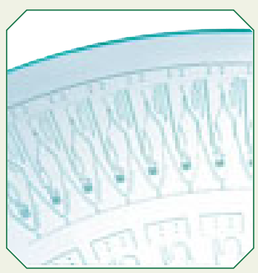
Niches and Nanotech

The future keeps getting smaller, and potential benefits loom large.

MICHAEL J. FELTON

The chemical enterprise—whether focused on producing and developing chemicals or analytical techniques—is exploring the new frontiers of the microscale and nanoscale. Instruments have been getting smaller and detection limits have been lowered. The move to interacting with the world at these very small dimensions is changing the nature of the modern laboratory, providing new life to existing tools and fertile ground for new methods of chemical analysis and production.

Computer on a Chip



The development of microtechnology began with innovation in the electronics industry. In 1947, the first transistor was invented, which allowed vacuum tubes to be replaced by a very small piece of germanium and, later, silicon. By 1954, the transistor radio was developed, but more-complicated electronics were difficult to make because wiring numerous transistors was labor-intensive and prone to errors. In July 1958, Jack Kilby at Texas Instruments decided to try to make an entire electrical circuit, not just the transistor, out of silicon, thus reducing the size and making circuits easier to produce. Shortly after, in January 1959, Robert Noyce at Fairchild Semiconductor independently developed an entire circuit on silicon. Both technologies were patented, but interest in the so-called integrated circuits waned.

Almost a decade later, in 1968, Noyce and fellow engineer Gorden Moore left Fairchild Semiconductor and started Intel Corp. Intel first produced silicon-based memory chips, but it was approached by a Japanese company, Busicom, to design and build 12 integrated-circuit chips for incorporation into a handheld calculator. An engineer at Intel, Ted Hoff, suggested designing one chip that could perform the function of all 12 chips. After negotiating with Busicom for the rights to the design of this first microprocessor, Intel marketed its 4004 integrated circuit as a "computer on a chip." The 4004 had 2300 transistors and had wires as small as 10 μm wide, but by 1982, Intel's 286 microprocessor had 134,000 transistors with wires as small as 1.5 μm. Today's integrated circuits can have hundreds of millions of transistors, and Texas Instruments and Intel have announced that new chips will be produced with features as small as 65 nm.

While engineers and scientists at Intel and other companies were making the "computer on a chip" trillions of times over, several companies were using the same fabrication techniques to produce very different devices. In 1968, H. C. Nathanson and colleagues at Westinghouse first demonstrated that 3-D structures could be made out of silicon using integrated-circuit fabrication techniques. In 1974, National Semiconductor applied the fabrication techniques to mass-produce strain gauges. These developments led to products such as microfabricated accelerometers, which are used in cars to trigger air bags during a crash.

Integrated-circuit fabrication techniques were applied to more than mechanical and electrical systems. One of the first liquid applications of microtechnology was ink-jet printing. The ink-jet concept was proven in 1878 in England by Lord Rayleigh and was finally transformed into working technology in 1951 by Siemens. However, these early printers produced continuous streams of ink, which wasted ink. In the late 1970s, several companies were researching drop-on-demand ink-jet printing, and in 1979, Canon succeeded, followed shortly by Hewlett-Packard. The ink-jet printer heads contain etched silicon wafers with microscopic channels that allow ink to flow to hundreds of nozzles.

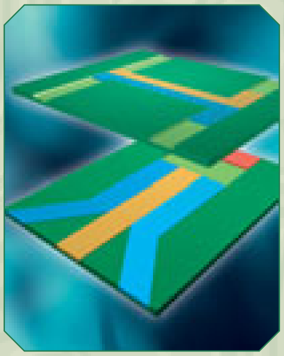
Lab-on-a-Chip

Making analytical instruments using integrated-circuit fabrication techniques was a conceptual leap. In 1975, Stanford University researcher S. C. Terry reported on an idea to make a gas chromatograph etched in silicon, but little was done about producing one. Much later, Stephen Fodor at Affymax used a technique similar to photolithography, which is used in making integrated circuits, to

Top: Richard E. Smalley (r), *Luminaries of the Chemical Sciences*, 2002

Center: Gyrolab microlaboratory disc, courtesy of Gyros AB

NICHES AND NANOTECH



Above: Microfluidics channel schematics, *Modern Drug Discovery*, 2002

make a microarray of oligonucleotides. Affymetrix was formed to commercialize the product, which was a dramatic success for biotechnology. Other companies developed competing microarray fabrication methods using ink-jet technology. For example, Agilent used Hewlett-Packard ink-jet technology to deliver DNA or proteins for making microarrays.

During the same period (late 1980s and early 1990s), Andreas Manz and others used silicon fabrication techniques to produce the first liquid pump on a chip, thus starting the field known as microfluidics. Manz coined the term µTAS, for micro total analytical system, to describe the goal of making microdevices that would perform analytical functions. Researchers soon replicated liquid chromatography within a microchannel, proving that analytical techniques could be replicated at this scale. Regardless of the terminology, the description is similar to the products that Intel, Canon, and Hewlett-Packard had developed to make computers and later printers on a chip.

New companies such as Aclara Biosciences, Caliper Technologies (now Caliper Life Sciences), Orchid Technologies, Gyros, and Cepheid, as well as integrated-circuit companies such as Motorola, began developing "lab-on-a-chip" products.

One of the first microfluidics products was the LabChip system jointly developed by Caliper Technologies and Agilent. Caliper, founded in 1995, developed a disposable microfluidic chip that could process multiple samples and developed a prototype reading instrument to obtain results from reactions on the chip. In the late 1990s, the company partnered with Hewlett-Packard. The partnership allowed Hewlett-Packard, which soon changed its laboratory instrument division name to Agilent Technologies, to apply its instrument expertise toward the refinement of the analyzing hardware that became the Agilent 2100 Bioanalyzer. In 1999, the Bioanalyzer and Caliper's LabChip microfluidic chips were introduced. Caliper's success raised new interest in microfluidics to replicate or develop new laboratory analytics. New companies such as Nanostream and established makers such as Waters are introducing new microfluidic-based versions of liquid chromatography. The same is true of gas chromatography; Agilent and others are producing microfabricated columns, and new companies such as SLS Micro are producing entire instruments consisting of microscale components.

A new generation of companies, started by researchers, is just beginning to introduce and develop products. George Whitesides, the Harvard University professor who invented soft lithography that uses poly(dimethylsiloxane), is behind a Massachusetts company, Surfacelogix. And Caltech researcher Stephen Quake has started a company called Fluidigm to commercialize his highly parallel microfluidic system that resembles computer microprocessors.

LARRY BOCK

Beginning with the biotechnology and Internet booms in the 1990s, new technology was not only in the domain of large corporations or universities—venture capitalism was becoming commonplace. And one of the most prolific and successful venture capitalists is Larry Bock. Bock began his career at Genentech, where he witnessed the biotechnology boom. But this son of an investment banker and gourmet chef found starting companies more rewarding. Bock founded and was the initial CEO of ARIAD Pharmaceuticals, Neurocrine Biosciences, Pharmacopeia, GenPharm International, Argonaut Technologies, Caliper Technologies, Illumina Technologies, Idun Pharmaceuticals, and Fast Track Systems. He also cofounded Athena Neurosciences, Vertex Pharmaceuticals, and Onyx Pharmaceuticals.

Several of these companies have become successful, one of which, Caliper Technologies (now Caliper Life Sciences), became one of the major microfluidic instrument makers. Bock is now executive chairman of the board of directors of Nanosys, which is working with numerous researchers on inorganic semiconductor-based nanotechnology.

Nanotechnology

The concept of nanotechnology was first succinctly explained by Richard Feynman in a lecture at Caltech on December 29, 1959, titled, "There is Plenty of Room at the Bottom." Feynman's view was that there was a vast amount of promise in building objects from the bottom up, from individual atoms, rather than the current situation, where technology can handle only millions of atoms at a time. Feynman is cited so often as the father of nanotechnology that it is easy to forget simply how prophetic he was. He stated, "In the year 2000, when they look back at this age, they will wonder why it was not until the year 1960 that anybody began seriously to move in this direction."

The term nanotechnology was coined in 1974 by Japanese researcher Norio Taniguchi, who was using energy beams to etch nanometer-scale channels at the University of Tokyo. He defined nanotechnology as "production technology to get the extra-high accuracy and ultrafine dimensions. . . . The smallest bit size of stock removal, accretion, or flow of materials is probably of one atom or one molecule, namely 0.1–0.2 nm in length."

Very little happened with the theory of nanotechnology until there was a way to see molecules and atoms at the nanometer level. Feynmen foresaw this in 1959 when he said, "For us to make more rapid progress is to make the electron microscope 100 times better." In 1981, researchers Gerd Binnig and Heinrich Rohrer at IBM's Zurich Research Laboratory invented the scanning tunneling microscope (STM). The device uses a probe with an extremely precise tip that is held in place by piezoelectric disks. The probe travels over a surface and measures the changing current caused by electrons that tunnel across the extremely small distance between the probe and the surface. The result is that atoms can finally be witnessed. Binnig and Rohrer won the Nobel Prize in Physics for the microscope in 1986.

The STM could be used only on surfaces and atoms that were conductors. In 1986, Binnig, Christopher Gerber, and Calvin Quate at IBM developed atomic force microscopy (AFM). Instead of using tunneling electrons to look at a surface, the AFM measures the deflection of the probe tip as it approaches atoms. Commercialization of STM and AFM, commonly lumped together as scanning probe microscopy (SPM), was led by Digital Instruments. In 1986, the company was formed and offered its Nanoscope STM, which sold for almost $100,000. Many other companies followed, such as Molecular Imaging, Omicron Nanotechnology, RHK Technology, Nanofactory, Asylum Research, JEOL, Leica, and Veeco (which is composed of former SPM companies ThermoMicroscopes, Digital Instruments, TopoMatrix, and Park Scientific).

IBM also found a new use for STM. In 1990, D. M. Eigler and E. K. Schweizer published an STM image of the letters I, B, and M spelled with 35 individual xenon atoms that were picked up and moved by STM. Being able to examine, and even move, atoms has brought about a revolution in material science and chemistry.

Nanoproducts

The new analytical technology has allowed new products to be developed. Micro- and nanoscale metal particles have been found to have either enhanced or completely unique properties compared with larger particles. For instance, microparticles of TiO_2 absorb or reflect UV radiation in new sunscreens, but they do not appear white like bulk TiO_2. Many companies are involved in developing new particles in a wide range of fields. One firm, Mach I, produced nanoscale magnetic and nonmagnetic iron particles for use as catalysts—the smaller particles have a much higher surface area than the traditional larger particles.

Some of the most promising new materials appear to be new forms of carbon, like buckyballs, carbon nanotubes, and nanoscale semiconductors, such as CdSe quantum dots. The road to the development of quantum dots, like integrated circuits, dates back to the late 1950s, when Herbert Kroemer at RCA theorized the possibility of a heterotransistor, in which positive and negative charges would move in a 2-D plane where two different semiconductors meet. In the 1970s, Kroemer and Zhores I. Alferov at the A. F. Ioffe Physico-Technical Institute in Russia independently developed a heterostructure laser, for which they were awarded the 2000 Nobel Prize in Physics. Research into the quantum effects of semiconductors continued, and in 1980, Alexander Ekimov and Alexei Efros at the Ioffe Institute observed quantum confinement in zero dimensions, which was also discovered by researchers led by L. Brus and R. Rossetti of Bell Labs. In the early 1990s, several papers discussed possible uses for the zero-dimensional quantum dots, which was borne out by research in communications technology and biology.

Several companies are now commercially producing quantum dots for biological use. The first entrant was QuantumDot, which was formed in 1998 on the basis of work done at the Massachusetts Institute of Technology and the University of California. In 2000, Evident Technologies was founded by colleagues who were working at Lockheed Martin's Advanced Concepts Research Division. Many other companies are interested in this area, with production technology being licensed from companies such as IBM as well as quantum-dot makers partnering with manufacturers such as Matsushita.

The other high-profile material of the nanotechnology field is carbon. In 1985, Robert Curl, Harold Kroto, and Richard Smalley discovered a new form of carbon with 60 atoms and shaped exactly like a soccer ball. This "buckminsterfullerene", as it was called, was very stable, and the researchers were even able to place metal atoms within the balls of carbon.

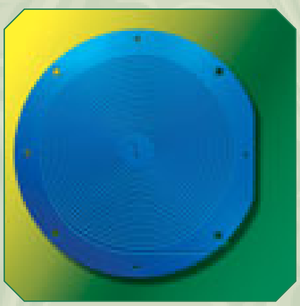
Production of C_{60} became commercially useful as research with it became increasingly widespread. For example, some fullerene-based solids can superconduct at reasonably high temperatures (20–40 K), and companies such as C Sixty are examining ways to use them as antioxidants and mitochondrial protectants. In 2002, Frontier Carbon Corp., partially owned by Mitsubishi Chemical Corp., opened the first fullerene plant in the world in Kitakyushu, Japan, to make 400 kg per year of fullerenes.

While investigating ways to make fullerenes, Sumio Iijima, a spectroscopist at NEC Japan, discovered what are known today as carbon nanotubes. Nanotubes exhibit unique properties such as either conducting electrons or behaving as a semiconductor, depending on their internal structure. Because of these properties, they have found use in many products, from preventing static buildup in plastic bags used for sensitive electronics to adding strength to plastics and concrete. New uses are being developed almost every day. In September 2003, NEC announced that it could reliably fabricate carbon nanotube transistors, which could revolutionize the electronics industry.

Carbon nanotubes are already being produced commercially by more than 16 companies, about half of them in the United States; and new factories are being built in Japan, Korea, China, and France. Current worldwide production in 2002 was more than 2.5 metric tons per day, a staggering amount considering each tube is mere femtograms.

Small problems

Microtechnology and nanotechnology have changed our world. And, although there may be problems down the road—for example, recent studies indicate that carbon nanotubes may cause damage to the lungs of rats, and cadmium-based quantum dots have been shown to kill rat liver cells when cadmium leaches from the dot—few are calling for the end to nanotechnology research. In fact, many countries are increasing their funding, including the United States through the U.S. National Nanotechnology Initiative. The trend is clear: The future is small. ◆



Above: MEMS-GC illustration, *Today's Chemist at Work*, 2002