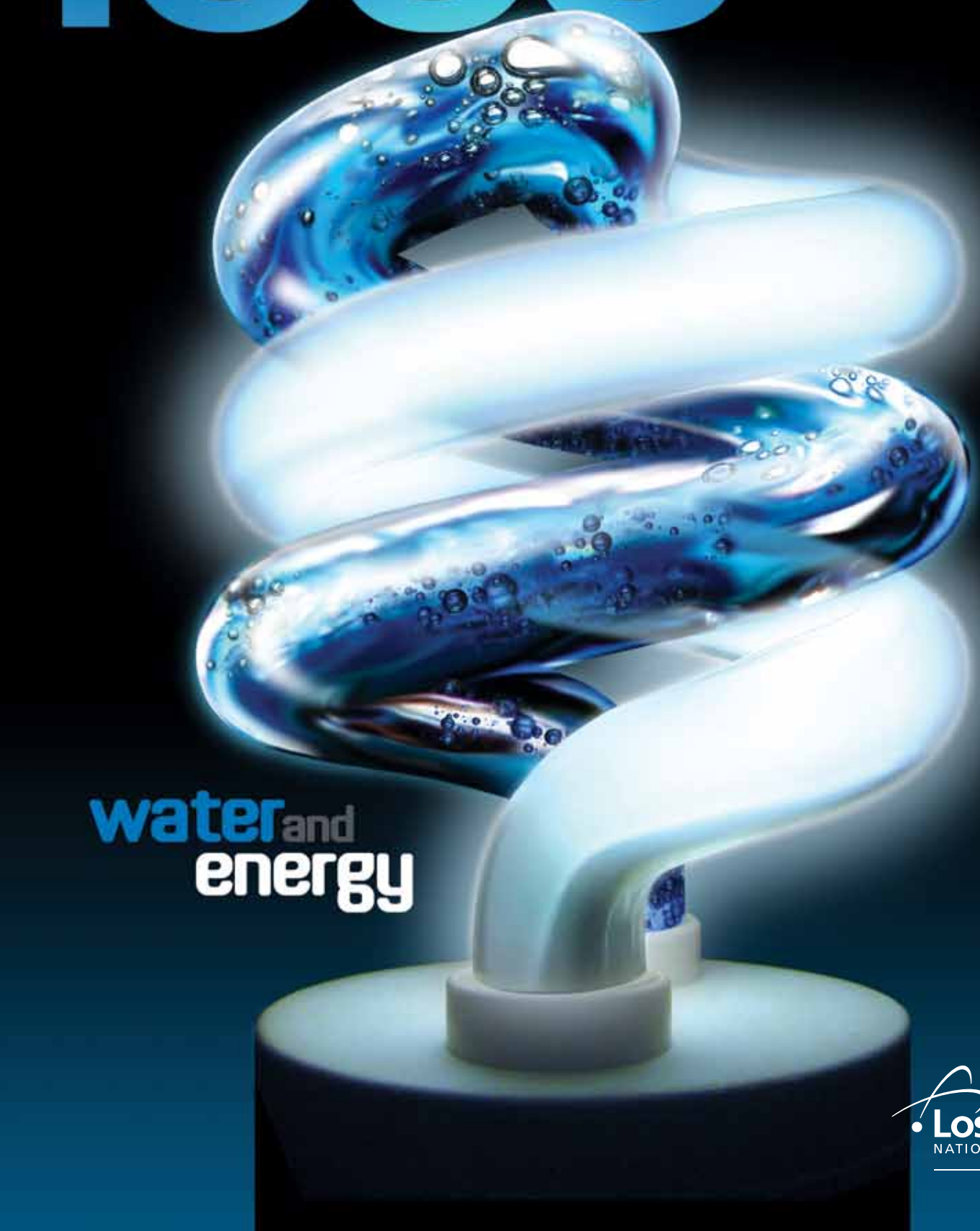
Los Alamos Science and Technology Magazine | January 2015

1663

Drug-resistant TB
Nature-inspired Polymers
MRI for Everyone
Mesoscale Maneuvers



water and energy

Los Alamos
NATIONAL LABORATORY
EST.1943

"Det Syke Barn" (The Sick Child), by Norwegian artist Edvard Munch, shows the artist's sister on her deathbed, stricken with tuberculosis (TB). Commonly called "consumption," TB was often romanticized as the disease of artists because so many of them died from it (Henry David Thoreau, Frédéric Chopin, John Keats, Robert Lewis Stevenson, and all five Brontë sisters, to name a few). Thought to be inherited, it was also believed to bestow heightened sensitivity on its sufferers, endowing them with artistic talent, and, as the cause of their flushed cheeks, sunken eyes, and waif-like physiques, enhancing their aesthetic beauty. Los Alamos theoretical biologists are working toward a better understanding of how *Mycobacterium tuberculosis* adapts to modern therapeutics. See "Fight of the 21st Century" on page 12.

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LOS ALAMOS SCIENCE AND TECHNOLOGY MAGAZINE

About the Cover:

Water and energy resources are interdependent. Water is needed to cool power plants and extract fossil fuels, while energy is needed to purify and distribute water. Any strain on either resource, therefore, produces a corresponding strain on the other. In particular, population growth in the American Southwest will continue to require more electrical power, thereby placing an additional water demand on the already drought-riddled West—a condition that is only expected to worsen with ongoing climate change. Los Alamos is working to understand and predict this complex interdependency to better manage critical resources in the 21st century.

About Our Name:

During World War II, all that the outside world knew of Los Alamos and its top-secret laboratory was the mailing address—P. O. Box 1663, Santa Fe, New Mexico. That box number, still part of our address, symbolizes our historic role in the nation's service.

About the LDRD Logo:

Laboratory Directed Research and Development (LDRD) is a competitive, internal program by which Los Alamos National Laboratory is authorized by Congress to invest in research and development that is both highly innovative and vital to our national interests. Whenever *1663* reports on research that received support from LDRD, this logo appears at the end of the article.

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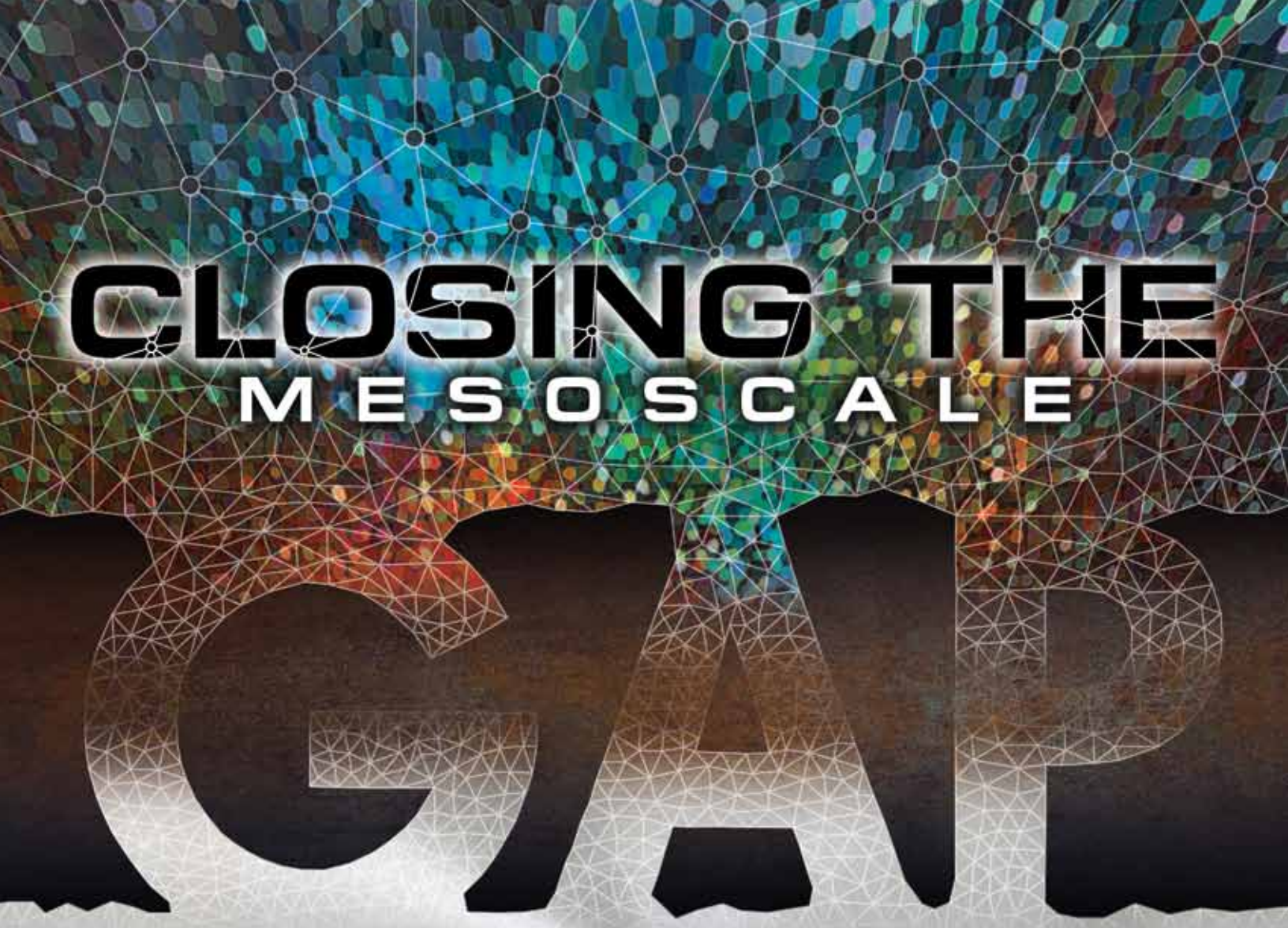
Features

Spotlights



CLOSING THE MESOSCALE GAP

Los Alamos makes a bold proposal to understand and control material properties

Cindy Bolme and Amy Clarke don't see themselves as revolutionaries, and neither of them is talking about a revolution. They're just helping to start one.

The two Los Alamos scientists are contributing to a body of knowledge that, once integrated into the science-technology culture, is likely to revolutionize how we discover, develop, and apply new materials. Bolme's work is the more explosive, with investigations into shock physics, high-pressure dynamics, and the behavior of materials under extreme conditions. Clarke wants anything but an explosion as she investigates how controlling fabrication and processing parameters can produce materials that behave as predicted.

Bolme and Clarke are part of a group of early-career technical staff engaged in what Los Alamos physicist Cris Barnes calls "science on the roadmap to MaRIE." Not a lady but an acronym for Matter-Radiation Interactions in Extremes, MaRIE is the multi-purpose, billion-dollar materials research complex and user facility proposed for Los Alamos National Laboratory.

MaRIE answers the mission need for an experimental facility that can accelerate the qualification, certification, and assessment of materials for national security and science solutions. A huge endeavor that would entail, at the very least, the construction of an electron accelerator, an x-ray free-electron laser, a diagnostic hall, and a materials fabrication facility, MaRIE would be separate from, but integrated with, existing Laboratory facilities and would eventually affect every program at the Lab in some way or another.

Barnes, who *does* see himself as a revolutionary, is the champion for MaRIE. Apart from managing the project, he is its staunchest and most vocal advocate, able to convey to scientists and laypeople alike the science and technology opportunities—and challenges—afforded by the momentous project. The roadmap that he helped create is a plan for all the experiments and projects that need to be proposed and completed to go from the Laboratory's current accelerator facility, LANSCE, to the future accelerator complex, MaRIE. If all goes well, the roadmap will help document the making of a global resource suited to the challenges of the 21st century.

An answer to mission need

The National Nuclear Security Administration (NNSA) is beginning to recognize that if it is to uphold its mission to "sustain a safe, secure, and effective nuclear deterrent," business cannot continue as usual. Many of the weapons in the U.S. nuclear stockpile have been in service well beyond their design lifetimes and will need to have parts and materials repaired, refurbished, or outright replaced to remain viable. Any new or modified part or material needs to be qualified and assessed, and the revamped weapon needs to be certified before it can return to service.

In principle, any aged material can be replaced with a brand-new material remanufactured to be identical to what was used originally, but remanufacturing can be very difficult and costly. Changing the material, however, or changing the process by which it is made raises questions about certifying its performance. If the only way to prove a material will maintain performance over its design lifetime is to wait a design lifetime and then see how it performs, the stockpile would become unsustainable. There is a mission need, therefore, to accelerate the qualification, assessment, and certification of parts and materials used for nuclear weapons, so when new materials and more flexible, better-understood, lower-cost, and certifiable processes become available, they can be readily utilized.

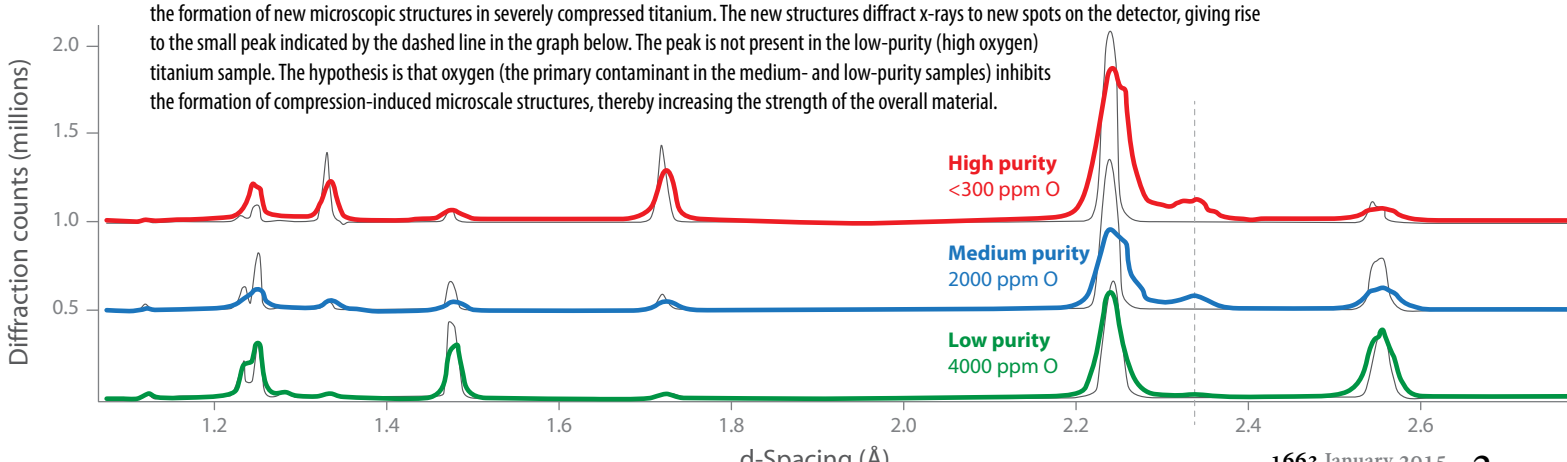
Part of the answer to that mission need is to test the part or material or weapon inside a supercomputer. Weapons scientists can run a simulation and expose the item to a lifetime of random insults, then see how it performs in a weapons simulation. If confident of the simulation results, they can repeat the experiment enough times to build an accurate picture of performance that the NNSA can use to certify (or not) the real item.

This idea of "validated simulation" was proposed in the 1990s for nuclear weapons stockpile stewardship, but it required a simulation capability that didn't exist at the time. Not only were the computers too slow, but the fundamental understanding of materials was too limited. Models could not capture the full range of real-material behaviors, and there was little data to guide the way to improve those models.

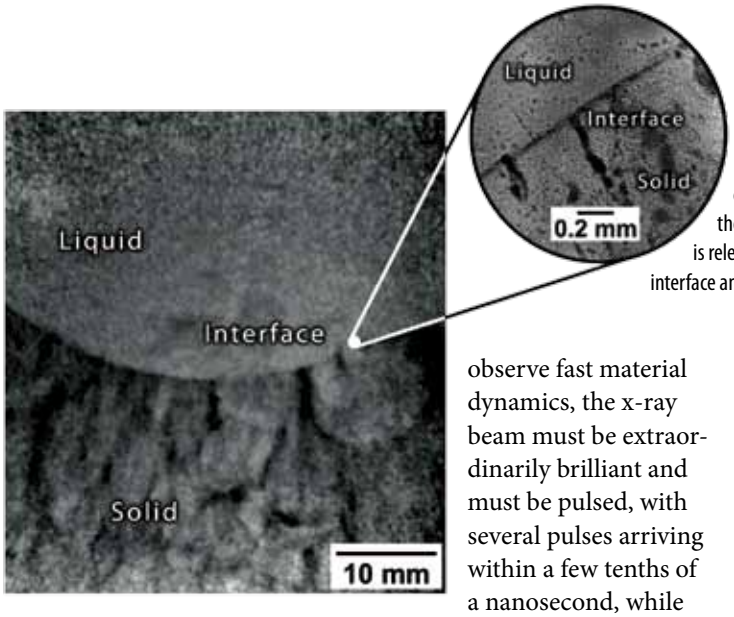
Research tools developed and built under stockpile stewardship since then—DARHT at Los Alamos, NIF at Lawrence Livermore National Laboratory, U1a at the Nevada National Security Site—have contributed greatly to our understanding of weapons materials, mostly by probing atomic and macroscopic distance scales. But between those two domains lies the so-called mesoscale, with physically distinct features—crystal grains, defects, voids, grain boundaries, and interfaces—on the order of 10^{-8} to 10^{-4} meters in size. Mesoscale features have a tremendous influence on a material's macroscopic behaviors and properties.

Unfortunately, the mesoscale is very difficult to probe—too large to be interrogated by atomic-scale probes and too small to be seen by macroscale tools. It's a difficult domain to understand theoretically or to model, too, because it's inherently inhomogeneous, and symmetry arguments that simplify calculations don't apply. Consequently, a gap remains in the understanding of mesoscale properties and responses, especially in extreme temperature, pressure, strain, chemical, electromagnetic, and radiation environments. Without that understanding, a material's behavior cannot be simulated with sufficient validity to allow certification.

Clearly, there is a need for a facility designed to look into and through the mesoscale and obtain data about the dynamic response of the materials used in nuclear weapons, from high explosives to plutonium. The facility would require a coherent x-ray source because x-rays diffract from mesoscale-sized structures, and coherent x-rays open the door to the greatest number of imaging and detection techniques. To



By recording the location and number of x-rays that diffract off her target and hit the detector, researcher Cindy Bolme and her team were able to "observe" the formation of new microscopic structures in severely compressed titanium. The new structures diffract x-rays to new spots on the detector, giving rise to the small peak indicated by the dashed line in the graph below. The peak is not present in the low-purity (high oxygen) titanium sample. The hypothesis is that oxygen (the primary contaminant in the medium- and low-purity samples) inhibits the formation of compression-induced microscale structures, thereby increasing the strength of the overall material.



Amy Clarke and her team use proton and x-ray radiography to make movies of a metal alloy as it cools and solidifies. Proton radiography images a large sample volume and can capture mesoscale and macroscale processes during solidification, as evident in this image of the liquid-solid interface in an aluminum-indium alloy. Information gleaned from such images is relevant for structural development and casting. (Inset) This x-ray image shows the liquid-solid interface and microscopic structural development at 50x higher resolution.

observe fast material dynamics, the x-ray beam must be extraordinarily brilliant and must be pulsed, with several pulses arriving within a few tenths of a nanosecond, while imaging the interior of thick metal samples would require exceptionally high-energy x-rays, on the order of 40–50 kilo-electron volts.

All of these attributes can be met by an x-ray free-electron laser, but one having what amounts to the highest-ever photon energy, the fastest-ever pulse repetition, and by far the largest-ever imaging volume. If built, it would be the most remarkable laser of its time.

Furthermore, though technically challenging, one can envision conducting dynamic experiments using x-ray diffraction, proton radiography, and electron radiography to probe a sample on several length scales simultaneously. Scientists would have the unprecedented ability to follow, in real time, the effect of, say, a shock wave on atomic-, meso- and macroscale structures. If there is also the capability to fabricate samples that have predetermined mesoscale structures, one could begin an experimental program with the intention of showing that materials with *these* types of internal structures, when in *those* environments, consistently behave *this* way. With sufficient data, simulations of material behaviors could achieve predictive capability, and the results of weapons simulations would be accepted with more confidence. This is the vision of MaRIE.

The accelerator complex, if approved, would not produce a beam for many years. The science being done in advance of MaRIE is therefore invaluable for filling in the mesoscale gap and for developing critical skills and expertise. On the day MaRIE opens its doors to a new and different future, experienced Los Alamos researchers can jump through feet first and hit the ground running.

Observations

Cindy Bolme loves it when new data crosses her laptop, be it from her own active experimental group or not. Any new data offers the possibility of increased insight into her current research interest, what may best be called "dynamically induced material transitions," or informally, "what happens when you hit a material really hard."

Bolme uses a technique known as x-ray diffraction to probe atom positions at discrete times after her sample is hit by, say, a powerful shock wave. Her x-ray source is the Linear Coherent Light Source at SLAC National Accelerator Laboratory—more than a million-billion times brighter than any airport security x-ray machine and currently the most brilliant x-ray source on the planet. X-rays flood her sample, and the small fraction that diffract coherently from its atom planes are detected, their positions and intensities analyzed to reveal the atomic-scale structures from which they scattered. Illumination of the sample before and during the shock compression allows her to measure relative changes and infer structural changes.

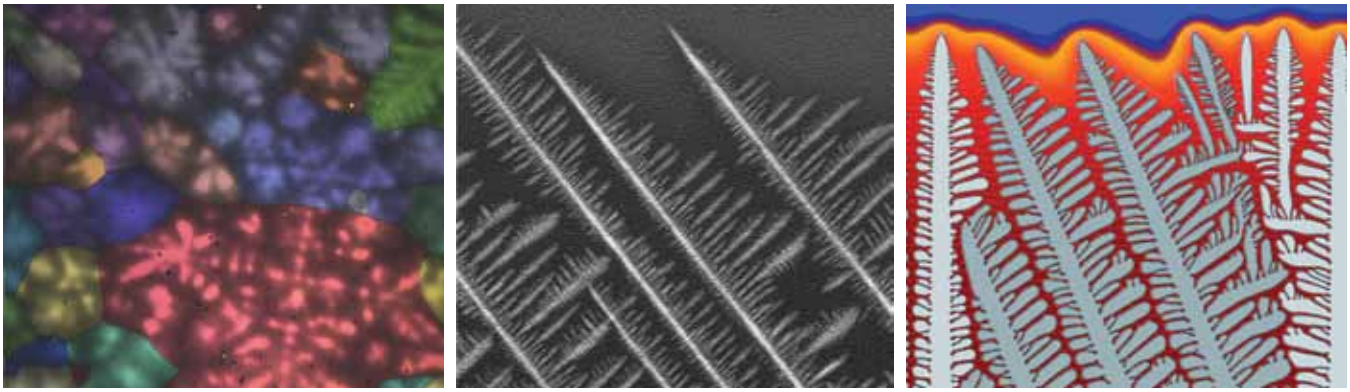
For example, last year she completed a series of experiments to investigate titanium, the lightweight yet strong metal of choice for golf clubs, dental implants, jet plane frames, and ship propellers.

"Any metallurgist will tell you that if you want to make titanium strong, add oxygen," Bolme says. "But why is that? What does the oxygen actually do?"

Under high stress, pure titanium can deform by undergoing a phase transition and by creating at least two types of structural defects, including twinning, in which a large group of atoms shift their positions slightly to form the mirror image of a neighboring group of atoms. The relative contribution from each of the three deformation mechanisms was not known, nor was their relative effect on titanium's strength, but Bolme wanted to find out. She also wanted to know how the relationship between titanium's defects and strength changed as a function of its purity.

Her x-ray diffraction studies showed that during compression, a secondary structure, consistent with twinning, grew within the pure titanium sample, implicating that defect as the primary reason for titanium's deformation. The studies also showed that a set of samples with progressively increased impurity levels had progressively fewer defect structures. It was

Amy Clarke



(Left) An electron-backscattered diffraction image shows microscopic structures called dendrites (tree-like patterns within the colored grains) in an as-cast uranium alloy. (Center) Controlled directional solidification can dramatically affect the evolution and formation of dendrites, as seen in this x-ray image of a tin-bismuth alloy. The tin-rich dendrites are the first structures to form at higher temperatures as the melt cools, resulting in a chemically segregated solidification microstructure that significantly impacts the properties and performance of the resulting alloy. (Right) A computer simulation follows dendritic growth competition in an aluminum-copper alloy during solidification. The darker gray dendrites in the center are being eliminated by their lighter gray neighbors. This process directly affects the development of grains and grain boundaries.

Simulation results courtesy of Alain Karma (Northeastern University) and Damien Tourret (LANL).

known that when oxygen enters the material as an impurity, an oxygen atom will settle into random, non-binding sites between the titanium atoms. These and other studies suggest that oxygenated titanium remains strong because oxygen atoms inhibit twinning, presumably because the randomly spaced oxygen atoms don't allow the mirror-symmetric titanium twins to form.

Would MaRIE aid Bolme in her research? "To be able to image the mesoscale structure directly?" she says, eyebrows raised. "Oh yeah."

Process

Amy Clarke understands deeply what most of us would recognize as true but have little appreciation for—that what you get depends on how you got it. The properties that we assign to a material—the yield strength of a metal, its ductility, or its crystallographic texture—are determined as much by how the material was initially made and processed as by its composition.

Clarke and her team are interested in metal-alloy solidification at different length scales, which is relevant for technologically important processes such as casting. She was fascinated to learn that when she and her team changed the thermal gradient across a sample and adjusted the rate at which the liquid-solid interface advances, they could control the microscopic structures that solidified from the melt and change their morphology. Indeed, the young scientist, winner of an early-career award that currently funds the bulk of her team's research, has had remarkable success in producing various predetermined structures within metal alloys.

"Material properties derive from these structures," she says. "Being able to control their morphological evolution is the first step in gaining control over the resulting material behaviors."

Cindy Bolme

Clarke's team uses x-rays, typically at the Advanced Photon Source at Argonne National Laboratory, to image the mesoscale and microscale structures that form in her samples. Working with the Los Alamos proton radiography (pRad) team, she is also helping to pioneer the use of pRad to make images of solidification processes. Because pRad has great penetrating power, the researchers are able to image large, thick samples and therefore study macroscale processes, complementing the Clarke team's x-ray work.

And if MaRIE affords her simultaneous x-ray and pRad interrogations? Clarke merely imagines the world of possibilities for materials-processing studies.

Status

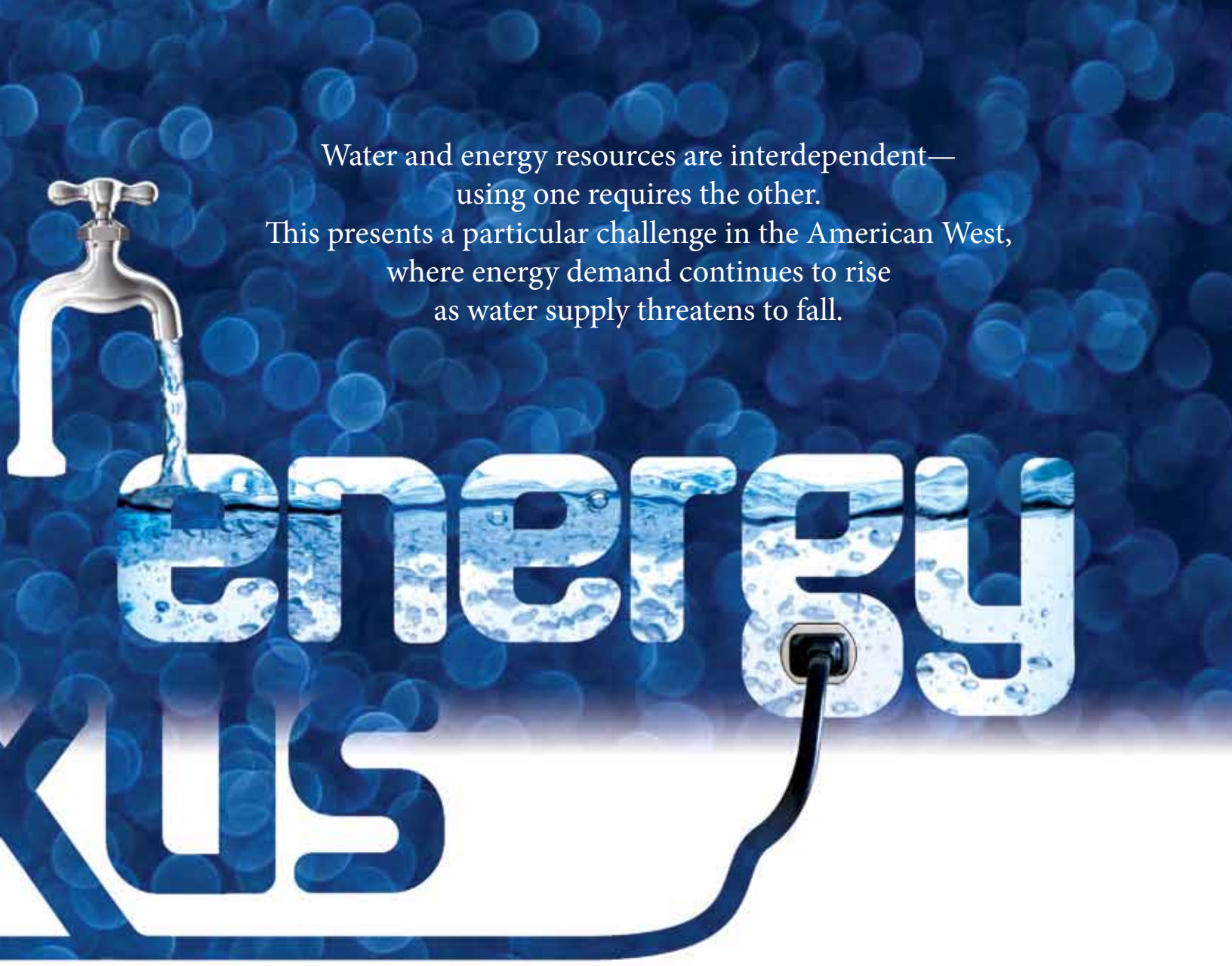
Though a top priority in some NNSA hallways, MaRIE is not yet approved as a project. Some only see the future complex through the focused lens of the weapons community; others see the broad scope of science tools represented by MaRIE and recognize that with the ability to control mesoscale structures comes the opportunity to create a more abundant future. Los Alamos is committed to submitting the case for the mission need by this summer.

MaRIE has already had a positive impact. In the words of its champion Barnes, "Whatever one thinks about the likelihood of an x-ray free-electron laser ever happening at Los Alamos, the recognition of the importance of the problem and the science challenges that it presents are leading us to do some really cool science and technology, now, today."

—Jay Schecker

California's mountains have risen by as much as 1.5 centimeters since early 2013, according to sensitive GPS measurements analyzed by the Scripps Institute of Oceanography. The cause? It's not due to increased magma pressure from deep underground or anything of that ilk; it's due to an exceptionally severe drought that spans California and much of the western United States. The drought means less water weighing down the land, and as a result, the West has risen by an amount that lines up with the amount of water lost during the rise—240 gigatons, or roughly the amount that melts from the entire Greenland ice sheet each year.

At the same time, the Colorado River—which provides drinking water to Los Angeles, San Diego, Phoenix, Tucson, Las Vegas, and more—is showing the effects of a 14-year drought. Its Lake Mead reservoir, America's largest, is now down to about three-eighths capacity, its lowest level since Hoover Dam was constructed in the 1930s. The U.S. Bureau of Reclamation predicts that the dam will produce as little as 1120 megawatts of hydropower by mid-2016, despite its 2074-megawatt capacity, due to diminished and oversubscribed river water. And with long-term rising temperatures, reservoir levels are expected to continue to decline because



of increased evaporation and reduced snowfall in the river's Rocky Mountain headwaters.

In all, 40 million Americans depend on the Colorado River's water, as do the farms that produce two-thirds of the nation's winter vegetables. To make up for its shortfall, residents and farmers increasingly draw from underground aquifers, which, for many aquifers in the West, do not recharge nearly fast enough to recover during a human lifetime. NASA satellite measurements confirm that water is rapidly depleting from the Colorado River Basin aquifer spanning western Colorado and eastern Utah, most of Arizona, and parts of California, New Mexico, Nevada, and Wyoming. No one knows exactly how much of its water remains. Yet back in California, farmers are currently withdrawing 62 percent more groundwater than usual—enough in 2014 alone to submerge Washington, D.C., under 90 meters of water.

The predicament does not end with agriculture and public water use. Energy production, broadly speaking, requires large quantities of water as well. Conversely, water usage requires large amounts of energy. Water is needed to cool thermoelectric power plants—coal, nuclear, gas, or

concentrated solar thermal—and extract fossil fuels from the ground. Energy is needed for water treatment and distribution to agricultural, industrial, and residential customers. The full interdependence is a complicated one, often with a compounding effect. For example, as more people move to the West, more electricity is needed. And higher temperatures brought on by climate change call for more air conditioning, which further amplifies the electrical demand. All this additional electricity requires additional water to cool the power plants, even as climate and weather changes induce increasingly severe water shortages. In turn, pumping and treating the additional water requires still more energy. The bottom line is this: any strain on either resource, water or energy, produces a corresponding strain on the other.

Naturally, this "water-energy nexus" has garnered the attention of the federal government, notably the Department of Energy (DOE), partly because water scarcity and variability could introduce vulnerabilities in the U.S. energy system. The DOE published a major report in the past year highlighting challenges associated with the water-energy nexus, identifying key efforts needed in technology, and addressing vulnerabilities and potential adaptation strategies. Taking on these challenges would require a partnership between the DOE and a broad range of external partners, including all levels of government, private-sector companies, academic institutions, and nongovernment organizations, as well as internal partners, the national laboratories. Los Alamos, for its part, has key modeling capabilities to predict and quantify various aspects of the water-energy nexus and valuable expertise in related areas such as drought ecology and wildfire modeling.

Colorado case study

In the early 2000s, before the current U.S. boom in natural gas and oil production was ushered in by horizontal drilling and hydraulic fracturing technologies, the DOE recognized that achieving energy independence might require developing harder-to-get resources. Their attention at the time was drawn to the Piceance Basin in northwestern Colorado, part of the Upper Colorado River Basin and home to one of the world's richest known oil-shale deposits.

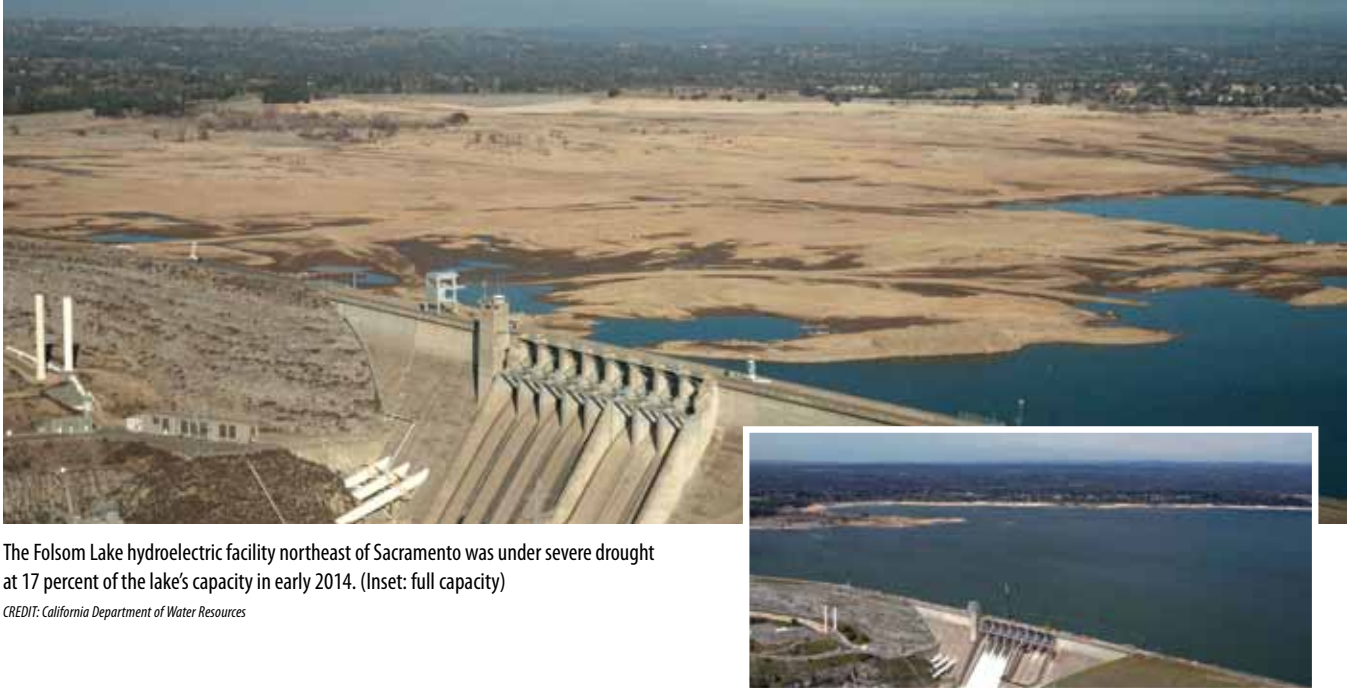
Oil shale is a type of rock that contains a mixture of organic chemicals called kerogen that can be converted into a liquid transportation fuel—a viable substitute for crude oil. But unlike crude oil, which can be directly extracted from underground reservoirs, this kerogen-rich fuel must first be separated from the rock before it can be extracted with conventional production wells. In their quest to investigate the efficacy of developing this potential resource, Shell Oil proposed a process of freezing enormous portions of the subsurface to isolate the oil recovery zone (to prevent groundwater contamination) and then heating the shale for several years to liberate its kerogen. Both the freezing and the heating would be extremely energy intensive, however, requiring significant additional electrical power production in the region. And that additional power production would likely place a prohibitive water and carbon premium on any transportation fuel produced.

The DOE originally asked Los Alamos to evaluate the water and carbon impacts of oil-shale development in the Piceance Basin. Although interest in oil shale soon waned at the DOE and in industry, the study provided an important opportunity to investigate the water impacts and requirements for increased thermoelectric power production in the region for any kind of development.

The Los Alamos research team, led by Andrew Wolfsberg, set out to investigate this representative nexus issue by assessing whether the river basin could provide a sufficient, reliable water supply under a variety of energy-production demands. Each such demand was characterized

Part of the Piceance Basin of northwestern Colorado. The Colorado River, Interstate 70, and many oil and gas sites can be seen.

CREDIT: EcoFlight



The Folsom Lake hydroelectric facility northeast of Sacramento was under severe drought at 17 percent of the lake's capacity in early 2014. (Inset: full capacity)

CREDIT: California Department of Water Resources

by its required daily water flow, which was assumed to be drawn from a hypothetical new water storage facility supplied by flows upstream of the Colorado-Utah border. The researchers would specify the size of the storage facility and simulate realistic river flows into it by taking into account the mountain precipitation that aggregates into a complex system of streams, river stretches, and existing reservoirs before reaching the new storage facility. They would then identify the maximum acceptable rate of withdrawal to prevent the new storage facility from dropping to useless levels (a "dead pool") during times of drought. By varying demands from different types of power production and introducing potential levels of climate change-induced variability, they could determine how much new water storage would be needed to accommodate each level of water use, even through a drought, under realistic flow conditions.

The river water supply to the reservoir was generated by a general hydrology model capable of analyzing the impacts of climate change on water availability and then calculating how much water could be safely removed for new energy development. The model spans the Colorado, Gunnison, and White Rivers, which form a complex system that currently includes nearly 800 man-made diversions, all calibrated to decades of input data from 89 weather stations, 105 stream gauges, and 18 reservior levels. The modeled rivers then experience diminished flows as a result of climate warming: less snowfall, earlier snowmelt, and greater evapotranspiration of rainfall (evaporation from land and transpiration through plants).

Would the water supply be adequate to support additional thermoelectric power production? To find out, Wolfsberg's team examined the simulated river flow and storage requirements near the Colorado-Utah border under a range of climate-change scenarios. The team found that a scenario with a 1°C rise in global temperatures throughout the study period would result in about 8 percent less cumulative river flow over the next 20 years, assuming all other conditions remain similar to the past. With a 2°C rise, the drop would be 16 percent. And the most extreme (but still plausible) climate-change scenario the team considered would produce a 25 percent cumulative reduction in river flow over 20 years.

"The remarkable thing we found is that, even for the same total amount of annual precipitation, the snowpack quantity, its minimum elevation, and the timing of its melt have a tremendous impact on how much flow makes it to the streams and reservoirs, and when," says Wolfsberg. "This, in turn, dramatically affects the availability of water for diversion at the times that it is needed."

Water use for power plant cooling depends on the type of power production and the technology invoked for cooling. Nuclear uses more than coal. Coal uses more than natural gas. And any type of fossil-fuel power plant will need more water with carbon capture and storage operations (CCS) than without. The researchers developed models of these differences to determine the size of the reservoir necessary to reliably supply the cooling water.

Andrew Wolfsberg

For example, if substantial electrical power production were added to the Upper Colorado region to meet growing energy demand in the West, say 4 gigawatts, then 50,000 acre-feet of additional water storage capacity should be sufficient for most types of power plant under current climate conditions. However, under a warmer future climate, the model projections indicate that significantly more storage would be needed for all types of power production other than natural gas combined-cycle technology and for any power production that includes CCS. The models make it easy to make such reevaluations with different assumptions about the power plant demands.

Aim for the best…

The Upper Colorado River Basin aside, the global population is growing and demanding more water and more energy. Meanwhile, climate change is exacerbating both the water shortfall and the energy demand. With these underlying causes decades or more away from abating, the water-energy nexus will only get more intense over time—that is, unless humanity can develop new technologies to reduce the amount of water spent on energy and vice versa. Indeed, the DOE and others are working on a number of promising technologies to help relieve the combined resource pressure.

A particularly important area for improved water-use efficiency is power plant cooling. The maximum efficiency of a thermoelectric power plant depends on two things. The first is the plant's high temperature, achieved by burning coal, for example, and used to convert water into high-energy steam and blow it through a turbine to generate electricity. The second is its low temperature, which is needed to condense the energy-spent steam back into water so that it can be pumped into the process anew.

In a world without water-use concerns, the easiest way to minimize the low temperature (and thereby maximize efficiency) is to divert surface freshwater from a nearby lake or river into the power plant. Heat from the plant is then transferred into this water, either by converting it to steam and allowing it to vent through the cooling towers or by sending it back into the lake or river. Neither option is suitable for a world with water-use concerns, however, since surface freshwater is either lost to the atmosphere as steam or returned to the lake or river at high temperature, causing significant ecological damage.

Fortunately, there are several ways to improve this approach to power plant cooling. For instance, certain substitutes for the standard water-steam power cycles produce less waste heat and therefore require less cooling. Alternatively, the waste heat emerging from the turbines could be put to use somehow, as in a heating system for a nearby industrial process, rather than expending it on vaporizing surface freshwater while the nearby industry gets its heat from the plant's electricity. The power plants could also install airflow-based cooling systems, or hybrid air and water cooling systems, instead of using only water.

In addition, the potential for energy-related water savings is not limited to electrical power plants. Hydraulic fracturing for fossil-fuel extraction, in which pressurized water is injected to fracture the rock and create a pathway for the oil or gas to get to the well bore, may be possible

Standard thermoelectric power plants, like this coal-fired plant in the United Kingdom, use freshwater for cooling to obtain a large temperature difference (between fuel-heated and cooled states) and correspondingly high efficiency. The heat transfers out of the plant and into the cooling water, producing steam. Much of the steam is recaptured for further use, but some is not and simply vents to the atmosphere. In this way, surface freshwater ceases to be available. (The vented steam may subsequently fall as rain, but that rain may fall over the ocean or may fall in a brief drizzle that produces no available surface water.)

Due to drought conditions, Lake Mead, the reservoir created by the Hoover Dam on the Colorado River, is currently less than half full and is on track to produce only about half of its designed hydroelectric generating capacity by 2016.

with highly brackish water from deep underground aquifers, or with other fluids, instead of freshwater—something Los Alamos is also investigating. And water-use efficiency can be improved in other areas, such as industrial processes, algal biofuel production, and carbon capture and storage.

Likewise, new technologies offer the potential for substantial energy savings in water processing. There are several systems under development, for example, to more efficiently process municipal wastewater. Once treated, municipal wastewater can be used for power plant cooling, as is the current cooling paradigm at the nation's largest power plant, the Palo Verde nuclear generating station outside of Phoenix. In addition, a number of efficiency-improving technologies are being explored for desalination, which could increase the freshwater supply from seawater and from brackish-water aquifers. Better yet, desalination plants could potentially be powered by the waste heat from power plants. These improvements and others are currently at various stages of development.

… but prepare for the worst

Meanwhile, Richard Middleton, a member of Wolfsberg's team at Los Alamos, is taking a new direction on the Piceance Basin research with a study of America's at-risk watersheds. In particular, he is interested in identifying how and when human use and climate change might push them past some "point of no return" and what we can do about it—critical information for policymakers.

"This is a serious energy and national security problem," says Middleton. "Many of our critical watersheds are already under severe stress. Then add projected changes in temperature, extremes of precipitation and drought, insect infestations, and climate-induced wildfires, and ask: Where are the tipping points that will disrupt our national water supplies for the long term?"

Middleton's research is designed to predict those tipping points and quantify the resulting changes in water supply and water quality, corresponding energy-resource impacts, and any other downstream effects. It leverages key model- and experiment-driven Los Alamos research, including how and why trees die; how and why wildfire spreads and what it does to watersheds; and advanced watershed-scale simulation to couple surface and subsurface water systems, accounting for climate change, vegetation dynamics, and complex feedbacks. By merging such components, Middleton is developing a new framework to reveal the tipping-point vulnerabilities and assess the effectiveness of various possible interventions, such as controlled burns or changes in aquifer management. If there's any combination of actions that will be particularly effective in protecting our coupled water and energy resources, he reasons, it's best to find out now.

"Obviously there are tough times ahead," he says. "And our best defense right now is knowledge—so we know what we're facing and how to focus our efforts." LDRD

—Craig Tyler

FIGHT of the 21st CENTURY

REMATCH

TUBERCULOSIS VS. HUMANITY

EXPOSURE OF TB'S SECRET STRATEGY COULD SHIFT THE ODDS MORE IN OUR FAVOR.

THE DISCOVERY OF STREPTOMYCIN in the mid-1940s turned the world on its ear. The broad application of this antibiotic drug abruptly reduced tuberculosis (TB) from the leading cause of death to a 20th century anachronism in the United States. Streptomycin and the arsenal of antibiotics discovered since are powerful tools in the fight against infectious disease. They, along with vaccines, are the best line of defense. But drug mismanagement, particularly over-prescription and misuse, can lead to resistance, reducing their ability to fight infection and actually strengthening the bacteria they were meant to kill. Tuberculosis is one of the diseases antibiotics have been helping the world beat, but it is showing worrisome trends in drug resistance.

In 1991, the World Health Organization (WHO) recognized the growing problem of TB and implemented a massive, globally coordinated effort to bring down the annual number of new infections and bring up the number of cured ones. Since that time, according to the latest WHO Global Tuberculosis Report, new cases are down by 41 percent and fatal outcomes have dropped by nearly half. So their strategy, which hinges on effective diagnosis, availability of drugs, and supervised adherence to treatment regiments, is working.

Still, over a million people die each year from TB. Roughly a third of the world's population is infected and nine million new infections occurred in 2013 alone. Don't know anyone with TB? That's because most infections occur in developing countries; in 2013, the highest incidences of fatal TB were in India, South Africa, Bangladesh, Pakistan, and Indonesia.

Tuberculosis is a contagious and airborne respiratory infection (though organs other than the lungs, such as the bones or lymph nodes, can be infected too). The causative agent, *Mycobacterium tuberculosis*, is a hearty species of bacteria that has plagued humans since time immemorial. Most infections are latent, meaning a person can be infected without developing the disease for a long time, sometimes throughout their life. However, about 10 percent of infected people develop the disease, or active TB, which is very dangerous and second only to human immunodeficiency virus (HIV) in the number of global deaths it causes each year. But TB and HIV aren't operating independently; in fact, they work in terrible synergy. First, HIV depresses the immune system, and then TB comes in as an opportunistic secondary infection and overwhelms the body's remaining defenses. Co-infection with HIV raises the likelihood of developing active TB by up to 20 times and accounts for a quarter of TB's death toll.

Co-infection with HIV is not the only thing driving TB's re-emergence, however. Recent decades have seen alarming increases in mortality due to new multidrug-resistant and extensively drug-resistant bacterial strains. Multidrug-resistant TB (MDR-TB) is defined as having resistance to the two most potent first-line drugs, isoniazid and rifampicin. Extensively drug-resistant TB (XDR-TB) is defined as having resistance to both of the first-line drugs, as well as other commonly used TB drugs. First identified during a highly lethal 2005 South African outbreak (98 percent dead within two weeks of diagnosis), XDR-TB has now been reported in 92 countries, including the United States. In recent years, there have been ominous, though rare and isolated, reports of totally drug-resistant TB strains that cannot be treated with any drugs at all.

Before antibiotics, public signs such as this one from England were a major component of tuberculosis control.

Drug resistance is usually diagnosed *in vitro*—that is, in a culture dish in a lab—which can take weeks, is difficult to do in the field, and can have poor sensitivity and specificity. On-demand molecular diagnostic tests are becoming increasingly available, but many of the resource-limited, hardest-hit regions still use the culture method. In addition, culturing relies on a single sample, which may underrepresent the composition of an individual infection. So while determining the best treatment for a patient depends on a drug-resistance profile, such profiles can be inaccurate and difficult to generate. Improved outcomes rely on improved speed and accuracy of diagnosis, which might be achieved with improved data.

This is where Los Alamos theoretical biologist Bette Korber and her team come in. Korber works primarily with HIV, which led first to an interest in TB and next to an opportunity to study it. In collaboration with the National Institutes of Health (NIH) and the International Tuberculosis Research Center in South Korea, Korber and colleagues collected data on as many TB strains as they could get their hands on. They then analyzed the strains' genetic codes, transmission routes, and drug-resistance profiles, searching for ways that drug-resistance diagnosis might be improved.

SICKNESS, STATEHOOD, AND SITE Y

AT THE PEAK OF THE LUNGER MIGRATION, NEARLY A THIRD OF NEW MEXICO'S POPULATION HAD ARRIVED ON THE WINDS OF THE WHITE PLAGUE

At the turn of the 20th century, tuberculosis, also called consumption, was the leading cause of death in the United States. With no effective drugs, doctors prescribed fresh air, sunshine, rest, a hearty diet, and cultivation of a cheerful attitude. Consumptives wheezed their way to the American Southwest on doctors' orders or by their own accord, with hopes that the salubrious climate would cleanse their lungs and restore their vigor.

New Mexico received these medical refugees, colloquially called "lungers," by the thousands. While Texas, its neighbor to the east, maintained that consumptives were explicitly unwelcome, New Mexico eagerly built tuberculosis hospitals, or sanatoria, to accommodate the coughing droves. Military hospitals led the movement, but soon private sanatoria abounded, due largely to tax incentives codified in the 1903 "Act to Encourage the Establishment of Sanatoria in the Territory of New Mexico." By 1908, the lunger movement was in full swing and the territory's governor, jockeying for federal recognition, proclaimed New Mexico "the nation's sanatorium."

At the peak of the lunger migration, nearly a third of New Mexico's population had arrived on the winds of the white plague. In fact, the influx of health seekers and their comparatively high rates of recovery—New Mexico claimed the lowest tuberculosis-related death rate in the country—were cited by territory officials in support of their ongoing petition for statehood, which was granted in 1912.

But it's not just New Mexico's state history that was touched by tuberculosis. Los Alamos and its shadowy first ambition, the Manhattan Project, were also influenced by lungers in numerous and lasting ways.

Photograph used with the permission of the Amon Carter Museum of American Art

Architect **John Gaw Meem** came to New Mexico as an invalid in 1920, having contracted tuberculosis on the heels of the Spanish flu. As he convalesced at Santa Fe's Sunmount Sanatorium, he grew enamored with the Spanish Pueblo Revival style of architecture. After his recovery, he stayed in Santa Fe and dedicated his career to the conservation of New Mexico's architectural heritage. He became a preeminent purveyor of historically faithful architecture and designed dozens of iconic buildings throughout the state. Early in his career, in 1928, Meem was commissioned by Ashley Pond, the founder of the Los Alamos Ranch School, to build the school's central building, an imposing lodge of upright logs. The school was purchased in 1943 by the United States Army for use as "Site Y," the code name used to scout locations for the Manhattan Project's research laboratory. Meem's now-famous Fuller Lodge still stands and is adjacent to the Los Alamos Historical Museum.

Also in residence at Sunmount Sanatorium circa 1920 was Dorothy Scarritt, a tubercular recent college grad from Missouri. During her recuperation, Dorothy liked Santa Fe so much that years later—after having recovered, married, moved to the Midwest, and become suddenly widowed—she returned, now **Dorothy McKibbin**, to raise her child. When the top-secret Manhattan Project came to northern New Mexico, Dorothy was hired by J. Robert Oppenheimer, the project's civilian director. Her title was "secretary" but she was essentially the gatekeeper for all new arrivals to "the hill," as Los Alamos was called. While overseeing the flow of scientists, technicians, their families, and supplies up the hill, she diligently and skillfully preserved the project's secrecy—unaware herself of its true scope—which was vital to its ultimate success.

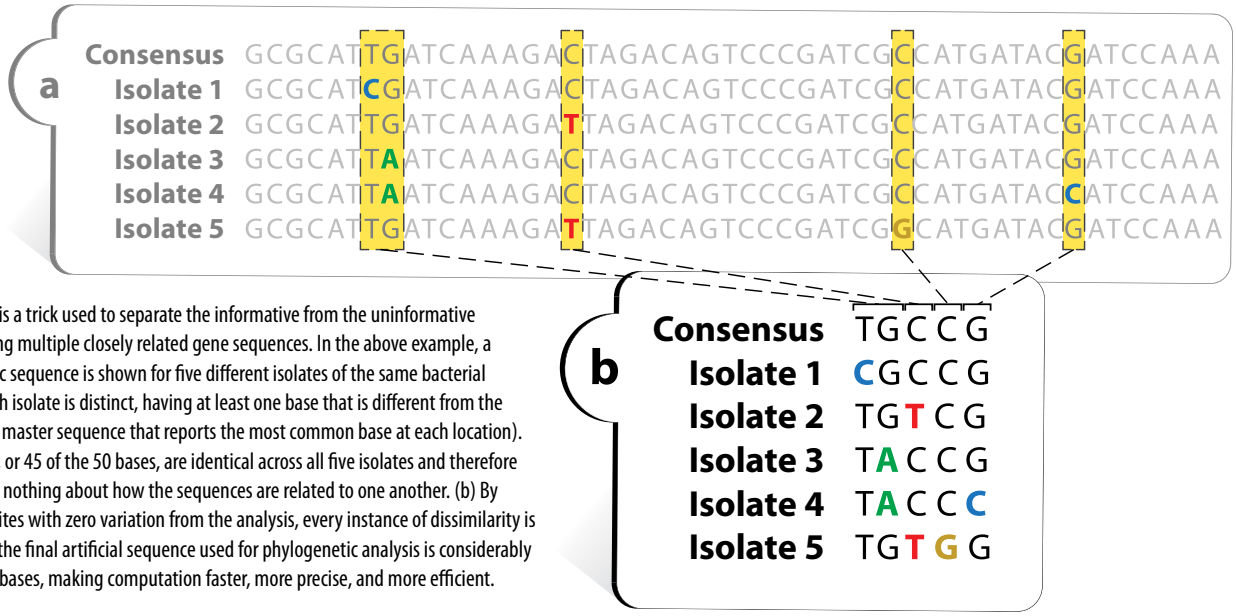
CREDIT: LANL archives

Photograph used with the permission of Melanie Jackson Agency, LLC

Tuberculosis nearly prevented the young **Richard Feynman**, famous physicist and Nobel laureate, from participating in the Manhattan Project. His wife, **Arline**, was terribly ill, and he would not leave her to come to Los Alamos. It was Oppenheimer who located a sanatorium in Albuquerque for her and who convinced Feynman that he could visit her on weekends while spending his workweek on the hill. Arline died from her illness in Albuquerque in June of 1945, just two months before the end of the war and nine months before streptomycin was proven as a cure.

CREDIT: LANL archives

Finally, **Oppenheimer** himself spent time recovering from tuberculosis in New Mexico. In 1922, just after graduating high school, he contracted severe dysentery while traveling in Europe and was sent to New Mexico with a chaperone to recuperate. Rather than snoozing in a chaise lounge, he traveled the hills by horseback and befriended local families. He so loved the culture, people, and landscape that when he was diagnosed with tuberculosis in 1928, he again came to northern New Mexico to recover. These health-seeking stints and subsequent visits were how he came to know the Los Alamos Ranch School and the Pajarito Plateau upon which it sat. So when General Leslie Groves asked if he had any thoughts on a good location for Site Y, Oppenheimer knew just the place.



Concatenation is a trick used to separate the informative from the uninformative when comparing multiple closely related gene sequences. In the above example, a 50-base genetic sequence is shown for five different isolates of the same bacterial species. (a) Each isolate is distinct, having at least one base that is different from the consensus (the master sequence that reports the most common base at each location). Ninety percent, or 45 of the 50 bases, are identical across all five isolates and therefore tell researchers nothing about how the sequences are related to one another. (b) By removing the sites with zero variation from the analysis, every instance of dissimilarity is preserved and the final artificial sequence used for phylogenetic analysis is considerably smaller, only 5 bases, making computation faster, more precise, and more efficient.

Minimizing here, maximizing there

M. tuberculosis comes in different classification types that are associated with particular geographic regions and clinical profiles. Determining which type a sample belongs to is done by looking for specific genetic markers that are diagnostic for that type. There are a few different kinds of tests that can be done, but they are limited in that they only look at part of the genome. Like the parable of the blind men trying to describe an elephant from touching only one part, important information is lost by not considering the whole. The Los Alamos team looked at whole genomes and compared what they saw to other researchers' reports of trunks, tails, and tusks.

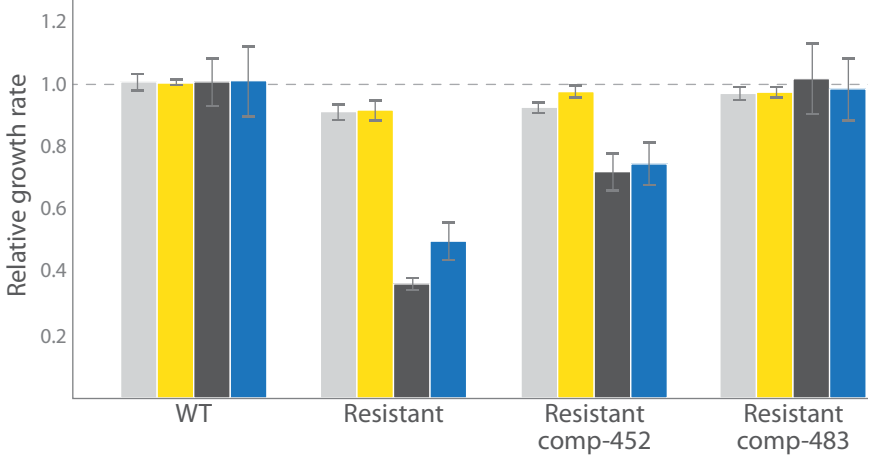
Viral immunologist Karina Yusim, a scientist in the group and expert in sequence analysis, wanted to use whole-genome sequence (WGS) data to put together a global evolutionary portrait of tuberculosis and map drug resistance within and between different outbreaks. The genome of *M. tuberculosis* is roughly four million bases long. (For comparison, influenza virus has 13.5 thousand bases and the human genome has 3.2 billion.) Comparing multiple strains on a genome level can be a bit tricky, so Shihai Feng, a programmer on Korber's team, wrote a computer code to reduce the amount of data without reducing its content by doing a data transformation called concatenation. Information about the origins and relatedness of genomes is gleaned from looking at the differences between genomes. Most of the four million bases are identical at each position across all strains (not surprising, given that all the strains were the same species, *M. tuberculosis*), but every so often one strain will have an A, for instance, where all the others have a G. This is a single nucleotide polymorphism, or SNP (pronounced "snip"). The SNPs are the variation, and the variation is they key, so by removing all the identical genome positions, each four-million-base genome was paired down to a more manageable size of roughly 18,000 variable bases.

That is still a relatively high number of SNPs. A handful of TB strains are very well studied, but because the Los Alamos researchers included all available WGSs, not just the well-studied ones, they discovered that some of the sequences had artifacts that looked like SNPs, but weren't. Feng, Yusim, and Korber developed a novel algorithm that would flag mutations suspected of being sequencing artifacts rather than SNPs of biological origin so they could omit those confirmed to be artifacts from further analysis.

Next they did a phylogenetic comparison of their concatenated WGS SNP data to the small subset of SNPs used by conventional methodology. Phylogenetic analysis compares numerous similar sequences and mathematically determines the most likely relationships between them to suggest patterns of evolution and transmission. They found that the inclusion of SNPs from the whole genome provided finer resolution of relationships between strains and could be important in figuring out how drug resistance evolves, which often involves just a single, well-placed SNP.

Greater than the sum of its parts

One of the most potent antibiotics against TB is the first-line drug rifampicin. It is also one to which TB becomes resistant most frequently. The TB gene *rpoB* (for RNA polymerase beta subunit) encodes the portion of RNA polymerase—an enzyme vital for bacterial reproduction—that rifampicin acts on. When rifampicin binds to a particular bulge on the enzyme's surface, it blocks a neighboring channel that contains newly synthesized RNA. If the RNA can't exit the channel, the enzyme becomes clogged and the



The cost of bacterial drug resistance and the restoration of fitness by compensatory mutation are most pronounced when resources are scarce—as would be the case in an ailing human body. Wild-type ("WT") *Mycobacterium smegmatis,* a close relative of *M. tuberculosis,* grows equally well in conditions of high sugar (white bars), low sugar (black bars), reduced carbon (yellow bars), and reduced carbon plus low sugar (blue bars). When a mutation conferring rifampicin resistance is introduced ("Resistant"), growth is significantly slowed for the low-sugar group and for the reduced-carbon plus low-sugar group. When either of two compensatory mutations are then added, either at position 452 ("Resistant comp-452") or at position 483 ("Resistant comp-483") within the *rpoC* gene, growth is either partially or completely restored, relative to the unaltered wild type.

bacteria can't grow. So if the bacteria want to prevent the action of the drug, one way to do that is to modify the shape of the particular bulge that rifampicin binds to so that it doesn't fit any more. And that's exactly what happens. Rifampicin resistance-conferring mutations all occur in a very narrow window in the middle of the *rpoB* gene, the part that encodes the bulge on the beta subunit bound by rifampicin. (This is not the case with other drugs.)

But resistance isn't free. It's been long understood that with acquisition of drug resistance there often comes a loss of fitness. The RNA polymerase enzyme's natural structure was optimized over eons of evolution, so to suddenly tweak its shape usually makes it less efficient and slows bacterial growth. However, the fitness defect is temporary while the drug resistance is not. Somehow, drug-resistant strains can regain fitness without losing resistance. Last year, it was finally revealed that the bacteria use a push-me-pull-you strategy, mutating a different part of the RNA polymerase to compensate for the shape change in *rpoB*.

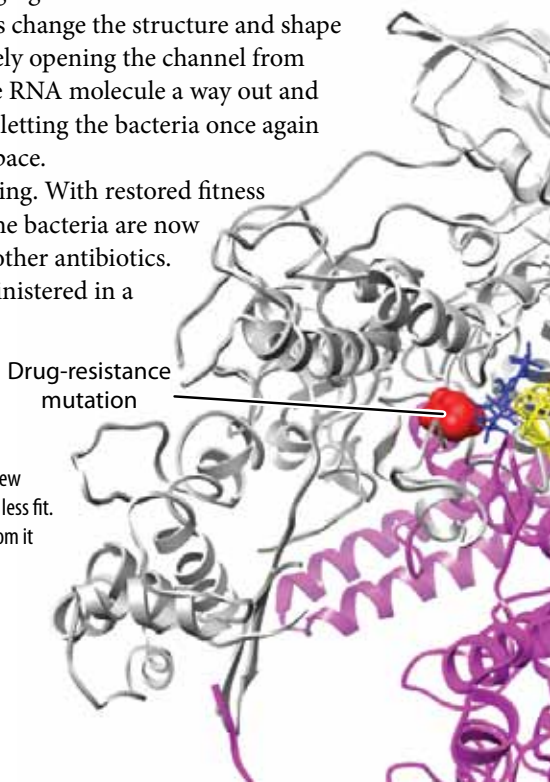
The Los Alamos team and its collaborators at NIH and in South Korea wanted to figure out just how these compensatory mutations worked. Korber and Yusim, together with Los Alamos physicist James Thieler (Korber and Theiler are not only colleagues, they happen to be married) looked at global TB WGS data as well as a set of data from highly antibiotic-treated patients in South Korea. When they compared patterns of mutation throughout the genome between drug-susceptible TB and drug-resistant TB, they found one gene stood out—it was the gene for a different part of the polymerase, called *rpoC*. Looking closely at *rpoC* gene sequences, they found that, although mutations in *rpoC* aren't required for rifampicin resistance, those mutations appeared most often in rifampicin-resistant strains and seemed to accompany particular *rpoB* mutations.

Korber's NIH collaborators put the identified *rpoC* mutations into *Mycobacterium smegmatis*, which is closely related to *M. tuberculosis* but easier and safer to work with, and then looked at bacterial growth. They showed that when *rpoB* is mutated for rifampicin resistance, growth declines, but when *rpoC* was also mutated, growth was mostly or completely restored. This showed that compensation was real, but it didn't offer much as to how it worked.

To determine that, Los Alamos structural biologist Chang-Shung Tung made a digital structural model of the *M. tuberculosis* RNA polymerase (RNAP) using RNAPs from other bacteria as a guide. "It wasn't hard to build the structure," he recalls. "The trick is to understand what's going on—how do these two mutations, which are physically far from each other, work together?"

Once again, the answer was in looking at the whole system instead of just one part. The protein structure itself provided few clues, but once Tung added DNA and RNA to the model—RNAP makes RNA molecules using a DNA template and interacts closely with both molecules—the mechanism became clear. It turned out the RNA was the mediator between the two mutations. The *rpoB* mutations causing resistance to rifampicin result in larger, bulkier amino acids being used to build that part of the enzyme, which has the channel-clogging effect associated with fitness loss. But the *rpoC* mutations change the structure and shape of the channel wall, effectively opening the channel from the other end. This gives the RNA molecule a way out and ungums the RNAP's works, letting the bacteria once again reproduce at an unfettered pace.

And there's another thing. With restored fitness and rifampicin resistance, the bacteria are now perfectly poised to take on other antibiotics. Rifampicin is typically administered in a



This 3D model of the RNA polymerase enzyme illustrates the mechanism of compensatory mutations in drug-resistant tuberculosis. The antibiotic rifampicin binds to the polymerase in such a way that nascent RNA (yellow), which is assembled in a special channel on the surface of the enzyme, cannot exit the enzyme complex, so bacterial growth stops. Tuberculosis achieves rifampicin resistance by altering the amino acids at this location (red), thereby changing the polymerase's shape and making the drug unable to bind. But the new shape still partially impedes the enzyme's function, so the resistant bacteria replicate slower than they did before—they have become less fit. Compensatory mutations (green), however, act at the other end of the channel, opening it up and giving the new RNA molecule the room it needs to leave the enzyme complex, thereby restoring fitness to the bacteria. Now they are both resistant and fit.

cocktail of several different drugs, which is very effective for drug-susceptible TB. But if the patient has rifampicin-resistant TB, the drug cocktail won't work as well and could actually increase the likelihood of resistance developing to the other drugs in the cocktail. This is one way patients progress from MDR-TB to XDR-TB.

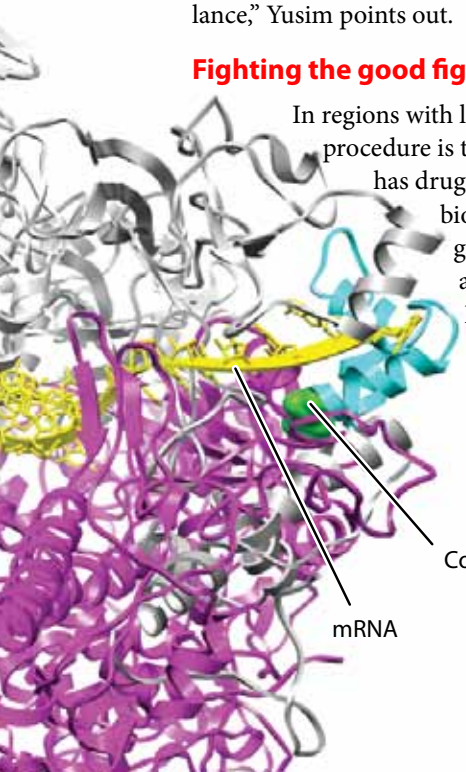
In addition to facilitating resistance to more drugs, compensated drug-resistant forms may also fuel transmission. In the Los Alamos group's analysis of the South Korean data, the same *rpoB-rpoC* mutation pair was found in samples from TB patients who had been treated in the same hospital. That means the resistant, compensated form was transmitted in the hospital. This was the first realization and documentation of compensatory mutations being involved in epidemic spread of TB.

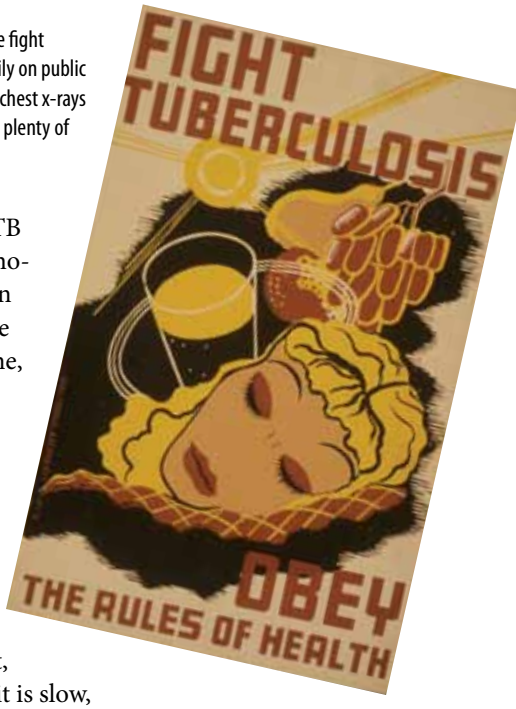
Knowing now that resistant, compensated TB was transmissible, Korber's group next looked at outbreak data from South Africa that had yielded multiple strains of XDR-TB. Revisiting the data revealed that *rpoB-rpoC* resistance and compensatory mutations also underlied these outbreaks. Because the samples didn't have drug-resistance mutations in common for drugs other than rifampicin, upon initial investigation, they were declared to represent independent instances of resistance acquisition. But the Los Alamos team found that all isolates did indeed carry the same *rpoB-rpoC* mutation pair. So resistant and compensated strains were being transmitted in South Africa as well.

The South Korean and South African studies led the group to conclude that compensated rifampicin-resistant strains with improved fitness were being transmitted, leading to subsequent acquisition of different levels of drug resistance in different people. So rifampicin-resistant strains with restored fitness may be fueling the global increase in MDR-TB and XDR-TB cases. "This highlights the importance of studying compensatory mutations and including them in diagnostic screening and epidemiological surveillance," Yusim points out.

Fighting the good fight

In regions with limited resources, the standard procedure is to assume a first-time TB patient has drug-susceptible TB and prescribe antibiotic drugs. But, as the Los Alamos group and others have shown, that assumption is often erroneous. Resistance begets resistance, compensation begets resistance, and both facilitate transmission, making first-time patients who are already resistant more and more common. And TB infections are not homogeneous—a person can be infected by multiple strains at the same time, so just because they coughed up drug-susceptible TB on the day they were tested doesn't mean they aren't dying from XDR-TB. And while testing often isn't done before treatment, even when it is done, it is slow, costly, and not always accurate. Yet skipping the test and going straight to the cocktail for patients who are already infected with resistant TB only compounds the global problem.





Before the age of antibiotics, the fight against tuberculosis relied heavily on public campaigns promoting frequent chest x-rays and healthy lifestyles, including plenty of sun, rest, and nutrition.

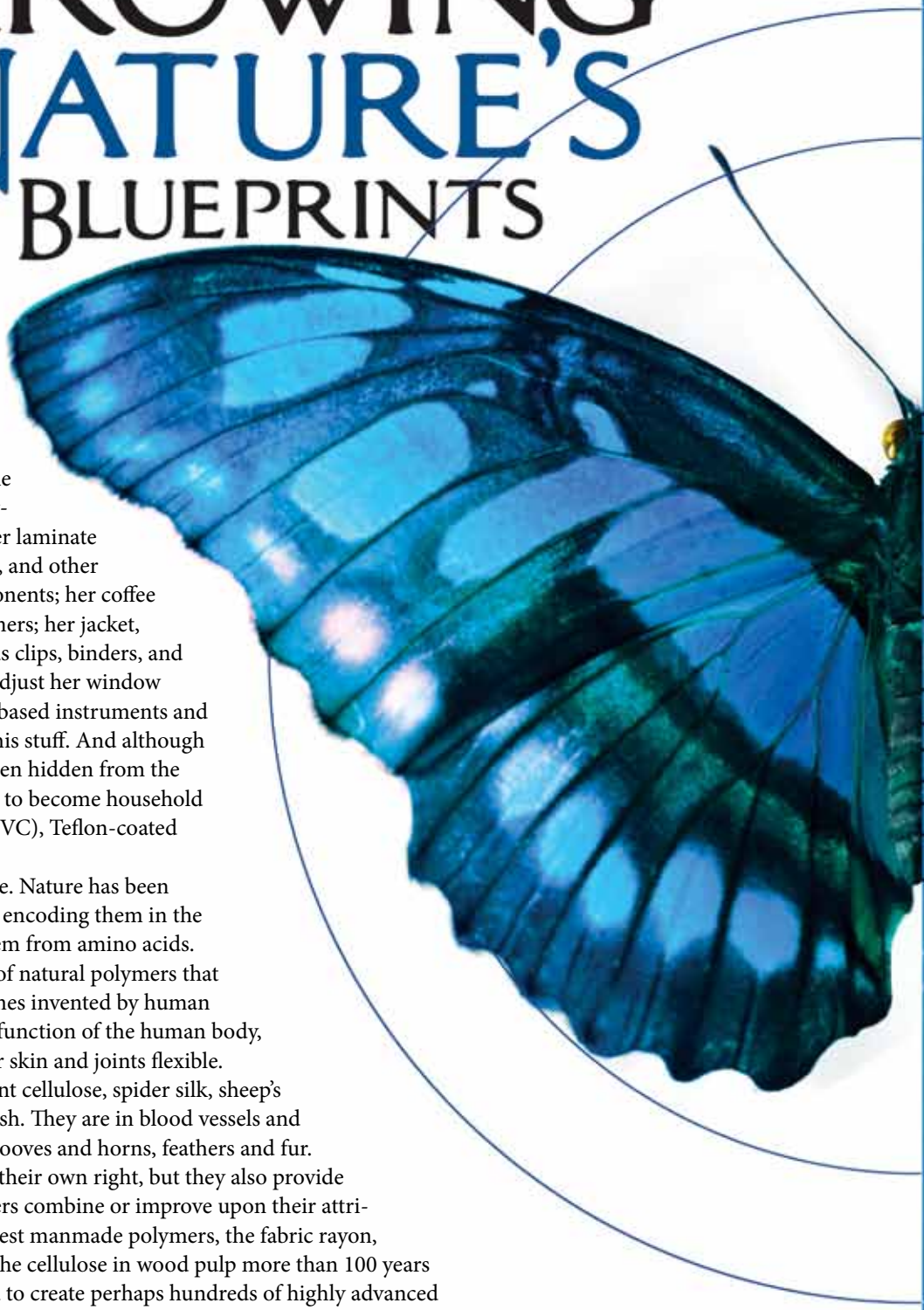
So tuberculosis is running rampant, drug-resistance is on the rise, compensation is fueling the fire—what is to be done? There is a commercial kit available, called Xpert MTB/RIF, which is very fast and very reliable and tests for *rpoB* mutations to identify rifampicin-resistant strains. It is backed by the WHO and is getting traction. But it doesn't detect all the possible resistance profiles, let alone the compensatory mutations. (These are both active research areas that are still incompletely defined and too complex for current standard testing.) It only looks at that narrow window in the *rpoB* gene that contains rifampicin-resistance sites. Still, it is a huge step in the right direction.

The infectious disease community has long been aware that emerging drug resistance is a serious problem in the fight against TB. The WHO has made tremendous progress in its massive global campaign to eradicate TB, which focuses heavily on the issue of resistance and early diagnosis. Korber's work, while not offering a quick fix, offers direction in terms of better understanding transmission of drug-resistant TB, the need for rapid diagnostics, and the role of fitness-restoring compensatory mutations.

"What we're saying," she says, "is that the key to global eradication lies in improved and increased clinical testing." More research is needed to develop on-demand multidrug-resistance panels and compensatory mutation tests. Her team's work adds emphasis to that need, bringing humanity one step closer to ending one of its deadliest diseases. LDRD

—Eleanor Hutterer

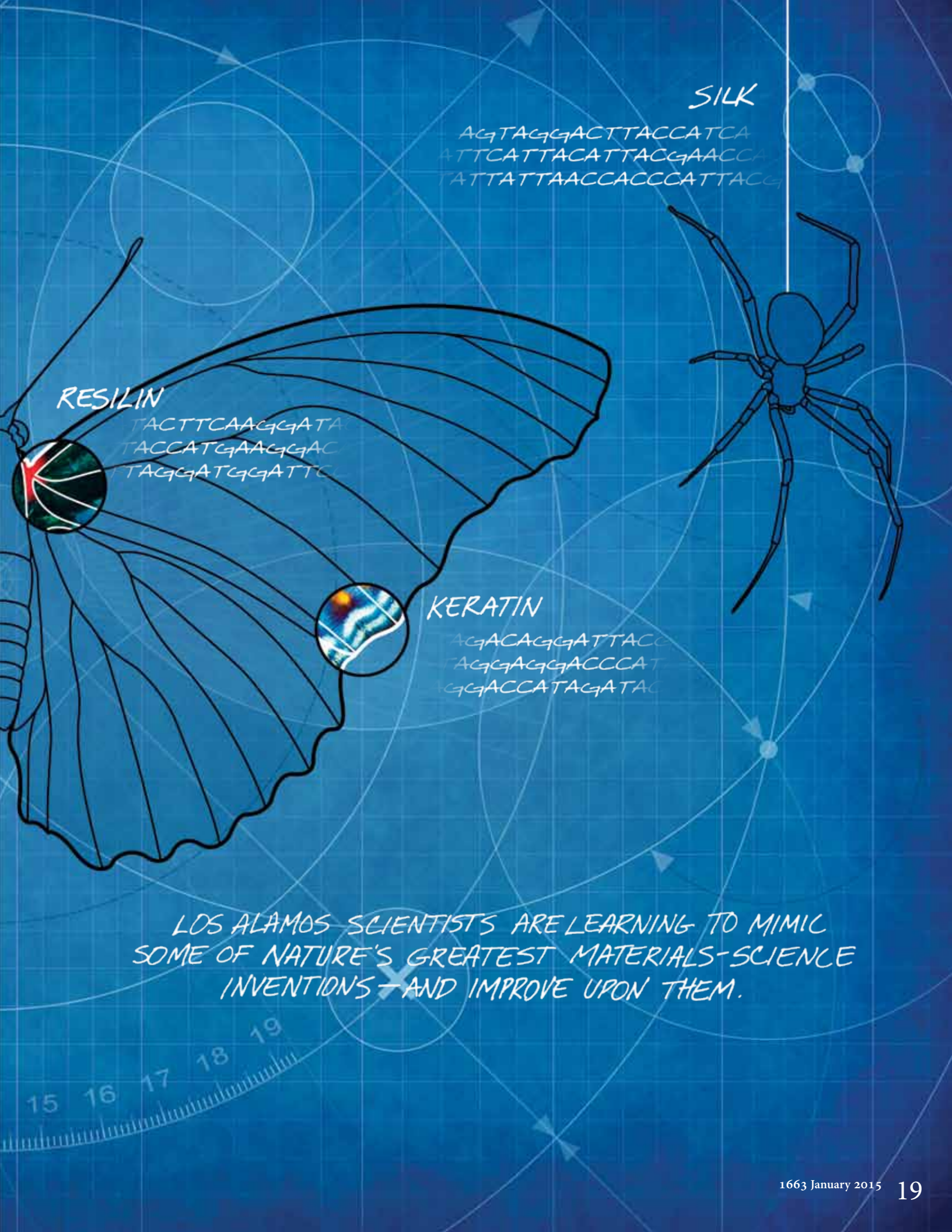
BORROWING NATURE'S BLUEPRINTS



"WE CAN'T DRIVE, we can't eat, we can't do much of anything without polymers," says Jennifer Martinez, a chemist with the Center for Integrated Nanotechnologies (CINT) at Los Alamos. She casually gestures at the multitude of polymer-containing objects within her own office—her laminate desk and plastic chairs; her phone, computer, and other devices, as well as their many internal components; her coffee thermos and assorted food and drink containers; her jacket, sunglasses, wristwatch, and shoes; the various clips, binders, and dispensers all around; and even the cord to adjust her window blinds. Then there's the plethora of polymer-based instruments and processes that went into manufacturing all this stuff. And although the pervasive use of synthetic polymers is often hidden from the average person, a few of them have managed to become household names, including polyvinyl chloride pipes (PVC), Teflon-coated pans, and nylon fabrics.

Yet polymers weren't invented by people. Nature has been using them much longer than humanity has, encoding them in the DNA of living organisms and assembling them from amino acids. In fact, evolution happened upon a number of natural polymers that are in many ways superior to the synthetic ones invented by human engineers. Some polymers are critical to the function of the human body, such as the elastin and collagen that keep our skin and joints flexible. Others are only found elsewhere, such as plant cellulose, spider silk, sheep's wool, or bioluminescent proteins from jellyfish. They are in blood vessels and bones, toenails and teeth, stalks and stems, hooves and horns, feathers and fur.

These natural polymers are valuable in their own right, but they also provide key inspiration to help scientists and engineers combine or improve upon their attributes for human use. Indeed, one of the earliest manmade polymers, the fabric rayon, was inspired by natural silk and made from the cellulose in wood pulp more than 100 years ago. Now, modern genetic tools stand poised to create perhaps hundreds of highly advanced synthetic polymers for mechanical and biological applications of all kinds. And researchers like Martinez are counting on nature to show them the way.



LOS ALAMOS SCIENTISTS ARE LEARNING TO MIMIC SOME OF NATURE'S GREATEST MATERIALS-SCIENCE INVENTIONS—AND IMPROVE UPON THEM.

Poly sci

Technically, a polymer is any large molecule formed as a sequence of repeated subunits. In a biological context, the subunits are generally simple biomolecules, such as sugars, fats, and amino acids, which can be arrayed into polymers called polysaccharides, lipids, and proteins, respectively. The subunits might also be nucleotides, in which case the polymer would be RNA or DNA. Or the subunits might be a variation on one of these themes. Synthetic polymers, too, are arrangements of different kinds of chemical subunits with varying complexity. The relatively simple synthetic polymer polypropylene, for example, is a common plastic with a subunit that's just a particular arrangement of three carbon atoms and six hydrogen atoms, nothing more.

Martinez is interested in simple proteins made from a specific sequence of 10 or 15 amino acids, say, repeated perhaps 100 times. Unlike more complex proteins, such as enzymes, that can contain tens of thousands of amino acids in a precise sequence, her preferred proteins are essentially polymers *of* polymers: repeating sequences of short amino-acid sequences. Yet even these relatively simple sequences can get out of control quickly. Out of 20 varieties of amino acids, even a sequence of just five of them allows for 20^5 or $20 \times 20 \times 20 \times 20 \times 20$ combinations—that's over three million possibilities. So the problem of designing polymers would be instantly unwieldy without some kind of starting point.

In living cells, that starting point is the genetic code. DNA carries the exact instruction sequence for arranging amino acids into proteins. Following suit, Martinez begins with known sequences of DNA that encode for proteins with valuable properties, and to those sequences she adds some closely related sequences with targeted variations in order to look for potential improvements on nature's original designs. She then employs a variety of laboratory techniques, working with viruses, bacteria, and yeast, to read the DNA segments and assemble the corresponding proteins.

Finally, calling upon a suite of sophisticated screening protocols that sort by temperature effects, fluorescence, pressure response, and other attributes, she screens her proteins for any that possess the desired properties. From there, she can tweak, refine, and repeat her way to material perfection.

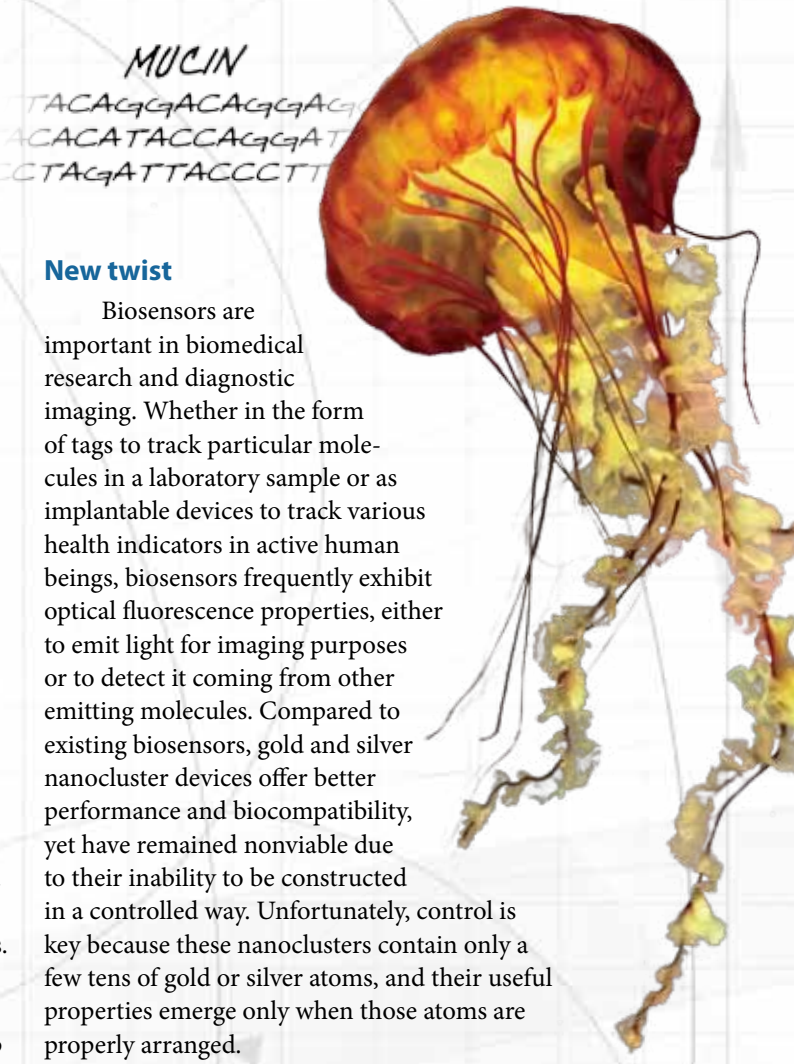
Inspired by nature

Natural polymers do some remarkable things. Take something as seemingly simple as human skin, for example. More than 75 percent of it is composed of collagen, in addition to elastin. Together, these two polymers give skin its strength, insulating properties, and tremendous flexibility—and allow it to ward off sagging and wrinkling for as long as the body is able to produce enough of them. The polymers also enable nerves to deliver sophisticated pressure sensitivity, allowing them to sense varying degrees of compression, stretching, twisting, and so forth. In addition, they form a barrier that is waterproof (and, therefore, largely pathogen-proof) from the outside but can secrete sweat at a regulated, adjustable rate from the inside. They allow for self-healing, with more collagen produced during wound repair. And another natural polymer in the skin, a common pigment called melanin, makes the skin optically responsive by absorbing harmful ultraviolet sunlight.

That's just human skin (and only a subset of its virtues at that). But nature has invented many other polymers with many other desirable attributes: the extreme tensile strength of spider silk and the insulating power of wool; the versatility of plant-based polymers, such as rubber and cotton; the optical iridescence of some beetles, bird feathers, and butterfly wings; the low-friction hardness of snake scales; the absorbency and transparency of jellyfish; and the adhesive properties of vegetable dextrin and boiled animal collagen (both used to make glue). All of these are purely natural resources derived from biological evolution, yet there is every reason to believe they can be improved by a deliberate human redesign.

Resilin, for example, is the enormously elastic protein responsible for the spring action of rapidly beating insect wings or jumping fleas. It is incredibly efficient at producing rebound motion without losing energy to heat and doesn't substantially degrade even after hundreds of millions of expansion-compression cycles. An Australian team recently extracted the gene for it from a fruit fly and re-expressed that gene in a laboratory setting. With some modifications, they developed a synthetic resilin that may find a home in a wide variety of applications, from athletic shoes to spinal implants.

Martinez anticipates many more revolutionary materials to be made possible by genetically engineering polymers. She is particularly motivated by the possibility of isolating the genetic sequences associated with various desirable attributes and then combining them in novel ways to make multifunctional materials.



"Suppose you could combine the optical glow from a bioluminescent fish with the pressure sensitivity of animal skins," says Martinez. "You can imagine engineering a new kind of flexible touch-screen that responds to different amounts of pressure by emitting different kinds of light. Or you could make a flexible body armor by combining the strength and elasticity of different natural polymers. Or you could engineer fiber-forming polymers with particular optical properties to make a solar energy-harvesting fabric. The possibilities are nearly endless. And that's not even considering the biomedical arena."

Replacement body parts

Because of their origins in living tissue, genetically encoded polymers naturally lend themselves to many potential biomedical applications. In the future, tooth fillings may no longer consist of foreign materials; they may instead consist of dentin that has been genetically designed to integrate with the tooth and accommodate new enamel. And bypass surgery to save a heart-attack patient may no longer require a real blood vessel grafted from the patient's arm or leg; it may instead be possible to construct an actual replacement blood vessel with genetically encoded polymers. That blood vessel could then trigger the growth of endothelial cells to line its interior and heal its own surgical seams.

"One of my favorite examples to illustrate the potential of genetically encoded materials is sprayable skin," says Martinez. Rather than treating a wound, possibly a very deep one, with a bandage, she envisions spraying a polymer that has been designed to seal the wound with a strong, flexible, and yet artificial skin. It would be largely based on the skin's natural collagen and would even produce the correct biochemical and mechanical cues to hasten the body's natural healing mechanisms by recruiting the correct sequence of cells. The wounded individual could then return to normal activity, fully protected, while the healing continues under the skin. "Inventing sprayable skin will require a lot of hard work by a lot of smart people," she says, "but there's nothing fundamentally preventing it."

Most of the new materials for products and biomedical uses are still a ways off. Right now, Martinez is working to develop the underlying techniques for creating genetically encoded polymers with valuable materials properties. Despite early indications of success, including polymers designed to control the fate of cells and others to act as fluorescing strain sensors, her efforts to make the physical materials of the future will take place mostly, well, in the future—with an interesting exception.

New twist

Biosensors are important in biomedical research and diagnostic imaging. Whether in the form of tags to track particular molecules in a laboratory sample or as implantable devices to track various health indicators in active human beings, biosensors frequently exhibit optical fluorescence properties, either to emit light for imaging purposes or to detect it coming from other emitting molecules. Compared to existing biosensors, gold and silver nanocluster devices offer better performance and biocompatibility, yet have remained nonviable due to their inability to be constructed in a controlled way. Unfortunately, control is key because these nanoclusters contain only a few tens of gold or silver atoms, and their useful properties emerge only when those atoms are properly arranged.

Martinez obtained the necessary control over nanocluster construction with the quintessential natural polymer: DNA. She and Los Alamos colleague James Werner designed and constructed specific DNA snippets to serve as scaffolding for the gold and silver atoms. They were then able to control the atoms' clustering by controlling the DNA code. The resulting nanoclusters may be used for biosensing, including national security applications such as detecting biothreat agents, and may even improve upon existing nanotechnology for solar energy harvesting.

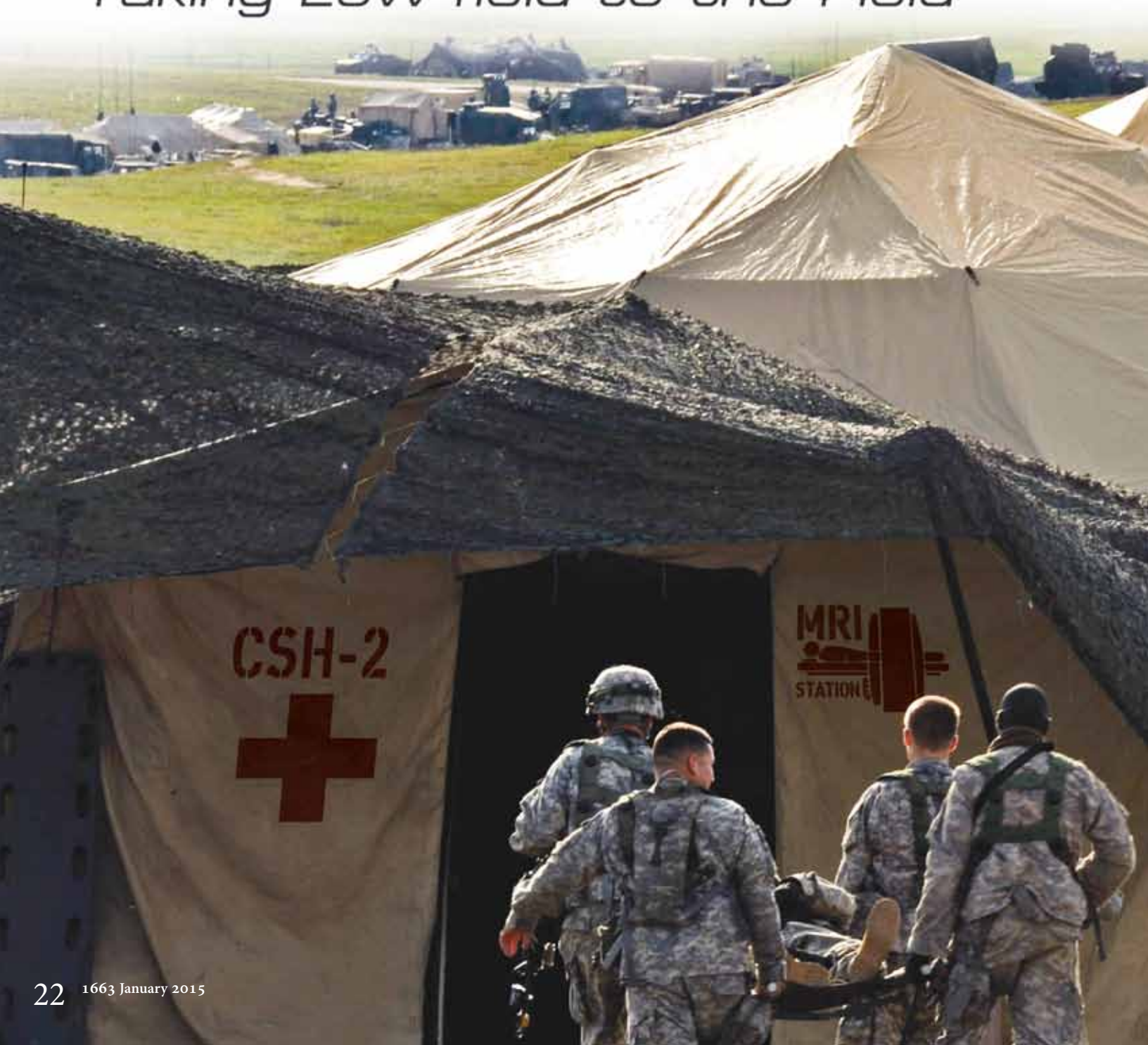
Yet such DNA scaffolding probably only represents the low-hanging fruit of the smart-polymer orchard. Martinez believes she and others will make the most profound polymer advances simply by mimicking and tweaking polymers already invented by nature. But does that make her feel unoriginal?

"Not at all," she says. "There's no shame in mimicking nature. It had a billion-year head start after all. But we're catching up now." LDRD

—Craig Tyler

MRI BATTLEFIELD

Taking Low-field to the Field



This Los Alamos ultra-low field brain scan was produced from within a metal-shielded room, for noise reduction.

There are some aspects of war that stand out as signatures of each specific conflict—the redcoats of the American Revolution, the trenches of the First World War. Sometimes they represent the human toll, such as how amputations are often associated with the American Civil War, even though the loss of limbs is prevalent in all military battles. What will emerge iconic from the contemporary war zones in Iraq and Afghanistan? The use of drones will likely be one thing, but another will almost certainly be the vast number of traumatic brain injuries (TBIs). In fact, the U.S. Department of Veterans Affairs, among others, is calling TBI the "signature wound" of the wars in Iraq and Afghanistan.

Since 2000, more than 300,000 U.S. military service members worldwide have sustained a TBI. Soldiers today have strong armor so they can survive close-range explosions that would have killed soldiers of earlier wars. They also have access to rapid medical care for other injuries and many quickly return to combat. However, head injuries that do not involve obvious wounds or loss of consciousness—which is often the case for mild TBIs, such as concussions—may go unnoticed. Although many patients recover from concussions completely, a fraction can have long-term effects including mood disorders and depression. And some studies suggest TBIs can increase the risk of post-traumatic stress.

Even when a head injury is suspected, there are few options for detection in a combat setting. Computerized tomography (CT) scanners—which use x-rays—are available in many combat-support hospitals but are less efficient at detecting the swelling or microscopic bleeding that may be associated with concussions. Magnetic Resonance Imaging (MRI) is often better at identifying these microscopic changes; however, the closest MRI machine to currently deployed service members in the Middle East and Afghanistan is at the U.S. military medical center in Landstuhl, Germany.

Traditional MRI machines have multiple advantages for detecting changes in soft tissue, and early intervention for even mild brain injuries has been shown to significantly improve a patient's long-term prognosis. However, these machines are expensive and their high magnetic fields are not safe for injuries involving metal (think shrapnel), which also rules out using them on unconscious patients for whom a medical history is unknown. Could weaker magnetic fields be used? Actually, yes. Los Alamos experts in ultra-low field MRI are developing smaller, less expensive systems that may be better suited for the battlefield setting and beyond.

Inner magnetism

The fundamental principle of MRI is the detection of magnetic resonance signals from atoms inside the body. Each atomic nucleus, like a bar magnet, has an intrinsic magnetism called a magnetic moment. When a large external magnetic field is applied, the magnetic moments of the nuclei interact with the field, causing many of them to align with it, akin to a compass needle aligning with the earth's magnetic field. Once these magnetic moments have been aligned, or polarized, the application of appropriate time-varying magnetic fields (typically radio frequency) then causes them to precess, or rotate, with a characteristic frequency dependent on the isotope of the atom and the strength of the magnetic fields applied. The density of signal from these nuclei and how it changes in a magnetic field can provide sensitive information about a material—for instance, distinguishing one type of tissue from another. The measurement of the rotating nuclei is called nuclear magnetic resonance (NMR). An MRI machine measures how the NMR signal is spatially encoded over an object and turns this information into an image.

Although nuclear resonance can be detected in most isotopes, MRI is often based on the single proton that comprises the nucleus of the most common isotope

Michelle Espy stands in the thick-walled doorway of her team's shielded ultra-low field MRI system.

of hydrogen, because it gives a strong signal and because hydrogen makes up 75 percent of the atoms in the human body. (Hydrogen is a major component of carbohydrates, fats, and proteins, and, of course, there are two hydrogen atoms in every water molecule.) Body tissues naturally have more water (and more hydrogen) than bone and can therefore be distinguished by a more intense signal; the decay of the signal also varies between tissues, and these differences manifest as contrast in an MRI image. In a brain injury, the buildup of fluid or blood can be identified by variability in the signal compared to healthy brain tissue.

"We are looking to understand how the magnetization varies in time to tell us about the chemical environment," explains physicist Michelle Espy, team leader for the Battlefield MRI project at Los Alamos. "For instance, the time it takes the protons to align is different in each type of tissue, such as grey matter, muscle, and white matter. These time-varying signatures also provide contrast and can be exploited by designing the imaging sequence and even varying the magnetic field strengths to highlight or suppress specific tissues."

How low can it go?

High-field MRI (HF MRI) machines use a single, static magnetic field both to polarize the magnetic moments in the sample and to detect the NMR signal. The resulting images are very high quality. However, HF MRI has drawbacks, too. The large magnetic fields (several teslas of magnetic field, roughly a thousand times the field strength at the surface of a typical refrigerator magnet) can exert great force on metal items. This creates a danger not only when there is metal inside the body being examined (such as metal implants or shrapnel) but also when there is metal anywhere in the same room as the scanner—a bobby pin can get pulled into an MRI machine at 40 mph. Furthermore, the radio-frequency fields used to manipulate the nuclei can cause heating in body tissues and are not generally considered safe for pregnant women or small children. In addition, HF magnets are expensive, heavy, and always on, so they require safe, separate spaces in which they can operate—and a constant supply of costly cryogenic liquids to keep them cold. For these reasons, HF MRI machines are normally only found in first-world countries that can afford the high cost and maintain the necessary infrastructure.

But an MRI does not need to have such strong magnets to be useful. A few groups around the world have pursued MRI at magnetic fields orders of magnitude lower than traditional MRI. Among them, Espy's team at Los Alamos has shown—and published in a recent book—that MRI at these very low magnetic fields can still produce images that are potentially useful for a doctor to determine the next course of action when assessing a patient.

The Los Alamos team's system uses two different field strengths—one to pre-polarize and a smaller one to collect the NMR signal. Its ultra-low field MRI (ULF MRI) uses pulsed magnetic fields from 0.1 tesla (T) down to 10 microteslas (10 μT, or 10 millionths of a tesla), and because fields are so low, the ULF MRI can safely produce images even in the presence of metal.

What's tricky about the ULF approach is getting enough signal from the rotating nuclei to make a good image. Imagine a bar magnet again, this time with a light on one pole, so that when it rotates about in the applied time-varying magnetic field, the light appears to flash like a lighthouse. If you could line up many lighthouses and synchronize their rotation so that all the lights point to you at once, you would have a much stronger signal to detect. As a higher magnetic field is applied, more magnetic moments can be aligned and synchronized, making a larger signal for detection. Conversely, when the magnetic fields are reduced, a smaller fraction of protons participate, and the signal is proportionally smaller.

The solution is twofold. First, the Los Alamos team applies a relatively strong pre-polarization field (0.01–0.1 T) to align as many protons as possible. Next, the pre-polarization field is turned off—unlike HF MRI, which uses a constant, uniform field—and the aligned nuclei then rotate in a much weaker field where they are detected. By applying a spatially varying magnetic field, the frequency of the signal becomes a function of position, and an image can be produced. Additionally, the behavior of the signal decay after the pre-polarization field is turned off is also a function of magnetic field strength.

"The Los Alamos group and others have indicated that ULF MRI can actually produce images with better contrast, albeit lower signal, than HF MRI, and that some anatomical characteristics might only be visible with the help of the lower fields," says Espy.

The second part of the ULF MRI approach is the incorporation of a superconducting quantum interference device (SQUID)—the most sensitive kind of magnetic field detector. The SQUID works by detecting the changing magnetic flux inside a superconducting loop. Espy and her colleagues, who actually call themselves the SQUID team, had used SQUIDs for years to measure brain function before they decided to try ULF MRI. For the last decade, they have refined their approach, and what they've discovered is that ultra-low fields coupled with SQUIDs can indeed make decent MRI images—as long as they can control the noise.

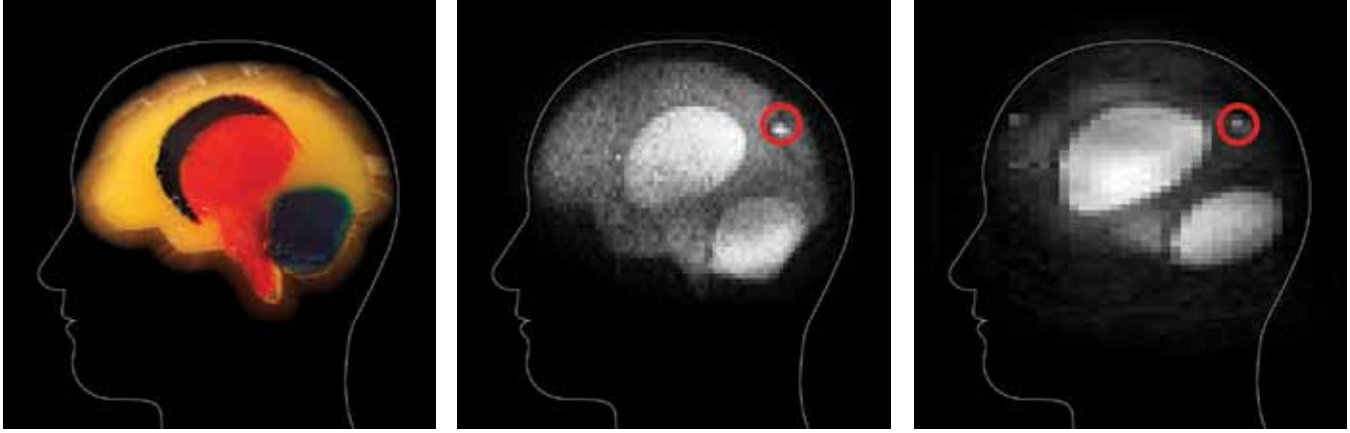
It's all about the noise

Unfortunately, the same sensitivity that allows a SQUID to pick up ULF MRI signals also causes it to pick up nearly everything else that might be nearby—making the ideal signal-to-noise ratio needed for a good image difficult to achieve.

"SQUIDs will respond to a truck driving by outside or a radio signal from 50 miles away," says Al Urbaitis, an engineer on the Los Alamos team. Even something as innocuous as a chair rolling across the room could cause significant disruption to the SQUID's ability to measure an NMR signal.

The SQUID team has constructed three MRI systems in its laboratory, all with significant external shielding in the form of a small room made from conductive metal to block external electromagnetic radiation. However, this shielding adds significant bulk to the system. Therefore, to adapt ULF MRI to a provisional combat-support hospital setting, the team would need a new approach to make the system smaller.

Per Magnelind (left) and Al Urbaitis stand beside the battlefield MRI system. The wooden framework supports the dynamic field-cancellation system they are developing to help prevent unwanted noise from interfering with the MRI measurements without a fully metal-shielded room. This framework makes the system easier to transport and a lot less expensive than their shielded system.



(Left) To test the new battlefield system, the SQUID team created a model of a brain made of gelatin and included indications of a bloodclot that would cause a stroke. (Center) Here, the shielded, ultra-low field MRI image shows enough resolution to identify the major parts of the brain as well as the bloodclot (circled). (Right) The unshielded battlefield MRI has significantly less resolution; however, the stroke bloodclot is still visible, indicating that this system might be enough for a doctor in the field to determine the next step in treatment.

By first characterizing the types of noise that could interfere with the MRI measurements, the team is working on a field-cancellation system built as a framework around the MRI instead of an entire metal room. This concept, similar to active noise-canceling headphones, would enable the system to emit its own noise at the same frequency but opposing phase to cancel out any unwanted noise.

"At present, the team has used a handful of coils to counter unwanted magnetic fields associated with the earth's magnetic field or low-frequency transient magnetic fields induced in nearby conducting materials," explains Per Magnelind, a physicist on the SQUID team. "But the hope is to expand this approach to an array of nodes attached to the sides of the MRI and distributed around the room to give the best coverage."

Beyond the battlefield

Although head trauma from military training accidents or roadside bombs in Iraq is a major problem that MRI can help, soldiers aren't the only people who could benefit from a less expensive, more transportable MRI machine. With this in mind, Espy and colleague Igor Savukov have been collaborating with Dr. Steve Schiff, a pediatric neurosurgeon at Pennsylvania State University. Schiff spends part of his time at a hospital in Uganda where he is studying and treating hydrocephalus, a condition in which cerebral fluid builds up in the skull, leading to brain swelling. Hydrocephalus can be congenital or acquired during infections from various tropical diseases, and when it occurs in people in developing countries where MRI is not widely available, little can be done. However, life-saving treatment, such as a shunt or surgical incision to help drain the fluid, could be possible with a ULF MRI image to indicate where the fluid buildup is and which approach is better suited. Although the images are not as high quality as those from an HF MRI system, they would likely show enough information to guide treatment.

Ultra-low field scans could be especially helpful for infants and children—even in developed countries. If children are hooked up to life-saving equipment, they often cannot have an MRI, and CT scans are never preferred for children due to the risk from x-ray radiation on their rapidly dividing cells. The ULF MRI system being developed by the SQUID team would be safer for infants and children at a fraction of the size and cost of a traditional MRI, making it more accessible to hospitals all over the world. SQUIDs, however, still require expensive, not-widely-available cryogenic liquids (nitrogen and helium) to cool their superconducting coils to their operating temperature of just 4 degrees above absolute zero. For this challenge, Savukov is working on a solution that would mean ditching the SQUID completely.

"An atomic magnetometer is a relatively new type of detector that has a similar sensitivity to a SQUID," says Savukov. He explains that the magnetometer uses lasers and a small glass cell filled with alkali-metal atoms, such as potassium. One laser serves to align potassium nuclei, while the second laser reads out the signal from their magnetic moments—with extremely high sensitivity—in response to changes in the magnetic field in the patient's tissues. The system Savukov has been developing has a lot of potential: not only does it eliminate the need for cryogenic liquids, but it also does not require as large a shielding system. The images, however, still need some improvement, so Savukov is working on stabilizing the magnetometer (which he made himself because atomic magnetometers, unlike SQUIDS, are not yet commercially available).

Overall, the last decade of ultra-low field work by the scientists at Los Alamos has shown not only that ULF MRI is possible, but also that it is competitive with HF systems in certain important contexts. Furthermore, their new battlefield prototype could make MRI accessible in combat hospitals and developing countries, demonstrating what Espy often says: "When it comes to the power of MRI, sometimes less is more." LDRD

—Rebecca McDonald

spotlights

Inside Alzheimer's Disease

Los Alamos neutron and x-ray physicist Jarek Majewski is at it again. He has used neutrons to probe biological structures associated with illnesses ranging from cholera to vascular disease [see the August 2011 and August 2014 issues of *1663*, respectively]. To that list, he and his Los Alamos colleague Ann Junghans, together with collaborators at the University of New Mexico, the Max Planck Institute for Neurological Research, and the Center for Neurodegenerative Diseases (the latter two in Germany) now add a mechanism that many researchers believe underlies Alzheimer's disease. The disease is America's sixth-largest killer and burdens the nation to the tune of $220 billion per year—more than 1 percent of GDP—plus another 17 billion hours of unpaid care, according to the U.S. Centers for Disease Control and Prevention and the Alzheimer's Association.

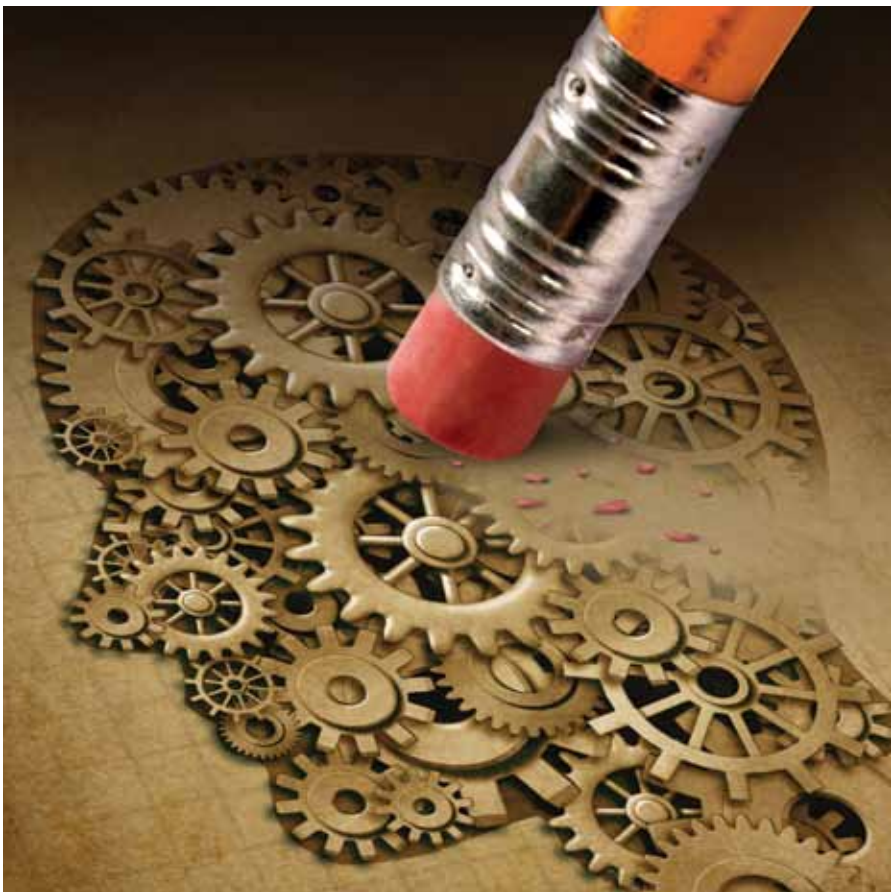
In the brains of patients suffering from Alzheimer's disease—examined post-mortem, of course—anomalous tangles of tau proteins and plaques of beta-amyloid protein fragments are always present. It is not clear whether these tangles and plaques directly cause the disease, but they, or their precursors, are believed to interfere with normal brain function by suppressing communication between neurons or simply disintegrating them. The tau and beta-amyloid proteins are present in healthy human brains as well, where they help stabilize microtubules in the nervous system and participate in cell growth, respectively. But the question is what causes them to accumulate into tangles and plaques in the brains of those suffering from the disease? In other words, what causes these proteins to assemble into larger structures that obstruct the cells' normal activities?

For atoms or molecules to assemble into larger structures like tangles and plaques, they must overcome certain energy barriers; when the aggregates are too small, they are unstable and will disassemble themselves. Sometimes, however, they receive help from tiny bits of solid matter to grow past the unstable phase, such as when clouds are seeded with particles to help raindrops aggregate out of water vapor. Other times, the help comes from environmental conditions, such as fluctuations in temperature, pressure, and electric charge. Something of this sort must be catalyzing the aggregation of beta-amyloid and tau molecules out of solution in Alzheimer's patients, and a theory that has been gaining traction suggests that electrical charges on neuron cell membranes may provide that catalyst.

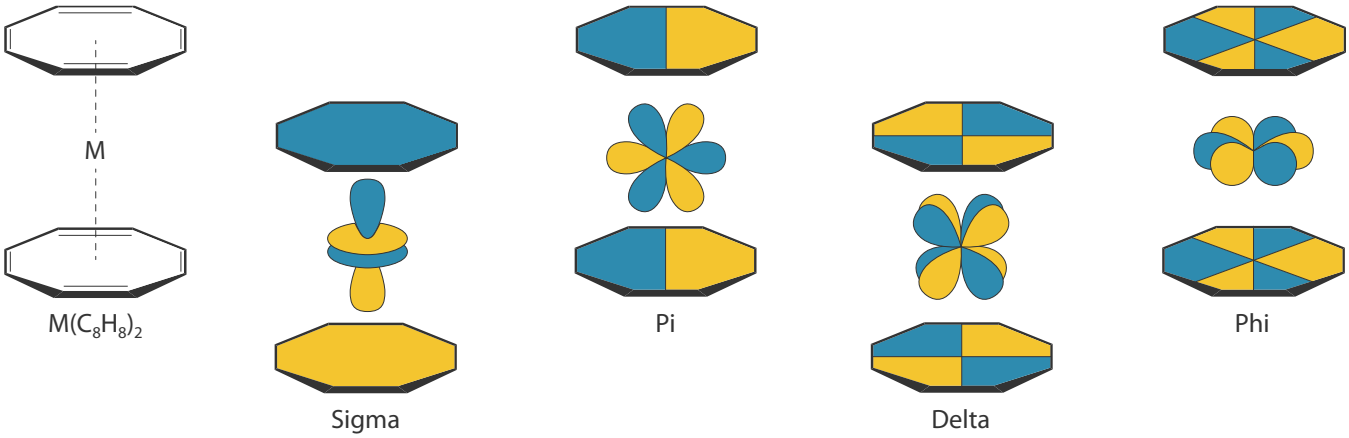
To investigate the theory, Majewski reflected x-rays and neutrons off of a simplified cell membrane after injecting human tau proteins into the adjacent fluid. He found that when the membrane is comprised of uncharged lipids, as is normally the case with the exteriors of young, healthy brain cells, the proteins do not significantly interact with it. But when the membrane contains negatively charged lipids, as are observed in old or injured cells, the tau proteins fold up into tighter configurations—a necessary first step in the aggregation of tau tangles—and wedge themselves between lipid molecules in the cell membrane. Similarly, beta-amyloid proteins anchor into the membrane and begin to aggregate and grow in the presence of the negatively charged lipids. Majewski and his team observed this directly in recent synchrotron x-ray experiments.

In other experimentation using grazing incidence x-ray diffraction and neutron reflectometry, Majewski revealed that the tau proteins broadly disrupt the lipid organization, creating weak spots and openings in the membrane. Such membrane disruptions can impair neuronal signaling and ultimately kill the brain cell—producing (or at least contributing to) the cognitive dysfunction of Alzheimer's patients.

In the absence of the disease, tau proteins bind to microtubules that run the length of the long, wire-like part of neurons, strengthening them and providing convenient roads for other molecules to travel. But if too many phosphate



Los Alamos research indicates that neuron membrane disruption may be responsible for the aberrant growths found in the brains of Alzheimer's patients and the neuronal damage that causes mental decline.



The sandwich complex consists of two flat layers of hydrocarbon atoms which sandwich the metal ion in between. When the metal is thorium, four types of covalent-bond symmetries have now been observed. Each is made by different arrangements of orbitals occupied by electrons involved in the bonding. The yellow and blue shading represent the phase of each orbital lobe, and only orbital lobes of the same phase form constructive interactions—i.e., covalent bonds. Where the metal orbital lobe of one phase (say, blue) is oriented towards a part of the hydrocarbon layer of the same phase (also blue), a bond is formed. The way the hydrocarbon-layer orbitals are split up, like slices of a pie, defines each type of bond—sigma with one slice, pi with two, delta with four, and now phi with six. Note that the pi bond has six visible orbital lobes but only two overlap to participate in bonding with each hydrocarbon layer, as defined by the proximity of matching phases (matching colors) between the thorium in the center and the hydrocarbon layers above and below. The phi bond utilizes the same metal orbital as the pi, but it is rotated in such a way that all six of its lobes overlap with the hydrocarbon-layer orbitals.

groups attach to the tau proteins, as occurs in the early stages of the disease (for unknown reasons), the proteins detach from the microtubules and begin to aggregate into tangles. The process appears to be accelerated by interaction with the interior of the cell membrane where negatively charged lipids are known to reside. Majewski simulated such "hyperphosphorylated" tau proteins in x-ray diffraction experiments with a mutant version of the human tau protein and found that the tau aggregation and lipid membrane disruption were accelerated relative to those for regular tau protein molecules. Then, once the tau aggregates have formed, the continuity of the cell membranes is compromised, killing the cells and making the disease worse over time.

The good news—if learning the mechanisms underlying a horribly debilitating disease can be viewed as good news—is that these studies strongly support the notion that interactions with neuron membranes lead to both neuron death and the formation of protein tangles and plaques. And if both problems have a common cause, they may also respond to a common treatment.

—Craig Tyler

Bond, Phi Bond

The principles of chemical bonding lie at the heart of chemistry and have been known since the early 20th century. Therefore, it's not every day that a chemist discovers a new type of chemical bond—but that's exactly what a team led by Los Alamos scientists Stosh Kozimor, Rich Martin, and Enrique Batista, together with Lawrence Berkeley National Laboratory (LBNL) scientist David Shuh, has done.

Prior to this work, covalent bonds (the kind where electrons are shared between atoms) were classified by just three types, named sigma, pi, and delta, which describe the different symmetries of the bonds that hold together molecules at an atomic level. The prize discovery of this work is a fourth type of covalent bond known as the phi bond. Theory had predicted the existence of the phi bond for the actinide metals—the 14 consecutive elements beginning with actinium at the bottom of the periodic table—but experimental proof remained elusive until the Los Alamos and LBNL team developed a way to make the new bond reveal itself. Part of the challenge inherent in studying these elements is the complex organization of their many electrons and the minor role that covalent bonding plays amidst overwhelming ionic forces, which dominate the overall chemical bonding picture. It can be hard to accurately pinpoint these subtle, yet important, covalent-bonding interactions.

The Advanced Light Source (ALS) beamline facility at LBNL allowed the team to take state-of-the-art x-ray absorption spectroscopy measurements on a pair of uranium- and thorium-containing molecules (both actinides). The technique works by examining electronic transitions in which an electron close to the atom's nucleus is excited to a higher-energy state by absorbing an energetic x-ray. When combined with detailed computational models, these transitions can be accurately correlated with a molecule's structure. The compounds—part of a class of molecules called a sandwich complex because the uranium or thorium is sandwiched between two ring-shaped hydrocarbon structures—were carefully chosen because their symmetry simplifies these transitions and allows the team to interpret the x-ray data more clearly.

The plan paid off when the first convincing experimental evidence of the phi bond showed up for the thorium sandwich

complex, as revealed by its elaborate, never-before-seen symmetry. The aptly named sandwich complex normally divides its bonding interactions into specific numbers of segments, like a club sandwich served whole, sliced in half, or sliced in quarters. But the thorium sandwich displayed six slices. No doubt, this new symmetry will be examined in much detail in the future.

Yet the motivation of the work wasn't simply to pin down an elusive form of bonding. It is part of a greater ongoing effort to understand the properties of actinide-containing materials, such as spent nuclear fuel components, in order to improve computer-based models which ultimately may lead to better nuclear separation and forensics technology. But no one can predict all the future benefits of a new scientific discovery, and this one is certainly a landmark for the chemistry of the actinides and the science of chemical bonding in general.

—Owen Summerscales

Mathematically Sound Investment

Education research shows that traditional teaching practices, such as covering a chapter a week to get through the textbook by the end of the year, often fall short of the real goal, which is learning. Studies show that it's worth investing time early on to build a solid conceptual foundation before pushing forward to more elaborate tasks.

For example, before children can understand an abstract concept, they must first understand it at the concrete and representational levels. Place three apples in front of a child, and she can pick them up and move them; she can feel and see that there are three distinct units of "apple" in front of her—that's concrete. Now show her a picture of three apples. She can't hold each apple, but she can still see three individual apples—that's representational. Now show her the number "3" without any apples—that's abstract. It seems obvious, but it's not; no matter the grade level, when undertaking a new subject, students benefit from a slow start.

The Los Alamos Math and Science Academy (MSA) sends Laboratory educators into public schools to improve how teachers teach. They train kindergarten through eighth-grade math and science teachers to lead their students through the levels of understanding to real comprehension. In so doing, the MSA supports the Laboratory's good neighbor pledge, which promotes economic development, excellence in education, and active employee engagement in the northern New Mexico community.

Single interventions are ineffective, so rather than a rote hour-long seminar, the MSA provides continual professional development for several years to both teachers and principals. "Educators should engage in professional development from day one, and it should continue throughout their career," says MSA veteran Lorenzo Gonzales. "You are teaching someone to think, you are actually structuring their brain. It's not a simple skill set to be memorized and repeated." With over 40 years of experience, Gonzales is the group's de facto guru. The other three members—Zachary Leonard, Monica Martinez-Archuleta, and Randy Merker—are all former math or science teachers and scholars. They scour the education research literature to identify the latest findings and successful strategies, then translate, hone, and integrate that information into what they call best teaching practices.

Solve the following word problem: Four educators want to teach math to 15,000 grade-schoolers over the course of 14 years. How many students must each educator tutor? Answer: 3,750 total, or 268 per educator per year. That student-teacher ratio, while common at large universities, won't work for elementary school. The formula for the MSA's success is to train the educators so that their investment is amplified with each new class. The program previously partnered with the Taos, Chama, Mora, Española, and Pojoaque school districts in northern New Mexico and is presently working with the Bureau of Indian Education, all with marked success. At the beginning of their work with Native American students in 2005, for example, just 12 percent of students at one school were deemed proficient at math, according to standardized tests. That number has consistently risen through the MSA's partnership and last year reached 56 percent. The numbers add up: the program is working.

And it's not just about how teachers teach, but also what teachers teach. Errors in comprehension are carried over and compounded when teachers don't have a solid understanding of the subject. To address deficits in content knowledge, the MSA brings in Richard Kitchen, a math education professor who spends eight Saturdays per school year teaching math to math teachers at the MSA.

The 2014–2015 academic year is the final year of New Mexico's transition to the Common Core State Standards (CCSS), the national overhaul of public education presently underway, and the members of the MSA have mixed feelings. On the one hand, the CCSS run parallel to the goals of the MSA, and having higher standards ought to result in higher proficiency statewide. On the other hand, they worry that while the bar has been raised, support for teachers statewide may come up short. As Gonzales points out, "High-performance schools have two things in common: opportunities for professional development and the expectation and allowance for teachers to take those opportunities. "While the rest of the state will have to step up to the CCSS, MSA-served schools in northern New Mexico should have a comparatively smooth transition.

—Eleanor Hutterer

To most people, a snack; to Los Alamos math-education-theory specialists, a representation of the concept "three."

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