Lawrence Livermore National Laboratory

October/November 2016

Science & Technology Review

PREDICTIVE MEDICINE ADVANCES CANCER RESEARCH

Also in this issue:

A New Look at Lithium Hydride

Chemical Biosensors Measure Brain Activity

Recovering Infrastructure after a Biological Attack

About the Cover

Through a historic partnership between the Department of Energy (DOE) and the National Cancer Institute (NCI), Lawrence Livermore is applying its expertise in high-performance computing (HPC) to advance cancer research and treatment. As the article beginning on p. 4 describes, the Laboratory plays a crucial role in the partnership's three pilot programs. In particular, Livermore experts are working in collaboration with NCI and other DOE labroatories to develop more advanced algorithms for improving predictive models, computational tools for better understanding cancer intiation, and data analytics techniques to search for patterns in vast amounts of patient data. The cover art combines an artist's rendering of circulating tumor cells in the blood of a cancer patient with computer circuitry (representing HPC) in the background.

Cover design: Amy E. Henke

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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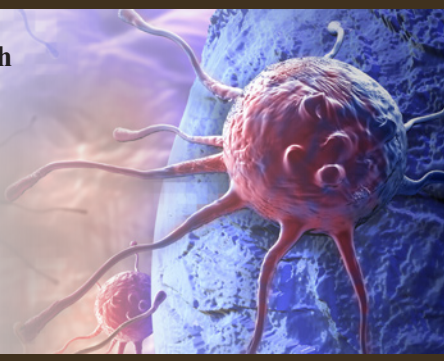
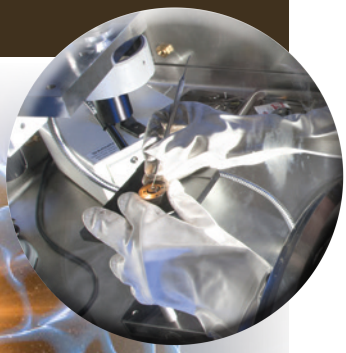


Research Highlights



Departments

Progress toward Ignition

In a paper published in the April 11, 2016, online issue of *Nature Physics*, researchers at Lawrence Livermore's National Ignition Facility (NIF) analyzed "high-foot" inertial confinement fusion (ICF) experiments that reached the highest levels of alpha-particle heating, or self-heating, achieved by any laser facility. Alpha-particle heating within deuterium–tritium (DT) targets is a key step on the path to ignition.

In the high-foot experiments, the early-time foot of the drive—the initial "picket" of the laser pulse—was approximately doubled as compared to the low-foot drive, thus launching a stronger and faster first shock and substantially reducing the implosion instabilities associated with low-foot experiments. Recent three-dimensional simulations of the fusion targets used in both high- and low-foot experiments have shown reasonable agreement with the experimental results, indicating an improved understanding of the implosions that can be used to guide future work toward ignition. "We have obtained a factor-of-two yield amplification from alpha heating, but more importantly, we see an array of evidence that symmetry control and engineering features are limiting further progress," says Omar Hurricane, ICF program chief scientist and lead author of the paper.

NIF provides insights and data for the National Nuclear Security Administration's science-based Stockpile Stewardship Program. Advances in ignition physics and performance also play a key role in fundamental science and potential energy applications.

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Examining Hydrogen at High Pressure

Hydrogen is the most abundant element found in the universe, making up nearly three-quarters of all matter, but many questions about the element remain. In a paper published in the April 15, 2016, edition of *Nature Communications*, a team of researchers, including scientists from Lawrence Livermore, the University of California (UC) at Berkeley, UC at Los Angeles, SLAC National Accelerator Laboratory, the University of Rostock in Germany, and Sandia National Laboratories, describe what happens to hydrogen at high pressure.

The team used an x-ray scattering technique to detect free electrons that appear in high-pressure shock waves formed when hydrogen is subjected to a high-energy laser beam. The experiments were conducted at Livermore's Jupiter Laser Facility using the two-beamed Janus laser. One beam launched a shock wave into the deuterium target, and a second beam created x rays that scattered off the shocked hydrogen. A crystal spectrometer spread the scattered x rays into a spectrum that was then compared to theoretical calculations. By conducting the same experiment at several pressures, the team established the specific pressure at which hydrogen turned from an insulator to a metal.

The researchers determined the hydrogen content at a variety of shock conditions, calculating how many deuterium molecules turned into single atoms—a process called dissociation. They found that the pressures at which their x-ray measurements indicated the appearance of free electrons (ionization) coincided with where dissociation occurred. Former Livermore graduate student and lead author of the paper, Paul Davis, says, "The details of how hydrogen dissociates under pressure and becomes electrically conductive are important for scientists seeking to understand planetary interiors and the dynamo action that causes their magnetic fields."

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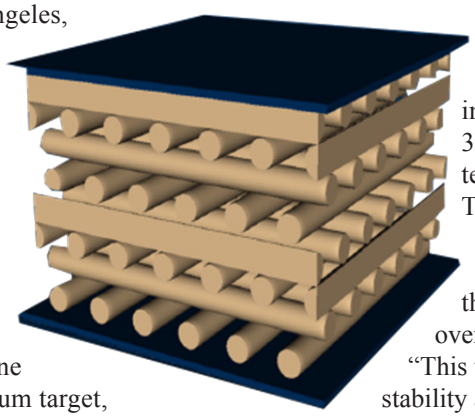
Printed Foam Outperforms Standard Materials

A study conducted by Lawrence Livermore material scientists found that foams produced through three-dimensional (3D) printing are more durable and offer longer mechanical performance than standard cellular solids. The research appears in the April 27, 2016, edition of *Scientific Reports*.

Foams are an important class of materials with applications ranging from thermal insulation and shock-absorbing support cushions to lightweight structural and floatation components. Conventional foams are created by processes that result in a nonuniform structure with significant variations in the size, shape, thickness, connectedness, and topology of constituent cells. As an improved alternative to conventional foam products, Lawrence Livermore scientists recently demonstrated how direct ink writing could be used to print 3D foams with uniform structures (see image below). "These foams offer tremendous flexibility in creating programmable architectures, customizable shape, and tunable mechanical response," says lead author Amitesh Maiti.



As part of the work, Lawrence Livermore researchers tested the new material's stability by conducting accelerated aging experiments in which samples of both conventional and 3D-printed foam were subjected to elevated temperatures under constant compressive stress. The stress condition, mechanical response, and permanent structural deformation of each sample were monitored for one year. The team then modeled the evolution of these properties over decades under ambient conditions. Maiti says, "This work strongly indicates the superior long-term stability and performance of the printed material and may result in 3D-printed foam replacing traditional foam in specific future applications."

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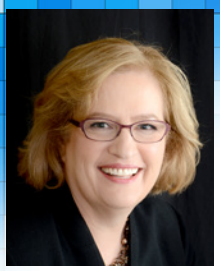
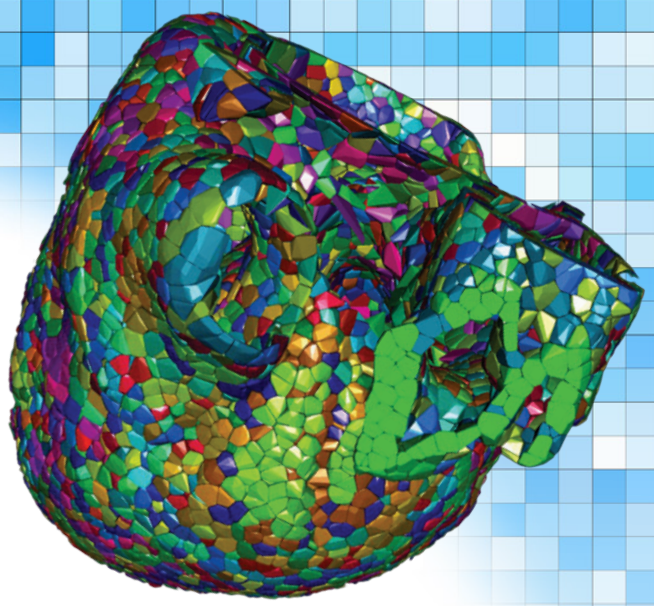
Commentary by Patricia Falcone



A New Paradigm for Medical Research



ONE of Lawrence Livermore's most significant contributions to the nation has undoubtedly been its prominent role in the ascendancy of the computer for scientific research. The Laboratory's insatiable demand for computational power helped drive the computer revolution and its rapid development into today's era of high-performance computing (HPC). Livermore computing experts have spurred advances in hardware, software, code development, and simulations of physical phenomena that today support the U.S. nuclear deterrent and advance technology and scientific discovery.

Perhaps less well known is Livermore's rich heritage in applied biological and biomedical research. In 1963, the Laboratory established a program to investigate how radiation and chemicals interact with human genetic material to produce mutations. We also worked with the Department of Energy (DOE) to establish the Human Genome Project and took on the effort to complete the mapping and sequencing of human chromosome 19. Over the past few decades, our researchers have helped change the biomedical world by developing instruments that sort cells and analyze DNA and by creating advanced simulations that mimic physiological functions, including a beating human heart.

Lawrence Livermore is now helping to lead the national effort to bring the most powerful HPC resources to bear on pressing medical issues. The initiative comes at a time of reduced pharmaceutical research and development outlays and increasing microbial resistance to antibiotics, as well as explosive growth in the quantity and complexity of biological and patient data. Livermore experts are showing how to analyze enormous and disparate data sets with new algorithms and specialized machines designed for analyzing and making sense of "big data."

As described in the article beginning on p. 4, Lawrence Livermore is proud to be a major collaborator in a groundbreaking partnership between DOE and the National Cancer Institute (NCI) that represents a revolutionary approach to enhanced understanding of human biology and health, the treatment and prevention of disease, and biosecurity. The effort leverages DOE's enormous investments in some of the world's most powerful supercomputers, large-scale simulation techniques, advanced software, and data analytics. Three pilot programs are focused on topics ranging from analysis of single molecules to entire human populations. Lawrence Livermore researchers play important roles in all three pilot programs.

The DOE–NCI partnership resides under the umbrella of the National Strategic Computing Initiative (NSCI), which outlines a cohesive federal investment strategy in HPC. As a lead NSCI agency, DOE has been exploring how to apply HPC to societal challenges. The computing resources resident in DOE national laboratories offer enormous potential for advancing breakthroughs in medicine and healthcare. In that respect, the partnership is also an essesntial element of the national Cancer Moonshot Initiative, which aims to accelerate effective treatment options for cancer.

Our participation in the DOE–NCI partnership is indicative of nearly all research efforts at the Laboratory, where collaborations predominate and thrive. For example, we are working with University of California (UC) institutions to apply HPC to other projects in cancer research, including the study of breast cancer metastasis. Our computer scientists and supercomputing capabilities are also integral as part of an effort with Norwegian researchers to analyze medical data to improve screening for cervical cancer. We are also in early discussions with the UC Office of the President and UC San Francisco to combine our strengths and possibly develop an innovative research facility in the San Francisco Bay Area that takes advantage of both HPC and biomedical expertise in the region to advance medical breakthroughs. Other discussions with pharmaceutical companies focus on collaborations designed to radically reduce the time required for drug discovery.

We are looking at a true revolution in medicine made possible by the convergence of HPC, big data, and biomedical research. In addition, our work on understanding complex biomedical systems through HPC helps inform the design of new computer architectures, algorithms, and computational approaches for national security applications. The results of these efforts may well be twofold: better health for all Americans through the development of "precision medicine" and improved HPC capabilities for tackling our biggest scientific challenges.

■ Patricia Falcone is deputy director for Science and Technology.

HIGH-PERFORMANCE COMPUTING TAKES AIM AT CANCER

A Department of Energy (DOE)–National Cancer Institute (NCI) partnership aims to significantly advance cancer research and treatment. This artist's rendering depicts circulating tumor cells in the blood of a cancer patient.

A historic partnership between the Department of Energy and the National Cancer Institute is applying the power of Lawrence Livermore supercomputers to tough problems in medical science.

COMBINING extraordinary processing capability with enormous storage capacity and advanced simulation and analytical software, supercomputers have become essential to national security, scientific discovery, engineering, technology, and industry. Some of the world's most powerful supercomputers are located at Lawrence Livermore, where they support the National Nuclear Security Administration's Stockpile Stewardship Program and make possible advances in areas such as materials science, chemistry, and energy, among others.

Livermore researchers have recently been calling national attention to applying the power of high-performance computing (HPC) to biology. According to Dave Rakestraw, head of Livermore's chemical, biological, and explosives security program, the Laboratory is fostering collaborations across academia, industry, and government that promote HPC as a revolutionary approach to improved understanding of human health. The effort focuses on countering biosecurity threats, overcoming infectious disease challenges, and laying foundations for the future of critical care.

Now, a historic partnership between the Department of Energy (DOE) and the National Cancer Institute (NCI) is applying the formidable computing resources at Livermore and other DOE national laboratories to advance cancer research and treatment. Announced in late 2015, the effort will help researchers and physicians better understand the complexity of cancer, choose the best treatment options for every patient, and reveal possible patterns hidden in vast patient and experimental data sets. The DOE–NCI agreement features three pilot programs that bring together nearly 100 cancer and biomedical researchers, computer scientists, and engineers. Livermore researchers are playing important roles in all three programs. Participants also include Argonne, Los Alamos, and Oak Ridge national laboratories; NCI's Frederick National Laboratory for Cancer Research (FNLCR); and the U.S. Department of Veterans Affairs.

"One of the goals of this partnership is to bring about a huge shift in how biological and medical research will be performed in the future," says Fred Streitz, director of Livermore's High Performance Computing Innovation Center. "We are investing in the computational tools needed to move the medical community toward a predictive approach to cancer,"

he says. "Such tools may help explain why one cancer treatment is successful with one patient but fails with the next." In that respect, the DOE–NCI partnership supports President Barack Obama's Precision Medicine Initiative, which promotes developing treatments for various medical conditions that take into account patients' individual variability in genes, microbiomes (the collection of microbes in or on the body), environment, health history, lifestyle, and diet.

The partnership is also a key element of the National Cancer Moonshot Initiative, which, under the direction of U.S. Vice President Joe Biden, seeks to double the rate of progress in the understanding, prevention, diagnosis, and treatment of cancer. On June 28, 2016, a summit for Cancer Moonshot was held at Howard University in Washington, D.C., that joined Vice President Biden with more than 350 researchers, oncologists, and care providers.

Jason Paragas, Livermore's director of innovation, was instrumental in bringing together high-level officials for the DOE–NCI cancer research partnership. He notes that the agreement is aligned with the National Strategic Computing Initiative, which is designed to ensure the United States continues leading the world in HPC over the coming decades. "NCI understands that the complexity of cancer initiation and growth demands the same computational approaches Livermore has spent decades developing for both national security and scientific discovery," says Paragas. "NCI managers recognize that the newer computational architectures inside the latest machines provide an opportunity to think about biology in a novel way by combining the best of simulation and data science."

According to Jim Brase, deputy associate director for science and technology in Lawrence Livermore's Computation Directorate, this partnership

Vice President Joe Biden holds the first meeting of the Cancer Moonshot Task Force as part of the federal initiative to double the rate of progress in the understanding, prevention, diagnosis, and treatment of cancer. The large-scale effort involves hundreds of researchers, oncologists, and care providers. (Photo courtesy of Pete Souza, White House.)

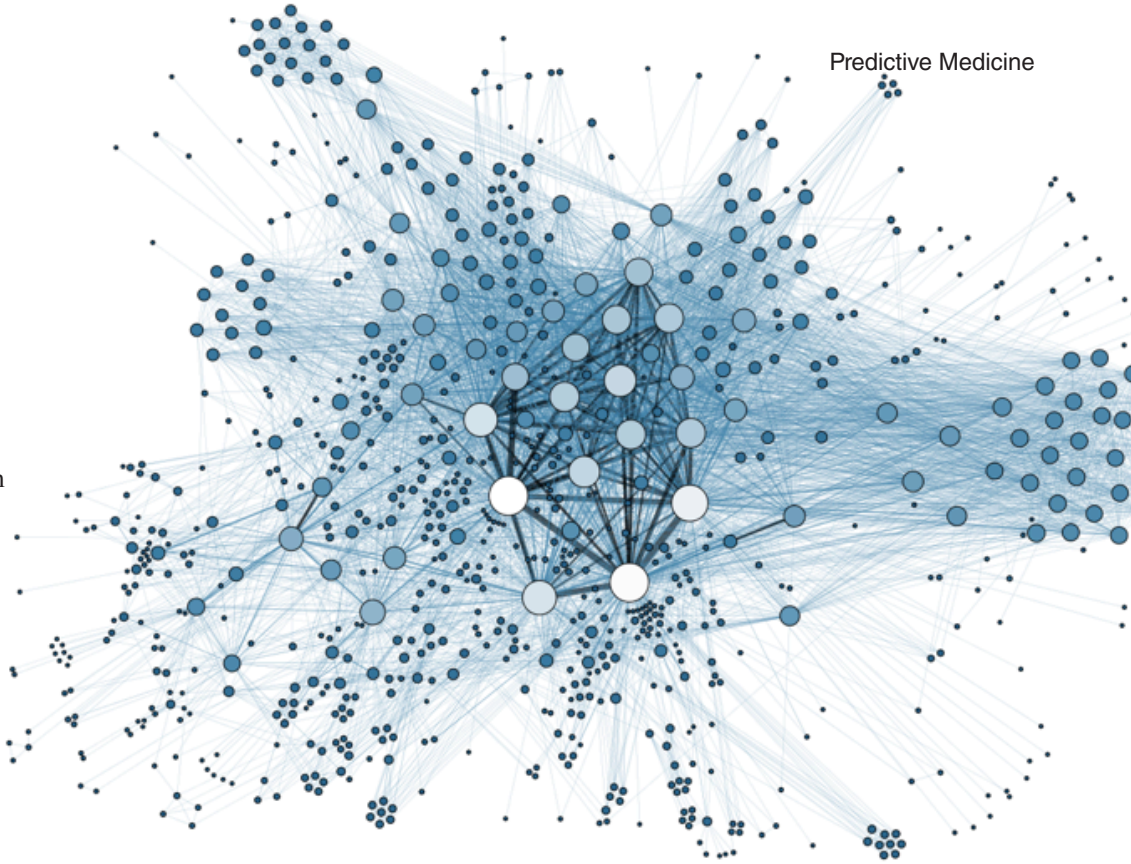
underscores how Livermore can work closely with research partners to advance medical breakthroughs. "Our expertise is in computing, not cancer," he says. "Medical advances in this area require an effective partnership with NCI."

Data May Reveal Patterns

Advanced data analytics—an approach that uses machine-learning algorithms to search for connections within vast amounts of data—is a key component of the DOE–NCI research. Recently, Livermore-developed deep-learning networks, based loosely on neural pathways in the human brain, have been used to create advanced models based on patterns buried deep within data sets. (See *S&TR*, June 2016, pp. 16–19.) Streitz says, "Merging data analytics and simulation could potentially transform how we do scientific research."

All three DOE–NCI pilot programs will develop advanced data analytics for large sets of patient, drug, experimental, and other cancer-related data to uncover correlations that are too complex for humans to discern. Each pilot will also be applying uncertainty quantification, a statistical process that increases confidence in the conclusions drawn from data analytics. The process, improved over the years by Lawrence Livermore weapons scientists, has been highly effective in stockpile stewardship work for assessing the expected performance of nuclear weapons systems without nuclear testing.

Amy Gryshuk, Director of Strategic Engagements and Alliance Management for Livermore's Physical and Life Sciences Directorate, and Eric Stahlberg, Director of the High Performance Computing Initiative at FNLCR, coordinate and provide project management for the three pilot programs, which are aimed at improving drug therapy for cancer patients, simulating human RAS proteins to facilitate cancer drug development, and analyzing extremely large NCI databases to optimize cancer therapies. "The DOE–NCI partnership is critical to the success of the program and has resulted in a unified and formidable endeavor that includes multiple institutions with diverse cultures, capabilities, and fields of research," says Gryshuk. The pilots will also identify requirements for future supercomputer architectures and data analytics software.



Livermore scientists are applying advanced machine-learning algorithms to search for connections within vast amounts of data. Shown here is a graph representing the metadata of thousands of archived documents, illustrating the complexity and expansive nature of data analytics. (Image courtesy of Martin Grandjean.)

Learning from Cancer Cell Cultures

The first pilot program is led by Rick Stevens at Argonne National Laboratory and Jim Doroshow at NCI, with bioinformatics scientist Jonathan Allen heading Livermore's participation. This team aims to outperform current methods for selecting cancer treatments through the development of algorithms that produce powerful new predictive models. The work includes both statistical and mechanistic models (how tumor cells promote unchecked cell growth and how cancer drugs interact with those cells). The models are expected to help researchers speedily and inexpensively predict the effectiveness of potential cancer drugs and more quickly identify and evaluate promising new pharmaceuticals. The pilot program also promises to provide new insights into tumor biology and critical cancer pathways.

For several years, Allen has been working on methods to rapidly detect and characterize pathogenic organisms such as viruses, bacteria, and fungi. Allen's team previously developed the Livermore Metagenomic Analysis Toolkit (LMAT), a group of software programs that quickly compares metagenomic data (environmental genetic material) to large collections of already sequenced human and microbial genomes. (See *S&TR*, October/November 2015, pp. 16–19.)

LMAT uses unique search algorithms that exploit large memory computer architectures such as those being implemented for the DOE–NCI research.

The computer models will be based on well-documented data generated by numerous cell lines—populations of cells taken from different human tumors and grown and maintained in a laboratory. Allen says, "We will look for key patterns such as molecular signatures that correlate with certain outcomes to build a model of the drugs' effectiveness at countering tumor growth."

The researchers will start with the NCI-60 tumor cell line to determine the tumors' response to thousands of available drugs. This group of 60 different human tumor cell lines includes leukemia, melanoma, and cancers of the lung, colon, brain, ovary, breast, prostate, and kidney. Studying tumor cell cultures is critical because "it's difficult to know what's happening inside a human tumor," explains Allen. Researchers expect to add data from other cell lines and from patient-derived xenograft (PDX) models, wherein cells from human tumors are transplanted to mice, to better capture details of how tumors grow and respond to different treatments. The long-range goal is to have more than 1,000 PDX models available for screening to study

Looking Forward to New Generations of Supercomputers

Livermore's suite of powerful unclassified supercomputers such as Catalyst, Cab, and Vulcan will play an important role in all three Department of Energy (DOE)–National Cancer Institute (NCI) pilot programs. Developed in partnership with Intel and Cray, the Laboratory's Catalyst machine has a unique architecture designed to collect, manage, and analyze vast quantities of data. "Catalyst serves as a test bed to optimize strategies for data-intensive computing," says Fred Streitz, director of Livermore's High Performance Computing Innovation Center (HPCIC).

The computing techniques developed during the pilot programs will be scaled to the next generation of supercomputers being produced as part of the Collaboration of Oak Ridge, Argonne, and Livermore (CORAL) effort. CORAL-class machines will be operating beginning in late 2017. Livermore's machine, Sierra, will be capable of at least 150 petaflops (10^{15} floating operations per second), 15 times the power of current supercomputers.

In June, the National Nuclear Security Administration (NNSA) and other government representatives dedicated a new supercomputing facility at Livermore. The $9.8 million facility, which adjoins the Livermore Valley Open Campus (LVOC), provides added flexibility to accommodate future advances in computer technology and meet a rapidly growing demand for unclassified high-performance computing (HPC). Home to HPCIC, the LVOC area facilitates collaborations with industry and academia. Next year, the facility will house a smaller, unclassified companion to Sierra to support academic alliances, the DOE–NCI partnership, and other efforts of national importance.

Researchers participating in the three pilot programs anticipate a formidable class of supercomputers still under design. The exascale machines will be capable of 1 billion billion calculations per second, a significant performance increase over existing systems. DOE's NNSA and Office of Science have launched the Exascale Computing Project, and the first exascale machines are scheduled to arrive in 2023.

The deputy associate director for science and technology in Livermore's Computation Directorate, Jim Brase, says, "CORAL machines will show us what exascale will look like. We already know that we need to scale our codes to exascale machines with new types of CPUs, GPUs, neurosynaptic chips, and other specialty processors inspired by the architecture of the human brain."

Officials from DOE's National Nuclear Security Administration (NNSA) and government representatives dedicate a new supercomputing facility at Lawrence Livermore. (from left) Michael Macial, mayor of Tracy, California; Charles Verdon, Lawrence Livermore's principal associate director for Weapons and Complex Integration; Kathleen Alexander, NNSA administrator; Pat Falcone, Lawrence Livermore's deputy director for Science and Technology; Nicole Nelson-Jean, NNSA Livermore Field Office manager; and John Marchand, mayor of Livermore, California. (Photo by Julie Russell.)

the tumors' heterogeneity. The resulting model repository will be used to characterize tumor viability and provide a computerized platform for testing new drugs.

Modeling Cancer Initiation Events

Livermore's Streitz and Dwight Nissley at NCI lead the second pilot program, which promises to deliver the computational advances necessary for understanding cancer initiation in RAS proteins located in cell membranes. Found in all human cells and organs, these proteins are involved in transmitting signals within cells and regulating diverse cell behaviors. When a RAS protein is switched on, it activates other proteins, which then trigger other genes involved in cell growth, differentiation, and survival. Under normal function, a RAS protein switches off after other proteins are switched on. However, RAS gene mutations can lead to proteins' permanent activation. These mutations are responsible for up to 30 percent of all human cancers, including some of the most deadly forms, such as pancreatic.

The fundamental mechanism by which RAS proteins initiate uncontrolled cell growth is still a mystery. NCI has large amounts of data on the physical, chemical, and biological characteristics of RAS genes and proteins, data which were obtained through x-ray crystallography, cryoelectron microscopy, and other imaging techniques. The team will couple experimental data with atomic-resolution molecular dynamics simulations to build a model of RAS protein biology in varying types of cell membranes. The RAS model will permit easy manipulation of particular tissues and simulate the effects of environmental and genetic factors present in human populations or specific to individuals.

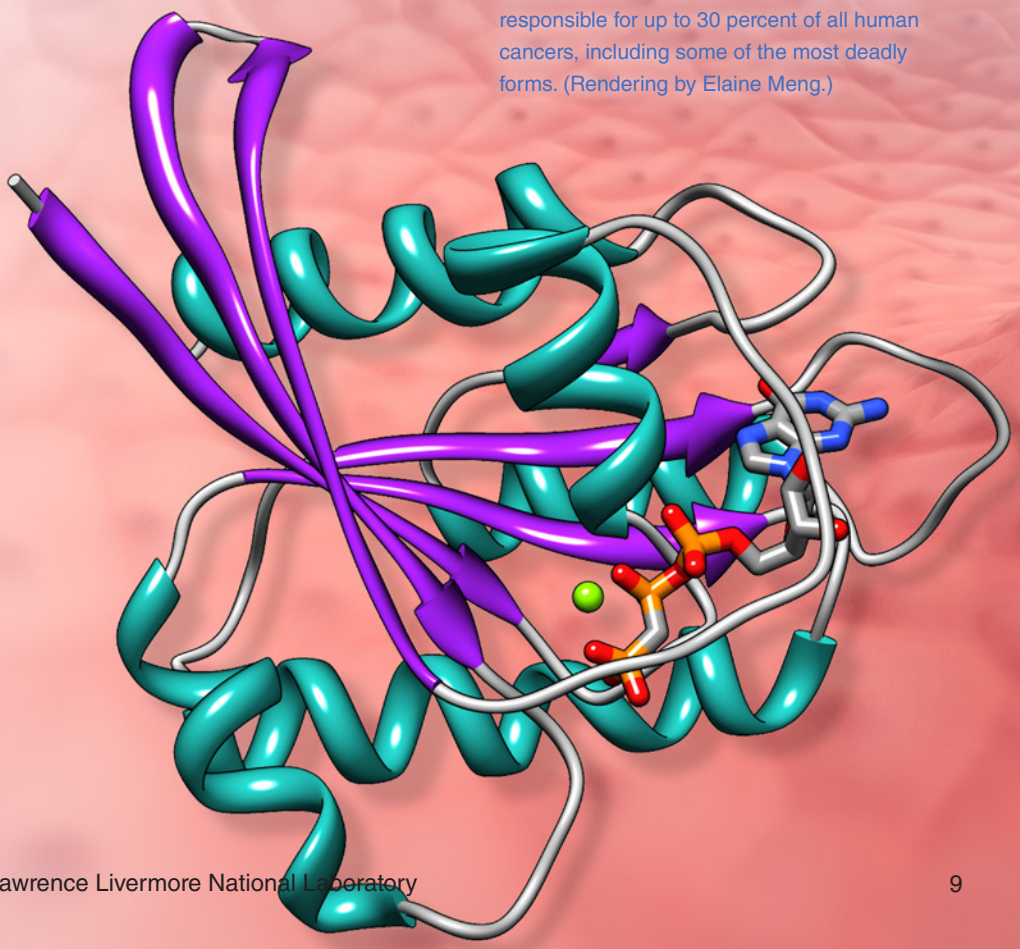
According to Streitz, a major advance in this area of research would be a comprehensive approach to explain the mechanisms of the protein and the onset of cancer. "Although RAS is found only in the cell membrane, it starts a cascade of events that involves many processes happening simultaneously," he says. "These events are not linear, so they cannot be modeled sequentially or simply. However, we can simulate the membrane environment and explore how it operates and interacts with other proteins and with cancer drugs."

The models will use machine-learning algorithms combined with uncertainty quantification to optimize the simulations of RAS interactions with RAF (a protein activated by RAS). The investigators plan to use the model's ability to predict the fundamental mechanism of RAS-driven cancer initiation and growth in the various tissue types to identify potential treatments for inhibiting RAS activation in normal cells.

As part of this effort, the team is developing algorithms that will automatically switch between atomistic and coarse-grained molecular dynamics, in essence, optimizing the resolution to maximize fidelity yet minimize run time. In addition, they will explore algorithms capable of autonomously generating hypotheses about signaling mechanisms. The hypotheses will then be validated through simulation, possibly identifying potential drug therapy sites among thousands of possible configurations. "This capability will be nothing short of revolutionary," says Streitz. "It will change the way we use predictive simulations."

Going Deep into Patient Records

The third pilot program, led by Gina Tourasi at Oak Ridge and Lynn Penberthy at NCI, takes a population-wide approach to cancer research. The research team is analyzing cancer patients' medical records to better understand treatment outcomes on a large scale. Livermore computational biologist and team member Todd Wasson



Found in all human cells and organs, RAS proteins, such as the one shown in this artist's rendering, are involved in transmitting signals within cells and regulating diverse cell behaviors. Mutations in RAS genes are responsible for up to 30 percent of all human cancers, including some of the most deadly forms. (Rendering by Elaine Meng.)

notes that patient privacy will be strictly observed. The team has begun studying 500,000 medical records from four states—Washington, Louisiana, Georgia, and Kentucky. The records are provided by NCI's Surveillance Epidemiology and End Results (SEER) program, which has been collecting data on cancer patients since 1973.

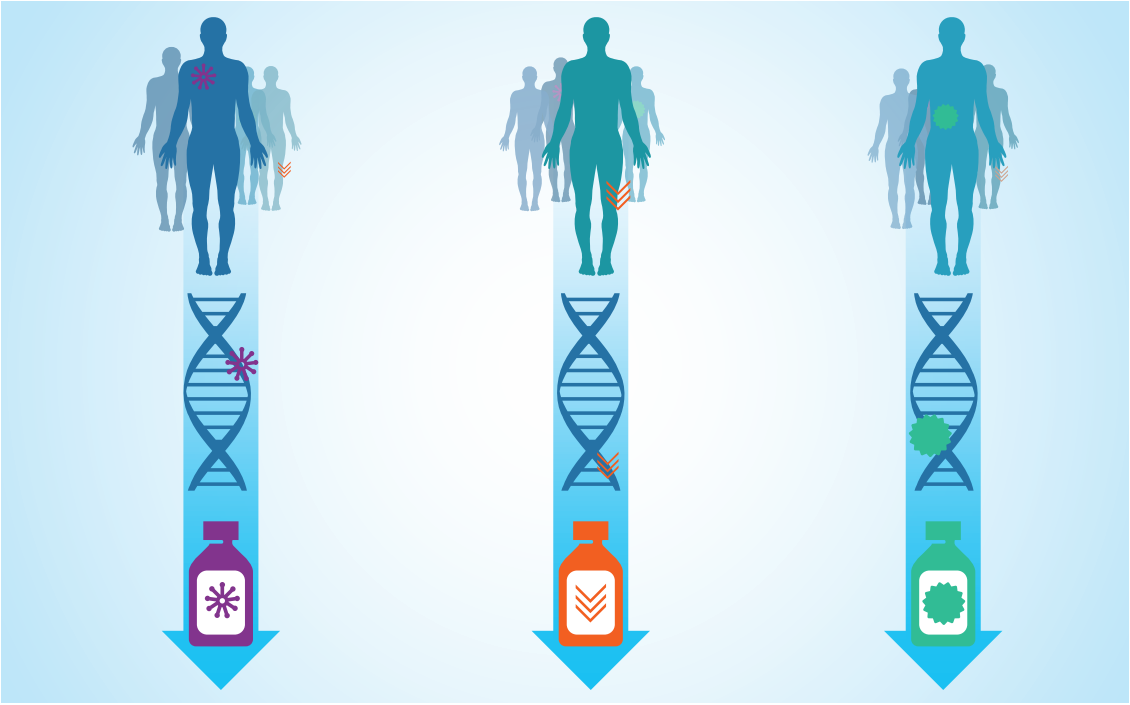
This pilot aims to develop processing tools for analyzing many different sets of medical records. Powerful machine-learning tools will search the data for patterns of how genetics, environment, lifestyle, and quality of health affect the progression, recurrence, and survival of cancers. The data include patient characteristics, pathology reports, specific treatment, survival, and cause of death. Since clinical text varies in writing style and expression, algorithmic development will focus on advanced machine-learning and deep-learning techniques to extract relevant features from clinical reports. In particular, investigators will be implementing natural-language processing, which enables computers to derive meaning from reports written in human languages. The machine-learning approaches could also be augmented with genomic data, images, and medical claims.

The results will help scientists improve cancer care at various levels—individuals, an entire population, or subgroups where there may be disparities in outcome. Investigators plan to produce an unprecedented predictive simulation capability. "We want to obtain a deeper understanding of cancer drivers and outcomes in the population," says Wasson. "We'll be looking at how different cancers respond to the same treatment and how a single type of cancer responds to different treatments." He says the long-term goal is to support personalized therapies, as part of the Precision Medicine Initiative. "We want to provide oncologists greater confidence when they recommend a particular treatment based on the type of cancer and the individual. We don't know what we will discover," says Wasson. The pilot program is also expected to advance machine-learning algorithms and scalable deep-learning tools for CORAL-class supercomputers and exascale-computing platforms (see box on p. 8) to permit efficient analysis of the millions of records expected annually in the cancer surveillance program.

Partnerships Are Critical to Success

The expected collaborations between biomedical researchers and clinicians and HPC teams will likely change the culture of medical research, according to Brase. "You need a big team to write codes and validate them," he observes. This approach points to the philosophy of E. O. Lawrence, who more than 60 years ago invented "team science," the proven concept of assembling a highly focused team of investigators from different disciplines to achieve a common, often difficult, goal.

Streitz predicts that as the value of HPC to cancer research becomes more evident, collaborations aimed at helping overcome medical challenges will become an increasingly important aspect



As depicted in this graphic, the goal of the Precision Medicine Initiative is to help physicians choose the best cancer treatment for patients by taking into account the individual variability in their genes, the microbes in and on their bodies, and their physical environment, health history, lifestyle, and diet. (Image courtesy of the National Cancer Institute.)

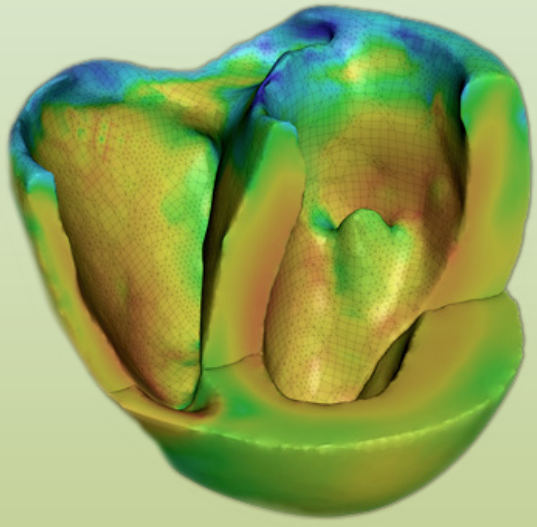
"Home-Grown" Efforts Thrive at Livermore

While the DOE–NCI programs are getting started, a number of internally funded projects are already underway at Livermore to build HPC capabilities across an increasing number of disciplines. The following three efforts are funded by the Laboratory Directed Research and Development (LDRD) Program, Livermore's single most important internal funding resource for fostering innovative science and technology.

Jonathan Allen leads an LDRD project, in collaboration with Argonne National Laboratory, the University of Chicago, and other research groups. Allen's team is working to predict the potential for hospital patients in intensive care units (ICUs) to develop antibiotic-resistant infections, a serious problem that has resulted from overuse of antibiotics. Some drug-resistant bacteria survive these treatments or mutate to become resistant, transforming simple diseases into killers. Allen's group has been studying collections of microbial genomes identified as resistant or susceptible to antibiotics to develop a predictive model of which ICU patients will become susceptible. The group's methods search massive amounts of genomic data to recognize important biological features, leading to better predictions of pathogen emergence. The team is developing an analytic framework for storing and searching terabytes (1 trillion or 10^{12} bytes) of genomic data and metadata.

Principal investigator Todd Wasson is working with the Research Division at Kaiser Permanente in Oakland, California, to predict the onset of sepsis in hospitalized patients. Sepsis is the body's overwhelming response to an infection, leading to potential tissue damage, organ failure, and death. Sepsis, which occurs in 1–2 percent of all hospitalized patients and 25 percent of ICU patients, is the most common cause of death in hospitalized patients. Early detection (and, ideally, prediction) is vital because the earlier the onset of sepsis is detected, the better the possible outcomes. Wasson is building a predictive model of sepsis occurrence by using patient data—for example, blood pressure, temperature, and medication—to determine whether the patient might enter a septic state while hospitalized. "The data are not massive but extremely variable and complex because people are heterogeneous and complicated," he observes.

A third LDRD-funded project, led by Sergio Wong, is aimed at enhancing Cardioid, the world's most detailed model of the electrophysiology of the human heart. (See *S&TR*, September 2012, pp. 22–25.) Developed in partnership with IBM, the code depicts the activation of each heart muscle cell and the cell-to-cell voltage transfer of up to 3 billion cells. It does so in near-real time and with unprecedented accuracy and resolution. For the first time, scientists are seeing how potentially fatal arrhythmias develop and are influenced by the administration of drugs and medical devices.



Cardioid is the world's most detailed simulation of the human heart in action and an example of high-performance computing applied to human health. The highly scalable code replicates the heart's electrical system, depicting the activation of each heart muscle cell in near-real time and with accuracy and resolution previously unavailable.

of Livermore's research portfolio. He observes that connecting the computational resources of DOE national laboratories to life-sciences projects may also help in developing responses to drug-resistant microbes, the ever-changing threat of bioterrorism, the intractability of other complex diseases in addition to cancer, and the rising cost of new pharmaceuticals. He emphasizes, "But we'll always need partners such as NCI to make the progress needed in these fields." With the help of HPC and the dedication of hundreds of scientists, doctors, and researchers, the scourge of cancer may, one day, have a cure.

—Arnie Heller

Key Words: bioinformatics; cancer; Cancer Moonshot Initiative; Cardioid; Collaboration of Oak Ridge, Argonne, and Livermore (CORAL); exascale; high-performance computing (HPC); High Performance Computing Innovation Center (HPCIC); Livermore Metagenomic Analysis Toolkit (LMAT); National Cancer Institute (NCI); Precision Medicine Initiative; RAS protein; Surveillance Epidemiology and End Results (SEER).

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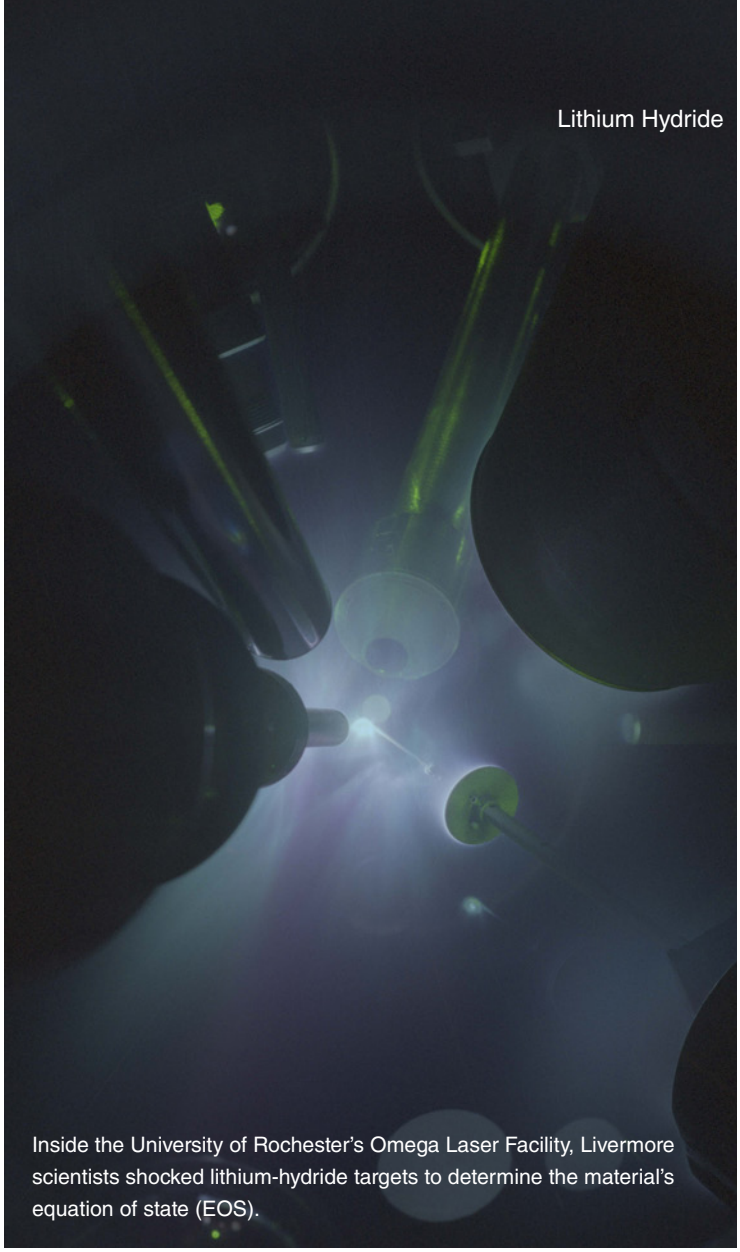
NEW INSIGHT INTO AN INTRIGUING MATERIAL

EXPERIMENT and simulation are two of the most powerful tools in a scientist's toolbox for delving into the mysteries of material properties. Recently, this formidable combination proved key to solving a conundrum about lithium hydride, the lightest ionic chemical compound.

For decades, modeling the equation of state (EOS) of materials at extreme conditions has presented a challenge to scientists. The EOS of a material describes the relationship between the thermodynamic conditions of pressure, density, and temperature, and under what set of these conditions the material changes from one phase (solid, liquid, or gas) to another. Previous experimental data for lithium hydride was limited, consisting of measurements from gas-gun experiments and three data points at higher pressures gathered from underground nuclear tests conducted many years ago.

The material, which has the smallest number of electrons for a chemical compound, has also proved difficult to simulate using theoretical models. "Various theoretical approximations predicted widely different equations of state at high pressures," explains Heather Whitley, a program coordinator for a two-year-long research effort focused on lithium hydride. "Because lithium hydride's constituent atoms are so light, the material is particularly sensitive to quantum effects. In addition, EOS models tend to differ in their treatment of the material's electrons, and few experimental constraints existed on the models at high pressure. These model discrepancies motivated us to investigate lithium hydride in more detail."

Lithium hydride is an interesting material for several reasons. With the highest hydrogen content of any hydride, it has potential applications for hydrogen storage and is a good material for shielding nuclear reactors. It also provides a useful benchmark for theoretical models of material, given the small number of electrons per atom in the system. Livermore physicists worked with collaborators at Sandia National Laboratories in Albuquerque, New Mexico, to more accurately constrain which EOS models for lithium hydride work best over a wide range of temperatures and pressures, opening the door to its potential use in numerous applications.



Inside the University of Rochester's Omega Laser Facility, Livermore scientists shocked lithium-hydride targets to determine the material's equation of state (EOS).

Hit It, Hit It Hard

Livermore physicist Amy Jenei, who led the experimental portion of the project, conducted the research at the University of Rochester's Omega Laser Facility in Rochester, New York. In a series of experiments, a small disk of lithium hydride was subjected to laser-generated shock waves, which hit the target material with supersonic velocity, taking the material to a new thermodynamic state with higher pressure, density, and temperature.

The series of experiments allowed the team to plot a set of high-pressure, high-density states—called a Hugoniot curve—for the material. Although the lithium hydride Hugoniot had been previously predicted using a variety of simplified computer models to describe its thermodynamic state, experimental data were sparse, and the three pre-existing highest pressure measurements, taken at pressures just above 10 megabars (1 megabar is the pressure of 1 million atmospheres, or 100 pascals), had substantial uncertainties. Jenei explains, "My job was to design lithium hydride targets, subject them to shock experiments at Omega, and obtain more reliable Hugoniot measurements that the modelers could have confidence in."

The challenge, Jenei adds, was not so much with the experiments themselves, which were conducted with an established technique, but in working with the air-sensitive material. Lithium

Physicist Amy Jenei assembles a lithium-hydride target inside a glovebox to protect the air-sensitive, hygroscopic material from contamination. (Photo by Randy Wong.)

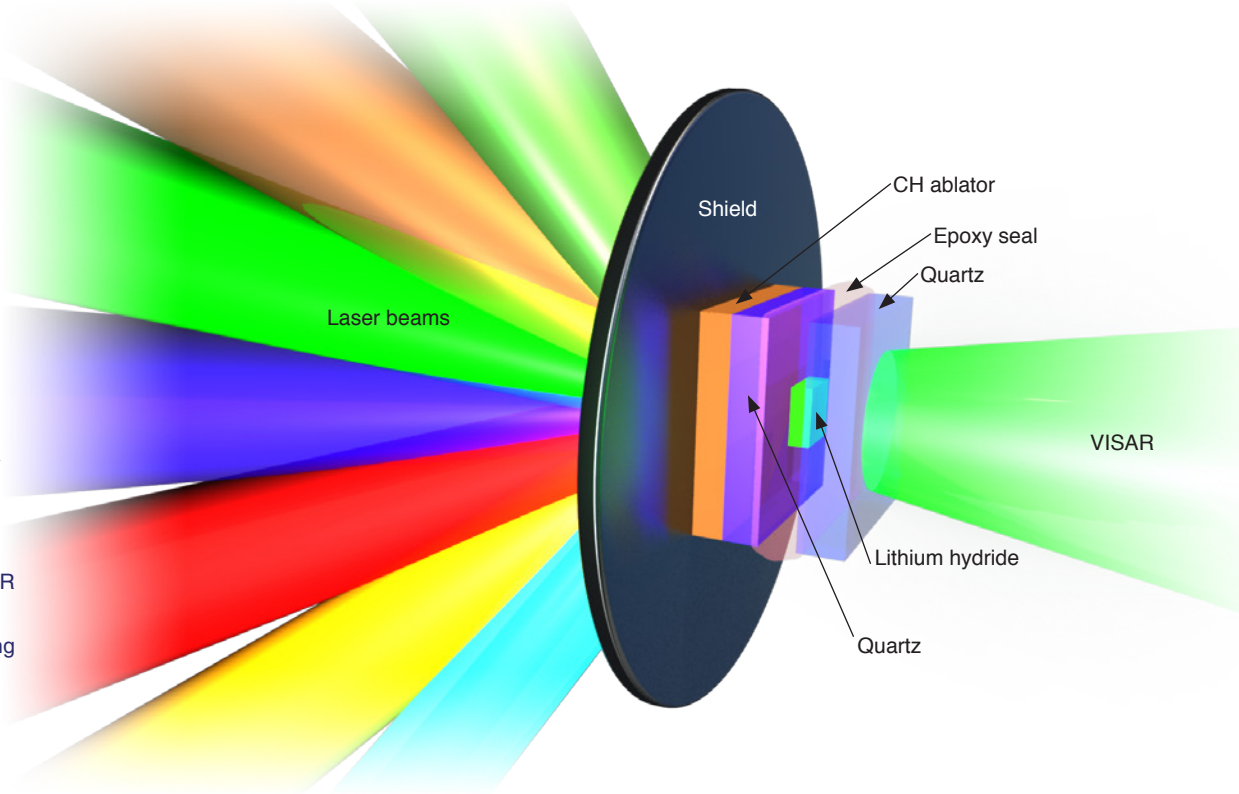
hydride is extremely hygroscopic—it reacts with moisture, which made it tricky to design and fabricate the targets and to ensure their integrity. After exploring different target designs for her experiments, Jenei decided on two. One design featured a disk of lithium hydride sandwiched between quartz plates, with the lithium hydride encased in mineral oil, containing a minimum amount of dissolved water, and epoxy. For the second design, the lithium-hydride disk was compressed to a few kilobars in a pressure cell, together with a thin quartz disk. "The quartz equation of state is well known from previous experiments, so we used it as a reference to determine the equation of state of lithium hydride," says Jenei.

The targets were driven to high pressure using up to 12 beams from the Omega laser, with pulses 1 to 1.6 nanoseconds in length and energies of 400 to 500 joules per beam. The laser energy created a shock in the quartz, which then passed into the lithium hydride. The velocity of the shock front as it passed through these materials was measured continuously using interferometry. In this study, measurements of the pressure, density, and temperature along the principal Hugoniot (the set of states reached in a single shock from ambient conditions) were extended up to 11 megabars. In the experiments with the target sandwiched between two quartz plates, the experimentalists gathered data for higher shock pressures as well, since the front end of the shock wave "rebounded" off the rear quartz, launching a second shock back into the already-compressed lithium hydride and generating even higher pressures. This measurement extended the secondary Hugoniot up to 13.8 megabars.

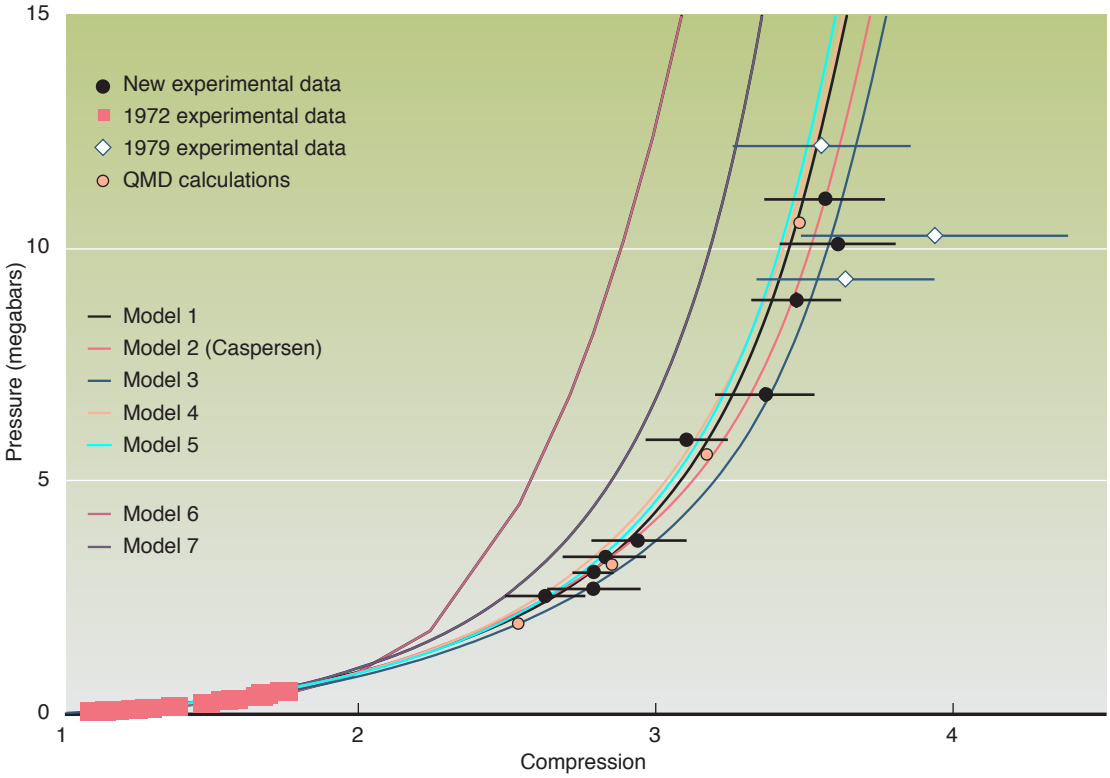
Taking It from First Principles

Theorists create models of what processes occur in materials under various thermodynamic conditions, working with "first principles" computer codes, called ab initio codes. Such codes calculate material properties based on the fundamental laws of physics. Results from the ab initio simulations are often used to define EOS models. The theoretical team, which included James Gaffney, Miguel Morales, Brian Wilson, and Jonathan Dubois, applied various methods to compute the thermodynamic properties of lithium hydride and investigate the validity of existing EOS models.

"To make the physics equations more tractable and solvable, physicists have to make educated approximations or assumptions. These approximations generally set a region of temperatures and densities where a given method is believed to be accurate," says Whitley. "We wanted to examine how various approximations affect the resulting thermodynamic properties so that we could determine



During an EOS experiment, Omega's intense laser beams ablate polystyrene (CH) to launch a shock in the quartz, which then passes into the lithium hydride. The pressure and particle velocity are continuous across the quartz–lithium-hydride boundary. In this "sandwich" design, the shock also passes from the sample into the back quartz plate, creating a second shock from the back plate into the sample and yielding higher pressures. Shock velocities were determined using a VISAR (velocity interferometer for any reflector) diagnostic. (Rendering by Adam Connell.)



This graph shows the Livermore team's new experimental results (black dots) compared to previously acquired data (red squares and blue diamonds), ab initio quantum molecular dynamics (QMD) calculations (orange dots), and several models of lithium-hydride's EOS. Models 1 through 5, including the one developed by Livermore's Kyle Caspersen, track well with the experimental results.

which existing EOS models were reasonable. This investigation also provided high-quality simulation data for developing new models."

The team compared four different ab initio codes—including ones based on quantum molecular dynamics—each of which takes a different approach to the problem. "Each code has different strengths when addressing equations of state for various regimes of temperature and pressure. Taken together, we could compare results over a broad range of existing models," says Whitley. In addition, the codes provided constraints, from which a new, more accurate EOS model could be built, a task that was undertaken by Livermore's Kyle Caspersen.

The team's anlysis showed that some models, including the one developed by Caspersen, clearly yielded results in better agreement with the Omega experimental data. Thus, the researchers are confident that they now have a good model for determining lithium hydride's EOS over the principal Hugoniot up to 11 megabars.

A Number of Firsts

Lawrence Livermore's counterparts at Sandia conducted similar exercises in both theory and experiment. The institution collaborated with Jenei to use Sandia's Z machine for compressing lithium-hydride targets to high pressures with intense magnetic fields. The results generated by Sandia's theoretical models matched those from Livermore. Whitley and her colleagues were very pleased. She says, "Through experiment and simulation, we resolved the major differences between EOS models."

The team's success has even greater implications. "To the best of my knowledge, this work is the first time in which the four ab initio calculation methods were compared at such a high level of detail," says Whitley. "It's also the first time this many ab initio methods have contributed directly to an EOS model that could then be compared to detailed experimental data. It was a procedure that worked well for lithium hydride, and could be applied to other materials."

Looking toward the future, the team plans to use the powerful laser beams at Lawrence Livermore's National Ignition Facility to shock lithium hydride to even higher pressures and test the EOS models in regimes beyond those available in past underground tests. These studies could bring about shocking—and intriguing—developments, to be sure.

—Ann Parker

Key Words: ab initio code, equation of state (EOS), Hugoniot curve, lithium hydride, National Ignition Facility, Omega Laser Facility, Z machine.

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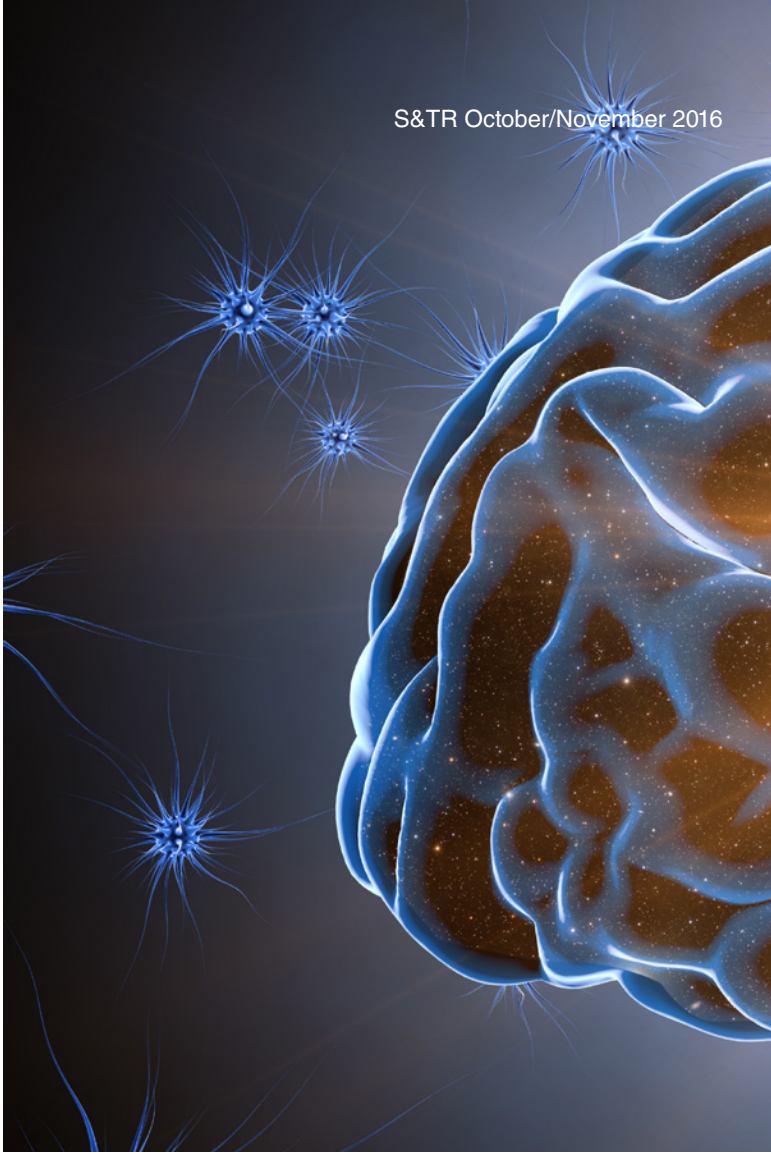
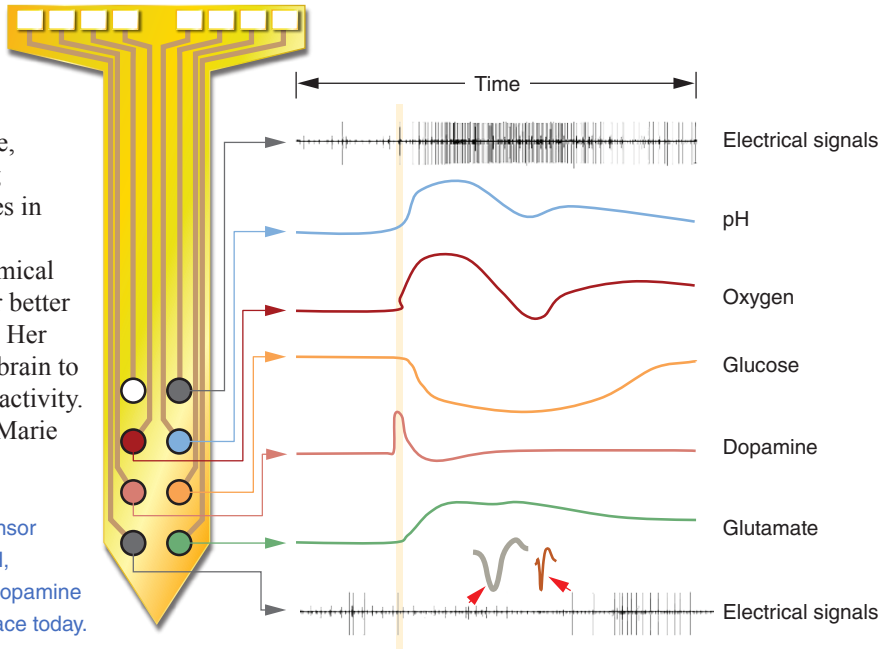
Peering into the Brain with Chemical Biosensors



THE human brain is a biological marvel that, when functioning properly, allows people to survive in endlessly changing environments, engage in complex behaviors, and live full and productive lives. Scientists estimate that the brain consists of between 80 and 100 billion neurons, with as many as 100 trillion interconnections among them. Impressively, more than 100 types of chemicals called neurotransmitters carry signals across these interconnections from one neuron to another, enabling the human body to carry out its requisite tasks.

For as much as scientists know about the brain and its sophisticated workings, many more aspects of this impressive organ remain a mystery. Measuring biochemical changes within the brain, for example, is slow and difficult. In fact, no tools exist today that allow scientists to continuously measure real-time changes in neurotransmitters, or most other chemicals in the body, for extended lengths of time. Yet research on conditions such as Parkinson's disease, chronic depression, post-traumatic stress disorder, and drug addiction suggests that their causes are related to imbalances in neurotransmitter production and behavior.

A group of researchers, led by Lawrence Livermore chemical engineer Vanessa Tolosa, is working to address the need for better technologies to study the chemical fluctuations in the body. Her team is developing biosensors that can be implanted in the brain to measure neurotransmitters as well as other signals of brain activity. In addition to Tolosa, the team includes Livermore's Anna Marie



Livermore researchers are developing a real-time biocompatible sensor array capable of simultaneously measuring several biomarkers—pH, oxygen, glucose, electrical activity, and neurotransmitters such as dopamine and glutamate—in the brain. No such sensor exists in the marketplace today.

Belle, Allison Yorita, Anna Ivanovskaya, Jeanie Pebbles, Supin Chen, Brian Baker, and Shalini Mabery, as well as collaborators from Aqua Regenerative Therapies, LLC, and the University of Illinois at Urbana–Champaign.

The work, funded by the Laboratory Directed Research and Development Program, could result in a powerful new tool for scientists to explore the etiology of brain diseases and a real-time monitoring capability for patients to manage their health conditions and adjust their treatment to match their brain activity. Biosensor implants could also open the door to groundbreaking treatments that target specific organs in the body while leaving the rest untouched. Such sensors could also provide an alternative to pharmaceuticals, which circulate throughout the entire body, increasing the risk of side effects.

One Sensor, Many Measurements

"More than 500 quadrillion chemical reactions happen in our bodies every day," says Tolosa, "across all size scales, from the single-cell level to the multi-organ level." Many diagnostic technologies, such as electrocardiography and electroencephalography, can record the body's electrical signals in real time through external sensors attached to a patient's skin. However, sensors that measure continuous, real-time chemical changes are much more difficult to engineer because they must be implanted in the body's internal tissues. Eventually the body rejects the sensor as a foreign object—a biologically incompatible material—limiting the device's lifetime.

Glucose sensors for diabetics are the most advanced real-time chemical monitoring system on the market (and the only sensors produced on a large scale), but they last only seven days before the body's defense mechanisms render the sensors ineffective and they must be replaced. Tolosa says, "Our goal is to develop continuous, real-time, biocompatible sensors that can measure multiple biomarkers on a single platform and that will last considerably longer than today's commercially available sensors." The team's sensor will be able to simultaneously measure physiological changes such as pH; oxygen level; glucose; electrical activity; and neurotransmitters, including

dopamine and glutamate, which are indicators of a person's ability and motivation to learn and form memories.

Previous work by Tolosa and others in Livermore's Neural Technologies Group has led Laboratory researchers to develop flexible, polymer-based implants capable of recording electrical signals in the brain and providing deep brain stimulation to help treat neural disorders such as depression. Lawrence Livermore makes these custom-built devices in-house, using the same photolithographic process that the electronics industry uses to manufacture integrated circuits. Tolosa's group is building on this past success by incorporating biosensor sites on the implant that can record chemical changes, as well. Biochemical indicators on the sensors react with the target chemical to produce a measurable signal.

Neurotransmitters are Unique

In her laboratory, chemist and postdoctoral scholar Anna Marie Belle is custom-building, testing, and characterizing biosensor prototypes. Detecting the target neurotransmitter requires establishing its specific electrochemical signature. Some important neurotransmitters are non-electroactive, meaning they do not have electrochemical signatures. To be detected, these neurotransmitters, the most common being glutamate, must react chemically with other molecules deposited within the biosensor. As part of the device testing process, Belle uses an enzyme known to react exclusively with glutamate to produce hydrogen peroxide. The hydrogen peroxide then reacts electrochemically with the sensor to release an electron whose signal is detected, amplified, and recorded by the sensor. More electron detections mean a higher glutamate level.

Belle can also detect other common non-electroactive neurotransmitters, such as choline and acetylcholine, by depositing enzymes specific to each neurotransmitter onto the implant's sensor sites. "This new platform is generic enough that all we have to do is switch out the enzyme," says Belle. For electroactive neurotransmitters such as norepinephrine and dopamine, Belle and other team members are experimenting with polymer coatings whose porosity allows the target chemical to pass through the coating and generate a signal at the sensor's electrode while filtering out all other neurotransmitters.

Livermore chemist Anna Marie Belle holds a sample case of chemical biosensors she fabricated for measuring neurotransmitters in the brain. (Photo by Randy Wong.)

Biosensors Have Potential

The team has tested their biosensor prototypes in animal brains and on iCHIP (in vitro chip-based human investigational platform), a silicon-based platform developed at Livermore that mimics several biological systems of a human body. (See *S&TR*, March 2014, pp. 16–19.) Currently, Belle is characterizing glutamate sensors—studying their responsiveness and lifetime in vivo and proving that the device selectively measures glutamate and not chemical artifacts. The tests are done by surgically implanting these biosensors into the brains of live rats, then recording and analyzing sensor signals several times a day over a period of days using a measurement platform that Belle developed. These biosensors detect very small, localized changes in glutamate concentration, providing far more data than current diagnostic techniques.

Belle's preliminary analysis of the data will help determine the efficacy, accuracy, and endurance of the prototype devices. Eventually, scientists will be able to use these advanced sensors to answer questions such as: how do the concentrations of neurotransmitters change as animals (and, eventually, humans) engage in various activities? How do stimuli and neurotransmitter measurements correlate in normal brains compared with those suffering from disease; drug addiction; post-traumatic stress disorder; or deep, chronic depression?

In addition, chemical biosensors may play a role in developing electroceuticals—bioelectronics medicine. Livermore has unique capabilities in protein engineering, biocompatible materials, advanced manufacturing, sensor development, and computational modeling that are poised to place the Laboratory at the forefront of this new area of biomedical research. "No one knows why electroceuticals work," says Tolosa. "What's missing is a way to monitor organs and the changes in neurotransmitter release and other chemicals during nerve stimulation." Although in its early stages of development, the Livermore biosensor could one day help reveal the root causes of various diseases and provide advanced treatments, allowing more people to live full and productive lives.

—Allan Chen

Key Words: acetylcholine, biosensor, brain, depression, dopamine, electroceutical, glucose, glutamate, iCHIP (in vitro chip-based human investigational platform), neurochemistry, neuron, neurotransmitter, pharmaceutical, post-traumatic stress disorder, serotonin.

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Biosensor prototypes have been tested on Livermore's iCHIP (in vitro chip-based human investigational platform)—a miniature external replication of the human body, integrating biology and engineering with a combination of microfluidics and multielectrode arrays. (Photo by Julie Russell.)

Rapid Recovery of Critical Infrastructure

AMERICANS take more than 3.5 billion trips on trains, commuter rails, and subways annually. Because public transportation systems have high traffic, expensive infrastructure, central location in large metropolitan areas or near tourist destinations, and economic importance, they could be likely targets for a terrorist attack.

Many transportation agencies are strengthening their emergency response capabilities to minimize the impact of a chemical, biological, or radiological (CBR) attack and quickly return a system to service. However, the restoration process is complex. First, response teams and laboratories must quickly and accurately collect and analyze hundreds to thousands of samples so they can identify the type of threat agent released and determine the extent of contamination. This phase of the process must then be followed by characterization of the agent, decontamination, and clearance before the system can be reoccupied.

Livermore has played a key role in several projects related to recovering critical infrastructure in the event of a CBR attack. (See *S&TR*, December 2006, pp. 10–12.) Funded by the Department of Homeland Security's Science and Technology Directorate, Livermore has recently been supporting an

Underground Transport Restoration (UTR) project to streamline the necessary steps for quickly responding to, remediating, and restoring an underground transportation system. The multilaboratory effort, which also includes Argonne, Sandia, Lawrence Berkeley, and Pacific Northwest national laboratories, as well as the Massachusetts Institute of Technology's (MIT's) Lincoln Laboratory, the Environmental Protection Agency (EPA), Bay Area Rapid Transit (BART), and New York City Transit (NYCT), focused on a simulated release of *Bacillus anthracis* (the bacterium that causes anthrax) using a surrogate material. The anthrax bacterium was chosen because its spores are surrounded by a tough outer shell that make the pathogen one of the most difficult biological agents to inactivate.

The information from this project is being compiled in a first-ever Web-based tool that guides response and recovery personnel through a step-by-step decision tree for bringing the affected transportation system back to full service. To develop the UTR decision framework, the Livermore team, led by Ellen Raber, builds on past experience developing CBR recovery plans and exploits expertise from both the scientific and operations areas at the Laboratory. "I hope all U.S. underground transportation systems—and potentially international systems—can use this framework as an emergency management tool," says Raber. "Users would have all the information they need compiled in one place prior to and during an emergency."

Surrogate Provides Insight

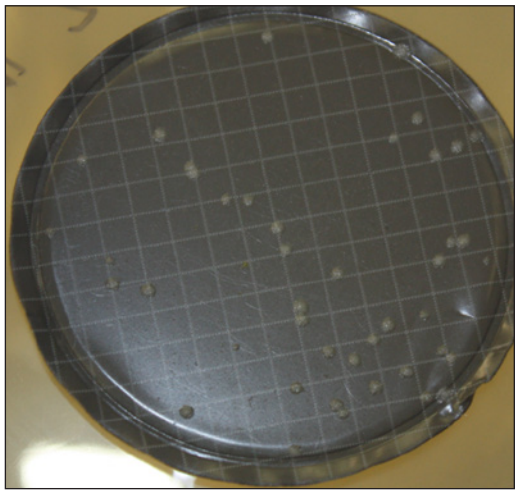
The UTR team is collaborating with transportation groups and supporting federal, state, and local regulatory agencies to develop the most rapid and efficient return-to-service strategy possible. Workshops, experiments, and technology demonstrations conducted with these key collaborators have permitted the team to gain specialized knowledge to optimize the recovery strategy. Environmental engineer Sal Mancieri has been responsible for overall coordination among the stakeholders.

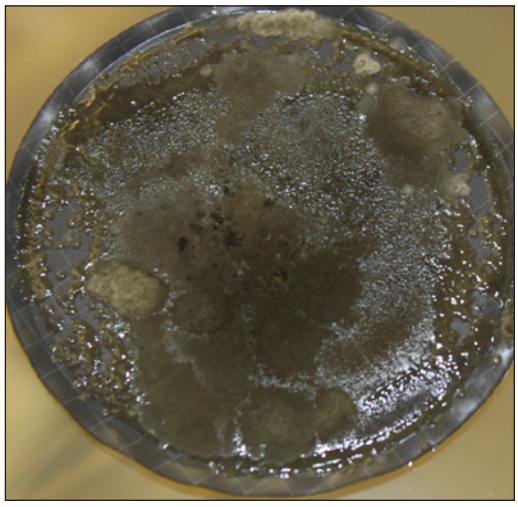
One such experiment in the New York City subway examined how a surrogate for *B. anthracis* might disperse throughout the nation's largest rapid transit system as a result of a terrorist attack. The Livermore team, led by chemical engineer Elizabeth Wheeler, designed the surrogate material, which was based on the Laboratory's patented DNA-tagged reagents for aerosol experiments (DNATrax). (See *S&TR*, October/November 2013, pp. 4–5.) DNATrax combines food additives approved by the U.S. Food and Drug Administration and unique nonviable DNA bar codes to produce microparticles that simulate biological threats in aerosol form. The UTR team also developed protocols and techniques for analyzing the subway samples and participated in the field experiments.

The field exercises, led by Argonne and MIT's Lincoln Laboratory, provided the UTR team with insight into dispersion and contamination pathways that allowed the researchers to develop options for quickly determining the extent of contamination and preventing further spread. These data, combined with models and simulations created and run by Argonne, provide transit agencies and response organizations with better tools for pre-planning and for optimizing characterization approaches in the event of an actual biological attack. This information is critical to developing the rapid return-to-service strategy.

Improved Sampling Processes

Recovery of an underground transportation system has six distinct phases: notification, first response, characterization, decontamination, clearance, and reoccupancy. Each of these phases is addressed in the UTR decision framework, which underlies the Web-based tool. Typically, trained personnel begin by immediately collecting samples from the air and surfaces in specified areas. Sample analysis assists in defining the extent of contamination and the biological attributes of the agent, including particle size, spore concentration, and viability. Event characterization helps evaluate the possible health risks and establish emergency measures and containment options.





(top) When target spores are added to clean samples, they prduce clear, distinct microbial colonies that are easy to analyze and identify. (bottom) When the same amount of spores are added to samples taken from a grimy, metal-contaminated environment, target colonies are difficult to distinguish from "background" microbial growth.

Minimizing the number of samples needed is key to reducing recovery time. The samples are typically cultured to detect target cell growth, an indication of whether live pathogens are still present. Pathogen colonies that develop must be confirmed by polymerase chain reaction (PCR) or other methods, increasing analysis time. Such anlyses typically take between 36 and 72 hours for confirmed results.

The Livermore team has identified key challenges when analyzing samples taken from grimy, urban environments. When microbes are extracted from a sample for culturing, residues and materials inherent in the environment, including other bacteria, are extracted, too. These bacteria also grow during incubation, potentially interfering with the growth and identification of the target bacteria colonies.

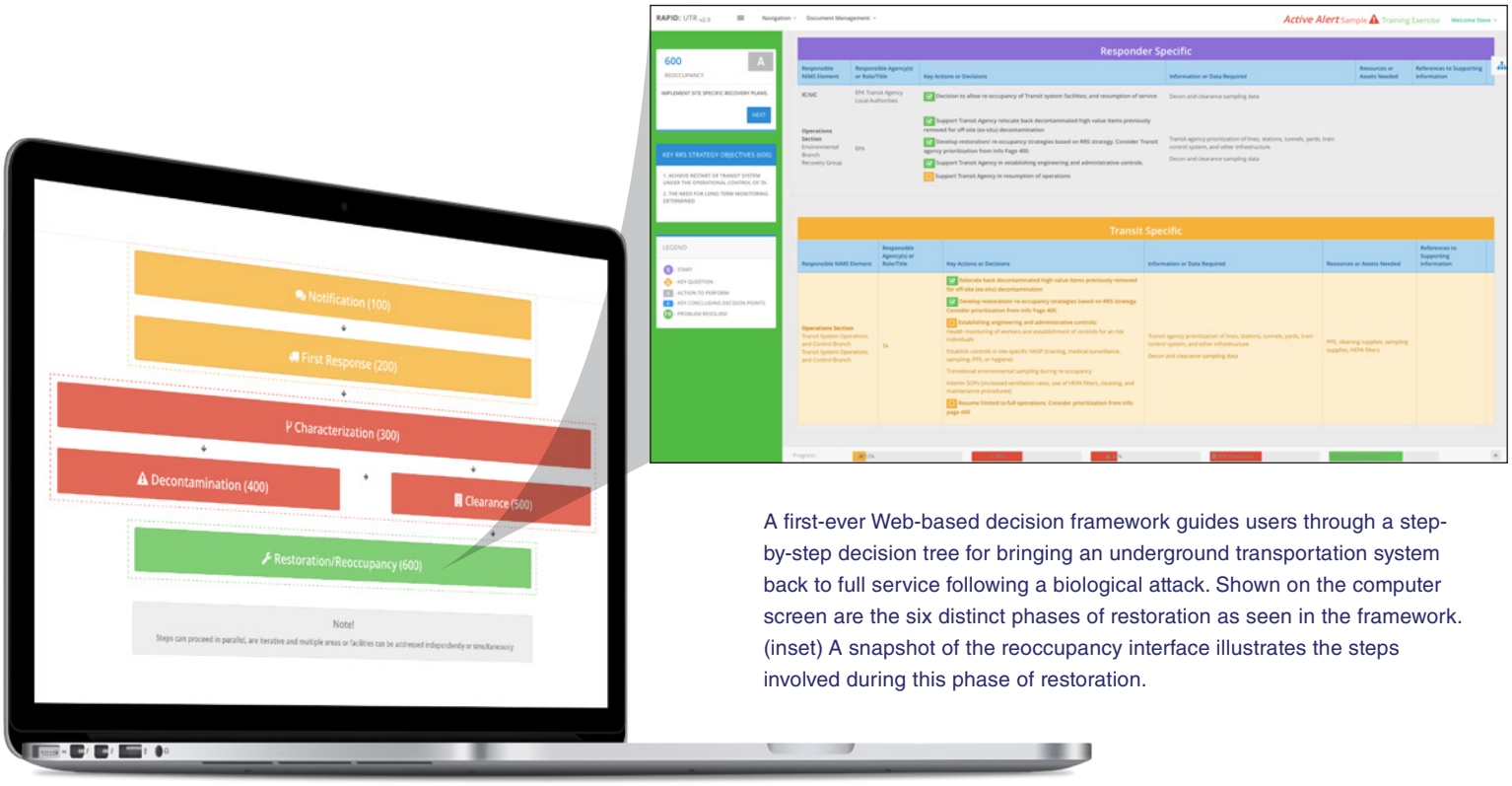
To save time, increase throughput, and achieve greater accuracy, the Livermore team has adapted the Laboratory-developed rapid viability PCR (RV-PCR) technique to work on samples collected from metal-laden environments. RV-PCR is a semi-automated procedure that uses the change in PCR response during a short, 9-hour culture process to detect viable spores or cells. (See *S&TR*, September 2010, pp. 16–19.)

Microbiologist Staci Kane led the effort to adapt the RV-PCR method for subway samples by increasing the culture volume and modifying the PCR conditions. The PCR process uses an enzyme to replicate and increase the amount of target bacterial DNA in a sample. The Livermore team added an extra PCR enzyme to overcome inhibition resulting from grime in the environment and better amplify the target DNA, thus reducing false-negative results. Once the biological threat is characterized, the most effective decontamination methods can be selected.

Neutralizing the Threat

Each of the five primary components of an underground transportation system—subway cars, control and support facilities, tunnels, yards, and stations—require a different decontamination approach because of the varying materials and assets in each area. Possible decontamination solutions for biological threats include oxidizers (such as hydrogen peroxide or chlorine dioxide), pH-amended bleach or dichlor, and methyl bromide (a colorless, odorless, nonflammable gas, used as a fumigant). For this project, EPA, along with Sandia National Laboratories, led laboratory and field evaluations to determine which decontamination process recommendations will be incorporated into the final decision framework.

Standardized decontamination methods for *B. anthracis* spores use corrosive oxidizers that can penetrate the bacterium's spore



A first-ever Web-based decision framework guides users through a step-by-step decision tree for bringing an underground transportation system back to full service following a biological attack. Shown on the computer screen are the six distinct phases of restoration as seen in the framework. (inset) A snapshot of the reoccupancy interface illustrates the steps involved during this phase of restoration.

coat and prevent germination and outgrowth. However, oxidizers can cause corrosion, compromising assets such as vents, pipes, and electronic components. As a result, this approach can be intrusive, costly, and labor intensive. Methyl bromide (once used to eliminate pests and termites for home fumigation) is a more effective, noncorrosive gas for eradicating bacterial spores, but the chemical is known to deplete Earth's ozone and is strictly regulated. Recently, an activated-charcoal filtration system was developed to collect methyl bromide after its release, so this gas is now a potential option for disinfecting corrosion-sensitive areas—cars and control rooms, for example—affected by *B. anthracis* spores. The UTR team is considering using liquid, gel, or fog-based oxidizers for decontaminating tunnel walls and train stations, since the areas are so large and the environments do not lend themselves to the gas approach. Decontaminants such as pH-amended bleach—a neutral pH solution—can be used as less corrosive, yet effective options.

Speedy Restoration Realized

The UTR decision framework tool aligns with the National Incident Management System—a guide that identifies a common incident management structure for agencies responding to national emergencies, including CBR attacks. Livermore will continue building on the framework to prepare site-specific biological response plans for the NYCT and BART systems, which will be the most comprehensive recovery plans to date.

"We hope that being prepared for CBR attacks is in itself a form of deterrent," says Bob Fischer, a Livermore UTR team member and environmental scientist who leads development of the Web application. "By having the capability to rapidly restore service, we will have reduced the effects of such an attack, if one were to occur."

—Lanie L. Helms

Key Words: anthrax; *Bacillus anthracis*; Bay Area Rapid Transit (BART); chemical, biological, or radiological (CBR); DNA-tagged reagents for aerosol experiments (DNATrax); methyl bromide; New York City Transit (NYCT); rapid viability polymerase chain reaction (RV-PCR); Underground Transport Restoration (UTR).

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Patents and Awards

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. For the full text of a patent, enter the seven-digit number in the search box at the U.S. Patent and Trademark Office's website (http://www.uspto.gov).

Patents

Iron-Based Amorphous Alloys and Methods of Synthesizing Iron-Based Amorphous Alloys
Cheng Kiong Saw, William A. Bauer, Jor-Shan Choi, Dan Day, Joseph C. Farmer
U.S. Patent 9,328,404 B2
May 3, 2016

Fluidics Platform and Method for Sample Preparation
W. Henry Benner, John M. Dzenitis
U.S. Patent 9,372,135 B1
June 21, 2016

Resonant Optical Transducers for In-Situ Gas Detection
Tiziana C. Bond, Garrett Cole, Lynford Goddard
U.S. Patent 9,377,399 B2
June 28, 2016

Mechanically Robust, Electrically Conductive Ultralow-Density Carbon Nanotube-Based Aerogels
Marcus A. Worsley, Theodore F. Baumann, Joe H. Satcher, Jr.
U.S. Patent 9,384,870 B2
July 5, 2016

Embedded-Monolith Armor
Michael W. McElfresh, Scott E. Groves, Mitchell L. Moffet, Louis P. Martin
U.S. Patent 9,395,159 B2
July 19, 2016

Nanoscale Structures on Optical Fiber for Surface Enhanced Raman Scattering and Methods Related Thereto
Xuan Yang, Tiziana C. Bond, Jerald Britten, Thomas C. Carlson, Nazar Ileri, Cindy Larson, Claire Gu
U.S. Patent 9,395,304 B2
July 19, 2016

Flexible Neural Interfaces with Integrated Stiffening Shank
Angela C. Tooker, Sarah H. Felix, Satinderpall S. Pannu, Kedar G. Shah, Heeral Sheth, Vanessa Tolosa
U.S. Patent 9,399,128 B2
July 26, 2016

Chip-Based Device for Parallel Sorting, Amplification, Detection, and Identification of Nucleic Acid Subsequences
Neil Reginald Beer, Billy W. Colston, Jr.
U.S. Patent 9,409,177 B2
August 9, 2016

Awards

Lawrence Livermore National Laboratory chemist **Dawn Shaughnessy** has been named **No. 9** on ***Fast Company* magazine's** Top 100 Most Creative People in Business for 2016. This year's list spans educators to scientists, jazz saxophonists to startup founders, fashion designers to rappers.

Shaughnessy is the principal investigator within Livermore's Heavy Element Group, where she has worked as a nuclear and radiochemist since 2002. In December 2015, the International Union of Pure and Applied Chemistry added three new elements to the periodic table that had been synthesized by a team of researchers led by Shaughnessy. Partnering with the Joint Institute for Nuclear Research in Russia, the group has discovered five new "superheavy" elements since 2004, bearing the atomic numbers 114 to 118. Element 116, Livermorium, was named after the Laboratory and the city where it resides.

Livermore scientists **Félicie Albert** and **Karis McFarlane** were selected by the **Department of Energy's** (DOE's) **Office of Science Early Career Research Program** (ECRP) to receive $2.5 million each over five years for their proposed research projects. ECRP, now in its seventh year, is designed to bolster the nation's scientific workforce by providing support to exceptional researchers during the crucial early career years, when many scientists do their most formative work. Livermore researchers have won 15 ECRP awards since its inception in 2010.

Albert, an experimental plasma physicist at the National Ignition Facility and expert in ultrafast x-ray sources and laser–plasma interactions, won the award for her work in laser-driven x-ray sources for high-energy-density science experiments. She will explore x-ray sources from laser–plasma accelerators to probe plasmas under extreme temperature and pressure conditions.

Karis McFarlane, a staff scientist at the Center for Accelerator Mass Spectrometry, was awarded a grant to study the impact of climate change on carbon cycling in tropical forests. She plans on joining the Next Generation Ecosystem Experiments-Tropics (NGEE-Tropics) project, headed by Lawrence Berkeley National Laboratory, to gather radiocarbon data on soil and tree roots.

Lawrence Livermore Director **Bill Goldstein** received the **Director of the Year Award** for fiscal year 2015 from the **Department of Energy's Office of Small and Disadvantaged Business Utilization** (OSDBU). Goldstein was honored for encouraging and promoting collaborations with small businesses at the Laboratory. Goldstein is the second annual honoree for this award, which recognizes a national laboratory director for displaying leadership and commitment to maximizing small business utilization through policies, procedures, and outreach, and creating an atmosphere of "small business first" throughout his or her organization.

Abstract

High-Performance Computing Takes Aim at Cancer

A partnership between the Department of Energy (DOE) and the National Cancer Institute (NCI) is aimed at applying the formidable computing resources of Livermore and other DOE national laboratories to advancing cancer research and treatment. Announced in late 2015, the partnership is designed to help researchers better understand the complexity of cancer, choose the best cancer treatment option for every patient, and discover relationships hidden in vast patient and experimental data sets. The DOE–NCI agreement features three pilot programs aimed at improving drug therapy for cancer patients, simulating human RAS genes and proteins to facilitate cancer drug development, and analyzing extremely large NCI databases to optimize cancer therapies. The pilot programs will also identify requirements for future supercomputer architectures and data analytics software. The partnership is a key element of the National Cancer Moonshot Initiative, which seeks to double the rate of progress in the understanding, prevention, diagnosis, and treatment of cancer. The partnership also supports President Barack Obama's Precision Medicine Initiative, which aims to take into account individual variability in genes, microbiomes, environment, health history, lifestyle, and diet to develop more targeted therapies. The agreement is also aligned with the National Strategic Computing Initiative, which is designed to ensure the United States continues leading the world in high-performance computing over the coming decades.

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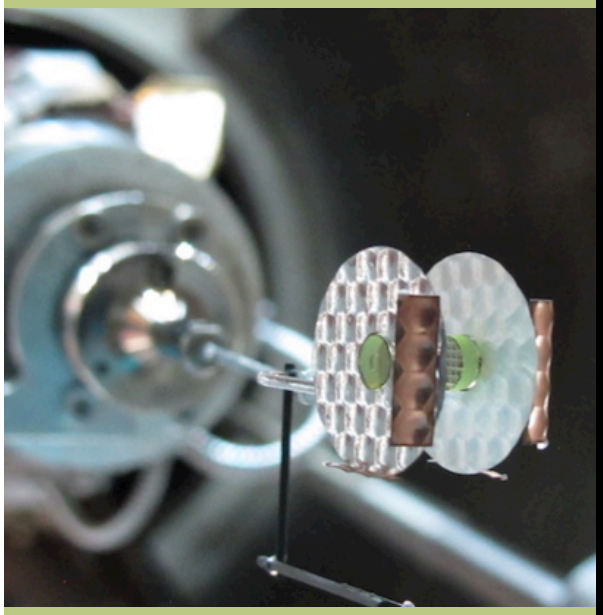
U.S. Government Printing Office: 2017/770-075-10022

Experiments Reveal Mysteries of the Cosmos



The extraordinary high-energy-density conditions produced at the National Ignition Facility allow researchers to study astrophysical phenomena at unprecedented regimes.

Also in December

- *Four new elements officially join the periodic table as a result of a longstanding partnership between Livermore and a research facility in Dubna, Russia.*
- *Computer simulations help scientists explore the complexity of the kinetic impact method for deflecting asteroids.*
- *Carbon nanotubes may be the key to developing protective, breathable clothing that safeguards against hazardous agents.*

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