Breakthroughs

Science. Technology. Innovation.

SUMMER 2002

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PACIFIC NORTHWEST NATIONAL LABORATORY

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Breakthroughs

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editor's screen

Engineers can predict exactly what will happen if a critical component in manufacturing equipment is installed incorrectly or if the carburetor fails in a sports car. They can "fly" a jumbo jet inside a computer, making minor adjustments as they go to fully test every component and how it affects overall performance. Machines easily are understood as a collection of systems and subsystems that follow the laws of chemistry and physics as they interact.

In this issue of *Breakthroughs*, we look at how scientists at Pacific Northwest National Laboratory are trying to build the same level of understanding of living systems and the machinery of life. With the help of advances in computational science, analytical tools and research instruments, scientists are embarking on a relatively new approach to biological research. Systems biology refers to the science of understanding and predicting the behaviors, roles and interactions within complex biological systems such as cells, organs or organisms. Eventually, this understanding could lead to innovative answers to environmental, energy and health challenges such as global warming or disease diagnosis and prevention.

This edition of *Breakthroughs* also features other solutions being developed by researchers at PNNL, including training programs for emergency first responders and mail handlers; the creative use of statistics in identifying biological pathogens, handwriting samples and potential airline safety issues; and a sensor fish for studying the effects of hydroelectric dams on salmon.

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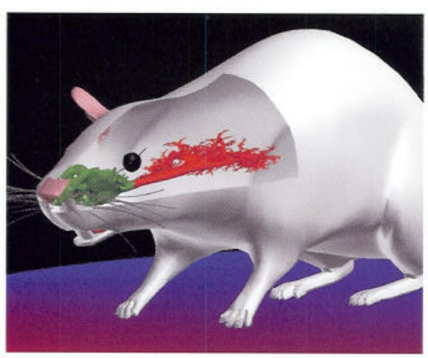
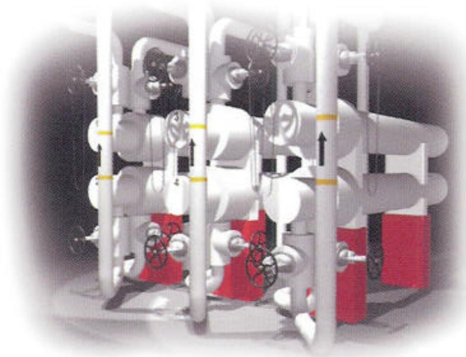


Energy system savings stack up

An energy management system developed at Pacific Northwest National Laboratory and installed at a New York Housing Authority boiler plant in Manhattan has led to cost savings of more than $300,000 in the first year.

Decision Support for Operations and Maintenance®, or DSOM®, is a state-of-the-art monitoring and diagnostic system that optimizes system performance. Under a contract with the New York City Housing Authority, the system went online in January 2001 at the Smith House central boiler plant, a facility that provides steam and hot water to 12 housing units totaling nearly a million square feet.



DSOM® originally was developed for the U.S. Marine Corps and has been installed at two major Corps facilities. In every case, DSOM® has improved process efficiency, reduced maintenance expenses, extended equipment life and cut energy consumption and associated emissions. The award-winning system is available commercially and could be used by process-based industries such as central district heating and cooling, steel and aluminum production, pulp and paper plants and pharmaceutical production. • **www.pnl.gov/dsom**

Climate monitoring goes mobile

Pacific Northwest National Laboratory scientists now have the capability to document atmospheric and climate change at locations nearly anywhere in the world, thanks to a new mobile atmospheric monitoring system developed at the Laboratory. The Pacific Northwest National Laboratory Atmospheric Remote Sensing Laboratory, called PARSL, is a complete climate-measuring system that can be taken to nearly any site quickly and easily. Scientists can conduct research wherever the need exists by simply loading the equipment on a flatbed trailer or placing it in a cargo container for ocean travel.

PARSL also allows scientists immediate access to newly gathered information. Data can be downloaded directly onto a compact disc or web site where it can be made available to scientists around the world. The PARSL suite of instruments will allow researchers to closely focus on key elements that contribute to climate change. In particular, scientists are interested in the amount of solar energy reaching the earth's surface and the atmospheric conditions that influence it. • **www.pnl.gov/news/2002/02-10.htm**

Fast glass!

Researchers at Pacific Northwest National Laboratory and the Savannah River Technology Center have developed a more efficient formula for vitrifying radioactive waste. Vitrification is a process that combines concentrated radioactive waste with glass-forming materials. Scientists at PNNL and SRTC have applied glass property models to develop a new frit or glass-forming material. This new formula, Frit 320, showed a melt rate 20 percent faster than the previous frit in small-scale melter tests. Frit 320 also allows more waste to be incorporated into the glass when combined with a new technology developed by SRTC and is expected to yield significantly higher melter throughput. By allowing more waste to be mixed into each batch of glass and producing it faster, this new glass formula may significantly reduce the cost of vitrifying waste, an integral part of cleaning up the nation's nuclear waste.

The Defense Waste Processing Facility at the Savannah River Site in South Carolina has incorporated Frit 320 into its operating plans for the future. •

Exploring the machinery of life

Pacific Northwest National Laboratory is building a systems biology program to unlock the mysteries of living systems. This new approach to biological research may lead to revolutionary solutions to challenges such as global warming, energy generation and treatment of diseases. We asked leaders in PNNL's systems biology program to discuss this effort with us. Our panel included Steven Wiley, who leads the Laboratory's Biomolecular Systems Initiative, and researchers representing various disciplines: Fred Brockman, microbial biology; Steve Colson, instrument development; Dave Dixon, computational biology; and Karin Rodland, proteomics.

How does systems biology differ from the conventional approach to biology?

Wiley: Systems biology attempts to understand how an organism works from an overall perspective. We're building this understanding starting from the molecular level. Conventional molecular biology is devoted to learning more about the parts—describing the structure, properties and interactions of the individual components. Systems biology looks at how the components work together as a system. Using the analogy of an automobile, systems biology is like understanding the different parts of a car and how the different parts work together to achieve motion.

Colson: It all starts with the word "system." Only recently have we had advances necessary to create models that could potentially be predictive at the level of a biological system. Systems could refer to a cell, to multiple cells, an organ or an organism. At all of those levels, the degree of complexity is substantial. We're really stretching the resources of biology, computer science and instrumentation to make progress in this area.

Rodland: To me, it is the opposite of reductionist biology. For a long time we made a lot of progress in biology by looking at one protein at a time and learning everything there was to know about it in isolation. Now we have to put those pieces together.

Dixon: As we integrate all of the data to describe a biological system, we also want to do a better job of predicting biological behavior. We need to see how proteins work together to form networks to make a living cell.

What problems can this approach eventually solve?

Rodland: My bias is health-related research. The only way to really understand the human body is from a systems biology standpoint. We learned from a reductionist approach to cancer research that cancer is not one disease with one cause. It is hundreds of diseases with hundreds of causes, not based on one gene or one cell, but dozens of genes acting in concert.

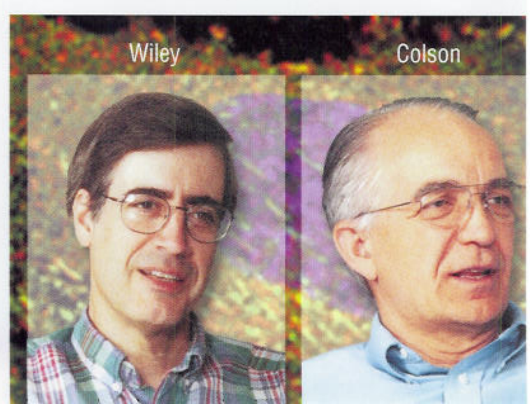
Wiley: I expect systems biology to allow us to both understand and productively manipulate biological systems. At this point, new drugs are tested on thousands of people. If they don't work, researchers go back to the drawing board because they don't know what needs to be changed. If we can make biology predictive, we can engineer cells in productive ways. You could help solve problems anywhere a living cell is involved—treating disease, understanding the implications of pollutants, removing carbon from the atmosphere and developing clean energy supplies.

Brockman: From my perspective, defining networks of carbon, energy and information flow between microorganisms will improve our ability to help solve environmental problems. In the long term, it will improve the predictive understanding of how microbial communities respond to and buffer changes in the natural environment. For example, we could influence microbial communities to subtly change the relative rates of chemical reactions relating to sulfur or carbon as a powerful way to reduce global warming. Systems biology also will speed the ability to carry out improved and new chemical processes using microbial communities in engineered environments such as bioreactors. For example, we could establish communities of microbes with the optimal structure and function to process waste streams, to produce chemicals from low-value raw materials or generate hydrogen as a source of clean energy for fuel cells.

Why is DOE interested?

Colson: DOE has big issues to solve. You can't address these problems one molecule at a time. We have to understand how systems work together if we are going to address global climate change or clean up complex contaminated environments or produce energy using microorganisms. We now have a much more powerful way of going after these issues.

Dixon: You can't really understand how to clean up contaminated sites if you don't fully understand the risk of low-dose radiation damage. It's not just one person doing experiments in a lab that will solve the real questions of systems biology, it's teams of scientists from many different disciplines working together. DOE and the national labs have the team approach and the tools—the big computers and the



big instruments—to do the large-scale science necessary for systems biology.

How does PNNL intend to contribute to DOE's Genomes to Life program?

Wiley: PNNL would like to be a primary driver. We would like to help define the experimental systems, the computational infrastructure and the instrumentation necessary to do systems biology. We feel we have the ideas to help DOE become preeminent in this area. We partnered with Oak Ridge National Laboratory to submit a proposal to the Genomes to Life program to do global analysis of protein complexes in cells. In our second proposal, we put forward a systems biology and computational approach for understanding complex microbial communities.

Brockman: One aspect of our plan deals with the tight integration of theory, experimentation and measurements. Classically, science always has had these three components, but now the idea is to go through the process very rapidly with the help of computers. Computers can design a sequence of experiments to effectively test ambiguous hypotheses. A computer can show how and where models are inadequate and help define parameters to go into that part of the model.

How are advancements in computational science and instrumentation critical to systems biology research?

Brockman: It's really clear that the reason biological knowledge has exploded in the past decade is the ability to make measurements and develop instrumentation to take those measurements. The number of new instruments and new types of measurements is increasing almost exponentially. It's almost incomprehensible. In the future, we'll depend more and more on computers and computation to deal with the flood of data from these new instruments.

Rodland: At any given time, the ability to answer questions is dependent upon the tools available to study the question.

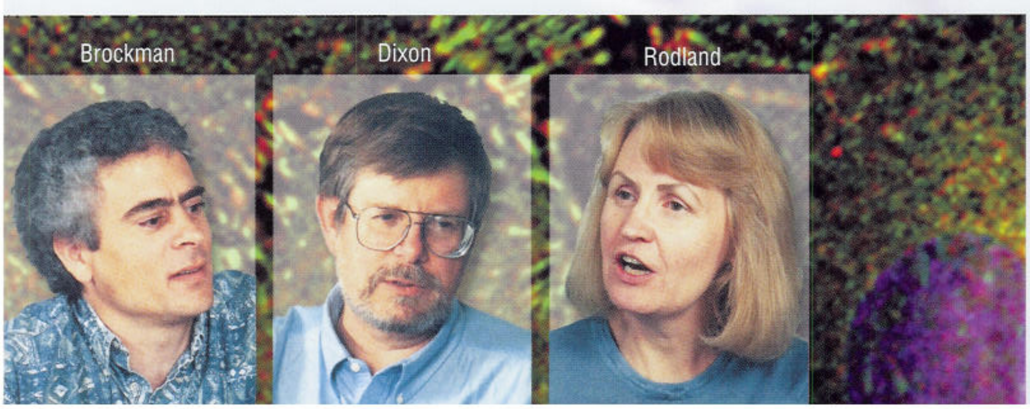
Why do you feel PNNL can be a leader in systems biology?

Wiley: We made a decision to do it. We made the investment and have the commitment behind the decision. We have real expertise in this area and we're building the teams to get the job done. The scientific community has known how to do this for 10 years. It simply requires long-term investments in instruments and computational infrastructure and faith in people.

Colson: PNNL has made substantial investments in new ventures for years. One brought the Environmental Molecular Sciences Laboratory (EMSL) here and it has some of the world's best instrumentation. Investments in systems biology allow us to go forward with DOE and other clients.

Dixon: We are one of the few DOE labs that understands how to run a user facility that is not built around a single instrument. EMSL allowed us to stick our foot into the waters of biology and now we can make more of a leap because of the investments we've made.

Wiley: And the organizational structure here is better for interdisciplinary research. Universities are bound more by departmental organizational structures. To get the engineering department to work with the life sciences department at a university is very difficult. The culture and structure here make it far easier to begin making progress.



Rodland: That's a real strength of PNNL. The communication and conversations between different components—computational science, optical experts, proteomics experts, toxicologists and biologists—have been going on here for years.

Where do you see this field in 10 years?

Dixon: It's my feeling that biology will look a lot more like high-energy physics. I think it will revolutionize how we solve biological problems, but it's going to be an interesting road. The transition will require individual scientists from disciplines that have been very individualistic to work together as a team. Biologists and chemists have never been known for working together to solve a problem, but physicists have.

Rodland: There also will be a new niche in data mining and data scavenging because so much data is generated by the systems biology approach. It will involve a whole new discipline of sorting, formatting and looking at data to figure out what it all means.

Dixon: Biology will become more of an information science. Advances will be made in gathering data and then synthesizing the information to tell the "biology story." How is the biological system working? What are the conceptual models that will allow us to design a new drug or modify an organism to do what we want it to do? These models will be on our computers, based on experimental data and validated with experimental data so we can take giant steps forward.

Brockman: In 10 years, I see systems biology as a dominant force in how biology is done. There is a tremendous opportunity for DOE to take a leadership role by drawing upon its ongoing investments in technology development and computation and the multidisciplinary scientific teams within the DOE national laboratory system. ●

For more detailed responses to these and other questions, see **www.pnl.gov/breakthroughs/sum02/systemsbio.html**

Super-*Shewanella*

It can convert soluble metals and compounds, like uranium, into insoluble forms. It can live aerobically, in the presence of oxygen, or anaerobically, without oxygen. It can grow naturally almost anywhere and does not cause disease in humans, animals or other organisms.

Introducing *Shewanella oneidensis* strain MR-1, a versatile bacterium that scientists at Pacific Northwest National Laboratory are studying in the Microbial Cell Project as a potential biological solution to Department of Energy sites contaminated during the manufacture of nuclear weapons.

"The Microbial Cell Project has two main objectives," said Yuri Gorby, a PNNL microbiologist involved in the project. "First we would like to find out how *Shewanella* works so it can be used to help remediate contaminated DOE sites. We also believe that understanding *Shewanella* may help explain how early life on earth developed and functioned."

Shewanella oneidensis strain MR-1 growing on the surface of the iron oxide mineral hematite.

Like human cells, microbes need fuel to survive. Both human and bacteria cells create adenosine triphosphate (ATP), the substance that fuels all cellular activity, in a process called respiration. Similar to a human breathing in oxygen and exhaling carbon dioxide, *Shewanella* has the ability to "inhale" certain metals as electron acceptors and "exhale" them in an altered state. For example, it can change oxidized uranium, which is water soluble, into reduced uranium, which is insoluble.

"*Shewanella* can enzymatically reduce metals like uranium, technetium and chromium—the same metals that are contaminating groundwater at DOE sites," Gorby said. "Because *Shewanella* can transform these metals from soluble form into precipitates, we're hoping to use it in a controlled system to help prevent contaminated groundwater from spreading into the Columbia River."

But first scientists working on the project must understand the intricacies of cell respiration in *Shewanella*. "We want to understand how this organism controls its ability to use different electron acceptors for respiration, how it senses these electron acceptors in the environment and what cellular components are involved in the electron transfer process that is the basis of respiration," Gorby said. The approach taken by PNNL scientists and their collaborators is to study the genes of *Shewanella* to determine all possible processes that can occur in the cell and then to study the proteins that actually catalyze electron transport and metal reduction.

Beyond investigating *Shewanella's* potential for remediating subsurface sediments and groundwaters contaminated with heavy metals and radionuclides, research on this scientifically evocative organism may yield insights into early life on earth and possibly life on other planets.

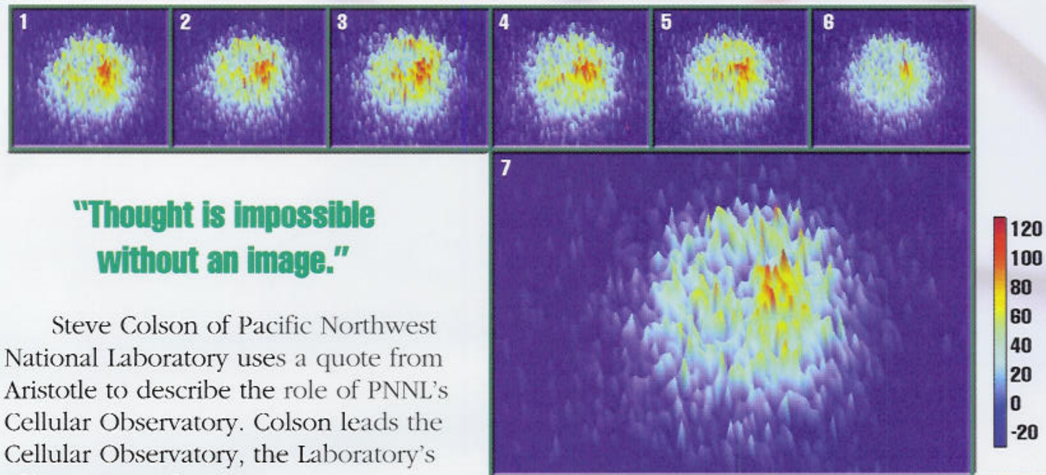
Iron, the principal electron acceptor for *Shewanella* and other metal-reducing bacteria thriving in environments lacking oxygen, is the fourth most abundant element on earth. Before bacteria and plants produced oxygen via photosynthesis, iron was likely the most abundant electron acceptor on prehistoric earth. Hence, metal-reducing organisms, like *Shewanella*, were likely to have developed before other respiratory organisms.

Recent hypotheses also suggest that life on other planets, such as the iron-rich planet Mars, probably includes metal-reducing bacteria. In any case, the Microbial Cell Project is contributing to the understanding of the fundamental processes of a scientifically fascinating and potentially useful bacterium, *Shewanella oneidensis* strain MR-1.

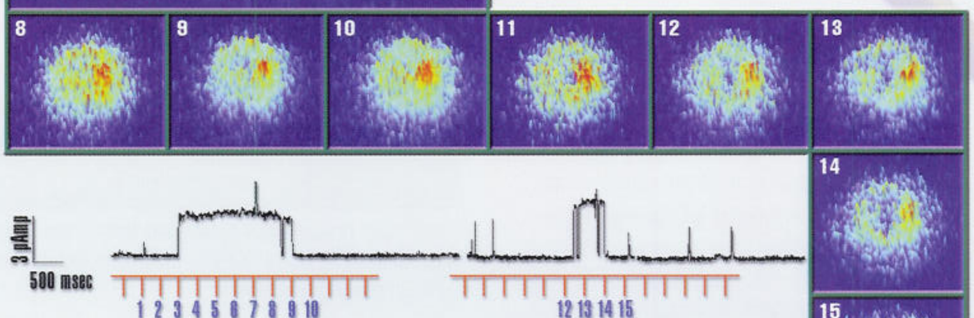
The Microbial Cell Project is part of the Genomes to Life program supported by DOE's Office of Biological and Environmental Research. Other participating institutions include Michigan State University, the University of Southern California, the University of Hawaii, Baylor College of Medicine, Oak Ridge National Laboratory and the Institute for Systems Biology.

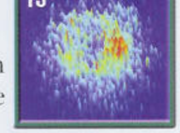
www.biomolecular.org/research/microbiology
www.shewanella.org

Seeing cells in a whole new way



Using advanced instruments, researchers simultaneously acquire single-channel current records and single-molecule fluorescence images at the tip of a patch pipette. Gathering this information over time allows them to study the channel as it becomes conductive when fluorescence-labeled subunits interact in the membrane. Changes in the fluorescence intensity reveal subtle changes in the conformation of the proteins that control the conductance of the channel.





"Thought is impossible without an image."

Steve Colson of Pacific Northwest National Laboratory uses a quote from Aristotle to describe the role of PNNL's Cellular Observatory. Colson leads the Cellular Observatory, the Laboratory's effort to provide advances in imaging tools needed for a systems biology approach to molecular and cellular biology. Eventually, these tools could help enable biological solutions to challenges in energy production and use, carbon management, bioremediation and bioterrorism.

"Cell function changes with time and in response to changes in its environment, so we need multi-functional instruments to observe biological processes in living systems, in real-time," said Colson. "By developing tools that allow researchers to study cellular functions—at the subcellular, cellular, tissue and organ scales—we can help accelerate discovery and understand the biochemical networks and pathways that carry out essential processes in living organisms."

One instrument developed as part of the Cellular Observatory is the compound confocal patch clamp microscope. This specialized microscope helps researchers understand important molecular processes that occur in the cell membrane, such as how channel proteins within the membrane regulate the passing of ions in and out of the cell. After attaching a pipette to a cell membrane, or "patch clamping" the membrane, researchers use this specialized instrument to look at the tiny piece of membrane between the walls of the pipette and measure the ion current passing through the channel proteins.

Proteins within the cell membranes work like sensors that automatically open the gates to admit certain ions. Calcium ions, for example, are important in regulating cell function. Scientists are trying to build a better understanding of how the proteins become conductive and how the cell is affected when ions flow across the cell membrane. In addition, researchers are investigating cell signals transmitted across the membrane. At times the mere presence of certain proteins outside the cell affects the chemistry and binding properties of proteins within it.

According to Colson, a national laboratory is uniquely suited to bring together the multidisciplinary teams needed to develop new instruments such as the compound confocal patch clamp microscope. The scientists involved with the Cellular Observatory represent disciplines in the biological sciences, the physical sciences and engineering and automation, as well as collaborators from other research institutions.

Because new research instruments must meet the needs of the researchers who will use them, there is a close coupling among those on the instrument development teams and the scientists doing biological research. By providing substantial advances in imaging, these new instruments and research capabilities will deliver detailed and quantitative information that can be used to develop, test and improve computer models of biological processes.

"The instruments are just one piece of the puzzle," Colson said. "We build project teams around biological problems. These teams drive all the aspects of the problems—imaging, modeling, proteomics and genomics, and the design of experiments." ●

www.biomolecular.org/research/cellob

Biology research goes *in silico*

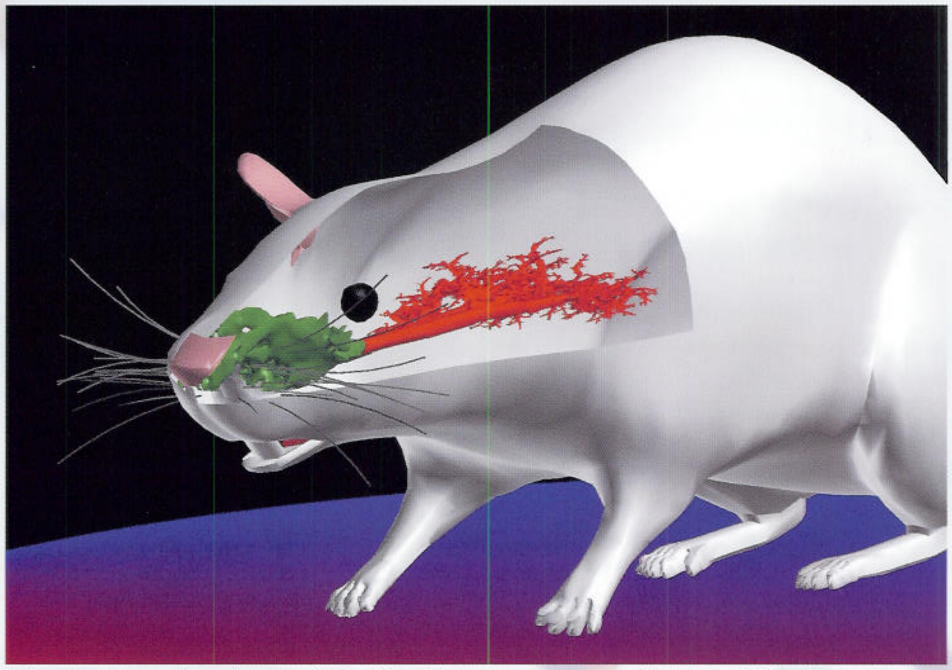
Long before a new jumbo jet takes off the runway, all of its systems and subsystems down to the tiniest of individual parts have been virtually designed, built and tested through the use of computer models and simulations. Similarly, Pacific Northwest National Laboratory is developing virtual cells that can be explored, tested and manipulated within the world of computers to make important discoveries in systems biology.

"Computational biology involves creating sophisticated mathematical and equation-based computer models and simulations to understand and predict how cells behave, interact and respond to their environments," said Dave Dixon, associate director of theory, modeling and simulation at the U.S. Department of Energy's William R. Wiley Environmental Molecular Sciences Laboratory (EMSL), a national scientific user facility operated by PNNL.

Dixon leads the Virtual Cell project, which is focused on integrating and analyzing biological data and developing and improving advanced computational models from the data. With the help of conceptual models, new drugs could be designed, for example, and capabilities of microorganisms could be harnessed to convert contaminants into less harmful substances or to efficiently generate energy by creating hydrogen.

The broad scope of the research includes atomic-level simulations of biomolecular complexes, network analysis and kinetic modeling of cell signaling and metabolic pathways, and development of bioinformatics tools for data mining and analysis with a focus on data from high throughput experiments.

In one study, researchers are using computational methods to simulate cellular signaling pathways and compare reactions that originate at the cell surface with those that begin within the cell. Because a mutant form of a specific protein complex called Ras is found in 30 percent of all human tumors, researchers are investigating how the Ras protein serves as a switch to control when cells develop and grow and how they differentiate from one another.



Laboratory researchers developed this virtual lung, a computer model that provides an unprecedented, three-dimensional view of how pollutants enter, travel through and collect in a rat's respiratory system.

Another group of researchers is using computational data analysis tools to statistically analyze biochemical data from some of the world's most powerful mass spectrometers at EMSL. "We're analyzing how protein networks within cells communicate with each other, using the same statistical approach that is used to analyze communication networks," said senior research scientist Bill Cannon.

"The Internet is a system of computers talking to one another in different ways," he said. "Similarly, we're trying to understand how cells communicate as part of a complete system." Cannon and his colleagues are using statistical tools related to network communications and artificial intelligence to study *Shewanella oneidensis* cells, which potentially could be used in bioremediation.

In yet another study, researchers use slices of images captured by a microscope to explore water density in cells and simulate radiation damage. In addition to understanding how radiation affects exposed cells, researchers are investigating how effects spread to adjacent cells, which is known as the bystander effect.

"There are a lot of opportunities for computational science, mathematics and statistics to bring together data sets and extract valuable information from the mountains of data collected," Dixon said. "The models we build help bring the pieces together and drive where the research is headed to get a description of a biological system."

For more on computational biology, see **www.biomolecular.org/research/virtualcell**. For more about the virtual lung, see **www.pnl.gov/news/2001/01-33.htm**

Paving the way for proteomics

A field of study that is only about five years old is beginning to blossom at Pacific Northwest National Laboratory. Proteomics is the systematic study of patterns of proteins expressed in living organisms.

"Where the genome is the blueprint of all the possible proteins within a cell, the proteome is the subset of those proteins that actually are made and change within a cell over time as the cells respond to their surrounding environment or disease," said Karin Rodland, a lead scientist in PNNL's proteomics program.

Rodland explained that there are two related and interdependent components of proteomics research at PNNL. The first has to do with developing uniquely powerful analytical tools that are being applied to help the U.S. Department of Energy. For example, the researchers at DOE's William R. Wiley Environmental Molecular Sciences Laboratory (EMSL) are working to identify all the proteins expressed by organisms such as *Deinococcus radiodurans*, one of the most radiation-resistant organisms known. As more is learned about how the proteins in this organism react to radioactivity, researchers might know more about how to protect people from exposure to radiation or reverse its effects.

The second component is more focused on human biology and health-related research. "As we track what groups of proteins do, we can begin to discover the disruptive influences that may cause problems in the cells," Rodland said. "Identifying the proteins that cause problems and removing or repairing them could help cure or prevent diseases such as cancer." By using proteomic tools developed at EMSL, researchers can compare proteins in normal cells with those of diseased cells.

In one project funded by the Department of Defense, PNNL's Rick Zangar is looking for early biomarkers of breast cancer by analyzing fluid discharged from the breast. In time, this research could lead to the development of a clinical test where a protein chip, or assay, could quickly determine if a patient is expressing the biomarkers for breast cancer.

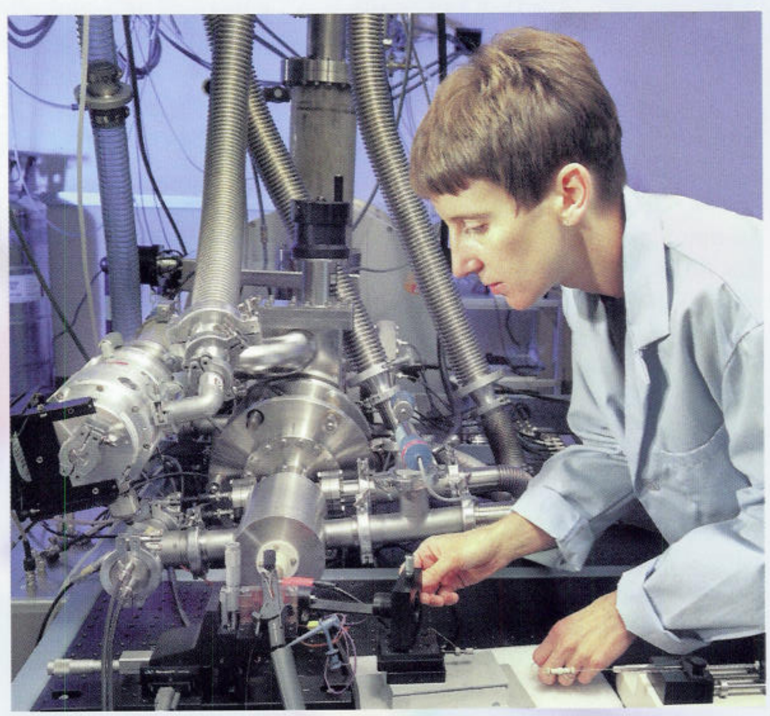
Another research project being proposed would compare the proteins expressed on the cell surface in different stages of ovarian cancer. By determining the differences between early-stage ovarian cancer with a cure rate of 95 percent and late-stage cancer that has only a 15 percent survival rate, researchers may be able to detect ovarian cancer earlier and keep it from progressing.

"These projects are examples of how the national laboratories push the frontiers," Rodland said. "We're developing the tools and starting the transition of applying those tools to meet real needs."

One such tool involves instrumentation that measures the mass of peptide fragments, or accurate mass tags, with the level of accuracy needed for protein identification. Researchers at EMSL are leading the world in developing these instruments. By identifying accurate mass tags, a proteome can be characterized with more confidence and with higher throughput than achieved by other methods.

In diagnostics, the future could lead to protein chips that could be used to quickly identify specific cancers based on blood or saliva samples. "You could identify the type of cancer, how far it progressed and match it with an extensive collection of drugs tailored specifically for the kind of tumor a patient may have," Rodland said. "Researchers around the world will jump on this approach, addressing one cancer at a time, until we begin to make a dent in the problem of targeting therapeutics specifically to the patient's cancer."

www.biomolecular.org/research/proteomics
www.pnl.gov/news/back/proteomicsoverview.htm
www.pnl.gov/news/back/proteomics.htm



Ljiljana Pasa-Tolic and her colleagues are providing new insight into the molecular basis of cancer by developing advanced proteome analysis capabilities.

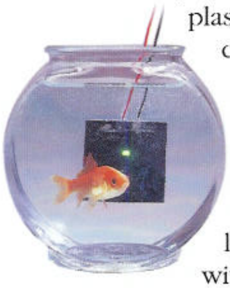
NOTABLE Achievements

Technology commercialization recognized nationally

The Federal Laboratory Consortium honored Pacific Northwest National Laboratory with three 2002 Excellence in Technology Transfer Awards. The FLC annually recognizes federal laboratories and their employees who have made significant contributions in transferring important federally funded technology into the private sector. With 51 awards, PNNL has been honored by the FLC more than any other federal laboratory since the recognition program began in 1984. Awards were given for:

Ultra-barrier coatings for flat-panel displays

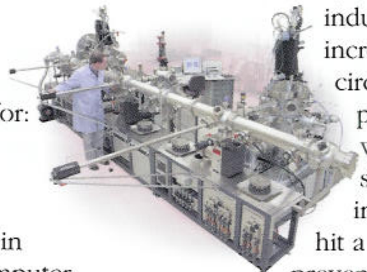
Glass electronic displays in cell phones, watches and computer monitors may soon be replaced with plastic, making electronic devices thinner, more rugged and lighter. PNNL developed an ultra-barrier coating technology that gives plastic the necessary levels of protection without affecting clarity.



In 1999, Battelle created a subsidiary to commercialize these products. Vitex Systems, Inc. soon attracted $15 million in investment from Mitsubishi Corp. and is bringing two products to market.

Advancing semiconductor materials development

For decades, the semiconductor industry has been increasing the amount of circuitry, or computing power, on a chip while reducing its size. However, the industry soon will hit a technical wall preventing additional size reduction unless methods can be found to create cost-effective "nanoscale" semiconductors.



PNNL's advanced work with molecular beam epitaxy, or MBE, has provided Motorola Labs with the ability to create the next generation of semiconductor wafers. MBE uses separately generated and controlled beams of atoms and molecules to deposit a thin film of crystalline material on a solid substrate. Motorola plans to have silicon wafers manufactured using this new technology and produce communication devices containing circuits on these wafers.

Radio frequency tags

Radio frequency tags are small, inexpensive and can be used to identify, inventory and track items. Ranging in size from a grain of rice to a credit card, they can be encoded with detailed information. PNNL has made significant advances to the technology, creating tags that can be read from distances up to 10 times further than previous tags.

WAVE ID
Wireless Solutions

In late 2000, Battelle created a new company, Wave ID, to manufacture, market and distribute the PNNL-developed RF tags. Within a year, Wave ID was acquired by Alien Technology, a fast-growing California-based company with a patented technology that dramatically reduces the cost of manufacturing electronic products.

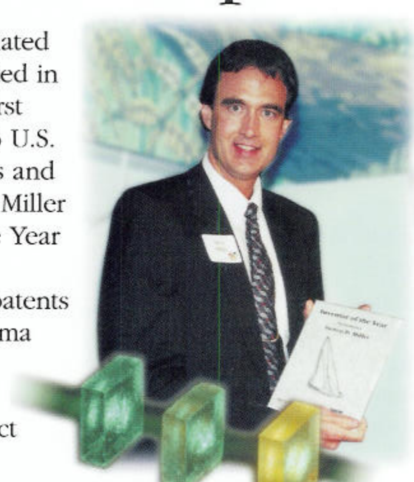
Battelle names top inventor for 2002

He developed a new Optically Stimulated Luminescence (OSL) technique that resulted in Pacific Northwest National Laboratory's first million-dollar royalty license. He holds 13 U.S. patents and has numerous foreign patents and patents pending. And, now PNNL's Steve Miller has been named Battelle's Inventor of the Year for 2002.

A staff scientist, Miller holds several patents on OSL, which has greatly improved gamma and beta dosimetry. His OSL research earned an R&D 100 award in 1992.

Following a successful research project with Landauer, Inc., the OSL technology was licensed to Landauer in 1994 for use in measuring occupational exposure to radiation.

In 1996, Miller helped found Sunna Systems Corporation to commercialize OSL for high-dose dosimetry applications. He received an R&D 100 award in 2000 for the Sunna high-dose dosimetry system.



The Inventor of the Year award honors a Battelle staff member who, through outstanding career achievements and creativity, has significantly expanded Battelle's intellectual property portfolio. Accordingly, this individual has enhanced Battelle's ability to commercialize technology to better serve its customers, the marketplace and society.

Miller designed and now manages an OSL laboratory at PNNL. The lab includes state-of-the-art lasers, optical systems and equipment to help build expertise in the fields of ionizing radiation detection, sensitive photon detection techniques and non-ionizing radiation. He currently is developing medical dosimetry products and high-dose dosimetry for food irradiation and medical product sterilization.

Stories on this page written by Lisa Brown, contributing writer.

Sensor Fish gets redesign

The Sensor Fish—originally packed into a six-inch-long rubbery fish shape nicknamed "flubber fish," this data collection device later resurfaced in the shape of a juvenile fish sized plastic tube. Both the original and the tube-shaped Sensor Fish employed computer electronics to measure the pressure and acceleration changes salmon smolts experience in the severe turbulence that forms the hydraulic environment of hydroelectric dams as they migrate down the Columbia River.

Pacific Northwest National Laboratory scientists are now miniaturizing the Sensor Fish so it can be surgically implanted in the bodies of real fish. "That way there's no question that it's reacting to flows like a real fish because it is inside a real fish," said Tom Carlson, who manages the project. As smaller components become available, researchers will finalize a new design that will be about one-quarter by one-and-a-half inches in size and one-fourth the cost of the tube-shaped Sensor Fish.

PNNL scientists have used the Sensor Fish to study spillway and turbine passage routes for migrating salmon at several Columbia River dams. Scientists are trying to determine what hydraulic conditions contribute to mortality rates at these dams and what alternatives, structural or operational, might reduce injuries to fish.

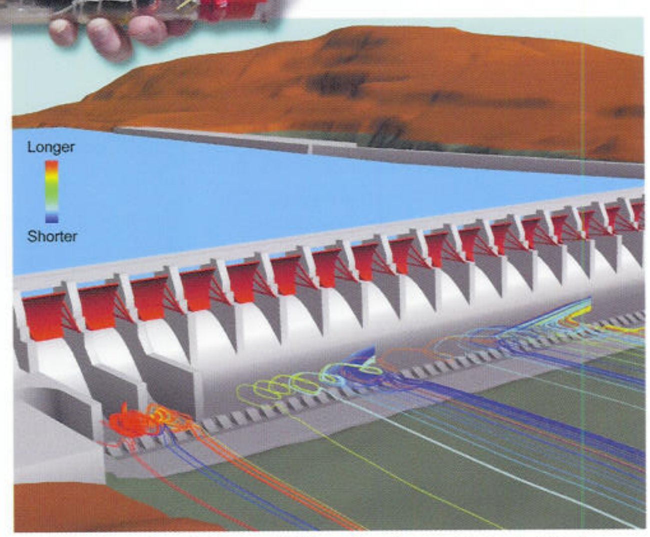
In addition to the accelerometers and pressure sensors that were part of the original Sensor Fish, the Sensor Fish implant will include devices called rate gyros. The combination of linear and angular accelerometers will mimic the environmental sensing functions of the inner ear of a fish. "We're hypothesizing that the vestibular system of fish may be disrupted during passage," Carlson said. The rate gyros would measure the rate of change in pitch, roll and yaw of the fish as it moves through the water. "A number of salmon smolts we see below stilling basins and turbines are temporarily disoriented. They're dizzy. As they move to the surface, toward the light, to re-orient, they become vulnerable to birds and other predation," Carlson said.

By implanting sensors in live fish, releasing the fish through dam passage routes such as spill or turbines and recovering the fish afterwards, scientists can link fish injuries to the conditions experienced during passage. "This technology will provide a unique capability for assessing these environments and help us to more quickly identify deleterious conditions and find solutions that will provide safer fish passage," Carlson said.

One drawback, the Sensor Fish does not record its location as it passes through the stilling basin, making it difficult to determine the location and type of hydraulic conditions it encounters. To make this connection, scientists use three-dimensional computational fluid dynamics (CFD) modeling to create predictive simulations of the hydraulic environment and link them to information gathered by the Sensor Fish. After dumping data from the Sensor Fish into a computer, researchers set up the same physical parameters and run the same scenarios in CFD models. The models use moving particles to represent the Sensor Fish and produce the same sets of statistics as the Sensor Fish.

"CFD results are realistic, but not exactly what the Sensor Fish experienced. The Sensor Fish provides the linkage between simulations and data on actual flow conditions. It measures what happens to a body that's moving in real fluid under actual operating conditions," said Marshall Richmond, chief engineer, who manages the CFD component of the project.

Comparing the two allows scientists to better understand the hydraulic conditions that may be responsible for fish injury and to make recommendations for improvements. "We are trying to develop this process to predict as accurately as possible how changes to dam operations and design will affect fish survival."

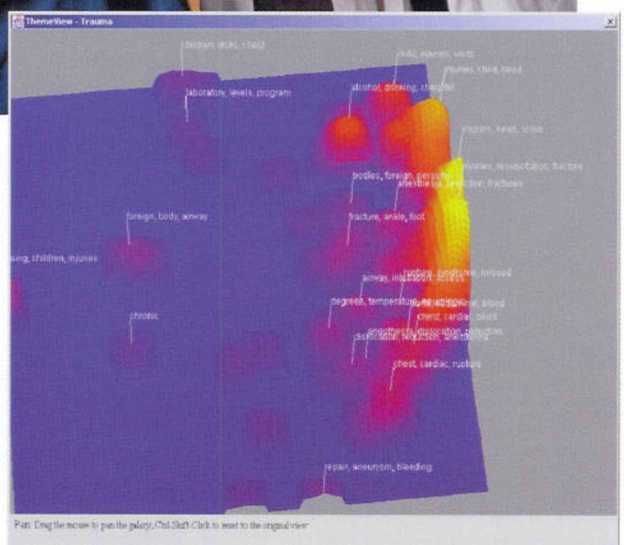


The lines are simulations of different pathways fish might take once in the spillway. Line colors signify relative time fish could spend in each pathway.

PNNL applies risk assessment techniques to health care

Hospitals are for healing. With the help of tools used in the nuclear, aerospace and chemical industries, researchers at Pacific Northwest National Laboratory are helping make sure they stay that way.

In response to a recent standard from the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), more than 18,000 accredited health care organizations in the U.S. and Canada are performing analyses and developing ways to prevent errors that could threaten patient safety. Groups affected by the new standard include not only hospitals, but also clinical laboratories, behavioral health centers, home care facilities and other accredited health care organizations.



Data visualization is a powerful technique that can be used to analyze patient safety issues and drug medication errors. In this example, visualization provides a graphic representation of themes that appear in journal articles about pediatric trauma care. Treatment records with similar topics appear close to one another and the most prevalent topic combinations are represented with the highest peaks.

Analysts at PNNL are assisting local hospitals in identifying and evaluating situations that may affect patient safety. "We identify frequency and consequence of failures in such a way that we can identify improvements to the system," said Jon Young, program manager for the project. Using risk assessment techniques to evaluate safety is not new to PNNL analysts, who have employed these techniques successfully in the nuclear, aerospace and chemical industries.

Risk assessment related to health care begins with looking at processes and data. "We're interested in finding the underlying problems that can cause mistakes," Young said. "These may be institutional or environmental and may cause other problems as well." Factors could include staff experience level, treatment protocols or interdepartmental communication.

Hospitals call underlying problems "latent failures," things that exist all the time, but don't become visible until something happens that acts as a catalyst. That's when patient safety may be threatened.

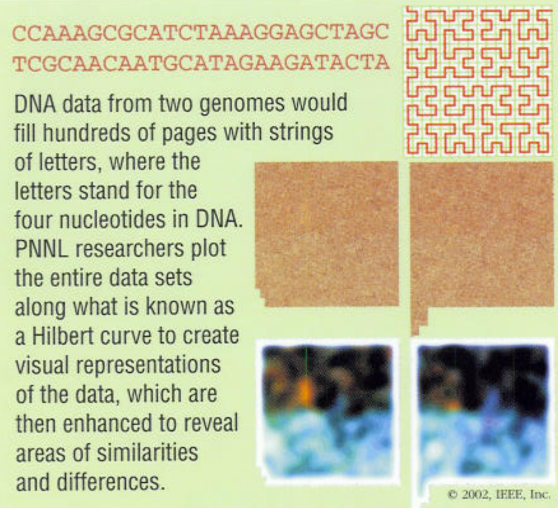
PNNL analysts are using risk analysis techniques to analyze existing processes related to patient safety. For example, hospitals already assess some patient safety issues, such as slips and falls, devising a management plan to deal with patient vulnerability. As part of the program, hospital staff might place a placard on the patient's door advising of high risk. "But what happens if the patient is taken to radiology and no one can see the placard?" Young asks. "This is an example of the kinds of things we're starting to find."

In another approach to patient safety, the Laboratory is applying powerful techniques to analyze data in a pilot study with U.S. Pharmacopia, an organization that collects data on medication errors from hospitals nationwide. "We're using our data mining and data visualization technologies to analyze medication error data and put them into a risk context," Young said. The pilot study is currently being funded by Battelle, which operates PNNL for the U.S. Department of Energy, and will expand if grant funding comes through. "This is an exciting opportunity to refine the understanding of errors because we'll have hundreds of thousands of records on medication errors," Young said. Eventually, study results may be published in a report and go back to member hospitals.

"We have other powerful risk analysis technologies we hope to apply in the future. This is just a starting point," Young said of PNNL's work with risk assessment at hospitals. Ultimately, analysts hope to apply risk analysis and data visualization techniques to help hospitals rank problems and determine which issues they'll address first and how.

science SPOTLIGHT

The color of genomes



DNA data from two genomes would fill hundreds of pages with strings of letters, where the letters stand for the four nucleotides in DNA. PNNL researchers plot the entire data sets along what is known as a Hilbert curve to create visual representations of the data, which are then enhanced to reveal areas of similarities and differences.

New visualization techniques developed by researchers at Pacific Northwest National Laboratory allow researchers to compare and analyze genomes using a powerful tool that computers cannot replace—the human brain.

By presenting a color-coded graphic representation of genomes, people can easily identify similarities and differences. This approach may help identify individual genes responsible for certain properties and characteristics.

"Our visualization method allows us to look at whole genomes, while most methods look at just part," said Pak Chung Wong, who leads the project. While developing the technique, Wong and colleagues Harlan Foote, Kwong Kwok Wong and Jim Thomas compared different strains of bacteria to determine what made them unique.

They began by assigning a color to each of the four nucleotides in DNA—adenine, cytosine, guanine and thymine. They created a graphic representation of the genome where each colored pixel represented a single nucleotide in the sequence.

"It didn't work," Wong said. He explained that individual nucleotides change so frequently that there was too much "noise" to recognize patterns.

So, the researchers began taking steps to reduce the noise, such as arranging the data in different curves. "The biological community has been mapping genomes from left to right because we read that way," Wong said. "The curves we use fold a one-dimensional genome sequence into a two-dimensional image, which allows neighboring nucleotides to appear near each other."

Researchers apply other digital image processes that make distinguishing features more apparent. For example, they apply smoothing filters and adjust the contrast and intensity.

The technique is useful in comparing multiple genomes because people can look at the images and easily spot the interesting areas that they would like to study in more detail using other methods. On the other hand, computational methods require each data set to be compared fully against every other data set, an expensive approach that generates pages and pages of data.

Beyond genomes, this visualization method could be applied to analyze other sequential data, such as brain wave data from an electroencephalogram or EEG.

A patent is pending on the visualization technique and PNNL is interested in identifying a company to develop user interfaces and software based on this approach. ●

World-class equipment for a world-class Lab

Pacific Northwest National Laboratory is in the process of adding the world's largest, highest-performing nuclear magnetic resonance spectrometer and one of the top supercomputers in the world to its suite of advanced equipment.

After nine years in development, a superconducting magnet, weighing 16 tons and standing 21 feet high, was delivered to PNNL in March. It is part of a 900 megahertz wide-bore nuclear magnetic resonance spectrometer. The NMR is a powerful scientific instrument that will enable scientists to make new discoveries in chemical, physical, biological and life sciences. When fully operational, it will be the world's largest, highest-performing NMR, enabling researchers to investigate larger and more complex molecules at resolutions never before available. This system could enhance understanding of basic molecular and cellular processes and how those relate to damage or repair to DNA, disease development and protein interactions.

The Hewlett-Packard Linux-based supercomputer will allow researchers to apply computational science to fundamental questions such as how radioactive waste can be processed and stored, and how proteins interact and behave in order to model a living cell. Calculations that now take a month to complete will take one day on the new system. When fully operational in 2003, the supercomputer will have 50 times more disk space and hold 15 times as much memory as PNNL's current supercomputer, one of the world's most powerful when installed in 1997. The new supercomputer, with a price tag of $24.5 million, will be roughly 9,100 times faster than a current personal computer.

Both pieces of custom-built equipment are being installed in the William R. Wiley Environmental Molecular Sciences Laboratory, a user facility operated by PNNL. Scientists from around the world will be granted access to the equipment through a competitive proposal process. ●

www.pnl.gov/news/2002/02-08.htm
www.pnl.gov/news/2002/computer.htm

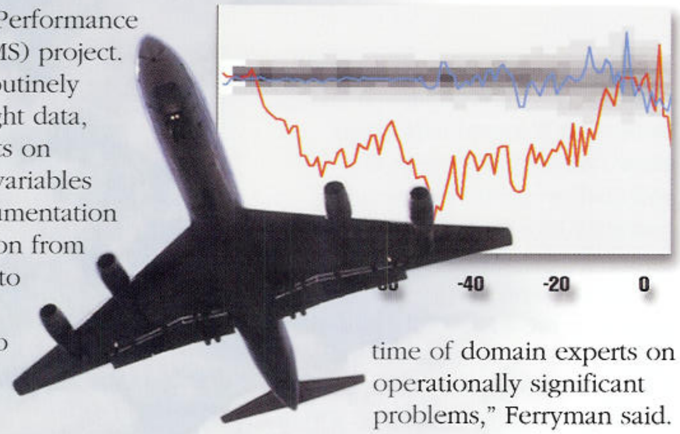
This story written by Lisa Brown, contributing writer.

Improving airline safety

In an ongoing project for NASA, Pacific Northwest National Laboratory statisticians developed a system for analyzing flight data recorded aboard commercial aircraft.

"We developed an 'atypical flight detector' to detect anomalous flights that show patterns different from the norm. These flights set up red flags for airline staff to ask if there's something about the flight that would warrant further investigation," said Tom Ferryman, who directs PNNL's work for the NASA Aviation Performance Measuring System (APMS) project.

Many air carriers routinely record performance flight data, collecting measurements on between 50 and 3,000 variables per second. "This instrumentation collects flight information from beginning to end, gate to gate, flight after flight. We had to find a way to sift through it quickly to focus the limited time of domain experts on operationally significant problems," Ferryman said.



PNNL statisticians developed algorithms to make sense of the data by clustering flights into typical and atypical patterns. "We look for all those things experts say happen, but ideally should not happen, like slowing down by putting the flaps or gear down early, and we enable airline experts to find these *envisioned things*. But the experts can't envision all possible errors," Ferryman said.

PNNL developed algorithms that find *unenvisioned conditions* the experts did not think to look for in flight data. In one exercise these algorithms uncovered asymmetry in engine output for a set of flights involving a particular aircraft. This can indicate mismatched throttles, a condition that degrades aircraft fuel efficiency. The air carrier had not been looking for this problem, but PNNL's algorithms found the unexpected.

When the optical disc used to record flight data is swapped off the airplane and into a computer loaded with the APMS software, atypical conditions are quickly apparent to airline experts. Airline safety personnel can further investigate to determine whether they are unsafe conditions.

Although the analysis uses sophisticated statistical techniques, flight operations and safety staff are shielded from the statistics by user-friendly and intuitive visual representations.

Statistical algorithms developed for APMS have other applications, including monitoring health patterns in communities, use in the financial industry or, possibly, different approaches to air carrier security.

ALGORITHMS

A new perspective on data

We live in the age of information. Analysts are among those inundated with data. But with the aid of powerful computing techniques, analysts can make sense of volumes of data that come in many forms—text, numbers, images, video, audio.

Statisticians at Pacific Northwest National Laboratory are marrying computational power with statistical techniques to sift through all these forms of data together. Their work is being applied in a variety of areas, such as analyzing handwriting and identifying bioagents.

Whether clients come in with existing data or PNNL gathers the data, statisticians help uncover hidden information through exploratory analysis, grouping like kinds of information and extracting key features. Using systematic sampling and experimental design techniques, they ensure data are reliable and will support confident decisions.

"We take varying types of information, whether it's text, video or audio and turn it into mathematical representations. Once we have a mathematical representation, we can apply our statistical techniques of clustering and data analysis," said Brent Pulsipher, who manages PNNL's statistical and quantitative sciences group.

PNNL statisticians use clustering algorithms to find groups that share a common feature in some dimension and "cluster" them together. "Many of our algorithms are self-clustering. We don't say 'group these into a certain category that relates to a certain feature.' The algorithms specify categories themselves," said Pulsipher. Identifying these groupings is called "lead generation" because it provides leads that may explain what is causing a problem.

In one project, statisticians are developing algorithms to identify handwriting samples. These algorithms quantify handwriting characteristics, such as density, height and slant. "We use statistical methods to test for similarities and differences between unknown and known handwriting samples," said Kris Jarman, who leads the effort.

In another project, statisticians are using algorithms with a biopathogen sensor being developed at the Laboratory called Matrix-Assisted Laser Desorption Ionization Mass Spectrometry (MALDI-MS). The algorithms quickly identify the unique features of questionable bacteria and categorize those features in real time according to pathogen type. In lab tests, these algorithms were more than 95 percent accurate in classifying bacteria strains.

Responding to terrorism

Even before Sept. 11, Pacific Northwest National Laboratory researchers were thinking of ways to combat terrorism. PNNL now contributes to the U.S. State Department's Diplomatic Security Service training program, teaching foreign firefighters, police and emergency medical personnel how to deal with weapons of mass destruction—chemical, biological and radiological—that may be used by terrorists. The training is offered to first responders in partner nations, generally in the capital, where the U.S. has an embassy or consulate.

The Laboratory, together with the Department of Energy's Hazardous Materials Management and Emergency Response Center (HAMMER), a training facility in Richland, Wash., has been involved with training military and civil support groups in chemical and biological warfare for the past few years. Its work with the U.S. State Department has been expanding most rapidly. "After watching the success of the Lab's international border security training program for the last three or four years, we decided to approach PNNL about training first responders," said Terry Jones of the Diplomatic Security Service Anti-Terrorism Assistance program.

The Anti-Terrorism Assistance program suggested the Laboratory develop a curriculum for operational training to complement the State Department's existing in-country classroom training for first responders.

Through hands-on training, emergency personnel learn how to respond to nuclear, chemical or biological attacks.

"The operational training we offer at HAMMER involves a series of field exercises to familiarize students with the basic concepts and materials of chemical, biological and radiological threats. It includes role-playing exercises to allow students to apply what they've learned," said Barbara Seiders, manager for the Laboratory's chemical and biological defense programs. For example, students study the basics of hazard identification and personal and group protection. The next day, they arrive at class to find a distressed employee who has just discovered a powdery white substance in the package she's opened. The culmination of the course, dubbed the "big, bad unknown exercise" is an all-day response to a simulated terrorist incident that gives students the opportunity to synthesize everything they've learned.

PNNL now offers two other components of the State Department's Anti-Terrorism Assistance program. The Laboratory supports one-week introductory training classes given in the foreign countries, providing instructors with expertise in radiological hazards and weapons of mass destruction. The Laboratory also has partnered with the State Department to develop a mail handling training for international mail handlers.

Prior to the World Trade Center bombings in September, the Anti-Terrorism Assistance program's plan included giving four two-week first responder courses in fiscal year 2002. Three months later, Seiders had five 19-day courses scheduled for the next nine months, beginning in March. "We're just glad we can help," she said.

Neither biological nor chemical agent...
Keeping mail safe in the 21st century

Snail mail may be an anachronism, but enough people still use traditional mail to make it a convenient tool for terrorists using bio-weapons that can be lethal in small quantities. And mail is an international affair.

"You can't think of bioterrorism only in the national arena. Bio-weapons in the mail can cross national boundaries very easily," said Ken Ames, project manager for an international mail handling course sponsored by the U.S. State Department and Diplomatic Security Service in association with Pacific Northwest National Laboratory and the U.S. Postal Inspection Service.

The course, Postal Chemical/Biological Incident Management, is part of the State Department's Anti-Terrorism Assistance program and has three purposes: to spread goodwill by helping foreign countries combat terrorism, to prevent the spread of bioterrorism attacks to the U.S. and to protect U.S. diplomats abroad.

The course is designed for people who might be the first to come into contact with biological or chemical contaminants sent through the mail or the consequences of such attacks. These include postal service workers, the public health community and first responders.

"One of our main goals is to get them thinking about what could happen in advance so they can have a plan for it," said Ames of PNNL. "We start by discussing how to identify a credible threat. In the U.S., we've had thousands of hoaxes for every actual threat so you need some way to weed out the hoaxes without missing the real thing."

Next, the class talks about what steps to take if the threat is credible. How should the suspicious mail be handled? What precautions should be taken if you've touched it? What information can you gather from the piece of mail? Who should you notify? What should you do if other people are in the building?

Other lessons include a history of anthrax incidents in the U.S. and how anthrax spores spread to other countries, appropriate public information before and after the event, basic medical response, such as conducting victim assessment and maintaining sanitation, interagency collaboration and contingency planning.

The four-day training ends with a hands-on exercise that ties together previous discussions. "Students role-play a scenario involving a suspicious piece of mail to get an idea of the follow-up required," Ames said.

More than 50 trainings are scheduled over the next two years in South America, Southeast Asia, Eastern Europe, the Middle East, Africa and Europe. ●

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