Lawrence Livermore National Laboratory

Science & Technology Review

October/November 2022

ACCELERATING ALS RESEARCH

Also in this issue:

Understanding Nature's Weak Nuclear Force

Assessing Intact Components

Sheltering from Airborne Hazards

About the Cover

Livermore researchers seek to understand the disease mechanism of amyotrophic lateral sclerosis (ALS) and, with that knowledge, identify therapies to cure this always-fatal disease. As the article beginning on p. 4 describes, the ALS research effort combines Laboratory core competencies in bioscience, engineering, computational modeling, and data science. The cover design represents this integrated effort by embedding computer code (1s and 0s) and a latticework structure (to represent materials science) within the tendrils of the neuron.

Cover design: Alii Diaz Cover artwork: Jake Long

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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October/November 2022

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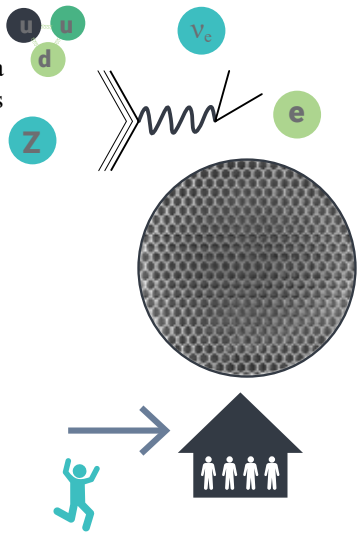
Research Highlights



Departments

Red Dwarf Physics to be Modeled

Red dwarfs represent the majority of stars in our galaxy, yet astrophysicists lack full understanding of the interior physics for this type of star. Heat from hydrogen fusion emanates from a red dwarf's core to its surface; but whether heat transport occurs through radiation (heat transfer through electromagnetic waves), convection (heat transfer by way of fluid currents), or both remains uncertain. Because a star's energy output is primarily determined by its mass, low-mass red dwarfs are relatively cool and dim. The smallest red dwarfs can burn for trillions of years, and energy transport near their surface is dominated by convection. At larger masses, the possibility of a radiative core increases, and energy is dispelled as electromagnetic waves.

In research published August 12, 2022, in *Physics of Plasmas*, Livermore scientists and a group of international researchers proposed an experiment to elucidate the nature of red dwarf interiors. "Understanding radiative properties of complex plasmas within a host star is crucial when judging the possibility of an exoplanet to host life—especially for red dwarfs, where the habitable zone is thought to be relatively close to the star itself due to low surface temperature," says Livermore co-author Tilo Doeppner.

The proposed experiment, to be conducted at the National Ignition Facility, would measure the opacity of dense hydrogen plasma by reducing implosion velocity, creating colder plasmas than necessary for sustained fusion reactions. Findings will help determine which interior regions of the stars are dominated by convective or radiative transport in addition to enhancing models of dense plasma behavior.

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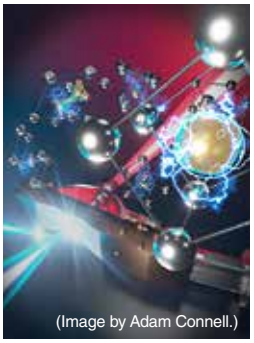
Smaller, Safer Samples for Testing

Studying uncommon, radioactive compounds deepens fundamental understanding of chemical elements and their behavior. With state-of-the-art characterization methods, scientists can perform physicochemical analyses with only milligrams of a substance. However, for the most scarce, unstable, and toxic ingredients, one milligram may outweigh annual production worldwide, posing logistical challenges of high cost and low availability of samples. Livermore scientists collaborated with researchers at Oregon State University to detail a new process for isolating rare, often hazardous, elements for further study. Their work was published on September 1, 2022, in *Nature Chemistry* and was selected as the journal's December cover story.

Led by Livermore's Gauthier Deblonde, the research team synthesized coordination complexes containing rare isotopes to enable detailed characterization of radioactive compounds while using as little as one thousandth the mass previously required. The study demonstrated that polyoxometalates (POMs) can be used to form crystallized metal–ligand complexes with multiple f-block elements, including transplutonium elements. Further, researchers found previously unnoticeable differences between their solution- and solid-state chemistries. The team produced and analyzed three new complexes of curium (a third of all described curium–ligand complexes since the element's discovery) and achieved several new POM complexes with lanthanide elements.


(Image by Adam Connell.)

"The simplicity, efficacy, and modularity of the newly proposed method are astonishing," says Deblonde. "The method significantly decreases the radiation exposure to workers, preserves the nation's isotope resources, and drastically cuts costs." The team's findings could help facilitate investigation of compounds using even rarer materials such as actinium, short-lived metal isotopes, and transcalifornium elements to uncover additional isotopic and bonding trends in a most inaccessible region of the periodic table.

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Extreme Pressure Yields Experimental First

As the world's most energetic laser, the National Ignition Facility (NIF) provides unique opportunities to investigate matter under extreme conditions. In a study published September 19, 2022, in *Nature Physics*, a research team led by Martin Gorman used NIF to observe how solid-state matter reacts to enormous pressures comparable to those of giant planetary cores. Computer simulations had predicted that materials such as magnesium will form novel phases of matter at immense pressures due to quantum mechanical forces beginning to dictate atomic and subatomic interactions. While the predictions shattered traditional understanding of bonding and crystallization, they had not been experimentally verified.

Employing NIF's shaped laser pulses, the team crushed a small sample of magnesium foil with pressure reaching 1.3 terapascals (TPa) to initiate a structural phase transition—an experimental first in the TPa compression regime. "Our observations confirm theoretical predictions for magnesium and demonstrate how TPa pressures—10 million times atmospheric pressure—force materials to adopt fundamentally new chemical and structural behaviors," says Gorman.

X-ray diffraction analysis revealed that valence electrons of magnesium atoms, which normally travel freely throughout the material, became localized to interatomic cavities under these conditions, forming crystalline, ionic salts in which electrons negatively charged ions. Direct observation of the phenomenon provides valuable insight into the way that valence–core and core–core electron interactions can influence material properties at high pressure. The success of this effort presents opportunities for further high-pressure research at the limits of experimental feasibility.

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Commentary by Amanda Askin

Creative Teams Solving Real-World Problems

THE past year as scientific editor of *Science and Technology Review* (*S&TR*) has enlightened me to the incredibly broad array of technical accomplishments at the Laboratory and the diverse and talented teams of people behind them. In seeking out articles for each issue, I've had the privilege and responsibility to reach out to members of the Laboratory community far beyond my own research area. The *S&TR* team and I have sought to ensure that readers learn about topics that are important for our national security missions and the community, reflect significant accomplishments and impacts, and share the diversity of the Laboratory's workforce and capabilities. I am delighted that this issue, coming near the end of my scientific editor assignment, presents outstanding examples of creative researchers working together and applying unique skills to further scientific knowledge and solve real-world problems.

The feature article showcases how researchers from across the Laboratory are engaged in research to tackle a debilitating disease, amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. ALS and other neurodegenerative diseases have devastating effects and touch thousands of new patients every year. Yet the cause of ALS remains unknown, and no cure exists. Laboratory experts leverage capabilities established to support Lawrence Livermore's diverse mission areas to partner with clinicians and others researching ALS and develop novel methods for understanding disease mechanisms and identifying potential treatments.

For example, machine-learning techniques supporting applications as diverse as high-energy-density experiment design and modeling, nuclear proliferation detection, and forensic science can also search medical records for drugs that could be repurposed to fight ALS and to investigate in vitro drug responses based on cell image data. Computational physicists use multiscale physics modeling frameworks from materials science applications to understand a protein that leads to one of the few consistent ALS indicators. Biologists who developed a brain-on-a-chip platform to study the effects of chemicals, viruses, and drugs now extend the platform to an ALS-on-a-chip technology that characterizes ALS-related protein aggregation. Experts who developed capabilities to study astronaut's microbiomes seek to apply those skills to examine environmental factors associated with disease progression. These projects take on the challenge of understanding a complex disease from multiple angles using diverse technical approaches reflecting the breadth of capabilities at the Laboratory.

The first of three research highlights in this issue recognizes research on another complex problem: achieving the most precise measurements of the weak nuclear force ever conducted. Nuclear experimentalists and theorists work together to advance confirmation that the W boson is solely responsible for beta decay, deepening understanding of a fundamental force of nature that plays a key role in nuclear fission and fusion. Measurements of the weak nuclear force are extremely challenging as the force operates at distances on the order of 10^{-18} meters. Only by significantly improving experimental design in parallel with adapting theoretical predictions were researchers able to validate their results.

The second research highlight describes how the Laboratory's Nondestructive Characterization Institute pulls together experts in different diagnostic technologies to address improved defect detection in high-Z materials and streamline the qualification process for additively manufactured components. The researchers apply new laser-plasma acceleration techniques to develop higher resolution imaging for high-density materials, develop methods to integrate multimodal data for enhanced images, and build platforms to generate 3D visualizations that allow researchers to better distinguish material defects in imaging data.

The third highlight outlines ways that radiation and health physics expertise combined with an understanding of nuclear fallout and the movement of aerosolized particles enabled Laboratory researchers to characterize the benefits of sheltering in the aftermath of a chemical, biological, radiological, or other airborne hazard. For the first time, researchers could assess the protective value of individual building attributes to identify which buildings provide the best protection for different hazards. The team also took a regional view to characterize the distribution of highly protective buildings and help real-time emergency response planning and execution.

The articles in this issue exemplify the Laboratory's ability to flexibly build technically diverse teams to tackle research challenges. This strength is something that I have appreciated in my own research, and I believe it will continue to enhance our ability to tackle evolving national security challenges.

■ Amanda Askin is a Global Security Systems Analyst and the 2022 *S&TR* Scientific Editor.

On July 4, 1939, baseball All-Star Lou Gehrig announced he would leave baseball after having been diagnosed with amyotrophic lateral sclerosis (ALS), commonly known as Lou Gehrig's disease. (Photo by Stanley Weston/Getty Images.)

Joining the Fight to Cure NEURODEGENERATIVE DISEASE

The Laboratory's cutting-edge capabilities and expertise offer new tools to study ALS disease mechanisms and fuel hope for a cure.

IN the late 1930s, beloved Major League Baseball (MLB) All-Star, Triple Crown winner, and record-breaking New York Yankees first baseman Henry "Lou" Gehrig began showing signs of rapidly deteriorating strength and agility. At the time, Gehrig—deemed the "Iron Horse" for his athletic prowess and grit—was at the height of his career. His diminishing performance left fans stunned and confused. Diagnosed with amyotrophic lateral sclerosis (ALS), Gehrig's decline was swift. Just a little more than two years after his symptoms began, Gehrig died at the age of 37, a promising life cut short by a cruel and little-known affliction, which thereafter would also be referred to as Lou Gehrig's disease.

Always fatal, and usually within two to five years, ALS is an adult-onset, progressive neurodegenerative disease in which motor neurons in the brain and spinal cord die. Over time, the loss of these cells prevents the brain from controlling or regulating muscle movement, not just in the arms and legs but in the muscles needed to speak, swallow, and eventually breathe. Yet, while the central nervous system is destroyed, the mind remains fully aware, cognizant of its ever more debilitated state. The cause of ALS is unknown, and no cure has been identified.

Gehrig's death brought ALS into public awareness, and since then strides have been taken to improve understanding of this insidious disease. However, many challenges remain as physicians, scientists, and researchers worldwide strive to determine a disease mechanism, identify possible biomarkers, and develop effective treatments.

One of the primary obstacles is that ALS disease pathogenesis is tricky. From patient to patient, how the disease presents itself, the course it follows, and the rate of progression differ. This scientific challenge is compounded by the disease's rarity. Whereas nearly 2 million people are diagnosed with cancer every year and 19 million are living with cancer at one time, only 6,000 people are diagnosed with ALS every year and 18,000 are living with the disease. Consequently, high-dollar funding opportunities from pharmaceutical companies are limited.

In 2019, Lawrence Livermore joined the fight alongside universities, research institutes, and healthcare partners to better characterize ALS through a strategic partnership between the Livermore Lab Foundation (LLF) and the ALS CURE Project, a nonprofit organization that

identifies and funds promising ALS research studies. (See the box on p. 7.) Sally Allen, LLF's executive director, says, "LLF is dedicated to facilitating the application of the Laboratory's unique capabilities for the public good. The nonprofit is a bridge to a broad range of stakeholders and provides an important mechanism to enable broader society to benefit from the Laboratory's expertise."

In the first year of the collaboration, initial efforts were focused on engagement. Former Lawrence Livermore scientist and strategic partnerships manager Amy Gryshuk led the Laboratory's ALS Research Initiative and was instrumental in identifying multidisciplinary projects with the potential for follow-on funding and fostering relationships with the ALS community. Gryshuk, who now serves as associate director for the Office of Strategic Alliances with Innovation Ventures at the University of California at San Francisco (UCSF), says, "We grew our professional relationships and scientific network and demonstrated what the Laboratory could contribute in the ALS space."

This early groundwork laid the foundation for a growing research portfolio that combines the Laboratory's core competencies in computational modeling, biosciences, engineering, and data sciences with the expertise of external clinicians and researchers. The Laboratory's goal is to help identify the ALS disease mechanism and potential prognostic and diagnostic biomarkers for ALS, establishing a target for therapy development that could lead to a cure.

Insight into "Confounding" Data

According to the U.S. Centers for Disease Control and Prevention, of the 6,000 people diagnosed with ALS each year, only about 5 to 10 percent can trace their diagnosis to inherited genetic factors. What's more, the disease is twice as prevalent among veterans. This alarming statistic was the impetus for the Laboratory's first ALS project, focused on assessing whether machine-learning (ML) approaches could be used to identify the lifetime risk, age of onset, and rate of disease progression in military personnel.

Led by Livermore computational engineer Priyadip Ray, the project was conducted in collaboration with colleagues at the Veterans Affairs (VA) Palo Alto Health Care System's ALS clinic and Center for Collaborative Healthcare Innovation. Ray says, "Over the course of a year, we established a good working relationship with the VA and finalized an agreement that would allow us to use de-identified ALS patient data from the VA's electronic health records, along with clinical data from the Pooled Resource Open-Access ALS Clinical Trials database, to explore the efficacy of machine-learning approaches for predicting factors related to ALS."

Typically, a patient's disease progression is based on the ALS functional rating score, a physician-based assessment of a patient's impairment. "We applied multimodal machine-learning approaches to identify risk factors that could serve as surrogate measures for the functional rating score," says Ray. "We showed that modeling long-range, complex correlations among different factors using patients' vital data could help predict disease progression."

This initial work set the stage for a larger project funded through the Department of Defense Congressionally Directed Medical Research Programs (DOD CDMRP) to identify Food and Drug Administration (FDA) approved medications that could be repurposed to slow ALS progression. Currently, the three FDA-approved drugs for ALS (Riluzole, Edaravone, and the recently added Relyvrio) can extend the survival time of patients temporarily. Ray says, "We know that off-target drugs have been used to treat other neurological diseases, so we're looking for instances in which off-target drugs could be successful with treating ALS."

ALS CURE Project co-founder Mike Piscotty presents a check to Livermore Lab Foundation representatives Dona Crawford and Sally Allen to fund strategic projects that apply the Laboratory's scientific and technical expertise to meet the challenges of ALS.

The Livermore team, which includes Jose Cadena, Andre Goncalves, Braden Soper, and Boya Zhang, first developed a baseline ML approach using an algorithm that assumes all confounding variables—factors that can affect both treatment and outcome but are not under direct study—are known. "For example, some drugs are not suitable for older patients, and younger patients tend to live longer," says Ray. "If you don't consider age as a confounder, then the data may suggest the medicine lengthens life rather than something else affecting the survival rate," says Ray. With their baseline approach, the team flagged promising classes of drugs for repurposing.

To reinforce the initial drug results, the team applied more sophisticated ML approaches. "We developed two other machine-learning algorithms that remove some of the assumptions embedded in the previous work," says Ray. While the baseline algorithm

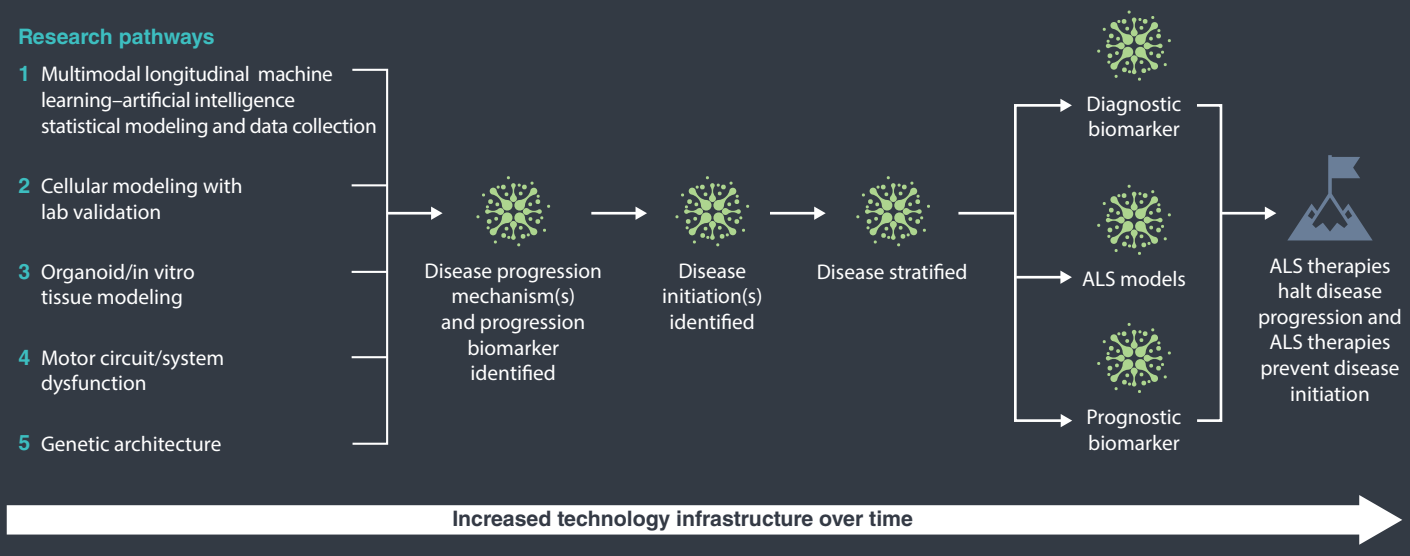
Partnering for A Cure

The triumph of the human spirit can enable people to turn tragedy into hope, heartache into purpose. The ALS CURE Project was founded by Livermore computer scientist Mike Piscotty and his son, Major League Baseball player Stephen Piscotty, in memory of wife and mother Gretchen (also a former Laboratory employee), who passed away from amyotrophic lateral sclerosis (ALS) in 2018. The nonprofit raises funds to support promising ALS research initiatives and build strong, international collaborations. Piscotty, who has been a project manager within the Laboratory's Information Technology Program for more than 30 years, says, "The ALS CURE Project brings independent researchers together to better understand the disease, its cause and progression, and ultimately, find a cure."

Recognizing the immense scientific capabilities and broad expertise that the Laboratory could bring to bear on ALS, Piscotty began exploring how to bring the two together. He engaged Laboratory management, including former Associate Director for Engineering Anantha Krishnan, who saw the potential benefits of applying the Laboratory's multidisciplinary approach to ALS research. Krishnan helped pave the way for the initiatives funded through the Livermore Lab Foundation (LLF). Sally Allen, LLF's executive director, says, "LLF's partnership with the ALS CURE Project demonstrates the value of having a philanthropic entity that can facilitate public–private partnerships at the Laboratory to help tackle some of today's most complex scientific challenges." Piscotty adds, "None of the amazing ALS work being done at the Laboratory would have been possible without the support of LLF and its Board of Directors."

Annually, the ALS CURE Project holds an ALS Innovation Symposium, where the top ALS researchers from around the world come together virtually to discuss potential research avenues. "We are not concerned with who gets credit but rather that the limited ALS research dollars are directed to the most promising opportunities," says Piscotty. "Through this event, we developed our Roadmap to Cure ALS, which serves as a guide for research grants focused on international collaborations." To date, the ALS CURE Project has sponsored $1.2 million in research efforts, and it is committed to seeing a cure become a reality. Piscotty says, "Before Gretchen died, I made a promise that we would continue to work towards a cure." For Piscotty and all those who have made this work possible, when that day comes, the ALS CURE Project will be complete.

Mike Piscotty started the ALS CURE Project in honor of his wife Gretchen, who passed away from the disease in 2018. In the background, his son, Major League Baseball player Stephen Piscotty, approaches the batting cage.



The ALS CURE Project's "Roadmap to Cure ALS" outlines key milestones and objectives in ALS research and serves as a guide for research grants for leading ALS organizations around the world.

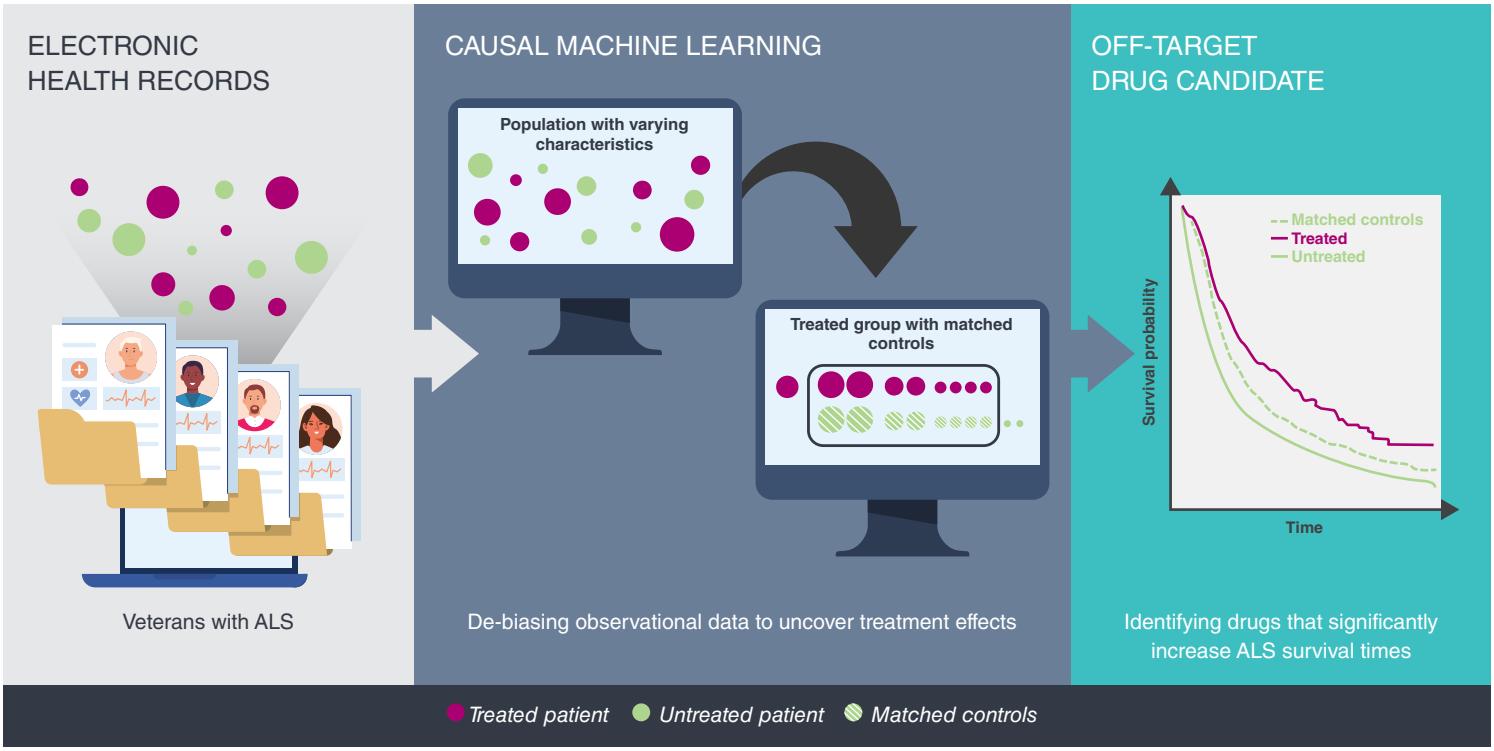
assumed all confounding variables were known, the second removes some of the assumptions, and the third considers "deconfounders." Ray explains, "Imagine trying to determine how much the actors typically cast in James Bond movies will affect a movie's revenue. A deconfounder machine-learning approach would take all the data and analyze how much of a factor the actors are versus other factors. Perhaps the actors' level of success in terms of revenue is less about the particular actors than about their being cast in James Bond movies." Such an approach would allow the team to uncover confounders in a data-driven manner rather than relying on human experts to identify them beforehand, which removes inadvertent biases. The team has run preliminary analyses on all three ML algorithms and has identified several promising drug repurposing candidates. "Our goal is to develop a suite of approaches in which we can reinforce the outcomes to identify specific drugs with confidence."

While randomized clinical trials are the ultimate gold standard in medical research, they are expensive to conduct. "This work will help us determine if we can emulate a randomized drug trial using retrospective patient data rather than having to recruit trial participants to determine effective drug repurposing. We can then focus limited funding resources on the most promising therapeutics," says Ray. The research team continues to engage with the VA and UCSF, which has an ALS clinic that could provide a large, separate patient data set for ML exploration. Researchers are also working with collaborators at Stanford University and the University of California at Los Angeles to investigate specific drugs and the biological mechanisms that drive the positive outcomes for ALS patients.

Proteins Could Be Key

Several years ago, as part of the National Cancer Moonshot Initiative, Laboratory researchers began investigating the process of cancer initiation in RAS (rat sarcoma virus) proteins. (See *S&TR*, October/November 2016, pp. 4–11.) The team coupled experimental data with atomic-resolution molecular dynamics simulations to build a model of RAS protein biology in varying types of cell membranes. Mike Piscotty, co-founder of the ALS CURE Project, says, "After reading about this work, I wondered if this same physics-based approach could be used to study the TDP-43 protein, which is present in 95 percent of ALS cases but is poorly understood."

TDP-43 (transactive response DNA-binding protein 43) is found in cell nuclei, including within nerve cells such as motor neurons, and is involved in RNA-related metabolism and gene expression. The protein is made up of 414 amino acids and



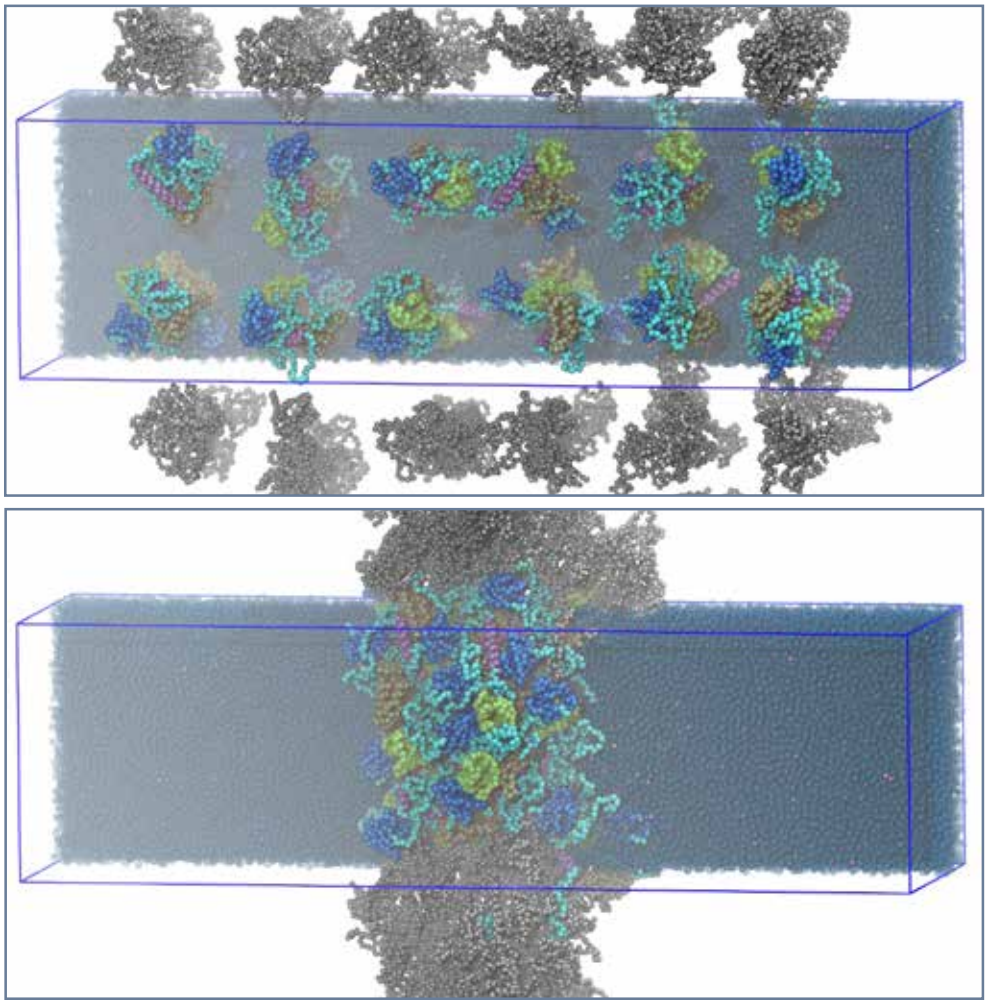
Livermore researchers are using machine-learning algorithms to find effective off-target drugs to treat ALS patients.

several functional domains—independent units of the polypeptide chain that allow the protein to perform its primary function. Although the amino acids dictate the folded 3D structure of the protein, structural rearrangements can occur. Previous research has shown that TDP-43 protein aggregation, wherein proteins misfold or cluster together to form stress granules, leads to plaque formation between nerve cells. These plaques cause motor neurons to die and are one of the few consistent observable indicators in ALS and other neurodegenerative diseases.

As a result, another project within the ALS research portfolio focused on developing an experimentally informed and validated physics-based multiscale modeling framework to understand the physics of TDP-43 protein phase separation and aggregation intra- and extracellularly. "Think of an egg with the yolk and surrounding white membrane," says Piscotty. "When TDP-43 stays in the nucleus of the cell, in this case, the yolk, the cellular process works well. But, if the protein moves out of the yolk and into the egg white, and then finds other proteins to bind with, the cell behaves differently. What we don't know is whether neurodegeneration is causing TDP-43 aggregation, or the other way around."

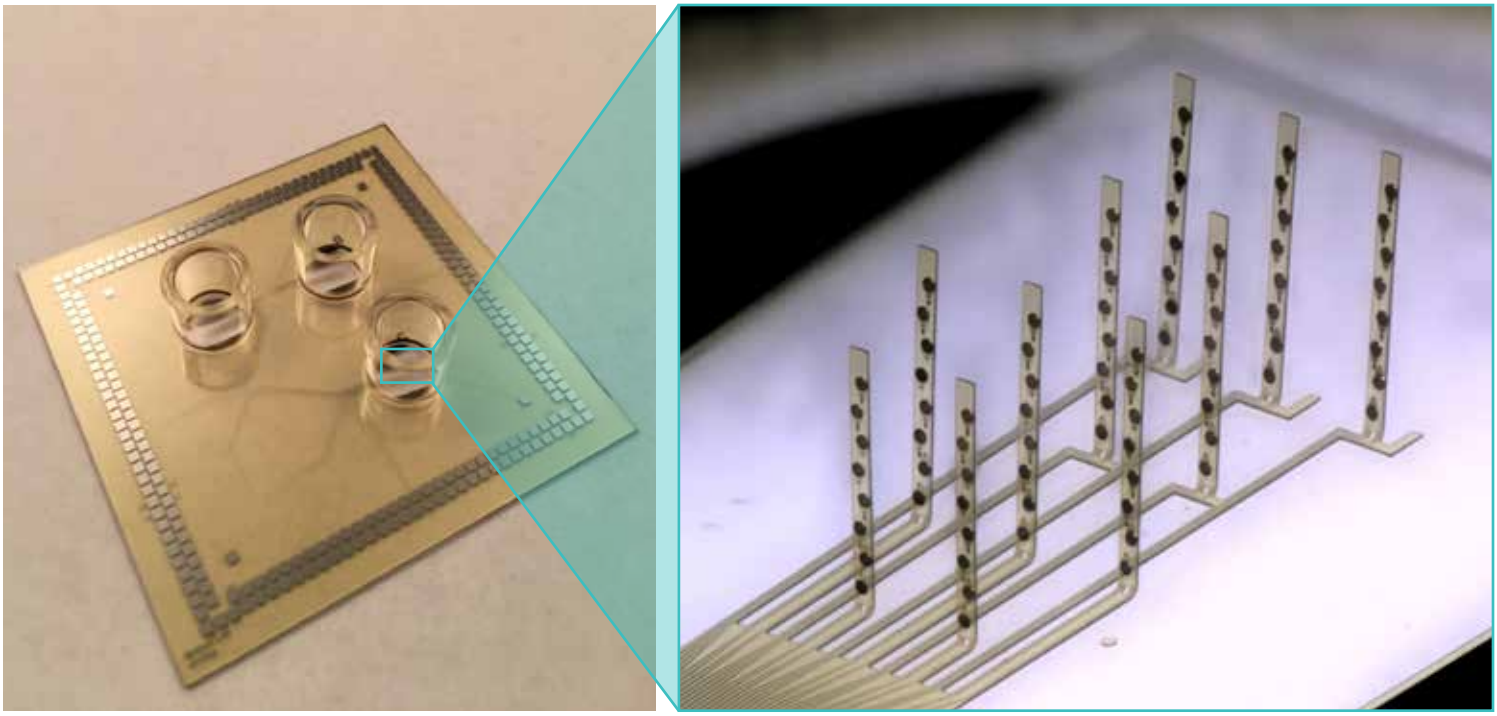
To help unravel this mystery, Livermore computational physicists Joel Berry and Helgi Ingolfsson are delving into the molecular dynamics of TDP-43 self- and cross-interactions. Berry's work focuses on developing macroscale models to simulate the liquid–liquid phase separation (LLPS) of TDP-43 proteins. "TDP-43–rich clusters are intracellular condensates—micrometer-scale, membraneless protein- and RNA-rich bodies that are typically liquidlike and are thought to commonly form and disassemble through cell-wide phase transitions," says Berry. "TDP-43 condensates and stress granules may form when these phase transitions are not properly regulated."

The team developed a full-length molecular model of TDP-43, including all



To better understand transactive response DNA-binding protein 43 (TDP-43) protein–protein interactions and assembly, Livermore computational scientists developed multiscale molecular dynamics models of a full-length TDP-43 protein (top). The coarse-grained molecular dynamics simulation shows 24 full-length TDP-43 proteins that are initially placed apart. As the simulation runs, the proteins quickly associate, forming larger assemblies that coalesce into a single assembly (bottom). Colors denote different protein structural domains.

414 amino acids, using select structures of the protein functional domains. Ingolfsson's expertise lies in all-atom and coarse-grained molecular dynamics simulations, which describe individual particles at high resolution. He says, "Data from higher resolution simulations serve as parameters for the larger-scale models." The course-grained, macroscale models, one of which is optimized for disordered proteins, explore the full-length protein's self-assembly process as well as protein–protein interactions—ranging from dozens to hundreds of proteins in assemblies—illustrating the role of protein self-affinity in LLPS and protein conformational evolution. Ingolfsson says, "Liquid–liquid phase separation has been extensively studied for physics and materials science applications but applying it to biology is new, and most work in this area is focused on experiments. Not many people have



Livermore's ALS-on-a-chip technology incorporates a 3D co-culture of motor neuron cells and glia (non-neuronal brain cells) grown and nourished inside experimental wells that sit on top of the microelectrode arrays (inset), which allow for noninvasive interrogation of the cells.

done this type of simulation work and at this scale." These simulations could play a crucial role in linking molecular-level interactions to aggregate behavior of protein assemblies, potentially giving insight into ALS mechanisms.

The team has secured additional funding through the DOD CDMRP to take this research to the next level. In collaboration with San Francisco–based research groups Gladstone Institutes and Prosetta Biosciences, the team will integrate computational models and data from experiments to study whether small molecule drugs that disrupt TDP-43 aggregation can have a neuroprotective effect. Ingolfsson says, "Establishing that small molecule compounds can restore TDP-43 nuclear localization would support further development of treatment options." Livermore colleagues working in the biosciences will contribute to this work, with a new capability for studying neuronal cells in vitro.

ALS-on-a-Chip

In 2014, Livermore researchers unveiled an innovative device called the in vitro chip-based human investigational platform (iCHIP)—an integrated system that combines primary human cells, tissue engineering, and microfluidics—to evaluate the effects of chemicals, viruses, and drugs on humans without relying on animal or human test subjects. (See *S&TR,* March 2014, pp. 16–19.). Through a strategic initiative funded by the Laboratory Directed Research and Development Program, this platform was later adapted to create the brain-on-a-chip technology, which simulates the central nervous system by recording activity from multiple brain cell types deposited and grown onto a small platform embedded with microelectrode arrays. (See *S&TR*, May 2019, pp. 4–11.)

As part of a third ALS research effort, Livermore biologists Nick Fischer and Heather Enright have further adapted the technology to deliver "ALS-on-a-chip." The device takes a closer look at the connection between ALS-related protein aggregation and stress granule formation from the experimental side. Fischer says, "Our system may provide a new tool to study the possible mechanism of protein aggregation on ALS disease progression, while also serving as a tool for evaluating new therapies."

ALS-on-a-chip incorporates a 3D co-culture of motor neuron cells and glia (non-neuronal brain cells) grown and nourished inside experimental wells that sit on top of the microelectrode arrays. The first phase of the project focused on establishing the culture conditions necessary to maintain the cells' viability and evaluating the network formation, cellular morphology, and functional signatures in vitro. The team will soon begin testing a handful of therapeutic candidates developed by collaborator

Prosetta Biosciences to assess how the drugs affect the network function.

Ideally, the platform will provide a controlled way of analyzing the onset of stress granule formation and tracking how the proteins affect the function of the motor neurons over periods of time ranging from hours to weeks. If the team can demonstrate how the functional signatures of the neural network correlate with structural changes within the motor neurons, the research could open new avenues for developing, testing, and validating promising therapeutics, including ones with potential to prevent or reverse stress granule formation.

The work shows promise, and in June 2022, Fischer began collaborating with the University Medical Center (UMC) at Utrecht in the Netherlands on a separate, but related project. The work will integrate the Laboratory's work with ALS-relevant 3D neuronal cultures and 3D multielectrode arrays with the expertise of UMC Utrecht in developing and characterizing ALS-relevant neuronal cells and brain organoids. "This work can give us amazing insight into a part of the body that cannot be evaluated while a person is living," says Piscotty. "Organoid and tissue arrays provide a noninvasive way to peek inside the brain to help us better understand disease mechanisms and accelerate therapeutic development."

Future Possibilities

The success of these early projects has generated momentum as the Laboratory finds more areas in which to contribute. Under a proposed collaboration with UCSF, Livermore researchers will investigate whether environmental factors may play a role in ALS disease mechanisms by studying the microbiomes of ALS patients. Previously, the Livermore team, led by biologist Crystal Jaing, studied associations between pathogens and various forms of cancer and worked with NASA to characterize the microbiomes of astronauts and the environment within the International Space Station. (See *S&TR*, January/February 2018, pp. 12–15.) "Using both computational and microbial data, we can look at patients' progression scores, diets, and general environment to explore whether there are factors within patients' microbiomes that could be contributing to disease onset and progression," says Jaing. CDMRP funding has been approved for the project, which includes collaborators from UCSF and Stanford. Team members look forward to applying their expertise to potentially identify opportunities for ALS prevention, early detection, and treatment.

Another pilot project recently funded by LLF uses ML approaches to stratify ALS patients based on in vitro drug response. Livermore computational engineer and principal investigator for the project, Alan Kaplan, says, "We will take imaging data from in vitro experiments and assess how a cell's appearance changes, such as shape and morphology, pre- and post-treatment and evaluate how the drugs are affecting the cells."

Image data is being provided by collaborators at the University of Sheffield in the United Kingdom. "My role is taking all the shape descriptions and data from each cell and using machine-learning approaches to distinguish patterns of how the cells change with which drugs," says Kaplan. ML allows the researchers to analyze hundreds of features computed per image. "Drug response is not uniform in the patient population. Therefore, we are developing methods that allow us to assess hundreds of morphological parameters per cell to determine potentially complex relationships that differ between patient subtypes." Ultimately, the team aims to generate an ML model that can stratify patients into subgroups based on correlations between the expression of pathological hallmarks in cells and their drug response to accelerate drug discovery.

Fueling Hope through Science

The breadth of capabilities and diverse approaches that Livermore is applying to tackle ALS research challenges and the external partnerships with medical providers and other disease experts are leading to new discoveries in disease pathogenesis. Piscotty says, "People should be proud of the work being done here and with strategic partners to advance research in this important area. The work under way to identify disease mechanisms and speed therapeutic development is a testament to what can be accomplished when we work together to achieve a common goal. This research can also be applied to other neurodegenerative diseases."

Since the ALS Research Initiative began, the Laboratory has gained recognition for the tools brought to the ALS fight. "In the Spring of 2021, LLF sponsored a Rae Dorough Speaker Series talk on neurodegenerative disease and what we have learned so far," says Dona Crawford, chair of the LLF Board of Directors. "The Laboratory has become a compelling partner in this space, a natural convener of multiple research efforts serving as a neutral, honest broker. We hope to make faster progress collectively than what would be possible individually." Piscotty adds, "The key for hope in the ALS community is to discover the target—the disease mechanism along with an ALS biomarker—that we can share with pharmaceutical companies to rapidly bring drugs to market to slow or even halt disease progression and in the future may even allow patients to regenerate movement." Bringing great minds together is an essential part of this work. Now, it is time to play ball.

—Caryn Meissner

Key Words: ALS CURE Project, ALS-on-a-chip, amyotrophic lateral sclerosis (ALS), biomarker, disease mechanism, Livermore Lab Foundation (LLF), Lou Gehrig's disease, machine learning (ML), microbiome, molecular dynamics, motor neuron, neurodegenerative disease, TDP-43 (transactive response DNA-binding protein 43).

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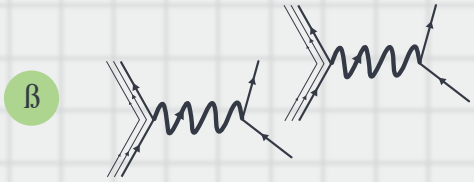
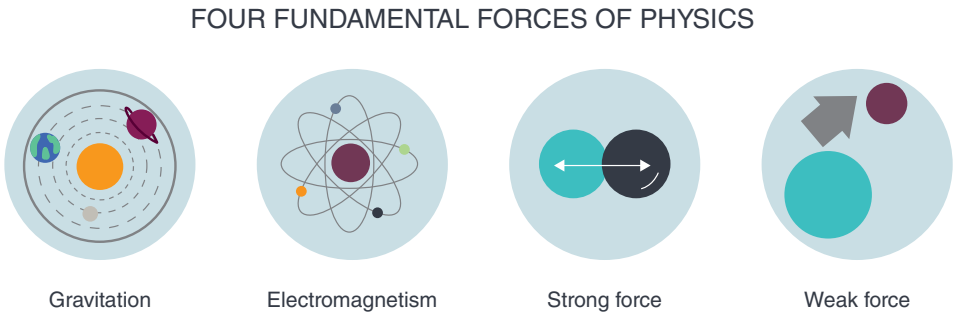


SMALL THINGS CONSIDERED

GRAVITY. Electromagnetism. The strong nuclear force. The weak nuclear force. Four fundamental forces of nature govern everything that happens in the universe. The first two are readily observed in everyday life. Detecting the latter two calls for a dive into subatomic realms. Whereas the strong nuclear force holds atomic nuclei together and operates at distances of about 10^{-15} meters (the diameter of a proton), the weak nuclear force operates at even shorter distances, approximately 10^{-18} meters, and can trigger radioactive decays that alter the proton and neutron content of a nucleus.



The fundamental forces of nature are gravitation, electromagnetic force, the strong force, and the weak force.

Of the four forces, the weak nuclear force is the least understood and most difficult to detect. A Lawrence Livermore team headed by physicist Nick Scielzo partnered with scientists from Argonne National Laboratory (ANL), Louisiana State University (LSU), and other universities to better characterize the weak force's foundations. Thanks to significant advances in experimental design and theoretical calculations, researchers are now on the road to a clearer understanding of the mysterious force.

In 1933, physicist Enrico Fermi proposed the weak nuclear force as a way to explain nuclear beta decay, the most common form of radioactivity. Today, this force forms a pillar of the "Standard Model," a set of mathematical equations that describe fundamental particles and forces of nature. The weak nuclear force acts through the short-distance exchange of heavy particles called W and Z bosons. During beta decay, a neutron spontaneously changes into a proton inside the nucleus, and the exchange of a W boson emits a beta particle (electron) and an antineutrino.

To explore the weak nuclear force, Scielzo's team required a beta-decaying nucleus that is accessible to experiments and that has properties well-predicted by the Standard Model. They chose the isotope lithium-8, with a half-life of 840 milliseconds. Lithium-8 decays to beryllium-8, which further breaks apart into two alpha particles. In the Standard Model prediction, the beta particle and antineutrino are emitted at a precise distribution of relative angles. Scielzo says, "The current Standard Model predicts that beta decays for lithium-8 are due solely to the W boson, but extensions to this model predict there could be contributions from other, as-of-yet-unseen particles. If these new particles exist, they would reveal themselves by altering the correlation between the directions of the emitted beta particle and antineutrino."

Feynman's diagram (represented in the illustration) provides researchers with an explanation of beta decay in quantum field theory.

Experimental Precision

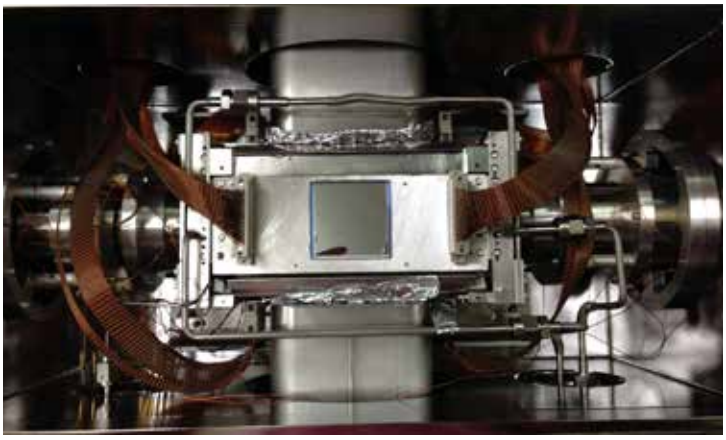
The lithium-8 experiments were conducted at ANL's ATLAS accelerator over a two-week period. Lithium ions produced in the accelerator are guided into the vacuum chamber of the Beta-decay Paul Trap (BPT). (See *S&TR*, September 2013, pp. 16–18.) An oscillating electric field created by electrodes confines the ions to a small area, floating in vacuum, where they decay. Numerous radiation detectors consisting of double-sided silicon strip detectors and plastic scintillators surrounding the trap measure the energies and directions of all emitted particles except the virtually undetectable antineutrino. However, the two emitted alpha particles carry information on the size and direction of nuclear recoil, which, together with the detection of the beta particle, allowed the team to reconstruct the antineutrino's heading and determine its angular correlation with the beta particle.

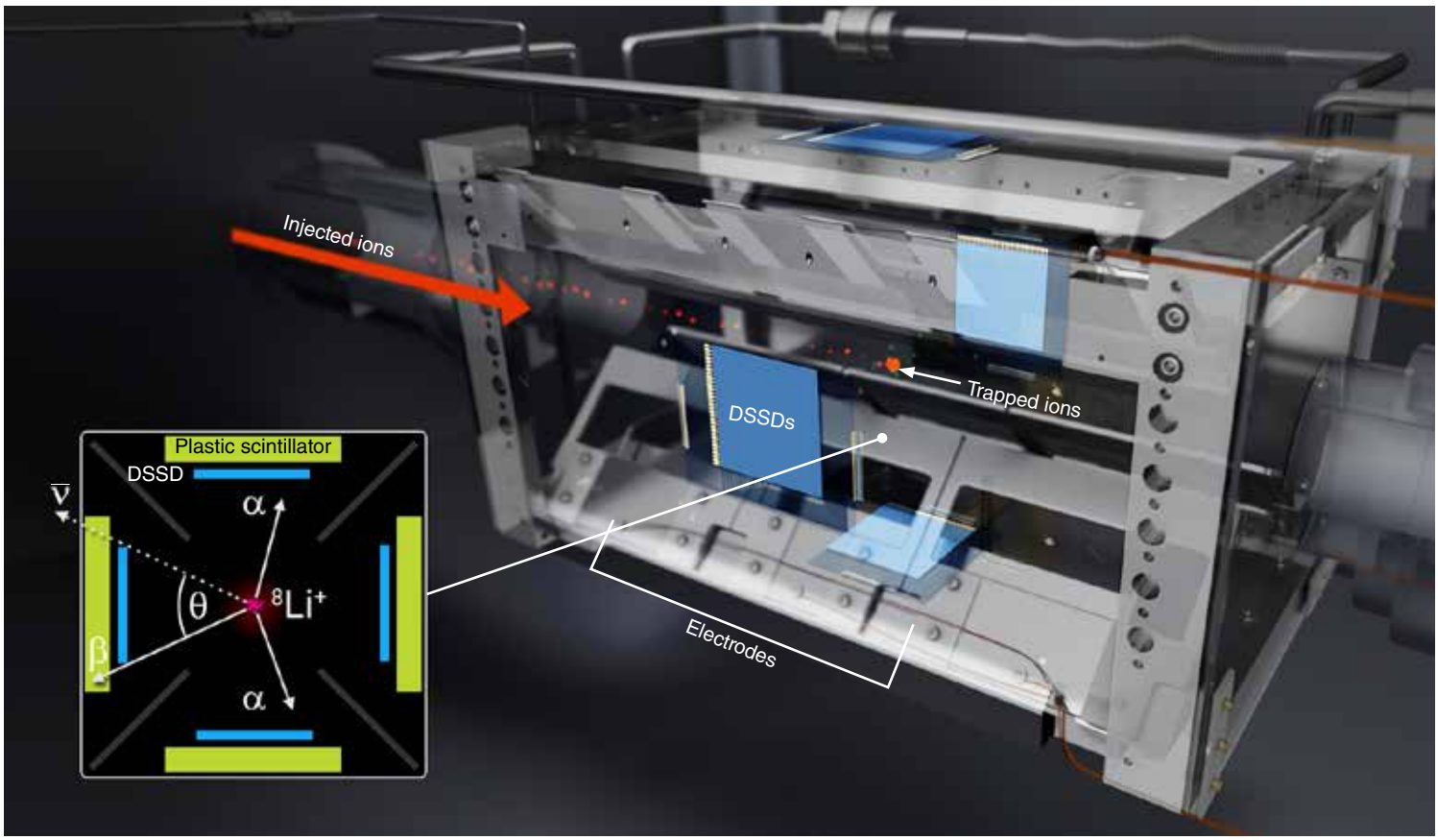
The team resolved the angular correlation between the beta particle and the neutrino to higher precision than ever before, sensitively probing the mechanisms driving the weak nuclear force. "Precision in these experiments was critical," Scielzo notes. Higher precision increases the likelihood of detecting subtle distortions caused by the hypothesized heavy, exotic bosons that may briefly pop into existence before decaying. Achieving such precision was no easy task.

To that end, Lawrence Livermore staff scientist Mary Burkey, then a University of Chicago graduate student, worked with the Laboratory's Scielzo, Aaron Gallant, and others to upgrade the BPT. She found a way to manage the impact of the electrodes' oscillating high voltages that were being picked up by the radiation detectors and corrupting the incoming decay signals, worsening the energy resolution, and blurring out the angular correlation. Burkey's solution was to install hundreds

The Beta-decay Paul Trap (BPT, pictured at right) captures the energy and direction of travel of all the particles except antineutrinos, which have no charge and essentially no mass.

Lithium-8 ions ($^8Li+$) are produced with an accelerator and injected into the BPT. The ions are confined in the BPT's center by strong electromagnetic fields produced by thin, segmented, planar electrodes. Decay products—two alpha (α) particles, one beta (β) particle—and an antineutrino ($\bar{\nu}$) are collected by double-sided silicon strip detectors (DSSDs) and plastic scintillators (not shown in larger diagram) surrounding the trap. The correlation angle (Θ) between β and $\bar{\nu}$ is recorded by researchers. (Image by Ryan Chen.)





of tiny notch filters—simple electrical components to filter out electrical signals at the same frequency as the BPT voltages. Data analysis revealed more challenges. She explains, "I spent most of my time comparing the data to extremely detailed simulations in which we try to take into account everything we possibly could—the nuclear physics, of course, but also the interactions of decay products with the detectors and the rest of the apparatus."

These groundbreaking experiments yielded extremely precise results, but certain aspects of the data seemed to conflict with the Standard Model. Were these differences due to something in the apparatus, or the data-gathering, or a bug in the data

analysis? Or was it new physics, something happening at such a small scale it had been undetectable with earlier experiments?

Theorists and Experimentalists Unite

Interpreting the results required an in-depth consideration of theory. Livermore nuclear theorist Grigor Sargsyan was still a doctoral student at LSU when he examined the experiments' theoretical aspects. "My role was to calculate the higher-order effects that become a significant source of uncertainty for this kind of precise measurement," he explains. "Imagine trying to measure the height of a 20-story building by throwing stones from the top and measuring the time it takes the stones to hit the ground. Only a stopwatch is needed to determine the height within a meter. But to know the height within millimeters, precise devices are required to exactly measure the start and end of the stone's journey. Higher-order effects such as air resistance and wind that are otherwise negligible would also be considered."

To calculate the higher-order effects in the lithium-8 beta decay, Sargsyan used the symmetry-adapted, no-core shell model—a modern ab initio model based on accepted physics principles. Implemented on supercomputers, such ab initio models consider all the complicated proton–neutron interactions in a nucleus. In a scientific first, Sargsyan and his doctoral advisor implemented calculations of the beta-decay higher-order effects into the symmetry-adapted model. "We found no previous theoretical calculations of these effects in the literature," says Sargsyan, "so we had to double and triple check each step to make sure our implementation was correct." Advancements in the nuclear theory that relates these calculations to measured nuclear moments allowed the researchers to calculate terms magnitudes smaller than the dominant decay effects. Scielzo notes, "This type of correction typically only contributes a 1 percent distortion in the decay, but when you are looking for 0.1 percent distortions, this is a big deal."

Theorists and experimentalists soon accepted that the discrepancies from the Standard Model they saw in the data arose from the physics that Sargsyan included in his calculations. In earlier experiments, the effects had been too small to acknowledge, but these ultraprecise experiments accounted for miniscule effects. Sargsyan says, "The experimentalists would show us how each of our calculations changed their interpretation of the results. We were happy to see that our predictions helped decrease the uncertainty on the final experimental values." Burkey adds, "Finally, we knew we weren't encountering a weird experimental issue, but 'missing' physics that hadn't been considered before." Scielzo adds, "This major advancement in our tests confirmed that the W boson is solely responsible for this type of decay. Our results, while consistent with the Standard Model, placed the strongest limit on a possible source of new physics and elevated the state of the art for precision measurements of this kind."

Enduring Research Benefits

The benefits of addressing cutting-edge, fundamental science questions are many. Scielzo notes that such efforts draw early career researchers into the Laboratory hiring pipeline. Both Burkey and Sargsyan began the project as graduate students, based their dissertations on this work, and joined the Laboratory as postdoctoral researchers. Both published back-to-back papers on their research in *Physical Review Letters*, with Burkey's paper on the weak interaction in lithium-8 beta decay receiving a 2022 Laboratory Director's Excellence in Publication Award. The skill sets and approaches developed in the project stand to benefit other Laboratory endeavors. "For instance, we can apply these types of high-precision methods to improve studies of the beta decay of fission products that serve as key diagnostics and signatures for the Laboratory's Stockpile Stewardship Program and nuclear forensics efforts," says Scielzo.

Meanwhile, fundamental research continues. In mid-2022, the team performed similar experiments using boron-8 (5 protons and 3 neutrons), a mirror nucleus to lithium-8 (3 protons and 5 neutrons) that also decays to beryllium-8. When switching from studying lithium-8 to boron-8, some of the higher-order corrections switch signs, allowing the team to isolate their impact and gain a better understanding of these small but important effects. Since boron-8 is responsible for most high-energy neutrinos emanating from the Sun, this research will also aid Earth-bound experiments studying solar neutrino oscillations.

"We're a small and nimble experimental effort and can switch directions easily and follow the most compelling science," says Scielzo. "We're pushing the precision on all sorts of beta decays. The finer we can measure, the more we learn, and the greater the opportunities to address different topics—from probing the nature of the weak force and looking for physics that may lie beyond the Standard Model to improving the nuclear data that underpins our national security efforts. Theorists and experimentalists working together make these kinds of advances happen."

– Ann Parker

Key Words: Ab initio model, alpha particle, Argonne National Laboratory (ANL), ATLAS, beryllium-8, beta decay, Beta-decay Paul Trap (BPT), beta particle, boron-8, lithium-8, neutrino, particle physics, Standard Model, W boson, weak nuclear force.

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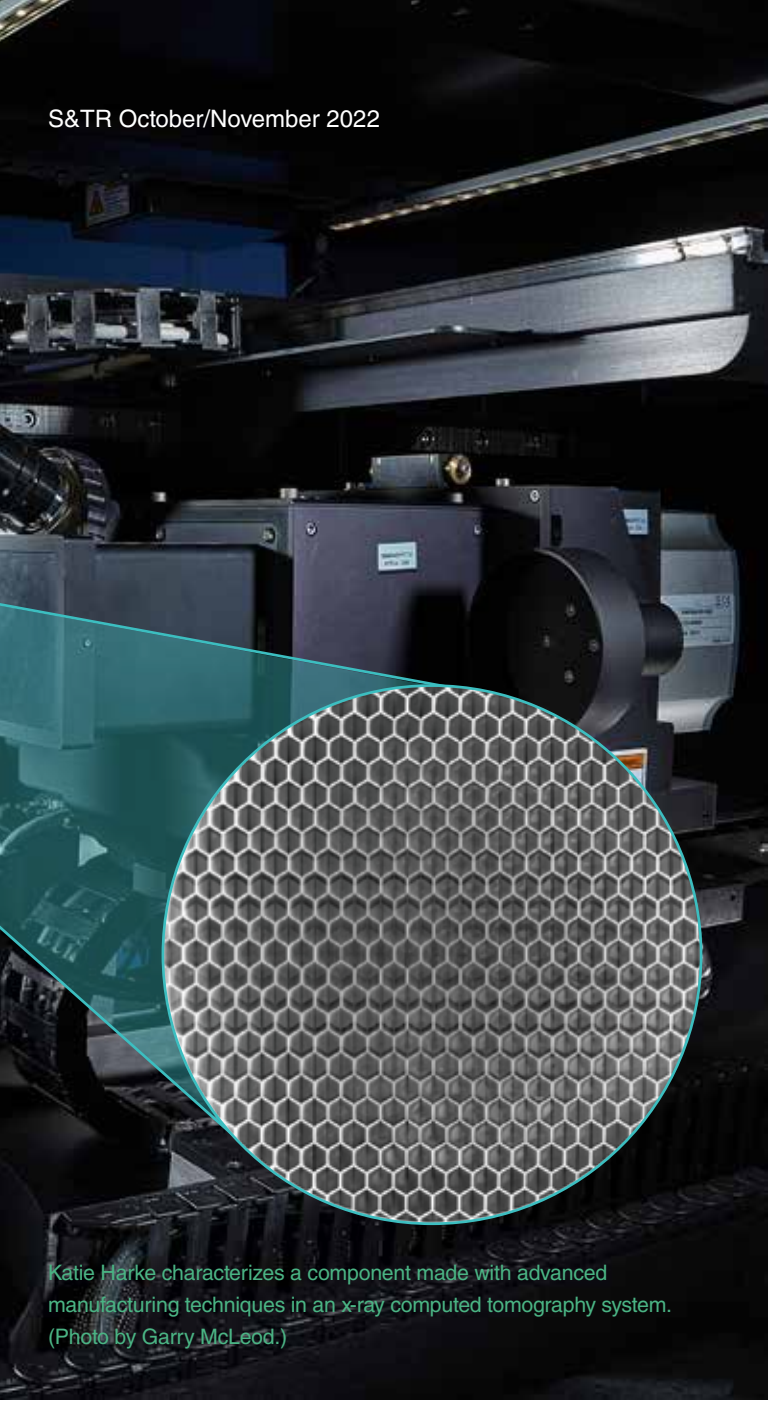
FROM PLASMA TO DIGITAL TWINS

MICROMETERS matter when aberrations smaller than the width of a hair can jeopardize an entire system. Whether working with semiconductors or optics, research teams from all disciplines at Livermore recognize that stringent standards of precision ensure operability of mission-critical equipment. Only after extensive testing can any component be qualified for its function. However, nearly all components require a thorough quality control process that keeps them intact and functional—no dissection allowed—from microscale objects replete with intricate details to additively manufactured parts built micrometers at a time.

At Livermore, this challenge goes to the Nondestructive Evaluation (NDE) group. "Put simply, our job is to look inside things. We check for irregularities and make sure physical components will function as intended," says NDE group leader Joe Tringe. The group has an array of techniques at its disposal for inspecting objects' interiors without disturbing them: computed tomography (CT), optical laser interferometry, and ultrasound, for example, can be used alone or in combination to gauge whether a component's physical and material properties fall within allowed tolerances.

Laser Precision

Metrology—the study of measurement—offers data-backed confidence for performance of the Laboratory's specialized components. Despite the breadth of diagnostic tools available to NDE scientists, data out is only as good as data in. This reality led Harry Martz, director of Livermore's Nondestructive



Katie Harke characterizes a component made with advanced manufacturing techniques in an x-ray computed tomography system. (Photo by Garry McLeod.)

Characterization Institute (NCI), in search of even higher-precision methods. NCI identifies requisite NDE processes for Livermore's diverse programs and coordinates with outside research institutions when additional development is needed. As part of a project funded by the Laboratory Directed Research and Development (LDRD) Program, Martz drew talent from Lawrence Berkeley National Laboratory as well as the United Kingdom–based Rutherford Appleton Laboratory and Manufacturing Technology Centre to focus on a class of notoriously camera-shy objects: x-ray resistant materials. The group addressed limitations of x-ray computed tomography (XCT)—used to digitally reconstruct objects in 3D from serial radiographs—when imaging high atomic number (high-Z) components. "We're trying to achieve higher spatial

The Berkeley Lab Laser Accelerator (BELLA) Center supported work to perform x-ray tomography of high-Z components. Optics in the foreground channel electron and laser beams that are fired toward a sample staged at the far side of the setup.

resolution and minimize uncertainty when imaging these materials to streamline the qualification and design cycle of additively manufactured components," says Martz.

Robust, high-Z materials such as the superalloy Inconel (used in rocket engines and heat exchangers) impede incident x rays, distorting radiographs. To ensure x rays fully penetrate Inconel components during evaluation, scientists must crank up x-ray energy to more than 1 megaelectronvolt (nearly 10 times higher than a standard chest x ray). Unfortunately, such powerful beams typically require large focal spot sizes. The result is a less precise probe, meaning minute imperfections in critical, additively manufactured components that could trigger mechanical failure—precisely the flaws that must be identified—could therefore evade detection.

Martz's team sought to produce high-energy x rays while maintaining minimal beam spot size to improve components' digital reconstructions. Martz explains, "Physics models have generally assumed a monoenergetic x-ray source when, in reality, lab-based x rays are polyenergetic, with energy distributed above and below the desired value. We need as close to a monoenergetic source as possible so subsequent image reconstruction excludes artifacts that deviate from ground truth." The team saw promise in the nascent method of laser–plasma acceleration (LPA) under development at the Berkeley Lab Laser Accelerator (BELLA) Center. Adapting BELLA's hardware for their experimental needs, the researchers set out to generate narrow-band x rays and perform CT with the method for the first time.

In the world of accelerator physics, LPA is the next big thing in a small package. A short, intense pulse of laser light is fired and split into two beams, the first of which is focused into a volume of gas to create a plasma. High electric field gradients then accelerate the plasma's electrons to ultrarelativistic velocities at a rate that is far more efficient than traditional linear accelerators. Meanwhile, the second beam is rerouted to collide with the produced electron beam to create energetic x rays through a phenomenon called inverse Compton scattering (ICS). X rays generated through ICS are used to produce radiographs.

The team probed a small, additively manufactured Inconel object using LPA-driven ICS, hoping to achieve more than 200 times greater spatial resolution than with conventional XCT. The setup's tunable, quasi-monoenergetic x-ray spectrum would reduce energy spread, providing more precise images of the stubborn material than ever before. "Unfortunately, research isn't always successful the first time around," says Martz. The group successfully acquired CT data, although neither the x-ray beam nor the CT resolution was as precise as they hoped. But Martz remains optimistic. "The work we did at BELLA was a worthwhile risk. Even without the crisp images we strove for, simply obtaining CT data with this new process is an achievement in its own right, and what we learned prepares us for the next attempt." Their project indicates promising evaluative capabilities by demonstrating the feasibility of a new NDE resource.

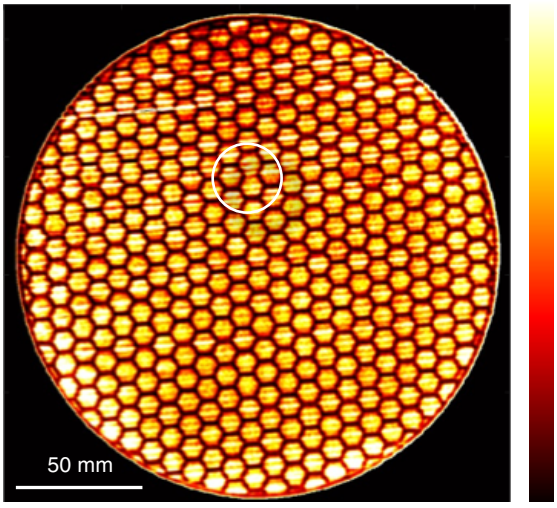
Putting It All Together

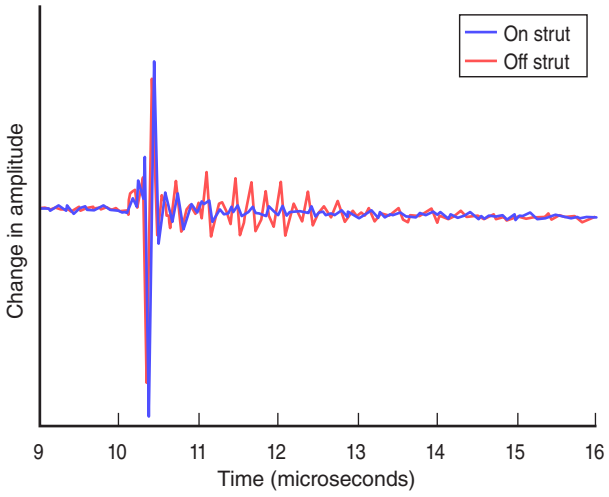
While Martz's group works to expand XCT capabilities, Tringe leads another LDRD project exploring NDE methods effective in other situations. "Ultrasound, while not well suited for many 3D imaging problems, is attuned to slight density changes and perceives cracks, voids, and layer thicknesses like no other method," says Tringe. "We wanted to combine the strengths of multiple modalities—XCT, ultrasound, neutron imaging, and so on—to provide the best quantitative data possible for critical components."

Tringe's team of NDE specialists and university collaborators tackled integration of data from multiple modalities into composite images, a task more complex than merely overlaying multiple images. Each modality is uniquely suited to detecting particular features and compositions, and each supports a different spatial resolution. "We have to decide which part of an image represents true physical boundary features—the dark side? the light side? somewhere else along the gradient?—and do so algorithmically for thousands of images. With XCT, we consider where within the object we're looking as well as the spot size, energy spectrum, and x-ray source scattering. For ultrasound, the determination can depend on material thickness and porosity."

Metrology is inextricably tied to uncertainty, but knowing the exact level of precision in one's methods can prove challenging. "In evaluating additively manufactured parts," says Tringe, "scientists require precise quantitative information from CT. They often are searching for subtle deviations in geometrically complex structures, not conspicuous changes in image contrast like in medical scans." The team determined how to quantify the uncertainty associated with multimodal measurement, comparing obtained readings to "exemplar" objects with verified dimensions to isolate the factors responsible for certain measurement errors.

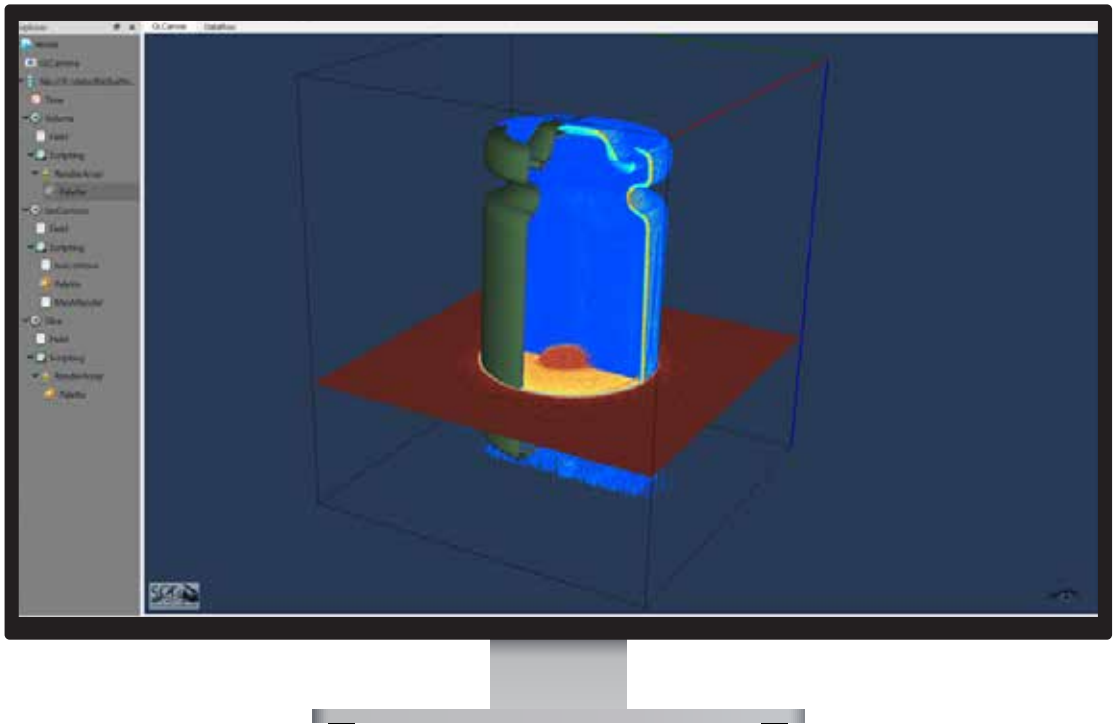
The research group also transformed multimodal data into true-to-life "digital twins," ultra-precise computed replicas of a component's structural and material properties. Using digital twins, scientists can simulate properties including heat transfer and physical deformation to ascertain a component's performance and longevity. "A good digital twin is better than a snapshot in time," says Martz,





Ultrasound can detect faults in repetitive structures where other nondestructive evaluation methods may fall short. (left) Echoes in a planar ultrasound C scan (represented as brightness) denote cavities in an additively manufactured titanium honeycomb, revealing a missing strut (circled). (right) A time-dependent ultrasound A scan measurement confirms the missing strut, indicated by incongruous waveforms.

who served as an adviser on the project. “For example, each time an airplane lands, rubber is stripped off the outer layer of its tire. With a digital twin, we can predict how friction and stress will impact the tire’s performance both in its current state and after repeated landings to determine when it might need replacement.”



Developed by researchers from the University of Utah and Lawrence Livermore, OpenViSUS software allows users to organize, analyze, visualize, and interact with multimodal 3D data as indicated in this image integrating x-ray and neutron scans of a battery, where different colors reflect different material densities.

Computational Foundations

Under Tringe’s leadership, the LDRD team developed a library of algorithms to combine data from XCT, ultrasound, and neutron imaging methods and visualize 3D component reconstructions. Using the numerical technique of forward projection to estimate unseen features, preliminary reconstructions were iteratively refined and rebuilt through a machine-learning model that adjusted geometry and reduced modality-specific artifacts. The team first tested their method on exemplars to further tune the computing process before applying it to additively manufactured components. The resulting model is more than the sum of its parts, reflecting the most confident readings obtained from each modality individually.

Equipped with a trove of data describing structure and composition, the researchers transformed statistics into a comprehensible, user-friendly form. Collaborating with the University of Utah, they built OpenViSUS, open-source software to organize, analyze, and visualize massive data sets—an improvement over existing third-party software that can buckle under processing requirements. Integrated with Livermore Tomography Tools, researchers can run OpenViSUS directly on a laptop to explore and interact with multimodal reconstructions of objects in 3D.

Optimum 3D visualization, however, is found in virtual reality (VR). “Unlike a computer screen, VR completely immerses you in a space,” says Tringe. Reconstructions of highly complex components such as truss structures contain hundreds of thousands of features. Computers can statistically sample slices of an object to check for defects, but defects just outside the sampled slice could be missed. “While we often defer to machines and statistics for consistency,” he says, “we still need a person in the loop to interact intuitively with the data. We could deploy multiple machine-learning algorithms that direct VR wearers to potential problem areas demanding inspection while fully immersed in the 3D structure.” Although VR is developing, the NDE team now has a valuable supply of data and exemplars for future use.

Through innovation and collaboration, Livermore continues to cultivate its strengths in NDE, computing, and additive manufacturing to ensure the safety and operability of national security infrastructure. The cutting-edge CT technique tested by Martz’s research team provides “meaningful NDE capability transfer to meet our program needs,” says Martz. Tringe reflects, “I’m proud of how this large team with diverse backgrounds cooperated on such a complex project, all while dispersed due to pandemic complications. Innovation in these critical processes allows Livermore to fulfill its stewardship duties to an ever-increasing standard of excellence.”

–Elliot Jaffe

Key Words: Additive manufacturing, computed tomography (CT), digital twin, high-z material, laser–plasma accelerator (LPA), multimodal reconstruction, nondestructive evaluation (NDE), OpenViSUS, qualification, surveillance, virtual reality (VR), x rays.

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SHELTERING SCIENCE SAVES LIVES

AFTER a blinding flash, a tall mushroom cloud of radioactive particles is unleashed near a city. Prevailing winds carry the fallout through the densely populated downtown and into nearby neighborhoods. People are working in offices or at home, running errands, or exercising outdoors. Quick decisions by authorities and first responders about how to shelter mean the difference between life and death. How can decision makers maximize the number of lives saved in the initial moments of a catastrophe?

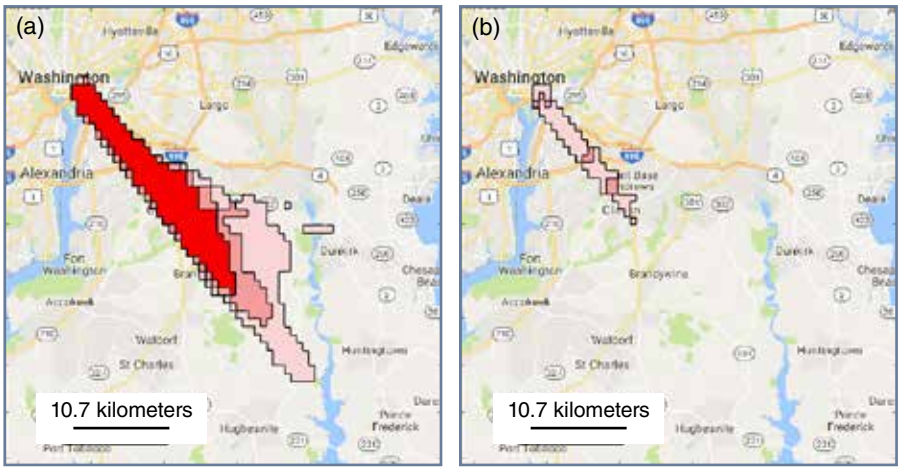
Lawrence Livermore researchers have worked for more than a decade to provide insights for a multifaceted emergency response, and in the process, they have advanced the science of sheltering and developed computer models to identify potentially life-saving strategies. Their efforts have provided actionable insights to protect people from many types of hazards, including radioactive hazards such as fallout from nuclear detonations, particles released from nuclear power plant accidents, and radiological dispersive devices (also called dirty bombs), in which radioactive particles are spread by an explosive device. Other hazards include industrial accidents discharging large clouds of hazardous chemicals, smoke from wildland or urban fires, and airborne-transmitted diseases such as COVID-19, Q-fever, Legionnaire's disease, and Valley fever.

Scientists must study many parameters to understand how sheltering can protect human life. "As an emergency response strategy, sheltering has not been studied as well as evacuation, but getting people into good shelters can save lives," says Livermore scientist Michael Dillon. "Most hazard assessments assume that everyone is outside. Being inside matters. Shelter can drastically change how many people are affected by outdoor hazards."

Sheltering studies conducted by a range of institutions over many decades have typically looked at protection provided by individual or a small number of buildings. Lawrence Livermore's research broadens earlier work by assessing the protection diversity provided by the current national building stock and considering options for improving response to specific threats. Livermore has provided advice to federal, state, and local agencies on how to use existing buildings to protect their populations from radioactive fallout, chemical, and biological hazards. "Sheltering can be used as a good response in so many different areas that a generalized approach may be the best strategy," says Dillon, "and a broad base of partners helps us get there. We are privileged to have great sponsors, collaborators, and end users." The list of partners includes Lawrence Berkeley, Oak Ridge, and Sandia national laboratories; private-sector partners; and agencies such as the Defense Threat Reduction Agency and the Department of Health and Human Services. Funding sources for the team's research and products include the Department of Energy—both the Office of Science and the National Nuclear Security Administration—the Department of Defense, the Department of Homeland Security (DHS), the Centers for Disease Control and Prevention, and the University of Texas.

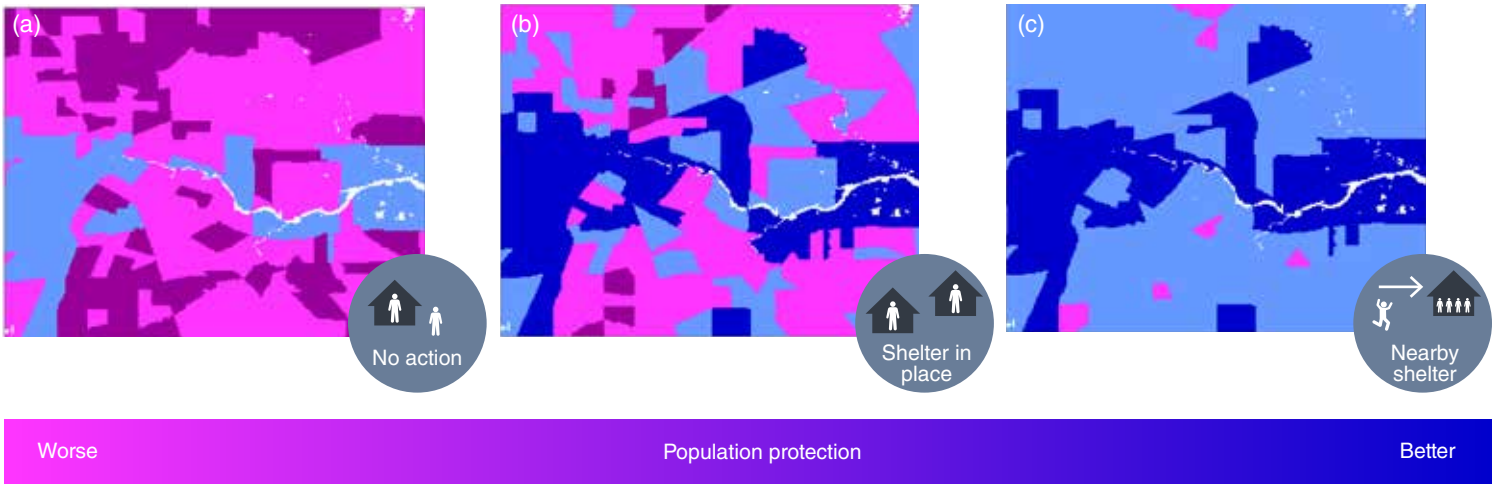
Building Details Matter

Specific properties of a building's design, construction, and operation affect how well it protects people from particular



Risk of Death	Probability
Near certain	90% or more
Likely	50% to 90%
Possible	10% to 50%

Regional Shelter Analysis products present the risk of dying due to fallout radiation exposure. Planning and real-time response visualization and analysis are designed to help officials understand outcomes of possible response strategies for their region. Figures a and b present two outcomes for the same region in a fallout incident. (a) More people remain outdoors and face a higher risk of death (dark red). (b) People shelter in place, and expected risk of death is reduced across the region.



Regional Shelter Analysis incorporates shelter quality into hazard assessments. In Figure a, for example, most people have relatively poor shelter (magenta). In Figure b, people choose to shelter in the closest buildings and have mixed levels of protection (magenta, light blue, dark blue), while in Figure c, people take shelter in nearby buildings such as churches or supermarkets that can offer better protection (light and dark blue).

hazards. For example, protection against nuclear fallout depends on the building size; the weight of the exterior and interior walls, ceiling, and floors; the presence or absence of a basement; as well as aperture (window and door) characteristics. Inhalation hazard protection requires an understanding of how air enters and leaves the building—moving through openings such as windows, doors, ventilation fans, and microscopic cracks in walls as well as, if present, the heating, ventilation, and air conditioning (HVAC) system. In addition, inhalation hazard protection also requires knowing how indoor airborne material may be deposited onto interior surfaces, how it can be filtered by HVAC or air cleaning equipment, and other ways the material will be removed from the air.

After identifying the key building properties, Livermore researchers and their collaborators estimated the protection that current U.S. buildings provide. First, they developed accurate, fast-running, physics-based models that estimate the protection for a single building and hazard. Specifically, Livermore researchers built the PFscreen model for nuclear fallout assessments while a separate, joint effort between Livermore and Lawrence Berkeley researchers developed novel inhalation hazard models. Next, the teams studied how buildings are built and operated in the United States, assembling key information on the range of modern building attributes needed to assess nuclear fallout and inhalation protection. They evaluated the protection for common building types—single family homes, supermarkets, and office buildings—by modeling the protection of more than 10,000 buildings. This approach enabled researchers to understand the average protection for each hazard that each building type provides as well as the variation of protection within a given building and among different buildings of the same type. Now, Livermore researchers and partners understand which building types, and locations within those building types, are best for sheltering for specific hazards—and which may leave people more exposed.

Further, researchers understand how practical actions can improve building protection and indoor air quality. For example, in many U.S. homes, the furnace can offer protection against hazardous smoke if the existing filter is replaced with a readily available, higher quality home furnace filter—rated at minimum efficiency reporting value 13 or better—and the home furnace fan is activated.

Considering the Hazard and Scenario

Livermore and Berkeley researchers also studied how building protection factors vary with specific hazards and scenarios. For example, inhalation hazard protection strongly depends on particle size, with buildings providing orders of magnitude more protection against larger (10-micrometers in diameter) particles than smaller ones (0.1-micrometers in diameter).

For all inhalation hazards, building protection increases with faster indoor airborne material removal rates. In addition, the short-term hazard (acute toxicity) of some chemicals, including many common industrial chemicals such as chlorine, ammonia, and hydrofluoric acid, depends strongly on the peak exposure. For these chemicals, buildings are particularly good at providing protection since they act as low-pass filters, smoothing out the chemical concentration time series and significantly reducing peak exposures. For these hazards, ensuring the toxic outdoor cloud has passed before occupants

leave a shelter is more important than prescribing a particular length of time to remain inside.

For nuclear fallout, building protection depends on the radiation spectra. The gamma radiation emitted from fallout particles will change over the first few days as the short-lived isotopes decay away forming new isotopes. Livermore researchers are investigating how the changing fallout spectra affects the corresponding building protection. This information assists researchers in determining the optimal time to evacuate sheltered populations based on the indoor radiation exposure rate for different building types.

Locating People is Key

Understanding which U.S. buildings offer the best protection provides only part of the puzzle. Knowing where people are located is also important when using sheltering as an emergency response tool. Prior approaches that simultaneously considered both building protection and population location have been computationally expensive, posing a challenge for emergency planning and response activities.

People in this building are well protected and so are least at risk.

People in these buildings are not well protected and so are most at risk.

In many regions, nonresidential buildings, such as offices, churches, and supermarkets (represented by a blue dot), provide much better fallout protection than the surrounding housing (magenta dots).

To meet this challenge, Livermore researchers have developed the Regional Shelter Analysis. This approach combines variations in both building protection and population location to create a set of shelter quality factors for a region or neighborhood. These factors can be used to rapidly scale the results of traditional, outdoor-only assessments, such as those produced by Livermore's National Atmospheric Release Advisory Center, to account for building protection and shelter posture. Resulting maps can indicate regions in which building protection is insufficient to avoid acute radiation injury if dangerous fallout was present. Emergency planners and responders can, therefore, focus efforts on these regions to prevent potentially life-threatening exposure. Fortunately, many regions have a few buildings nearby—such as a church, supermarket, or school—that provide much better protection than the surrounding buildings.

Livermore has extended the Regional Shelter Analysis approach to also account for variations in population demographics and individual sensitivity to the hazard. A recent paper extended the original Regional Shelter Analysis method to show that the spatial distributions of many natural airborne disease outbreaks were well predicted by the Regional Shelter Analysis method combined with physics-based modeling.

Dillon and colleagues are developing planning and real-time response visualization and analysis. Their results will help officials better manage emergencies by identifying which regions could be affected and indicating expected benefits of possible response strategies. Dillon and his team aim to provide useful and technically defensible products to help planners should outdoor hazards occur. "We strive to meet this ongoing challenge," he says. "Sheltering can save lives, and the Laboratory's attention to basic science and computer modeling will show the way."

—Allan Chen

Key Words: Airborne disease; Centers for Disease Control and Prevention; Defense Threat Reduction Agency; Department of Health and Human Services; Department of Homeland Security; heating, ventilation, and air conditioning (HVAC) system; National Nuclear Security Administration; nuclear fallout; PFscreen model; sheltering.

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

Patents

Cylindrical Microelectrode Array for Neural Stimulation and Recording
Kedar G. Shah, Supin Chen, Sarah H. Felix, Satinderpall S. Pannu, Susant Patra, Vanessa Tolosa, Angela C. Tooker, Jason Jones
U.S. Patent 11,357,975 B2
June 14, 2022

Laser-Driven Hydrothermal Processing
Raymond P. Mariella, Jr., Alexander M. Rubenchik, Mary A. Norton
U.S. Patent 11,358,237 B2
June 14, 2022

Water Purification
Ryan P. Brisbin, Jenny Zhou, Allan S. Chang, Tiziana C. Bond, Aaron J. Simon, Lars Voss
U.S. Patent 11,358,880 B2
June 14, 2022

System and Method for Using Ultramicroporous Carbon for the Selective Removal of Nitrate with Capacitive Deionization
Patrick Campbell, Maira Cerón Hernández, Steven Hawks, Colin Loeb, Tuan Anh Pham, Michael Stadermann
U.S. Patent 11,358,883 B2
June 14, 2022

System and Method for Liquid Crystal Display System Incorporating Wire Grid Polarizers for Large Scale and Large Volume Stereolithography
Eric B. Duoss, James Oakdale, Nicholas Anthony Rodriguez, Hongtao Song, Richard Crawford, Carolyn Seepersad, Morgan Chen
U.S. Patent 11,360,348 B2
June 14, 2022

Heat and Fire Resistant Gel Seal
Erik P. Brown
U.S. Patent 11,364,398 B2
June 21, 2022

Photoconductive Charge Trapping Apparatus
Stephen Sampayan, Paulius Vytautas Grivickas, Krisin Cortella Sampayan
U.S. Patent 11,366,401 B2
June 21, 2022

Awards

Three Livermore scientists received the **Department of Energy's (DOE's) Office of Science Early Career Research Program Award**. Awardees typically receive $500,000 annually for five years to support promising research projects. **John Despotopulos**, a staff researcher in the Nuclear and Chemical Sciences Division, was recognized for work investigating heavy elements and stellar nucleosynthesis. **Timofey Frolov**, physicist in the Materials Science Division, was nominated for research into computationally modeling material interfaces of alloys. **Mimi Yung**, deputy group leader within the Biosciences and Biotechnology Division, was recognized for research into protein compartmentalization systems and genetically engineered microorganisms.

The **DOE** granted two Livermore scientists—**Sofia Quaglioni** and **Jennifer Pett-Ridge**—the **E. O. Lawrence Award** for exceptional achievement among mid-career researchers in DOE focus areas. Quaglioni, who has been with the Laboratory over 15 years, serves as Nuclear Data and Theory group leader in the Nuclear and Chemical Sciences Division. She was recognized for substantial contributions in quantum and computational physics that bear strong implications to inertial fusion and astrophysics understanding. Senior staff scientist Pett-Ridge, who has been at the Laboratory for 17 years and is a group leader for the Environmental Isotope Systems Group in the Nuclear and Chemical Sciences Division, was lauded for her research in quantitative microbial ecology and for heading efforts to understand the impact of climate change on the environmental biogeochemical roles of microorganisms.

Abstract

Joining the Fight against Neurodegenerative Disease

Always fatal, amyotrophic lateral sclerosis (ALS) is an adult-onset, progressive neurodegenerative disease with no known cause or cure. In 2019, Lawrence Livermore joined the fight alongside universities, research institutes, and healthcare partners to better characterize ALS through a strategic partnership between the Livermore Lab Foundation and the ALS CURE Project, a nonprofit organization that identifies and funds promising ALS research studies. A growing portfolio of research combines the Laboratory's core competencies in computational modeling, biosciences, engineering, and data sciences with the expertise of external clinicians and researchers to advance understanding of disease pathogenesis. Researchers aim to help identify an ALS disease mechanism and potential prognostic and diagnostic biomarkers for ALS, establishing a target for therapy development.

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U.S. Government Printing Office: 2023-770-075-20027

W87-1 Modification Program

Lawrence Livermore will deliver the first newly manufactured warhead in three decades—transforming the nuclear security enterprise through innovative collaborations in the process.

Also in an upcoming issue:

- *Strategic latency anticipates how emergent technologies might impact national security.*
- *Discovery Science Program experiments reveal iron's properties under extreme conditions.*
- *A new 3D printing technique supports microbial characterization and function.*

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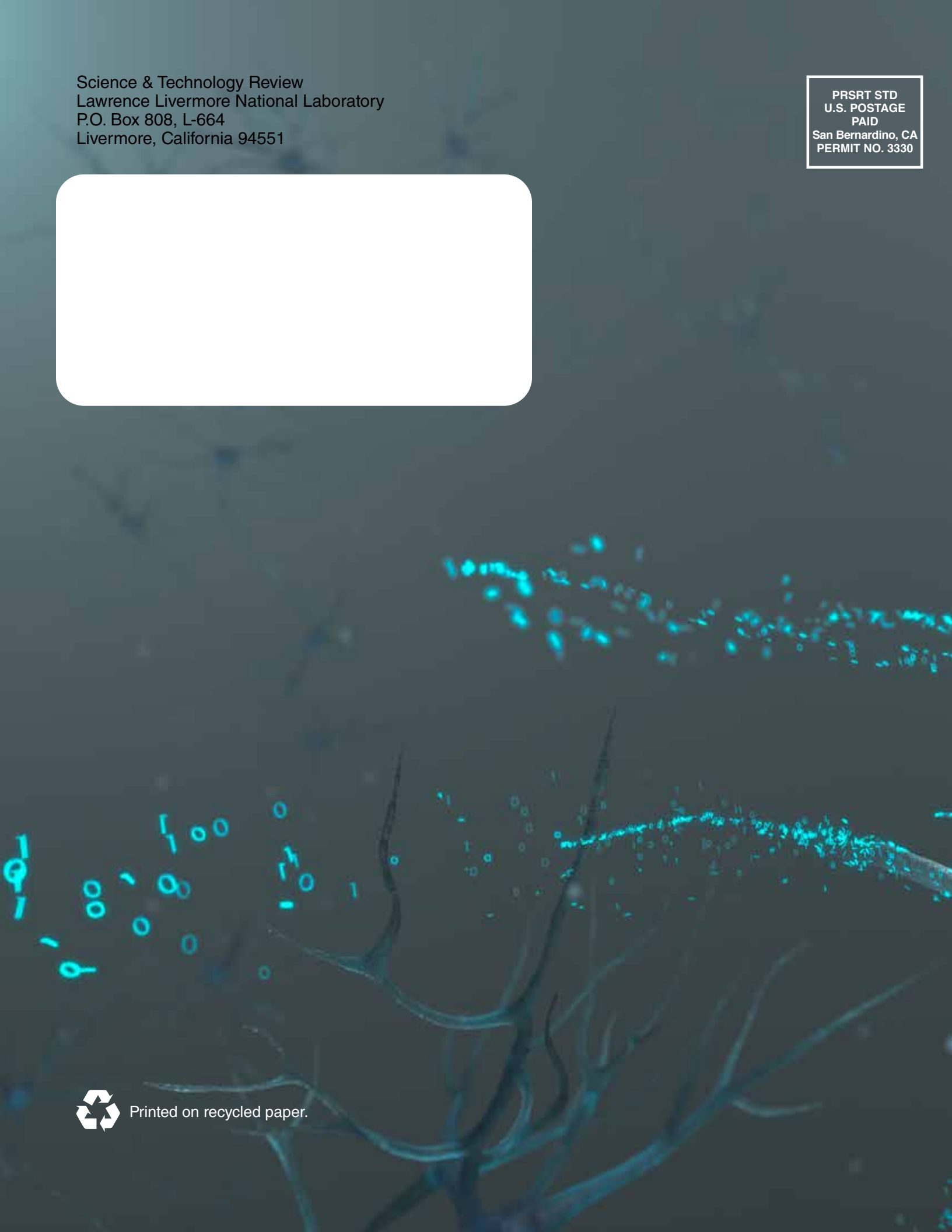

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