LBL-PUB--742/3-94

THE ADVANCED LIGHT SOURCE

rica's
scienc

MASTER

LAWRENCE BERKELEY LABORATORY

America's brightest light comes from the Advanced Light Source (ALS), a national facility for scientific research, product development, and manufacturing. Completed in 1993, the ALS produces light in the ultraviolet and x-ray regions of the spectrum. Its extreme brightness provides opportunities for scientific and technical progress not possible anywhere else.

THE ADVANCED LIGHT SOURCE

america's brightest light for science and industry

The ALS is located at Lawrence Berkeley Laboratory (LBL), a national laboratory operated by the University of California for the U.S. Department of Energy. Founded in 1931 by Professor Ernest O. Lawrence, LBL supports a wide range of unclassified research activities in the physical, biological, and environmental sciences and in engineering and mathematics. Its dedication to scientific excellence has garnered a host of awards—including nine Nobel prizes. What's more, LBL research has spawned entirely new industries such as nuclear medicine and medical imaging. And its pioneering research in energy conservation has saved the nation billions of dollars.

In today's competitive marketplace, LBL serves the national interest by establishing partnerships with U.S. industry. Productive collaborations can lead to new and viable technologies that contribute value to the U.S. economy. In keeping with its commitment to forging such relationships, LBL welcomes industrial research and development teams to the ALS.

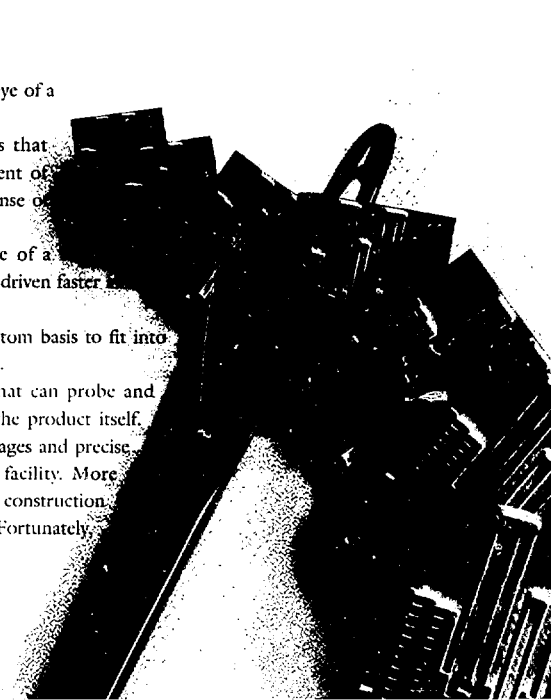
Technology is poised on the brink of a major revolution—one in which vital machine components and industrial processes will be drastically miniaturized. Industrialized nations are vying for leadership in this revolution—and the huge economic rewards the leaders will reap.

THE ALS a tool to launch a revolution

Soon to become commonplace are:

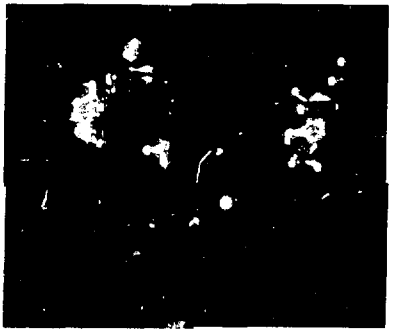
- Motors so tiny they can pass through the eye of a needle.
- Fingernail-size computer memory chips that hold a billion bits of information or the equivalent of 30,000 double-spaced typed pages. (The most dense of today's chips hold about 4 million bits.)
- Microscopic reaction chambers, the size of a few grains of sand, in which chemical reactions can be driven faster and more efficiently than in conventional equipment.
- Pharmaceuticals designed on an atom-by-atom basis to fit into and disable active sites in disease-causing organisms.

Developing these products requires a tool that can probe and manipulate matter on a scale at least as small as the product itself. The tool must allow industry to make detailed images and precise measurements—and even serve as a production facility. More than a dozen such facilities are planned or under construction around the world, almost all in Europe and Asia. Fortunately, the U.S. has completed one of the first—the ALS.



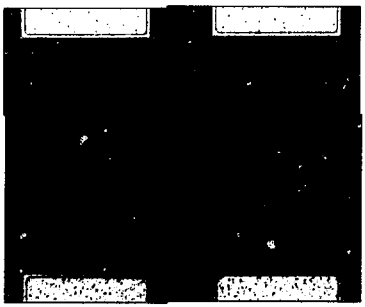
America's premier light source. It known as synchrotron radiation to structure, composition, and proper- and biological specimens.

THE ALS ADVANTAGE



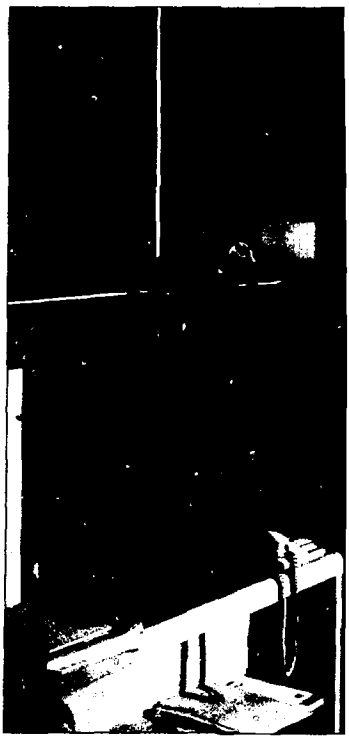
decade, synchrotron have delivered huge many of the tech- drive industrial new pharmaceuticals designed rather than trial and error. Electronic erials are being on a near-atomic scale. And precision microscopic components for the fiber-optics industry.

But amazing as they seem, these feats are only a [illegible] can achieve. Why? Because the ALS has a big advantage over [illegible] It produces light a hundred times brighter than the best of [illegible] brightness means that ALS light [illegible] better spatial and spectral resolu[illegible] your work.



In fact, experience shows that [illegible] improvement in the brightness of [illegible] not only advances current technology [illegible] new applications that before were [illegible] ALS user, you may well become [illegible] next pioneers.

How the ALS Works



When fast-moving charged particles such as electrons travel a curved path, they emit light. This is the principle governing the operation of the ALS. It accelerates an electron beam to nearly the speed of light and maintains it at constant energy inside a storage ring. Hundreds of precision electromagnets focus and bend the electron beam as it circles the ring more than a million times per second.

As the electrons travel in their circular orbit, they emit synchrotron light in the ultraviolet and x-ray range of the spectrum. This light is directed through beamlines to individual user workstations.

In some sections of the storage ring, the electron beam passes through special permanent-magnet arrays called undulators or wigglers, which cause it to oscillate from side to side many times. This additional wiggling motion generates synchrotron light a hundred times as bright as the best sources to date and a hundred million times as bright as a beam from the most powerful x-ray tube.

MEETING THE USER'S NEEDS

Most companies cannot afford to invest the millions of dollars required to develop a synchrotron light source of their own. But they need not commit tremendous resources to working at the ALS—an easily accessible shared facility that meets industrial standards. Because the ALS is a DOE national user facility, it is free to industrial users conducting nonproprietary research. (For proprietary usage, there is a modest charge to cover costs.)

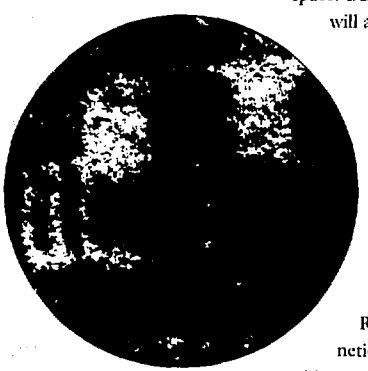
As an ALS user, you can conduct research or product development at a workstation designed to meet your requirements. Plans call for 10 custom workstations in the first two years of ALS operations. Eventually up to 100 will be available for simultaneous use.

Whether your company is in the Fortune 500 or a sole proprietorship, you can take advantage of the opportunities the ALS has to offer. We are committed to helping you make the most of America's brightest synchrotron radiation. A few potential applications of the ALS are described on the following pages.

Building Faster, More Powerful Computers

More Bits on a Disk

The ALS can help U.S. industry maintain its share of the giant market for mass storage media—worth $50 billion annually. To stay competitive, companies must find ways to pack more and more data onto magnetic storage disks. The smallest data bits today measure about 1 × 10 microns (millionths of a meter). At this size, around 23 million of them fit into a square centimeter of disk space. But industry trends indicate that, over the next decade, storage density will approach 1.5 billion bits per square centimeter.



Crucial to increased storage density is the development of novel magnetic materials on which smaller bits can be packed more tightly. And just as important are materials to make read heads that are sensitive enough to decipher the ever-shrinking bits. The evaluation of materials is a task that the ALS is uniquely equipped to support.

Designers at the ALS and their industrial partners are working on a beamline that will deliver ultrabright circularly polarized synchrotron radiation. This light has a right- or left-handedness that makes it ideal for investigating magnetic materials. Researchers will be able to use the polarized light to study the magnetic properties of complex materials and even produce images of the bits on a disk.

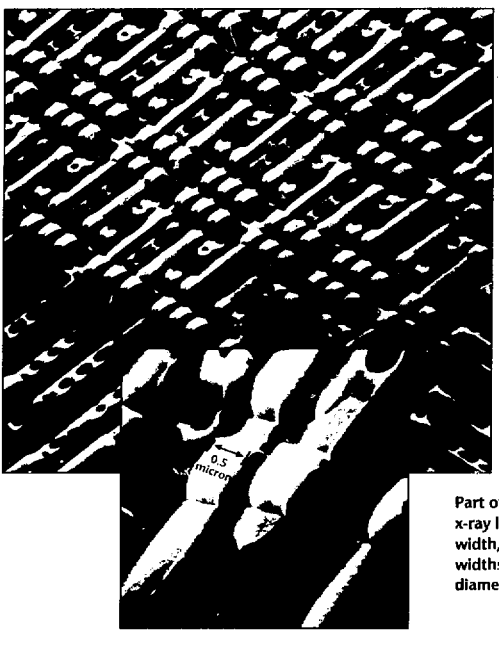
Image of data bits on a magnetic storage disk was obtained by using circularly polarized light.

More Circuits on a Chip

The race for dominance in making chips to drive computers will be won by companies that can pack the most circuitry into the smallest area. And what's at stake is a worldwide market worth more than $80 billion per year.

The problem for chip makers is that conventional manufacturing methods are being pushed to their limits when it comes to squeezing more circuits onto a chip. These methods are based on optical lithography, in which visible or ultraviolet light shines through a stencil-like mask to start the process of etching circuits onto silicon wafers. To make chips "denser" with more complex circuitry, manufacturers must be able to etch finer features than ever before and decrease the spacing between them. One way this feat can be achieved is by extending lithography to use the short wavelengths of extreme ultraviolet (EUV) light.

But EUV lithography systems are susceptible to flaws so tiny they cannot be discovered by traditional optical testing. The success of EUV lithography depends on developing techniques for "at wavelength" testing—testing performed at the wavelength at which the lithography system operates. This is the strength of the ALS.



LBL's Center for X-Ray Optics plans two ALS beamlines with workstations for optics testing. Both are open to industrial research. At one workstation, researchers can measure optical properties such as reflectivity, optical efficiency, and refractive index. At the other, they can take advantage of the laser-like EUV light from an undulator. The near-coherence of this light makes it useful in interferometry, a method for measuring the curvature and smoothness of reflective optics.

Part of an experimental chip manufactured through x-ray lithography. The blow-up shows a 0.5-micron line width, but the technique is expected to achieve line widths around 0.1 micron (one-thousandth the diameter of a human hair).

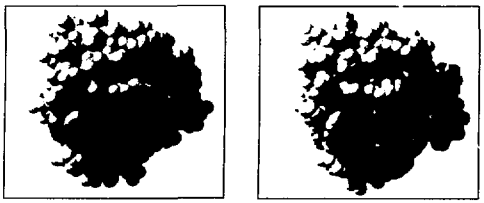
One in three Americans now living will eventually have cancer, and the cost for its treatment amounts to about $35 billion per year. Fighting this disease and reducing its costs rank as top priorities in the U.S. These are battles that the ALS can help to win.

TURNING OFF CANCER

Much of today's cancer research focuses on several genes known to play a crucial role in regulating human cell growth. One of these is the *ras* gene. A normal *ras* gene holds the code for creating an on-off switch—a protein that tells cells when to start and stop growing and dividing. But sometimes the code undergoes a mutation, transforming the gene into a cancer-causing *ras* oncogene. Proteins created by the oncogene, known as oncoproteins, lose their ability to turn off the cell division signal, a disaster that can lead to the formation of deadly tumors. *Ras* oncogene is common in human tumors. It is found in about half of human colon cancers and in most pancreatic cancers, two of the five deadliest malignancies among U.S. cancer victims.

Sung-Hou Kim of LBL led the research team that determined the structure of the *ras* protein using x-ray crystallography.

An international team based at LBL set out to unravel the mystery of how the *ras* oncoprotein does its deadly work. They used synchrotron light in a process called x-ray crystallography—currently the most successful way to get structural information about complex molecules in the human body. The researchers aimed x rays at crystals of both the normal and mutated forms of the *ras* protein. Subsequent analysis of the

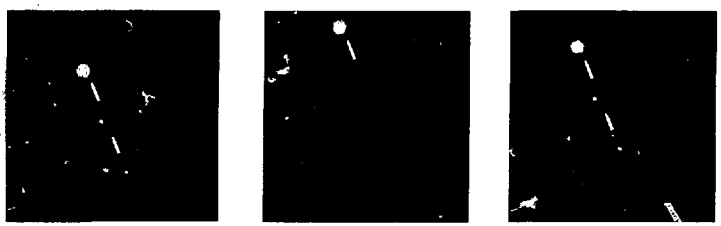


From protein crystallographic data obtained using synchrotron light, scientists developed computer images portraying *ras* protein molecules in three dimensions. When switched on (left), the protein tells the cell to grow and divide. When switched off (right), the protein stops cell division and waits for a new "on" signal.

pattern of the diffracted x rays yielded highly accurate data on the position of the atoms in the proteins.

By analyzing differences in the *ras* protein structures, the research team discovered how the on-off switch works and what happens when it goes awry (see illustration). Now that this disease-causing mechanism is understood at the atomic level, industry can focus on designing and synthesizing therapeutic molecules to counteract it.

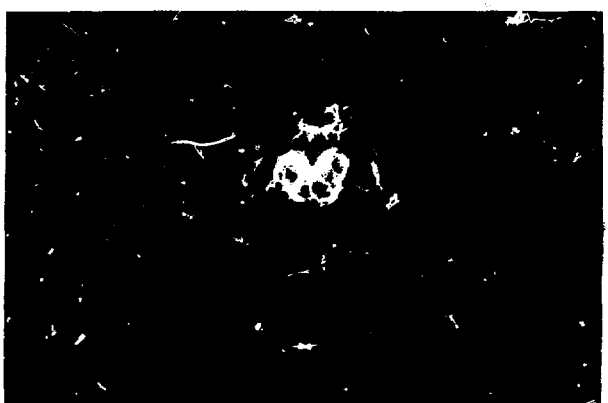
The *ras* protein is one of perhaps 100,000 proteins in human cells, and many of them play a role in disease. Yet only a small fraction of these protein structures have been solved. It is clear that synchrotron light is just beginning to fill the huge demand for a high-quality protein crystallography tool.



The on-off switch for cell growth and division centers on two loops that are part of the *ras* protein structure. In a normal protein, the signal is turned off when one loop holds in place a small chemical compound containing three linked phosphates while a second loop cuts off the third phosphate (left and center). In the cancer-causing *ras* oncoprotein, mutations alter the structure and prevent the holding or cutting mechanism from working correctly (right); the unsevered phosphate locks the protein in its "on" position, and the cell keeps growing and dividing.

Recognizing this demand, ALS planners are establishing a protein crystallography facility that offers analytical services to industry. A beamline delivering x rays from a wiggler source will serve three automated workstations built for high-quality data collection combined with fast sample turnaround. Also planned are computers for data analysis and laboratory space for sample preparation. Designed for ease of use, the facility will be dedicated to the convenience of users.

Developing Drugs by Design, Not Chance

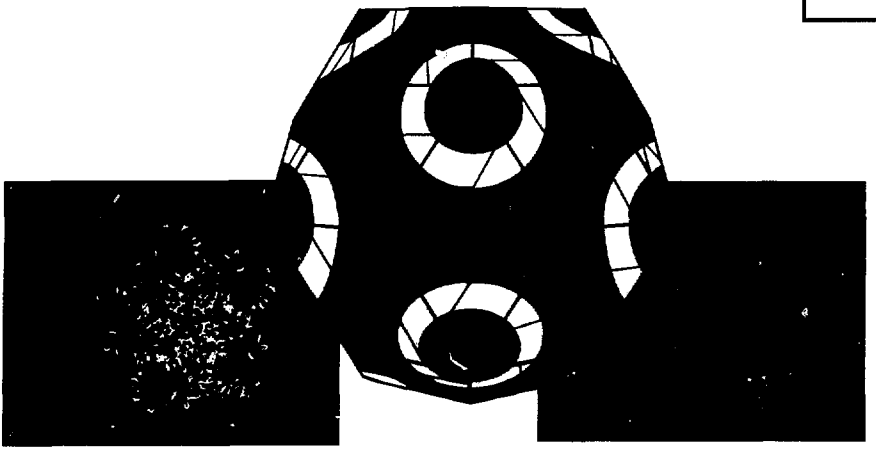


Computer model of HIV protease structure incorporates an inhibitory molecule (in yellow). The inhibitor was developed through structure-based drug design to bind at the active site of the protease and prevent normal viral function.

Most drugs on the market today were discovered by trial and error. Pharmaceutical companies typically screen 20,000–40,000 compounds to find a single promising lead. And for every 4,000 leads, often no more than one becomes a marketable drug. It's no wonder the pharmaceutical industry is seeking ways to streamline this long, expensive process. Companies that succeed have much to gain in this market worth more than $150 billion per year worldwide.

To make drug development more efficient, many companies are turning to structure-based drug design—an approach based on improved understanding of the molecular interactions that underlie diseases. Structure-based design has enabled promising candidate drugs to reach human testing in less than 4 years—a vast improvement over the typical 10-year development cycle.

The starting point of this approach is not the drug but its molecular target. First, scientists gather detailed information about the three-dimensional structure of a substance known to play a key role in a disease. The method of choice is x-ray crystallography—soon to be offered as an analytical service at the ALS. Then scientists turn to their computers to design custom drug molecules that will fit the active site of the target and alter its activity. The tighter the fit, the longer a drug will



X-ray crystallography studies with synchrotron radiation showed that the protein coat of many human cold viruses consists of 12 "pentameric caps," each containing five copies of three different coat proteins. The computer reconstruction on the left illustrates one of these fivefold-symmetric units, with red, green, and blue used to denote the proteins. One such unit occupies each of the 12 vertices of a 20-sided polyhedron (as shown in the right-hand structure). Deep canyons (gray areas in the center structure) encircle each fivefold axis and are sites where the virus can attach itself to a host cell.

remain bound to its target and the more potent it will be. Furthermore, a good fit will make the drug less likely to interact with structures other than the target, thus minimizing side effects.

This structure-based approach is being used to design inhibiting molecules that act on the protease enzyme made by the AIDS-causing virus HIV. This enzyme is necessary for the accurate assembly of viral particles and their spread from cell to cell. X-ray crystallography provides structural information about the HIV protease structure alone and bound with various inhibitors. In some cases, computer analysis of these structures has led to drug candidates that are now in clinical trials.

Drug designers are also tackling the common cold. To infect a cell, a cold virus must first bind to one of the cell's surface molecules. Using the structure-based approach, designers learned that the binding sites are relatively small areas at the bottom of "canyons" on the viral surface. Now they're concentrating on designing drugs that will block the attachment of healthy cells at these canyon sites.

The ALS is the drug designer's natural ally. Its unprecedented brightness makes it possible to collect high-quality x-ray crystallography data more rapidly than ever. Automated workstations at the x-ray crystallography facility will speed production and give ALS users the edge in the race to develop new drugs.

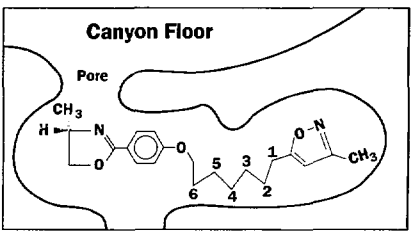
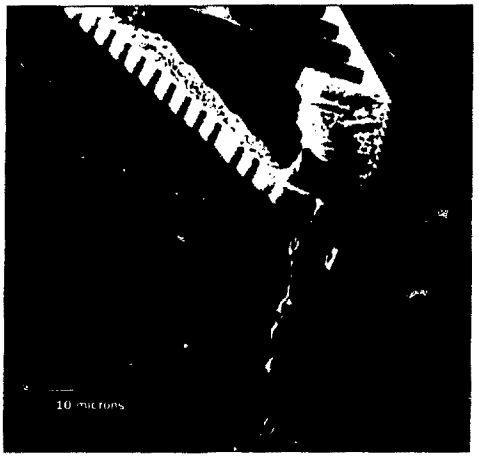


Diagram shows the tight fit of an inhibiting drug bound to a canyon floor in a viral protein coat. The drug prevents infection by keeping the virus from binding with a cell. Because many disease-causing viruses have similar structures, this strategy may be useful in treating a number of viral diseases, including influenza and cancer.

MANUFACTURING MICROSCOPIC MACHINES



This tweezer-like microgripper holds a euglena, a microscopic single-celled animal measuring only 7 × 40 microns.

Imagine a motor that can pass through the eye of a needle or a tweezer that can grasp a single-celled organism. Surprising as it might seem, devices this small not only exist—they're manufactured commercially! Today's market for microscopic machines and parts is estimated at $500 million, with the potential to reach $10 billion by the year 2000.

Among the micromachines now in use are speck-size sensors for detecting pressure, acceleration, vapors, temperature, and sound. These microsensors have applications in medicine, for example, to measure the pressure gradient at heart valves or the velocity of blood cells. And in automobiles they are used as acceleration detectors for triggering air bags or adjusting engine performance. An especially promising micromachine is the "chemical plant on a chip"—a tiny reaction chamber only as big as a few grains of sand built into a silicon wafer. Already demonstrated effective for DNA replication, this little device promotes fast reactions and has low power requirements because of its small volume. It could find use in "on-the-spot" manufacture of chemicals that can't be stored or shipped in active form.

The amazing thing about micromachines is not their size alone, but also the economies of scale achieved in their manufacture. Thousands at a time can be made on a silicon wafer for a few cents each.

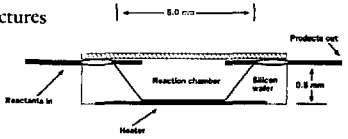
This microstructure, fabricated at the ALS by deep-etch x-ray lithography, could be used in the manufacture of thermal sensing units for automobile engines. The high precision of the lithography process enables complex structures like this to be manufactured with submicron accuracy.

Until recently, most of these tiny devices were made by surface micromachining—conventional lithography combined with thin-film deposition or etching. Micromachines made this way are delicate structures no thicker than a dust particle (2 or 3 microns) and therefore impractical for many uses. But a newer technique, deep-etch x-ray lithography, now produces sturdier devices up to 1000 microns thick—very tall in relation to their length or width. By making these devices more practical, this technique can lead to thousands of new applications, expanding a novelty to an industry of substance.

How does deep-etch x-ray lithography differ from the conventional variety? A major difference is the use of synchrotron radiation—essential for sculpting taller, sturdier micromachines rather than "flat" ones. But to do so, the synchrotron radiation must have three qualities:

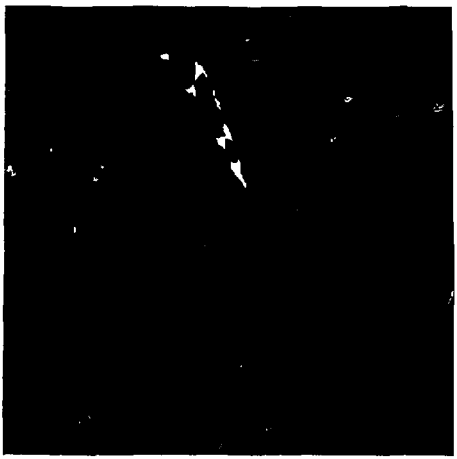
- A high degree of collimation (parallelism).
- High flux (amount of energy delivered).
- Suitable wavelengths to penetrate in depth.

Eager to take advantage of these qualities at the ALS, research teams are planning a deep-etch x-ray lithography facility where users can fabricate micromachines on an industrial scale.



Prototype chemical-reaction chamber etched into a silicon wafer. The chamber is just one component of a miniature microflow system, essentially a "chemical plant on a chip." Other components include tiny ultrasonic pumps, mixers, and resistive heaters—each the size of a few grains of sand.

SEARCHING FOR THE PERFECT POLYMER



What do milk bottles, golf carts, and bullet-proof vests have in common? They're all made of polymers—a class of chain-like chemical compounds representing more than 75% of the U.S. petrochemical industry's production. The worldwide market for polymers exceeds $500 billion annually.

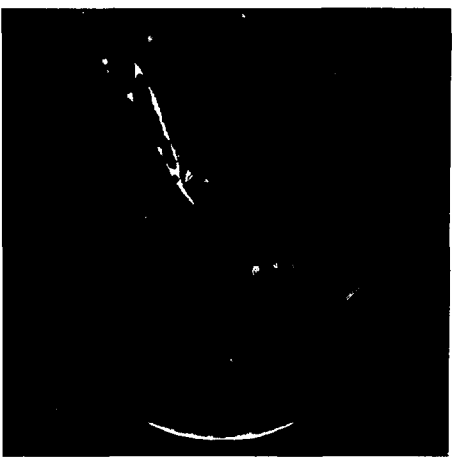
Polymers turn up just about everywhere—in food packaging, automobiles, aircraft, textiles, sporting goods, and many more end products. But industrial chemists never stop looking for the perfect polymer—one with exactly the right combination of properties to fit an application.

To achieve this ideal, chemists must scrutinize a polymer's structure, which is strongly tied to its properties. By using a special form of x-ray microscopy called XANES,* they can produce pictures revealing such details as the chemical (valence) state of elements in the polymer and the orientation of polymer components. The XANES technique can even distinguish among chemical groups such as C-C, C=C, and C≡C, in which only the bond between two carbon atoms differs.

The ALS is an ideal tool for polymer XANES microscopy because its undulator-produced x rays are America's brightest. For this reason, you can focus a high concentration of x rays on an extremely small spot, achieving better spatial resolution than ever before. And the spectral

* X-ray absorption near-edge structure.

resolution is equally good; you can select a very narrow band of the spectrum from the x-ray beam and still have a high enough intensity of light to give reasonable exposure times. This work will also benefit from the x rays' linear polarization, the characteristic most useful for determining the orientation of polymer-chain components. With these virtues, the ALS might be just the key to finding the perfect polymer.



These two XANES images show the same Kevlar® fiber section. Kevlar is a polymer used in over 200 applications including tires, aircraft, missile cases, and bullet-proof fabrics. The butterfly pattern was produced by exposing the sample to linearly polarized synchrotron radiation at a wavelength strongly absorbed by Kevlar's aromatic chemical groups. The pattern shows that the aromatic components have a radial (spoke-like) orientation. The reversal in contrast between the two images is a result of rotating the direction of polarization by 90°.

NEW TOOL, NEW OPPORTUNITIES

A tool of immense versatility, the ALS offers industry a wealth of pioneering technology. Its brighter synchrotron radiation lets you use traditional research techniques such as protein crystallography and microscopy more effectively than ever before. And it puts at your disposal forefront technologies now made practical by synchrotron radiation:

- Quality testing of x-ray optics.
- Imaging of magnetic materials by circularly polarized light.
- Micromachining through deep-etch x-ray lithography.

Contact us now to learn more about the ALS and the opportunities it offers. We're committed to helping you take advantage of America's brightest synchrotron radiation.

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Credits

Page 1: The microstructure passing through the needle's eye is a representation of an electromechanical filter fabricated by the Berkeley Sensor and Actuator Center, University of California, Berkeley, CA.

Page 2: (Left) Computer-generated image of the structural backbone of the normal *ras* protein, based on work done by S.-H. Kim of LBL using synchrotron radiation. The *ras* protein plays an important role in regulating cell growth in humans. (Right) Computer-generated model of superoxide dismutase, the enzyme discovered to be defective in patients with Lou Gehrig's disease. The image was produced by J. Tainer, M. Pique, H. Parge, and E. Getzoff, Scripps Research Institute, based on their x-ray crystallography studies at Stanford Synchrotron Radiation Laboratory, Stanford, CA.

Page 3: (Top Left) A zeolite "cage" with a small molecule trapped inside. Zeolites have tremendous importance as catalysts in petroleum refining and other fields. Their catalytic activity is directly related to the details of their 3-D structure, which can often be determined only with synchrotron-generated x rays. Image courtesy of Brookhaven National Laboratory. (Bottom Left) An electrostatic micromotor fabricated by Y. Tai and R. Muller of the Berkeley Sensor and Actuator Center, University of California, Berkeley, CA. (Right) Image of a *Plasmodium falciparum* parasite-infected human red blood cell produced by M. Moronne and C. Magowan of LBL at the National Synchrotron Light Source, Upton, NY.

Pages 4-5: M. Fryer of LBL reviews data from the x-ray microprobe beamline at the ALS.

Page 6: Image of magnetic bits on a magnetic storage disk was produced by IBM Almaden Research Center and the University of Wisconsin, Milwaukee, at Stanford Synchrotron Radiation Laboratory, Stanford, CA.

Page 7: Part of an experimental chip made by scientists from IBM Research.

Page 9: (Top) Computer-generated images of *ras* protein molecules courtesy of S.-H. Kim of LBL.

Page 10: HIV protease image based on work by H. Bellamy, H. Luecke, and M. Soltis at Stanford Synchrotron Radiation Laboratory, Stanford, CA.

Page 11: Computer reconstruction of human cold virus based on research by M. G. Rossmann, Purdue University, conducted at Cornell High Energy Synchrotron Source, Ithaca, NY; National Synchrotron Light Source, Upton, NY; Stanford Synchrotron Radiation Laboratory, Stanford, CA; Synchrotron Radiation Source, Daresbury, UK; and European Molecular Biology Outstation at Deutches Elektronen-Synchrotron, Hamburg, Germany. Illustrations by K. Schuster, Purdue University.

Page 12: Microgripper made by C. Kim, A. Pisano, and R. Muller of the Berkeley Sensor and Actuator Center, University of California, Berkeley, CA.

Page 13: (Top) Microstructure fabricated at the ALS by C. Khan Malek and K. H. Jackson of the Center for X-Ray Optics, LBL; and R. Brennen and M. Hecht of the Jet Propulsion Laboratory. (Bottom) Prototype biochemical reaction chamber fabricated at the Berkeley Sensor and Actuator Center, University of California, Berkeley, CA.

Page 14-15: Polymer images produced by H. Ade, North Carolina State University, and B. Hsiao, DuPont, at the National Synchrotron Light Source, Upton, NY. The researchers gratefully acknowledge the assistance of their coworkers at the State University of New York, Stony Brook; IBM; LBL; and the National Synchrotron Light Source. H. Ade and B. Hsiao, Science **262**, 1428 (1993).

Page 15: Kevlar™ is a registered trademark of DuPont.

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