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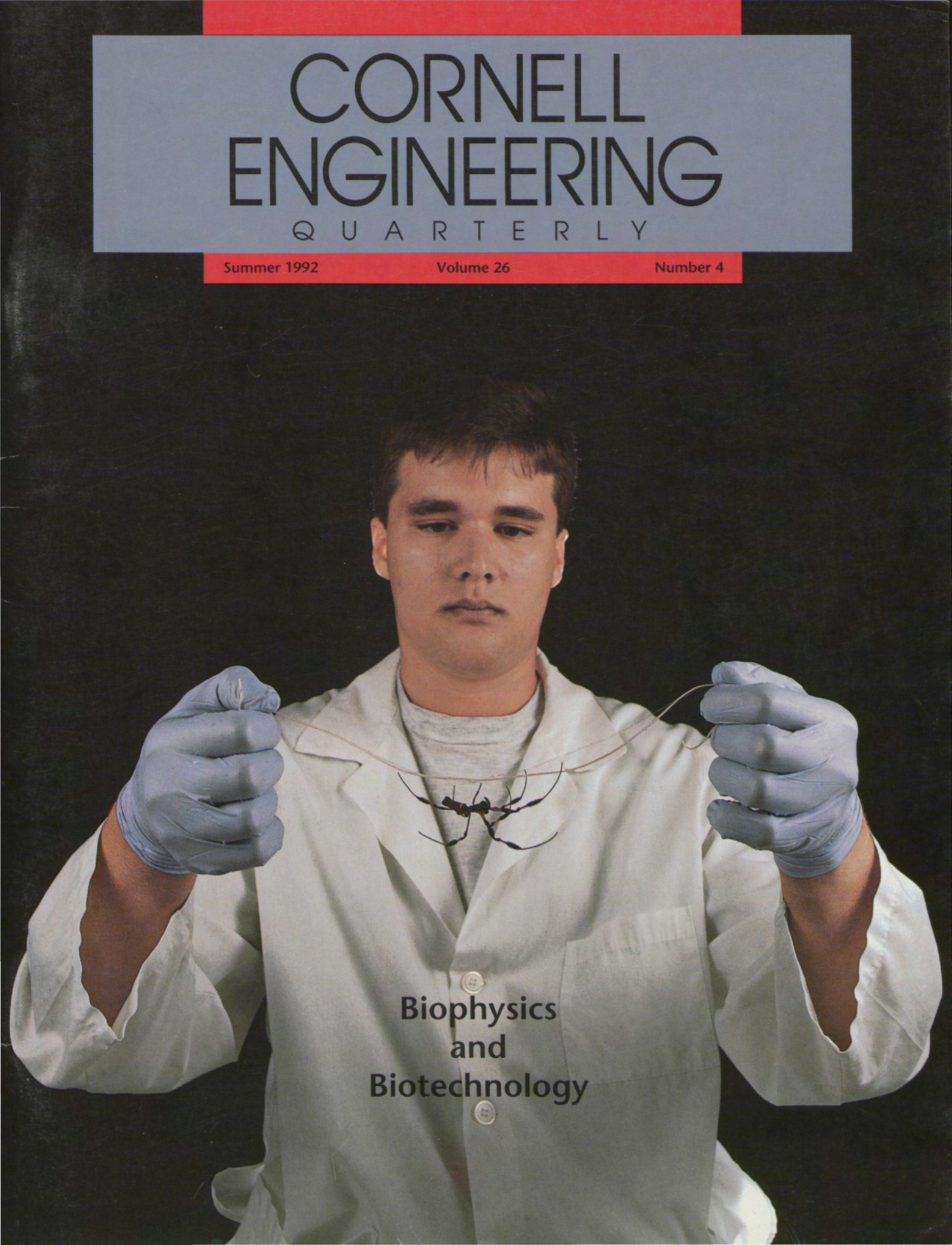

Biophysics and Biotechnology

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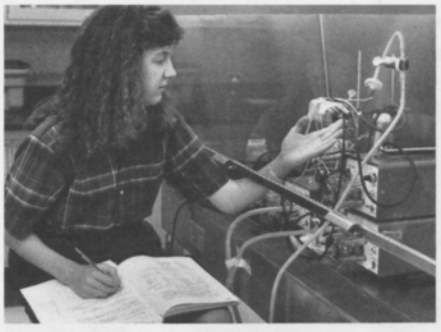

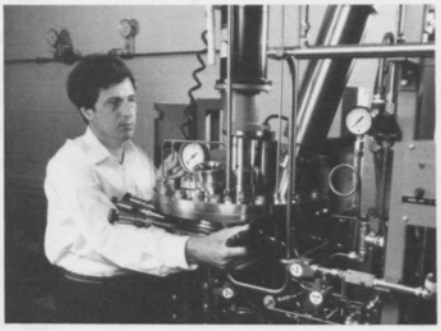

Cover: Edward Ray, an undergraduate majoring in biochemistry, works with a golden orb weaver spider (Nephila clavipes) *as part of a research team in Lynn Jelinski's laboratory that seeks to discover why spider web is stronger than steel.*

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BIOPHYSICS AND BIOTECHNOLOGY AT CORNELL

by Lynn W. Jelinski

"Biophysics and biotechnology, together, already contribute greatly to the quality of life."

Biophysics and biotechnology occupy the fertile ground where biology, physics, chemistry, and engineering all come together. Biological organisms, assemblies, and molecules are highly complex entities whose study presents some of the most exciting challenges in the physical sciences today. At the same time, applications of biotechnology and biophysics are at the cutting edge of work in engineering. The relationship between research in biology and the physical sciences, on the one hand, and the development of engineering applications, on the other, results in new discoveries about how biological systems work and novel inventions of products and processes.

Biophysics is the study of biological systems by physical methods and principles. Understanding biological processes at their most fundamental level requires a detailed knowledge of molecular structure and function. Powerful physical techniques such as x-ray crystallography, optical spectroscopy, and magnetic resonance imaging are used to advance the frontiers of biological science.

Biophysics also provides some of the major underpinnings of biotechnology, which, in the broadest sense, is the use of biological organisms and techniques to produce products. Biotechnology has already taken root in many areas of industrial society and over the next few years its impact can be expected to grow rapidly. Part of this impact will involve health care, but biotechnology is also being used as a cost-effective way to remedy environmental ills, to reduce dependence on chemical pesticides and fertilizers, and to improve the nutritive value of food. Biophysics and biotechnology, together, already contribute greatly to the quality of life.

The Programs in Biophysics and Biotechnology

The Biophysics Program, directed by Watt Webb, is a confederation of faculty members from a wide range of departments and fields

Biotechnology at Cornell reaches far beyond the 171,000-square-foot Biotechnology Building, which is located on the central campus. More than one-fifth of Cornell's faculty is involved in bio-related research.

Chemistry professor Barbara Baird and undergraduate Walter Yang Chi work on a biophysics project. Interdisciplinary cooperation is a hallmark of research at Cornell.

who have drawn together over the last twenty years in order to address the needs of research and training in the area of biophysics. Members of the Biophysics Program carry out research in areas such as chemical kinetics, the molecular dynamics of cell-surface receptors, neurotransmitters, and second-messenger signalling. The program supports a weekly Biophysics Seminar Series that brings renowned speakers to the Cornell campus and serves as a meeting place for students and faculty in the biophysics community. A training grant from the National Institutes of Health provides support for ten graduate students whose research involves the molecular physics of biological systems. The interdisciplinary character of the program provides students with a rich educational opportunity.

The Biotechnology Program, which I direct, is a Center for Advanced Technology (CAT) funded by the New York State Science and Technology Foundation and industrial partners. While the Biotechnology Program also has an NIH training grant, its orientation is very different from that of the Biophysics Program. Its mission is to ensure that the results of Cornell's research in biotechnology are transferred to industry, resulting in economic development and an ultimate benefit to society. Research and development activities are carried out by interdisciplinary faculty clusters that focus on specific problems such as the environment, agriculture, food science and nutrition, and health care.

The Biotechnology Program is housed in the 171,000-square-foot Biotechnology Building, which was completed in 1988. It has well equipped laboratories that provide a wide range of analytical and biotechnological services to the Cornell community and to industry in New York State. These include facilities for protein analysis and synthesis, oligonucleotide synthesis, computer and molecular graphics, fermentation, flow cytometry and video microscopy, development of monoclonal antibodies, and plant-cell culture and transformation services.

Biotechnology, Remediation, and Stewardship of the Environment

Many of the people who do research in biophysics and biotechnology are motivated by a concern for the quality of the environment. Stewardship of the environment is one of the foremost concerns facing the nation and the world. Bioremediation, the use of biological organisms and processes to detoxify polluted soil and water, offers great promise as a cost-effective in-situ method for cleaning up industrial wastes that have been spilled or improperly disposed of. In his article on bioremediation (pages 7–10), Eugene Madsen highlights the research of members of the Biotechnology Program's Faculty Cluster on the Environment. He points out the irony of using the same tools of science, technology, and engineering that have created environmental pollution to help eliminate it. But he makes a case that the convergence of current research initiatives will result in a powerful new tool, bioremediation, to cope with industrial ills.

Jean Hunter's article (page 11) further highlights the interrelationship between the envi-

Researchers at Cornell have produced high-densithy maps of the tomato genome. Such maps will ultimately contribute to the quality of many fruits and vegetables.

The "gene gun," which grew out of an interdisciplinary collaboration that was partially funded by the Biotechnology Program, modifies genetic structure by shooting DNA-coated metal particles into cells. Here it is being used by Rosa Spivey, a research support specialist in the Plant Science Center.

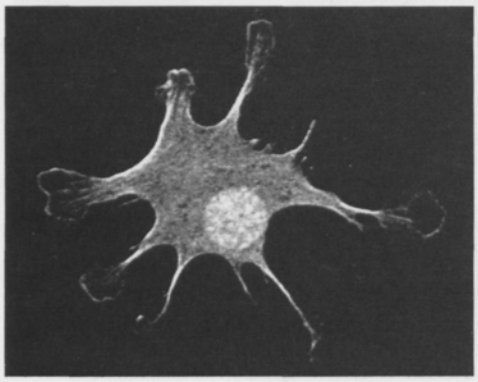
ronment, food science, and agriculture. Her research seeks to create processes for producing value-added products from food-processing and agricultural wastes. She has focused on whey, a by-product of the manufacture of cheese, and shows that suitable biological processes can produce valuable organic solvents while solving a waste disposal problem. Her research elegantly captures the essence of the emerging field of industrial ecology, which promulgates a holistic, systems approach to manufacturing in which the waste from one process becomes the raw material for another.

Understanding the Structure of Biological Molecules

Research involving biological macromolecules benefits from a number of outstanding resources at Cornell. Among them are the Cornell High Energy Synchrotron Source (CHESS) and the Cornell National Supercomputer Facility. The high-quality macromolecular crystallography that can be carried out at CHESS has contributed to determining the structure of the human cold virus, and plays a part in ongoing pharmacological research (see page 25). The Cornell National Supercomputer Facility provides the massive computing power required by studies of protein folding and simulation of the molecular dynamics of macromolecules.

How proteins fold is one of the key biophysical problems of the decade. It can be thought of by analogy to origami, the Japanese art of folding paper into complex artistic shapes. In the protein-folding problem, we want to be able to predict the three-dimensional structure of a protein molecule by simply knowing the linear arrangement of its constituent amino acids. It is as if we were given an unfolded origami bird, without being told what it was, and asked to recreate the original shape from the flattened-out sheet.

When the techniques of biotechnology are used to produce proteins, it sometimes happens that the molecules do not fold properly and are useless for the purpose intended. Consequently, a solution of the protein-folding problem has enormous implications, especially



Confocal microscopy, available in the Biotechnology Program's Flow Cytometry and Video Imaging Facility, provides three-dimensional images of living and fixed cells. This image is of a fibroblast cell.

for the making of designer drugs, carefully tailored to affect certain molecules. In his article on the subject (pages 32–36), Harold Scheraga describes computational approaches to overcoming the major stumbling block—the problem of multiple minima, or "valleys," in the energy landscape.

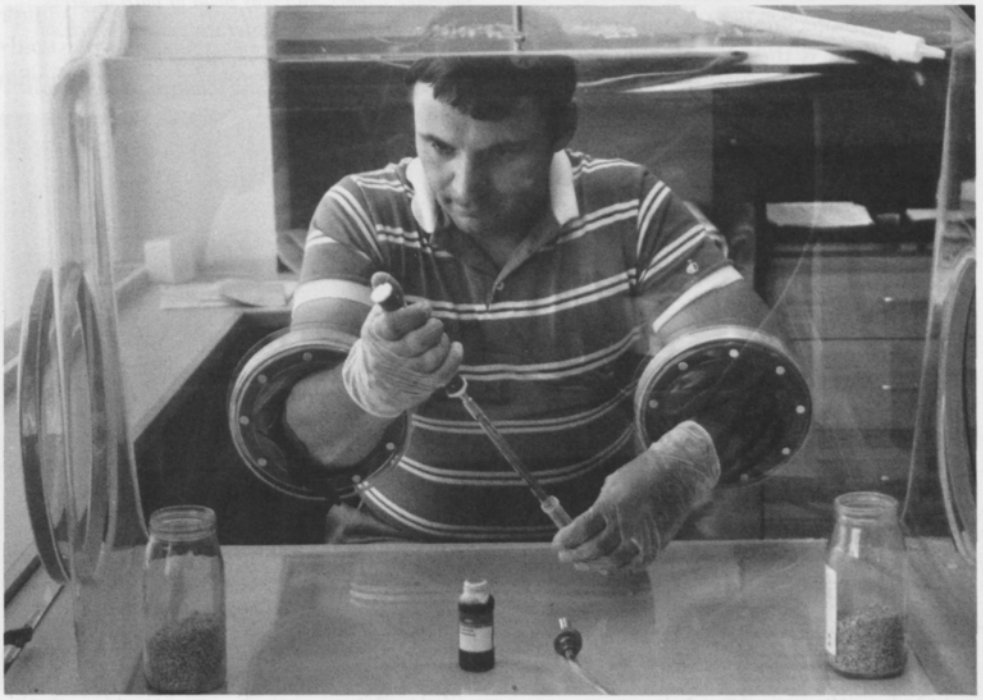
Research on Cells and Larger Systems

Operating at the interface between the cellular and subcellular level is the Developmental Resource for Biophysical Imaging Optoelectronics, featured in the article by Watt Webb (pages 12–17). Webb describes how state-of-the-art instrumentation can be developed and applied to biological assemblies to understand the microscopic motion of macromolecules on living cells and mechanical transduction by biological cells, as well as other biophysical phenomena. One especially promising technique is two-photon laser scanning fluorescence microscopy, which can provide remarkable three-dimensional resolution of living cells.

The deformability of red blood cells, investigated by Harold Craighead and Richard E. Waugh (page 18), makes use of another remarkable resource available on the Cornell campus: the National Nanofabrication Facility. The NNF is a research center specializing in the fabrication of structures with dimensions smaller than 0.1 micron, and this work is a good example of the contribution the NNF can make to research involving the behavior of cells.

Michael Shuler's innovative approach to determining the toxicity of pollutants also operates at the level of the cell, making use of the techniques of chemical engineering (pages 19–24). Shuler and his coworkers have constructed an apparatus containing interconnected cell cultures, representing various organs, which can be thought of as a surrogate animal. He shows how this novel bioreactor can be used in conjunction with computer modeling to better understand the distribution and biotransformation of drugs and pollutants such as naphthalene and dioxin.

At the scale of entire biological systems, Donald Bartel's work seeks to improve the longevity of artificial joint replacements for knees and hips (pages 26–31). Problems arise from the body's reaction to polyethylene debris that is produced when the two articulating surfaces rub together. Bartel's analysis of the mechanics of joint function is oriented toward better design that will minimize the production of such debris.



Ted Thannhauser directs the Biotechnology Program's Analytical Chemistry and Peptide/DNA Synthesis Facility. The ability to analyze and synthesize peptides, proteins, and DNA is essential to modern research in biotechnology.

". . . many projects will have practical applications in the near term."

Out of the Laboratory and into the Marketplace

The articles in this issue of the *Quarterly* illustrate the exciting diversity and innovative depth of Cornell's research in biotechnology and biophysics. All across campus, at the Geneva Experiment Station, and at the Medical College, nearly four hundred faculty members are involved in research related to biophysics or biotechnology. At the hub of this massive effort is the Cornell Biotechnology Program, which coordinates directly funded research projects with total expenditures of about $2.3 million per year. But funding for all of Cornell's initiatives in the area totals many times that figure.

Although much of this research is basic, guided primarily by scientific curiosity, many projects will have practical applications in the near term. More and more developments made in academic laboratories are ready for commercial development. During the past five years, over a quarter of all small businesses that were spun off from Cornell research involved some aspect of biotechnology. A revolution is brewing, and within the next few years industrial processes involving biological techniques will change our lives.

Lynn W. Jelinski is a professor of engineering and director of the Biotechnology Program. She studied as an undergraduate at Duke University and completed her doctorate at the University of Hawaii. She held postdoctoral and staff fellow positions at the National Institutes of Health prior to joining AT&T Bell Laboratories in 1980. While at Bell, Jelinski performed fundamental research in biophysics and in polymer science and was head of both departments. Her research interests include nuclear magnetic resonance, imaging of biophysical systems, biopolymers, and biomedical materials. She joined the Cornell faculty in 1991. Jelinski is a fellow of the American Physical Society, a member of the advisory board of Chemical Abstracts Service, and a member of the National Academy of Sciences' panel on biomolecular and self-assembling materials. She is past chair of the Experimental NMR Conference, of the Advisory Board of the High Field NMR Facility at Massachusetts Institute of Technology, and of the National Academy of Sciences Colloquium on Industrial Ecology.

BIOREMEDIATION OF ENVIRONMENTAL POLLUTANTS

by Eugene L. Madsen

When a tree falls in the forest, when crop residues are left in the fields, and even when spilled gasoline soaks into the ground, microorganisms go to work. Just as humans eat food to sustain life, microorganisms digest nonliving organic materials, using an astounding diversity of enzymes. In the process of deriving carbon and energy for their own use, microorganisms recycle essential nutrients such as nitrogen and phosphorus to the other species with which they share the biosphere.

Before the twentieth century, naturally occurring biodegradation was able to maintain the biosphere in a relatively steady state. Myriads of microbial processes digested different types of biomass derived directly or indirectly from photosynthesis, so that organic substances seldom accumulated to cause environmental pollution. But then human beings developed the ability to synthesize chemicals industrially and these processes were put to use on a large scale to serve the needs of a rapidly increasing population. The rate at which petroleum-derived solvents, pesticides, and other synthetic chemicals were produced outpaced naturally occurring processes of biodegradation. This has thrown many ecosystems into an unsteady state and has threatened human health.

Increasing expertise in analytical chemistry and toxicology has contributed to an understanding of the problems of environmental pollution, and remedies are now being sought. Both physical and chemical processes may be essential to pollution-control technologies, but controlled biodegradation also offers significant promise.

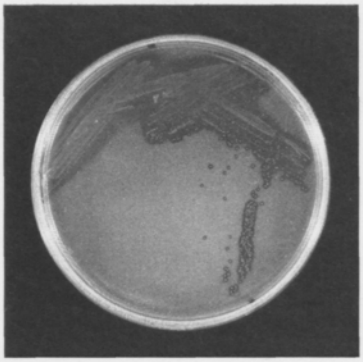
The Relationship between Bioremediation and Biodegradation

Bioremediation is the intentional use of biodegradation processes to eliminate environmental pollutants from sites where they have been spilled or dumped. Bioremediation has been used in municipal sewage-treatment systems for over a century. Here, microbial growth in filters, tanks, and digesters removes carbonaceous, nitrogenous, and other materials from water before it is is discharged into rivers, lakes, and oceans. But the growing need for ways to prevent or repair environmental

"Before the twentieth century, naturally occurring biodegradation was able to maintain the biosphere in a relatively steady state."

Bioremediation has long been used in the treatment of municipal sewage at facilities such as the Blue Plains Wastewater Treatment Plant in Washington, DC. ***(Courtesy of the District of Columbia Department of Public Works)***

damage requires increasingly sophisticated approaches to bioremediation, which depends on a detailed understanding of biodegradation. In order to achieve such an understanding, researchers are studying the environmental factors that affect the metabolism of organic compounds and examining the biochemical bases of microbial metabolism.



Bacteria breaking down polycyclic aromatic hydrocarbon create clear zones around their colonies in this petri dish. The polycyclic aromatic hydrocarbon was applied as a uniform white coating, and the areas where it has been consumed appear darker. The white streaks and dots are bacterial colonies.

Martin Alexander, of the Department of Soil, Crop, and Atmospheric Sciences, has found that major insights into microbiological processes can be gained by adding chemical pollutants to flasks that contain samples of soil, sediment, and water from a variety of different sources. The rate at which these pollutants are metabolized depends on the naturally occurring microbial populations. Using these and other techniques, Alexander and his coworkers have demonstrated that the susceptibility of pollutants to biodegradation depends on whether they occur in a solid form, or dissolved, or are ad- or absorbed onto some substrate. Results of this research may lead to strategies for enhancing biodegradability by increasing the availability of pollutants to microorganisms.

In Cornell's Section of Microbiology, William C. Ghiorse and I are investigating microbial processes and other factors that affect the fate of pollutants in the field. We are concerned with polycyclic aromatic hydrocarbons, an important class of pollutants that commonly contaminate soil and groundwater. By carefully interpreting patterns in microbiological populations and their activities in aquifer sediments, we have been able to demonstrate that polycyclic aromatic hydrocarbons do, in fact, undergo natural biodegradation in the groundwater of our study site.

Among the most pervasive and toxic environmental contaminants are halogenated organic solvents, such as tetrachloroethene. The chlorine in these compounds is the source of their toxicity and resistance to biodegradation. But major breakthroughs made in the past few years show that highly chlorinated compounds can be metabolized, particularly by anaerobic microorganisms. James M. Gossett, in the School of Civil and Environmental Engineering, has been working with Stephen H. Zinder, of the Section of Microbiology, to understand the complexities of a microbial community that completely dechlorinates tetrachloroethene, leaving only nontoxic products.

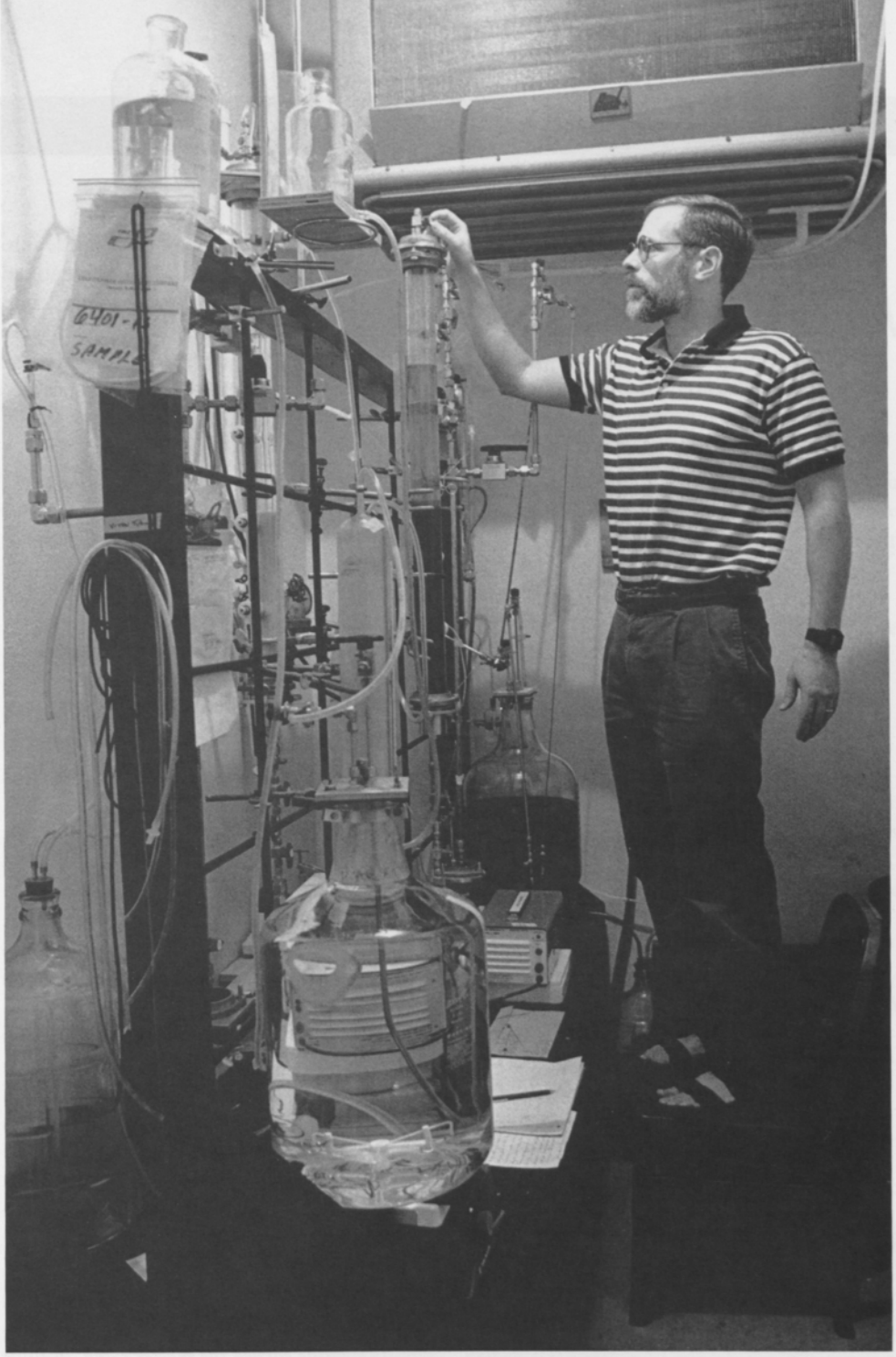
Steps toward Applications for Bioremediation

Microbial processes may be used to treat environmental contaminants *in situ*, or the contaminants may be drawn into some type of containment vessel (a bioreactor) and treated *ex situ*. Each of these approaches may, in turn, exploit solid-, slurry-, or vapor-phase systems for encouraging microorganisms to proliferate and metabolize the contaminants. Choice of strategy takes into account the characteristics of the contaminant (its molecular structure, solubility, volatility, and susceptibility to microbial attack), the nature of the contaminated site (its geology, hydrology, soil type, and climate), and the microbial process that will be exploited (whether a pure culture or a mixed culture, and the conditions needed to maintain growth).

A well-known example of in-situ bioremediation is the project carried out jointly by the U.S. Environmental Protection Agency and the Exxon Oil Corporation following the accidental release of crude oil in Prince William Sound, Alaska, in March 1989. In addition to beach washing, which physically removed some of the spill, a source of nitrogen and phosphorus was applied to overcome nutrient limitations and thus encourage native bacteria to degrade the oil. Chemical analysis demonstrated that microbial communities were effective in metabolizing the crude oil.

Two faculty members of the Department of Agricultural and Biological Engineering are conducting research that involves ex-situ bioremediation. Larry P. Walker is studying the solid-phase processes that take place in composting. By quantifying and mathematically modeling the complex physical, chemical, and biological changes that occur during the decomposition of organic waste, he hopes to find ways of optimizing biodegradation. William J. Jewell has developed an ex-situ, slurry-phase system of bioreactors for completely detoxifying halogenated compounds such as tetrachloroethene, trichloroethene, and vinyl chloride (see *Engineering: Cornell Quarterly*, Autumn 1990). A pilot system has been operating for more than a year, purifying twenty liters of contaminated water every day.

In most bioremediation scenarios, the active microorganisms form a film, held to-



James Gossett, of the School of Civil and Environmental Engineering, is developing a bacterial culture that rapidly degrades chlorinated solvents. The culture derives from microorganisms originally found in a municipal sewage-treatment facility, but continual selection, over the course of six years, has increased the rate at which chlorinated solvents are degraded by a factor of fifty to one hundred. Anaerobic metabolism of the solvents involves complex relationships among a community of microorganisms; Gossett and his students are now investigating the requirements and capabilities of the system. Their research holds great promise for the remediation of contaminated groundwaters.

gether by extracellular polymers, that coats a supporting substrate. It is these biofilms, as they are known, that are the fundamental active unit of biodegradation. A collaboration between Leonard W. Lion, of the School of Civil and Environmental Engineering, Michael L. Shuler, of the School of Chemical Engineering, and William C. Ghiorse, of the Section of Microbiology, seeks to develop a mechanistic understanding of how the components of biofilms contribute to their effectiveness in waste-treatment systems.

Engineering Better Organisms for Bioremediation

The tools of molecular biology and genetic engineering may contribute substantially to the progress of bioremediation. A knowledge of both the molecular mechanics of enzymatic attack and the influence of molecular structure on the biodegradability of synthetic chemicals is essential for augmenting the detoxification capabilities of bioreactors. Once such matters are understood, it becomes possible to optimize conditions under which reactions take place or to

engineer microorganisms that carry out these reactions more efficiently.

In a few well-defined instances there is already enough biochemical and genetic information so that the efficiency with which microbes metabolize pollutants can be improved through genetic engineering. A research group working under K. N. Timmis, in Braunschweig, Germany, has redesigned the genes of an aerobic bacterium, increasing its ability to attack aromatic compounds. Jane Gibson, of Cornell's Section of Biochemistry, Molecular and Cell Biology, is engaged in similar work, together with former Cornellian C. S. Harwood, who is now at the University of Iowa. Gibson and Harwood worked out the biochemical steps used by *Rhodopseudomonas palustris*, a photosynthetic bacterium, to degrade aromatic compounds under anaerobic conditions. Then, using molecular methods, they identified the genes that code for metabolism of these compounds. Ultimately, they hope to construct bacterial strains that can utilize toxic compounds more rapidly.

Once the molecular details of microbially mediated reactions are adequately understood, rapid advances are possible through genetic engineering. Work carried out by David Wilson, of the Section of Biochemistry, Molecular and Cell Biology, provides a good example of what can be done. First, Wilson deciphered the structure and function of enzymes that convert the polymers found in cellulose into their constituent subunits. Then he identified the genes involved in cellulose biodegradation and engineered a cellulose-degrading enzyme with a ten-fold increase in activity. This suggests the impact that molecular techniques may have on bioremediation.

"Society now faces the challenge of using the same tools of science, technology, and engineering that have created environmental pollution to help eliminate it."

Perspective on the Future

The very idea of "bioremediation" is a commentary on the state of industrial society. Remedies for problems of environmental pollution can only be necessary because the biodegradation capabilities of naturally evolved microorganisms have become inadequate. Society now faces the challenge of using the same tools of science, technology, and engineering that have created environmental pollution to help eliminate it. But there is reason for optimism, for bioremediation is a powerful tool, and further research and development can only make it stronger.

Eugene L. Madsen is a senior research associate in the Section of Microbiology in Cornell's Division of Biological Sciences. He holds undergraduate degrees from Oregon State University and the University of California at Santa Cruz; he earned the master's and doctorate at Cornell.

After completing his Ph.D. in soil science, microbiology, and ecology, Madsen held postdoctoral appointments at Rutgers University and Pennsylvania State University. He also served as senior microbiologist at MSI Detoxification Inc., in Bozeman, Montana, before joining the research staff at Cornell in 1989. Madsen's research interests include groundwater microbiology, microbial metabolism of organic pollutants, and strategies for measuring microbiological processes in situ. He is a member of the Panel on In-Situ Bioremediation, which is a committee of the National Academy of Science's Water Science and Technology Board.

Useful Solvents from Dairy Wastes

by Jean B. Hunter

The best way to dispose of waste materials does not just render them harmless, but makes them into something useful. This is the rationale behind a broad effort, in the Department of Agricultural and Biological Engineering, to find ways of making value-added products from food and agricultural wastes.

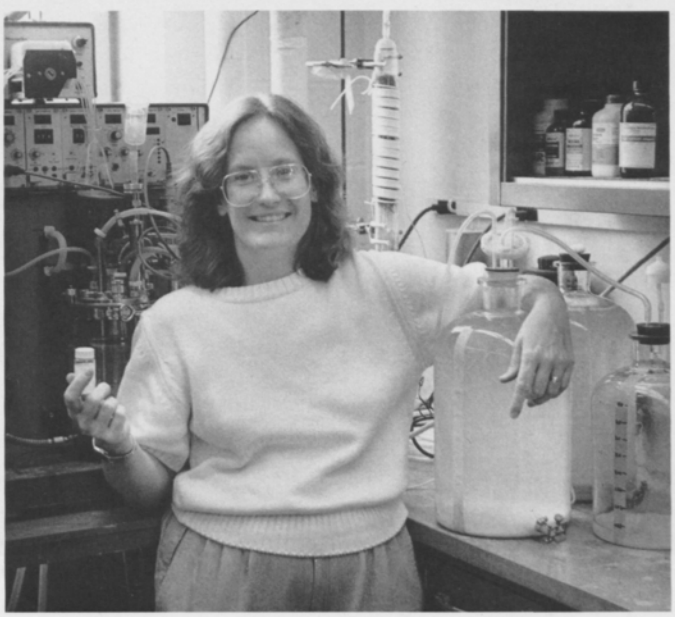
A case in point is research aimed at deriving acetone, butanol, and ethanol from whey, a waste product that results from the manufacture of cheese. Valuable proteins are usually removed by ultrafiltration, but the residual whey permeate still contains 3 to 5 percent lactose, 0.2 to 1 percent lactic acid, and up to 1 percent salts. This is a significant source of pollution in regions with a substantial dairy industry, in part because of its high biological oxygen demand (BOD), which is in the range of 30,000 to 50,000 parts per million.

A technique that promises to derive useful solvents from whey while rendering the balance of the waste stream relatively harmless involves biodegradation with the soil bacterium *Clostridium acetobutylicum*. First isolated by British microbiologist Chaim Weizmann, who later became the first president of Israel, this microorganism will metabolize both lactose and lactic acid, will tolerate high acidity, and will work efficiently with a dilute substrate.

Unlike fermentation with yeast to produce ethanol, fermentation with *C. acetobutylicum* proceeds in three stages. Initially, the bacteria take in sugars and give off acetic and butyric acids, reproducing rapidly. As acid concentrations attain toxic levels, the bacteria switch to a new metabolic strategy, reassimilating the acids along with the remaining sugars to produce solvents (acetone, butanol, and ethanol), while growing very slowly. As the end of fermentation approaches, the combination of butanol toxicity and nutrient depletion causes the cells to produce spores and then die.

In a continuous fermentation process, bacteria in all three metabolic states are present, and overall productivity is sensitive to the relative equilibrium among the three populations.

With the help of my students, Irshad Ahmed, Francisco Diez-Gonzalez, and Armando Solis, I have undertaken research to gain a better understanding of how *C. acetobutylicum* interacts with its environment, in the hope of engineering an economical process for continuous solvent production from whey permeate. We are also looking for energy-efficient methods to recover butanol directly from the fermentation. By selective removal of the volatile solvents, we can reduce their toxic effects and increase the rate of solvent formation.



Our current system incorporates a two-stage continuous process, in which a small acidogenic fermentor feeds a larger solventogenic fermentor. Part of the slow-growing solventogenic cells from the second stage are recycled. In this way we have achieved cell densities that are three to five times greater than those attainable in cultures that do not involve recycling, with a production of up to 1.2 grams of butanol per hour, per liter of fermentor volume. By gas stripping of culture broth in a packed column, we have recovered a two-phase condensate, one phase containing 80 percent butanol by weight. We are now trying to increase the rate of butanol removal so that it keeps pace with the rate of butanol synthesis.

We do not expect solvents produced from whey to be cheaper than those synthesized from petrochemicals. But profits from these materials could certainly defray the cost of cleaning up whey permeate before it is discharged into the environment.

Jean B. Hunter is an assistant professor in the Department of Agricultural and Biological Engineering.

THE BIOLOGICAL PHYSICS OF CELLS

Research in the Developmental Resource for Biophysical Imaging Optoelectronics

by Watt W. Webb

". . . it has been necessary to pioneer new techniques in order to study the molecular dynamics of cellular functions."

In living cells, a very small number of macromolecules—sometimes only one—can stimulate a global response. The signals generated by sparse molecular receptors are so tiny that they are often obscured by the complex chemical environment of the whole cell's life processes. The experimental demands of this fundamental frontier frequently exceed the best available measurement capability, and it has been necessary to pioneer new techniques in order to study the molecular dynamics of cellular functions.

Several years ago, the universal significance of biological problems began drawing my research interests away from popular problems in condensed-matter physics. The sensitive experimental strategies that I had developed for observing the dynamics of small numbers of particles, atoms, molecules, or photons in tiny mesoscopic systems appeared ideal for studying molecular signals in living cells. Experience has validated this concept, and over the years my colleagues and I have studied molecular mechanisms of transmembrane signaling, sensory transduction, possible molecular mechanisms of memory, regulation of development, mechanisms of gene regulation, biomolecular motor mechanisms, and function of membrane receptor molecules. This paper summarizes some recent accomplishments of graduate students, postdoctoral associates, and collaborators working in my laboratory.

How Protein Molecules Percolate and Perambulate on the Cell

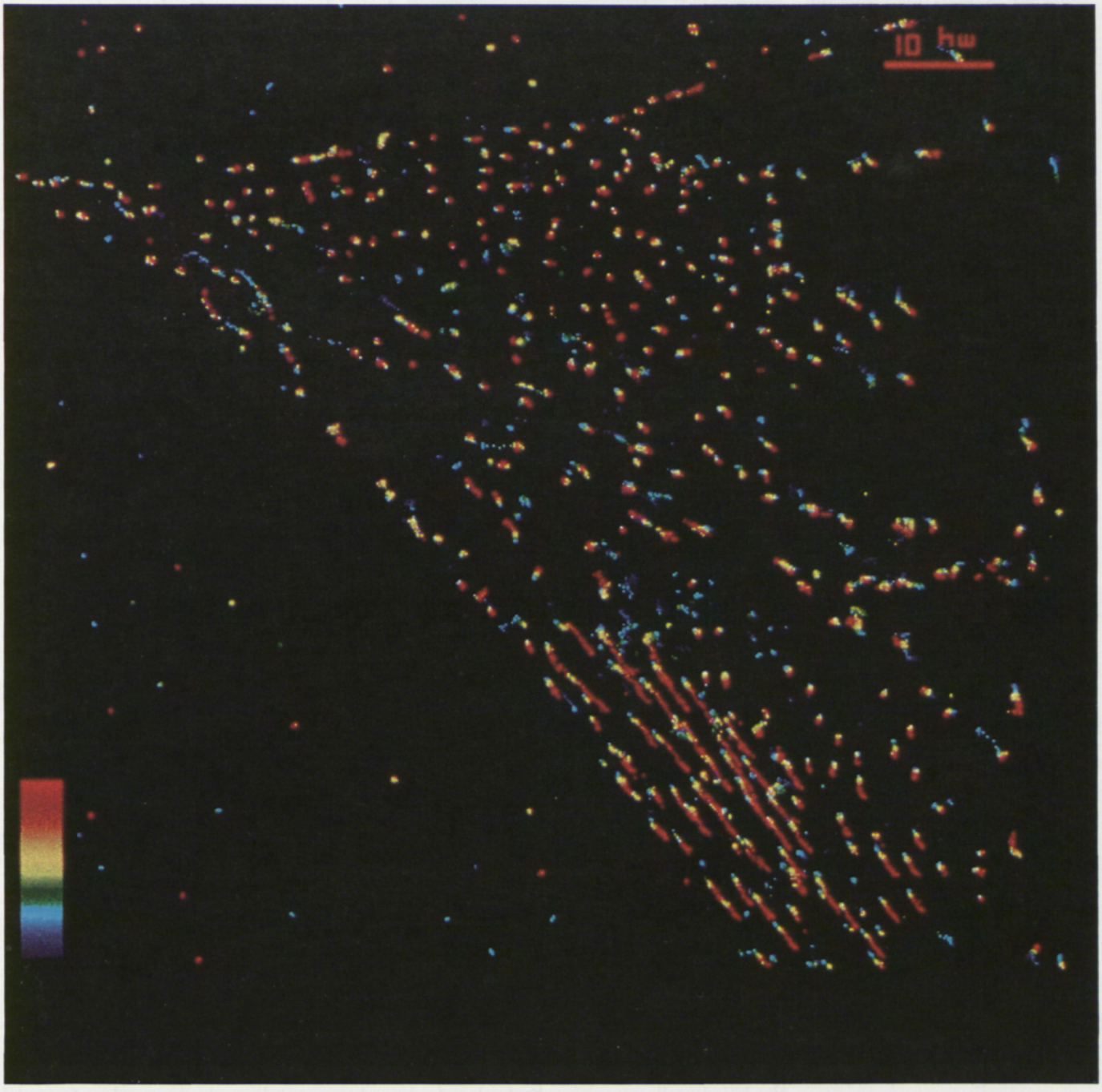
The microscopic motion of macromolecules on and in living cells is necessary for the intense traffic of information that governs cellular function. An important example is the diffusion of the low-density lipoprotein (LDL) molecule on the cell surface, which plays a part in the regulation of serum cholesterol—a function that is essential to health. Earlier experiments had shown that the diffusion of nearly all cell-surface proteins is orders-of-magnitude slower than fluid physics would predict for a two-dimensional lipid membrane. So the questions arose: What are the extra restraints, and what is their biological significance? To study this problem, a bright fluorescent marker for LDL was developed. This made it possible to detect and locate individual receptor molecules to within 30 nanometers. With the help of digital technology for image acquisition and processing, as well as new computer algorithms, thousands of LDL receptor molecules were tracked simultaneously as they followed trajectories on the surface of human cells with mutations that cause hypercholesterolemia.

This research showed that cell-surface protein diffusion is generally restricted by random energy barriers through which the molecules percolate (see Figure 1). Biological regulation of these percolation barriers appears to be an active, energy-consuming process whose molecular origins have yet to be understood. Active biomolecular motors not only drive flows involving a number of neighboring molecules, but also the independent motions of single molecules.

In a collaboration with chemistry professor Barbara Baird and her student James Slattery, my graduate students, Ingrid Brust-Mascher and Toni Feder, have found that simple thermally activated percolation accurately describes the restrained diffusion of the immunoglobulin E receptor, which binds allergen particles. In fact, we think the same physical mechanism accounts for most restraints on cell-surface diffusion. New research aims to identify the molecules involved in the diffusive restraints and in the active locomotion of some cell-surface molecules.

Figure 1. Low-density lipoprotein (LDL) molecules on a living cell. LDL molecules, which contain cholesterol, attach themselves to the cell surface at LDL-receptor sites and then unload their cargo into the cell. They migrate along the surface and cluster together before making a delivery.

This image shows LDL molecules that were treated so that they would fluoresce under the microscope. One hundred fifty exposures, made 1.6 seconds apart, were colored to show the movement of the LDL molecules from blue, at the beginning of the run, to red, at the end. Note how a number of molecules are moving in a coordinated fashion at the upper right, while many others are relatively quiescent, and a few are moving independently.



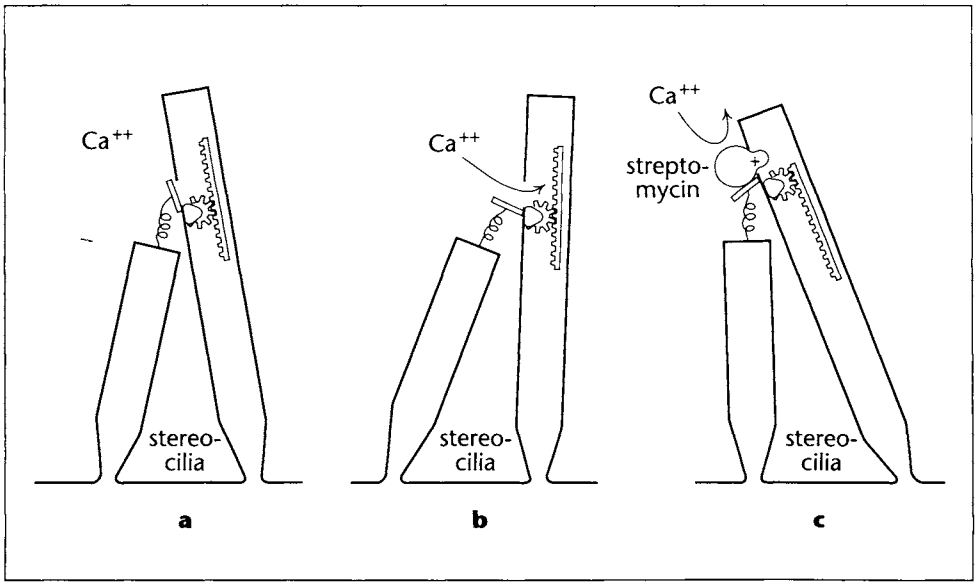


Figure 2. A model of the mechanosensitive ion channel responsible for auditory transduction in the inner ear. There are fifty channel molecules per hair cell, in the walls of the stereocilia that compose the hair bundle. A stretch-sensitive ion channel, shown in the closed position in (a), is opened by the displacement of the stereocilia (b). This allows calcium ions to enter the cell, sending a signal to the auditory nerve. If a streptomycin molecule lodges in an open ion channel (c), calcium ions can no longer enter and the transmission of auditory signals is interrupted.

Transduction between Mechanical, Chemical, and Electrical Energy

Two kinds of mechanical transduction are common in biological cells: chemomechanical and mechanoelectrical. The molecular motors that empower muscle and cellular mobility are chemomechanical transducers. They convert chemical energy from the hydrolysis of ATP (adenosine triphosphate) into the mechanical work of the muscles. Mechanoelectrical transducers vitalize the sensory processes in the inner ear that make possible the perception of sound and acceleration.

Auditory transduction depends on a microscopic organelle, the hair bundle, that is displaced by the motion of fluid in the inner ear and stimulated to generate an electrical signal. To learn more about the molecular mechanisms of this process, Winifried Denk, a former graduate student, developed a microinterferometer capable of detecting the displacement of a hair bundle on a subatomic scale. He demonstrated that hair-bundle displacement opens a stretch-sensitive ion channel in the cell membrane, increasing the flow of ion current through the membrane, depolarizing the cell and transmitting a signal to the nervous system. This mechanoelectrical transduction mechanism is so sensitive that spontaneous thermal motion of just a few nanometers causes the hair bundle to generate a background noise that acts as a threshold to audibility.

Denk and I also studied the effects of streptomycin, an antibiotic that has long been known for its ototoxicity, in order to probe the molecular properties of the mechanosensitive channel. Our work showed that streptomycin molecules inhibit the mechanical motion that closes the ion channel, and established the statistical thermodynamics of the mechanosensitive molecular mechanism of auditory transduction (see Figure 2).

Mechanosensitive ion channels have also been found in cells that play no part in sensory perception. While working to determine how they function, graduate student Lorinda Opsahl discovered mechanosensitivity in a fungal peptide antibiotic, alamethicin, which she introduced into a pure lipid membrane. The alamethicin molecules formed channels through the membrane by joining together like the staves of an open-ended barrel. To study the mechanosensitivity of the channels, she used a patch of membrane as a barrier between two volumes of salt water that contained extra alamethicin. When the patch is stretched by applying a pressure difference, work done by tension in the membrane adds more staves, increasing the diameter of the channels and allowing more ions to pass across the membrane. This simple mechanochemical transfer of molecules between salt water and membrane may be a factor in the mechanosensitivity of cells.

Two-Photon Laser Scanning Fluorescence Microscopy

Confocal laser microscopy has long provided a powerful quantitative tool for measuring molecular concentrations and motions in cells. The specimen to be examined is treated with a fluorophore—a substance that will fluoresce when appropriately excited. A laser beam is then focused through a microscope in such a way that it narrows down to a focal point at the apex of a cone of light and then expands in the form of another cone. The laser excites the fluorophore—most strongly at the focal point, which is fixed on the intended target. A pinhole in the image plane cuts out most of the extraneous background fluorescence and limits the visible image to a small area around the focal point. If the focused beam is made to scan the specimen in a raster pattern, the resulting fluorescence can be digitized by a computer and used to compose a detailed image on a television screen. If such images are made at a succession of different depths within the specimen, a three-dimensional model can be constructed.

Unfortunately, this method has one problem: the double cone of laser radiation excites molecules, creating background fluorescence and inducing photodamage, all along its path through the specimen—even though the light that reaches the detector is limited by the pinhole filter to only that coming from the small focal volume at the apex of the cone. To excite photochemical reactions only at the focal point (and incidentally, to overcome the bleaching problem), I worked with graduate students Winifried Denk and James Strickler to develop two-photon excitation for laser scanning fluorescence microscopy.

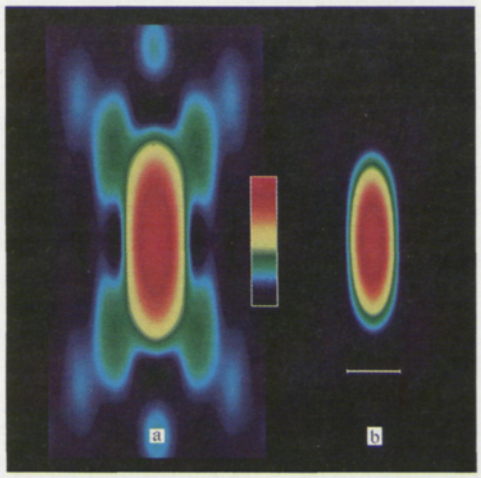


Figure 3. A comparison of one- and two-photon laser microscopy. These computer-generated images represent excitation profiles perpendicular to the focal plane. The color shows the range within which fluorescence occurs, with decreasing intensity from red to blue. With one-photon microscopy (a), considerable fluorescence occurs in the cones of light on either side of the focal point (the blue and green regions). With two-photon microscopy (b), the area of fluorescence is confined to a narrow ellipse.

This technology is based on a simple concept in nonlinear optical physics that was first explained by Maria Goeppert-Mayer in 1931, but had no practical application until the recent development of femtosecond-pulse mode-locked lasers. A molecule that will fluoresce when excited by a single photon in the ultraviolet range may also fluoresce when excited by two photons of red light—each with half the energy—provided they arrive at essentially the same time. When a stream of 100-femtosecond pulses of red laser light is strongly focused in a microscope, enough photons ar-

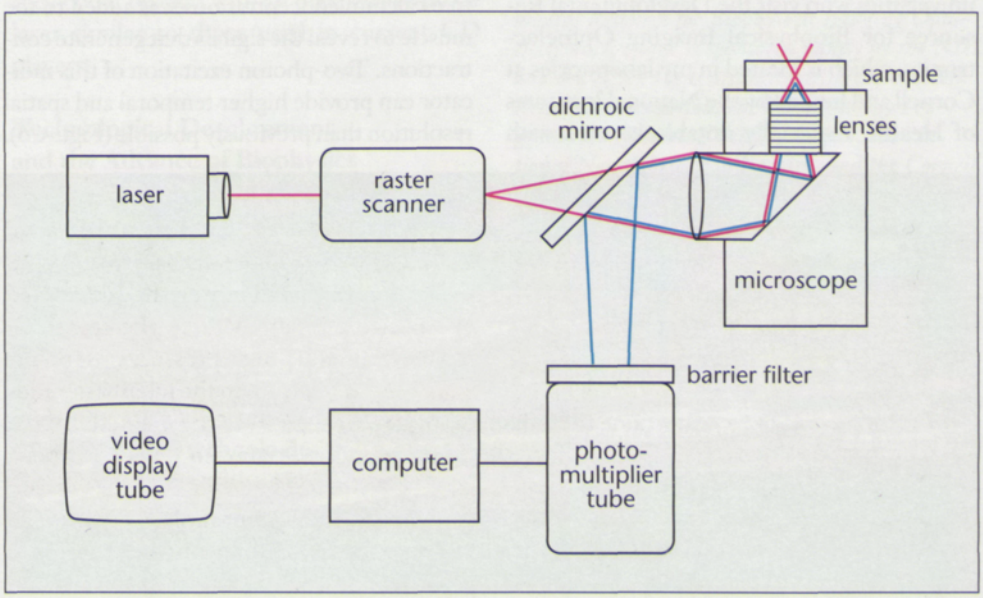


Figure 4. A schematic representation of the two-photon laser scanning microscope. A narrow laser beam, made to move in a raster pattern, passes through a dichroic mirror on its way to the microscope, where it is focused down to a size capable of scanning features on a single cell. The fluorescence that the laser beam provokes passes back through the microscope to the dichroic mirror, where it is reflected into a photomultiplier tube through a barrier filter that removes unwanted wavelengths. Information from the photomultiplier tube is fed into a computer, which organizes it into a raster pattern that produces an image on the video display tube.

rive at the focal point simultaneously for some pairs to activate the fluorophore, producing an image. Inasmuch as the probability of fluorescence increases quadratically with the intensity of excitation, fluorescence is practically limited to the focal point. This means that a crystal-clear image is produced without the need for a pinhole to mask out extraneous fluorescence, and cellular damage does not extend through the entire specimen.

Nonlinear laser microscopy utilizing two-photon excitation provides remarkable measurement capabilities for biophysical research applications. Three-dimensional diffusion of fluids inside cells can be measured by photobleaching a fluorescent marker in the tiny ellipsoidal focal volume and measuring the rate at which fresh fluorophore diffuses in to replace it. Caged neurotransmitters and bioeffector molecules (such as carbamylcholine, ATP, cyclic nucleotides, inositol triphosphate, calcium and magnesium ions) can be released photolytically with great precision at specified locations where treatment is desired. The first practical imaging of fluorescence decay times has recently been achieved with two-photon excitation in the laser scanning microscope; this was accomplished by David Piston, a postdoctoral associate, and David Sandison, a graduate student in my laboratory.

Several important biological applications have been pioneered through a collaboration between Piston and biophysicists from other universities who visit the Developmental Resource for Biophysical Imaging Optoelectronics, which is located in my laboratories at Cornell and funded by the National Institutes of Health. Especially notable is work with

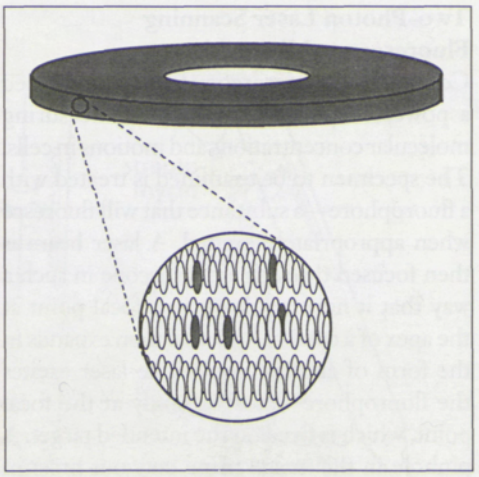


Figure 5 (right). Three-dimensional information storage on an optical disk. Multiple layers of refractive dots could hold up to 10^{12} bits of information per cubic centimeter in a write-once, read-many format.

Robert Summers of the State University of New York at Buffalo, which involved imaging the chromosomes in the developing embryos of sea urchins—and following the cells as they go through several successive stages of mitosis. The goal of this work is to detect the first systematic clues in the organization of the embryo that guide its development into the complete animal.

In addition, collaborative studies with Jon Lederer of the University of Maryland School of Medicine have used two-photon microscopy to analyze physiological signaling in individual heart-muscle cells. To show the energy state of the muscle cell, high-resolution maps of oxygen potential were made using NADH (nicotinamide-adenine dinucleotide) fluorescence. Also, a fluorescent indicator of free calcium concentrations was added to the muscle to reveal the signals that generate contractions. Two-photon excitation of this indicator can provide higher temporal and spatial resolution than previously possible (Figure 6).

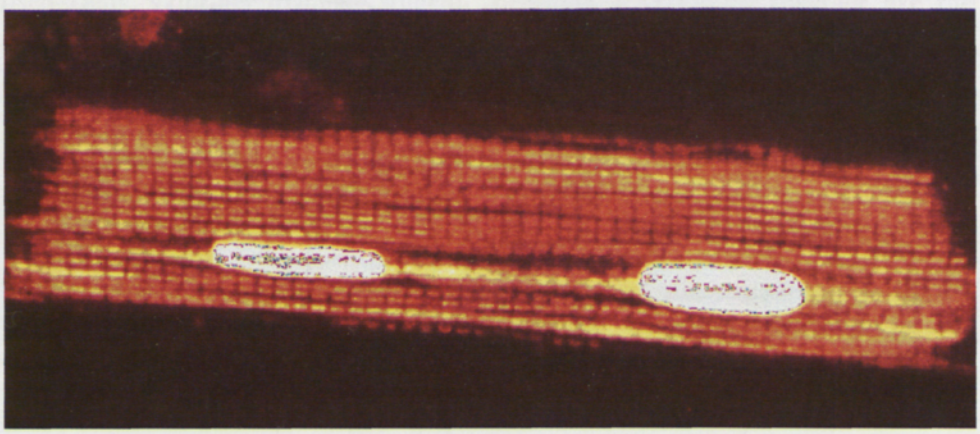


Figure 6. A living heart-muscle cell as imaged with a two-photon scanning laser microscope. The two whitish areas are the cell's nuclei. The little yellow rectangles are mitochondria, which store energy. The dark vertical bands between the mitochondria are sarcomeres,which show the periodicity of the contractile structure. The associated sarcoplasmic reticulum releases calcium ions when stimulated by an electric pulse, causing the muscle fibers to contract.

A Spin-Off with Implications for Information Technology

An unexpected spin-off into a nonbiological application is being advanced by graduate student and entrepreneur James Strickler. He has found that two-photon excitation of ultraviolet-sensitive photoresist polymers can create internal dots of increased refraction that can be detected by laser scanning microscopy. This effect makes possible three-dimensional optical information storage using multiple layers of dots. The dots can be as small as 1 cubic micron, permitting up to 10^{12} bits of information per cubic centimeter to be stored in a write-once, read-many (WORM) format similar to magneto-optical disk memory (see Figure 5).

Presently, commercial development of the WORM may be inhibited by the high cost and complexity of the 100-femtosecond writing laser. While the potential of two-photon laser microscopy for biomedical research can justify the expense of the lasers currently in use, the commercialization of multilayer WORM media calls for the development of more affordable 100-femtosecond, 100-megahertz, pulsed mode-locked lasers.

The refractive dots are read by a scanning differential-interference-contrast (DIC) laser microscopy that is capable of detecting changes in refraction of 1 percent. Disks with about thirty layers of optical memory could be manufactured with an adaptation of the technology currently used for ROM compact disks, and they could be read with an inexpensive diode laser similar to those used in current CD players.

Technological Development and the Advance of Biophysics

The ability to conduct "impossible" experiments in biological physics has been advanced by new technologies that make it possible to observe individual molecules in membranes of living cells, to map subnanometer motions, and to conduct, at the submicron level, analytical chemistry and chemical surgery or pharmacology on living cells. Modern physical optics, new laser technologies, and interactive digital computers with massive memories all play a part. Further technological developments can be expected to open up a new era of research on the physics of the life process.

Watt W. Webb is a professor in the School of Applied and Engineering Physics and the Division of Biological Sciences. A specialist in biophysics and chemical physics, Webb was educated at the Massachusetts Institute of Technology, earning the B.S. degree in engineering administration in 1947 and the Sc.D. in metallurgy in 1955. Engineering development at Union Carbide Corporation, before his doctorate, led to subsequent research in solid-state physics. When he left to join the Cornell faculty in 1961, he was the assistant director of research.

At Cornell, Webb is director of the Developmental Resource for Biophysical Imaging Optoelectronics, which is sponsored jointly by the NIH and the NSF. He is affiliated with the Cornell Research Foundation, the Biotechnology Program, the Materials Science Center, the National Nanofabrication Facility, and the Cornell National Supercomputing Facility. He has been a Guggenheim fellow and a scholar in residence at the NIH Fogarty International Center for Advanced Study. He is a fellow of the American Physical Society (APS) and the American Association for the Advancement of Science, and a founding fellow the American Institute for Medical and Biological Engineering. He is also a member of the American Society for Cell Biology, the Biophysical Society, the Society of General Physiology, and the Society of Photo-Optical Instrumentation Engineers. In 1991 he received the $5,000 Biological Physics Prize from the APS in recognition of his work.

"Further technological developments can be expected to open up a new era of research on the physics of the life process."

Squeezing Blood Cells

Biological Research with Nanofabrication

by Harold Craighead and Richard E. Waugh

Red blood cells are produced in bone marrow. When they are mature, they pass through small pores in the marrow's endothelial cells, which separate the tissue compartment from the circulatory system. For the body to keep the proper number and type of blood cells in circulation, they must not be released too early. Researchers have noticed that the deformability of blood cells increases as they mature, and it seems likely that this is part of the mechanism by which the release of cells is regulated. Immature cells apparently remain in the marrow until they are flexible enough to squeeze through the pores.

Since the marrow is not accessible for observation, we designed an experiment to test this hypothesis in vitro. Making use of the microfabrication technology available at the National Nanofabrication Facility, we developed a system that enabled us to measure the physical requirements for the passage of cells through pores.

To fabricate a pore of the right dimensions, we began by thinning down part of a silicon wafer to produce a window about one micron thick, using photolithography and anisotropic etching. Then we used electron beam lithography and reactive ion etching to cut through this window, forming a pore at the center of a tiny disk that remained attached to the surrounding silicon at two points (see Figure). The disk was glued to the tip of a glass micropipette with a water-resistant adhesive and then freed from its matrix.

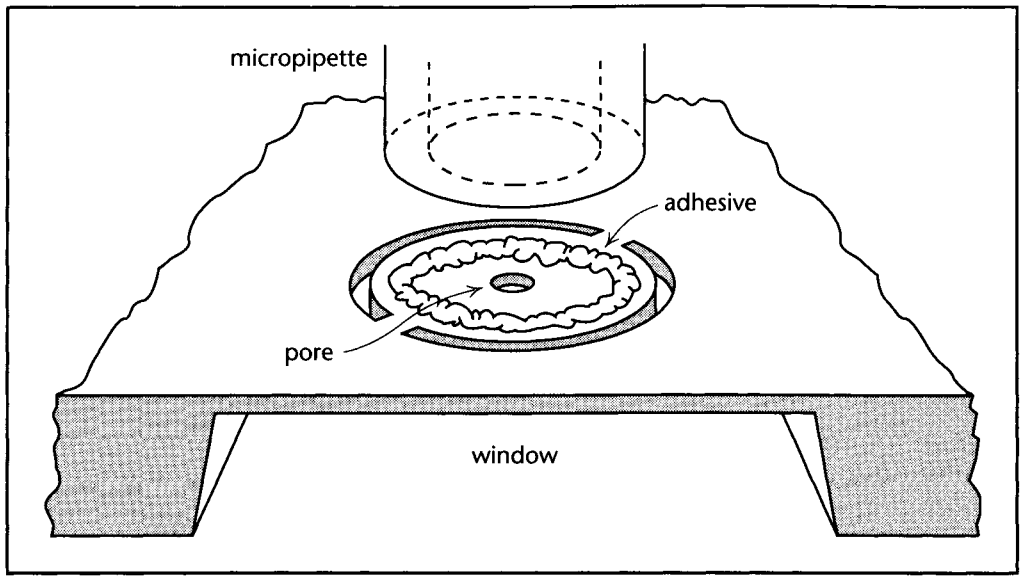
To conduct the experiment, we inserted the pipette with the pore on its tip into a chamber on the stage of a light microscope. Both the pipette and the chamber were filled with physiological saline. Blood cells were put into the chamber and pressure in the pipette was lowered so that they would be sucked toward the pore. The pressure difference was controlled with a water manometer so that we could look at the time it took for a cell to get through the pore as a function of the driving pressure. In addition, we used pores of different sizes.

We found that the pressure and time required for a cell to traverse the pore increased, as expected, with cell stiffness. Variation among immature cells was considerable—probably reflecting variation in relative maturity within the population. But the difference between immature cells and mature cells was significant.

If a pore had a diameter of 1.4 microns and the pressure was about 2 percent of that generated by the heart, all of the mature cells—and none of the immature cells—would pass through. This ability to differentiate between cells of differing deformability increases when the pore is smaller and diminishes when the pore is bigger. It is thought that the body deals with blood loss or anemia by opening the pores in the marrow endothelium to release more blood cells. Judging from our experiments, this should result in more immature cells entering the circulatory system—a fact that has been clinically observed.

More work will be required to explore all the ramifications of pore size on the supply and quality of blood cells, but the results we have already obtained clearly support the view that cell deformability plays a central role in controlling the release of red blood cells from bone marrow.

Harold Craighead is a professor in the School of Applied and Engineering Physics and director of the National Nanofabrication Facility. Richard C. Waugh is an associate professor in the Department of Biophysics at the University of Rochester.



SURROGATE ANIMALS FOR LABORATORY TESTS

by Michael L. Shuler

Current procedures for determining the toxicity of hazardous chemicals leave much to be desired. The most common way to assess the risk of both natural and synthetic compounds is to observe their effects on live animals, such as rats and mice. But in addition to raising troublesome ethical questions, this technique yields results that are expensive to obtain and difficult to interpret.

One serious methodological problem involves cross-species extrapolation. As shown in Table I, it takes hundreds of times more dioxin to kill hamsters than to kill guinea pigs. Other species fall between these extremes, but it is hard to know which species' sensitivity is most similar to that of humans.

Another problem is extrapolation to low doses. If we want to know what dosage will cause but one new cancer per million, we would need, for a statistically valid estimate, more than ten million animals. Since this is not feasible, it is customary to determine the effect of a relatively high dose on a smaller number of animals. An extrapolation over three or four orders of magnitude is then made from this data.

Because of these impediments to a straightforward interpretation, it is necessary to make assumptions about how laboratory findings apply to human beings. A man is not just a big mouse. Extrapolation requires models that take into account differences in sensitivity, relative size, and dosage. This is a serious matter, for different models can result in widely varying regulatory limits (see Table II).

These problems illustrate the need to understand mechanisms of toxicity at the molecular level as well as relate them to whole-animal physiology. Lisa Sweeney, Naheed Mufti, John Babish, and I have been working in this direction. We are building a model that will allow the rational prediction of toxicological responses to varying doses in humans.

A Cell-Culture Analog to a Computer Simulation

One way to avoid the difficulties of research with live animals is to use a computer simulation. Physiologically-based pharmacokinetic models (known as PBPKs) have been developed to predict the distribution and biotransformation of drugs. These computer models, which incorporate many principles of chemical engineering, divide the body into various compartments that correspond to different

". . . different models can result in widely varying regulatory limits."

Table I
DIFFERENCES IN TOXICITY AMONG SPECIES

Species	*LD_{50} (TCDD mg/kg)**
Guinea pig	0.6–2.5
Mink	4
Rat	22–320
Monkey	<70
Rabbit	115–275
Mouse	114–280
Dog	>100–<3,000
Hamster	1,150–5,000
Human	?

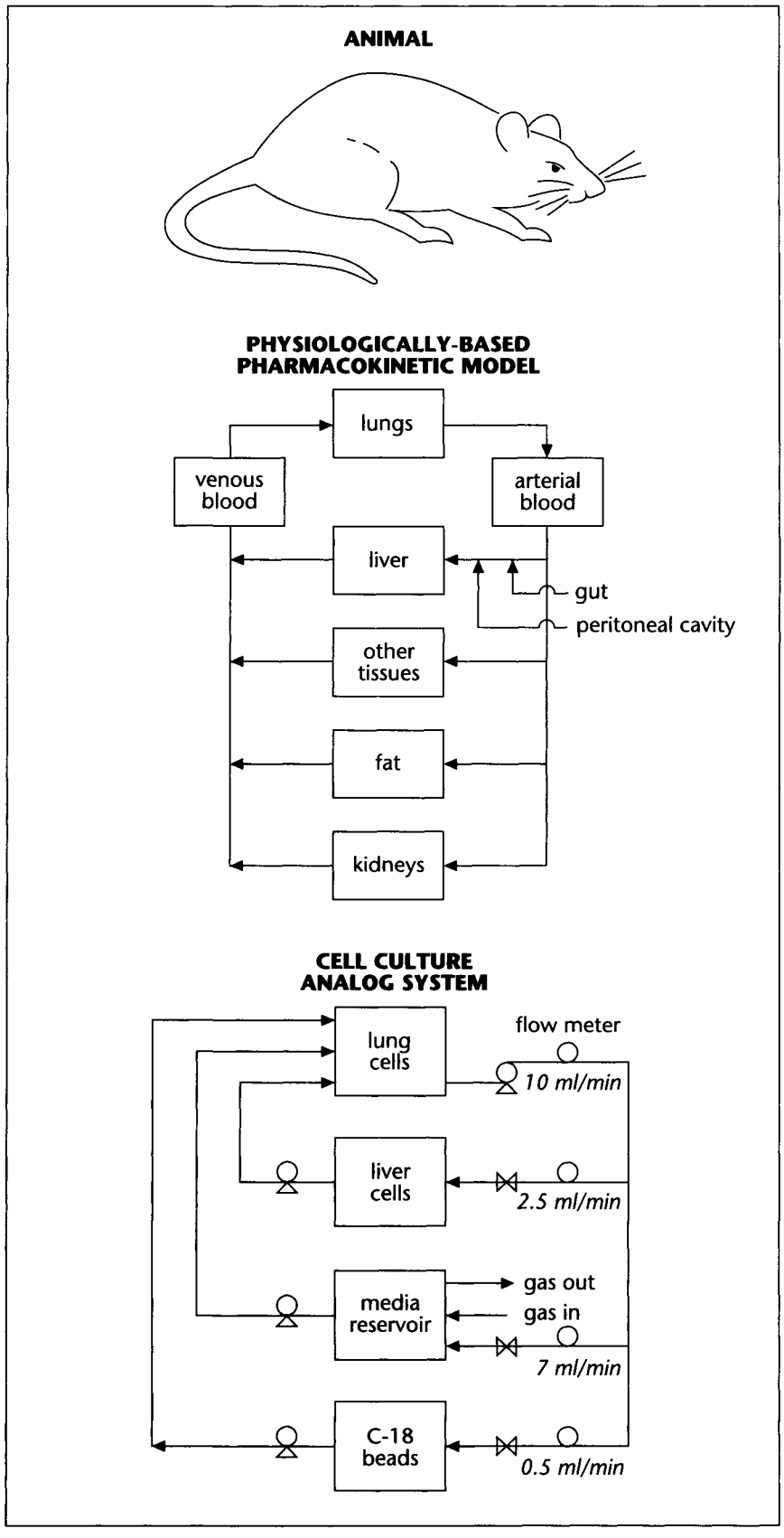
** The dose of TCDD (dioxin) that causes death in half the subjects, in milligrams per kilogram.*

Table II
ACCEPTED LEVELS OF TCDD INTAKE

Country/ organization	*Picograms per kilogram of body weight per day*
United States (E.P.A)	0.006
Germany	1.0
Netherlands	4.0
Canada	10.0
World Health Organization	10.0

Differences between species in the toxicity of TCDD (a kind of dioxin) leads to sharply differing estimates of what is safe for humans.

Figure 1. Three systems for evaluating toxicity.



types of tissue. Compartments that simulate the function of organs such as liver, lungs, muscle, fat, and kidneys are connected by a simulated circulatory system. The model includes realistic estimates of organ size and flow rates between compartments, as well as algorithms to predict the concentration in each compartment. The effects of a particular drug or chemical can be studied by inputting its kinetics of conversion.

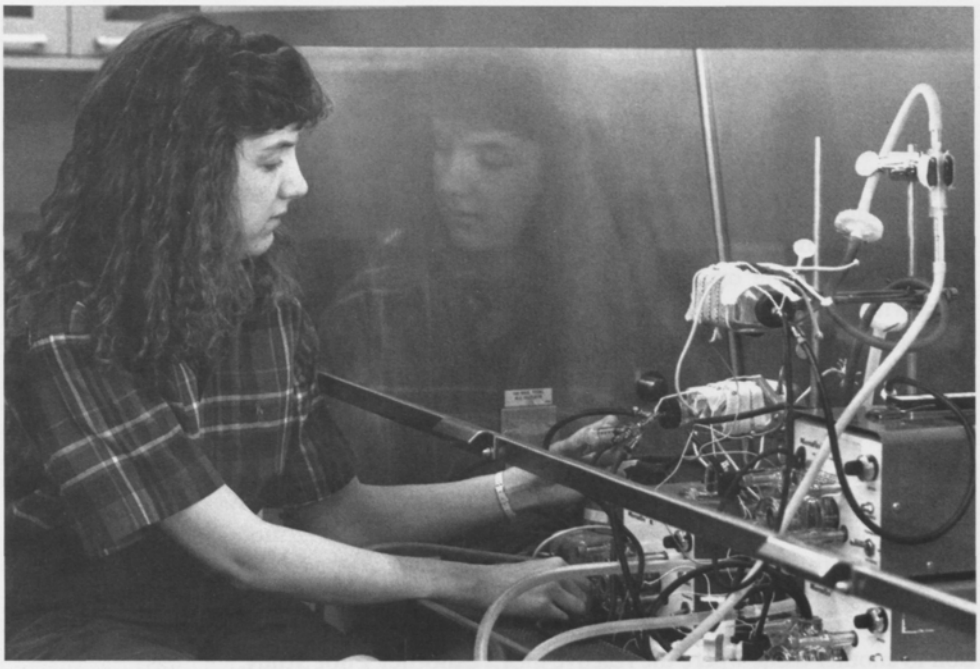
So far, the usefulness of PBPK models has been limited. They describe well the flow between organs, and they are generally satisfactory in describing the ingestion, inhalation, or absorption of a compound. Thus, they have aided in determining the best doses and schedules for administering chemotherapeutic drugs. But PBPK models have not lent themselves to good a priori predictions of metabolism or secondary chemical reactions.

One day in 1989, when I was preparing for a visit from Lisa Sweeney, who was about to begin graduate study with me, I suddenly realized that it would be possible to build a cell-culture analog of a PBPK. Where a PBPK model specifies a liver compartment, the cell-culture analog would have a chamber with living liver cells. Instead of a mathematical connection between symbolic compartments, the analog system would have multiple interacting chambers with a circulating culture medium.

The Advantages of Testing with Surrogate Animals

An apparatus containing interconnected cell cultures of various organs can be thought of as a surrogate animal. It offers a number of advantages over testing procedures that depend on live animals, PBPK models, and other in-vitro techniques.

The use of cell cultures means that metabolism is accurately represented. By simply measuring concentrations in and out of a cell chamber, "black box" kinetics can be determined, and interactions among cell types can be observed. In addition, cells can be removed from the chambers for examination. The induction of enzyme systems, changes in genetic information, and other processes can be monitored and related to hypotheses about mechanisms at the cellular level. Of course, cells cultured outside the body may not behave in precisely



Graduate student Lisa Sweeney works with a prototype cell-culture analog device.

the same way as they would inside the body, and conclusions need to be interpreted with this caution. Nevertheless, the cell-culture analog device can provide metabolic detail unavailable in a PBPK, and it should mimic real animals with unprecedented accuracy.

Most other in-vitro systems use cultures that contain only one type of cell, although a few use cells of multiple types. But in all of these methods, the fluid is static; and in none of them is the ratio of cell types to one another and to the fluid physiologically correct. Moreover, the cell-culture analog system differs from other in-vitro systems by allowing dosing in a manner that is directly analogous to animal studies (such as milligrams of chemical per kilogram of body-weight equivalent). Time-dependent responses can be followed. Different exposures and different routes of exposure can be simulated (such as eight hours of inhalation of a chemical at a specific concentration followed by sixteen hours of no exposure, or ingestion three times a day). Just as an animal is examined by a pathologist after such a study, the cell-culture analog system can be studied histologically.

With a metabolically, mechanistically accurate model, extrapolation to low doses can be done much more rationally. Such a system can be used with human cells as well as animal cells. As noted in Table 1, the dose of dioxin that would be lethal for fifty percent of a human population is unknown, and an experiment on humans to determine this value is ethically unthinkable. Yet similar experiments on both mouse and human cell analog systems can be done readily. Thus, the cell-culture analog system should greatly facilitate the extrapolation of dose response across species.

A Pilot Study of the Toxicity of Naphthalene

Realizing the need of additional expertise, Lisa Sweeney and I persuaded John Babish, of the Department of Pharmacology at the Cornell College of Veterinary Medicine, to join our team. With support from Cornell's Biotechnology Program and a starter grant from the National Science Foundation, the three of us have initiated studies to test the viability of the cell-culture surrogate animal.

One of our first efforts concerned the toxicology of naphthalene, a commercially important chemical derived from coal tar and petroleum. We knew that naphthalene had unusual species and tissue specificity. Mice are approximately seven times more sensitive to naphthalene than rats. The tissue-binding of radio-labeled naphthalene is not predictive of its toxicity among various cell types, although different levels of tissue binding with lung cells is correlated with toxicity.

It is thought that the toxic effects come, not from naphthalene itself, but from its oxides. The liver is rich in the enzyme family known as P-450 monooxygenases, and these enzymes catalyze the oxidation of the naphthalene. The Clara cells in the lungs are sensitive to these products, and the binding of naphthalene oxide to cellular protein is toxic. Naphthalene oxides can, however, react with glutathione to form a nontoxic product. Furthermore, naphthalene molecules can spontaneously rearrange themselves to form 1-naphthol, and they can be converted enzymatically to 1,2-dihydrodiol.

To investigate this relatively complex situation, we have used information available from the literature to construct a PBPK for a mouse challenged with naphthalene. This is the first PBPK to deal with the production of a reactive metabolite in one organ and its circulation to another tissue where the reactive metabolite can interact at a secondary site. The results of this computer simulation, in which no adjustable parameters were used, compare favorably with data from animals.

The PBPK model makes a number of important predictions that cannot be confirmed with existing data. It suggests, for example, that naphthalene toxicity is primarily due to reactive metabolites transported from the liver to the lung by the circulation of blood. This is a situation that can be studied with the cell-culture surrogate because it allows us to combine cell types from different species. A single component can be changed while the rest of the system remains the same. To find out the reasons for the difference in sensitivity between rats and mice, we can compare the performance of a system with a rat liver and a mouse lung, a mouse liver and a rat lung, or a mouse liver and a mouse lung. Moreover, liver-derived cells that preferentially produce a certain metabolite can be used to compare the toxicity of different metabolites of a single compound.

This research is currently being conducted using a prototype cell-culture analog device, shown schematically in Figure 1. The system has been operated successfully under restricted conditions with two different cell types, but more detailed studies remain to be done.

Another Pilot Study, on the Toxicity of Dioxin

In a parallel project, postdoctoral associate Xin-Fang Ma, graduate student Naheed Mufti, John Babish, and I are examining the toxicity of dioxin on human cells. We have found that TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) is responsible for the induction of P450IA1, one of the monooxygenase enzymes (also known as a cytochrome), through a complicated, multistep process (see Figure 2). Dioxin (TCDD) enters the cell by simple diffusion.

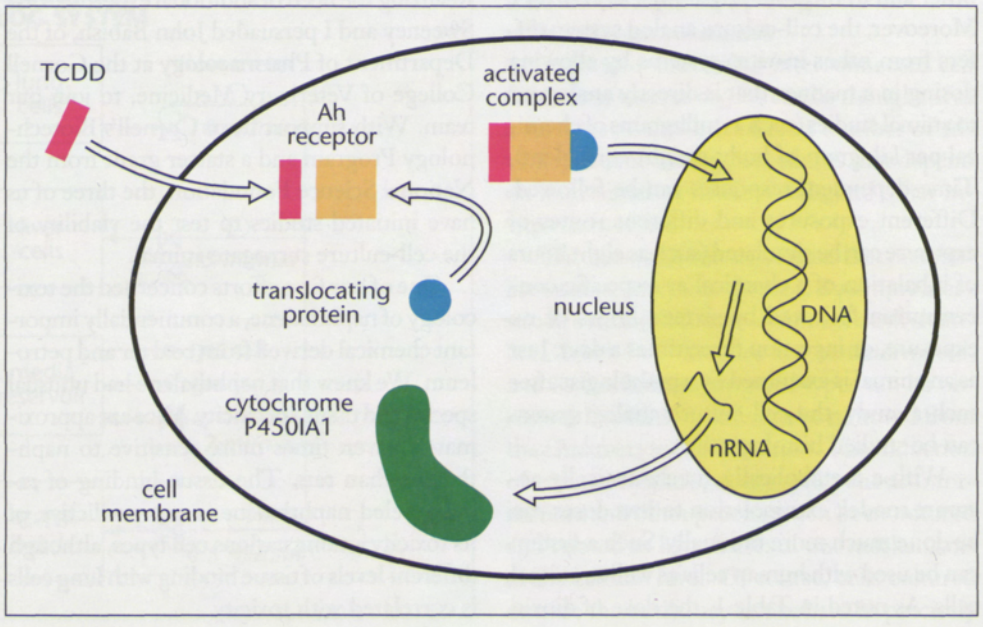


Figure 2. Induction of P450IA1. Dioxin (TCDD) enters the cell and joins a receptor protein and a translocating protein to form a complex that enters the nucleus, where it induces a messenger RNA molecule that serves as a template for the P450IA1 enzyme.

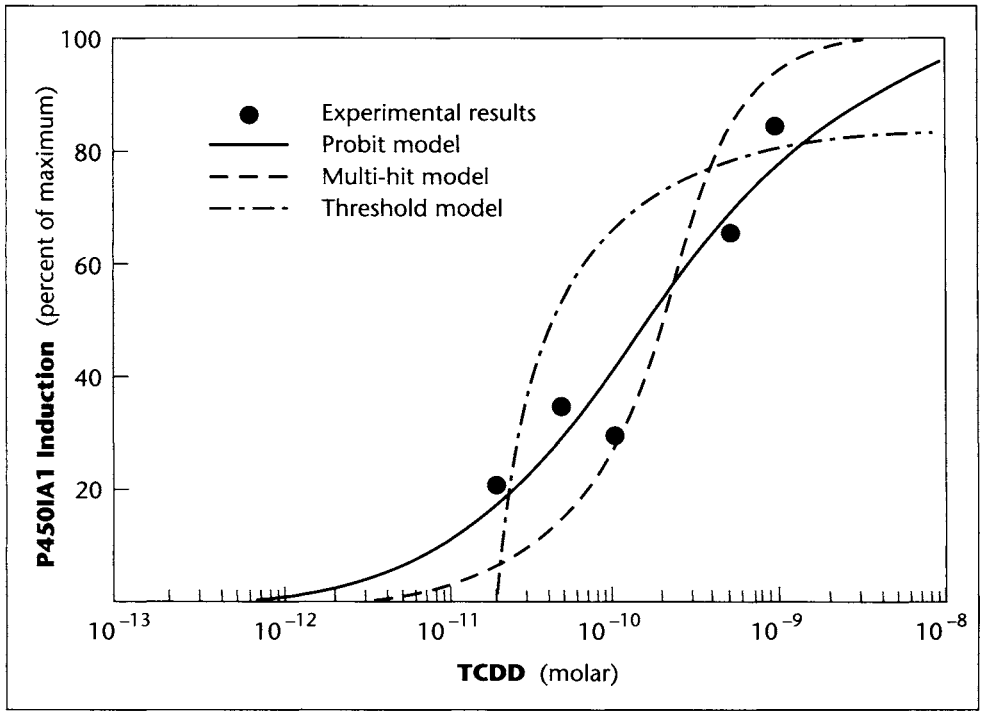


Figure 3. Three models used to define safe levels of dioxin compared with experimental results. In the Probit model, $P(D) = \Phi[(\log D - \mu)/\sigma]$, and in the Multi-hit model, $P(D) \simeq (\lambda D)^k/k!$, where $P(D)$ is the probability of a response at a particular dose level, Φ is the standard normal integral from $-\infty$ to x, μ is the mean, σ is the standard deviation, λ is an unknown rate constant, and k is the number of hits on a receptor required for a response. In the threshold model, there is no induction for doses less than a threshold value, D^*, while for higher doses, D, the response is $B \log (D/D^*)$, where B is a fitting parameter. The risk of exposure to TCDD (in picograms per kilogram per day), is 0.186 according to the Probit model, 0.041 according to the Multi-hit model, and 4.0 according to the threshold model.

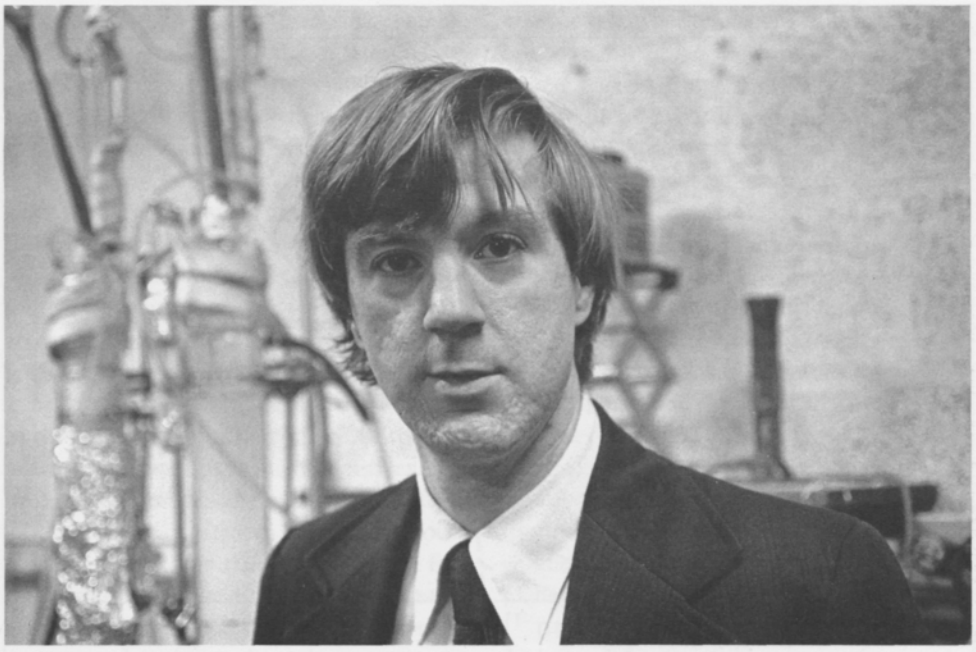
Inside the cell it may join a receptor protein and a translocating protein to form a complex that crosses the nuclear membrane and enters the cell's nucleus. There, the complex may interact with the DNA that contains the cell's genetic information, "turning on" a gene that induces the formation of a messenger molecule (mRNA). This molecule then leaves the nucleus and serves as a template for the formation of a protein—in this case, the enzyme P450IA1. It is capable of producing many molecules of this enzyme.

Since this mechanism requires a series of binding and translocation events that may or may not take place, the relationship between the input of TCDD and the induction of P450IA1 is not linear. The cell-culture analog device is useful in this situation, because it gives an empirical measure of induction. We used it to study the induction of P450IA1 in a human lymphoblastoma cell line, and found that at a 0.01 nanomolar concentration of TCDD, the amount of P450IA1 induced was indistinguishable from the uninduced, basal level. Only when the concentration of TCDD was greater than this threshold did the amount of P450IA1 begin to rise (see Figure 3).

This result suggests that many models used to assess risk are unnecessarily conservative. These models, which extrapolate to low doses from observations made at high doses, generate "virtual safe doses" that vary by many orders of magnitude. While a 0.01 nanomolar concentration of TCDD would be judged unsafe according to all of these models, actual experiment shows that only when TCDD is increased beyond this threshold amount does P450IA1 rise above the basal level. Without any knowledge of the molecular mechanisms involved, a regulatory agency would have to err on the side of caution and establish a very conservative "virtual safe dose." With an understanding of the actual mechanisms, the agency could base regulations on a more realistic estimate.

In this particular case, however, the issue is probably academic. While P450IA1 induction is a convenient way to measure cellular response, it is unlikely that this mechanism is directly involved in the formation of human cancers. Cancers are caused by cell division that escapes the body's normal control mechanisms. We know that changes in the control of mechanisms for cellular replication and division are influenced by changes in protein phosphorylation, and so we are now turning our attention to this subject.

We are developing mechanistic interpre-



"The appropriate regulation of processes and products, so as to insure public safety . . . is one of the most important issues facing industrialized society."

tations of the way protein phosphorylation at tyrosine residues, which involves specific enzymes called tyrosine kinases, responds to TCDD exposure. We are using a combination of standard static cell-culture experiments, PBPK models, and a cell-culture analog device. In this device we will use transformed, but not tumorogenic, human cell lines. We plan to use a lymphoblastoma cell line in a blood compartment, a hepatoblastoma in a liver compartment, and a kertinocyte in a skin compartment.

Toward More Rational Grounds for Regulation

One of our primary motivations in developing the cell-culture animal surrogate system is to learn, through using this device, how molecular-level mechanisms inside the cell relate to whole-animal physiology. This knowledge is relevant to the rational development of regulations for both toxic substances and prescription drugs. The appropriate regulation of processes and products, so as to insure public safety while still permitting reasonable production and utilization, is one of the most important issues facing industrialized society. We expect that the techniques we are developing will provide improved information to decision makers, so that they can develop regulations grounded in a more realistic appraisal of toxic and pharmacological effects.

Michael L. Shuler is the Samuel B. Eckert Professor of Chemical Engineering. He studied at the University of Notre Dame as an undergraduate; he joined the Cornell faculty in 1974 after completing his doctoral work at the University of Minnesota. His research focuses on biochemical engineering, use of genetically altered cells, plant cells, novel biological reactors, mathematical models of cell growth, bioremediation, and the insect cell–baculovirus system to synthesize biopesticides and proteins.

A member of the graduate fields in food science and in microbiology, as well as in chemical engineering, Shuler has been active in the development of the Biotechnology Institute and Program. He was the founding editor-in-chief of Biotechnology Progress *and is currently on the editorial boards of three other journals. He is a member of the American Chemical Society, the American Institute of Chemical Engineers (AIChE), the American Society for Microbiology, and the American Society of Pharmacology. In 1989 he was inducted into the National Academy of Sciences, and in 1991 he received the Professional Progress Award from the AIChE. He is a founding fellow of the American Institute for Medical and Biological Engineering.*

Macromolecular Crystallography

at the Cornell High Energy Synchrotron Source

People who study the structure of large molecules and membranes come from all over to use the Cornell High Energy Synchrotron Source (CHESS). It is widely acknowledged that CHESS provides the most intense x-ray beams in the world, and several experimental stations at CHESS are particularly well-suited to macromolecular crystallography. Using one of these stations, a team headed by Michael Rossmann of Purdue University worked out the structure of human rhinovirus 14 (see *Engineering: Cornell Quarterly* 20(4): 44-49), the first mammalian virus ever deciphered.

Ironically, the radiation that makes such feats possible is a byproduct of another field of research—high-energy physics. The Cornell Electron Storage Ring accelerates electrons and positrons at energies in excess of five billion volts and smashes them together to investigate the properties of the *b* quark. The acceleration of the particles causes them to emit radiation over the whole electromagnetic spectrum—including the intense x-radiation that has proven so useful for studying molecular structure.

CHESS was established to harness these intense x-ray beams and make them available to a broad community of users. As a national facility, CHESS is available to a diverse group of experimentalists from a wide variety of disciplines. It is used, to an increasing extent, for research in the biological sciences.

The National Institutes of Health has established a Research Resource called MacCHESS to promote macromolecular crystallography. The support group formed under its aegis has helped provide the environment in which seminal work, such as solving the structure of the cold virus, could be performed. Other work to which MacCHESS has made a significant contribution has yielded exciting information on the structures and phases of lipid membranes.

The MacCHESS team has shown that an x-ray diffraction picture can be taken in a single pass of the electron beam as it circles the storage ring—a mere 100 picoseconds. This experiment was performed to show the potential of synchrotron radiation for investigating biological processes.

Several large pharmaceutical companies are active users of CHESS, and much of the work in macromolecular crystallography is related to their programs of research on the synthesis of antiviral drugs. A Bio-level Hazard 3 Facility has been constructed with funds from the National Institutes of Health. Located adjacent to a very-high-intensity macromolecular crystallographic station, this facility makes it possible to investigate the structure of sensitive viruses and their derivatives in a secure and protected environment. Currently, CHESS is the only synchrotron radiation facility in the world that has this capability.

The areas covered by biological research at CHESS represent a wide range of interests, and there is a highly productive interaction between the academic community and colleagues in the pharmaceutical industry.

This article is based on information furnished by Boris W. Batterman, director of the Cornell High Energy Synchrotron Source.

POLYETHYLENE COMPONENTS FOR HIP AND KNEE REPLACEMENTS

by Donald L. Bartel

"The principal constraint on the longevity of total joint replacements is the body's reaction to debris generated by damage to the articulating surfaces."

Total joint replacement has become a common surgical procedure. When the bones that articulate in hips and knees are damaged through injury, disease, or normal wear and tear, they are replaced with joints made of steel, ceramic, or plastic. In general, these artificial joints perform remarkably well. They provide an excellent range of motion, permitting the recipients to engage in most everyday activities, and greatly reduce, if not eliminate, the pain associated with damaged joints. Long-term follow-up shows that joint replacements can be expected to perform well for ten to fifteen years. Through mechanical analysis and improved design, the biomechanics group at the Sibley School of Mechanical and Aerospace Engineering hopes to extend this period.

How Joint Replacements Wear Out

The principal constraint on the longevity of total joint replacements is the body's reaction to debris generated by damage to the articulating surfaces. In most contemporary designs, a convex metal component articulates with a concave, ultrahigh-molecular-weight polyethylene component. In some hip replacements, a ceramic (Al_2O_3) is used instead of metal for the ball portion of the joint.

Over time, debris is generated by the motion of the components under loads transferred across the joint. This debris, which is mostly polyethylene, migrates to the surrounding soft tissue, where it eventually triggers a biological reaction. When the body deals with the debris it also releases agents that attack the bone, generally near the interface with the implant. As a result, the joint becomes more susceptible to infection and bone resorption, which loosens the prosthetic components. The ten or fifteen years that it takes for a critical amount of debris to accumulate is, in effect, the useful life of the joint.

There are two aspects to this problem—one mechanical and the other biological. The debris is generated by mechanical processes, and the amount of debris is a function of the materials used and the geometry of the articulating surfaces. The body's response to the debris is the biological side of the problem. To understand the relevant biochemical processes, it is necessary to find out which materials are most detrimental, to identify the consequences of shape and size, and to determine how much debris is needed to evoke the body's reaction.

During the past ten years, my students and I have collaborated with the Department of Biomechanics at the Hospital for Special Surgery, in New York City, to develop total joint replacements with greater longevity. Our goal, which is to decrease the damage that occurs at articulating surfaces, requires a comprehensive approach. Objective measures must be used to evaluate the in-vivo performance of components; the mechanical properties of polyethylene must be determined; the stresses caused by contact between the metal and plastic components must be understood; and designs must be developed that minimize surface damage while, at the same time, maximizing overall function and facilitating surgical implantation. Knowledge of these parameters is essential for designers who wish to develop better prostheses, as well as for surgeons who wish to make informed choices between contemporary designs.

Structural Analysis of Polyethylene Components

Our research has concentrated on the polyethylene components of implants because they are especially susceptible to surface damage and because the body seems to be more sensitive to polyethylene debris than to metallic debris. Structural analysis of these components requires the specification of geometry, material properties, and loads.

Figure 1 (left). A total hip replacement. The metal ball articulates with a polyethylene socket, which is backed with metal in this design.

Figure 2 (below). A total knee replacement. The curved metal condyles articulate with the polyethylene tibial component, which is metal-backed. The articulating surfaces of the plastic and metal components are curved in two directions. This controls the direction of the load on the plastic component and reduces the stresses that result from contact.

The geometry of polyethylene components varies from design to design. In hip joints (Figure 1), the contact occurs between a nearly conforming ball and socket. The components of total knee replacements (Figure 2) are much less conforming, as a class, but there is great variation depending on the goals of designers. All designs must allow the tibia to rotate about its axis with respect to the femur, but how much it can twist from side to side depends on the conformity of the articulation. And here there are trade-offs. Some conformity is desirable, especially when the cruciate ligaments inside the knee joint are destroyed or removed. If the articulating surfaces are too conforming, however, excessive constraint will restrict freedom of motion and introduce forces that can loosen the implant. Less constraint may be required if the posterior cruciate ligament is retained, but if it is achieved by decreasing the conformity of the articulating surfaces, the likelihood of surface damage is increased.

Polyethylene components may be backed with metal to more evenly distribute loads to the supporting bone. In this case, the methods used to attach the material to its backing can have a pronounced effect on the stresses that cause debris. Contact between the polyethylene and its metal backing, as well as between the articulating surfaces, must be considered. This introduces nonlinearities into the structural analysis because the contact area at both interfaces changes with loading. If the plastic component is firmly bonded to the metal backing, stresses due to contact are reduced. Some components are molded to the metal to achieve this condition. In other designs, the plastic and metal interlock according to various schemes. Molded attachment is relatively easy to model, but interlocking attachment can be quite difficult.

The load on a joint is much greater than the functional load applied to the limb of which it is a part. For example, the force of a foot hitting the floor during normal gait is about 1.25 times body weight, but the contact force between the bones at the knee is three to four times body weight. The forces at the joint are magnified because the large moments about the joint produced by the functional loads must be resisted by muscle forces through tendons which lie close to the joint and consequently have small moment arms with respect to the joint. As hip and knee joints are flexed or extended, the area of contact moves across the articulating surfaces. The stress-strain relationship is nonlinear and adds yet another level of nonlinearity to the structural analysis.

As a further complication, the material properties of the polyethylene used in an implant change over the course of time. On the whole, it becomes stiffer; but stiffness does not increase uniformly throughout the thickness of the component. The stiffening is greater near the articulating surface of the implant and near the metal backing. Since the distribution of material properties at the time of implantation is similar to the shear stress distributions

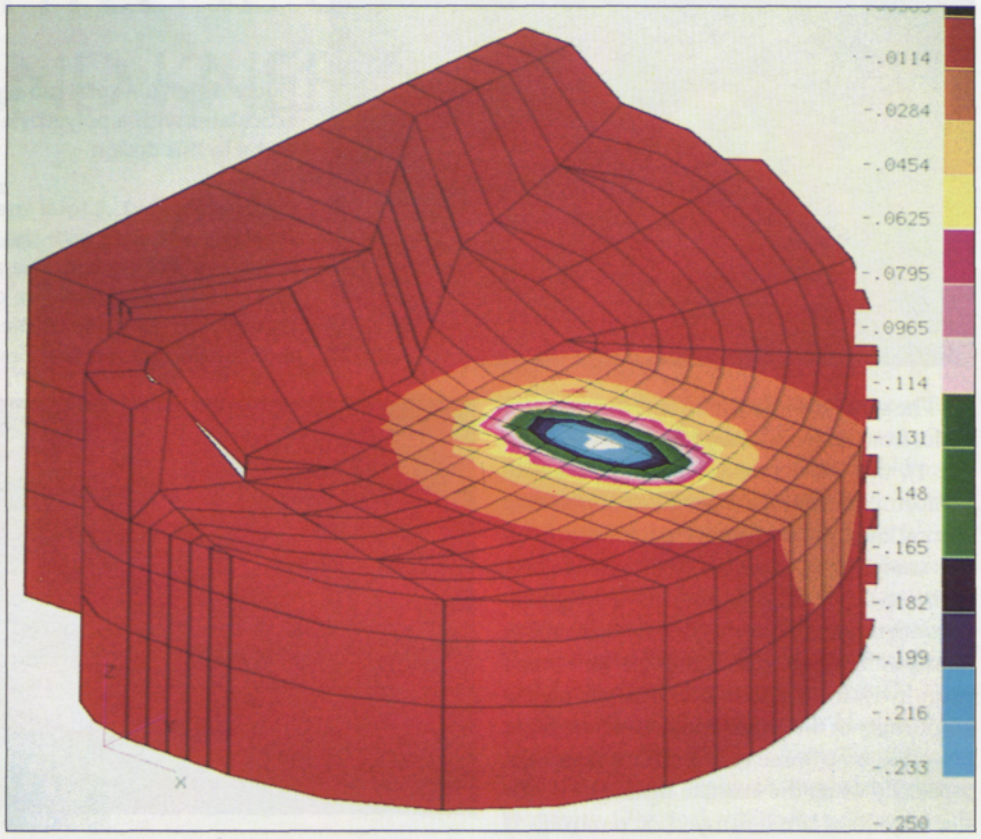


Figure 3. A finite-element model of a plastic component with a relatively flat articulating surface. The stresses shown here are in the *z* direction and indicate the area of contact. The stresses are large because the flat surface results in nonconforming contact.

through the thickness of the component, the nature of the changes suggests that they come about, at least in part, because of the loading on the prosthesis. When the stiffness of the polyethylene increases, the articulating metal component does not indent it as deeply and the contact area decreases, augmenting the stresses that cause damage. In addition, polyethylene undergoes oxidative degradation in the chemical environment of the body. This degradation, whose rate is influenced by the methods used to process the polyethylene and the radiation used to sterilize the component after manufacture, also increases stiffness.

Thus, a complete structural analysis of the polyethylene components must be iterative so as to account for the changing properties of the material and their effects on the stresses that cause debris. Research being conducted at the Hospital for Special Surgery is sorting out the effects of radiation, oxidative degradation, and loading on the material properties of polyethylene. At the Sibley School of Mechanical and Aerospace Engineering, we are developing models based on data from the hospital that allow us to predict how the properties of components will change over time.

Designing Implants for Better Performance

Our analyses make it possible to quantify the differences between various designs and to correlate these with differences in clinical performance.

Finite element models show how the conformity of tibial components is related to stress and damage. When the articulating surface is relatively flat (see Figure 3), contact with the metal component is nonconforming and stresses are great. In addition to the contact stresses, which are normal to the articulating surface, other stresses are tangent to the surface (Figure 4). These stresses are compressive near the center of contact and tensile near the edge of contact. There are also large tensile stresses at the outside edge of the component, which increase when the component is made thinner and the load is applied closer to the edge (Figure 5). This edge loading is minimized by the more conforming geometry of prostheses such as the one shown in Figure 2.

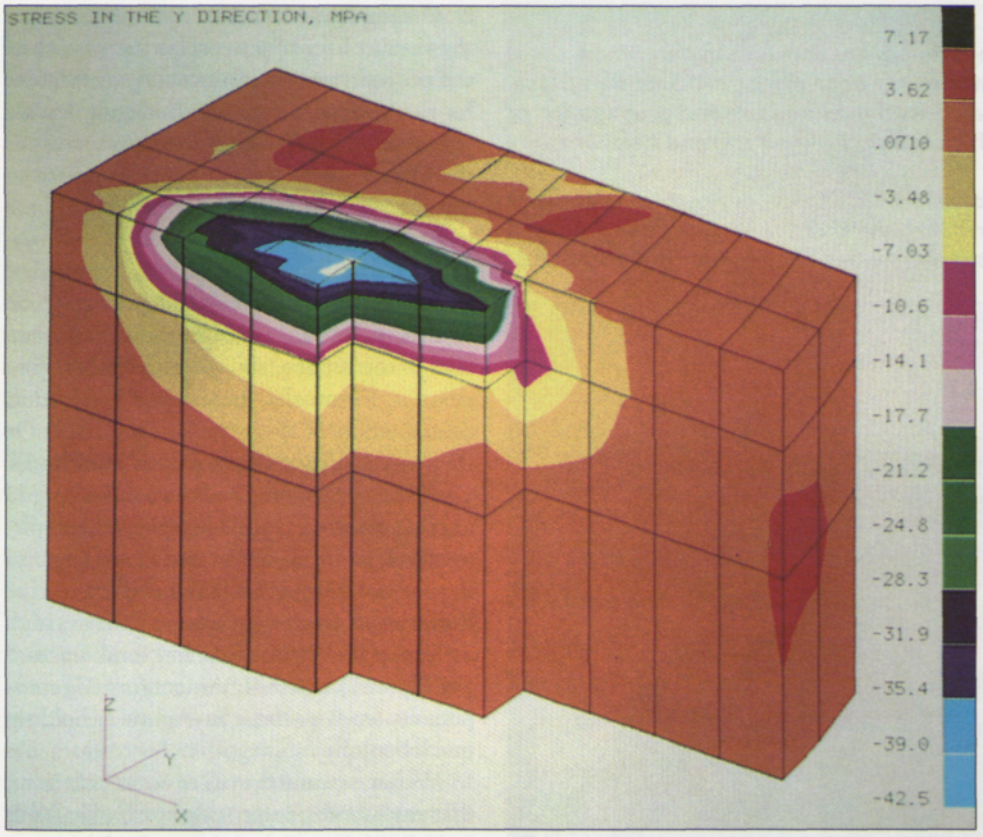


Figure 4. A section of the component showing the stresses in the *y* direction. On the contact surface these stresses are compressive at the center of contact and tensile at the edge of contact. The stresses are also tensile on the outside edge of the component.

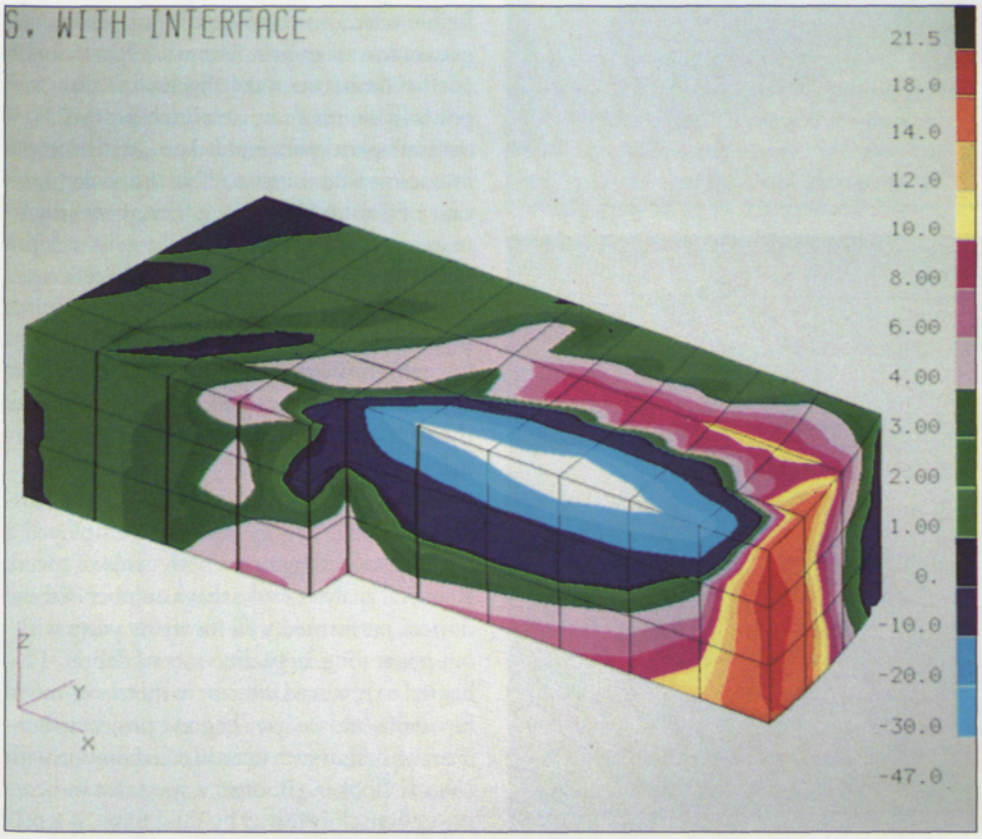
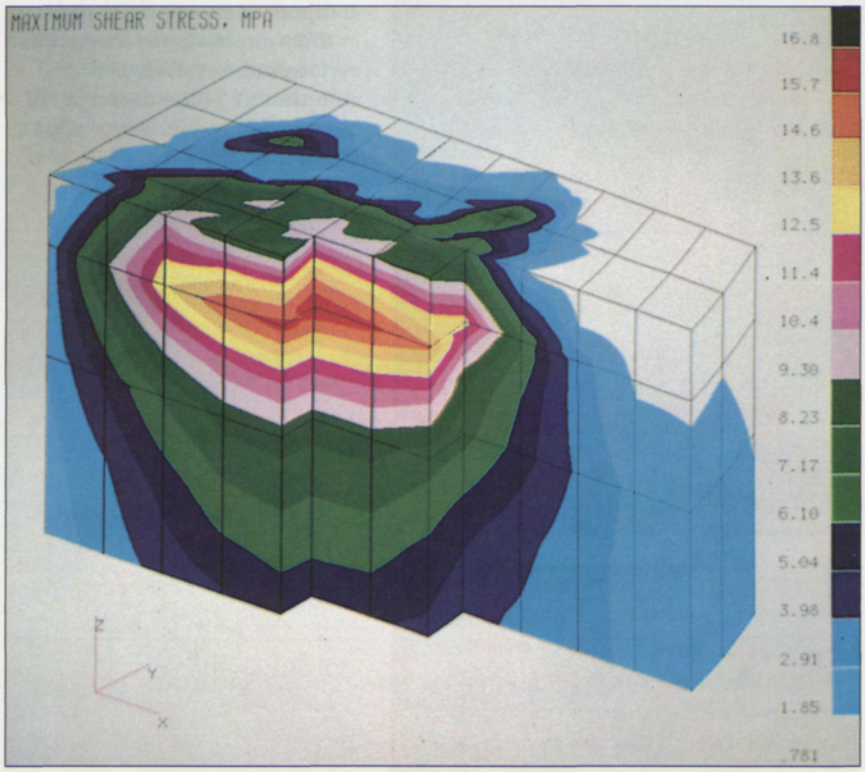
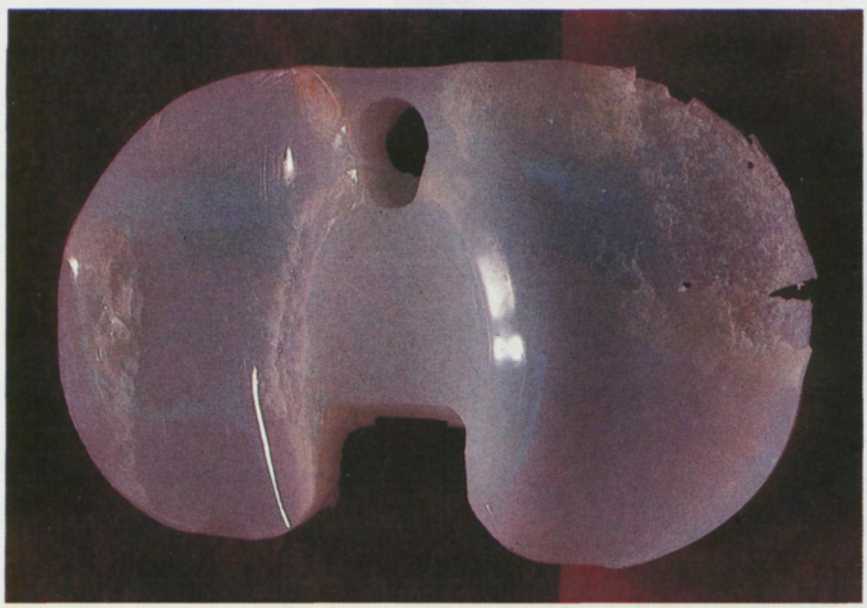


Figure 5. The stresses described in Figure 4 are increased when the component is made thinnner and the load is applied closer to the edge.

Figure 6 (above). A section of the component showing the maximum shear stresses, which occur about 1 millimeter beneath the articulating surface. These stresses are associated with the initiation and propagation of subsurface cracks, which can result in pitting and delamination.

Figure 7 (below). A retrieved component. The damage, which consists of cracking at the edge, delamination of a portion of the surface, and pitting, is consistent with the stress analyses depicted in Figures 3 through 6.





During flexion and extension of the joint, the contact area moves across the surface of the polyethylene component. A given point on the surface is subjected to compressive stress, then tensile stress, then zero stress as the knee is bent, and the same sequence in reverse when the knee is straightened. These stresses, acting tangent to the surface, are associated with cracks that propagate normal to the surface. But there are also large shear stresses (Figure 6), which promote cracks parallel to the surface, about one millimeter beneath it. Eventually, these cracks can lead to delamination of the articulating surface. Or they may propagate toward the surface under alternate compression and tension, leading to the formation of a pit. Delamination and pitting both produce debris that can migrate into the surrounding tissue. We have found that thin, less-conforming components have a high incidence of delamination and frank fracture (see Figure 7), whereas more conforming components (such as those in Figure 2) hold up much better.

We have assumed, in all of our calculations, that any lubrication provided by bodily fluids intruding between the components has a negligible effect on the stresses that lead to the generation of debris. But while the friction coefficient between cobalt-chrome alloy and polyethylene is quite small (about 0.025), it may still play a part in the damage that occurs in conforming joints such as the socket portion of a total hip replacement. One way of reducing the friction would be to develop a means of maintaining fluid-film lubrication between the ball and the socket of this joint, using normal joint fluids. The conditions are not favorable, however, because the load does not completely reverse, and the ball oscillates through a relatively small angle during normal activities.

Some early total hip replacements, implanted about twenty years ago, employed a ball and socket that were both made of metal. Retrieval analysis shows that a number of these devices performed well for many years without generating large amounts of debris. This has led to renewed interest in metal-on-metal hip joints, and we have begun a project to analyze and design such units in collaboration with John F. Booker. (Booker, a specialist in bearing systems lubricated by fluid films, is a col-

league at the Sibley School of Mechanical and Aerospace Engineering.) Preliminary analyses suggest that fluid films between the articulating components are quite thin—of the same order as the deformations in the metal cup. Consequently, the design of these devices will have to be based on the theory of elastohydrodynamic lubrication. The techniques developed in this project will also be relevant to fluid-film lubrication of other material combinations, such as metal on polyethylene, ceramic on polyethylene, and ceramic on ceramic.

The Final Test of Implants: How Well They Really Work

All the analysis and design work takes place in the context of ongoing clinical and biological analysis. At the Hospital for Special Surgery, every component that is removed from a patient is examined by staff engineers in the Department of Biomechanics. In addition, the sockets of total hip replacements are monitored radiographically to determine the amount of wear as a function of the time of implantation. Such analyses are essential for determining the various mechanisms that contribute to the generation of debris. In addition, when revision is necessary, specimens of tissue surrounding the joint are collected and analyzed to find the amount, type, and shape of debris particles. Such studies provide essential information, which, along with engineering analysis and design, form a basis for developing the next generation of total joint replacements. It should be possible, in the near future, to design artificial joints that will provide at least twenty years of pain-free function.

Donald L. Bartel holds a joint appointment as professor of engineering in Cornell's Sibley School of Mechanical and Aerospace Engineering and as senior scientist in the Department of Biomechanics of the Hospital for Special Surgery, which is the orthopaedic affiliate of Cornell's Medical College.

After earning bachelor's and master's degrees at the University of Illinois, Bartel taught engineering, mathematics, and physics at Black Hawk Junior College in Moline, Illinois, for two years. He then entered a doctoral program in mechanics and hydraulics at the University of Iowa, receiving the Ph.D. and joining the Cornell faculty in 1969. His research interests include biomechanics, design optimization and reliability, and computer-aided design.
Bartel was a Guggenheim fellow and visiting scientist in the Department of Orthopaedics at the Mayo Clinic in Rochester, Minnesota, in 1976–77. In 1976 he was appointed visiting scientist at the Hospital for Special Surgery in New York City and has had a continuing affiliation with the hospital since then. He was recently elected a fellow of the American Society for Mechanical Engineers, in recognition of his accomplishments in both education and research.

"It should be possible, in the near future, to design artificial joints that will provide at least twenty years of pain-free function."

THE MULTIPLE-MINIMA PROBLEM IN PROTEIN FOLDING

by Harold A. Scheraga

"One of the goals of modern biophysical chemistry is to be able to predict the conformations that different molecules will assume when allowed to find their lowest-energy states."

Large organic molecules have a special property that enables them to play fundamental roles in the life process. They fold up. The places at which they fold are the bonds between their constituent atoms. The forms that the segments of a molecule can assume, as they rotate around these bonds, are theoretically infinite in number. But in fact molecules tend to settle into shapes—or conformations, as they are technically called—that are most favorable from an energetic point of view.

One of the goals of modern biophysical chemistry is to be able to predict the conformations that different molecules will assume when allowed to find their lowest-energy states. For simple molecules, which contain only a modest number of atoms, the conformation corresponding to the lowest energy can be determined quite easily. But finding the lowest-energy conformation for large molecules, which may be composed of thousands of atoms, requires sophisticated computational methods and extremely powerful computers.

Basic Outline of the Folding Problem

Polypeptides are long, chain-like organic molecules consisting of a sequence of amino acids that fold up to become biologically active protein molecules. For a number of years, my colleagues and I have been studying the way that polypeptide chains fold.

The thermodynamic hypothesis used to calculate the most stable conformation of a biological macromolecule derives from Christian Anfinsen's experiments on ribonuclease, for which he won the Nobel Prize in 1972. The technique involves generating a chain in an arbitrary conformation (using either Cartesian coordinates or internal coordinates), calculating its conformational energy, and then finding ways to minimize this energy until the lowest value, or global minimum, is located. Numerous procedures have been developed to accomplish this, and we have evaluated three (AMBER, CHARMM, and ECEPP) by comparison with each other and with experimental results. (ECEPP, on which the work discussed in this article is based, stands for Empirical Conformational Energy Program for Peptides.)

To complete the calculation of the free energy of the system, it is necessary to take entropy into account. This involves not only conformational fluctuations, but also the distribution and configuration of solvent molecules around a given conformation of the chain—the potential of mean force. While individual water molecules have been used to introduce the effect of hydration, the computations can be greatly simplified by using either a hydration-shell model or a solvent-exposed surface-area model. The speed and efficiency of our new algorithm to compute solvent-exposed surface area now makes it possible to optimize a combined function, such as ECEPP, plus free energy of hydration.

Unfortunately, this whole procedure leads only to the local minimum nearest the arbitrary conformation that was used as a starting point. Organic macromolecules can fold into a bewildering variety of different shapes, including many that differ very little in energy from the one corresponding to the global minimum. But the shapes corresponding to these local minima are not necessarily similar to each other, and they may be separated from each other by higher-energy conformations.

To find the global minimum—the lowest energy state of all, which corresponds to the most stable conformation of the molecule—one must, in principle, find all the local minima, and then pick the lowest. Since this requires an amount of computation that taxes the best of computers, we have sought ways to eliminate, early in the game, conformations that are unlikely contenders. We are developing methods for searching conformational space that will discover, with maximum effi-

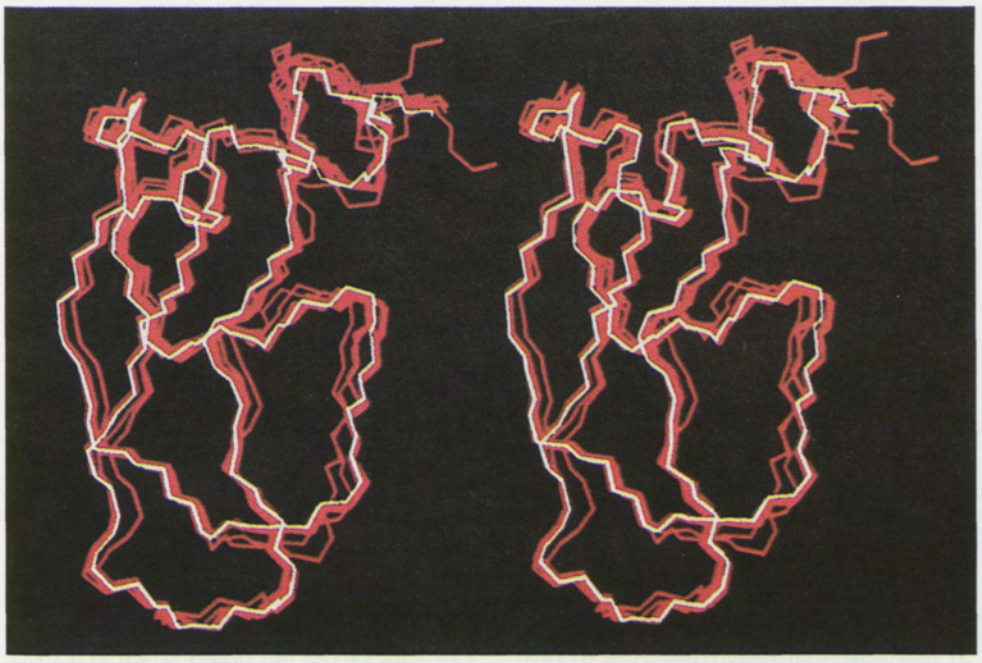


Figure 1. The structure of bovine pancreatic trypsin inhibitor (BPTI). The red lines show computed versions of the lowest-energy conformation of BPTI, oriented for optimal superposition with each other and with the native structure of BPTI, which is shown in white. The native structure is determined by x-ray diffraction.

This stereo presentation allows viewers to see the structure in three dimensions without the aid of any special apparatus. By relaxing the eyes into the position normally used when looking into the distance, it is possible to align the left image, as seen by the left eye, and the right image, as seen by the right eye, so that they appear as a single, three-dimensional object. The page should be held directly in front of the eyes, about 15 inches away. It may help to hold a card between the two images, so that each can be seen by one eye only.

ciency, the potential well where the global minimum lies. Several methods have been developed and used with some measure of success.

Building Up the Chain from Its Constituent Parts

One obvious approach is to consider the polypeptide chain as broken up into its constituent parts and then rebuild it. The energies of the smallest fragments are minimized, and then these fragments are combined into larger segments, whose energies are, in turn, minimized. Since the lowest-energy conformation of a larger fragment does not necessarily contain the conformations of its constituent parts that have the lowest energy in isolation, it is necessary to retain an ensemble of conformations at each stage of the build-up procedure. As the fragments become larger and larger, more and more of the long-range interactions are built into the computations.

The smallest fragment is the terminally-blocked amino-acid residue. A complete search of the conformational space of this molecule identifies all local energy minima. Terminally-blocked dipeptides are then built from all combinations of local minima of the two terminally-blocked amino-acid residues, and their energies are minimized. This minimization introduces the inter-residue interactions that had not yet appeared in the calculations involving the single residues.

Continuation of this process until the whole polypeptide chain is generated would lead to an enormous number of possible conformations. To avoid this, unacceptable conformations are dropped from the ensemble at each stage. Those deleted are high-energy conformations and hypothetical conformations with constituents whose overlapping parts are not identical.

This technique has been applied to open-chain and cyclic oligopeptides and to fibrous and globular proteins. Examples include the pentapeptide enkephalin, as a single chain and in a crystalline array; the cyclic decapeptide gramicidin S; the collagen-like poly(Gly-Pro-Pro); and the fifty-eight–residue bovine pancreatic trypsin inhibitor (BPTI). The computed structures of these molecules have been verified using x-ray diffraction or two-dimensional nuclear-magnetic resonance methods (see Figure 1).

Self-Consistent Electrostatic Field and Monte Carlo Methods

Another way to reduce the volume of calculations that need to be carried out is to assume that low-energy conformations must have favorable electrostatic interactions. Electrostatic energy is only one of the types of energy that

come into play in determining conformations, but the self-consistent electrostatic field (SCEF) method assumes it to be the most important one. Under this approximation, the peptide dipoles must be optimally oriented in the local electrostatic field, although the whole molecule contributes to the local electrostatic field at any given point. The implementation of this method begins with a minimization of the total ECEPP energy of an arbitrary starting conformation. The orientations of all peptide-bond dipoles with respect to the local electrostatic field in this locally minimized conformation are examined, and the one that is least acceptable is reoriented. This alters the conformation of the chain, whose total ECEPP energy is then minimized. Repeated iterations of this procedure rapidly led to the global minimum (an a-helical conformation) of a twenty-residue poly(L-alanine) chain.

The usual Metropolis Monte Carlo procedure does not search conformational space efficiently, and so we introduced Monte-Carlo-plus-energy-minimization (MCM), which searches only the space of the local energy minima. Here again, a starting conformation is chosen randomly, and its total ECEPP energy is minimized. Then backbone and dihedral angles are randomly selected, and random changes (ranging from –180° to +180°) are made in these dihedral angles. The energy of this altered conformation is then minimized, and the Metropolis criterion is used to determine whether or not to accept it. The procedure is then repeated. In eighteen randomly selected starting conformations of the pentapeptide Met-enkephalin, the MCM procedure led to an identical global minimum.

By combining the best features of the SCEF and MCM methods, implemented by thermal perturbations, we developed the electrostatically-driven Monte Carlo (EDMC) procedure. This technique has been able to obtain the right-handed a-helical (global) minimum conformation of a twenty-residue poly(L-alanine) chain by starting from many randomly chosen initial conformations including the fully extended chain and the *left-handed* a-helical form. It has also been applied successfully to Met-enkephalin and to the twenty-residue membrane-bound portion of melittin.

Another procedure designed to overcome the inefficiency of Metropolis Monte Carlo is based on adaptive importance sampling. The partition function for a polypeptide is evaluated by a Monte Carlo procedure, and average properties of the molecule are then computed from this function. Conformational space is searched with a probability distribution function that is adjusted at each stage to concentrate the sampling in regions where the partition function is largest. In late iterations of the procedure, the probability distribution converges on the Boltzmann distribution. Application to Met-enkephalin led to the low-energy conformation obtained with the methods described previously.

Building Up from Below to Find the Global Minimum

A significantly different procedure, similar in spirit to a technique pioneered by Gordon Crippen (who received his doctorate from Cornell), carries out optimization in a space of high dimensionality, where the obstacles of three-dimensional space are easier to surmount, and then the system is relaxed back into three dimensions.

This procedure depends on the fact that the energy of interaction Eij between every pair of atoms i and j depends only on their separation dij. Thus, when Eij is assigned its minimum value, the total energy of the molecule $E = S\ Eij$ is also minimized. But the outcome of this process does not correspond to a structure that can exist in three-dimensional space. Therefore, the system is relaxed back to three dimensions, with an accompanying *rise* in energy. In other words, the global minimum is approached from below, rather than from above, as in the previously described procedures.

According to a theorem propounded by mathemetician Leonard Blumenthal, a set of n points (the n atoms) in $(n–1)$-dimensional space is embeddable in three dimensions so long as three necessary and sufficient conditions hold true.

1. The set must include four points (p_1, p_2, p_3, p_4) that are exactly three-dimensional. (These points might be, for example, a planar peptide group or an external regular tetrahedron.)
2. The four-dimensional volume formed by the simplex of points (p_1, p_2, p_3, p_4, p_i) must be zero for all $i = 1,...,n$.

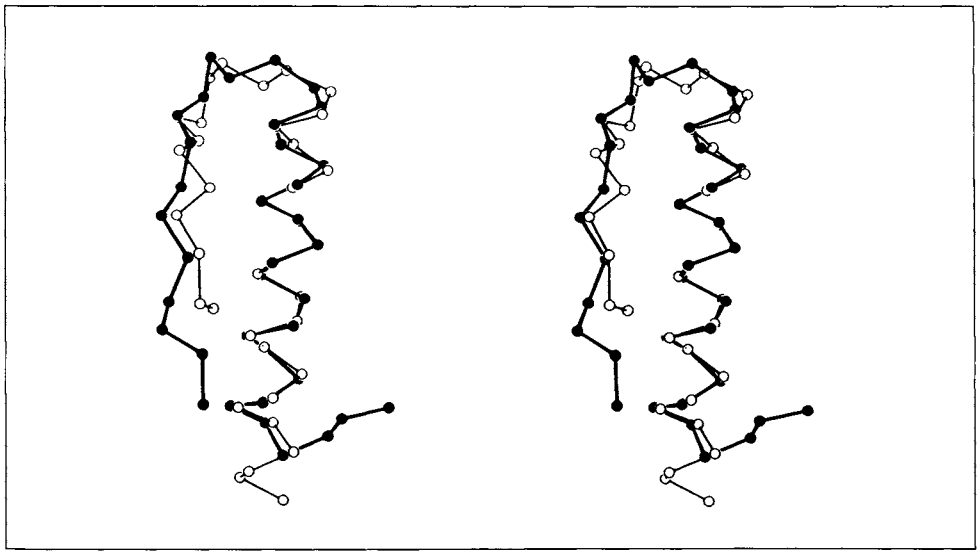


Figure 2. Avian pancreatic polypeptide. This stereo view compares the lowest-energy structure as computed by PRISM (open circles) with the structure as revealed by x-ray diffraction (solid circles).

3. The five-dimensional volume formed by the simplex of points $(p_1, p_2, p_3, p_4, p_i, p_j)$ must be zero for all $i,j = 1,...,n$.

Based on this theorem, and using distances as the variables, the global minimum can be found as the objective function F is minimized,

$$F = w_E F_E + w_{4D} F_{4D} + w_{5D} F_{5D} + W_B F_B$$

where each w is a weighting factor, FE is the ECEPP energy, $F4D$ and F_5D are Cayley-Menger determinant constraints on the four- and five-dimensional volumes, and FB incorporates information setting upper and lower bounds for the distances. Application of this procedure led to the same (global) minimum-energy structures that were obtained by the MCM and EDMC procedures.

Using Empirical Observations to Limit the Options

Various properties of amino acids and peptides, including structural information obtained from x-ray diffraction studies of crystalline proteins, can be used as aids in the search of conformational space. For example, the observation that certain pairs of amino acids "prefer" to adopt b-turn structures or contact each other in globular proteins limits the expected folding patterns. A factor analysis of numerous properties of amino acid residues has helped identify those that affect conformation.

One procedure that takes advantage of such information is pattern-recognition-based importance-sampling minimization (PRISM), which increases the efficiency of the build-up procedure. Instead of minimizing energy at each step, which is computationally expensive, PRISM searches conformational space by building up with probabilities and not minimizing energy until the end. The conformational space of each residue is divided into four regions, with no undefined "coil" state. In order to take the interaction between residues into account, at least minimally, attention is focused on tripeptides. Each residue is allowed to adopt one of four possible conformations, which means that a tripeptide can have 4^3 possible conformations for any given amino acid sequence. The probability of each of these conformations is assessed in accordance with data obtained from structures of proteins determined by x-ray diffraction and an analysis of amino acid properties in terms of ten orthogonal factors. The whole chain is then built up from the N terminus, using the most probable tripeptide conformations and adding residues one at a time so that they overlap properly. In this manner, individual tripeptide probabilities determine the probabilities of the whole polypeptide chain. In work carried out thus far, we have retained the ten most probable chain states and randomly selected, for each one, twenty conformations calculated according to a bivariate Gaussian distribution. The energies of these two hundred conformations are then minimized. For the thirty-six-residue avian pancreatic polypeptide, the lowest-energy conformation, as calculated by PRISM, was similar to the structure revealed by x-ray diffraction (see Figure 2).

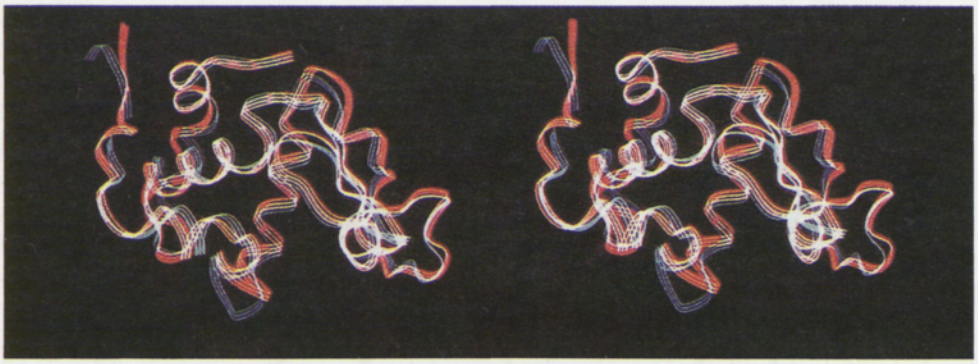


Figure 3. The structure of a-lactalbumin. Distance constraints obtained from the homologous protein, lysozyme, were incorporated into the computations that yielded the version shown in blue. The structure revealed by x-ray diffraction is shown in red.

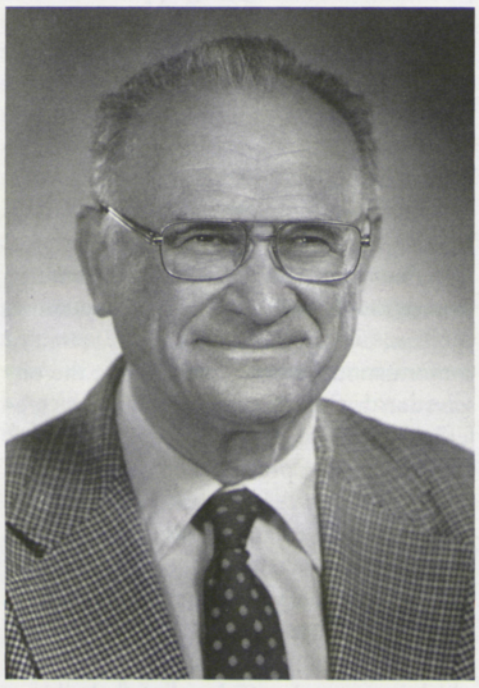
Homologous proteins have been used to obtain distance constraints. Figure 3 illustrates the agreement between the x-ray and calculated structures of a-lactalbumin, based on the x-ray structure of the homologous protein, lysozyme.

Flattening Out the Potential-Energy Surface with the Diffusion Equation Method

Yet another approach to the multiple-minima problem involves the deformation of the potential-energy surface so that only one minimum—the global minimum—remains. Reversal of the deformation leads to a trajectory of positions of the global minimum until the original potential-energy surface is reached, and the global minimum of the original function identified. This method has been applied to several mathematical functions, to clusters of Lennard-Jones particles, and to terminally blocked alanine and Met-enkephalin. The deformation is achieved by solving the diffusion equation, with the original potential function as the initial boundary condition.

In the case of Lennard-Jones particles, it has been estimated that there are some 10^{45} local minima for a cluster of fifty-five particles—the global minimum being the MacKay icosahedron. This global minimum was attained in about four hundred seconds on the IBM 3090 computer. Since there are 159 degrees of freedom for a fifty-five-particle cluster, a similar amount of computing time should be sufficient to locate the global minimum for a twenty-six-residue polypeptide. This suggests that the solution of the multiple-minima problem for polypeptides may be within reach. With improvements in the potential-energy functions, a general understanding of protein folding may be just around the corner.

Harold A. Scheraga is the George W. and Grace L. Todd Professor of Chemistry. He joined the Cornell faculty in 1947, after earning the doctorate at Duke University and spending a postdoctoral year at Harvard Medical School. His research has focused on the physical chemistry of proteins and other macromolecules, the chemistry of blood clotting and growth factors, and the structure of water and dilute aqueous solutions. He has been a visiting scholar in Australia, Japan, and Israel, where he was affiliated with the Weizmann Institute of Science from 1972 through 1978. He has given numerous distinguished lectures, served on many advisory panels, and has received a number of prestigious awards. He has authored two books and more than 850 articles. He is a member of the National Academy of Sciences and the American Academy of Arts and Sciences.



■ New appointments in the College of Engineering for academic year 1992–93 include the following:

John E. Hopcroft, the Joseph C. Ford Professor of Computer Science, has been named associate dean for college affairs, succeeding K. Bingham Cady, who is returning to full-time teaching and research in the Program in Nuclear Science and Engineering.

A leader in theoretical computer science, Hopcroft is internationally recognized for his books and research accomplishments. He is currently an editor or advisory-board member for *Algorithmica*, *Information and Control*, *Information Sciences*, *Journal of Computer and System Science*, *Discrete and Computational Geometry*, *Annual Reviews*, and the Oxford University Press.

Hopcroft is a fellow of the American Association for the Advancement of Science and the Institute of Electrical and Electronics Engineers. He is a member of the National Academy of Sciences, the New York Academy of Sciences, the Society for Industrial and Applied Mathematics, and the Association for Computing Machinery, which honored him with the 1986 Turing Award for fundamental achievements in the design and analysis of algorithms and data structures. He was recently appointed to the National Science Board.

Hopcroft received the bachelor's degree from Seattle University; he earned the master's and doctoral degrees at Stanford. He was on the faculty of Princeton University for three years before coming to Cornell in 1967.

Juris Hartmanis, the Walter R. Read Professor of Engineering, has been named to succeed Hopcroft as chair of the Department of Computer Science. This will be his third term in that post, which he filled from 1965 to 1971 and from 1977 to 1982.

Hartmanis studied as an undergraduate at the University of Marburg in Germany; he earned the master's degree at the University of Kansas and the Ph.D. in mathematics at California Institute of Technology. He taught at Ohio State University and worked as a research scientist at the General Electric Research Laboratory before coming to Cornell to chair the newly founded department of Computer Science.

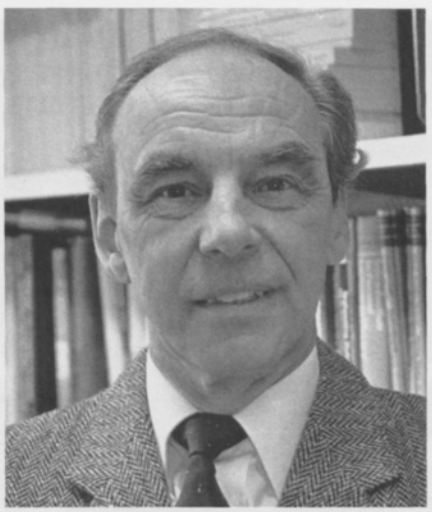
In 1980 he was appointed the Walter R. Read Professor of Engineering. He is a fellow of the American Academy of Arts and Sciences and the American Association for the Advancement of Science, a member of the National Academy of Engineering, and a foreign member of the Latvian Academy of Science. He is also a member of the New York Academy of Sciences, the American Mathematical Society, the Association for Computing Machinery, and Sigma Xi.

Franklin K. Moore, the Joseph C. Ford Professor of Mechanical Engineering, has been appointed director of the Sibley School of Mechanical and Aerospace Engineering. He succeeds Francis C. Moon who was director for five years.

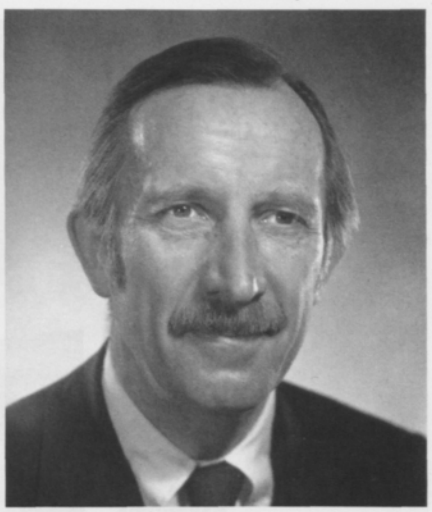
Moore studies fluid dynamics, turbomachinery, and heat transfer. A member of the National Academy of Engineering, he was cited by the academy for "pioneering fundamental research in fluid mechanics and continuing innovative engineering contributions." Moore is a fellow of the Society of Mechanical Engineers and the American Institute of Aeronautics and Astronautics and a member of the Aeronautics and Space Engineering Board of the National Research Council.

Educated at Cornell, Moore earned the B.S. in mechanical engineering (with distinction) in 1944 and the Ph.D. in aerospace engineering in 1949. After receiving his doctoral degree, he was an aeronautical research scientist at the National Advisory Committee for Aeronautics, which later became the National Aeronautics and Space Administration, and he was director of the aerosciences division at the Cornell Aeronautics Laboratory (now CALSPAN, Inc.). He joined the Cornell faculty in 1965.

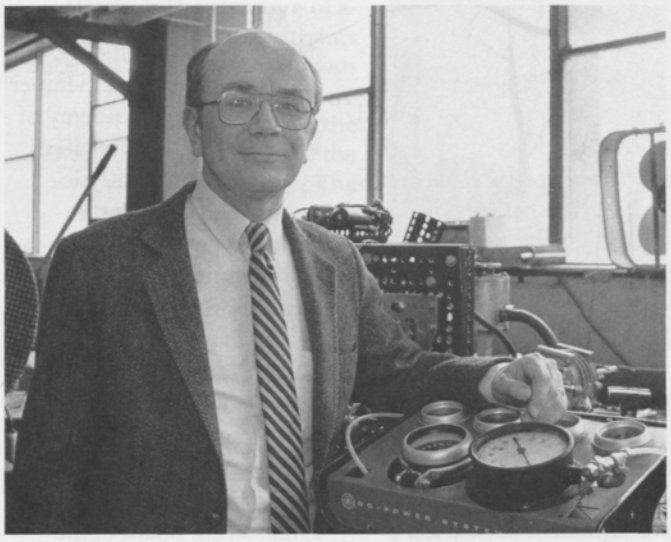
Hopcroft



Hartmanis



Moore



George

Albert R. George has been named the first John F. Carr Professor of Mechanical Engineering.

George, who holds B.S. and Ph.D. degrees from Princeton University, joined the Cornell faculty in 1965. His research interests include acoustics and noise control, fluid dynamics, aerodynamics, and automotive engineering. George is an associate fellow of the American Institute of Aeronautics and Astronautics and a member of the American Helicopter Society, the American Society of Mechanical Engineers, and the Society of Automotive Engineers (SAE), whose Wind-Noise Committee he chairs. He has been faculty advisor for the Formula SAE car project since Cornell began competing in 1987.

The chair is one of two funded by John F. Carr '41(AE) and Helen Ziegler Carr '41(HumEc) through provisions in their wills. The other endowment is the Helen L. Carr Professor of Human Ecology, held by Professor Stephen Ceci, a specialist in child development. The Carrs chose to support professorships because, as John Carr explained, they feel that people make the difference in a university.

Joseph M. Ballantyne has been appointed to direct the Semiconductor Research Corporation's Center of Excellence in Microscience and Technology at Cornell. A cooperative organization of U.S. companies, SRC provides support for research programs at several universities.

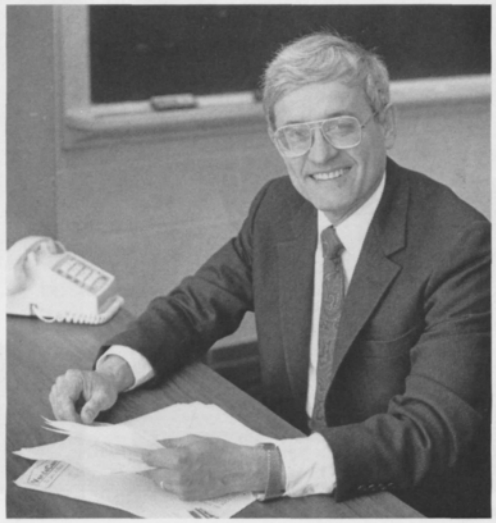
Ballantyne, who succeeds James W. Mayer, joined the Cornell faculty in 1964. He was director of the School of Electrical Engineering from 1980 to 1984 and served as Cornell's vice-president for research and advanced studies from 1984 to 1989. His research interests are optoelectronic materials and devices, integrated optics, and submicrometer lithography.

■ Three members of the faculty retired in 1992.

James W. Mayer has been named the Francis N. Bard Professor of Materials Science Emeritus. He will join the faculty at Arizona State University in the fall.

Mayer, who holds B.S. and Ph.D. degrees from Purdue University, came to Cornell in 1980 from California Institute of Technology. Before that he worked at the Hughes Research Laboratories in Malibu, California, on ion implantation and semiconductor nuclear-particle detectors. He has been a visiting scientist at the Technische Hochschule in Munich, Germany; the Chalk River Nuclear Laboratories in Ontario, Canada; the Institute of Physics of the University of Modena, Italy; the Research Institute for Physics in Stockholm, Sweden; and the University of Catania, Italy. His studies have included ion channeling, Rutherford backscattering spectrometry, the epitaxial growth of semiconductors, thin-film reactions, and silicide formation. In 1981 he received the Von Hippel Award of the Materials Research Society and, in 1986,

Mayer



Ballantyne

the Silver Medal of the University of Catania. He was awarded an honorary doctorate from the State University of New York at Albany in 1988.

Mayer is a fellow of the American Physical Society and the Institute of Electrical and Electronics Engineers, a member of the National Academy of Engineering, and a scientific member of the Böhmische Physical Society.

Shan-fu Shen has retired from the Sibley School of Mechanical and Aerospace Engineering after thirty-one years in the College of Engineering. He was named the John Edson Sweet Professor of Engineering Emeritus.

Shen received his bachelor's degree in 1941 from the National Central University in China and his doctorate from Massachusetts Institute of Technology in 1949. Before coming to Cornell in 1961, he served on the faculty of the University of Maryland.

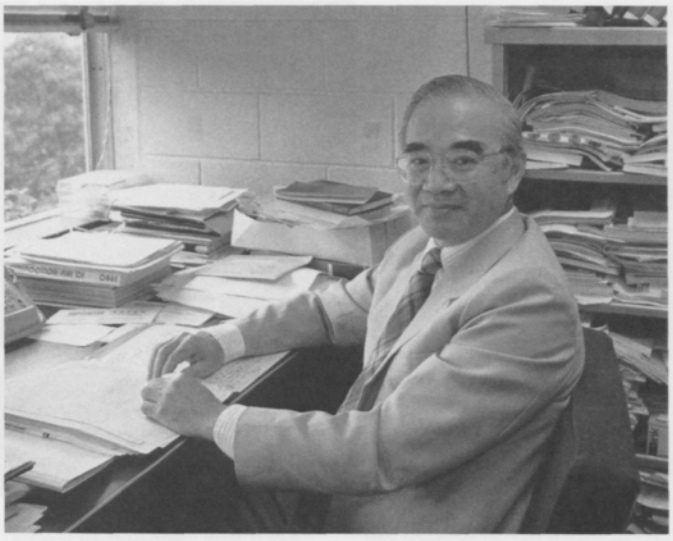
Shen's research interests include aerodynamics, fluid mechanics, and computational techniques. Recently, he was a consultant to the David Taylor Ship Research and Development Center of the U.S. Navy on matters concerning the seaworthiness of marine vessels on rough seas, the dynamics of giant helicopters with circulation-controlled rotors, and design modification of aircraft for carrier landing.

Shen was a Guggenheim fellow at the Eidgenössiche Technische Hochschule, in Zürich, in 1957; he was a visiting professor at the University of Paris in 1964 and 1969, at the Technical University of Vienna in 1977, and at the Institute of Space Sciences of the University of Tokyo in 1984–85.

In 1985, Shen received the Humboldt Prize and was elected to the National Academy of Engineering. He is also a member of the Academia Sinica (Republic of China), a fellow of the Washington Academy of Sciences, and a corresponding member of the International Academy of Astronautics.

Charles B. Wharton, who joined the Cornell faculty in 1967, has been named Professor of Electrical Engineering Emeritus.

Wharton holds B.S. and M.S. degrees from the University of California at Berkeley. An experimentalist by inclination, Wharton did research on microwaves and high-energy ion accelerators at Berkeley and later joined a group that began investigating the possibility of controlled fusion. When this group moved to Lawrence Livermore National Laboratories to begin research on magnetic mirror confinement, he headed the diagnostics development program and invented or developed many of the microwave diagnostic instruments now used in fusion experiments.

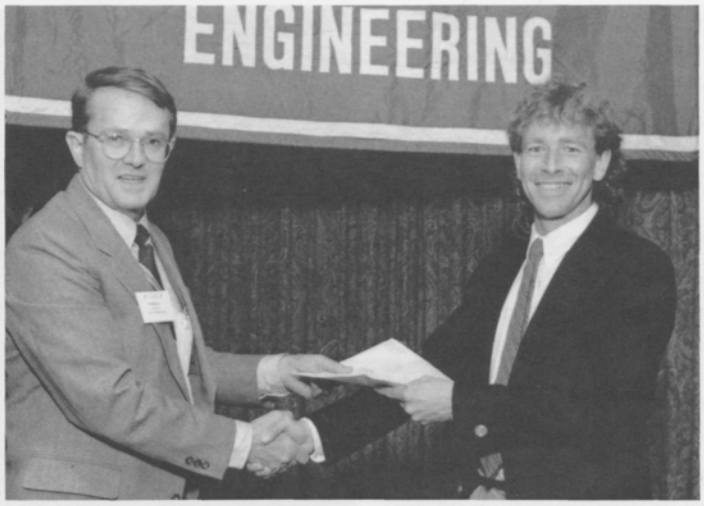


Shen

In 1962 Wharton joined an experimental physics group at the General Atomic Company. There, he participated in front-line experimental research including the first verification of Landau damping and discovery of the plasma wave echo.

In 1959–60 Wharton was a visiting scientist at the Max Planck Institute in Munich, Germany, and at the Atomic Energy Research Establishment in Harwell, England. He has been active in consulting and served as a director of the International School of Plasma Physics in Varenna, Italy. In 1973 he received the Humboldt Prize. He is a fellow of the American Physical Society and the Institute of Electrical and Electronics Engineers.

Wharton



David F. Delchamps (right) receives the Excellence in Teaching award from engineering dean William B. Streett.

■ ***David F. Delchamps***, an associate professor in the School of Electrical Engineering, has been named winner of the 1992 Excellence in Teaching Award.

The award, which includes a prize of $2,000, is sponsored by the Cornell Society of Engineers and the Cornell chapter of Tau Beta Pi, the national student honorary society in engineering. The recipient is chosen on the basis of student nominations.

Delchamps, who holds a B.S.E. from Princeton and S.M. and Ph.D. degrees from Harvard, joined the Cornell faculty in 1982 and has pursued research in the area of control and systems theory, with special emphasis on the theory of estimation and control for nonlinear systems. He is affiliated with the Center for Applied Mathematics at Cornell and is a member of the Institute of Electrical and Electronics Engineers and the American Mathematical Society. He won a National Science Foundation Presidential Young Investigator Award in 1984. He has also won several teaching awards, including the School of Electrical Engineering's Excellence in Teaching Award.

■ Five faculty members were chosen to receive the 1992 Dean's Prizes for Excellence and Innovation in Teaching. Each prize includes a cash award of $1,200.

Keith E. Gubbins, the Thomas R. Briggs Professor of Engineering in the School of Chemical Engineering, has consistently been one of the most respected teachers in the college. Students mention his professionalism, his organization of lecture material, his excellent presentations, his fairness, and his keen interest in making sure that the material is understood.

Andy L. Ruina, associate professor in the Department of Theoretical and Applied Mechanics, was cited for distinction in teaching undergraduate dynamics in T&AM 203. Students were impressed by his ability to communicate profound ideas by focusing on the operation of everyday objects.

Mary J. Sansalone, associate professor in the School of Civil and Environmental Engineering, was recognized for exceptional dedication to student learning in all phases of student-faculty interaction. She has motivated high school students and college freshmen to study engineering and has successfully addressed the special concerns of minority students. The Cornell student chapter of the American Society of Civil Engineers, with Sansalone as advisor, was selected as the best student chapter in the United States.

Charles H. K. Williamson, assistant professor in the Sibley School of Mechanical and Aerospace Engineering, was recognized for his outstanding teaching in lectures and laboratories and for exemplifying the ideal of involving students in the research life of the university.

Frank W. Wise, assistant professor in the School of Applied and Engineering Physics, was cited for revamping A&EP 264, "Computer-Instrumentation Design." He upgraded the computers used in the course and reprogrammed

Gubbins

Ruina

Sansalone

Williamson

all the assignments and programs. He also arranged for staff members of the Engineering Communications Program to help the students improve their technical writing.

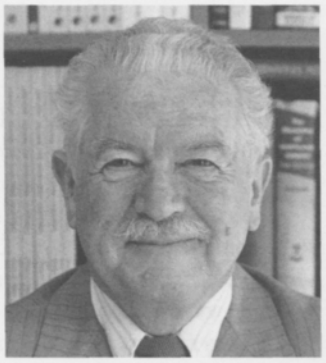
■ ***Sidney Leibovich***, the Samuel B. Eckert Professor of Mechanical and Aerospace Engineering, has been elected a fellow of the American Academy of Arts and Sciences.

An internationally recognized specialist in the field of fluid mechanics, Leibovich's research interests include fluid dynamics, wave propagation, and air-sea interactions; he is an authority on nonlinear waves.

Leibovich, who joined the Cornell faculty in 1966, is a member of the graduate Fields of Applied Mathematics, Theoretical and Applied Mechanics, Mechanical Engineering, and Aerospace Engineering. He has been a visiting scientist at the Weizmann Institute of Technology (Rehovot, Israel), and a British Science Research Council senior visiting fellow at the University of St. Andrews (Scotland). Leibovich is also a fellow of the American Physical Society and the American Society of Mechanical Engineers. He is a member of the Congress Committee of the International Union of Theoretical and Applied Mechanics and is chair of the delegation to its general assembly. He also serves as chair of the U.S. National Committee of Theoretical and Applied Mechanics.

Wise

Leibovich



Slate

White

■ Professor emeritus ***Floyd O. Slate***, of the School of Civil and Environmental Engineering, was elected to honorary membership in the American Concrete Institute. The ACI's highest award, honorary membership recognizes "persons of eminence in [the] field or those who perform extraordinary meritorious service to the Institute." Only 132 individuals, including Slate, have been elected to honorary membership since 1926, when this award was established. Slate was recognized for his distinguished career as an educator, his pioneering research in the behavior of cement and concrete, and his worldwide efforts in developing improved cement-based, low-cost housing.

Slate, who joined the Cornell faculty in 1949, has acted as a consultant to industry, primarily on concrete and other engineering materials, and has lectured and participated in seminars and workshops on six continents. He has researched and implemented low-cost housing in more than seventy countries, and at Cornell he organized a multidisciplinary program in low-cost housing for developing nations. He is the author of two books and about eighty technical papers. He has received many other awards from the ACI, and in 1986 he was chosen for the college's Excellence in Teaching Award.

■ ***Richard N. White***, the James A. Friend Family Distinguished Professor of Engineering in the School of Civil and Environmental Engineering, was recently elected to the National Academy of Engineering. White, who earned B.S., M.S., and Ph.D. degrees at the University of Wisconsin, joined the Cornell faculty in 1961. His research focuses on concrete structures, earthquake engineering, model analysis, and nuclear structures. He has been a visiting professor at the University of California at Berkeley (1974–75) and a staff associate at Gulf General Atomic (1967–68). At Cornell he has served as director of the School of Civil and Environmental Engineering and associate dean for undergraduate programs. White is a fellow of the American Concrete Institute and the American Society of Civil Engineers and a member of the National Society of Professional Engineers, the American Society for Engineering Education, and the Earthquake Engineering Research Institute. He was a co-recipient of the Collingwood Prize awarded by the ASCE, was the first recipient of the Cornell Society of Engineers Excellence in Teaching award, has co-authored five books, and is a registered professional engineer in the state of New York. He received the Joe W. Kelly Award of ACI in March 1992 and also was elected to the ACI Board of Direction at that time.

■ Several faculty members have received awards from the National Science Foundation.

Three junior faculty members in the College of Engineering received 1991 Presidential Young Investigator (PYI) awards from the National Science Foundation. This brings to thirty-six the total number of PYI awards made to Cornell engineering faculty members since the program began five years ago—representing about 5 percent of all engineering PYI awards nationwide.

New PYIs include ***James Engstrom***, chemical engineering; ***Niels Otani***, electrical engineering; and ***Éva Tardos***, operations research and industrial engineering. ***Nicolas Zabaras***, who joined the Cornell faculty last year in mechanical and aerospace engineering, also received a PYI award in 1991 while a member of the faculty at the University of Minnesota.

The awards provide $25,000 in research funding each year for five years. To encourage university-industry cooperation, NSF also provides up to $37,500 per year to match outside funding on a dollar-for-dollar basis, which brings the possible total support per recipient to $100,000 per year.

Engstrom's research focuses on developing a fundamental understanding of materials-processing operations that involve gas-surface interactions. These interactions include many chemical and physical surface-modification techniques of current interest, such as plasma etching, chemical vapor deposition, and molecular-beam epitaxy.

Otani uses computer simulation to study a range of plasma phenomena, including those occurring in nuclear fusion reactors, those found in the earth's ionosphere and magnetosphere, and those in and around the sun.

Tardos is working on the design and analysis of algorithms for fundamental problems of combinatorial optimization in both sequential and parallel settings, and problems related to linear and integer programming. She is also interested in the minimization of submodular functions and computational complexity theory.

Zabaras is developing accurate and innovative mathematical techniques for realistic engineering simulation and design of manufacturing processes.

The purpose of the Presidential Young Investigator awards is to support promising young researchers and encourage them to remain in academia.

Beginning in 1992, the National Science Foundation has replaced its Presidential Young Investigator Awards with two new programs to support outstanding science and engineering faculty: the Presidential Faculty Fellows Program (PFF) and the National Science Foundation Young Investigator Program (NYI). The new NYI program offers the same funding and similar eligibility requirements as the former PYI awards. Objectives are to recognize outstanding young faculty members in science and engineering, to enhance the academic careers of recent Ph.D. recipients by providing flexible support for research and teaching, and to foster contact and cooperation between academia and industry.

Three faculty members in the College of Engineering were selected for 1992 NYI awards: ***Joel D. Brock***,

Engstrom

Otani

Tardos

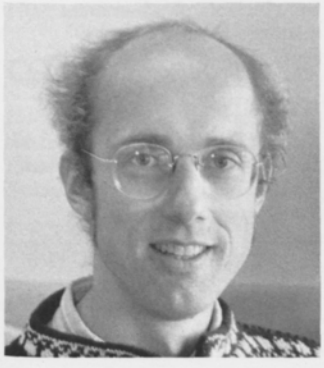
Zabaras

applied and engineering physics; ***Miriam Leeser***, electrical engineering; and ***Paul Pedersen***, computer science.

Brock's research involves using x-ray scattering techniques to study the role of symmetry, competing interactions, and spatial dimensionality in determining the structure, stability, and cooperative behavior of condensed matter.

Brock

Leeser



Pedersen

Leeser plans to concentrate on tools for generating floating point arithmetic designs. These tools should improve the quality of implementation and explore hardware and software boundaries and tradeoffs. Theorem-proving techniques will be applied to these design problems. Her work will result in a toolkit to aid designers in developing floating point arithmetic hardware and software.

Pedersen's research is in the general area of computational mathematics, which is a distinct and rapidly growing field that overlaps constructive mathematics, applied mathematics, theoretical computer science, and engineering.

■ Other recent faculty honors include the following:

Joseph A. Burns, professor of theoretical and applied mechanics and of astronomy, has been elected a fellow of the American Geophysical Union. Burns, who received the Ph.D. from Cornell, spent a postdoctoral year at NASA's Goddard Space Flight Center. His research interests include dynamics of the solar system, celestial mechanics, planetary satellites and rings, comets, and space exploration. He was recently appointed chair of the National Research Council's Committee on Planetary and Lunar Exploration.

Four faculty members in the School of Civil and Environmental Engineering have recently been honored. They are Peter Gergely, Kenneth C. Hover, Daniel P. Loucks, and William McGuire.

Peter Gergely was awarded an honorary doctorate from the Technical University of Budapest, where he began his undergraduate education. Interrupted by the Hungarian uprising of 1956, he completed his bachelor's degree at McGill University in Montreal. He earned the M.S. and Ph.D. degrees at the University of Illinois and joined the Cornell faculty in 1963. His research focuses on earthquake engineering, structural mechanics and dynamics, structural shells, and reinforced concrete.

Kenneth C. Hover was elected a fellow of the American Concrete Institute. After receiving bachelor's and master's degrees from the University of Cincinnati, Hover spent three years as an officer in the U.S. Army Corps of Engineers, serving as a unit leader. Then he joined a structural design firm and became interested in the analysis and rehabilitation of deteriorated concrete. This led him to Cornell, where he completed his doctorate and joined the faculty in 1984.

The German government has conferred on ***Daniel P. Loucks*** the prestigious U.S. Senior Scientist Award (known as a "Humboldt Prize"), which includes a research stay at a German university. Loucks, who joined the Cornell faculty in 1965, has primary research interests in interactive computer graphics and systems for water-resource and environmental management.

Professor emeritus ***William McGuire*** received two prestigious awards: the Shortridge Hardesty Award from the American Society of Civil Engineers and the 1992 T. R. Higgins Lectureship Award from the American Institute of Steel Construction. McGuire served in the Navy in World War II and spent two years practicing structural design before joining the Cornell faculty in 1949. His research centers on the application of interactive computer graphics to problems in structural engineering and structural mechanics.

FACULTY PUBLICATIONS

Current research activities at the Cornell University College of Engineering are represented by the following publications and conference papers that appeared or were presented during the three-month period January through March 1992. (Earlier entries omitted from previous Quarterly *listings are included here with the year of publication in parentheses.) The names of Cornell personnel are in italics.*

AGRICULTURAL AND BIOLOGICAL ENGINEERING

Cooke, J. R., and *E. T. Sobel.* (1991*a*). *ExamBuilder™ 1.0: A MathWriter™ 2.0 module for building examinations.* Pacific Grove, CA: Wadsworth, Inc.

____. (1991*b*). *MathWriter™ 2.0: The scientific word processor for the Macintosh.* Pacific Grove, CA: Brooks/Cole Publishing Company.

Delwiche, S. R., K. H. Norris, and *R. E. Pitt.* 1992. Temperature sensitivity of near-infrared scattering transmittance spectra of water-adsorbed starch and cellulose. *Applied Spectroscopy* 46:782–89.

Knowlton, K. F., R. E. Pitt, and *D. G. Fox.* 1992. Dynamic model prediction of the value of reduced solubility of alfalfa silage protein for lactating dairy cows. *Journal of Dairy Science* 75:1507–16.

Pitt, R. E. 1992*a*. Thermodynamics and intracellular ice formation. In *Advances in low-temperature biology*, ed. P. L. Steponkus, pp. 63–99. London: JAI Press Ltd.

____. 1992*b*. Viscoelastic properties of fruits and vegetables. In *Viscoelastic properties of food*, ed. M. A. Rao and J. Steffe, pp. 49–76. Essex, U. K.: Elsevier.

Pitt, R. E., M. Chandrasekaran, and *J. E. Parks.* 1992. Performance of a kinetic model for intracellular ice formation based on the extent of supercooling. *Cryobiology* 29:359–73.

van de Giesen, N., T. S. Steenhuis, L. W. Fitzgerald, M. E. Jensen, and J. Wolf. 1992. *U.S.-financed irrigation and drainage research: Applications for developing countries.* Irrigation Support Project for Asia and the Near East Report no. 44. Washington, DC: U.S. Agency for International Development.

APPLIED AND ENGINEERING PHYSICS

Bilderback, D. H., B. W. Batterman, M. J. Bedzyk, J. Brock, K. Finkelstein, R. Headrick, and *Q. Shen.* 1992. High-flux x-ray undulator radiation from proposed B factory storage rings at Cornell University. *Review of Scientific Instruments* 63(1):1590–93.

DiTusa, J. F., K. Lin, M. Park, M. S. Isaacson, and *J. M. Parpia.* 1992*a*. Finite-size effects in the low-temperature resistivity of CuCr films. *Physical Review Letters* 68(5):678–81.

____. 1992*b*. Role of phonon dimensionality on electron-phonon scattering rates. *Physical Review Letters* 68(8):1156–59.

Hopsfield, A., *P. Clancy, M. Teter*, and U.-W. Wang. 1992. Molecular dynamics using approximate kinetic energy functionals. Paper read at General Meeting, American Physical Society, 15–20 March 1992, in Indianapolis, IN.

Nelkin, M. 1992. In what sense is turbulence an unsolved problem? *Science* 255:566–70.

Reznik, G., and *M. Isaacson.* 1992. A technique for fabrication of textured thin carbon substrates. *Ultramicroscopy* 40:181–85.

CHEMICAL ENGINEERING

Bussell, S. J., D. L. Koch, and *D. A. Hammer.* 1992. Hydrodynamic interactions between proteins in biological membranes. Paper read at 1992 Meeting, American Society for Biochemistry and Molecular Biology/Biophysical Society, 9–13 February 1992, in Houston, TX.

Carpenter, J. K., and *P. H. Steen.* 1992. Planar-flow spin-casting of molten metals: Process behavior. *Journal of Materials Science* 27:215–25.

Carter, R. N., and *A. B. Anton.* 1992. Magnitude and effects of adsorbent temperature nonuniformities in temperature-programmed desorption. *Journal of Vacuum Science and Technology A* 10:344.

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A NOTE TO OUR READERS

A year has passed since we began publishing the *Quarterly* in its new format, and we would like to know how we are doing. When we adopted the eight-and-a-half-by-eleven design, we expected a deluge of reaction. But this never happened. One old-timer grumbled that with the loss of the nine-inch-square format the *Quarterly* had come to look so much like everything else that he almost threw it in the trash along with his junk mail. Another reader, who wrote to ask a favor, mentioned in passing that the new format looked nice. And that was the entire response to our face lift.

If no news is good news, most people must like our new look. But are they satisfied with the way we present the material? We have recently found that some readers consider the articles too technical and would like to see them made more accessible. This would involve a significant change in the character of the magazine, which we would not want to undertake without careful consideration.

We have always tried to aim the *Quarterly* at the "technically trained nonspecialist," making the assumption that people who are interested in engineering research and education have some background in science and mathematics. It might have been a long time since they sat in chemistry and physics classes, but we have assumed that they could follow a semitechnical argument and would find it a mind-stretching experience.

To pitch the articles toward a wider readership, we might have to write them ourselves. Faculty members who are used to writing for scholarly journals sometimes find it difficult to address a more popular audience. We try to reshape their work, encouraging them to explain technical details and to show the relevance of their research in a broader context. But we cannot rewrite a story completely, for the person who signs an article has a right to say how it should be.

Some of the best magazines published by other engineering colleges are written by their own staff members. Reporters interview people who conduct new and exciting research and then write about it in a style that they deem appropriate to their audience. The *Quarterly* is almost alone in featuring articles written by the faculty members themselves.

While it is impressive to have stories that come "straight from the horse's mouth," it is also important to have stories that readers can understand. We try to achieve both goals, but may not always succeed.

Should we continue with faculty-written articles pitched at a fairly high level, or should we change to staff-written articles that are accessible to practically everyone? Should we find some compromise between these extremes? Are there other alternatives? We would appreciate hearing the opinions of our readers.—DP

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