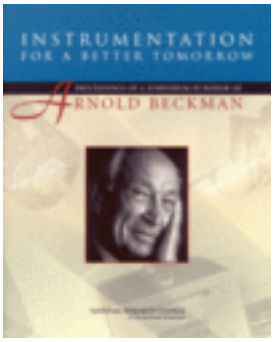

Instrumentation for a Better Tomorrow: Proceedings of a Symposium in Honor of Arnold Beckman

National Research Council

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INSTRUMENTATION FOR A BETTER TOMORROW

PROCEEDINGS OF A SYMPOSIUM IN HONOR OF ARNOLD BECKMAN

Board on Physics and Astronomy
Division on Engineering and Physical Sciences

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Among the many individuals to whom we express our heartfelt thanks and appreciations, we specially recognize the following: Jacqueline Dorrance and Kathlene Williams of the Arnold and Mabel Beckman Foundation; Amber Westberg of the Arnold and Mabel Beckman Center; James C. Osborne, Pat Ashton, and Sarah Nessl of Beckman Coulter, Inc.; Charles Casey and A.J. Ribes of the American Chemical Society; Robert Lukens, David Brock, and Robert Hicks of the Chemical Heritage Foundation; Gerald Gallwas of the Board of the Arnold and Mabel Beckman Foundation; Barbara Schlein of the President's Office at the National Academy of Engineering; Sharon Baker of the Chancellor's Office at the University of California at Irvine; and all of the dedicated staff at the National Academies' Board on Physics and Astronomy, including Timothy Meyer, Richard Rowberg, Don Shapero, and Pamela Lewis. Finally, conversations with the staff of the Institute of Medicine and the Beckman Institute at the University of Illinois at Urbana-Champaign and with Francis J. DiSalvo, David C. Clarke, Laura Greene, Frances Hellman, Venkatesh Narayanamurti, Richard Smalley, Paul Ferrara, Harry Gray, Nathan Rosenberg, and Dragana Brzakovic were invaluable.

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity and evidence. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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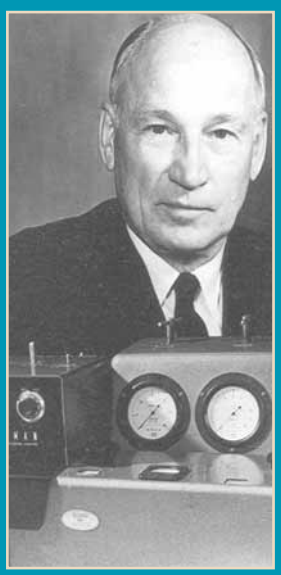
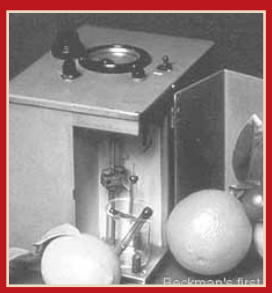
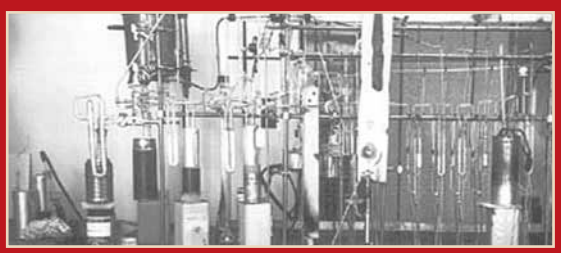


Arnold Beckman





A Better Tomorrow

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FOREWORD

On November 15, 2004, the National Academies sponsored a symposium at the Arnold and Mabel Beckman Center in Irvine, California, in honor of Arnold O. Beckman, the renowned inventor and philanthropist, who had died earlier that year at age 104. The title of the symposium was "Instrumentation for a Better Tomorrow," and it focused on the more practical, applied side of instrumentation, as was the focus of Arnold Beckman's career. Over the course of the day, the symposium participants were treated to a wide-ranging and inspiring overview of the role that research instrumentation has played, and will continue to play, in improving our lives. Many of the most important scientific and technological advances of the twentieth century were the product of devices that extended human observations and manipulations into new realms. Furthermore, many of these instruments have found applications far beyond the research laboratory, changing our lives in ways large and small. We benefit from advances in instrumentation every time we drive a car, shop at a store, go to the doctor, or turn on a computer or a television.

The importance of instrumentation in research has grown immensely since Arnold Beckman, then a professor at the California Institute of Technology, marketed his first commercially successful instrument in 1935—an electronic meter designed originally to measure the acidity of lemon juice. Today, the conduct of most research is essentially inseparable from the use of reliable, high-performance, and integrated research tools. Indeed, instrumentation has become so important in research that instrument development has itself become the subject of research, creating a positive feedback loop that has accelerated the pace of scientific and technological progress.

"simplify, innovate, and automate"

One of the guiding mottos of Dr. Beckman's commercial enterprises was "simplify, innovate, and automate," and each of these three admonitions was an important theme of instrument development throughout Dr. Beckman's career. Though the phenomena being studied in modern research laboratories are extraordinarily complex, an essential component of understanding has been to abstract some aspect of a phenomenon that can be observed or measured. Once recognized and quantified, this aspect can be used to help construct an understanding of the phenomenon in its full complexity. In the atmospheric sciences, for example, new instruments developed in recent decades, such as infrared spectrometers and flame ionization detectors used with gas chromatographs, have revealed a dynamism in the atmosphere that previously had been unsuspected. The major and minor constituents of the atmosphere interact with one another and with substances injected into the

Beckman's scientific instruments capitalized early on the capabilities of infrared light. Many technological applications of infrared light have since followed, including common remote controls. Courtesy of Wikipedia.

atmosphere in complex, unanticipated, and important ways. The revolution in the atmospheric sciences catalyzed by these instruments has led not only to greater understanding but to worldwide policies designed to protect the atmosphere from degradation.

The second of Dr. Beckman's guiding principles, "innovation," has become a centerpiece of advanced instrumentation. At the time of Dr. Beckman's first commercial enterprises, innovation in instrumentation was not perceived as a central part of the enterprise. Today, that attitude is gone. Researchers have realized that advances in instrumentation can be the key to both new discoveries and better technologies. For example, the instruments used to design, manufacture, and test integrated circuits have become as much the object of research as the integrated circuits themselves.

Researchers have realized that advances in instrumentation can be the key to both new discoveries and better technologies.

Finally, the drive to automate the observation and measurement of phenomena also has created new and often unanticipated opportunities. Though automation risks removing the researcher from the phenomena being studied, it can create capabilities not achievable in any other way. In the biomedical sciences, for example, analysis of thousands of genes and proteins interacting in complex ways is possible only through massive automation.

In general, instrumentation and research have a symbiotic relationship. Scientific and technological advances lead to new instruments, while important scientific and technological problems stimulate the development of new instruments. Instruments developed for one area of research often find application in other areas, both in the research enterprise and in the broader society.

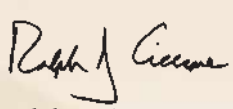
The summary of the symposium presented in this publication consists of three parts. Part I provides two perspectives on Dr. Beckman's life and accomplishments—one from his daughter, Pat Beckman, and the other from his biographer, Arnold Thackray. Together, these two personal reminiscences offer an insightful portrait of a remarkable man.

Part II consists of summaries of seven talks delivered at the symposium on various areas of modern instrumentation, from powerful x-ray light sources to magnetic resonance imaging devices to biosensors on tiny manufactured chips.

Part III presents a panel discussion of Dr. Beckman's contributions to science and of the vision of instrumentation and research that has emerged from his efforts.

The two of us can speak for everyone at the symposium in expressing our deep appreciation of and admiration for Dr. Beckman's accomplishments and convictions. By commemorating his life, we celebrate the work of a man who made the world a different and better place.

Wm. A. Wulf
President, National Academy of Engineering



Ralph J. Cicerone
President, National Academy of Sciences

Beckman

PART I

A DAUGHTER'S REMEMBRANCES

By Pat Beckman

Thank you very much for sponsoring this symposium. Dad would have been thrilled by the honor.

He left an enormous legacy that will always be larger than life. It began with his first job when he was six years old—he had to brush the flies off the noses of the big plow horses that his father the blacksmith was shoeing. He had lots of promise—midwestern values; good grades; he loved school; he was musically talented. The seeds of Dad's greatness and genius were sown very early.

When he was a kid, Dad decided he wanted to be a scientist. So he had cards made up that said, "Arnold Beckman, chief scientist." When he moved to Bloomington to attend high school, he decided that he wanted the corner back bedroom, so he painted his bedroom white, because all labs are white. But it took four coats, because he didn't understand that you have to use a primer.

He had great confidence. Once I asked him if he ever felt a lack of confidence, and he said no. Maybe that confidence came from his days of riding the rails. When he was coming out West, he would jump off a freight train, go to the back door of a café in town, ask for a job as a dishwasher, and work and quit after earning a bag of food. Then he would get back on the freight train until the next little western town. He learned to be self-sufficient.

He studied electronics at Bell Labs in New York, and he understood the electronics he was learning. When it came time to build the first pH meter, he made a fast, dependable, and accurate instrument that changed science forever. Of course, it didn't stop with the acidimeter. Dad went on to build a whole industry of fast, accurate, and dependable instruments. It was the melding of chemistry and electronics that first established his legacy.

His second legacy was a very successful melding of scientific knowledge and business acumen. Dad never quite admitted he was a businessman. He used to say that he backed into business. Rather, he would tell you that he was a problem solver, and of course he was a very good one.

In the 1970s, my parents set up a foundation. Beckman Instruments became enormously successful and world-renowned. It was sold in 1982 to SmithKline Corporation, the pharmaceutical house in Philadelphia, which then became SmithKline Beckman. Dad was now a very wealthy man. He used that wealth to build five centers and institutes at the University of Illinois, Caltech, Stanford, the City of Hope, and the Beckman Laser Institute here at the

University of California at Irvine. He said that scientists had been good to him by using his instruments so he would give back to them through the funding of the Beckman institutes and centers and many other scientific establishments. In September 1977, Dad said that the foundation had originally been established for the purpose of supporting basic scientific research, primarily in the fields of chemistry, biochemistry, and medicine.

After my mother died, in 1989, Dad placed the foundation in perpetuity. Its mission became "preserving and enhancing the capital assets and distributing only revenue to support leading-edge research in the fields of chemistry and life sciences broadly interpreted, and particularly to foster the invention of methods, instruments, and material that open up new avenues of research and application in these disciplines and related sciences." Dad wrote that when he was 90 years old.

The last paragraph of his philosophy statement is also instructive. Dad was aware that the funds in his foundation would grow and wanted those funds to support research, education, and facilities at the five Beckman institutes and centers. He also wanted to fund other institutions and did—so many that I won't recount here. But specifically they "should be primarily for research purposes and should be given for a limited time, one to three years." Then, my father said that his preference was to favor young investigators, new ideas, and a variety of projects, rather than fund large, established ones of long duration. Some of the variety of programs funded by the Arnold and Mabel Beckman Foundation are the Beckman Young Investigators Program for promising young faculty, the Beckman Scholars Program for undergraduate students, the research technologies initiatives, and in the past an Orange-County-wide, hands-on science program for elementary school children, to name just a few.

My father was always consistent. He had a set of what he called "The Rules That Govern My Life," which have been printed on a small foldover card. The first rule is and has always been, "Maintain absolute integrity at all times." That meant integrity in all things, such as when results do not match hypotheses in research.

But he also could poke fun at himself. I'll close with one of his favorite stories about integrity. Two men owned a store together. One day a patron came in to purchase an item. He paid for the item with a $20 bill. As the owner went to put the $20 in the cash register, he noticed that there were two new $20 bills stuck together. The owner wondered: Should he give the extra $20 to his co-owner, or should he pocket it himself?

Thank you and enjoy the rest of your day.

FINDING THE SWEET SPOT OF OPPORTUNITY

By Arnold Thackray, President, Chemical Heritage Foundation

Dr. Thackray (Ph.D., Cambridge University, 1966) has held faculty appointments at Oxford, Harvard, and the Hebrew University of Jerusalem. He was founding chair of the Department of History and Sociology of Science at the University of Pennsylvania. Dr. Thackray's scholarly interests lie in the historiography of science and in understanding technology, medicine, and science as elements of modern culture. He served as editor of Isis, *the official journal of the History of Science Society, and as editor of* Osiris. *Dr. Thackray is coauthor of the definitive biography* Arnold O. Beckman: 100 Years of Excellence. *He is a fellow of the Royal Society of Chemistry and of the Royal Historical Society. Dr. Thackray was the founding director of the Chemical Heritage Foundation.*

It is very special privilege and pleasure to be here on this beautiful day and in this beautiful place. It brings back memories of my first encounter with Dr. Beckman in his office on Jamboree Road, when this center was just a gleam in his eye. It's also a pleasure to be here because of the wonderful subject that is before us—the future and the promise of instrumentation. We've already heard that there is much to look forward to. What I want to do is set the context for you, paint in the background.

There are three important reasons for talking about Arnold Beckman and instrumentation at this symposium. The first is that instrumentation is a concealed subject; it's not something that you encounter in your day-to-day life. The second reason is that science looks toward the future, not the past. The third is that change is shaped by individuals.

Chemistry and instrumentation are both concealed. "Intel inside" is a great phrase. The Intel inside was put there by chemist Gordon Moore, who achieved what he did because of the knowledge and experience gained while in Beckman's employ. But when you think of Intel inside, you don't think of chemistry. Modern biotechnology is similar. Companies like Biogen and Amgen were conceptualized and created by Ph.D. chemists. The products of chemistry are everywhere, but chemistry itself is concealed. Instrumentation is even more concealed. Instrumentation is the tool or enabler with which you shape a product. But people tend to think about the lemon juice, not the juicer.

Second, science is forward looking. It's about what are you going to publish next week. If something is in the past, let's forget about it. But that is a terrible cultural loss. If there were no past associations among the people in this room, this would be a very poor meeting. Business is also forward looking. People look to tomorrow's bottom line. In addition, for the last 200 years we've been remorselessly specializing and differentiating, knowing more

FIGURE 1 (Above) The Beckman brothers, Arnold (center), Frederick, and Roland. (Right) George Beckman's blacksmith shop in Cullom, Illinois. Courtesy of the Beckman family.

and more about less and less. That makes it even harder to get a sense of the larger picture, which is one of the things that history brings us.

Finally, significant change is shaped by individuals. Change is not the result of vast, impersonal forces. Individuals intuit, act on, and exemplify the larger currents and opportunities in our world and catalyze what happens. Think of Russian history without Stalin, German history without Hitler, or U.S. or British history without Roosevelt or Churchill. And the significance of the individual is equally true in science. Think of Newton, Darwin, and Watson and Crick. Think of William Henry Perkin, whose discovery of mauve in the mid-nineteenth century created modern high-tech, industry-based science. Think of Fritz Haber at the start of the twentieth century, who personified German high-tech, professional expertise. Haber is the man who keeps half the world alive through his discovery of ammonia synthesis, which is fundamental to our ability to feed the world using modern fertilizers.

He was another individual who changed the world forever.

Arnold Beckman also intuited and acted upon the larger current in science and society. He was another individual who changed the world forever and, unlike some of the people I mentioned, changed it for the good.

Arnold Orville Beckman was a blacksmith's son, born in 1900 in Cullom, Illinois. He was simultaneously the baby and the firstborn, an unusual combination. His father's first wife had died after his two half-brothers were born *(see Figure 1)*. His father remarried, and Arnold was both the baby of the family and the firstborn—a younger sister followed. Then, when he was 12, his mother died, which was a tremendous blow in his life. We can only speculate about the psychological impact of being simultaneously the baby and the first born and then having his mother die, as we ponder the deep roots of his lifelong drive.

The world of 1900 was fundamentally rural. In 1900, 50 percent of people worked on farms, compared with 2 percent today. The great change has been not only in manufacturing but in the knowledge sector. Today the knowledge sector is the largest growth sector of our economy. Dr. Beckman recognized this trend very early on. Here in Irvine, for example, I don't see farms, factories, or smokestacks. I see the knowledge industry exemplified. This center itself is a sort of temple to the knowledge industry, and Arnold Beckman recognized that development.

Throughout his life he had an eye for the sweet spot of opportunity. Even as a very young man, he was able to excel. At the age of 14, after winning a scholarship to University High School in nearby Bloomington, he persuaded his father and family to move to Bloomington. Most people would have said "I'm where I am, and my education is what it is." But he moved the family, and in Bloomington he was the best student in his graduating class, achieving the highest average ever attained in his high school. And because there was a college in the town, he already had two and a half years of college chemistry under his belt at the age of 18.

Furthermore, his family was financially constrained, so he had to earn money. If you wanted someone to play at a dance on a Saturday night, the Beckman Orchestra would do that. Pat mentioned that he set up a chemistry consulting business. He played the piano at the local movie theater. He was a young man with very high energy levels and imagination, and he was going to seize his opportunities.

In 1918 he joined the Marines. Patriotic fervor was a reality, and Arnold Beckman was set to head off to Germany. But you needed a boat, and there weren't many boats in Illinois, so he departed for Brooklyn. There he met Mabel Meinzer of Brooklyn at a Red Cross dinner for the Marines on Thanksgiving Day in 1918. Mabel brought an enormous set of complementary talents to their marriage, which lasted for 64 years, until Mabel's death in 1989.

Before Beckman could set sail, the war was over. He moved back to Illinois and began studying chemistry, though he actually graduated with a degree in chemical engineering in 1922, from the University of Illinois. The University of Illinois at that time was the central chemical powerhouse of the land, which again reveals his instinct for finding the sweet spot of opportunity. He was editor of the *Illinois Chemist*, a very substantial publication. And he was making a mark on campus. For example, after World War I cut off the supply of organic chemicals from Germany, students worked in the summer making organic chemicals for sale, and Beckman participated in this activity. It helped to finance the chemistry department and gave the students practical experience—a powerful combination.

When he graduated from college, he wrote, "The world had a too cold and forbidding front when I was thinking of starting into business, so I decided to linger here at the schoolhouse. This graduate business is the real essence of education." In 1922, opting for graduate school was an unusual and risky choice, whereas today we are used to it. He was admitted to the Massachusetts Institute of Technology, but he decided to go to the California Institute of Technology. In retrospect Caltech was a great place to go, but Caltech was all of 4 years old at that time, so this also was a risky decision. The only problem was that Mabel was in Brooklyn. So after a year he dropped out, went to New York, and found a job at Bell Labs. There he was part of the founding research group and worked for Walter Shewhart, the great guru of quality control, whose disciple Edward Deming is more familiar today. So he was learning not only about electronics but also about quality control.

He moved back to Caltech in 1926, a year after his marriage to Mabel, and received his Ph.D. in 1928. Then he was asked to join the faculty—a great honor given the faculty's small size. He specialized in glass blowing and apparatus building. He was active in the hands-on aspect of chemistry, and of course chemistry is a very hands-on science.

But if you look at Arnold Beckman in this period, he was very restless. He was engaged in various ventures, but he did not entirely know where he was going. Where he ended up, of course, was with the pH meter.

That story, which I'll discuss in a moment, is very well known. But there were always many other facets to his life. He had a growing family. As his business grew, so did the responsibility of being a local, national, and global citizen. He participated in charity campaigns and was a key player in the smog understanding and elimination program. He was Orange County man of the year and on the Caltech board. He met with three different U.S. presidents and in the later

Prototype 1938 television from GE. Courtesy of Darryl Hock.

stages of his life became very active in philanthropy. He had an extraordinarily full and diverse life at every moment.

There are four aspects of Dr. Beckman's life and work that I would like to discuss this morning. First is his inventive restlessness. Second, his contributions to chemists' tools. Third, the new biology. And, fourth, the electronic future.

While he was in graduate school at Caltech he kept a journal of patentable ideas. Some of you know that he was something of an infamous speeder in cars during his life. His first patent, in 1927, was for a device that would sound a buzzer and alert the driver when the car reached a preset speed. It's an early version of cruise control. Chrysler was interested enough in it to talk with him about a license, though the talks didn't go anywhere.

Other potentially patentable ideas from his graduate school journal were an alarm for a typewriter to signal when it is nearing the bottom of a piece of paper, the use of electron beams to record sound on motion picture film, an electronic organ, a system for maintaining butter at optimal spreading temperature, whitening toothpaste that uses dyes instead of bleaches, and a self-sharpening pencil. He was not your average Caltech graduate student; he was someone with a remarkable inventive restlessness.

At the same time he was working on his Ph.D., on the photochemistry of hydrogen azide, with Roscoe Dickinson. To conduct his experiments, Arnold Beckman needed some very precise measurements and found that commonly available thermometers weren't sufficient. This led to his first publication, which described a new piece of apparatus, a quartz-fiber manometer. Meanwhile, he was working with A.A. Noyes, one of the great luminaries of Caltech, on a new periodic table. It was based on ions and energy groups and represented nothing less than an attempt to rewrite the periodic table. This work was presented at the Pacific Division of the American Association for the Advancement of Science and appeared in 1927 in the Proceedings of the National Academy of Sciences.

In the 1930s Dr. Beckman met Lee De Forest, the inventor of the vacuum tube, who was inaugurating the electronic age. De Forest was living in Hollywood and trying to develop tel-

evision. His concept was to use metal-coated film to reproduce sound and pictures, and to produce the required film in the needed volume he turned to Dr. Beckman, who developed a film-coating machine that he patented. De Forest's system didn't go anywhere, but it gave Dr. Beckman an opportunity to interact with probably the leading inventor of the period.

During this period, Dr. Beckman also was an expert witness. His consulting activities added about $150 a month to his assistant professor's salary. That doesn't sound like a lot, but it was 50 percent of his salary. As he oversaw the design and construction of the family house in Altadena, this was very welcome. And speaking of the sweet spot of opportunity, one of the most important cases he worked on was brought by a young district attorney named Earl Warren, later chief justice of the U.S. Supreme Court, involving an outrageous scam in the oil industry.

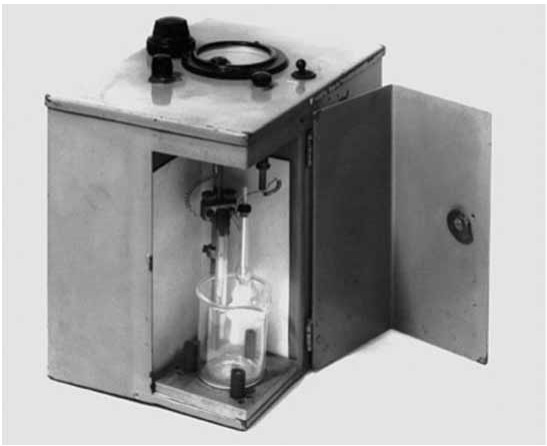


FIGURE 2 Arnold Beckman's first integrated pH meter, the acidimeter, circa 1934. Courtesy of Beckman Coulter, Inc.

The next thing Dr. Beckman pursued was postal meters. A local company, grandly called the National Postal Meter Company, had a problem with its inks, and Dr. Beckman developed a nonclogging formulation for the company. Then he decided to go into business to produce the ink himself, because people were having difficulties with the composition of the ink. He set up a subsidiary, the National Inking Appliance Company, in which he was vice president and general manager. Of course, he began thinking of other options. He developed a typewriter ribbon that is continuously reinked, an ink-loaded ribbon bobbin, and an ink-soaked sponge. But this was in 1936, and his work in inking was interrupted by the pH meter.

Dr. Beckman invented the pH meter, which was first called the acidimeter, in 1934 (*see Figure 2*). A friend on the *Illinois Chemist*, Glen Joseph, came to his old colleague with a problem. Joseph, a chemist working with the citrus industry, needed to find a way to measure the acidity of lemon juice. He tried using a hydrogen electrode, but it quickly fouled because of the sulfur dioxide preservative in the juice. A glass electrode would work better, but it produced a very weak signal.

Courtesy of Beckman Coulter, Inc.

Dr. Beckman's knowledge of electronics allowed him to make an electronic amplifier so that the rugged glass electrode method could be used to measure pH. Then he again began looking for the sweet spot of opportunity. He traveled the country seeking buyers for the pH meter, though he did not meet with much enthusiasm. But in Philadelphia Arthur H. Thomas, a big instrument supplier, told him that maybe 600 meters could be sold over several years. There's my business, Dr. Beckman said. But the business grew much faster than expected. By the late 1930s he was stepping out from Caltech and going full-time into business.

The difference between innovation and invention is that an invention is an idea, whereas an innovation is an idea out in the world.

This was just as the storm clouds of World War II were gathering. During the war his firm developed the first spectrophotometer produced in large quantities, the DU spectrometer. By now the company making these instruments was called National Technical Laboratories, but Dr. Beckman did not own the company, which raises interesting issues about inventors, entrepreneurs, and financiers. Dr. Beckman was simultaneously a very small shareholder and the major producer of ideas for this company.

By 1941 and 1942, National Technical Laboratories was becoming a large firm, and the directors were saying, Don't rock the boat. But Dr. Beckman saw opportunities, and he found a way to pursue them. By the end of World War II he had founded and was the boss of two other companies. One was Arnold O. Beckman, Inc., which made oxygen analyzers, and the other was Helipot Corporation, which made the Helipot variable potentiometer. These devices were coming into their own.

The development of chemists' tools was a theme throughout Dr. Beckman's life. An important aspect of innovation is whether you can get society to adopt an idea. The difference between innovation and invention is that an invention is an idea, whereas an innovation is an idea out in the world. There's a crucial difference between those two things.

FIGURE 3 Dr. Beckman shown with an early Beckman DU spectrophotometer, circa 1953. Courtesy of Beckman Coulter, Inc.

The development of chemists' tools would be enough for one life. That, however, was only the beginning, because the DU spectrometer marked the beginnings of Dr. Beckman's move toward the new biology *(see Figure 3)*. The Nobel laureate Bruce Merrifield said many years later that the most important instrument ever developed in the advancement of the biosciences was the DU. A different form of testimony comes from Carl Djerassi, an inventor of the birth control pill. He once said that the reason he went to work for the Mexico-based firm Syntex was because when he visited the company, to his amazement it had a DU. Syntex, by the way, in many ways was the first biotech company. As early as 1960 it had started an Institute for Molecular Biology in Palo Alto.

Another very early purchaser of the DU was Erwin Chargaff, the legendary biochemist and perhaps the world's leading expert on DNA at that time. With the DU, Chargaff was able to measure the relative abundance of the different bases in DNA. This resulted in Chargaff's rules, which established that the pairs of bases in DNA almost always occurred in equal amounts. This key insight led directly to Watson and Crick's determination of the structure of DNA. James Watson himself wrote:

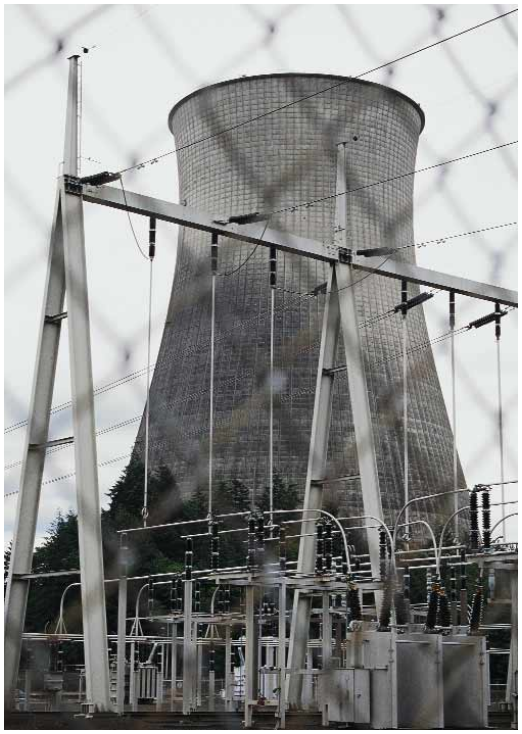
> *I can see . . . that our pursuit of the chemical underpinnings of biology has depended as much on the invention of new instrumentation and experimental procedures as on the generation of new experimental results and new ideas. Arnold Beckman's contribution to science and to society came, in part, from his rare talent for creating these new instruments and his decision to make them available to industry and science alike.*

The new biology also extended into the clinic. In the 1960s, Arnold Beckman led the charge for his firm's entry into clinical instrumental markets, where laboratory scientists used instruments to put modern medical information into the hands of clinical practi-

tioners. And Beckman Coulter continues along this path today with such products as the automated DNA synthesizer and other instrumental platforms for genomics.

Even with the new biology, Dr. Beckman was just getting started. Beginning in the 1930s and especially in the 1950s, he led his firm in profoundly important new directions connected with the emergence of the modern electronic age. Initially, the guts of the pH meter became products in themselves. Dr. Beckman realized that he had a powerful measuring device in the amplification circuits used in the meter, which made it a superb microammeter. He began producing the microammeter as a product in itself. For example, it found considerable service in monitoring the performance of early nuclear reactors. This led him to other kinds of electronic devices. The helical potentiometer was a component of the pH meter for which Dr. Beckman had a patent. During World War II, engineers developing radar discovered that the available variable potentiometers were not accurate enough. So Dr. Beckman set up a new company, the Helipot Company, to produce helical potentiometers during the war and after and began serving a booming market.

In the 1950s, Dr. Beckman was creating electronic measuring devices, advanced electronic components, laboratory and industrial automation, digital computing, and semiconductor technologies. In all of these areas, he was ahead of his time, but he had seen the sweet spot of opportunity. If you follow this thread out, in the 1970s, Beckman Instruments was, for instance, the global leader in the production of liquid crystal displays. The systems division of Beckman Instruments produced both analog and digital computers serving a variety of customers, including oil refineries, NASA, the Air Force, and aerospace companies.

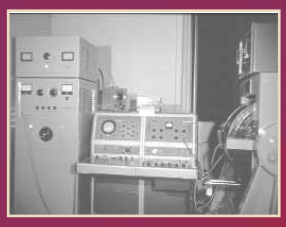


Even with all of this, we haven't touched upon the birth of Silicon Valley. Next year is the fiftieth anniversary of William Shockley's momentous phone call to Arnold Beckman, along with the fortieth anniversary of Moore's law. In 1955, Shockley, who was trying to develop the transistor, called Dr. Beckman and said, "I'm leaving Bell Labs. I need someone to back me." Arnold Beckman became the 100 percent funder of Shockley's semiconductor laboratories. Shockley also said, "There are only going to be about a dozen of us, and I don't really want to be in Pasadena. I'm awfully attached to my mother, who lives in Palo Alto. Do you mind if I set up there?" Another company acquired by Dr. Beckman, the centrifuge manufacturer Spinco, was already in Palo Alto, so Dr. Beckman said, "I suppose so." That's how the silicon got to Silicon Valley. Shockley went in a direction that did not have commercial utility, but under the influence of Arnold Beckman he hired the best people. These individuals went from Shockley to Fairchild to Intel and into all the rest of what became Silicon Valley. These were the people who understood where to go with this technology, and Dr. Beckman made this history possible.

A Beckman ad from 1960 read like this: "Since the year one there has been no change in the scientific method. Only the tools are different. Our job—providing them. . . . One day the present science of electronics will be supplemented or replaced. Still newer technologies will need even more advanced instruments to implement them. Our catalog for the future? We're working on it now." That's a wonderful text for our discussions today. Our task is to take up the challenge that Dr. Beckman laid out more than 40 years ago.

Beckman

PART II



A LIFETIME OF EXPERIENCE IN THE GROWTH OF MODERN INSTRUMENTATION FOR ORGANIC CHEMISTRY

By John D. Roberts, Professor Emeritus of Chemistry, California Institute of Technology

Dr. Roberts (Ph.D., UCLA, 1944) began his career as a National Research Council fellow and instructor at Harvard University. He joined Caltech as a professor of organic chemistry in 1953 and became chair of Chemistry and Chemical Engineering (1963-1968) and vice president, provost, and dean of the faculty. During his tenure at Caltech, he was a friend and colleague of Arnold O. Beckman. Dr. Roberts is a member of the National Academy of Sciences. He has received the Welch Award, the National Medal of Science (1990), and the ACS Arthur C. Cope Award. Dr. Roberts has authored more than 500 research publications, including 10 books. His current research involves applications of nuclear magnetic resonance spectroscopy to physical organic chemistry.

Arnold Beckman created new ways of analysis that truly revolutionized how chemical, biochemical, and medical research are done. Near the beginning of this revolution, I used a Beckman pH meter at UCLA in 1938 and subsequently a newly minted DU visible-ultraviolet spectrophotometer in undergraduate research.

In 1938, organic chemistry was characterizing its products just as for the previous 100 years. For solids: melting points, elemental analysis, and molecular weights. For liquids: boiling points, densities, and refractive indices. Indeed, a Zeiss refractometer was our only instrument for characterizing liquids.

Later, at MIT, a DU spectrometer served me well, but it was not widely applicable to the compounds I was studying. Infrared was better, and MIT's spectroscopist had a Perkin-Elmer single-beam infrared spectrometer, which was more applicable but difficult to use. Here, "simplify, innovate, automate" produced double-beam infrared spectrometers, first marketed by Baird Associates and later by Beckman and Perkin-Elmer. Infrared then took over most organic characterization by storm. However, only 3 to 4 years later, nuclear magnetic resonance (NMR) stirred up its own hurricane of interest.

Early refractometer, circa 1920. Courtesy of Richard A. Paselk, Humboldt State University.

What was different? Both infrared and NMR provide spectral regions characteristic of particular structural elements, but NMR offers more of them. The phenomenon

FIGURE 5 40-MHz iron magnet, probe, and sample (1954).

Arnold Beckman created new ways of analysis that truly revolutionized how chemical, biochemical, and medical research are done.

of spin-spin splitting allows determination of local structural environments of many kinds of functional groups. Quantitative analysis by infrared requires reference samples and calibration, while for NMR, the relative integrated intensities of spectral peaks of NMR spectra can be quite accurate. NMR has the advantage, except for two particulars. First, infrared absorptions are easier to understand than excitation and detection of nuclear magnetic states. Second is the cost differential, with NMR being more expensive by a factor of 10 to perhaps 500 or so on the high end. Cost might seem to depress NMR sales, but chemistry departments in research universities normally have between $5 million and $15 million or more invested in NMR equipment.

Fifty years following the first commercial NMR spectrometers, innovation seems not to be slowing but speeding up. We now trace the evolution of NMR instrumentation from the era of throwing switches, turning knobs, and pressing buttons to computer-driven black boxes with no user-serviceable parts inside.

How does NMR work? First, know that most NMR spectra are taken of hydrogen nuclei (protons). Hydrogen is generally abundant in organic compounds, and protons are the best NMR-active nuclei to observe. Consequently, the first commercial NMR spectrometers were primarily focused on proton spectra.

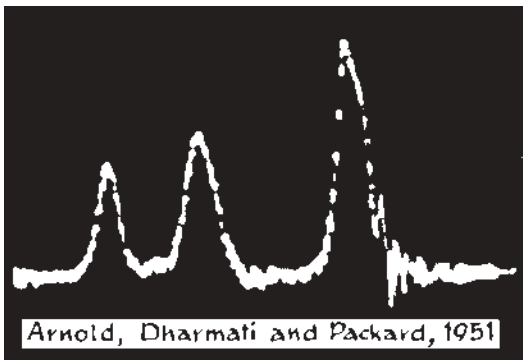


FIGURE 4 First published proton NMR spectrum of ethyl alcohol.

When an atomic nucleus in a magnetic field is exposed to photons that have an energy corresponding to the difference in energy between two possible orientations of its magnetic moment, it will resonate—that is, its magnetic moment will rapidly change orientation, in the process first absorbing energy and then radiating it. Only a finite number of different orientations are possible for the magnetic moments of any such nucleus in a magnetic field, each orientation having its own characteristic energy. This process occurs at a very precise frequency, $\nu = \gamma B_0$, where γ is the nuclear constant for the nuclei undergoing absorption of energy and B_0 is the strength of the magnetic field at the nucleus. The common way to detect the absorption of energy is with a receiver coil tuned to the frequency, ν.

FIGURE 6 40-MHz console, magnet, and power supply (1954).

One-of-a-kind NMR spectrometers have been constructed in several laboratories, but our concern here are the commercial instruments sparked by Felix Bloch and his co-workers at Stanford in conjunction with Varian Associates. Bloch shared a Nobel prize with Edward Purcell (Harvard) for condensed-state NMR. His instrument was geared to liquid samples and well suited for commercial development. Initial customers were chemical and petroleum laboratories. DuPont was sufficiently impressed by a 1951 proton spectrum of ethyl alcohol *(see Figure 4)* to advance $10,000 to Varian to facilitate completion of its first commercial spectrometer.

The spectrum shown in Figure 4 is crude but informative in showing three peaks, the area under which is in a ratio of 1:2:3 as suits the structure $HO\text{-}CH_2\text{-}CH_3$. Clearly, the OH proton resonance peak is on the left, the CH_2 resonances in the middle, and the CH_3 resonances on the right. No other physical procedure is so simple and clear in confirming the structure of a liquid molecule.

An early commercial NMR had an electromagnet weighing about 1,500 lbs., water-cooled with 12-in. pole faces, operating at 9,400 gauss *(Figure 5)*. The sample was contained in a 5-mm glass tube surrounded by oscillator and receiver coils at right angles to one another. The console *(Figure 6)* has the 40-MHz oscillator and receiver controls (driven by knobs, dials, and buttons, not by a computer); to the left is the power supply for the magnet. Atop the console is a Hewlett-Packard audio oscillator—its first product of the instrument revolution.

The more detailed alcohol spectrum *(Figure 7)* illustrates three important things NMR does for organic chemists. First, it shows the same three groups of protons as in Figure 4 separated in frequency by chemical shifts. Chemical-shift differences result largely from differences in diamagnetic shielding of the protons by nearby valence electrons. Chemical shifts are reasonably predictable and useful in structural analyses.

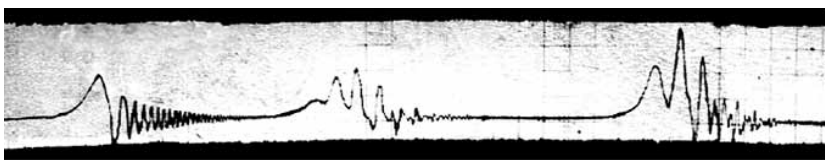


FIGURE 7 Proton spectrum of ethanol taken in 1955 with our first generation spectrometer.

FIGURE 9 Varian A-60 (60 MHz) spectrometer, the first real hands-on NMR instrument for everyone. Sitting at the spectrometer is Edward L. Ginzton, former chairman and CEO of Varian, Inc.; standing left to right is Tim Kingston; Wesley A. Anderson, NMR spectroscopist from Varian, Inc., who was involved with Fourier-transform NMR; Andy Baker; George Schulke; John Moran; James N. Shoolery, director of the Varian NMR Applications Laboratory, who worked closely with potential customers to show how Varian spectrometers could be used in their own applications; and Bob Gang. Photo taken in 1961.

Then, the three groups of protons are resolved into multiple peaks, seen in Figure 7, each resulting from spin-spin splittings. Without explaining the complexities, such splittings tell much about what other magnetic nuclei are close to a nucleus of interest, usually one to three connecting bonds away.

Last, note that the OH hydrogen of alcohol in Figure 7 shows no splitting. This is an additional example of NMR's unusual powers, here in connection with reaction rates. If the intermolecular exchange of the OH protons is fast, a single OH resonance will result. With purified alcohol, the OH line becomes a triplet, which indicates that intermolecular exchange occurs less than once every 0.01 seconds.

Research on such exchange processes requires good temperature control not available on the early spectrometers. Here, I turned instrument developer and designed a vacuum-jacketed, temperature-controlled probe *(Figure 8)*, which, in improved form, is standard on almost all modern NMR instruments.

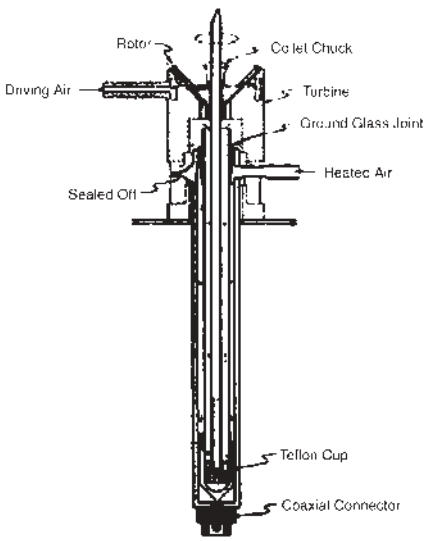


FIGURE 8 Vacuum-jacketed, temperature-controlled NMR probe.

"Simplify, innovate," was achieved by Varian Associates' A-60 spectrometer *(Figure 9)*, the first hands-on, easy-to-operate NMR machine. Its major flaw was vacuum-tube electronics. Trouble meant changing and rechanging tubes until order was restored. Despite this, the A-60 was immensely successful and allowed any interested organic chemist to use NMR. The A-60 spectral charts were standard. Varian published two volumes of sample proton spectra, which were very useful, and that was great low-key advertising.

At that point in history, one might have concluded that the NMR spectrometer problem had been solved—it only needed modern electronics, and a perfect hands-on NMR machine would emerge. However, new vistas opened up. One was ^{13}C spectra. The ^{12}C nucleus has no magnetic moment and no NMR signals. However, ^{13}C is an important nucleus for chemical work, but it has a low abundance in nature, 1.3 percent, and a nuclear moment 1/4 that of protons. Consequently, it gives weak NMR signals at the natural abundance level. Acetic acid *(Figure 10)* gave the first ^{13}C spectrum at that level.

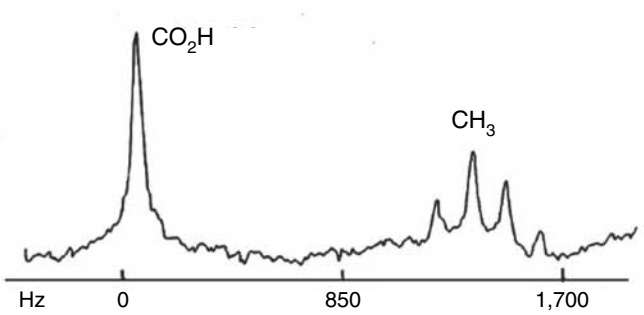


FIGURE 10 ^{13}C NMR spectrum of acetic acid.

The CO_2H carbon peak is on the left and the CH_3 carbon is on the right, split into four by the three attached protons. Such spectra, even if noisy and poorly resolved, whetted the interest of chemists in ^{13}C. However, the very weak ^{13}C signals required improvements in stability and enhancement by repetition and averaging.

The first spectrometer combining ultrastability and time averaging for ^{13}C looked different from an A-60. It incorporated a Hewlett-Packard digital-frequency sweep oscillator and was called the DFS-60 *(Figure 11)*. With it, useful spectra could be taken on quite large molecules, such as cholesterol.

Spectra of ^{15}N at its low natural abundance (0.3 percent) and a magnetic moment 1/10 that of protons were a greater challenge. The first ^{15}N spectrum taken at natural abundance concentration was the single resonance of liquid hydrazine taken in the DFS spectrometer at 6 MHz. Why not use abundant ^{14}N nuclei? They give NMR spectra, but the signals are too broad to be useful. Routine ^{15}N spectra required three major improvements: First, commercial development of superconducting magnets with fields 5 to 15 times stronger were needed to achieve greater magnetization of the ^{15}N nuclei.

Pulse FT NMR was the next giant step in NMR technology, where nuclei are flipped to upper magnetic states by powerful, very short pulses. A short enough pulse (microseconds) excites protons with very different chemical shifts. The decay of the magnetization induced in the sample is recorded digitally and usually takes a few seconds for protons at room temperature. The result is a free-

FIGURE 11 The DFS-60 NMR spectrometer, the first routine ^{13}C instrument, used time averaging. Photo taken in 1966.

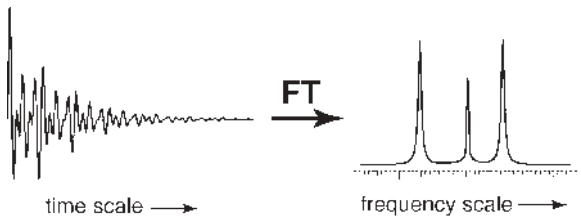


FIGURE 12 A multifrequency free induction decay (FID) and its Fourier transform.

induction decay (FID) *(Figure 12)*. The frequencies in this decay can be extracted with the Fourier transform (FT). For multiple frequencies, the decay is complex, but FT delivers resonance positions and their relative intensities. Computation of an FT for even a few digitized points is difficult, because many sin and cos values are required. Finally, fast computers were needed before this innovation could be implemented for NMR.

These elements together led to a useful spectrometer for ^{15}N at the natural abundance level with a superconducting magnet. An ^{15}N spectrum of the amide nitrogens of vitamin B_{12} is shown in Figure 13. The peaks go downward, because the γ constant of ^{15}N is negative.

Another giant step was massaging FIDs with pulses or continuous radiation to change the decaying magnetizations. An example, a two-dimensional correlation spectroscopy (COSY) plot *(Figure 14)* of nonexchanging ethyl alcohol, shows the chemical shifts and which of the hydrogens split each other. Spots on the diagonal show chemical shifts. The off-diagonal spots denote splittings, if any. Protons separated by three bonds split each other's resonances, but HO and CH_3 groups separated by five bonds do not split each other. With complicated molecules, COSY is a very important tool for analyzing splittings. Currently, probably 500 or more programs, like COSY, are available for massaging FIDs to improve the information content of NMR spectra.

What next? A relentless war to increase sensitivity by reducing electronic noise in the pickup coils. One way is to cool receiver coils and preamps close to liquid helium temperatures without cooling the sample. Both leading NMR purveyors, Varian and Bruker, offer this complex and expensive option, where the helium used for cooling is recycled. Signal-to-noise is improved by a factor of 3 or 4. An obvious way to increase the sensitivity of NMR detection, which advantageously spreads peaks separated by chemical shifts farther apart, is to use higher magnetic fields. Commercial NMR started with iron magnets at 30 MHz, but now almost all

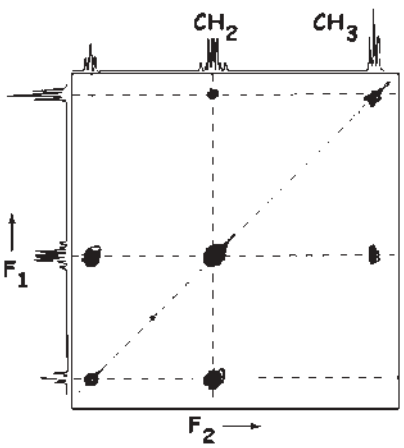


FIGURE 14 Two-dimensional correlation spectroscopy (COSY) plot of ethanol.

commercial spectrometers use superconducting magnets. The current highest field is a 900-MHz Bruker self-shielded magnet. This is a super technological accomplishment that provides a 30-fold (compared with 50 years ago) enhancement in field strength.

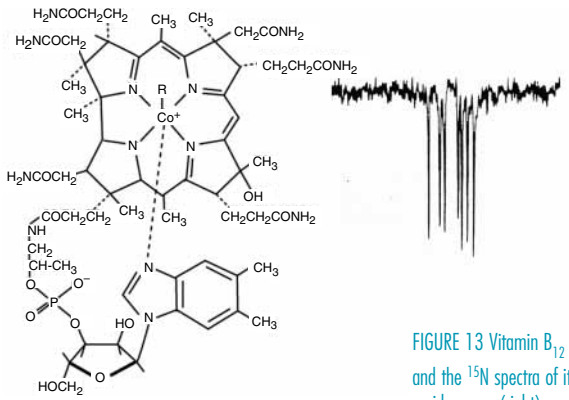


FIGURE 13 Vitamin B_{12} (left) and the ^{15}N spectra of its amide group (right).

Where do we go from here? One innovative approach is the extraordinary BOOMERANG spectrometer developed at Caltech by Daniel P. Weitekamp. Figure 15 shows a proton NMR prototype about the size of a coffee mug, operating at 7,000 gauss (27 MHz) with a 2.6-mm sample. It is a force-detection NMR (FDNMR) spectrometer. How does it work? The magnets are unusually shaped, but it has the customary excitation coil. The detection system is different. Basically, magnets detect the changes of force on excitation and decay of the magnetic nuclei in the sample. The changes in force are transmitted mechanically to a vibrating silicon plate, the resulting picometer changes in vibration amplitude are detected by an optical interferometer, and the FID is turned into a spectrum by FTs.

Where do we need this new detection scheme? It is the preferred method for obtaining spectra of very small samples. The changes in signal-to-noise ratio plotted on a log scale for calculated inductive-coil detection as a function of sample size compared with changes in signal-to-noise ratio for force detection show the latter is much better for very small samples. Weitekamp's goal is to be able to obtain an NMR spectrum for a single molecule.

How can the FDNMR spectrometers be made smaller? Put them on a chip! Such chips are being developed at Caltech's Jet Propulsion Laboratory, and we may eventually be able to send NMR spectrometers to Mars!

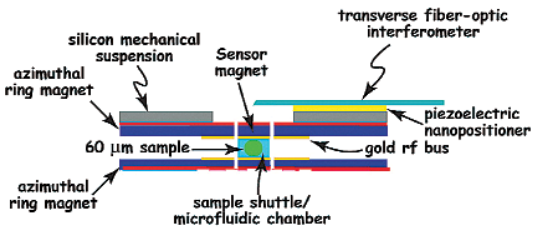


FIGURE 15 Cross section of a force-detection NMR (FDNMR) magnet on a chip.

It is fair to conclude that NMR is very much alive, and even after 50 years of commercial development, it is not yet mature. Still a teenager with great promise ahead!

MOLECULAR AND SYSTEMS BIOLOGY

By Leroy Hood, President, Institute for Systems Biology

Dr. Hood (M.D., Johns Hopkins, 1964; Ph.D., Caltech, 1968) began his career at Caltech, where he and his colleagues pioneered four instruments that comprise the technological foundation for contemporary molecular biology. In particular, the DNA sequencer revolutionized genomics by allowing the rapid automated sequencing of DNA. While at Caltech, Dr. Hood and others worked with Arnold O. Beckman to organize the Beckman Institute in 1986. In 2000, Dr. Hood cofounded the Institute for Systems Biology in Seattle. He has been honored with numerous academic and scientific awards for his study of immune diversity, continuing development of instrumentation, improvements to diagnostic methods, and efforts to open doors for new treatments and cures. Dr. Hood is a member of the National Academy of Sciences, the Institute of Medicine, and the American Association of Arts and Sciences.

You need to use frontier problems in biology to drive the kinds of technology you want to develop.

I was at Caltech for 30 years—four years as an undergraduate, four years as a graduate student, and then 22 years as a faculty member. During that time, I participated in four transformational developments in biology: the creation of new technologies, genome biology, systems biology, and personalized medicine. Each of these advances should be seen as nothing less than a paradigm shift in the biological sciences, with all of these paradigm changes driven by changes in technology.

When I became an assistant professor at Caltech in 1970, I divided my time equally between biomedical research and the development of new instruments, despite some resistance from the department. However, the two should not necessarily be seen as distinct. You need to use frontier problems in biology to drive the kinds of technology you want to develop. And once you've developed those technologies, they in turn allow you to remove the shrouds of confusion from these frontier areas.

One of the first instruments that my colleagues and I successfully developed was a device to determine the amino acid sequence of proteins. With a sensitivity much greater than any previously available instrument, the device allowed us to look at biologically interesting proteins that had theretofore been invisible. With University of California, San Francisco, professor Stanley Prusiner, we sequenced the proteins involved in prion diseases—work that helped Prusiner win the Nobel Prize in 1997. We sequenced the protein erythropoietin, a hormone that stimulates the production of red blood cells and was one of the first billion-dollar products in the biotechnology industry. We also sequenced proteins involved in neurotransmission, stem cell development, and immune reactions.

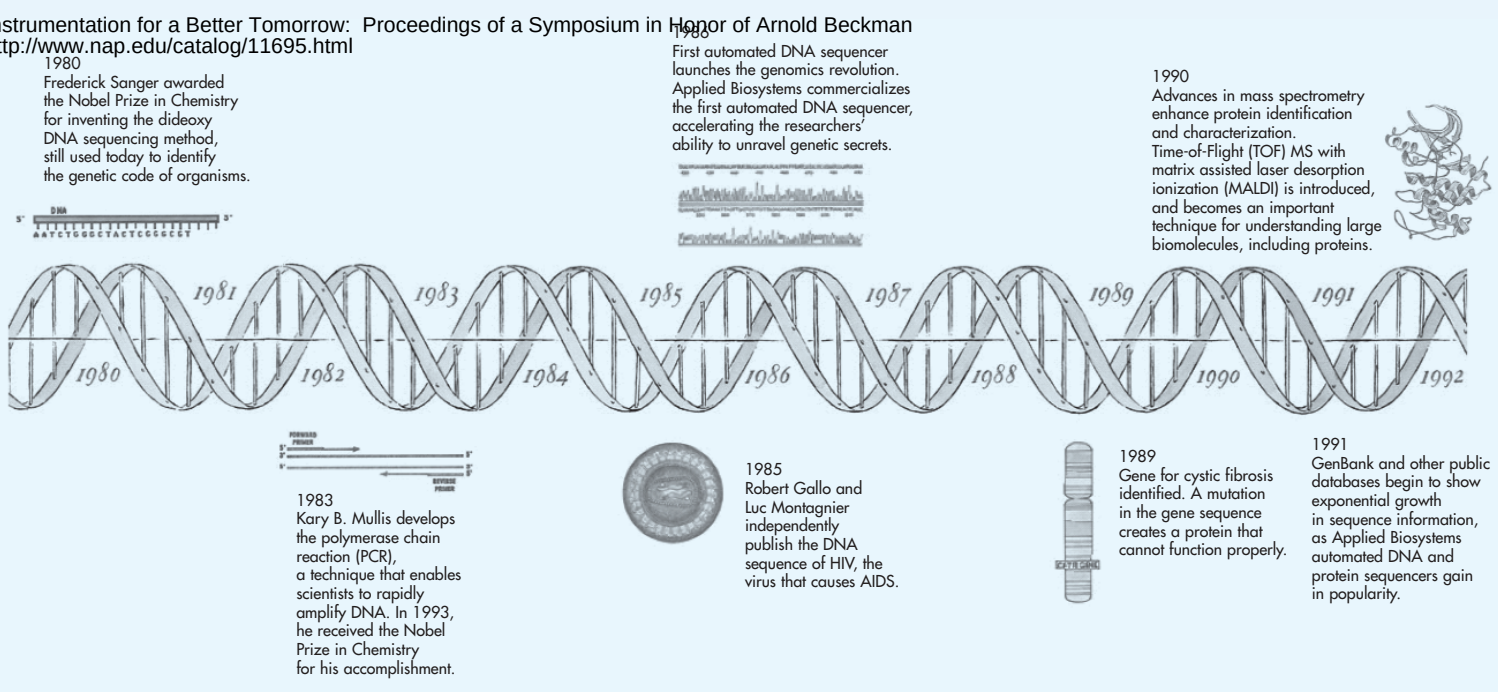
It was a remarkable time; we had this instrument that let us go out and survey the field of all these things that hadn't been looked at before.

We also developed a device to synthesize proteins from their constituent amino acids. This instrument was critical, for example in synthesizing part of an important protein in the AIDS virus, which in turn led to the development of the first protease inhibitor for the virus. The protein synthesizer also played a key role in the development of the polymerase chain reaction (PCR) because it enabled the construction of the oligonucleotide primers that are essential to the amplification of targeted DNA regions. PCR never would have happened if it had not been possible to synthesize DNA very readily.

In the late 1970s, I began thinking about commercializing some of the instruments I was developing. The president of Caltech emphasized that the fundamental role of the university was scholarship and education, not the commercialization of instruments, so I began exploring options on my own. I went to 19 different instrument companies and presented a vision of how instruments were going to transform biology. I was 0 for 19. In fact, I went to Beckman Instruments three times, and the last time a manager said, "We're just not interested." About that same time, Arnold Beckman, who was no longer directing Beckman Instruments, heard me give a lecture, and his reaction was "This is really interesting. This is just what Beckman Instruments needs." I should point out, this raises a really interesting question about companies. What happens when the creative driving force of the company isn't at the helm anymore? Is it really better to start new companies?

That's what I did. I participated in the founding of a new company, Applied Biosystems, which commercialized the instruments we were developing and is now a world-leading company in the field of molecular instrumentation.

One of the most important instruments commercialized by Applied Biosystems was the automated DNA sequencer, which could determine the sequence of nucleotides in DNA molecules. This got me into the next big adventure of my life, which was the Human Genome Project. Launched in 1990, the project completed an initial draft of the human genome in 2000, and a final draft in 2003. Essential to the project's success was the automated DNA sequencer developed by Applied Biosystems. The development of the instrument began in earnest in 1982 through a multidisciplinary effort involving biologists, chemists, computer scientists, and engineers. I realized that the tools of biology



couldn't be developed just by biologists any more; we had to integrate our partners from other disciplines (*see Figure 16* for the development of analytic methods).

This project convinced me that a cross-disciplinary environment could foster major advances in biology. Such an environment was difficult to establish at Caltech, so in 1992, I moved to the University of Washington to establish a new department of molecular biotechnology. The department brought together faculty members working on proteomics—the global analysis of proteins—cell sorting, protein synthesizers, and other sensitive, high-throughput instruments. We had good tools, a good computational infrastructure, and a cross-disciplinary environment, and the idea of biology as an information science was just beginning to emerge.

With the necessary components of a more comprehensive approach to biomedical problems becoming available, I turned my attention to the best way to approach complex biomedical problems. Systems biology is the idea that we can look at all of the elements of a system. There are two main types of digital information in biological systems. One is the genes that make proteins, and these proteins often create networks that do things like signal transduction of information from outside a cell. The second type of digital information is the regulatory elements that interact with a class of proteins called transcription factors—they regulate the expression of proteins and help to create networks of physiological and developmental order. These two types of information lie at the heart of systems biology. To take advantage of the many new opportunities offered by this perspective, I cofounded the Institute for System Biology in 2000.

Instruments now being developed are specifically focused on a systems biology perspective. For example, we are involved in efforts to use nanotechnologies to sequence single DNA molecules, which would eliminate the need to produce a large number of identical DNA

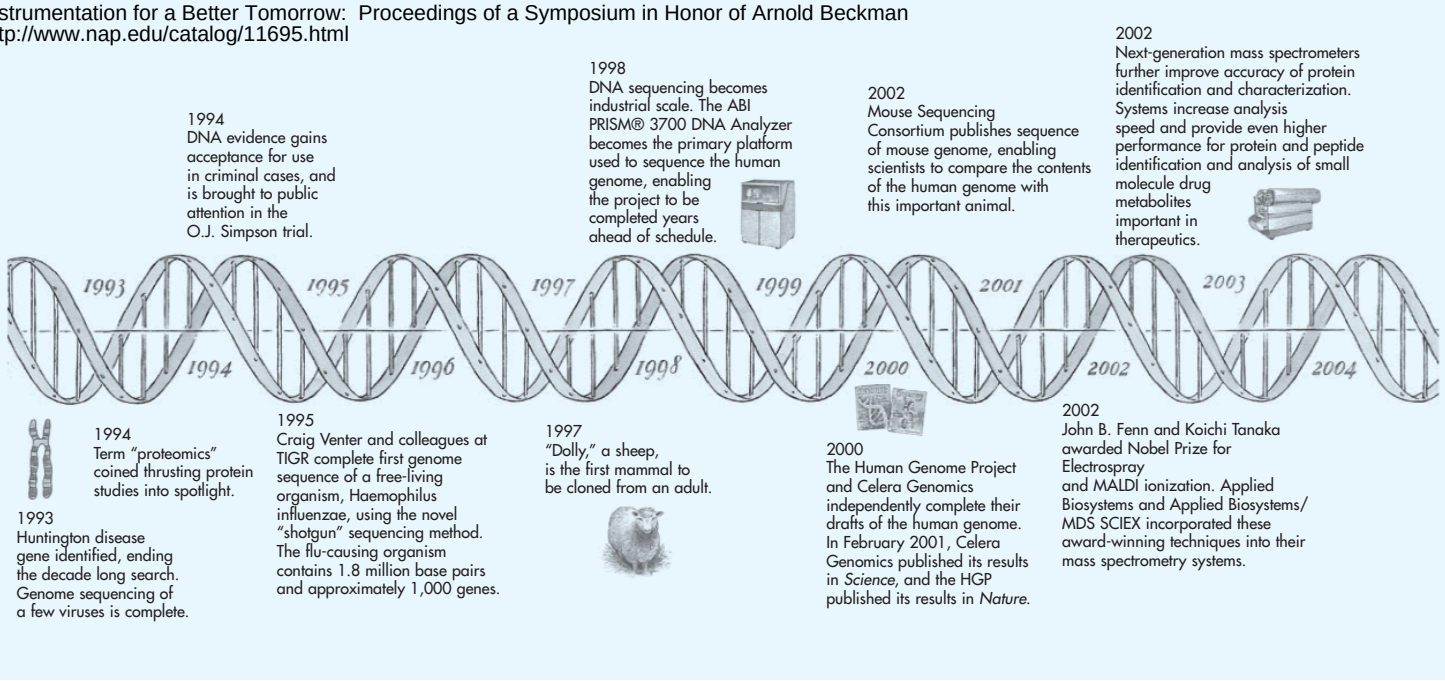


FIGURE 16 A pictorial timeline illustrating the rapid development of genetic analysis techniques.

molecules for sequencing. My prediction is that within 10 years we will be able to sequence the complete human genome inexpensively and rapidly. We are also working on instruments that will be able to analyze the individual RNA molecules in a cell (such instruments would indicate which genes are turned on and making proteins) as well as on an integrated "nanolab" that would subject the contents of a single cell to a variety of diagnostic tests.

In turn, these new instruments will make possible the coming era of personalized medicine. Patients would have their DNA sequences analyzed and undergo a profiling of the functioning of their cells using material from a simple blood test. We'll look at your DNA and make predictions about your future health. And we'll look at your blood as a window to health and disease.

Disease arises as a consequence of modified biological networks. When you modify the network, you modify the patterns of gene expression, which constitutes a molecular signature that differentiates health from disease. We can design a drug strategy that moves a network back toward its more normal behavior.

This new approach to medicine will have profound consequences for the health care and pharmaceutical industries, I predict. The medicine of today and the medicine of the future are going to be radically different. For example, I think in the next 10 years big pharma is going to be entirely restructured. I don't think it will be able to respond to the new kinds of medicine we will see.

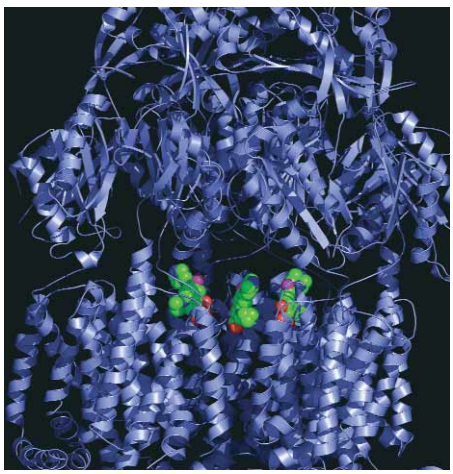
At the same time, the new medicine will have a powerful effect on the lives of individuals. If you put the medicine of the future, which I think is 10 to 20 years off, together with things that are happening in aging and neurobiology, I think we're going to significantly increase the productive lifespan of individuals over the next 20 years.

COMPELLING SCIENCE AND SYNCHROTRON X-RAY SOURCES

By Gabrielle G. Long, Associate Director, Experimental Facilities Division, Advanced Photon Source, Argonne National Laboratory

Dr. Long (Ph.D., Polytechnic Institute of Brooklyn, 1972) is an expert in x-ray scattering techniques and the microstructure of materials. She is currently associate director at the Advanced Photon Source, one of the nation's most powerful light sources, which is utilized by thousands of biological and physical scientists each year. She is a fellow of the American Physical Society and has been a member of the Materials Research Society's Public Affairs Committee and the Department of Energy's Basic Energy Sciences Advisory Committee. Before joining Argonne, Dr. Long was group leader at the National Institute of Standards and Technology's Center for Neutron Research. She has been named a Maria Goeppert-Mayer Distinguished Scholar. She is also an expert in designing and operating world-class instruments that serve many scientific disciplines simultaneously.

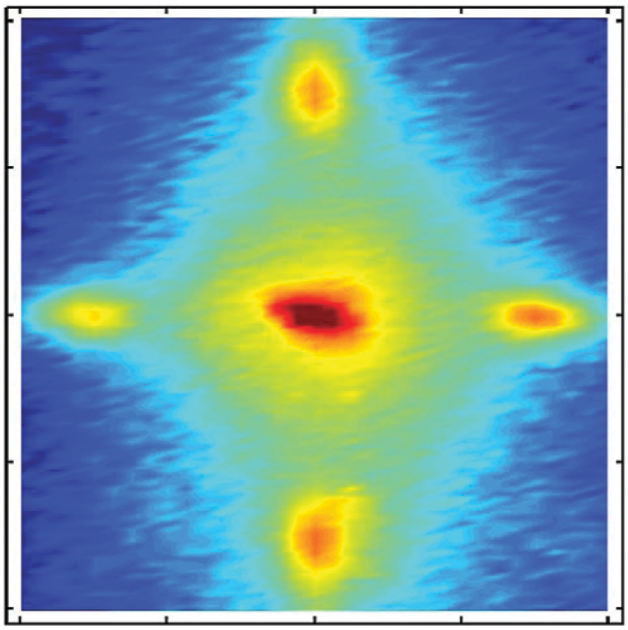
Historically, x-ray research has been propelled by compelling scientific questions and by the push of powerful x-ray source technology. Hand in hand with x-ray source technology are the spectrometers, optics, detectors, and fast electronics that similarly enable the success of the scientific endeavor. In keeping with the symposium's theme, "Instrumentation for a Better Tomorrow," I would like to illustrate the interplay between important scientific results and the instrumentation that made them possible by selecting some achievements arising from a single technique, x-ray inelastic scattering, from the 1920s until today and speculating on what may become possible with future synchrotron sources now on the horizon.



X-ray crystallography image of the AcrB protein complex, a bacteria that repels a wide range of antibiotics. Courtesy of Lawrence Livermore National Laboratory.

As the name implies, x-ray scattering involves x-rays impinging on matter and researchers observing the way they scatter. Elastic x-ray scattering occurs when the x-ray photons bounce off the object with no loss of energy; it can be used to characterize the static properties of physical systems. The atomic arrangement within the system can be derived from the angles at which the x-rays reflect, with x-ray crystallography being an important example of elastic x-ray scattering. Inelastic x-ray scattering, by contrast, involves observing how much of the x-rays' energy is absorbed and allows probing the dynamics of physical systems to learn about the excitations that determine physical properties.

Some of the earliest inelastic x-ray scattering experiments led to discoveries of great significance. In 1929, Compton (inelastic x-ray) scattering experiments on beryllium provided the first evidence for the validity of Fermi-Dirac, as opposed to Maxwell-Boltzmann, electron momentum distributions (DuMond, 1929). Since those early days, inelastic x-ray scattering has developed into a probe of collective electron excitations, structural chemistry and resonant excitations, and partial phonon densities of states.



X-ray scattering from ferroelectric stripe domains in a thin film of lead titanate three unit cells thick. Courtesy of Argonne National Laboratory.

From the discovery of x-rays in 1895 by Röntgen until the early 1970s, x-ray sources and x-ray instrumentation changed little. Laboratory x-ray generators accelerated electrons from tungsten filament cathodes toward copper or molybdenum (or other metal) anodes. These 1-kW machines remained the mainstay of x-ray laboratories until the invention of the rotating anode x-ray generator. By rotating the hot spot of the anode away from the impinging electron beam, the power of laboratory x-ray generators increased from 1 kW to 12 kW and upward. Typically, progress in x-ray sources has been marked by increases of at least one and usually many orders of magnitude in power and intensity.

The next important development came in the form of x-ray optics, in which crystal analyzers were bent to collect and focus the x-rays. Research included core electron excitations in low-Z materials. These x-ray Raman experiments (Black, 1990) offer the sensitivity of soft x-rays together with the penetration of hard x-rays. Thus, they deliver otherwise inaccessible information on the electronic structure from deep within materials rather than from the surface.

During the 1970s, first-generation synchrotron x-ray sources, such as the Stanford Synchrotron Radiation Laboratory (SSRL), came into operation. Circulating electrons in the storage ring produced intense x-ray beams that were used for physical measurements. While elementary particle physicists studied the newly discovered J/Y particle, which

determined the energy at which the ring was operated, the production of x-rays was ancillary. Later, SSRL became a dedicated x-ray source, but we turn our attention now to the second-generation source at Brookhaven, the National Synchrotron Light Source (NSLS). The NSLS was built for the purpose of producing x-ray light. It made use of x-ray beams primarily from bending magnets. The NSLS delivered x-rays six orders of magnitude more intense than x-rays from rotating anodes.

Along with the creation of intense x-ray sources, the development of optimized optics and detection methods played an important role in enabling x-ray inelastic scattering experiments. The back-scattering geometry and the development of spherically bent crystal analyzers (Dorner et al., 1986) contributed greatly to making experiments more efficient, robust, and ultimately practical. Also, as the photon flux increased, so did the demands of the science, from 1 eV to 0.1 eV and, finally, to approximately 1 meV resolution (Burkel, 2000), stimulating the development of a new generation of novel monochromators (Sinn et al., 2001).

Three premier synchrotron sources of hard x-rays are now in operation: the European Synchrotron Radiation Facility (ESRF), in France; the Super Photon Ring 8-GeV (or SPring-8), in Japan; and the Advanced Photon Source (APS), in the United States. Third-generation synchrotron x-ray sources primarily make use of radiation from insertion devices placed in straight sections between the bending magnets. These insertion devices—wigglers and undulators—are long devices that deflect the electrons rapidly back and forth and consequently deliver additional photon intensity. The new science coming from the APS depends on its unique beam characteristics. A very high degree of collimation makes it possible to efficiently monochromate hard x-ray beams to the approximately 1 meV mentioned above. These beams are used for inelastic x-ray scattering studies of lattice dynamics, which until then could be studied only by neutron scattering. Today, inelastic x-ray scattering is used to probe dynamics such as the collective vibrations (phonons) in a crystal, valence

FIGURE 17 Novel sample environments enable research into matter under extreme conditions within Earth. Inelastic x-ray scattering from levitated (containerless) molten alumina at high temperature is used to gain information on the liquid dynamics within Earth's mantle. The levitated liquid aluminum oxide sample in a supercooled state at approximately 1800°C is shown.

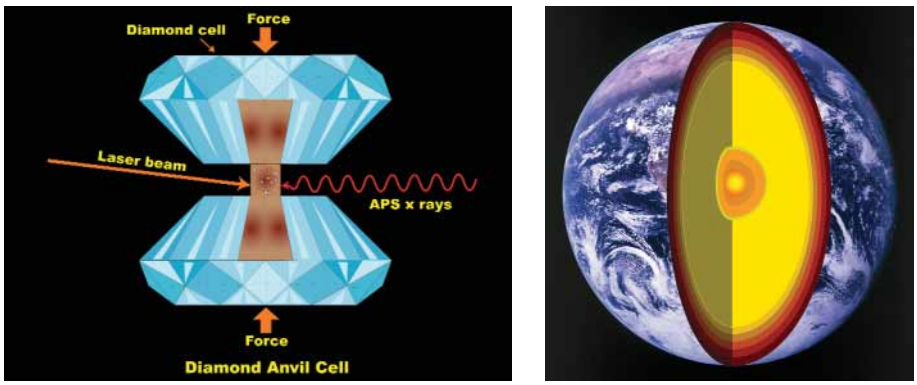


FIGURE 18 (Above left) Nuclear resonant inelastic x-ray scattering from iron and iron compounds at high temperature and high pressure in a diamond anvil cell (Above right) is used to study the geophysics of Earth's core.

electrons near the Fermi level, excitations monitored through a nuclear resonance, core and valence electrons, and spin-polarized electrons related to magnetism.

Inelastic x-ray scattering now probes materials with unusual non-Fermi-like behavior, such as the high critical temperature (high-T_c) superconductors. New calculation techniques are used to describe these materials, which are compared with measurements of the electronic excitation spectrum. Techniques such as angle-resolved photoemission are surface- rather than bulk-sensitive and suffer from final state effects and/or sample charging. Inelastic x-ray scattering has none of these limitations and is used successfully to measure charge excitations as a function of incident photon energy. Inelastic x-ray scattering results (Hill et al., 1998) on Nd_2CuO_4, for example, indicate the presence of a charge-transfer-type excitation involving the oxygen 2p and Cu 3d orbitals; they compare well with cluster calculations for the CuO planes in high-T_c materials.

In another area, both the spectroscopy and the sample levitation technique were novel. Molten aluminum oxide is of interest for modeling Earth's mantle, for optimizing aluminum production, and for confining nuclear waste. Kinematic restrictions on neutron scattering make it impossible to reach acoustic modes in liquid oxides, and the high-temperature regime is inaccessible by light scattering because of black-body radiation. Another factor making it difficult to obtain data is the chemical reactivity of aluminum oxide, which melts at about 2327 K and is an extremely aggressive material in the liquid state, precluding the use of traditional containers and forcing the scattering measurements to be performed in a containerless environment. Aluminum spheres 3 mm in diameter

Over the years, innovative developments in x-ray sources and instrumentation have greatly enlarged the parameter space in our physical world that can be explored.

were suspended in an oxygen gas jet and heated with a laser to between 2300 and 3100 K *(Figure 17)*. The high momentum-transfer data (Sinn et al., 2003) were well described by kinetic theory, but it was found unexpectedly that the viscosity increased in the hydrodynamic limit, where it had been expected to decrease. The results provide a description of liquid dynamics in relatively uncharted regions between hydrodynamics and kinetic theory.

Nuclear resonance inelastic x-ray scattering (NRIXS) (Sturhahn, 2004) became possible and even practical with the advent of the third-generation sources. One of the ways in which a nucleus can reach an excited state is by the absorption of a photon. Such an excitation is important when the energy of the photon is very close to the difference between the nuclear ground state and a nuclear excited state. By using samples enriched with nuclear isotopes that have large resonant cross sections and special timing techniques, one can perform nuclear resonant inelastic scattering to study lattice dynamics. NRIXS gives access to the partial phonon density of states of the resonant isotope only, thereby delivering unique isotope selectivity (Sturhahn et al., 1995). This has proven important in two very different areas: geophysics and biophysics.

In geophysics, nuclear resonant inelastic scattering is providing the phonon density of states in iron and iron compounds at high pressures and high temperatures. The data deliver essential information needed to characterize iron deep within Earth *(Figure 18)*. Iron, which is abundant in Earth, transforms from a bcc phase (a-Fe) to an fcc phase (g-Fe) at moderate pressures and temperatures, to an hcp phase (e-Fe) at higher pressures. With NRIXS, it was possible to measure the phonon density of states directly as a function of pressure and temperature and to compare the thermodynamic and elastic parameters directly with Debye's model. It was found that g-Fe has lower Debye temperatures and average sound velocities than e-Fe (Shen et al., 2004).

Inelastic x-ray scattering measurements are making profound contributions in another unanticipated area—biophysics. Vibrational spectroscopy probes the structure, dynamics, and reactivity of biological molecules, which has so far been done using resonance Raman, infrared, and femtosecond coherence spectroscopies. Limitations on those methods include selection rules that prevent the observation of many important active-site vibrations and difficulties in the assignment of the observed vibrational frequencies with expected normal modes. To meet these challenges, nuclear resonant vibrational spectroscopy reveals the complete vibrational spectrum of a probe nucleus. It can select a single atom from a complex molecule because only the vibrational dynamics of the probe nucleus contribute to the detected signal. It is now being used to identify and characterize

iron-ligand modes at protein active sites (Leu et al., 2004). For heme proteins, these include in-plane iron vibrations that had not been reported in resonance Raman experiments and the iron-imidazole stretch that had not been identified in six-coordinate proteins. Such identifications are a crucial step toward quantifying the reactive energetics of iron porphyrins and heme proteins.

Over the years, innovative developments in x-ray sources and instrumentation have greatly enlarged the parameter space in our physical world that can be explored. These developments led to a rich interaction between the experimental opportunities and the grand challenges that face many fields of science. Today, we can measure an exceedingly broad range of parameters, from those relevant to the functioning of proteins to parameters relevant to geophysics deep within Earth. These developments have also enabled crystal structure determinations from micrometer-sized crystals and have revolutionized protein crystallography, opening the door to the high-throughput determination of protein structure. With the realization of fourth-generation x-ray sources, the peak brightness will be 10 orders of magnitude greater than current synchrotrons, the x-ray light will be coherent, and the pulses will be three orders of magnitude shorter. The possibility of going beyond meV toward meV would open up another regime for inelastic x-ray scattering.

REFERENCES

Black, D.R. 1990. Ph.D. dissertation, Colorado State University.

Burkel, E. 2000. Rep. Prog. Phys. 63: 171-232.

Dorner, B., E. Burkel, and J. Peisl. 1986. Nucl. Instrum. Methods A 246: 450-451.

DuMond, J.W.M. 1929. Phys. Rev. 33: 643-658.

Hill, J.P., C.-C. Kao, W.A.L. Caliebe, M. Matsubara, A. Kotani, J.L. Peng, and R.L. Greene. 1998. Phys. Rev. Lett. 80: 4967-4970.

Leu, B.M., M.Z. Zgierski, G.R.A. Wyllie, W.R. Scheidt, W. Sturhahn, E.E. Alp, S.M. Durbin, and J.T. Sage. 2004. J. Am. Chem. Soc. 126: 4211-4227.

Shen, G., W. Sturhahn, E.E. Alp, J. Zhao, T.S. Tollner, V.B. Prakapenka, Y. Meng, and H.-R. Mao. 2004. Phys. Chem. Minerals 31: 353-359.

Sinn, H., E.E. Alp, J. Barraza, G. Bortel, E. Burkel, D. Shu, W. Sturhahn, J.P. Sutter, T.S. Toellner, and J. Zhao. 2001. Nucl. Inst. Methods A467: 1545-1548.

Sinn, H., B. Glorieux, L. Hennet, A. Atalas, M. Hu, E.E. Alp, F.J. Bermejo, D.L. Price, and M.-L. Saboungi. 2003. Science 299: 2047-2049.

Sturhahn, W. 2004. J. Phys. Condens. Mat. 16: S497-S530.

Sturhahn, W., T.S. Toellner, E.E. Alp, X. Zhang, M. Ando, Y. Yoda, S. Kikuta, M. Seto, C.W. Kimball, and B. Dabrowski. 1995. Phys. Rev. Lett. 74: 3832.

CHEMISTRY AT THE NANOSCALE FRONTIER

By Chad Mirkin, Professor of Chemistry and Director of the Institute for Nanotechnology, Northwestern University

Dr. Mirkin (Ph.D., Penn State, 1989) researches methods for controlling the architecture of molecules and materials on the 1- to 100-nm length scale and for utilizing such structures in the development of analytical tools. Dr. Mirkin joined the faculty at Northwestern in 1991; in 1997 he became Charles E. and Emma H. Morrison Professor of Chemistry. He has won numerous awards, including the ACS Nobel Signature Award, the Raymond and Beverly Sackler Prize in the Physical Sciences, and the Discover 2000 Innovation of the Year Award. In 1992, Dr. Mirkin received the Young Investigator Award from the Arnold and Mabel Beckman Foundation. In 1997, he was corecipient of a prestigious BF Goodrich Collegiate Inventors Award for one of the three most outstanding collegiate inventions in all of medicine, science, and engineering. Dr. Mirkin has helped found two companies, Nanosphere, Inc., and NanoInk, Inc.

At sizes below about 100 nanometers, materials have very different properties than they do at larger scales. That is one of the exciting aspects of the rapidly growing field of nanotechnology, which seeks to put these novel properties to use in the form of new functional materials and devices.

For example, consider the technology called dip-pen nanolithography, which we invented in 1999 *(Figures 19 and 20)*. This technology can be seen as a distant descendant of some of the inking technologies Arnold Beckman invented early in his career. Nanoscale cantilevers are constructed using lithography on silicon chips. At the end of each microscopic cantilever is a sharp tip that functions as a nanoscopic pen to transfer a soluble substance to a substrate. Different microscopic ink wells can be used to ink different pens, and the cantilevers in large arrays can be controlled individually. It's a fantastic research tool that is beginning to become a powerful commercial nanofabrication and production tool. It can work on almost any substrate, and we can put multiple functionalities on a single nanochip. We can use it as the world's smallest printing device to build and study structures composed of almost any material on the nanoscopic scale *(Figure 20)*.

For instance, we have been using dip-pen nanolithography to print on the scale of biological systems, so that one can begin to build multivalent architectures that can interface with, for example, the surfaces of cells. This is going to allow researchers to probe some of the most fundamental cellular processes, including adhesion, movement, signaling, growth, differentiation, and death. In the physical sciences, the technology can be used to build or repair the masks used for microelectronic circuits. It can even be used to repair individual circuits. For instance, one early application of the technology has been to

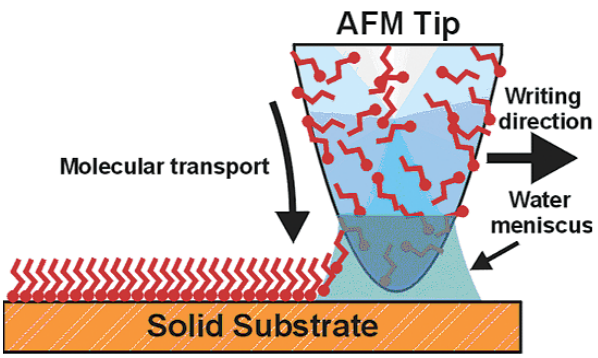


FIGURE 19 A cartoon diagram of dip-pen nanolithography. The atomic-force microscope (AFM) is coated with the molecules in solution and then dragged across the solid substrate. Molecular transport causes an orderly monolayer to be deposited on the surface, enabling the creation of complex nanoscale patterns and structures.

detect and repair defects in plasma screen televisions. The idea is not to compete with existing semiconductor technologies but rather to provide a complementary tool that provides capabilities not available with conventional semiconductor fabrication tools. These capabilities include ultrahigh resolution, registration, and the ability to interface hard and soft matter.

A start-up company called NanoInk, Inc., is pursuing a number of commercial applications of the technology. In 1999 there was only one lab in the world using this technology. Today, because of their efforts and ours, there are more than 60 users of dip-pen nanolithography in 18 countries.

The sensitivity and selectivity of nanotechnologies offer many other opportunities. One is in the area of personalized medicine, which Leroy Hood discussed in his presentation. Diagnostic tools based on nanomaterials can measure very low concentrations of biological molecules that serve as markers of health or disease. Our goal is to use these tools to decentralize diagnostics; we would like to move diagnostic technologies to the doctor's office, the post office, the battlefield, and maybe even the home. Today we think of diagnostic technologies as very advanced, but in many respects we're still in the Stone Age. We can't go to the doctor and immediately get screened for different types of diseases. Rather, the doctor takes a sample of blood or urine and sends it to an outside lab, and it takes two days to two weeks to get the results.

The holy grail of these efforts is to develop a detection technology that is as sensitive as the polymerase chain reaction (PCR) for nucleic acids without requiring the enzymatic amplification of target molecules. Moreover, we want these systems to be general for all analytes, including proteins, small molecules, and metal ions. I believe that nanomaterials may be one of the only routes to fast, reliable, robust systems that do not involve the hassles of PCR and that provide the targeted generality. My group has been working on various detection systems based on nanoparticles. In one system, called the bar code assay, particles that have specific DNA strands and antibodies on their surface can detect proteins at

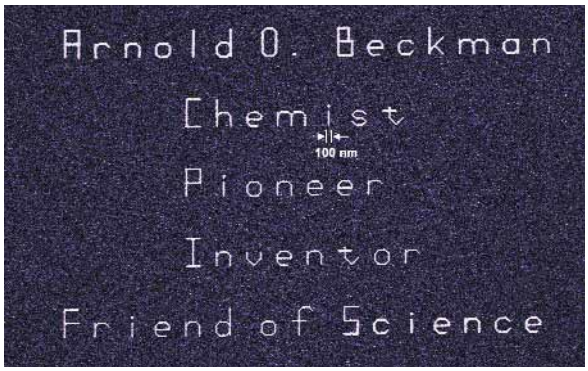


FIGURE 20 A fitting example of the capabilities of dip-pen nanolithography.

3-attomolar concentrations—six orders of magnitude more sensitive than conventional ELISA and Western blot assays. This extraordinary sensitivity is allowing medical researchers to identify and validate new biomarkers for neurodegenerative diseases such as Alzheimer's disease, HIV, and many forms of cancer. Another start-up company, Nanosphere, is seeking to create a universal platform that uses these approaches in diagnostic systems. The goal is a mobile diagnostic platform with target generality, high stability, high selectivity, and high sensitivity that can be maintained and operated by relatively low-skilled personnel.

We seek to identify and validate new markers for many debilitating diseases that cannot be studied with conventional tools, which do not possess the requisite sensitivity. This technology will change the way the medical community thinks about diagnostic systems—what they can consider as a marker, the types of markers that can be validated, the samples that can be used, and where they can use the marker.

NANOSCALE SCIENCE AND ENGINEERING

By Michael L. Roukes, founding director, Kavli Nanoscience Institute and professor of physics, applied physics, and bioengineering, California Institute of Technology

Dr. Roukes (Ph.D., Cornell, 1985) joined the Quantum Structures Research Group of Bell Laboratories after his dissertation and in 1992 joined the physics faculty of Caltech, where he established laboratories for the fabrication and study of nanoscale structures. His research group focuses on the scientific foundations for nanotechnology, specifically, nanoelectromechanical systems (NEMS). Among his activities, Dr. Roukes is cofounder, vice president, and chief technology officer of Nanotechnica Corporation and cofounder and codirector of the Caltech Initiative in Computational Molecular Biology. A fellow of the American Physical Society, he was a Lillian M. Gilbreth lecturer of the National Academy of Engineering in 2002.

It has become much easier for Caltech professors to spin off commercial enterprises since Arnold Beckman's time as a faculty member. But cross-disciplinary research still remains somewhat of a challenge. As a physicist, I'm slowly learning how to transition my own work from fundamental studies into applications relevant for the medical and life sciences. In this process, interdisciplinary collaborations are key.

The underlying focus of most of my current efforts is the creation of new tools from nanotechnology for biomedical and life sciences research. Today, we should probably characterize most ongoing work as "nanoscience," rather than nanotechnology. What's mostly been done so far is science that still needs to be transitioned into technology. My view is that this transitioning is going to be driven by the corporate sector rather than by university researchers. Why? Well, a major endeavor here is the development of nanosystems, complex and integrated devices analogous to computer chips. These will enable large-scale genomics and proteomics discovery to be carried out universally. The future era that this technology will enable is going to stand in contrast to today's paradigm, which involves centralized research at large technology-intensive centers. Today's organization of resources is, of course, necessary for economy of scale. But tomorrow's chips will put this technology in the hands of every able researcher, and that is certain to lead to an explosion in our knowledge base.

Unlike computer chips, these nanosystem chips must consist of far more than simply semiconductor elements of today's computer chips. Rather, they fuse a variety of different technologies from completely different fields—for example, microfluidics, biochemistry, photonics, and electrochemistry. These extra dimensions of complexity require entirely new avenues for integration and mass production. Collectively, industry has hardly started in this area. Even within the university research community, realizing this new technol-

ogy requires new, highly collaborative forms of doing science. The good news on this front is that the early phases of this are already well under way *(Figure 21)*.

Ultimately, a single nanosystem biochip will contain many thousands of biological sensors. To characterize future devices, only a few such chips are necessary. But to make real and innovative progress that has relevance to biological and medical discovery, such chips need to be produced en masse. In short, they must become commodities, since their useful life under the conditions of operation will be short. For example, their small plumbing, pores, and sensors typically become fouled with biological materials after just a few experiments or the effectiveness of their preprogrammed surface chemistry fades. We will literally need boxes of these chips to fuel the coming era of discovery and clinical application. The demand for such quantities, even from the basic biological and medical research communities, will from the outset outstrip the capability of university fabrication centers to produce them.

What does "nano" bring to the table here? A key element of these chips is that they must be able to detect biological molecules at very low concentrations—even down to the level of single molecules, which is, after all, the "quantum" of biochemical information exchanged within cells and organelles. Today, the conventional way of detecting specific molecules in proteomics is predominantly mass spectrometry, but the state of the art in mass spectrometry is a system that fills a good fraction of a room and typically requires something like 100 million molecules to achieve detection. That is very different from the single-molecule paradigm that nanotechnology is poised to enable.

Recently, we developed a nanomechanical device capable of registering the adsorption of individual macromolecules, one by one, on its surface. The next step is to take this capability from the realm of the fundamental physics lab into a setting where it can be applied to biological problems, that is, the realm of proteomics. This new approach might ultimately complement, or even replace, mass spectrometry as we know it today. It is certainly not a short-term goal, but it is a worthy one, which we think is probably achievable within the next 5 years or so. This dream is fueling our research today.

Another major challenge that my collaborators and I are focusing on is shrinking analytical instruments—specifically, bioarray detectors—to the size of an individual cell. Since cells are anywhere from a fraction of a micron to hundreds of microns across, the individual sensors absolutely must be at the nanoscale. The motivation here is not simply to achieve some form of nanoscale feat: It is to match the scale of detection—within both the spatial and temporal domains—to that on which cellular processes occur. One can liken

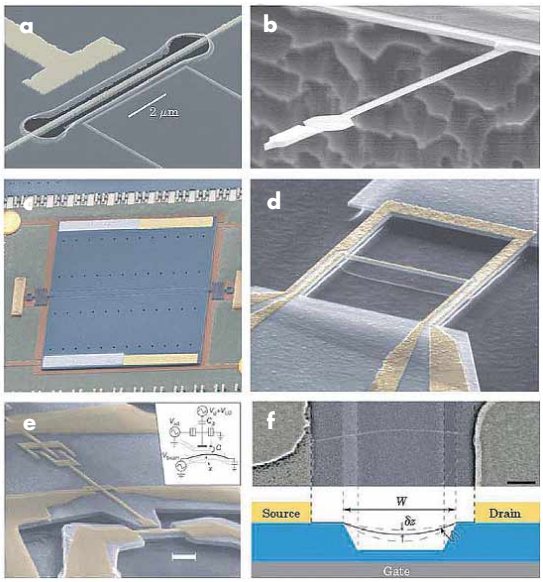


FIGURE 21 Nanoelectromechanical devices are starting to approach the ultimate quantum mechanical limits for detecting the exciting motion at the nanoscale: (a) A 20-MHz nanomechanical resonator capacitively coupled to a single-electron transistor (Keith Schwab, Laboratory for Physical Sciences). The resonator's motion induces a charge on the gate electrode of the single-electron transistor; the resulting changes in the conductance can be directly monitored. (b) An ultrasensitive magnetic force detector that has been used to detect a single electron spin (Dan Rugar, IBM). When a given electron spin is the right distance from the magnetic cantilever tip and therefore exposed to the right steady magnetic field, a resonance occurs, causing the electron spin to flip direction and generating a small change in force that can be monitored by interferometric observation of the cantilever oscillations. (c) A torsional resonator used to study Casimir forces and look for possible corrections to Newtonian gravitation at short-length scales (Ricardo Decca, Indiana University–Purdue University, Indianapolis). (d) A parametric radio-frequency mechanical amplifier that provides a thousandfold boost of signal displacements at 17 MHz (Michael Roukes, Caltech). (e) A 116-MHz nanomechanical resonator coupled to a single-electron transistor (Andrew Cleland, University of California, Santa Barbara). (f) A tunable carbon nanotube resonator operating at 3 to 300 MHz that exploits the strain dependence of electron transport through a suspended carbon nanotube (Paul McEuen, Cornell University).

the cell to a computer chip; its "logic gates" are individual biochemical processes that, concatenated, form biological regulatory networks. Signaling, or information exchange between individual logic gates (or subnetworks), is mediated by "bits" of information that may involve only the aforementioned fundamental "quanta" represented by single molecules. Information flow happens at the millisecond, or even microsecond, scale—the scale of the underlying biochemical reactions.

How can we tap into this vast and prolific information stream, ongoing within even the smallest and most primitive of cells? Certainly today's gene chips and protein chips are too large and far too slow to follow biochemical processes in real time. Also, they require large quantities of DNA or proteins to produce a signal. For DNA, if we're willing to wait and add extra steps to the observation process, we can employ the polymerase chain reaction (PCR) to amplify the individual bits (nucleic acid molecules) of information exchanged. But for proteins, no such amplification trick exists, so we clearly need techniques to sense at the single-molecule level. Given this technology chasm, today's proteomics and systems biology typically are carried out by homogenizing (that is, averaging) information from millions or billions of cells to have enough signal to detect in conventional assays. The dream of nanobiotechnology is, instead, to monitor the processes of individual cells in real time and to do this simultaneously on the cells of entire systems: organelles, immune systems, organisms.

As Lee Hood mentioned, a group of us have formed the NanoSystems Biology Alliance to take concrete steps today toward realizing this dream. Many significant individual elements of the technology exist, but they have yet to be integrated and deployed in a single device. This Alliance is a collaboration among seven West Coast-based scientists. We are adapting devices from nanophysics and nanochemistry, such as nanowires, nanocantilevers, optical tweezers, and atomic force microscopes, to observe and measure the behavior of single cells. Microfluidics is an underlying technology that ties all of this together. It enables cells to be placed within wells on chips outfitted with nanosensors that bind to particular proteins or nucleic acids—for example, those that the cell secretes during part of the cell cycle or in response to stimuli. Proteins produced by the cell bind to these nanosensors and change their mechanical or electrical properties, which can then be measured in the electrical domain by electronic transducers integrated within the chip. The overarching principle here is that it is now feasible to make devices so small and so sensitive that we can resolve individual binding events—that is, resolve the individual biochemical bits of information exchanged by the cell. And because it is feasible to do this quickly, we can follow the stochastic chemistry of life processes in real time.

"New directions in science are launched by new tools much more often than by new concepts."

—Freeman Dyson

One early supporter of our own work in this domain has been the Department of Defense (specifically DARPA), which has been interested in the development of first, simplest realizations such as chips to detect biopathogens. I see many potential applications of this technology—the payoff is certain to be immense. One possibility is high-throughput drug screening, in which the responses of particular cells are measured to detect drugs effective against various diseases. The responses of individual cells also could be measured when they are exposed to toxins or pathogens. But the really exciting coming era, for me, will be when these chips become commonplace in everyone's homes and lives—just like today's computer chips. They will be the enablers of the inevitable, coming era of personalized medicine. The changes they will bring to medicine and health care will be profound.

Let me conclude by quoting Freeman Dyson on the importance of new technologies. "New directions in science are launched by new tools much more often than by new concepts," Dyson wrote. "The effect of a concept-driven revolution is to explain old things in new ways. The effect of a tool-driven revolution is to discover new things that have to be explained." Nanoscience is now revealing new domains within our natural world, and these new domains will produce advances that are only the faintest of glimmers today

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FORENSIC SCIENCE AND TECHNOLOGY

By Robert E. Gaensslen, Professor, Director of Graduate Studies, Head of the Program in Forensic Science, University of Illinois at Chicago

Dr. Gaensslen (Ph.D., Cornell, 1971) is an expert in biological evidence examination, DNA forensic technology, and forensic laboratory approaches in the criminal justice system. He has coauthored seven books, coauthored nine chapters in edited volumes, and published over 60 papers in the refereed scientific literature. He has also organized, coordinated, and participated in dozens of workshops and training courses for forensic science laboratory and law enforcement personnel. Dr. Gaensslen is a fellow of the Criminalistics Section, American Academy of Forensic Sciences. He has received the Paul L. Kirk Distinguished Criminalist Award from the Criminalistics Section and was made a distinguished fellow by the Academy in 2000. He is a life member of the Northeastern Association of Forensic Scientists.

I assure you that we are returning to the macro level for the next half hour. Within the field of forensic science, criminalistics can be organized according to the kinds of evidence examined in a crime lab. Using this scheme, let me sort the field into chemical, biological, trace, and pattern evidence.

Instrumental analysis is deeply interwoven with the analysis of chemical, trace, and biological evidence. Forensic investigators who are analyzing materials from a crime scene typically have three goals: classification, individualization, and reconstruction. They are particularly interested in establishing the uniqueness of a piece of evidence. People in quality control think about how to make things the same, but I don't know anyone else who works on materials who thinks about how to render things unique!

With chemical evidence, the basic task is to identify a material. What is this, and how much is there? Chemical analysis can be further broken down into two categories: elemental analysis and organic compound analysis. Both are particularly dependent on instruments. A good example is identifying gunshot residue. Gunshot residue can consist of smoke, debris, foreign particles, or other substances. These materials are emitted by a gun and are deposited on the hand of the shooter or on anyone or anything else in the vicinity. Law enforce-

ment personnel are very interested in the analysis of gunshot residue in the hope that the results of such an analysis will show that someone fired a weapon. Unfortunately, even if the identification of gunshot residue is rigorous, it does not prove that the hand fired the weapon—only that the hand was in the vicinity.

Beckman Instruments executives examine mass spectrometer in 1953. Courtesy Beckman Coulter, Inc.

In the 1970s many forensic labs became interested in a technique known as neutron activation analysis to identify materials. But it proved less useful than anticipated. The cost and difficulty of the technique were part of the problem, and it promised more than it could deliver. There were so many variables associated with the elemental profiles of materials that it proved very difficult to establish uniqueness. This is an example of a technique that comes along that is instrument-based and chases applications.

The identification of organic compounds has been revolutionized by instrumental methods.

Today gunshot residue is usually analyzed using a combination of scanning electron microscopy to visualize the particles and a technique known as energy dispersive x-ray analysis to analyze elemental constituents. It is the combination that lets you make the identification. But the problem of linking the residue to the shooter remains. The presence of gunshot residue on a hand does not make that person the shooter, and that's the question the police are interested in answering.

Varian CP-3800 Gas chromatograph. Courtesy of Varian, Inc.

The identification of organic compounds has been revolutionized by instrumental methods. The methods used most often include gas chromatography and liquid chromatography with mass spectrometry. Much of this work involves identifying illicit drugs. For example, the Chicago lab of the Illinois State Police

handles about 5,000 cases per month, of which more than 4,000 are drug cases. And agents will tell you that they are getting only 1 or 2 percent of the drug traffic. The illicit drug problem continues to dominate the lab landscape.

The workhorse instrument in the lab for the analysis of trace materials has always been the microscope, which provides a rapid, convenient, and nondestructive method for viewing such materials as hairs, fibers, and paint. A microscope can be used to identify and sometimes partly to individualize these materials, but caution is warranted. For example, many forensic examiners recognize that hair samples cannot be individualized, but some of them nevertheless have testified with a greater degree of confidence than was warranted. When DNA evidence became available, these mistaken identifications became apparent. Quite a few reputations of labs and examiners, whether they acted out of ignorance or because of misguided efforts to please prosecutors, have been destroyed in the process.

We are natural beneficiaries of the legacy of Dr. Beckman.

Today, analysis of biological evidence consists mostly of DNA profiling. However, an essential element of this profiling is the sampling and identification steps that precede the actual analysis of DNA. An important consequence of DNA profiling has been the enablement of constructing databases of offenders. Every state in the nation has passed legislation mandating the databasing of DNA profiles of criminals. Some databases include only those convicted of sexual assaults, while others include all felony offenders, and the trend is in the direction of databasing more people, not fewer.

Despite relatively efficient typing or profiling methods, databasing and casework demands have overwhelmed many forensics laboratories. Part of the reason is that the front-end processing of material is still very labor intensive. It requires judgment and is difficult to automate. The federal government and the states are working to alleviate this problem. Meanwhile, there are many opportunities for automation and innovation to address databasing bottlenecks.

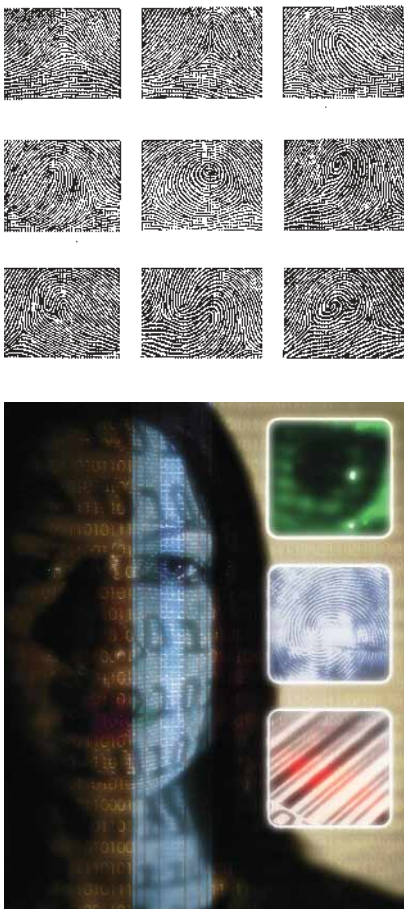


FIGURE 22 The sophistication of modern law enforcement has greatly increased with the advent of new technologies. Computer databases of fingerprints, chemical testing, and genetic analysis are among the many advanced tools used in such investigations.

A critical issue for forensic laboratories is the admissibility of forensic evidence in court. The 1992 Supreme Court case *Daubert v. Merrell Dow Pharmaceuticals* addressed this concern. The case established that scientific evidence presented in a court has to have a solid scientific underpinning, and it established guidelines for making this determination. Establishing the scientific underpinnings for a particular argument can be particularly difficult for pattern evidence. Even in the case of fingerprints, which are widely accepted as being unique, the scientific validity of that uniqueness has never been demonstrated. Biometric specialists are now addressing this issue, but considerable work still needs to be done to establish standards and techniques for the use of fingerprint evidence *(Figure 22)*.

Another example involves identifying bullets from particular firearms. Each handgun or rifle makes distinctive marks on the casing of a bullet, and these marks can be observed and assessed to determine if a bullet was fired from a particular gun. Recently, I have been participating in experiments on consecutively manufactured gun barrels to determine the extent to which any two firearms can be distinguished. The marks are different, but not by much.

Forensic science is by definition an applied enterprise, using scientific, technological, and analytical methods to answer questions that are involved in legal and regulatory matters. We are natural beneficiaries of the legacy of Dr. Beckman.

CLINICAL MEDICINE

By T. Vincent Shankey, Advanced Technology Center, Beckman Coulter, Inc.

Dr. Shankey (Ph.D., University of Florida School of Medicine, 1977) studied the structure and function of IgM antibodies for his dissertation. Before joining the Advanced Technology Center at Beckman Coulter, Inc., in 2001, he was the director of research for the Urology Department and scientific director of the Clinical Flow Cytometry Laboratory at Loyola University Medical Center near Chicago, Illinois, for more than 13 years. His research has utilized both flow and image cytometry and focused on genomic instability and patterns of evolutionary changes in bladder and prostate cancers. His clinical experience in cytometry included DNA content analyses of human tumors. Since joining the Advanced Technology Center, Dr. Shankey has worked on signal transduction pathways in human cancers, focusing on the development of unique biomarkers for molecularly targeted therapeutics.

When I was a graduate student, I spent many hours in front of a centrifuge built by Spinco, the centrifuge company acquired by Arnold O. Beckman in 1954. When we have been in science for a while we tend to forget how science evolved to the point where it is today. We forget that before the analytical techniques were developed to study protein-protein interactions, the gold standard was the analytical centrifuge.

Tabletop centrifuge. Courtesy of Wikipedia.

Another key instrument developed in the 1940s and 1950s was the flow cytometer *(Figure 23)*. At that time, researchers and physicians wishing to do counts of blood cells had to rely on manual counts in counting chambers, with differential blood smears to assess white cell populations. These counts were statistically hard to reproduce and relied on the technical ability of the person using the microscope.

A significant development was the development of a cell counter by Walter Coulter in Chicago. He and Arnold Beckman shared a number of characteristics. They were both curious about how ideas worked. They also were inspired by technological challenges. As Coulter is reported to have said, "Challenges are good, and we sure had our share of good."

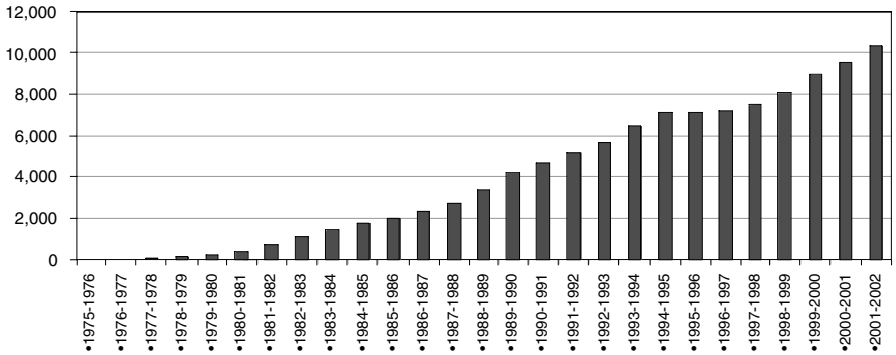


FIGURE 23 Publications using the keyword "flow cytometry" from PubMed; shown are 62,496 references from 1975 to 2002.

Important work on flow cytometry was also done at Los Alamos National Laboratory in New Mexico, which remains the home today of the National Flow Cytometry Resource. Since the 1950s, a research group there has worked on many of the technologies underlying flow cytometry, such as hydrodynamic focusing of cells being carried in a fluid stream *(Figure 24)*.

The addition of laser detectors to flow cytometers in 1972 marked another critical advance. The combination of multiple lasers and detectors made possible several commercially successful machines marketed by Becton, Dickinson and Company and by Coulter during this period *(Figure 25)*.

In flow cytometry, individual cells travel in suspension past excitation sources, usually a laser, in a liquid medium. As it passes by the excitation source, each cell scatters some of the source light but also often emits light as fluorescence. Physical and chemical characteristics such as cell structure, cell size, and particle morphology can be measured from the scattering. While fluorescence may occur naturally, cells are usually stained with fluorescent dyes that bind specifically to cellular constituents. The intensity of the resulting fluorescence emission is measured at several wavelengths simultaneously to identify the quantities of specific components of the cells. The outputs of this method are frequency histograms and dot plots. Frequency histograms display relative fluorescence or scattered light signals plotted against the number of events, whereas dot plots show one dot or point related to the amount of two parameters (identified on the x- and y-axis of the plot) for each cell that passed through the instrument.

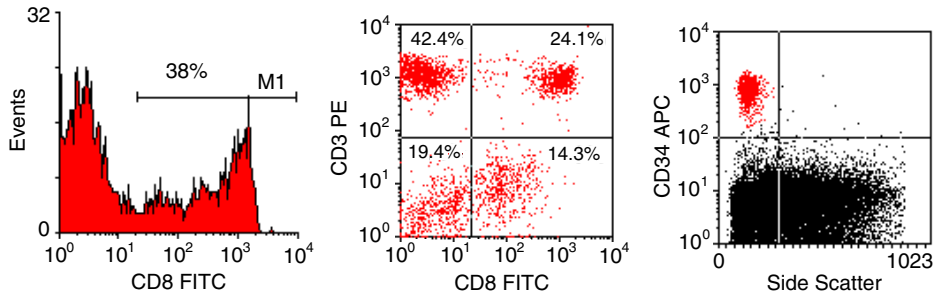


FIGURE 24 Flow cytometry data analysis. Left-hand plot shows a one-color histogram plot of CD8 expression by peripheral blood (PB) lymphocytes. Approximately 38 percent of events fall between the marker boundaries and are therefore regarded as CD8 positive. The center plot also shows CD8 expression on PB lymphocytes, but depicts the relationship between CD8 and the T-cell marker CD3. It is apparent that the CD8 positive population depicted by the histogram contains two CD3-defined subpopulations (CD3 positive and CD3 negative), and that the CD3 negative fraction (lower right quadrant) expresses CD8 at a lower intensity than the CD3 positive fraction (upper right quadrant). The right-hand plot shows a population of CD34 ositive stem cells plotted against side scatter.

Today flow cytometers are used in a wide variety of applications. One of the most important is known as immunophenotyping—detecting the types and numbers of immune system cells in a blood sample. For example, one hallmark of HIV infection is the loss of a distinct subpopulation of T cells called CD4 cells. This particular disease, I've been told, has sold more flow cytometers than any other disease.

Flow cytometers also are used in many other applications. For example, when a patient comes to a doctor's office with what appears to be leukemia or lymphoma, the disease is characterized using multiple sets of cell surface markers. Treatments then can be tailored to the particular form of the disease. If we characterize people, we know the first line of treatment to use. This has been one of the first instances of personalized medicine.

Flow cytometry also has been critically important in detecting what is called minimal residual disease. After a patient completes a course of therapy, a biological sample is taken from the patient to see how many tumor cells remain. The number of diseased cells remaining suggests how likely the patient is to respond to continued treatment. You get a predictive value out of this technology *(Figure 26)*.

The continued development of flow cytometry offers great potential. The first step is to define what the goals of an instrument are. The users of an instrument need to talk to people who are building an instrument and say, "This is what we need. Build us an instrument that will answer those questions." Otherwise, companies frequently build machines to answer questions that you don't have.

FIGURE 25 A color photograph of a flow cytometer showing the multiple colors of lasers.

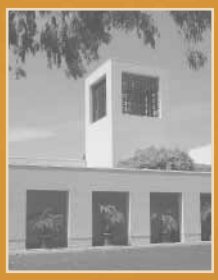
Ease of use is often as important as the capabilities of an instrument. For example, as HIV infection becomes a critical problem around the world, the use of instruments in many different settings must be considered. We need to monitor biomarkers to know when to start giving people therapies, and then monitor when to increase or decrease those therapies. To achieve this goal, instruments need to be straightforward and robust, with relatively automatic data analysis and interpretation. Also needed are strict standards and controls, so that the instrument will function as desired. While the instrument itself may appear to be relatively unsophisticated, the package itself needs to be very sophisticated.

For research purposes, technological capabilities are important, and instrument developers are building machines with greatly enhanced capabilities. Also, flow technologies and imaging technologies are being merged to allow researchers to examine subcellular components. Such analyses can be very complex, which is very useful in the translational effort to discover new things.

FIGURE 26 The EPICS ALTRA flow cytometer is a powerful and flexible cell sorter. Courtesy of the Beckman Coulter, Inc.

Beckman

PART III



THE EVOLVING RELATIONSHIP BETWEEN INSTRUMENTATION AND RESEARCH—A PANEL DISCUSSION[1]

Panel Participants: William Ballhaus,[2] Robert Gaensslen, Leroy Hood, Gabrielle Long, John Roberts, Michael Roukes, Vincent Shankey, Wm. A. Wulf[3]

William Wulf: I'm a computer scientist, and my career has pretty well corresponded with Moore's law. For 45 years it feels as if I've been sitting on the 50-yard line watching an incredible increase in technology. One byproduct of such rapid change has been that I have heard some really bad predictions about what's going to happen in the future. When technology is changing as rapidly as it has for 45 years, making predictions about the future can be dangerous. That said, I've suggested to the panel that we spend some time looking into the future.

Gabrielle Long: At the end of my talk I was discussing the linear coherent light source, which is essentially the x-ray laser. Such an instrument will create many opportunities, which I would put into two categories: chemistry and biology. The x-rays from this kind of device come in pulses and will be extremely short, on the order of a few femtoseconds. Chemists will be able to activate reactions and then watch the products go through various intermediaries to get back to the ground state. That kind of experiment is going to be very much possible with the linear coherent light source. It will open up an area of chemistry that we are only beginning to glimpse today.

Regarding biology, we're used to doing structural work on biological materials that have been crystallized, and crystallography has been enormously successful. The dream, however, is to be able to do structural analysis on a single molecule. When we finally have enough coherent photons in a single pulse, the molecule may fly apart from the impact, but it will not fly apart until we find what its structure is. Understanding these kinds of

[1] As prepared by Steven Olson.

[2] William F. Ballhaus, Sr., former president, Beckman Instruments, Inc. Dr. Ballhaus (Ph.D., California Institute of Technology, 1947) began his career in aircraft design and engineering at Douglas Aircraft, Inc., around the time of World War II; he then joined Northrop Corporation in 1953 as chief engineer and became executive vice president in 1961. In 1965, Arnold O. Beckman recruited Dr. Ballhaus as his successor to operate Beckman Instruments, Inc. Under Dr. Ballhaus's leadership, Beckman Instruments, Inc., made the transition from government contract work to the emerging markets of medical and biotechnology. He remained president of Beckman Instruments until 1983, when the company merged with SmithKline Corporation. Since then Dr. Ballhaus has served as president of International Numatics, Inc. He is an elected member of the National Academy of Engineering and is a fellow of the American Institute of Aeronautics and Astronautics.

[3] Wm. A. Wulf, president, National Academy of Engineering, and vice chair, National Research Council. Dr. Wulf (Ph.D., University of Virginia, 1968) is on leave from the University of Virginia, Charlottesville, where he is AT&T Professor of Engineering and Applied Sciences. Among his activities at the university are a complete revision of the undergraduate computer science curriculum, research on computer architecture and computer security, and an effort to assist humanities scholars exploit information technology. Dr. Wulf has had a distinguished professional career that includes serving as assistant director of the National Science Foundation; chair and chief executive officer of Tartan Laboratories, Inc., Pittsburgh; and professor of computer science at Carnegie Mellon University, Pittsburgh. He is the author of more than 80 papers and technical reports, has written three books, and holds one U.S. patent.

structures at a level never before possible will enable us to explore areas of biology that are not now accessible.

Leroy Hood: Biology has its own Moore's law, which is that all types of biological information will undergo an exponential expansion. The fascinating question is how we can use this information to gain some understanding of organisms.

I think the bottom line is systems biology, which will dominate the twenty-first century in powerful ways. It is imperative that we develop techniques that will enable us to do global analyses of biological systems. One of the enormous challenges in doing such analyses is dynamics. Biology is all about transitions, whether developmental, physiological, or even evolutionary. Can we understand these dynamic transitions?

Another big challenge is discovering how cells interact in complicated ways to create the properties seen in living organisms. At the institute we're using immune system cells because you can put them together in various ways, which makes an ideal model system. This enables us to digitize biology. We can interrogate individual molecules and cells. We will be able to put combinations of cells together and see how they create emergent properties.

Another thing is controversial but I am convinced it will happen. Through computational methods we will be able to fold all proteins and see what their likely behaviors are. Furthermore, we'll be able to deduce the circuitry of life. We'll be able to recreate protein networks and gene regulatory networks.

What we won't know from these computational networks is how the environment impinges on biological systems. So there always will be a marriage of experimental and theoretical science. In fact, all biology needs to be grounded in experimental data.

Within 10 years or so we will have aspects of the predictive medicine I've been describing. And in 15 years or so we'll be in the exponential phase of the advance of preventive medicine. Once we develop these tools, we'll be able to say that if you start taking these pills at age

38, you won't have to worry about this disease. I'm a skeptic about training people to stay out of the sun, stop smoking, and quit eating too much.

Finally, a lot of the big problems in the world have to do with food. I think these approaches will absolutely transform agriculture. Nutrition is really in the dark ages. If there was ever a discipline that desperately needed a systems approach, it's nutrition. These are enormous applications.

William Ballhaus: One thing that most people don't know about Arnold Beckman is that his company had the first bioengineers. When I was working with Douglas Aircraft, one of the finest aeronautical engineers I worked with was Curt Miller. We had both received scholarships to go to Caltech—I got my doctoral degree, and he got his master's degree. When it was over, I asked Curt what he wanted to do, and he said he wanted to be a medical doctor. And so he went to medical school for 3 years and then did a residency for a couple more.

"If I could choose one word that I would attribute to Dr. Beckman, it would be measurement."

—William Ballhaus

In 1965, when I became president of Beckman Instruments, I happened to see a mutual friend of ours, and I asked where Curt was. He said that he was working at Aerojet, and so I called him the next day and asked him whether he would like to be director of medicine for Beckman Instruments. He was a medical doctor and an aeronautical engineer, so I had him sit down with our chief scientist and tell him what the medical profession needs. I said that I wanted them to develop a set of instruments that medical doctors can use. That created a medical instruments department that became one of the fastest growing parts of the corporation.

If I could choose one word that I would attribute to Dr. Beckman, it would be measurement. But the demands made of measurement vary. When you look at what the electronics people have been doing, they have been packing more and more capability onto smaller and smaller things. Pretty soon the electronics people are going to have everything on nothing. But if you look at biology, billions and billions of proteins have to be analyzed and measured, so there is no question that bioengineering is going to be the future.

John Roberts: I feel very much like an anachronism in this discussion, because my focus on chemistry is entirely different. After I was a provost, I had to find some way of getting back into science. I did a little work on MRI, but I had to compete with patients for an MRI machine, and that didn't work out well at all. I also could not get the kinds of graduate students and postdocs that other people have in abundance. I had to work primarily with undergraduates. So I had to think about research in a different way, because you can't give an

undergraduate some of these tasks and get very much done in the course of a summer fellowship. I had to go back to some of the elements of organic chemistry and work on problems that were not well known.

One of these problems involved the structure of proteins. People don't always realize that the interior of protein is not filled with water but with something else, and the forces are very different. We started to study some of the simplest things you can study, the most favorable conformations around single bonds. In doing that, we discovered some quite unexpected things. In some compounds, two negative charges tend to want to be close together rather than far apart in aprotic solvents. These things are interesting, and they may have applications.

"Nano is a methodology. . . . The difference is that nano is a methodology that allows us to interact predictively with individual molecules."

—Michael Roukes

My point is that we shouldn't abandon basic chemistry completely. Lots of what's there has not been exploited well enough, and we don't understand it well. I'm enjoying this work very much. We had nine people working this summer, so there is a role for this kind of research activity.

Michael Roukes: I'm not going to propose that the next big thing after nano is pico. Nano is a methodology. Chemists could claim that they have been doing nano for a couple of centuries. The difference is that nano is a methodology that allows us to interact predictively with individual molecules.

Many things that are glimmers in the eyes of scientists who are in the field today are going to become robust in the same way that measuring tools Beckman built were brought into routine laboratory use. For example, one exciting possibility is doing dynamical measurements at the nano scale, really understanding at the level of single molecules the interactions in individual cells. We could follow this process in real time and understand its properties by building up statistical aggregates of individual entities.

I also believe that the Norman Rockwell picture of the family practitioner is going to fade into the sunset. Instead, you're going to plug your real-time attributes into a cold, calculating, massive database and out will pop a quantitative assessment of your physiological state, your proclivities for the future, and the preventive measures you should take to avoid disease. Part of the transition to that era will be the ability to mass produce these nano devices robustly. Ultimately I believe that these devices will be implanted in our bodies and will monitor our physiological state in real time. This will be transformational.

Robert Gaensslen: I'm at the applied end of this discussion. One trend will be to get a lot of the measurement, technology, and scientific testing out of the lab and into the field. There's no reason why a very sophisticated machine cannot be put in the hands of a cop, as long as the data go back to the lab and the cop isn't responsible for figuring out what the data mean. If some of these technologies can be boxed up, they can be complete black boxes for crime scene investigators, which would create huge efficiencies.

We need to learn how to individualize trace evidence. That would make trace evidence much more valuable. Showing that two red fibers have a common origin does not come up in every case, but where it does come up it's important.

Regarding biological evidence, if all of the predictions I've heard come true, you can bet that the FBI is going to have one of the receivers for these devices that are implanted in people. How much information are you willing to give to law enforcement, or are you willing to let law enforcement have in a databank in order to keep you safe? These are important public policy questions that ultimately the citizenry is going to have to answer. The freer the society, the more crime it will tolerate. There's little crime in Singapore, but there's not much freedom either. Some law enforcement people are already saying, "Why don't we put all suspects in the databank right now?" The British do this, and they get a lot more hits on suspects. Are you going to have half, three quarters, or all of your population databanked? That's a public policy question. You could catch every criminal who leaves biological evidence. But is that what we want? Do you want the FBI to know about your health status and when you're likely to have that next heart attack? I don't. It's a matter of how much you trust your government and how much you think the government, on the basis of its past behavior, has given you reason to trust it.

Arnold Thackray: I have a question for the panel. If you look at innovative organizations, probably the most successful long-term innovative organization in the world has been the Catholic Church, though we don't usually think of it in those terms. The last time I checked it had more members and a longer history than most other organizations. Universities are about the only other organizations that are serious competitors. Closer to home, General Electric set up an industrial lab in 1901, and the last time I checked GE was doing okay as a company. DuPont, too, has reinvented itself two or three times. So I don't think you can just push innovation entirely off to small companies.

Leroy Hood: All of the big companies I know, such as GE and IBM, tend not to innovate. They buy innovations that other people have created and then take that innovation to the

The Arnold and Mabel Beckman Center of the National Academies. Courtesy of the Beckman Center of the National Academies.

point of proof. Don't get me wrong. Big companies are very good at adapting to opportunities and integrating things that have been proven. And organizations like the church and universities are enormously innovative in the context of a bureaucracy that has been honed to do what they set out to do. My point is not that big organizations can't innovate. But they innovate around the conditions that their administrative structures have set in place.

I do have a wonderful model for academia and industry that is based on what Jack Whitehead did with the Whitehead Institute at MIT. What persuaded him to establish this institute at MIT was David Baltimore—he found a soulmate who had a common view. He was tough with MIT, because the university was anxious to take this $150 million and go with it. He said, no, my institute is going to be entirely independent from MIT except for a couple of things. One was jointly recruited faculty, which was important for quality control. The second was that the provost had veto power over the choice of the director, which was also a quality control provision. But in all major regards—managing the budget, personnel, the ability to make decisions about how to use resources—the Whitehead Institute was totally independent.

I would argue that the Whitehead is the best example of a really successful research institute in the world today. Even more important, MIT has enormously benefited from the Whitehead. A large percentage of its biology faculty has come via the Whitehead. And the institute could be enormously flexible. When Eric Lander was considering leaving the Whitehead, the institute decided to make an enormous contribution to his work in a mat-

ter of less than a week. Can you imagine any kind of academic institution making that kind of decision?

I think educational institutions are great and I don't want to replace them. But we need to think of innovative ways for them to create new kinds of opportunity.

John Roberts: I've been a consultant with DuPont for 56 years and I know something about what happened. They got into the instrumentation field with protein synthesizers and so on, and they had good instruments but did not have the commitment to finish them. They did some very innovative things, but they are generally not very good at doing the kind of thing that Lee Hood is talking about.

With respect to advances in forensic chemistry, I have a question. I want to hear about how these esoteric and complicated new methods can be presented to juries. I'd also like to hear about preventative work, rather than solving evidential problems afterward.

Robert Gaensslen: There are two schools of thought about how to testify. The O.J. Simpson trial is philosophy A. You try to teach everyone everything you know about the subject. It doesn't work. Everyone's eyes glaze over, and nobody knows what you're talking about. The second philosophy is that you give the jury the bottom line. It's his DNA. That's all they need to know. You can say a few words about how you came to this conclusion. They're not going to understand exactly what you did. But if you're credible and come from a credible laboratory, they're going to believe you.

The other thing to understand about an expert witness is that science does not fall within the realm of what courts call judicial notice. The judge is willing to admit that the sun will rise tomorrow, and you don't have to bring an expert to testify about that. But everything else is your opinion. So when you go to court, you're up there by yourself, and this is your opinion, and the jury can totally disbelieve you, no matter how good the science is. Look at what happened in the Simpson trial. I'm convinced that the DNA was right, though there was sloppiness in the case, but the jury simply disregarded the DNA evidence, and they are entirely entitled to do that.

Prevention is a good idea. The biggest cause of violent crime in the United States is the drug problem. It's huge. Nothing else makes a dent. I've been in this field for 35 years now, and the problem was about the same in 1970 as it is now. The drugs may change, but the problem doesn't change. This is something that is hardwired into human nature that we have to do

"The judge is willing to admit that the sun will rise tomorrow, and you don't have to bring an expert to testify about that. But everything else is your opinion."

—Robert Gaensslen

something about. It's obvious that we can't just burn down coca fields in Bolivia and solve this problem. There's demand, and in every generation the demand seems to stay the same. It eats up resources like you can't imagine—laboratory resources, prosecutors, jails, prisons.

Michael Roukes: I want to say something about the invasiveness of having our medical profiles accessible to large numbers of people. It seems inevitable to me. It's not a matter of whether it's going to happen—it is going to happen. Futurists talk about two different populations—people with technology, and people without. I have great faith in humankind that we have the collective will to make things better, and I think science can harness that will.

"Does the person who's identifying a drug need to know how a gas chromatograph/mass spectrometer works? It's an open question."

—Robert Gaensslen

Leroy Hood: The predictive part of medicine does bring tremendous ethical dilemmas. But they're ethical dilemmas only if you can't prevent disease. If you can, who cares whether you have that defect, because you can take care of it.

Audience member: I'd like to ask about sophisticated instruments being black boxes with no user-serviceable components. Is that a good or a bad thing?

John Roberts: I once wrote a book that essentially said, "If you want to learn about NMR, buy this book. If you're not interested and you're willing to let things be black boxes, don't buy it." We're willing to accept the computer as a black box, even though it may freeze up on us from time to time and we get mad at it. But with NMR, and with I don't know how many other modalities, I don't know how we're going to handle the problems of people not understanding what's going on inside these things. Maybe you can make instruments so reliable and so able to interpret the data that all you have to do is have it print out a complete diagnosis of what you've done; maybe it will even tell you where you've made a mistake.

I've had a scientific argument with a man who claims that he can measure NMR splittings to hundredths of a hertz. But according to theory, that would require listening to the free induction decays (FIDs) for 100 seconds. It turns out that you can't listen to an FID for 100 seconds because it seldom lasts more than 4 or 5 seconds. So how do you resolve that question? But when you run a spectrum, you get printouts of results to 0.001 Hz. That's the digital resolution, but it doesn't correspond to reality. I don't know how to deal with the problem of people believing what the computer tells them, even if the accuracy of the results does not correspond to the printouts. This is a major problem with quantum calculations.

Michael Roukes: There are at least two camps of people. There are the experts who are developing instrumentation and want to open up the hood and supercharge whatever's in there. But once the car is built, there's a large population that wants to use it to go somewhere. Both groups have happily coexisted in the past, and both will in the future. If your explicit question is whether I think that 20 years from now we'll have single-atom MRI and it will be robust, the answer is, "I hope so."

Leroy Hood: There are three stages of instrument technology. The first stage is the prototype. Then there is a stage when an instrument is made robust. And then there is the period when you move an instrument into an automated context.

You need much more understanding of an instrument at the early, immature stage. If you think about the three kinds of major technologies in genomics, for example, they range from immature to teenage to relatively mature. Proteomics is very immature, and you have to understand it very well before you know what to believe. DNA arrays are intermediate—you need to understand the statistics. DNA sequencing is now a very mature technology.

Robert Gaensslen: There's another angle of this that comes into play in forensics labs. Forensic labs use these machines in their mature stages to look at specimens for which the machines were not designed. It's fine if you're looking at cell lines and if you know you have a single source. But most of the forensic people doing these analyses don't fully understand what these machines are doing, even if they have Ph.D.s.

Furthermore, when something is owned by a company, the company is not necessarily going to tell you what's going on in the box beyond a certain point, when things become proprietary. This also becomes an issue in court involving how much

an analyst who is testifying needs to know. Does the person who's identifying a drug need to know how a gas chromatograph/mass spectrometer works? It's an open question.

Vincent Shankey: What is our role as scientists and what is the role of scientific institutions in trying to make our culture more scientifically sophisticated?
Leroy Hood: My philosophy has always been that one of the obligations of a scientist is to transfer knowledge to society through K-12 science education. In Seattle we've set up a K-12 science education program that is focused on innovation, inquiry, and teacher training. The program includes the entire set of elementary schools in Seattle—72 schools, 1,100 teachers, and 23,000 students. Almost 100 percent of the teachers have been instructed, and test scores for science in the elementary program have changed in a striking way. We have a similar program for middle school. In high school it's more difficult. What we've done there is to develop modules for systems biology. The kids work with these graphical networks, and they love it. And the teachers love it, because it's something new and not recycled. If every scientist made a commitment to helping K-12 science education in his or her own community, it would change a lot of the suspicion and hostility.

NSF is designing a series of kits that are really great. Our inquiry-based teacher training is organized around those kits. I always argue that the most important thing students should acquire is the ability to do analytic thinking. But one thing I worry about is how deep the understanding of the teachers and kids is. Another problem is that in the early stages our program was supported by a $2 million NSF grant that has since expired. Where does the money come from to continue to support the program? The school district has more than enough money to support this program, but it's all entitled. So I spend a lot of time raising money to keep this going. But in the long term, if you can't integrate these programs into the school system, they won't be viable.

I've looked at a bunch of programs in systems biology, and you really have to have one passionate leader who is willing to spend a lot of time and make it happen. For example, at Princeton, David Botstein has single-handedly fostered tremendous relationships among physics, engineering, and mathematics, and I think Princeton is creating a really terrific program. He came in with a mandate to do that. How you make the environment receptive for that kind of change is an issue many schools are facing today.

William Wulf: Well, I think this has been a wonderful symposium. I believe this is the first time I have heard the prefix yocto used, which I think stands for times 10 to the minus twenty-fourth. With that, I'd like to adjourn this session and the symposium. Thank you, and let's thank the panel!

THE ARNOLD AND MABEL BECKMAN CENTER OF THE NATIONAL ACADEMIES

A refined and relaxing environment for sharing knowledge, for learning, and for growth, the Beckman Center is adjacent to the University of California, Irvine *(Figure 27)*. Made possible by gifts from the Arnold and Mabel Beckman Foundation and the Irvine Company, the Beckman Center was originally conceived to serve and benefit the National Academy of Sciences, the National Academy of Engineering, the Institute of Medicine, and the National Research Council. Today it serves as a nexus for international collaboration in a wide range of intellectual pursuits dedicated to the advancements of science, medicine, engineering, and technology and the study of their social, economic, and environmental implications. The Beckman Center is also home to the offices of the Arnold and Mabel Beckman Foundation.

The Beckman Center was specifically designed to accommodate both short-term and long-term committee meetings, workshops, conferences, and symposia large and small. A variety of conference rooms and public spaces provide the flexibility to meet the needs of any size gathering and its agenda, including area for pre-function receptions, plenary sessions, lectures, breakout meetings, board meetings, and dining and social activities. Each conference room has its own private terrace or balcony where attendees can enjoy the near-perfect California weather during breaks, ensuring each meeting is as pleasant as it is productive.

FIGURE 27 The fresh air and warm sunshine of the southern California coast invite guests to relax during breaks on the patios, terraces, and balconies, which have been designed in harmony with the center's natural environment. Courtesy of the Beckman Center of the National Academies.

One wing of the first floor of the Beckman Center is home to a special historical exhibit sponsored by the Foundation in honor of Dr. Beckman's revolutionary tools. As Dr. Beckman said, "I've done more for science in general by making instruments available for thousands to use than what I could do in my own laboratory by myself."

With colorful illustrations, striking period photographs, and a lively narrative, the exhibit showcases the broad impact that Arnold Beckman's development has had on science and society. The exhibit traces the roots of scientific instrumentation from antiquity through alchemy to the first chemical revolution—brought about by Boyle and Lavoisier with their systematic approach to measuring and controlling the processes of chemical reactions. The exhibit even includes several of the original instruments first developed by Arnold Beckman, including the pH meter and the DU spectrophotometer.

As the exhibit concludes,

> *Across his long life, the world in which Arnold O. Beckman has lived was radically changed through the development of science and technology. Arnold O. Beckman was no passive observer of these profound changes. Through his leadership, Beckman's firms helped to create the new technological "ages" that reshaped life in the twentieth century.*

The Beckman Center is an appropriate and lasting element of the legacy that Arnold O. Beckman gifted society. As the venue for the "Instrumentation for a Better Tomorrow" symposium, it was perfect.