis of these complex problems."

Building Confidence in Simulated Solutions

The capabilities provided by Livermore's high-performance computers enable computational engineers such as Ferencz, Glascoe, and Kokko to validate codes quickly and efficiently and apply those calculations to many classes of problems. "Our advanced computing resources often exceed industrial capabilities," says Ferencz. "As a result, we can run multiple, detailed simulations simultaneously with much shorter turnaround times."

When researchers can obtain complex results in days instead of weeks, they can also dedicate more time to understanding an input parameter's effect on code sensitivity. "Sensitivity studies are an important part of the analysis process," says Kokko. "Investigating how results vary with assumptions across many scenarios helps us build confidence in our results."

Studies that help validate the performance of computational codes are propelling viable, novel solutions to some of the nation's greatest challenges. Says Kokko, "We have a responsibility to our sponsors to deliver accurate, reliable data so they can confidently make decisions regarding our national security."

—Caryn Meissner

Key Words: ALE3D code, arbitrary Lagrangian–Eulerian (ALE) technique, computational engineering, embedded grid, ParaDyn code.

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In this section, we list recent patents issued to and awards received by Laboratory employees. Our goal is to showcase the distinguished scientific and technical achievements of our employees as well as to indicate the scale and scope of the work done at the Laboratory.

Patents

Method for Warning of Radiological and Chemical Agents Using Detection Paints on a Vehicle Surface

Joseph C. Farmer, James L. Brunk, S. Daniel Day
U.S. Patent 8,143,063 B2
March 27, 2012
This paint is mixed with an indicator material, which provides a warning when radiological or chemical substances are present, and a thermoactivation material. The paint can be applied to a surface that is then monitored for indications of radiological or chemical substances. It also can be connected to a vehicle such that the indicator material carried by the paint provides a warning when radiological or chemical substances are present.

Hybrid Compton Camera/Coded Aperture Imaging System

Lucian Mihailescu, Kai M. Vetter
U.S. Patent 8,153,986 B2
April 10, 2012
In this system, an array of imagers is positioned behind an array of detectors relative to an expected trajectory of incoming radiation. Incoming radiation is detected and recorded by either the Compton or coded-aperture imaging method.

UWB Dual Burst Transmit Driver

Gregory E. Dallum, Garth C. Pratt, Peter C. Haugen, James M. Zumstein, Mark L. Vigars, Carlos E. Romero
U.S. Patent 8,160,118 B2
April 17, 2012
A dual-burst transmitter for ultrawideband (UWB) communication systems generates a pair of precisely spaced radio-frequency (RF) bursts from a single-trigger event. An input trigger pulse produces an initial oscillator pulse and a delayed one in a dual-trigger generator. The two pulses drive a gated RF burst (power output) oscillator. A bias driver circuit gates the output oscillator on and off and sets the burst packet width. The bias driver also shifts the drive signal to the level required for the RF output device.

Methods for Gas Detection Using Stationary Hyperspectral Imaging Sensors

James L. Conger, John R. Henderson
U.S. Patent 8,165,340 B2
April 24, 2012
This method uses data from a hyperspectral imaging (HSI) sensor to produce HSI data cubes of one location at two different times. The second HSI data cube is subtracted pixel by pixel from the first cube to produce a raw difference cube. The raw difference cube is calibrated and used with at least one spectral band for a gas of interest to produce a detection image and determine whether the gas is present. Results from the examination can then be output. Other methods, systems, and computer programs for detecting the presence of a gas are also described.

Pyrophoric Metal–Carbon Foam Composites and Methods of Making the Same

Alexander E. Gash, Joe H. Satcher, Jr., Randall L. Simpson, Theodore F. Baumann, Marcus A. Worsley
U.S. Patent 8,172,964 B2
May 8, 2012
With this method for creating a pyrophoric material according to one embodiment, a carbon foam is thermally activated to create micropores therein. The activated carbon foam is contacted with a liquid solution that includes a metal salt to deposit metal ions in the foam. The metal ions are then reduced to metal particles. A pyrophoric material can be made from a pyrophoric metal–carbon foam composite. The carbon foam has micropores and mesopores with metal particles in them, and its surface area is greater than or equal to about 2,000 square meters per gram. Additional methods and materials are also described.

Electrochemical Formation of Hydroxide for Enhancing Carbon Dioxide and Acid Gas Uptake by a Solution

Gregory Hudson Rau
U.S. Patent 8,177,946 B2
May 15, 2012
This system uses a water electrolysis cell to form a metal hydroxide from a metal carbonate. The electrolysis cell has an acid-producing anode and a hydroxyl-producing cathode immersed in a water solution with sufficient ionic content to allow an electric current to pass between the cathode and anode. A metal carbonate, in particular, water-insoluble calcium carbonate or magnesium carbonate, is placed near the acid-producing anode. A direct-current electric voltage generates acid at the anode and hydroxyl ions at the cathode. The acid dissolves at least part of the metal carbonate into metal and carbonate ions. The metal ions travel toward the cathode and combine with the hydroxyl ions to form the metal hydroxide. The carbonate ions travel toward the anode and form carbonic acid and/or water and carbon dioxide. Among its many uses, the metal hydroxide can absorb acid gases such as carbon dioxide from a gas mixture. The invention can also generate hydrogen and oxidative gases such as oxygen or chlorine.

Multiple Frequency Method for Operating Electrochemical Sensors

Louis P. Martin
U.S. Patent 8,177,957 B2
May 15, 2012
A multiple-frequency method for operating a sensor uses calibration information to measure a parameter of interest. The sensor is excited at first and second frequencies to provide two responses. The response at the second frequency is combined with the calibration information to produce a calculated concentration of the interfering parameters. The response at the first frequency, the calculated concentration of the interfering parameters, and the calibration information are then used to measure the desired parameter.

Diagnosis and Assessment of Skeletal Related Disease Using Calcium-41

Darren J. Hillegonds, John S. Vogel, Robert L. Fitzgerald, Leonard J. Deftos, David Herold, Douglas W. Burton
U.S. Patent 8,178,076 B2
May 15, 2012
This method uses the radioactive isotope calcium-41 to determine a patient's calcium metabolism. Once the isotope is administered and sufficient time has elapsed for calcium-41 to disseminate in the patient's system, a sample of the radioactive isotope is obtained. The sample's calcium content is then isolated in a form suitable for precisely measuring the sample's isotopic calcium concentration and determining the parameters of calcium metabolism in the patient.

Absolute Nuclear Material Assay

Manoj K. Prasad, Neal J. Snyderman, Mark S. Rowland
U.S. Patent 8,180,013 B2
May 15, 2012
This method involves counting neutrons from an unknown source and comparing the measured count distributions to a model to provide an absolute nuclear material assay. One approach uses a random sampling of analytically computed fission-chain distributions to generate a continuous time-evolving sequence of event counts by spreading the fission-chain distribution in time.

Real Time Gamma-Ray Signature Identifier

Mark Rowland, Tom B. Gosnell, Cheryl Ham, Dwight Perkins, James Wong
U.S. Patent 8,180,579 B2
May 15, 2012
A real-time gamma-ray signature and source identification method uses principal components analysis to transform and substantially reduce one or more comprehensive spectral libraries of nuclear material types and configurations into corresponding signatures. Each individual predetermined spectrum is indexed in principal component space. An unknown gamma-ray signature may then be compared with the concise representatives to either find a match or characterize the signature by performing a single regression or simple projection into principal component space using all the library entries. This method substantially reduces processing time and computing resources and enables real-time characterization and/or identification of an unknown gamma-ray signature.

Method of Fabricating Conductive Electrodes on the Front and Backside of a Thin Film Structure

Phillipe J. Tabada, Melody Tabada, Satinderpall S. Pannu
U.S. Patent 8,183,111 B1
May 22, 2012
In this method for fabricating a thin-film device with conductive front- and back-side electrodes or contacts, top-side cavities are formed on a dielectric layer. A metal layer deposited on the dielectric layer fills the cavities. Defined metal structures are then etched from the metal layer to include the cavity-filled metal, and a second dielectric layer is deposited over the metal structures. Additional levels of defined structures may be formed in a similar manner with connecting metal structures between levels. After a final dielectric layer is deposited, the top surface of a metal structure in an uppermost metal layer is exposed through the final dielectric layer to form a front-side electrode. A bottom surface of a cavity-filled portion of a metal structure in a lowermost metal layer is also exposed through the first dielectric layer to form a back-side electrode.

Shape Memory System with Integrated Actuation Using Embedded Particles

Patrick R. Buckley, Duncan J. Maitland
U.S. Patent 8,187,252 B2
May 29, 2012
This shape-memory material with integrated actuation uses embedded particles. One embodiment provides an apparatus with a shape-memory material body and magnetic pieces therein. Another embodiment provides a method for actuating a device to perform an activity on a subject. The shape-memory material body is placed in a desired position with regard to the subject. This material body can be formed in a specific primary shape and reformed into a secondary stable shape. It can also be actuated to recover the specific primary shape, including magnetic pieces in the shape-memory material body. The shape-memory material body can be actuated using these magnetic pieces, causing it to recover the specific primary shape and perform the activity on the subject.

Energetic Composite and System with Enhanced Mechanical Sensitivity to Initiation of Self-Sustained Reaction

Alexander E. Gash, Troy W. Barbee, Jr.
U.S. Patent 8,187,398 B2
May 29, 2012
An energetic composite and system uses amassed energetic multilayer pieces that are formed from cutting, scoring, breaking, crushing, or shearing one or more mechanically activated, monolithic energetic multilayers. These macroscale sheets of multilayer films enhance the sensitivity of the energetic composite and system allowing for mechanical initiation of a self-sustained reaction. In particular, mechanical initiation of the energetic composition may be achieved with significantly lower mechanical energy inputs than that typically required for initiating the monolithic energetic multilayers from which it is derived.

Corrosion Resistant Neutron Absorbing Coatings

Jor-Shan Choi, Joseph C. Farmer, Chuck K. Lee, Jeffrey Walker, Paige Russell, Jon Kirkwood, Nancy Yang, Victor Champagne
U.S. Patent 8,187,720 B2
May 29, 2012
In this method of forming a corrosion-resistant neutron-absorbing coating, a spray, deposition, sputtering, or welding process forms a composite material and a neutron-absorbing material.

Awards

Lynn Seppala, an optical designer in the Engineering Directorate, was named a **senior member** of the **Optical Society of America** (OSA), an international society for optics and photonics scientists, engineers, educators, and business leaders. Senior membership status recognizes members with more than 10 years of significant experience and professional accomplishments or service in their fields.

Seppala, who supports the National Ignition Facility, received the elevated status in recognition of his contributions to optics research. He also was a key contributor to the optical design of the Large Synoptic Survey Telescope (LSST), an 8.4-meter-diameter telescope being built on Cerro Pachón in Chile. In 2020, when LSST is operational, it will be the world's largest light-gathering astronomical telescope. In addition, Seppala chaired the OSA optical design technical group from 1990 to 1992.

An article written by Livermore scientist **Ellen Raber** and five other researchers was named **2011 Risk Management Paper of the Year** by ***Human and Ecological Risk Assessment*** (*HERA*). In selecting the chemical remediation paper as the year's top article, the editors of *HERA* wrote, "This paper gives salient management actions should airports experience terrorists' release of toxic substances into airport environments."

The paper, "Developing Health-Based Pre-planning Clearance Goals for Airport Remediation following a Chemical Terrorist Attack: Decision Criteria for Multipathway Exposure Routes," appeared in the January–February 2011 edition of *HERA*. In addition to Raber, the coauthors included project leader and lead author **Annetta Watson**, a senior scientist in toxicology at Oak Ridge National Laboratory; two former Laboratory employees, toxicologist **Linda Hall** and chemist **Adam Love**; **Fredrick Dolislager**, a senior research associate at the University of Tennessee in Knoxville; and **Veronique Hauschild**, a toxicologist with the U.S. Army Public Health Command. The research project, which was funded by the Department of Homeland Security, was performed as a national case study in partnership with Los Angeles International Airport.

Frédéric Pérez, a postdoctoral researcher in Livermore's Physical and Life Sciences Directorate, is one of three recipients of the **2012 Ph.D. Research Award** from the **Plasma Physics Division** of the **European Physical Society**. The award was created in 2005 to recognize exceptional work performed by young scientists.

Pérez was honored for work on his doctoral thesis, "Study of Supra-Thermal Electron Transport in Solid or Compressed Matter for the Fast-Ignitor Scheme." In his research, he focused on experimentally addressing some of the physics involved in the fast-ignition concept for laser-driven nuclear fusion—in particular, on measuring and better understanding electron generation and propagation into plasma.

Abstracts

Building New Vaccines for the 21st Century

Infectious diseases can cause catastrophic levels of illness and death worldwide. The nanolipoprotein particle (NLP) technology developed at Lawrence Livermore can be used to rapidly produce vaccines to counter infectious biological agents, whether they occur naturally or are released intentionally. Traditional vaccines are made with weakened or killed viruses or bacteria and are thus not suitable for treating diseases such as anthrax because they pose safety concerns and can have significant side effects. An alternative approach uses antigens, proteins from the targeted pathogen. Such subunit vaccines, however, have low potency and require adjuvants—chemicals that boost the immune system response but can also be toxic. Laboratory scientists have shown that nickel-chelated NLPs can act as a stable platform to bind antigens and adjuvants, delivering measured amounts of each substance to the immune system. NLPs are also the centerpiece of a Livermore collaboration with Loyola University in Chicago, Illinois, to develop a novel anthrax vaccine. Another research effort is developing NLP antigen–adjuvant vaccines optimized for *Burkholderia* and *Francisella tularensis*, bacteria regarded as viable biological warfare agents.

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A Flexible Foundation for High-Energy-Density Science

The National Ignition Facility (NIF) provides unique capabilities for exploring fundamental questions relevant to high-energy-density (HED) science, including such areas as stockpile stewardship, planetary physics, and astrophysics. By developing standardized target, diagnostics, and laser configurations, researchers facilitate a variety of experiments with precisely controlled inputs. HED experiments on NIF are being compared directly to high-performance computing simulations, providing essential validation of complex models and occasionally discovering a new phenomenon. Recent NIF experiments have explored the material properties of tantalum and diamond and radiation flow through various geometries and materials. These experiments highlight how researchers are using NIF to better understand material behavior at extreme temperatures and pressures.

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Coming Next Issue

Livermore Wins Six R&D 100 Awards

2012 R&D 100 50th ANNIVERSARY

In *R&D Magazine*'s annual competition for the top industrial inventions, Laboratory researchers won awards for the following technologies:

- High-Velocity Laser-Accelerated Deposition
- Laser Energy Optimization by Precision Adjustments to the Radiant Distribution
- Plastic Scintillators for Neutron and Gamma Discrimination
- Snowflake Power Divertor
- Multiplexed Photonic Doppler Velocimetry
- NanoSHIELD Coating

Also in October/November

• A new diagnostic called the all-optical probe dome measured material implosions at unprecedented velocities in a subscale integrated weapons experiment.

• Using sophisticated computer modeling techniques, researchers can readily evaluate methods for neutralizing toxic chemical warfare agents.

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