SANDIA TECHNOLOGY

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Sandia Pursues

Biotechnology

Molecular Integrated Microsystems

Powering Devices from Living Systems

Sandia National Laboratories

What is LDRD ?

Sandia's world-class science, technology, and engineering work define its value to the nation. These capabilities must remain on the cutting edge because the security of the US depends directly upon them. Sandia's Laboratory Directed Research and Development (LDRD) Program provides the flexibility to invest in long-term, high-risk, and potentially high-payoff research and development that stretch the Labs' science and technology capabilities.

LDRD supports Sandia's four primary strategic objectives: nuclear weapons; nonproliferation and materials control; energy and critical infrastructure; and emerging national security threats. LDRD also promotes creative and innovative research and development by funding initiatives that are discretionary, short-term, and often high-risk, and that attract exceptional research talent across many disciplines.

LDRD funding is intended to invigorate and extend Labs' expertise within disciplines identified to be the core of technical competence at Sandia. It may also be used to: (1) create or accelerate the development of a technical expertise within programs deemed important to the future of the Laboratories, DOE, and the nation; (2) focus on the development of technical expertise within programs with potential future importance for the Laboratories; or (3) extend the boundaries of the Laboratories' research into fertile new areas.

ON THE COVER: Biotechnology has arrived at Sandia, with a number of top researchers applying their talents to difficult problems probing into the secrets of life itself. This collage by Douglas Prout includes DNA sequences, molecules, regulatory pathways and a conceptual device to harvest glucose. The images give some glimpse of the sweep of work gearing up at Sandia for the next few years.

Sandia Technology is a quarterly journal published by Sandia National Laboratories. Sandia is a multiprogram engineering and science laboratory operated by Sandia Corporation, a Lockheed Martin company, for the Department of Energy. With main facilities in Albuquerque, New Mexico, and Livermore, California, Sandia has broad-based research and development responsibilities for nuclear weapons, arms control, energy, the environment, economic competitiveness, and other areas of importance to the needs of the nation. The Laboratories' principal mission is to support national defense policies, by ensuring that the nuclear weapon stockpile meets the highest standards of safety, reliability, security, use control, and military performance. For more information on Sandia, see our Web site at *http://www.sandia.gov.*

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FROM THE Editor

Dear Readers:

Biotechnology — the combination of biology with materials science, physics, computational analysis and simulation, microfabrication and Sandia's unique capabilities in systems integration — has arrived with a vengance at the Labs. As the stories in this issue attest, the problems posed are difficult. But successes are already beginning to emerge.

Sandia champions for this issue were Julia Phillips, director of the Labs' Physical and Chemical Sciences center in New Mexico, and Len Napolitano, director for Sandia's center for Exploratory Systems and Development in California. Both were gracious in sharing time from their busy schedules to help with this issue and in offering constructive suggestions for its improvement.

Most of the writing in this issue is from Chris Burroughs, who originally reported on these subjects for a series of articles in our employee publication, the LAB NEWS. Her stories reveal some of the approaches now being taken and some of the theoretical issues involved. Neal Singer also contributed to this issue with his coverage of an approach to bring sight to the blind and of Sandia's role in the Department of Energy's new Genomes to Life project.

The biotechnology initiative at the Labs has resulted in a new vocabulary for many of its researchers, new problems to address, and to some extent, a new culture for our research community. The potential for success is exciting.

Will Keener
Editor

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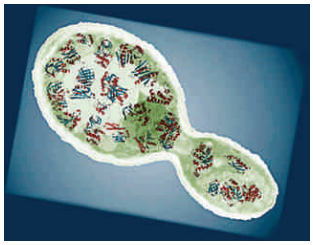
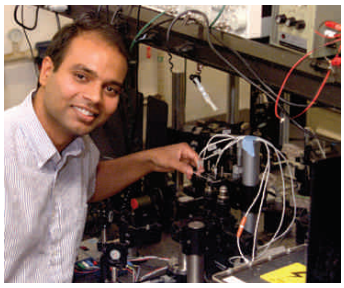
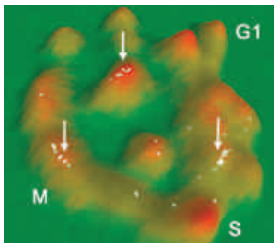






Sandia Pursues Biotechnology

By Chris Burroughs

"The same way computers dominated the past 20 years, biology is going to dominate this new century like nothing else will. How can Sandia not go into biology?"

Bill Camp, Director, Computers, Computation, Information & Math Center

Sandia National Laboratories is expanding its work in biotechnology to push scientific discovery and development into such areas as the creation of new materials and to help in America's war on terrorism.

Biotechnology — the coming together of computing, informatics and traditional physical, engineering, and chemical sciences with biology — is making new and complex types of research possible. Sensors, computing, nanoscience, robotics and materials science are all benefiting from the influx of biologically-rooted approaches into their worlds, just as the biological sciences are advancing from radically new approaches enabled by computation and the physical, chemical and engineering sciences.

One example is Sandia's work in mathematical and computational modeling to help biologists understand bio-systems at unprecedented levels of detail including the complex genomic and proteomic machinery of the cell. Such work is critical to advances in medicines and materials and is leading to new, biologically inspired, algorithms in other areas, explains Bill Camp, director of the Labs' Computation, Information & Math center.

The focus on biotech at Sandia started about three years ago when Al Romig, Sandia Vice President for Science & Technology and Partnerships, and Mim John, Vice President for the Sandia California Laboratory, began advocating expanded research efforts in the new field. The two felt that Sandia could have an even a greater impact on keeping the United States safe by adding biology to the science and technology base at Sandia for nuclear weapons and other purposes.

Al Romig

"I am very excited about how biotechnologies will be key enablers of nanotechnologies and lead to new materials and devices. To stay at the cutting edge of nanoscience, materials science and micro- and nano-devices, we must invest in biotechnologies."

Al Romig
Vice President,
Science & Technology
and Partnerships

"Atoms-up Engineering"

Work to construct a joint Sandia and Los Alamos National Laboratory Center for Integrated Nano-Technologies (CINT) also complements the decision to add biology as a focus. For several years scientists and engineers have seen the possibilities for "atoms-up engineering" — the ability to design and fabricate new materials beginning at the atomic level. Says Sandia President C. Paul Robinson, "The CINT goal of integrating the unique properties of nanotechnology into the macroscopic world is critically important if we are to realize the full benefit of nanoscale physics, chemistry and biology."

Sandia had a "clear mission driver" for pursuing biotech — countering bioterrorism and biowarfare, explains Romig. "We knew that long before 9/11. And we have a lot of intrinsic strengths that make us a competitive biotech player — sensors, electronics, mathematical algorithms, and computational ability. It only makes sense that we do this."

A second part of the vision, Romig says, is the bio-nano-information interface. "I am very excited about how biotechnologies will be key enablers of nanotechnologies and lead to new materials and devices," Romig says. "To stay at the cutting edge of nanoscience, materials science and micro- and nano-devices, we must invest in biotechnologies. I would bet that someday bio-inspired materials and devices will appear in Sandia-designed national security systems and nuclear weapons."

Sandia has pursued some biotech research for more than 10 years. Among the first projects, were an insulin pump and a noninvasive glucose monitor. Others included a bio-cavity laser, prosthetics, decontamination foam and the Rapid Syndrome Validation Project (Vol. 4 No. 2). But no concerted effort existed to use this technology in a big way.

In 1999 John and Romig sponsored a study for top leaders at Sandia to determine if Sandia should play a role in the biotech arena and, if so, what areas should be Sandia's focus. Len Napolitano from Sandia California was chosen to lead the study.

"And, by the way…

"We spent three months exploring what the role of biotechnology should be in addressing Sandia's current and future national security mission needs," Napolitano says. "We concluded that biotech at Sandia is inescapable. We were obligated. We couldn't avoid it. And, by the way, it was already here."

"Many current capabilities were already integrating biotech — materials sciences, computational analysis and simulation, physical diagnostic techniques, micro-fabrication, technology integration — and we anticipate that future missions will require even more biocapabilities," Napolitano says.

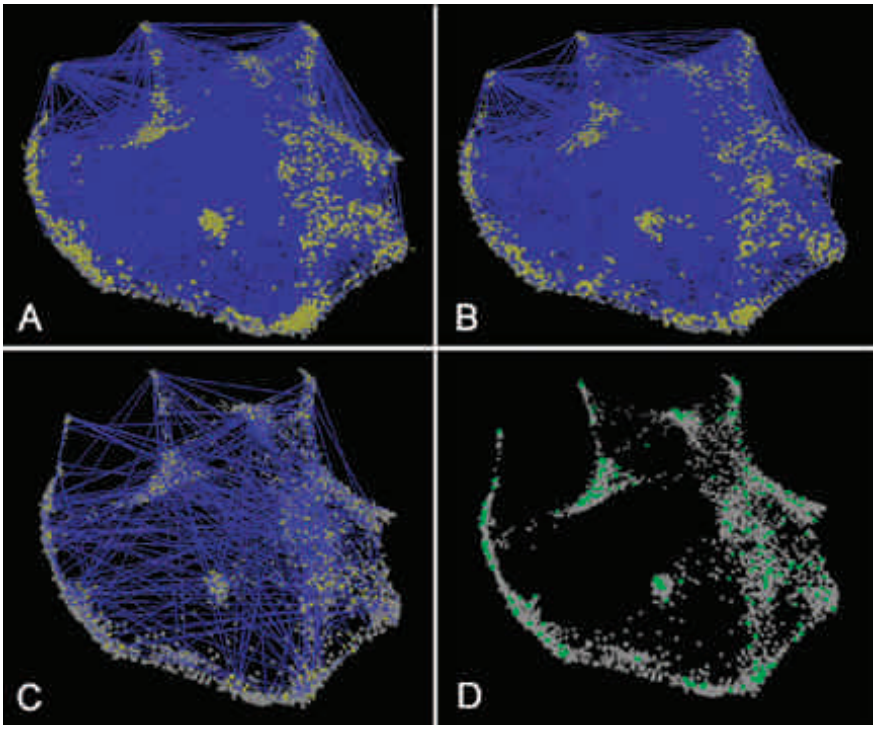
In 2000 a Biotech Science & Technology Council was created to lead Sandia's efforts to transform the Labs into the biotechnical laboratory of choice for national security problems. Also, three new departments, representing primary research endeavors, were formed to focus on biotech. In 2001 a biotechnology portfolio was established as part Sandia's internally funded LDRD program to provide seed funding for this new science and technology area. LDRD funding was established for:

- The Interfacial Bioscience Grand Challenge, focused on the development of new bioanalytical tools for the study of membrane protein structure and function. (See page 8.)
- The Molecular Integrated Microsystems Grand Challenge, which has as a goal the first-ever programmable microsystem devices for protein and peptide analysis. (See page 5.)

"Sandia's success was largely due to our unique computational capabilities..."

Grant Heffelfinger
Deputy Director for Materials Science and Technology

Software visualization of gene clusters in yeast cell and how proteins interact.

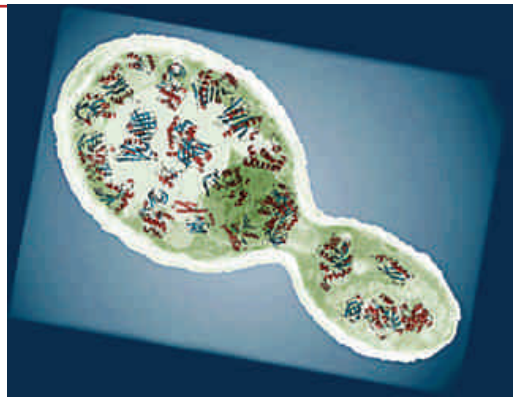


•The Bio-MicroFuel Cell Grand Challenge that will develop new compact power sources that can operate using fuels from biological sources. (See page 13.)

This fiscal year, biotechnology investment is about five percent of Sandia's research budget, which is considered to be a threshold level for developing new competencies. "We will be working in the 'sweet spots' in physical and bio areas where we have expertise and where there is the greatest need," Romig says.

Explosion of biological data

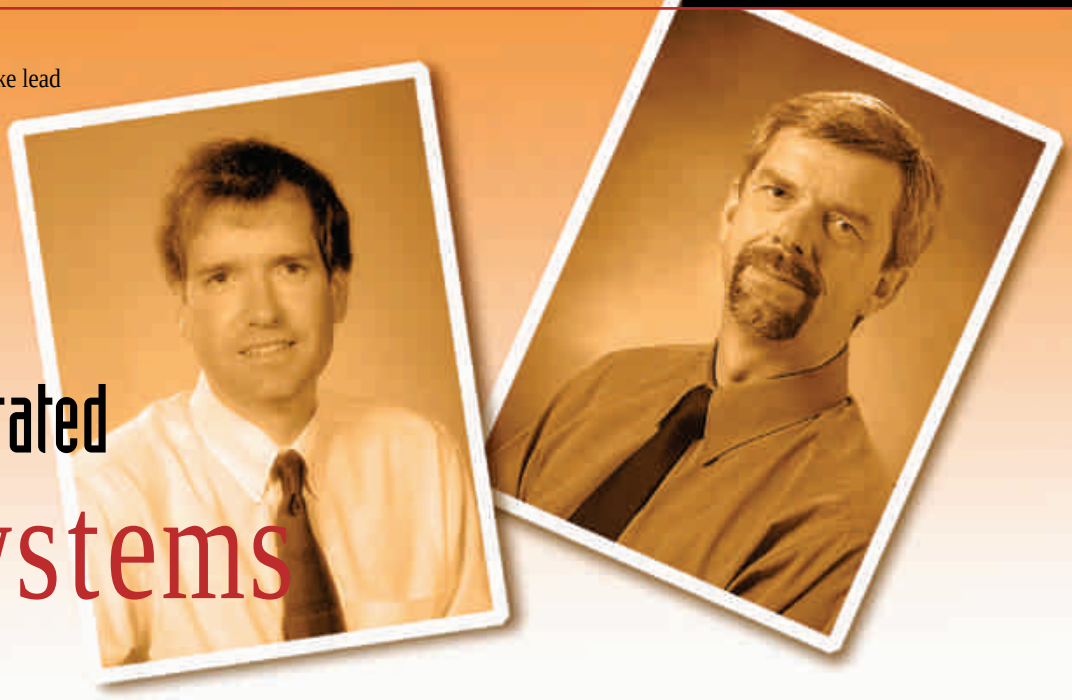
"This will be activities like understanding how bioagents and other pathogens attack and penetrate cell membranes, bioinformatics to 'mine and understand' the emerging explosion of biological data, and computational biology to tie all this understanding together in working models of cells and higher order structures. This will have direct and major impact on our bioterrorisim efforts and will also have important medical spinoffs." (See page 19.)



Synechococcus under an optical microscope.

For Sandia to succeed in its biotech endeavors, the Labs will have to partner more with other laboratories, universities, and hospitals. "We can't do this alone," Romig says. "We are not going to grow a major life sciences program here. We'll have to have interdisciplinary scientists and form lots of partnerships."

Following Romig's partnering theme, Camp and Grant Heffelfinger, Deputy Director for Materials Science and Technology in Sandia's Materials and Process Science center, point to Sandia's leadership of a major new multi-institutional project. (See page 22.) It will be funded over the next three years at $19.1 million by DOE's Office of Biological and Environmental Science — evidence Sandia's presence is beginning to be felt in this vital arena. Says Heffelfinger, "Sandia's success was largely due to our unique computational capabilities — which we coupled with the biosciences strengths of our partners — together with the vision to attack boldly a critical environmental problem. We seek no less than to understand at a genome and proteome level the carbon fixing abilities of *Synechococcus*, a naturally occurring organism. We then intend to use that understanding to develop strategies to help address the increase of carbon dioxide in the Earth's atmosphere."



Len Napolitano (left) and Terry Michalske lead the MIMS Grand Challenge.

Molecular Integrated Microsystems

By Chris Burroughs & Nancy Garcia

The next generation of microsystems may be like nothing anyone has ever seen.

Researchers at Sandia are pursuing a revolutionary approach to building microsystems — combining functions found in biological and nanoscale systems with manufacturable materials. The ultimate result may be the first programmable Molecular Integrated Microsystems (MIMS.) Such devices could be used for rapid chemical and biochemical analysis in sensors and for encoded optical interconnects to route optical energy on demand.

The research is funded internally as the LDRD MIMS Grand Challenge. Sandia's Terry Michalske in New Mexico and Len Napolitano in California are its leaders.

"A programmable system is a new vision for microsystems," says Michalske, a senior manager in the Labs' Integrated Nanotechnology group. "Our goal is to be able to reconfigure the architecture and tune the functions of microsystems, on-the-fly. This approach combines new developments in biotechnology and materials science to provide the methods needed to control materials and manipulate molecules at the nanometer scale. The ability to manipulate nanoscale structures is at the heart of the next revolution in programmable microsystems."

Over the past decade, Sandia has taken a pioneering role in the movement from traditional macroscale components and devices to fully miniaturized engineering systems. "We are now taking advantage of microscale addressability to locally control materials properties and molecular interactions within the microsystem itself," says Michalske, who is also Director of the Center for Integrated Nanotechnologies, a joint Sandia-Los Alomos National Laboratory center funded by DOE.

µProLab – sorting and separating

The grand challenge was initiated more than three years ago with the goal of developing the technical basis for the next generation of biochemical analysis and integrated optical microsystems. The biochemical analysis portion of the project is focused on new approaches to sort and separate small quantities of proteins in complex biochemical mixtures using the µProLab — Sandia's on-chip protein lab. The µProLab will concentrate dilute protein samples and do on-chip biochemical separations, similar to what Sandia's "chem-lab-on-a-chip," formally called µChemlab™, does with deadly chemicals. (See page 6.)

"...the team has already demonstrated that key components of protein analyses can be completed in a matter of minutes."

Len Napolitano
Director, Center for Exploratory Systems and Development

"The ability to rapidly analyze protein signatures is a critical component of Sandia's approach for detecting and mitigating bio-threats," says Napolitano, director of Sandia's Center for Exploratory Systems and Development. "Traditional methods for analyzing the protein signatures involve labor-intensive and time-consuming techniques, such as multidimensional chemical separations. Using new technologies, the team has already demonstrated that key components of protein analyses can be completed in a matter of minutes."

The programmable optical interconnect objective for MIMS is to write new optical paths, "on demand." The MIMS team has already demonstrated the ability to route on-chip optical signals in a programmable fashion. This new capability to create optical connections has important implications for spectroscopic analysis in chip-based chemical and biological analysis. It may lead to new ways to control access to information in weapons systems or secure data networks, as well.

Microchannel success

Napolitano notes that the MIMS project has already had several successes. Researchers can reconfigure a microfluid channel in real-time and can use electrical signals to manipulate proteins within those channels. In fact, some MIMS technologies are already licensed for commercial use while others are in negotiation.

"Our work over the past couple of years has brought us closer to our goal of building workable MIMS," he says.

The current goal is to build and demonstrate complete architectures and use science understanding to extend and increase programmable capabilities. The MIMS Grand Challenge project received high praise from its external advisory panel of members representing universities, National Institutes of Health, Department of Defense, National Science Foundation, and DOE. The panel noted that, "At this stage of the project you have a terrific technology. What you are doing with this program is important science and promising technology."

"We believe there have been some very significant accomplishments thus far," the panel said in a report. "Further, we were impressed with the talent of the technical people that presented to us, as well as your breadth of understanding of what others are doing in this field. We feel that you have the promise here to wow biologists."

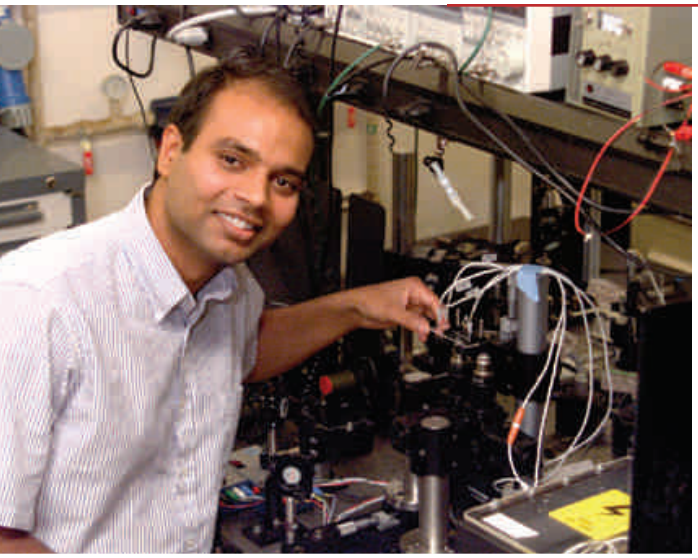
µProLab speeds protein sorting

If a cell typically contains 10,000 to 100,000 proteins or subcomponent peptides, then determining the distinct identities of only a few can be like looking for a proverbial needle in a haystack.

The task is even harder if the starting material is hardly more than a few cells. Then, provided the target has been sorted out, how does one manipulate that small amount to analyze it further? Standard screening currently requires cumbersome and lengthy processing steps, using equipment the size of kitchen appliances.

Sandia researcher Anup Singh and colleagues in the Labs' Biosystems Research department are developing microfabricated devices for protein and peptide analysis, dubbed a µProLab. The work is funded as part of the Molecular Integrated Microsystems (MIMS) Grand Challenge by the LDRD project.

The team has found, Singh says, that "by miniaturizing, we can actually do better." Using microchannels a few centimeters long, and in some cases just a few millimeters long, on glass chips, Sandia has demonstrated separation of multiple proteins and peptides



Anup Singh detecting protein separations.

in 30-45 seconds. That's one-tenth the time it would take if performed in longer columns or gels, and with only a thousandth of the starting sample amount needed for laboratory-bench-top-scale separations.

Liquid chromatography uses porous matrix-filled tubes called chromatography columns to separate molecules based on their interaction as liquid passes through under applied pressure or electric field. Different types of proteins interact differently with the column materials and drip out at different times, forming isolated "peaks."

Researchers have learned that separations can be tailored to a protein's different physical properties by selection of the material used for the spongelike matrix and the liquid used to rinse it through the column.

MIMS aims to integrate steps needed to sort and identify small amounts of proteins or peptides by "addressing" smart materials on chip assemblies to "do certain things at certain times in a certain place," Singh explains. In addition to running chromatography and other separations at the microscale, the chips will include components such as valves to control movement of fluids and concentrators. This will permit pre- and post-analysis concentration of dilute samples.

Singh hit upon his patent-applied preconcentrator invention by serendipity. He was working determinedly to get ready for a conference presentation. A minuscule, picoliter-sized protein sample he'd injected onto a microchannel that had been carefully packed with porous beads should have emerged, based on theory, after an electric field was applied. Anup suspected the initial sample injection didn't work. He used a hand-held syringe to push the fluid out of the channel. The detector happened to still be on, and to his surprise it registered a huge peak of concentrated protein.

"If not for that conference, I might not have discovered it," he says.

Electrokinetic trapping

He and collaborators termed the technique "electrokinetic trapping." Sharp, concentrated peaks form by using an electric field to focus charged analytes into a small spot in the separation channel. The preconcentration technique is addressable and reversible. Proteins can be trapped and concentrated at specific locations by turning the voltage on and released by turning the voltage off. Investigators, including Tim Shepodd of Sandia's Materials Chemistry department, have created in-place sieving gels by using ultraviolet light. The light polymerizes a porous matrix, whose composition can be fine-tuned for various separations. Select locations can be polymerized by using a mask.

For controlling flow through a branching array of intersecting channels, Sandia Microfluidics department researcher Brian Kirby has used a moving plug of polymerized material to shuttle flow through a bypass, thus creating a sort of check valve.

The team plans to combine separation techniques to "fingerprint" proteins, such as cytokines, as is currently done in bench-top processes, separating by both charge and size dimensions. Already, Singh and Biosystems Research coworkers Jongyoon Han and Dan Throckmorton have seen separation speed and efficiencies in a single dimension 10-fold greater than the larger techniques allow.

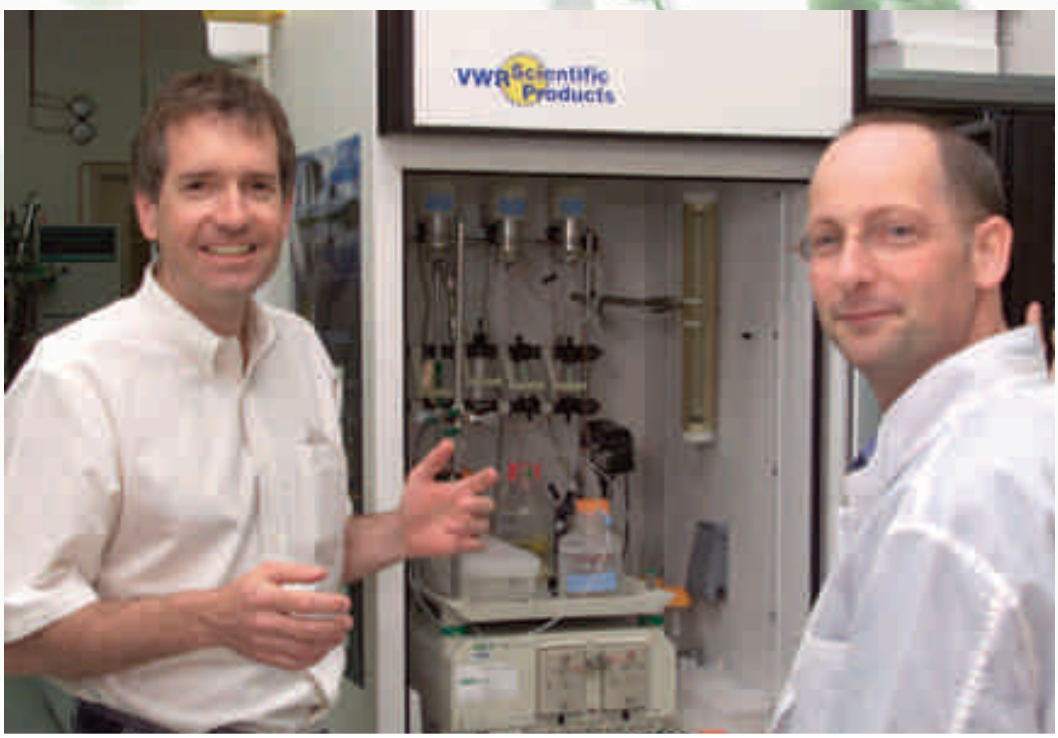
"We hope to cut the time, overall, 10- to 100-fold," he says, "and work with a small sample — possibly a few cells." The ultimate goal is that, once sorted by charge and size, a spot of protein can be microfluidically transported to a mass spectrometer for analysis of its constituent elements. Ideally this will occur through a completely automatic transfer when the device integration is complete.

> MIMS aims to integrate steps needed to sort and identify small amounts of proteins or peptides by "addressing" smart materials on chip assemblies to "do certain things at certain times in a certain place."
>
> Anup Singh
> Biosystems Research Department

Understanding Protein Interactions

By Chris Burroughs

A Sandia team is seeking to understand protein interactions, a research avenue that may lead to new ways of detecting biotoxins or of making drugs that will block them.



Len Napolitano with Joe Schoeninger (right) discussing Interfacial Bioscience Grand Challenge.

A team of about 30 scientists from Sandia National Laboratories in New Mexico and California is striving to better comprehend the mechanisms of "intoxication and signaling," through which biological agents — such as anthrax or botulism — might enter cells and try to kill them or interfere with the body's internal signaling system. The research project — called the Interfacial Bioscience Grand Challenge — is part of a two-and-a-half-year-old internally funded LDRD effort.

A cell membrane is a water-insoluble lipid bilayer surrounding a cell. It is studded with membrane proteins that control what goes in or out of the cell. In order for a bacterial toxin to penetrate a membrane protein, it must first bind to a receptor on the cell membrane. A pore is then created through which the toxic agent migrates into the cell.

"Because deadly biological agents enter cells in this fashion, finding a way to obstruct their entry would have a large scientific impact," says Len Napolitano, project manager. "It would be a significant contribution to biomedicine and could be an important bioterrorism countermeasure."

Joe Schoeninger, Sandia's principal investigator for the Grand Challenge, agrees: "If you go after a difficult problem, you might as well go after an important difficult problem."

"The completion of the human genome project has created a unique opportunity for breakthrough technologies with broad impact in chemical and biological defense and healthcare."

Len Napolitano, Director, Center for Exploratory Systems and Development

When a pathogen exploits the presence of a protein on a cell membrane to infect the cell, or a toxin specifically docks against a surface protein like an interlocking puzzle piece, the cell often spews out short-lived messenger compounds. A goal of the project is to better understand such signal pathways — the series of molecules that relay information between and within cells — something like a "bucket brigade" lining up to quench a fire.

Integrating Technologies

At the heart of the project is development of unique experimental and computational capabilities for understanding membrane protein structure. The challenge is to integrate a group of technologies that can provide structural and functional information about membrane systems at the molecular level. These technologies include methods for determining protein structure using mass spectrometry; a suite of novel scanning probe microscopes; and state-of-the-art membrane-simulation capabilities using massively parallel computers.

"The completion of the human genome project has created a unique opportunity for breakthrough technologies with broad impact in chemical and biological defense and healthcare," Napolitano says. "Based on Sandia's existing capabilities in bioanalytical technology, computer science and surface science, this project is directed to developing new technologies for analyzing the interactions of cell membrane systems, creating a unique niche for Sandia in biotechnology."

"We think there's room for some cross-cutting efforts that are going to be valuable in this area," says Schoeniger. "We're trying to develop new experimental and computational tools and take steps to integrate them."

As part of the Grand Challenge, the researchers ask three key scientific questions:

- What is the structure of the membrane protein when it is situated in the membrane?
- How does the structure change in response to a signal or an intoxicating agent?
- How does this structure change the function of the protein?

Three Technical Cores

To answer these questions, the project was organized with three technical cores: imaging, structure, and simulation.

- The imaging core team uses scanning probe microscopy and single-molecule biophysical measurement to connect structural changes with function.
- The structure core is based on a new technology for determining protein structure originally developed by Sandia/California researcher Malin Young and her collaborators at the University of California/San Francisco, the Buck Institute and Chiron Corporation. It uses protein chemistry and mass spectrometry methods to obtain structural information about protein molecules in different functional states.
- The simulation core provides computational tools to develop computer simulations and models of toxin and signal-molecule interactions with cell membranes.

The project made significant progress toward both experimental and computational goals during its first year. One example was implementation of an automated experimental and data analysis pipeline that will determine intra-atomic distances in membrane proteins. This was done through the use of chemical crosslinkers and Fourier Transform Ion Cyclotron Resonance Mass Spectrometry. These crosslinkers consist of two reactive groups joined by a linker arm of a certain length, used like a molecular caliper. The end groups can react with certain

Malin Young: From chemistry to structure.

The team has also written specialized software to use crosslinking information to build structure models, allowing further experimental refinement.

amino acid residues on the protein, but only if these residues are the right distance apart. Modern ultrasensitive, high-resolution mass spectrometry can determine, in hindsight, which residues were linked, and therefore how far apart they are. Different crosslinkers are used to determine the range of distances between different residues on the protein.

This is an entirely new methodology that has only been made possible in the past couple of years through advances in mass spectrometry and data analysis, Napolitano explains. "Using the unique capabilities of the mass spectrometry, we can ionize and fragment the whole protein to find out what parts are crosslinked to, and thus close to, other parts."

The team has also written specialized software to use crosslinking information to build structure models, allowing further experimental refinement.

Molecular Dynamics

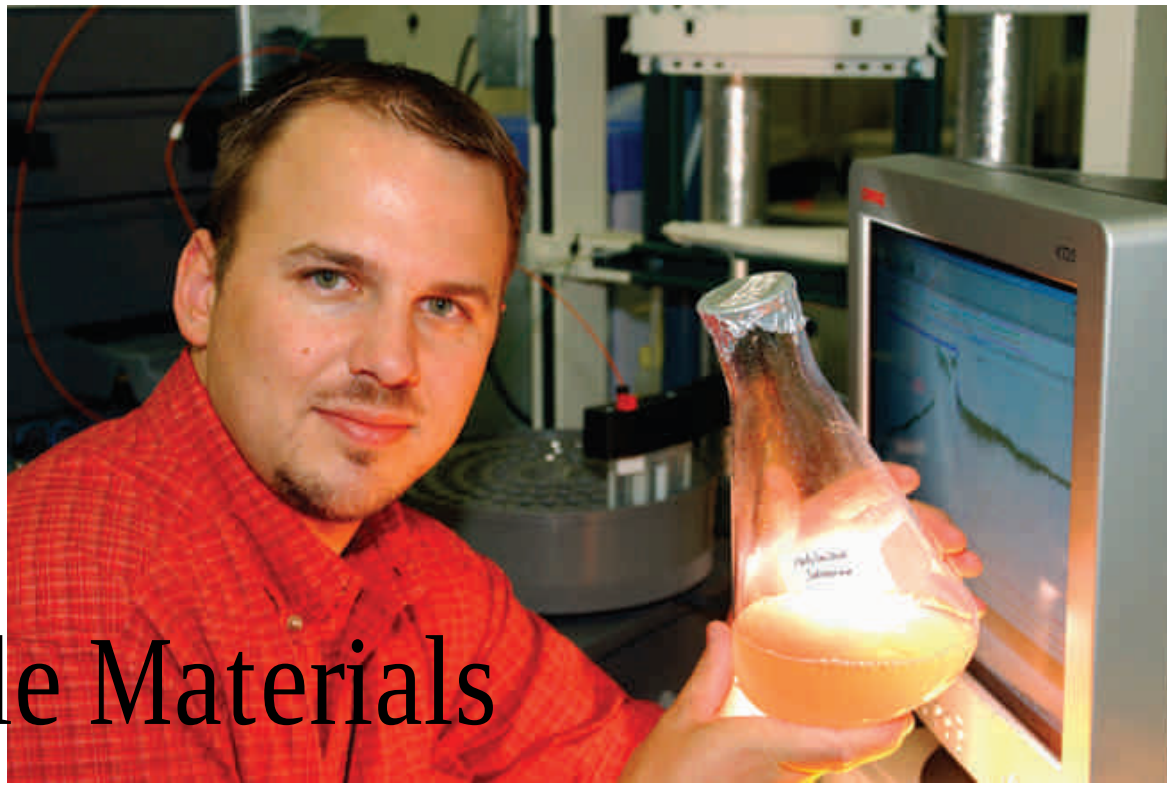
Under way as part of the project is a state-of-the-art computer code simulation of the molecular dynamics and energetics of membrane proteins. Used with Sandia's massively parallel computer, C-plant, and running on 100 processors, it can simulate one nanosecond of protein motion per day. Simulation time scales on the order of 100 nanoseconds and nonequilibrium simulation techniques, will allow a whole new range of biophysical problems to be addressed, including the significant changes in structure related to signaling.

At the same time, data analysis has been automated for researching the structural twists and turns of a model protein system — the light-sensitive visual protein rhodopsin — which is closely related to proteins that viruses interact with when they attack immune systems.

Using an atomic force microscope (AFM) in Albuquerque, the team was able to take images of single, isolated pores formed by cholera toxin molecules bound to the membrane. This shows the feasibility of using the AFM to study interactions of toxins with membranes at the single-molecule level. Sandia team members are collaborating with leading universities to look at the role of membrane proteins in normal neuro-transmitter function and after exposure to nerve agents (such as botulism, a toxin that shuts down the firing of neurons to cause paralysis).

An external advisory committee, composed of bioscientists from universities and the National Institutes of Health said in a report that the project was "very possible, very powerful, unique. No one else in the world has assembled the team and resources you have here and focused these on the highly compelling and daunting challenge of membrane proteins."

"You have huge potential for significant payoff and recognition, especially in the application of mass spectrometry and chemical crosslinking to membrane structure determination," the committee concluded. "If you reach your goals, Sandia National Labs will be the definitive cutting edge in a tremendously important area of bioscience."



George Bachand is part of a Sandia team studying motor proteins.

Imitating Nature with Adaptable Materials

Imagine a new "smart" material that can "heal" itself like a living system.

Synthetic materials tend to have static structures and are not capable of adapting to a changing environment. In contrast, living systems have the ability to create, heal, reconfigure and dismantle. It may sound like science fiction, but to Sandia molecular biologist George Bachand manufactured materials that can heal themselves may be just around the research corner.

Bachand is working with fellow Sandia researchers Jun Liu and Bruce Bunker of the Biomolecular Materials and Interfaces department and a team on a project called "Active Assembly of Dynamic and Adaptable Materials." Its goal is to identify and learn how to exploit key strategies used by living systems to develop materials that can be programmed to assemble and disassemble in controlled environments.

The Nanoscale Science, Engineering and Technology Initiative, through the Division of Materials Sciences and Engineering, Office of Basic Energy Sciences at the Department of Energy funds the project.

"With this project we are attempting to break the walls between living and nonliving systems at the nano-scale," Bachand says. "We are looking at designing materials that have properties of living cells."

As part of the project, the researchers are studying how to mimic the dynamic assembly and active transport of living systems in new materials. "The research moves material sciences from static structures to a regime in which materials can be assembled and reconfigured in response to external stimuli," Bachand says.

Smart, dynamic, adaptable

With this understanding, a new generation of "smart," dynamic and adaptable materials could emerge. As a first step, the researchers plan to use or modify key components from living systems and integrate and control those components in artificial microfluidic environments.

Specifically, they will be looking at motor proteins — considered to be Nature's means for transporting cargo within living cells — as the active components in the new dynamic nanomaterials. The species Bachand is studying is *kinesin*, a linear motor protein that walks along fibers in a "hand-over-hand" fashion for

"This work holds the promise of opening up a completely new branch of material science in which the nanostructures that can be produced will only be limited by our imagination."

George Bachand
Biomolecular Materials and Interfaces Department

hundreds of steps. *Kinesin* motor proteins are among the fastest and most efficient of motor proteins.

The motor proteins are produced through standard genetic engineering methods. Using a DNA sequence for a target protein, the specific gene that encodes the motor protein is isolated. The gene is then placed into *Escherichia coli*, where the motor protein is expressed and purified by liquid chromatography.

Bachand became particularly familiar with motor proteins while working as a research associate at Cornell University. There, as part of a team, he used motor proteins derived from enzymes to power a nano-propeller made of nickel in a solution. The entire device, including the motor and propeller on a nickel post, was comparable in size to some virus particles.

Bachand joined Sandia in 2001, becoming the Labs' first molecular biologist. Besides working on the Active Assembly of Dynamic and Adaptable Materials project, he plans to continue his efforts in using living motor proteins to power nanoelectromechanical (NEMS) systems.

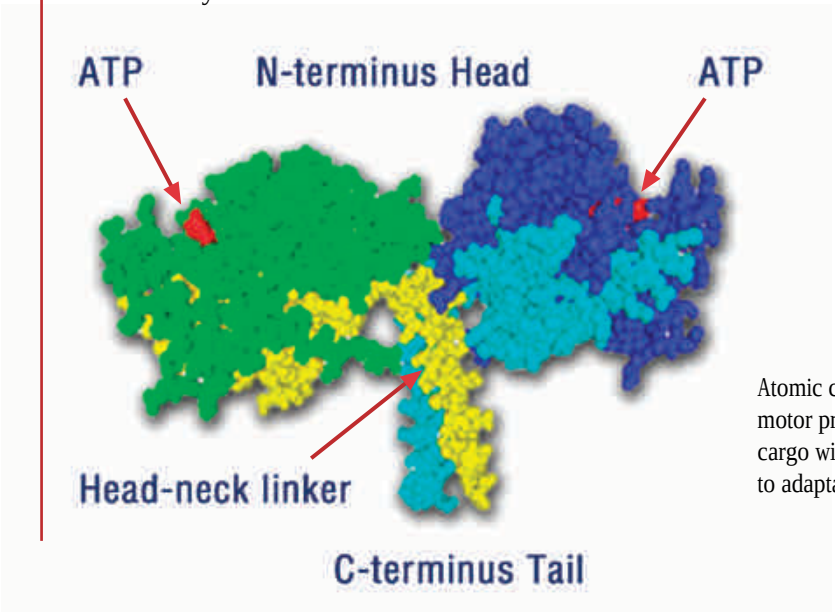
"Both research efforts will give us valuable understanding of motor proteins and how they work and a means for controlling the activity of proteins in synthetic systems," Bachand says.

Chemical energy to mechanical motion

While Bachand has cloned *kinesin* motor proteins in his lab, he still needs to characterize them to better understand how they bind and move. Over the next couple of years, he will perform biochemical and biophysical analyses of the motor proteins, which should provide him insight into the structural and mechanical features of the motor protein enzymes that are critical for conversion of chemical energy into mechanical motion.

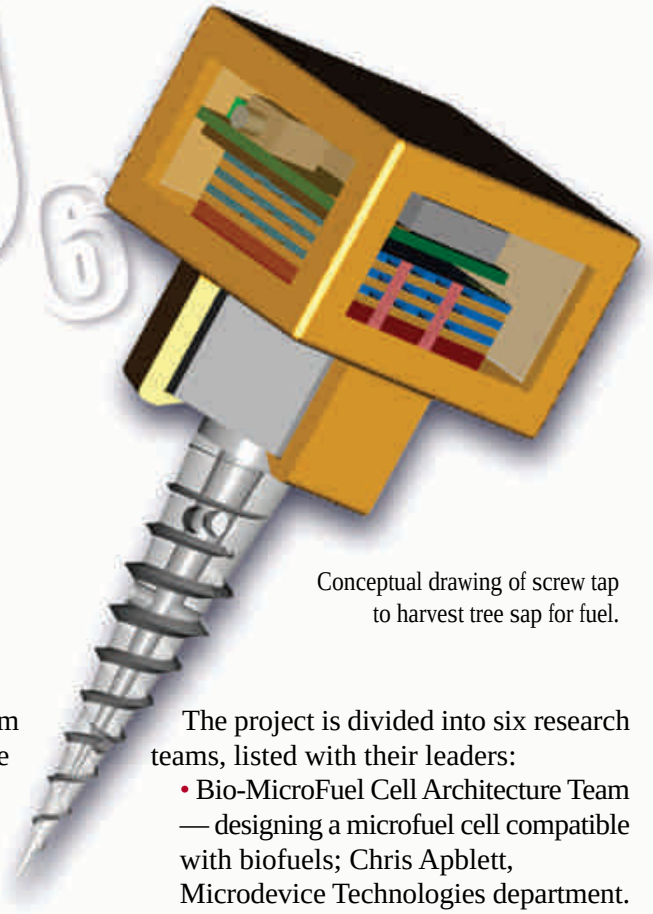
He will also genetically engineer these proteins to survive in synthetic systems, as well as provide mechanisms to control motor functions such as starting/stopping and cargo pick-up/delivery. Bachand notes that if he and the other researchers can understand key design criteria used by living systems, they will be able to identify basic concepts that will allow them to develop artificial materials and systems that may ultimately surpass the survivability and functionality constraints of existing biological systems.

"This work holds the promise of opening up a completely new branch of material science in which the nanostructures that can be produced will only be limited by our imagination," Bachand says.



Atomic crystal structure of *kinesins*, motor proteins that transport cargo within cells and a key to adaptable materials.

Powering devices from Living Systems



Conceptual drawing of screw tap to harvest tree sap for fuel.

Tomorrow's sensors, communication devices and other microelectronics technology may be powered by life. That is, powered by glucose obtained from living biological systems, ranging from human skin to plant tissues.

Sandia researchers Doug Loy, Jim Hudgens and Kent Schubert are leading a three-year project to develop new compact power sources fueled by biological hosts such as plants or animals. It could fill a need for uninterrupted autonomous power for applications where batteries are too large or too short-lived.

"We are initially looking at 'harvesting' glucose from living plants to serve as the power source for sensors," says Schubert, manager of Sandia's Microdevice Technologies department.

LDRD funds the Bio-MicroFuel Cell Grand Challenge.

A fuel cell is an energy conversion device that converts a chemical fuel, typically hydrogen and oxygen, into electricity. Instead of hydrogen, the fuel for the bio-microfuel cell will be glucose from living systems. Like a hydrogen-oxygen fuel cell, the primary emission is water. The biofuel cell will also create a small amount of carbon dioxide.

Power from Plants

Unlike a hydrogen fuel cell, which has to be refueled periodically, the bio-microfuel cell will continue to produce electricity as long as the plant or other biological host remains alive.

The project is divided into six research teams, listed with their leaders:

- Bio-MicroFuel Cell Architecture Team — designing a microfuel cell compatible with biofuels; Chris Apblett, Microdevice Technologies department.
- Membrane Materials, Fabrication and Testing Team — making membranes more robust and compatible with microfabrication techniques; Chris Cornelius, Catalysis and Chemical Technologies department.
- Bio-Microsystem Interfaces & Surface Compatibilization Team — engineering the interface for harvesting the fuel; Susan Brozik and Jeb Flemming, Microsensors Science and Technology department.
- Electrodes/Electrochemistry Team — focusing on the oxidation of the fuel and incorporating the electrode structures into the micro-architecture; David Ingersoll, Power Source Technology group.
- Biological Materials Team — working on integrating new bio-selective membranes and engineered enzymes; Andy Walker, Biosystems Research department.
- Systems Integration Team — integrating components into one system; Jim Hudgens, Integrated Microsystems department.

Chris Apblett conducts an experiment on a bio-microfuel cell.

"Micro-sized direct methanol fuel cells are under development for consumer electronics such as laptop computers and cell phones. In attempting to work with glucose or other bio fuels, the Sandia project is attempting to go even further."

Kent Schubert, Manager, Microdevice Technologies Department

To date the researchers have built several operational microfuel cells. They separately have demonstrated the feasibility of converting glucose to electricity, but have not yet powered a microfuel cell with glucose. Researchers are simultaneously developing two types of catalysts — one made from enzymes and one from precious metals.

The enzymatic approach makes use of enzymes found in nature to break down glucose and its by-products. The research goal is to develop long-lived methods to immobilize the approriate enzymes to catalyze the fuel oxidation reaction and efficiently withdraw the electrons released during that reaction. Ensembles of enzymes could potentially extract all of the available electrons in glucose. Precious metal catalysts, a more traditional approach, can also be used. This approach is more susceptible to poisoning, however. In its final form, the fully integrated system is expected to be the size of a small matchbox with a "harvester" tail protruding. The harvester will be a simple input device such as a short needle penetrating into a living biological source, like a plant or a tree. Whatever the source, glucose-containing fluid will be drawn from the biological host. Then the glucose will be oxidized in an electrochemical cell, producing electricity and water.

The goal of the project is to produce a 100 milli-Watt bio-microfuel cell in as small a package as possible, sufficient to power small devices. With breakthroughs in a few key technical areas, it may be possible to achieve output power densities of 100 milli-Watts per square centimeter.

Interdisciplinary approach

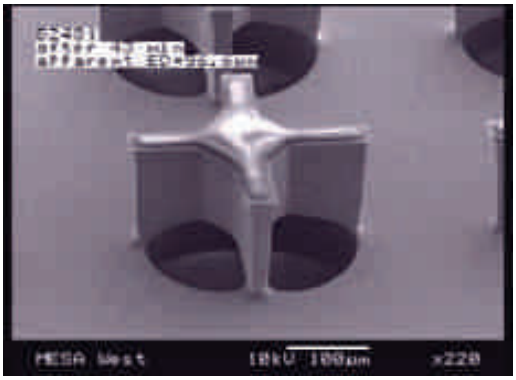
"The results of this work will have a profound impact on our nation's security and potentially our economic prosperity," says Sandia Vice President for Science Technology & Partnerships Al Romig. "Without the interdisciplinary collaboration between physical and biological disciplines, these results would not be possible."

Loy, a member of Sandia's Chemical and Biological Technologies department, sees a lot of potential uses for the bio-microfuel cell. "We anticipate the bio-microfuel cell will have a number of spin-off markets, particularly in the health care arena," Loy says. "Such devices could be used, for example, to power pacemakers, using glucose in a patient's blood as the fuel source."

The project comes with several "grand challenges" to overcome, Schubert says.

"Although many people and a lot of money have been devoted for many years to the development of microfuel cells that burn hydrogen gas, it is noteworthy that such devices are not yet commercially available," Schubert says. "Micro-sized direct methanol fuel cells are under development for consumer electronics such as laptop computers and cell phones. Though some may be close, none are on the market yet. In attempting to work with glucose or other bio fuels, the Sandia project is attempting to go even further."

"There are several major technical challenges facing the bio-microfuel cell team, but we've already come a long way." Schubert says. The team has already developed and demonstrated several micro fuel cell architectures, catching up with competitors who have been working the field



Microneedle, fabricated from silicon, is designed to harvest glucose from soft plant parts.

Currently, the team is collaborating with a number of different university groups in specialized areas.

for many years. They have built two different types of structures for harvesting glucose from plants and are beginning to test them. The team has shown good progress in developing new proton exchange membrane materials.

"We've demonstrated power from glucose in a meso-sized fuel cell and are working on transferring this to the micro fuel cells," says Schubert. "Our California team members have demonstrated 'direct wiring' of glucose oxidase enzymes to a gold electrode, and produced currents in a half-cell that far outstrip the best results in the literature. Our systems guys have come up with a prototype system concept and are working to make sure that components and advances developed by the various team members will function together in the prototype."

The bio-microfuel cell team is actively seeking partners for development of this technology. Currently, the team is collaborating with a number of different university groups in specialized areas, plus interacting with potential customers who could help fund the development. "No development partners are on board yet, but we have had promising discussions with different groups within the federal government and inquiries from commercial firms," says Schubert

How a Bio-microfuel Cell Works

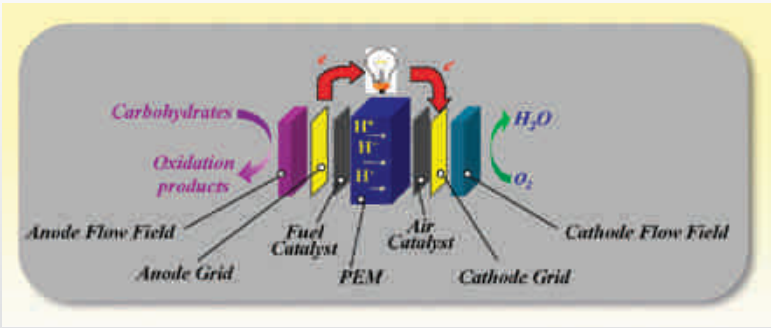
By tapping into a plant or animal, the bio-microfuel cell seeks to incorporate a "fuel tank" that refills itself.

The bio-microfuel cell being developed by researchers at Sandia works like a battery. While a battery is a "closed" system, that is its lifetime is fixed by the amount of reactants packaged inside it, the fuel cell is an "open" system. This means that its fuel is supplied on a semi-continuous basis and can be renewed by changing or refilling the fuel tank. By tapping into a plant or animal, the bio-microfuel cell seeks to incorporate a "fuel tank" that refills itself.

At the heart of the fuel cell, fuel oxidation and oxygen reduction take place at the anode and cathode, respectively. Catalysts are incorporated into the electrodes to facilitate the reactions. A proton exchange membrane (PEM) separates the oxidation and reduction reactions and allows the use of the electrons released at the anode during oxidation in an external circuit. The protons are transported through the membrane to complete the circuit inside the fuel cell. Electrons are received back again from the external circuit at the cathode, where they react with the protons and oxygen atoms to produce water.

In the case of the bio-microfuel cell, the fuel is glucose — a common natural sugar. When a glucose molecule comes in contact with the catalyst, it splits into two, releasing two protons and two electrons. Sandia researchers are looking at different types of catalysts for oxidizing glucose — one made of the enzyme glucose oxidase and another made of a precious metal.

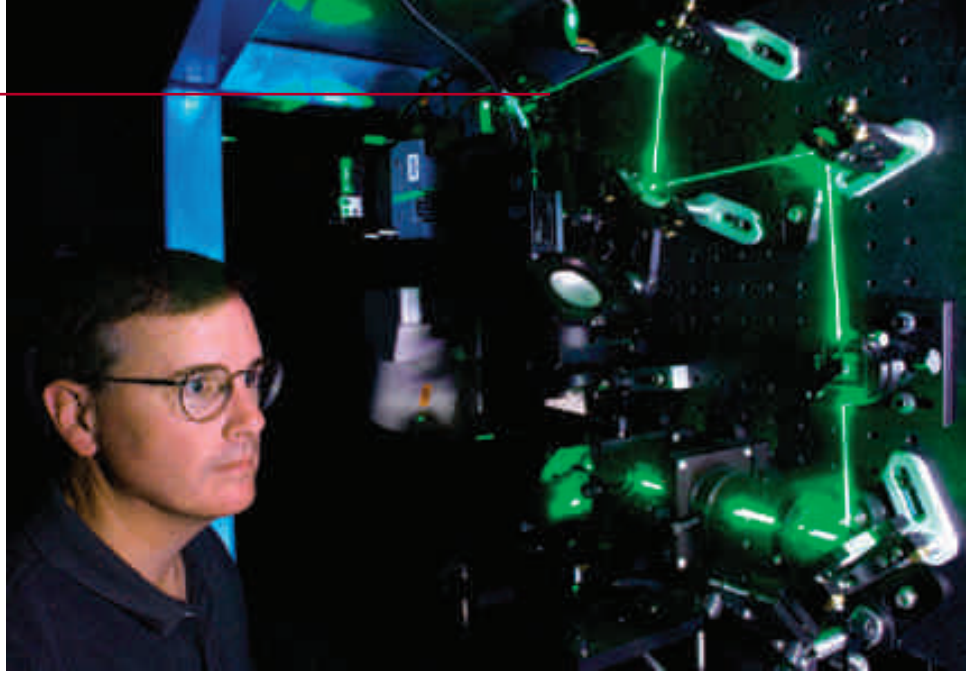
Researchers would also like to develop catalysts to harvest more protons and electrons from the by-products produced in the first oxidation reaction. In theory, researchers should be able to harvest 24 electrons from a glucose molecule by using the appropriate catalysts.



Bio-microfuel Cell main elements

Microarray technology helps diagnose, prevent illness

By Chris Burroughs



Mike Sinclair and his Hyperspectral Microarray Scanner.

Sandia National Laboratories and the University of New Mexico researchers are working together to gain a greater understanding of genomics and ultimately to find new ways to diagnose, treat and prevent illnesses.

Two Sandia researchers, George Davidson and David Haaland, have been collaborating with University of New Mexico (UNM) researchers on projects using several of the same microarray scanning and computing technologies.

One research endeavor — initially funded through an internal Sandia LDRD award and followed by grants from the W.M. Keck Foundation and National Institutes of Health — involves Sandia, the UNM Cancer Research and Treatment Center (CRTC), and UNM High Performance Computing Education and Research Center (HPCERC). Using Sandia-developed software and computing capabilities, researchers are evaluating thousands of genes from some of the 100,000 tissue samples from leukemia patients maintained at the CRTC.

Eventually, the new Sandia microarray scanning technology will allow for higher throughput in these studies. The goal is to determine why coded gene information in some cells leads to production of cancerous cells. This is information that will be useful for assigning patients to different treatment protocols and may ultimately lead to the development of drugs specifically targeted to fight these cancers.

In another project, Haaland, a senior scientist in Sandia's Chemical and Biological Sensing, Imaging and Analysis department, and Davidson, of the Computation, Computers, Information and Mathematics center, are collaborating with Maggie Werner-Washburne, a UNM biology professor. Their goal is to improve microarray analysis techniques and interpretation of data from microarray experiments. Focusing on yeast cells, the fundamental research is now promising to provide better understanding of how cells transition from a quiescent to a growing state. This transition is involved in wound response, cancer, germination of spores, and the complex response of cells to bioagents. This applied research is contributing to enhanced instruments and sensors to combat bio-threats.

University partnership begins

Sandia's work with Werner-Washburne came first, emerging from discussions while she was the program director for Microbial Genetics at the National Science Foundation in Washington, D.C. She returned to UNM to help create and lead a group of like-minded researchers interested in exploiting the genomics revolution and helping New Mexico laboratories develop these technologies. Davidson and Werner-Washburne developed strong ties between the biology department and Sandia, including training of students and building the required equipment. The work was partially funded by a three-year University Research LDRD grant that began in 1999.

The project had three objectives — the most important being the establishment of viable biotech research collaborations between the two institutions. The second goal was to enable local microarray experiments and to develop the methods and process controls

"As a result of our Sandia collaborations, we have been able to take a systems approach to this problem. There are very few laboratories in the country that effectively incorporate biologists, computer scientists, chemists, mathematicians, and engineers at this level."

Dr. Maggie Werner-Washburne
UNM Professor of Biology

necessary to achieve high-quality results. The third was to research the issues of gene expression of yeast cells in quiescence and during re-entry into the cell cycle.

"The collaborations between Sandia and UNM have been quite successful," Davidson says. "Importantly, we jointly developed the ability to conduct and analyze microarray experiments using either commercial gene array membranes or arrays printed on glass slides at the UNM Biology Department."

It became apparent that the commercial scanners for reading these arrays could be greatly improved, which led to Haaland's involvement. "Maggie and I talked about our research when we would run into each other in our neighborhood park. At the time Maggie was working with microarray technology using two fluorescent dyes to study gene expression of yeast cells, and I was doing hyperspectral imaging in the infrared," Haaland says. "It became apparent that the hyperspectral imaging could be useful in Maggie's efforts."

Werner-Washburne says that the Sandia collaborations started during their walks in the park have been particularly rewarding. "As a result of our Sandia collaborations, we have been able to take a systems approach to this problem," she says. "There are very few laboratories in the country that effectively incorporate biologists, computer scientists, chemists, mathematicians, and engineers at this level. It is the future of genomics, and we have a unique opportunity to make important contributions and have fun at the same time."

Microarrays and leukemia

About a year into the Sandia/Werner-Washburne project, the W.M. Keck Foundation of California awarded the UNM Health Sciences Center, which has the largest leukemia tissue repository in the world, and Sandia a $1 million grant to apply microarray research to leukemia.

"The attractive part of the proposal was the combination of high-performance computing capability and instrumentation technologies at Sandia with the unique tissue repositories at UNM," says Davidson. This potent combination is directed toward learning what causes the cancer and which drugs and therapies might be tailored to each individual patient for optimal treatment.

"It is our hope for the future that such studies will allow us to develop specific and more effective therapies targeted to each individual patient," says Cheryl Willman, M.D., CRTC director and principal investigator of the Keck grant.

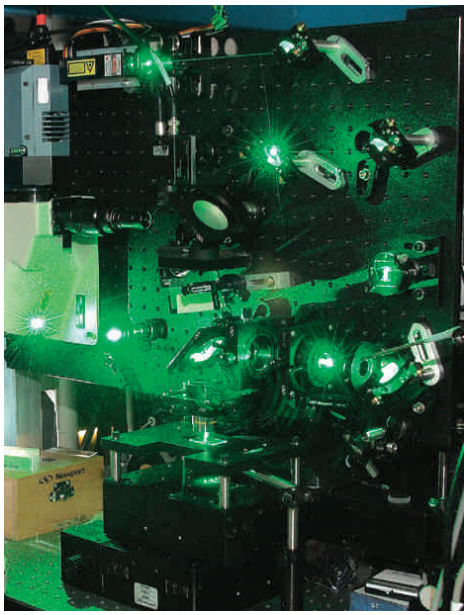
Of the $1 million, UNM received 70 percent, Sandia 30 percent. The CRTC handles all clinical interactions and the laboratory preparations, including scanning the slides with commercial equipment. Those data are then analyzed, using new methods developed at Sandia, and independently by the computer scientists from the HPCERC.

"Sandia's high throughput methodology, from the microarray scanners to the mathematical tools for data extraction, will have a major impact on a variety of bioscience and technology studies, from basic research of disease to mitigating the biothreat from emergent diseases and terrorism," says Sandia's Vice President for Science-Technology & Partnerships Al Romig. "It's simply another example of Sandia's expertise in physical science, engineering, and computing applied to biological problems. It represents a true scientific win-win. There are problems that are intractable with traditional tools of bioscience, yet attacking them allows Sandia to nurture its own competencies to the benefit of all of our national security problems."

What is genomics?

Genomics is generally defined as the study of genes — coded lengths of DNA material that provide blueprint information for a cell — and how they function. Recent advances in genomics are bringing about a revolution in our understanding of the molecular mechanisms of disease, including the complex interplay of genetic and environmental factors. Genomics is also stimulating the discovery of breakthrough healthcare products by revealing thousands of new biological targets for the development of drugs, and by giving scientists innovative ways to design new drugs, vaccines and therapeutics.

Source: Pharmaceutical Research and Manufacturers of America (PhRMA)



Tools of the Trade

Sandia and UNM have also produced better scanning technology by developing a new kind of scanner called a hyper-spectral imager.

The genome microarray studies being done by Sandia and the University of New Mexico (UNM) rely on two major enabling technologies: arrayers and scanners that read the information from the arrays.

The Keck-funded research uses commercially available arrayers. Laboratory arrayers give researchers the option to create custom arrays and to work with organisms for which commercial arrays are not yet available.

"One of our first steps was to get access to an arrayer. We ordered the parts and built it over about a week with a group of undergraduates," says Sandia's George Davidson.

The initial arrayer has been replaced with a faster commercial machine, but it served as the main research tool for developing all of the arraying protocols that are now standard in biology professor Maggie Werner-Washburne's laboratory at UNM.

The instrument is a robot, which moves metal pins, first dipping them into reservoirs of DNA, one gene per reservoir, and then tapping the nano-liter quantities onto the surfaces of up to 100 glass slides. Thousands of spots containing different DNA genes are laid out in each array on 100-200 micrometer centers.

After a slide is printed, samples of RNA from the target cells are prepared and translated into DNA that is complementary to the gene that originally coded the RNA molecule. These cDNA molecules are tagged with a fluorescent marker and incubated above the spots of DNA on the array.

The cDNA find the corresponding gene printed on the array and bind together in a process called competitive hybridization. Interrogation of the array with a fluorescent scanning device measures the concentration of the cDNA corresponding to each gene in the cell.

Typical Experiment

In a typical DNA microarray experiment, the relative expression levels of all protein-encoding genes are compared between two states of a cell. In this type of experiment, cDNA is labeled with two different fluorescent molecules (Cy3 and Cy5). The labeled cDNAs are combined and hybridized to the DNA printed on the microarray. Then the microarray is washed, dried, and read using green and red lasers in a commercial scanner to excite the two different fluorescent labeling molecules.

Using specialized computer software, the intensity of the emission peaks of both the Cy3 and Cy5 targets in each gene spot are visualized as green and red. The resulting data are then analyzed with a variety of techniques, including VxInsight, data-mining software developed at Sandia.

Werner-Washburne notes that her UNM research "now has over $1.5 million in new funding from the National Science Foundation and National Institutes of Health that wouldn't have been possible without the arrayer that George Davidson and our students built."

Sandia and UNM have also produced better scanning technology by developing a new kind of scanner called a hyperspectral imager.

Sandia researcher David Haaland says the scientists found many problems with the existing microarray scanner technology, including a need for greater sensitivity for low-expressed genes and the fact that comparisons between microarray experiments are limited due to poor reproducibility.

"But our main issue was slide fluorescence from impurities," he says. "The slides had spectral interferences that resulted in extraneous light causing loss of quantitative accuracy."

Haaland needed a device that would eliminate the influences of the impurities and provide much more accurate data that could be fed into the computers for analysis. He turned to fellow Sandian Mike Sinclair, known for co-inventing the Polychromator (see SANDIA TECHNOLOGY Vol. 4, No. 3.)

Among its advantages: greater accuracy and improved rejection of stray light.

Hyperspectral Microarray Scanner

After analyzing several approaches to array scanning, Sinclair developed a design and built the Hyperspectral Microarray Scanner for Microarray Analysis, primarily from commercial parts. The scanner he developed is potentially more sensitive than any commercial microarray scanners. Among its advantages: greater accuracy and improved rejection of stray light.

With the help of Jeri Timlin and Gary Jones at Sandia, Sinclair had a working device that was providing almost pure data from the slides provided by UNM's Werner-Washburne and the UNM Cancer Research and Treatment Center.

He can put what appears to be a clean slide with only the DNA samples in the hyperspectral microarray scanner, and after illuminating it with one or more lasers, see several impurities in the slide.

"I built this machine, but it is still amazing to use it and see all this information pop out on what looked like a clear glass slide," Sinclair says. The hyperspectral microarray scanner provides Sinclair with huge data files that are put on CDs. Haaland, Timlin and George Davidson then do analysis, using Sandia-developed algorithms and software.

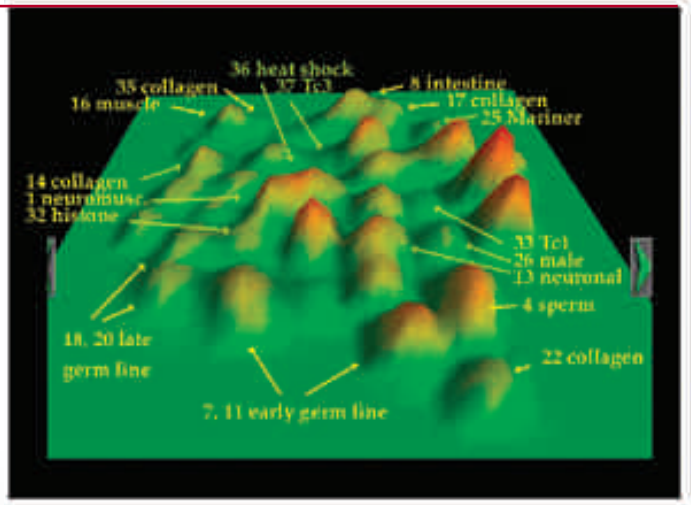
Currently, Sinclair is building a second, improved hyperspectral microarray scanner to study a seaborne bacteria, *Synechococcus*, as part of the recently announced Department of Energy "Genomes to Life" project. (See page 22.)

VxInsight analyzes data

Many approaches have been taken in analyzing, archiving, and annotating the data to determine gene relationships.

The Sandia team is using tools from researcher David Haaland's chemometrics research, linear and nonlinear classifiers, vector support machines and Sandia's VxInsight data-mining software. This software, which visualizes complex data into topographic map form, has also been successfully used at other genomic research centers.

"We've used VxInsight for a long time at Sandia for various projects," said Sandia researcher George Davidson. To make it applicable to genomics, however, the software had to be made even more sophisticated. Some of that development was the direct result of working with the UNM projects. Other parts sprang from Sandia's collaboration with the Stanford Medical School, which uses VxInsight for genomic research. "Many of the recently added capabilities were required to analyze the UNM leukemia data. These same techniques will be useful in the new Genomes to Life research that has just been awarded," says Davidson.



A gene expression map created by VxInsight. Three dimensional mountains represent gene classes that are enriched.

"Sandia is poised to begin making major contributions in biology; the researchers in New Mexico and California have a real opportunity now that we have been awarded the Genome to Life grant," Davidson says. "Certainly, the larger Sandia experience and capabilities grew from many sources, but David's and my research have benefited from the UNM collaborations."

Prototype array may eventurlly be inserted in retina of blind patient

A Thousand Points of Light

By Neal Singer

Enabling the blind to see — a task once thought the province of miracles — is the goal of a technical team that includes Sandia National Laboratories, four other national labs, a private company, and two universities.

The idea, funded by a $9 million, three-year grant from the Department of Energy's Office of Biological and Environmental Research, is to create 1,000 points of light through 1,000 tiny MEMS [microelectro-mechanical systems] electrodes. The electrodes will be positioned on the retinas of those blinded by diseases such as age-related macular degeneration and retinitis pigmentosa.

These diseases damage rods and cones in the eye that normally convert light to electrical impulses, but leave intact the neural paths to the brain that transport electrical signals. Eventually the input from rods and cones ceases, but 70 to 90 percent of nerve structures set up to receive those inputs remain intact.

"The aim is to bring a blind person to the point where he or she can read, move around objects in the house, and do basic household chores," says Sandia project leader Kurt Wessendorf. "They won't be able to drive cars, at least in the near future, because instead of millions of pixels, they'll see approximately a thousand. The images will come a little slowly and appear yellow. But people who are blind will see."

Tiny Camera and Transmitter

The plan is to lodge a tiny camera and radio-frequency transmitter integrated in the frame of a patient's glasses to transmit information and power to tiny electro-mechanical module devices placed within the eyeball. The electrode array, placed on the surface of the retina will electrically stimulate retinal nerves. The nerves then will send electrical impulses to the brain for processing.

Dean Cole, a biomedical engineer, directs the project at DOE's Office of Biological and Environmental Research in Washington, D.C. "Blindness is a devastating problem and we felt that the modern conjunction of materials science with micro- and nanotechnologies in our multidisciplinary national labs offers possibilities for advances where before people had hit brick walls," he explains.

The Sandia approach is to attach a MEMS chip on the retina made of LIGA and surface micro-machined silicon parts. (LIGA parts are metal, plastic, or ceramics and are made using lithography, electroplating and molding.) The idea is to directly stimulate some of the nerve endings within the retina to produce images good enough to read large print and to distinguish between objects in a room.

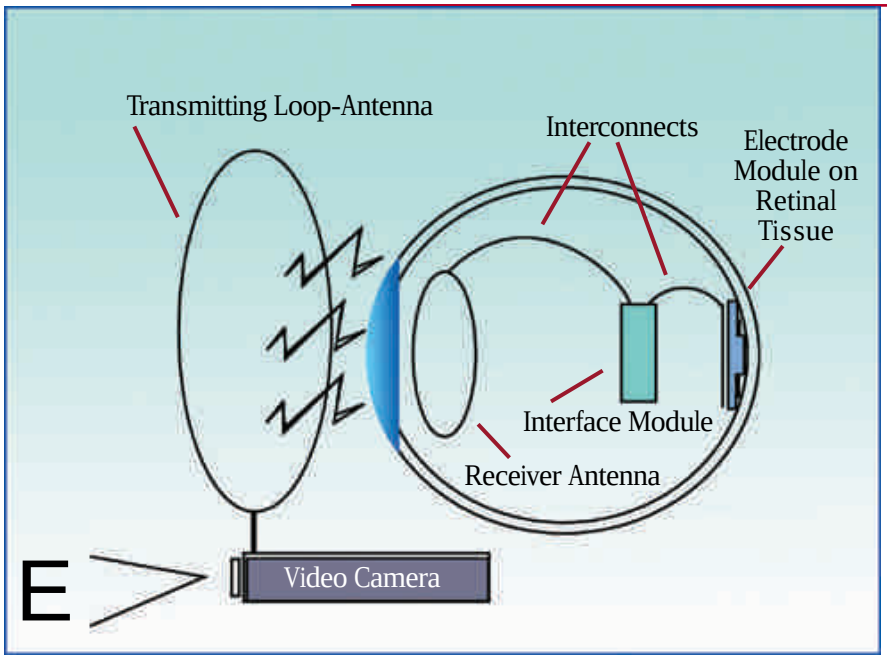
"Compared to the elegance of the original biological design, what we're doing is extremely crude," says Wessendorf. "We are trying to build retinal implants in the form of electrode arrays that sit on the retina and stimulate the nerves that the eye's rods and cones formerly served."

Difficult but achievable realm

The size of cones and rods, as well as nerve connections, are in the low micron range — a difficult but achievable realm for scientists used to working with micromachines. "We'll use a crude, shotgun approach that fires groups of nerves. In the long run, of course, we'd like to stimulate each individual nerve," says Mike Daily, manager of the Labs' Integrated Microsystems department.

Goals of the project increase from 10-by-10 electrode arrays to 33-by-33 arrays by 2004.

The project started at Johns Hopkins University under medical doctor and researcher Mark Humayun. When Humayun began the



A drawing of a retinal prosthesis implant shows the imaging camera at bottom (possibly situated on frame of glasses), transmitting power and information to modules within the eyeball.

"Integrating microdevices into the human eye is incredibly challenging because of the need for high-reliability operation over decades in a saline environment."

Mike Daily, Integrated Microsystem Department

Intraocular Retinal Prosthesis Group at Doheny Retina Institute at the University of Southern California (USC), the project moved with him. Teaming with Eli Greenbaum at Oak Ridge, the pair visited a number of national labs. Like Johnny Appleseeds of ideas, they tossed out seeds of thought and ultimately arranged to have each lab work on a different aspect of the electrode array/retina interface.

Says Humayun, "There is a considerable amount of advanced technology literally on the shelf or already being used for defense purposes that we could use to help solve blindness and greatly propel forward the entire field of medicine."

Other national labs involvement:

- Oak Ridge National Laboratory will manage the multi-laboratory effort and test components developed by the other labs;
- Argonne National Laboratory will investigate the viability of diamond-based electrode arrays and biocompatible coatings;
- Lawrence Livermore National Laboratory will experiment with rubberized electrode arrays; and
- Los Alamos National Laboratory will model and simulate neural paths from the retina to the brain.

Need for reliability

USC personnel will implant the devices and test their medical effectiveness. Second Sight, located in Santa Clarita, Calif., will commercially produce the finished system. North Carolina State University in Raleigh leads the development of the in-situ medical electronics.

Says Sandia's Daily, "Integrating microdevices into the human eye is incredibly challenging because of the need for high-reliability operation over decades in a saline environment. Bio-MEMS interfaces and biocompatibility issues drive much of the effort, particularly in the packaging of the microsystem." In this case, 'packaging' refers to sealing and securing a microdevice in place and linking it electronically and physically with its environment.

The rods and cones of the retina lie beneath nerves. The tissue housing the nerves is relatively clear, says Wessendorf. "We're investigating which electronic waveforms will best stimulate these nerves." There are other issues, he adds.

The overall project, underway since October 2001, is expected to identify the most promising implantation technologies. "The question is, who's going to engineer the best system that works in the real world?" says Daily.

Over a five-year period, says Dean Cole, the project will begin with goggles and move in the direction of corneal implants, aiming if all goes well to prepare five patients for the procedure before the project's end. After that, he says, "The FDA will say they want 100 patients for long-term studies and DOE will get out and leave the project in the hands of industry."

Two hundred thousand eyes — primarily in the elderly — in the US are blinded each year by macular degeneration. One baby in 4,000 demonstrates retinitis pigmentosa. Wessendorf and co-inventors Murat Okandan, David Stein, and Michael Rightley, Ramona Myers and Thomas Lemp all participate in the project.

Sandia Leads 'Genomes to Life' Program

By Neal Singer

Sandia will lead one of five major research programs — and participate in two others — announced this fall by the Department of Energy (DOE) for what it terms "post-genomic" research.

"One could hardly imagine when the Energy Department began the Human Genome project in the '80s that the resulting information and technologies could yield such diverse benefits," said DOE Secretary Spencer Abraham this fall in announcing Genomes to Life.

This new research initiative is expected to provide "biotechnology solutions to help produce clean energy, clean up the environment, and contribute to the President's policy on climate change," he added.

Grant Heffelfinger, Deputy Director for Materials Science & Technology in Sandia's Materials and Process Science center, heads one of five Genomes to Life programs now under way. The program involves $19.1 million over three years to understand the capture of carbon in sea-borne bacterium called *Synechococcus*.

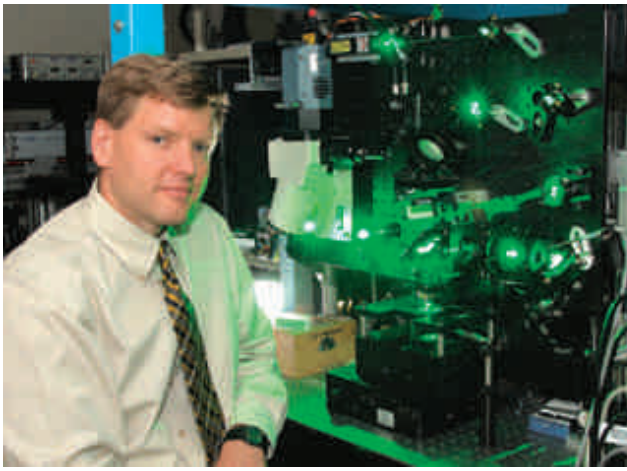
Experimental and computational

The program is a combined experimental and computational effort that emphasizes developing and applying new computational tools and methods. The experimental effort will provide the biology and data to drive computational development. The program also will develop and apply new data measurement and statistical methods to analyze microarray experiments.

The Sandia-led project brings together a formidable collection of research institutions, including Sandia, Oak Ridge National Laboratory, Lawrence Berkeley National Laboratory, Los Alamos National Laboratory, National Center for Genome Resources in Santa Fe, NM, the University of California at San Diego, the University of Tennessee at Knoxville, the University of Michigan at Ann Arbor, the Molecular Science Institute in Berkeley, California, the University of California at Santa Barbara, and the University of Illinois at Urbana-Champaign.

Of the total for this project, more than $8 million comes to Sandia. Other monies will be distributed among the ten research partners.

The reason that Sandia — not particularly known for biological expertise — was awarded the leadership role, says Heffelfinger, is the Genomes to Life program's emphasis on developing and applying computational methods to life science problems relevant to



Grant Heffelfinger

DOE's missions. In fact, the program is jointly sponsored by two of the Office of Science's programs, Biological and Environmental Research and Advanced Scientific Computing Research.

Computational Capabilities

One of the Genomes to Life key goals is to develop computational capabilities. (See page 24.) "Our proposal, though it has a biological title, is based on our world-class computing and experiment-analysis expertise — abilities we've proven time and time again. So it makes sense for Sandia to lead what I think of as the lead Genomes to Life computational capabilities project."

The research addresses a longstanding focus of biological oceanography — understanding, predicting, and perhaps manipulating carbon-fixation in the oceans. It is clear that oceanic microorganisms play a key role in the global environmental response to man-made generation of CO_2 into the atmosphere. However, the carbon-fixation mechanisms in these microorganisms are poorly understood. The Sandia project will investigate the carbon-capturing behavior of this abundant marine organism to learn more about environmental responses. By the end of the project, Heffelfinger's goal is development and prototyping of "a set of computational capabilities to enable the advancement of life science research for DOE's missions."

The program will use advanced computation, genomic information, and other resources to "take advantage of solutions that nature has already devised to help solve problems in energy production, environmental cleanup, and carbon cycling," according to the DOE. "Through a systems approach to biology at the interface of the biological, physical, and computational sciences, the program seeks to understand entire living organisms and their interactions with the environment."

Heffelfinger's goal is development and prototyping of "a set of computational capabilities to enable the advancement of life science research for DOE's missions."

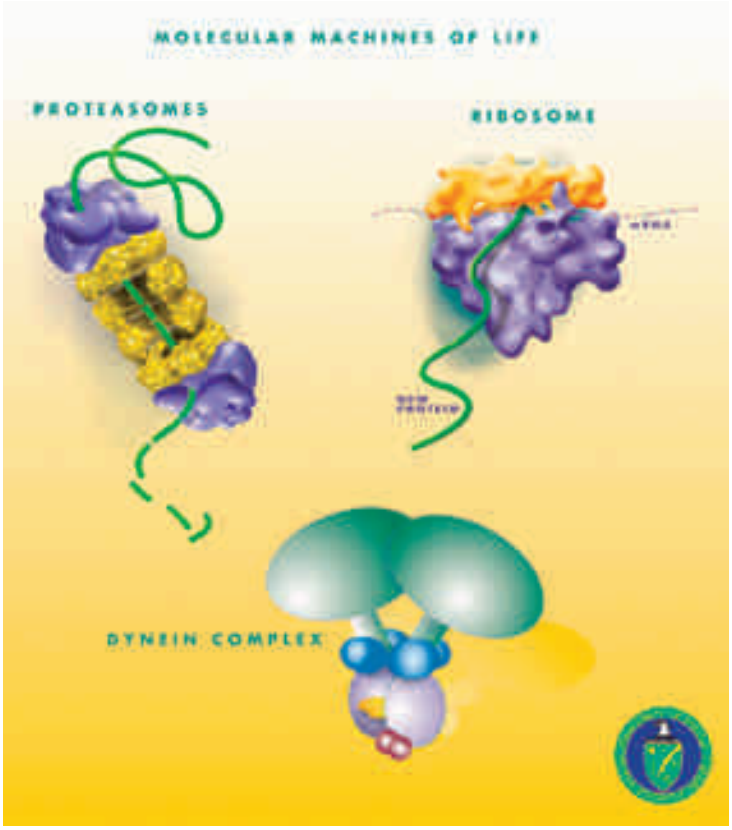
Other projects in which Sandia is formally involved are led by:

- Oak Ridge, which received $23.4 million over three years to develop a program for identification and characterization of protein complexes, and
- Lawrence Berkeley National Laboratory, which received $36.6 million over five years for work involving metal- and radionuclide-reducing bacteria.

A whole-systems VIEW

Secretary of Energy Spencer Abraham

Building on the successes of its "Human Genome Project," the Department of Energy (DOE) has initiated an ambitious program to achieve the most far-reaching of all biological goals: a fundamental, comprehensive, and systematic understanding of life.



DOE's "Genomes to Life" program is aimed toward a comprehensive, integrated view of biology at a whole-systems level. The DOE offices of Biological and Environmental Research and Advanced Scientific Computing Research have formed a strategic alliance to meet this challenge.

Secretary of Energy Spencer Abraham announced the new project in Washington last fall. Funding will total $103 million over the next five years. Research will be conducted at six national laboratories, including Sandia; 16 universities and research hospitals; and four private research institutes.

The plan for the program is to use DNA sequences from microbes and higher organisms, including humans, as starting points for systematically tackling questions about the essential processes of living systems. Advanced technological and computational resources will help to identify and understand the underlying mechanisms that enable organisms to develop, survive, carry out their normal functions and reproduce under myriad environmental conditions.

This approach ultimately will foster an integrated and predictive understanding of biological systems and offer insights into how both microbial and human cells respond to environmental changes. The applications of this level of knowledge will help DOE fulfill its broad missions in energy, environmental remediation, and the protection of human health.

GTL Goals

Specific Genomes to Life goals are to:
- identify the protein machines that carry out critical life functions,
- characterize the gene regulatory networks that control these machines,
- explore complex microbial communities in their natural environments to provide a foundation for understanding and using their remarkably diverse capabilities, and
- develop the computational capabilities to integrate and understand these data and begin to model complex biological systems.

"To stay at the cutting edge of nanoscience, materials science and micro- and nano-devices, we must invest in biotechnologies. I would bet that someday bio-inspired materials and devices will appear in Sandia designed national security systems and nuclear weapons."

Al Romig,
Sandia Vice President for
Science & Technology and Partnerships

Sandia is a multiprogram laboratory operated by Sandia Corporation, a Lockheed Martin Company, for the United States Department of Energy's National Nuclear Security Administration under contract DE-AC04-94AL85000

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