The Incredible Shrinking Laboratory

Microchips may revolutionize chemistry as they did computers

By CORINNA WU

Once, computers were monolithic machines that churned out just a few calculations per minute. Since then, microchips have put a much faster computer on nearly every desktop.

Dozens of companies are hoping that similar chips can do for chemistry laboratories what they have done for computers. Using the techniques of the semiconductor industry, researchers are etching microscopic labs onto the surfaces of chips made of glass, plastic, and silicon.

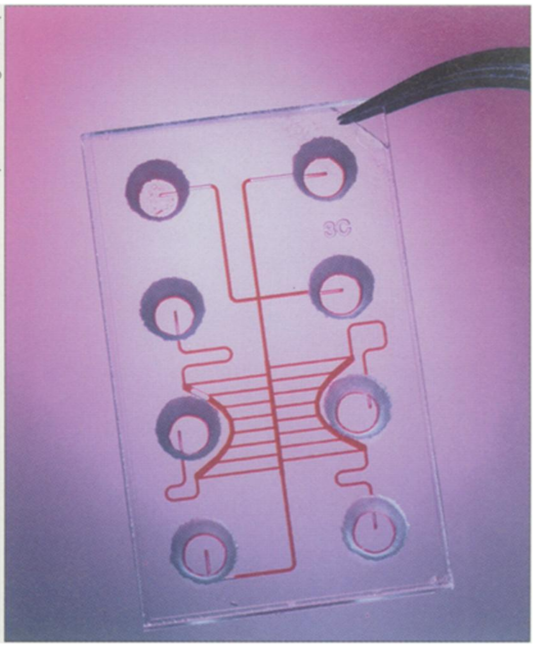
Instead of shuttling electrons back and forth as chips do in computers, the chemistry chips move minuscule amounts of fluid—volumes of millionths or even trillionths of a liter—through labyrinths of tiny channels and chambers equipped with pumps, valves, and filters. A computer choreographs the complex interaction of these components.

These chips could allow scientists to conduct biochemical analyses with greater accuracy than is now possible and in a fraction of the time. Instead of dealing with beakers, test tubes, and Bunsen burners, scientists could simply inject a small sample into a machine containing a microchip and wait a few minutes for the results to appear on a computer screen.

Several chemistry chip manufacturers are making substantial progress toward this goal. Pharmaceutical companies have taken a particular interest in chip technology, putting millions of dollars into developmental research.

The idea of chemistry chips began as a response to two research trends: genomics and combinatorial chemistry, says Michael R. Knapp, vice president of science and technology at Caliper Technologies Corp. in Palo Alto, Calif. The drive to sequence and identify all the genes in organisms—the Human Genome Project being the most prominent example—provided an incentive for entrepreneurs to develop ways to rapidly analyze large numbers of DNA samples (SN: 3/8/97, p. 144).

"There's a clear need to do thousands—if not tens of thousands—of genes at one time," says Paul Heaney, senior director of new technology and applications at Orchid Biocomputer in Princeton, N.J. Chips can accomplish these repetitive tasks quickly and cheaply, while requiring only small amounts of sample, he says.



Caliper Technologies Corp.

A network of channels connects eight reaction chambers etched into a thin glass chip.

At the same time, the techniques of combinatorial chemistry have radically changed the way drug companies look for new drug candidates. Instead of painstakingly synthesizing compounds one at a time and testing each individually for therapeutic activity, scientists simultaneously make small quantities of hundreds of related substances by systematically combining a range of chemical ingredients. They then screen the resulting libraries of compounds for biochemical activity.

The faster and easier this screening can be done, the better it is for a pharmaceutical company's bottom line.

Microchips may also be able to improve accuracy. Traditional chemistry labs are "open systems," says Jing Cheng of Nanogen, a biotechnology company in San Diego, Calif. Even though some steps in a complex process may be automated, a person has to intervene at several points, often moving materials from one container to another.

Not only can material be lost when it is moved, but an open system carries the risk of contamination. In contrast, after the sample is added to a microchip system, the analysis takes place entirely within the chip.

Chips may also be valuable to forensic scientists, who often have only small amounts of material to analyze, and hospital laboratories, where there is a need for accurate, automated diagnostic tests. The chips could be made disposable to prevent cross-contamination among samples.

Companies are approaching chip design from different angles. For example, Caliper Technologies is developing custom chips made from glass, plastic, or silicon that "miniaturize more conventional ways of doing experiments," says Knapp. "We can design whatever we want in miniature and recreate any experiment we can do on the lab bench."

Other groups are developing more generic chips that can be adapted for a wide variety of analyses.

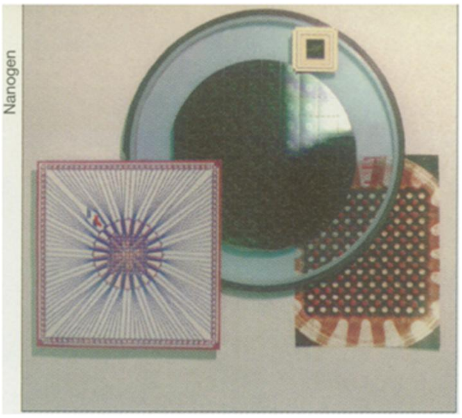
Researchers face the challenge of scaling down the pumps, valves, and reaction vessels found in larger lab devices. The chip components may not correspond to those available in traditional chemistry laboratories. There is no miniature centrifuge in a chip, for example, says Knapp. In fact, the chips generally have no moving parts at all.

Instead of using motors to move material around on a chip, a common strategy takes advantage of the charged, ionic nature of the cells and molecules themselves.

One trick is to use electrophoresis, a widely used technique for separating molecules by size. In the large-scale method, an electric voltage pulls DNA samples through a porous gel, moving different-size fragments at different rates and causing them to separate as marathon runners do in a race.

On a microchip, a simple pump might consist of electrodes that apply a voltage to pull cells and fluids through channels. Similarly, a miniature valve could use a voltage to block a fluid's flow. The valves in Orchid's chips are simply breaks in the capillaries that hold back fluids with surface tension. To restart the flow, electrodes protruding into the capillaries give the fluid an electric stimulus, overcoming the tension.

Orchid's 5-centimeter-square chips have a 12-by-12 array of chambers connected to form a "fluidic network," says Heaney. Made of multiple layers of glass or plastic, the chips are designed to perform as many as 144 simultaneous chemical reactions. In a three-layer chip, for example, the top layer contains the electronic connections, the middle layer the channels that distribute the fluids, and the bottom layer the chambers where chemical reactions take place.



Nanogen

Semiconductor microchips could form the heart of fast, accurate diagnostic devices.

In the June NATURE BIOTECHNOLOGY, Cheng and his Nanogen colleagues describe a chip designed to isolate the bacterium *Escherichia coli* from a blood sample and remove the microbe's DNA. The DNA is then analyzed by another chip. This type of sample preparation is one of the most difficult steps for researchers developing chip-based systems, Cheng says.

Their silicon chip, one millimeter on a side, carries 25 round, platinum electrodes arranged in a 5-by-5 array. The chip is connected to two tubes: one carries solutions to the chip and the other escorts them away.

A blood sample passes through the chip while an oscillating pattern of electric voltage is applied to the electrodes. Chemicals added to the chip adjust the blood's electrical properties so that a voltage pulls blood cells in one direction and bacteria in the other.

Through trial and error, Cheng and his colleagues found that an electric field with a frequency of 10 kiloHertz caused bacteria to collect on the electrodes and red and white blood cells to gather in the spaces between. A fluid pumped in over the chip washes the blood cells away.

Then, pulses of electric current break apart the bacteria, releasing their innards. An enzyme solution eats away the proteins in the cells, leaving the DNA and RNA intact. The resulting melange of molecules is then pumped out, and the genetic material is analyzed by another chip.

The 25-electrode chip can also be used to separate cervical cancer cells from blood cells, Cheng and his colleagues report in the June 1 ANALYTICAL CHEMISTRY. "We are creating a platform for many different assays," he says.

Chip makers have found that miniaturizing chemical processes results in a set of problems different from those routinely encountered in a conventional laboratory. For example, Knapp says, "There's so much wall space compared to the volume of the sample that the wall exerts a chemical impact." Molecules or biological cells inside a chip so frequently encounter the material that contains them that they may undergo unwanted chemical reactions.

Many companies prefer to make microchips out of glass, which interacts the least with samples. Plastic is cheap, which makes it a good choice for disposable chips, says Knapp, but it has more surface reactions and may not be as durable as other materials.

Silicon dissipates heat better than glass, getting rid of temperature variations that can push cells where they are not supposed to go. To mask the reactivity of the silicon surface, researchers have developed various ways to put down barrier layers. For example, Peter Wilding of the University of Pennsylvania School of Medicine in Philadelphia, who has been working on chemistry chips for more than a decade, uses silicon dioxide to "passivate the surface." At Nanogen, scientists deposit a gel on the walls that makes the silicon nonstick.

These Lilliputian laboratories also come with their own "miniature plumbing problem," says Heaney. The physics and engineering principles that apply to fluids moving on a microscopic scale are so different from conventional properties that they have been given their own name: microfluidics. "When you put fluids in small spaces, things happen that surprise you," says Knapp.

Caliper is working towards creating a device about the size of a toaster that could serve as a personal laboratory workstation—"a Nintendo machine for the lab," Knapp says. A scientist could simply plug in a cartridge containing the chip appropriate for a test. Because the machine would be connected to a computer, "it not only does the experiment for you but collects the data, too."

Indeed, says Wilding, companies will have to package the chips in convenient devices. "The real breakthrough will not be in the demonstration of the technology but in the completion of a system that people can use," he says.

Eventually, the chips may even find their way into home health-testing kits, says Cheng.

Now that home computers are commonplace, home chemistry labs might not be far behind. □