Innovations

The next chip-based revolution

Caliper Technologies Corp.

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Physicists have particle accelerators, structural biologists have synchrotrons, and astronomers have radio telescopes. Pity molecular biologists, stuck thinking that a PCR machine, a glorified heating block, is the height of technological innovation.

Help is at hand in the form of Caliper Technologies Corp. (Palo Alto, California). Caliper is one of several young companies putting microfluidic versions of your favorite laboratory procedure onto glass or plastic chips. The tiny channels on the chips can withstand proportionately huge voltage differences, so standard procedures whip by: perhaps a minute for a DNA fragment separation or a few seconds for an enzyme assay. The devices could also revolutionize both medical diagnostics and high-throughput screening of drug candidates.

Goodbye test tubes

"If you go through a standard laboratory it is unbelievably primitive," says Michael Knapp, Vice President for Science and Technology at Caliper. "So we looked around for alternatives to the standard test tubes and beakers and pipettes." The Caliper team found their vision of the future in the form of J. Michael Ramsey of Oakridge National Laboratory in Tennessee. Ramsey had started with capillary electrophoresis (CE), which is used for the separation of small molecules that diffuse too rapidly when standard, slower separation techniques are used. Although CE had never replaced common and simple techniques such as agarose gels, Knapp felt that with Ramsey's innovations such a takeover was possible.

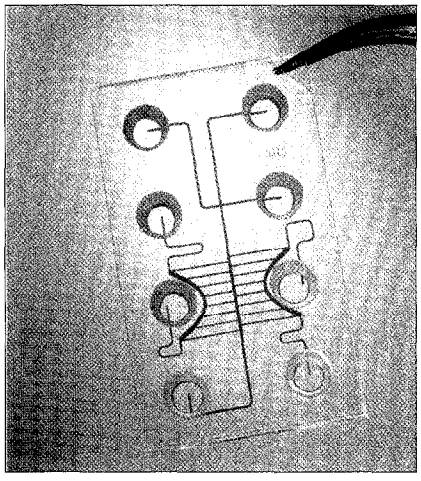
Ramsey and others had made a long-awaited mental leap from biology to materials science. The necessary micromachining methods had been devised decades ago for computer chips, and the new experimental concept was simple: by placing CE on a glass chip the researchers defined the logic of their experiment (Figure 1). "You can create a device of arbitrary complexity that can become the instruction set of an experiment," says Knapp.

The basic technique of molecular biology — the endless movement of colorless liquids — is what the new chips do best. Each reservoir on a chip is a source of buffer, enzyme, substrate, inhibitor or DNA, or a sink for waste. Fluid movement out of a reservoir occurs by electro-osmosis, a phenomenon from the world of CE in which ions associated with the channel surface move in response to a voltage change, and drag bulk fluid with them because of viscous drag. Voltage changes are used to first bring reactants together by electro-osmosis, and then separate products by electrophoresis. Valves are simply the channel junctions: Control of the voltage from all four directions can keep a liquid trapped between junctions, or flowing straight or around a corner (Figure 2).

Coming soon to a lab near you

The Caliper machine that runs the chips has the color, size and lines of a Macintosh computer. "You can imagine putting it on your desktop and a scientist will look like any other office worker," says George Church (Harvard Medical School, Boston, Massachusetts, and a member of Caliper's scientific advisory board). But this box — dubbed the Macarena — contains both electronics and a confocal optical system using laser-induced fluorescence. The ~2 cm × 2 cm glass chip is inserted on the top of the machine, slotting into the 16 pins that control voltage levels in the reservoirs. The Macarena is scheduled for release towards the end of 1998. Pricing has not been set, but Knapp says the box "need not cost much more than $10,000, and the chips need only be a few dollars each."

Figure 1



The layout of a Caliper chip. Voltage changes at the reservoirs, seen here as large circles, cause fluid to move into the microchannels, which in this image are filled with a red dye. Channel junctions act as valves, and stretches of channels between junctions can act as reaction chambers or separation columns. Image courtesy of Caliper.

"The function is dependent on the chip you put in there; it becomes a personal laboratory," says Knapp. "The Macarena is almost a peripheral: it's a way of getting information about chemicals into a computer." Possible functions include DNA separations, sequencing, PCR, receptor binding, enzyme inhibition, and immunoassays.

The delay in releasing the Macarena is more about developing a marketing plan than developing the product. Caliper faces a cultural challenge in convincing thousands of molecular biologists to trade in their trusty electrophoresis boxes and racks of eppendorf tubes.

Church, for one, is ready for the Macarena. "I think it will be like mini-gels," he says. "People realized they were inexpensive, didn't take up much space, and broke down the inertia barrier of running a gel. This takes the process one step further."

Figure 2

Delivery of serial, parallel samples using voltage-controlled flow. As fluid flows upwards from the reservoir at bottom right, voltage changes at the channel junction shunt 140 pl aliquots of liquid to the left. Samples of ~16 pl are removed from these aliquots and moved in parallel towards the bottom of the image. Such a design could be useful in high throughput screening, where multiple identical samples are required. Image courtesy of Caliper.

The Macarena was designed, says Knapp, to do standard techniques but to do more of them faster. But that may be enough to translate into new protocols. "A lot of things are possible with current methods, but just very difficult and expensive," says Church. With the Macarena, he says, "maybe there will be a feedback loop, so you can re-run experiments. If that involved reconnecting machines you would be reluctant to do it. You wouldn't try out ten protocols a day for 100 days. With this you could."

"One of the promises is great integration, where you have a number of steps dovetailed together," says Church. For example, both Caliper and Soane BioSciences (Hayward, California) have successfully combined PCR followed by electrophoresis and product detection. All this, on a single chip and with no human intervention, takes less than 20 minutes. The results come out as clean peaks on a computer screen.

For ion-exchange or affinity chromatography the channels can be filled with beads. The packing is no easy task, so PerSeptive Biosystems, Inc. (Framingham, Massachusetts) has replaced the beads with etched cubes of silicon. The cubes are evenly spaced, never move, and are easy to make: etching thousands of objects on one chip involves the same amount of work as etching one object. Deep etching reduces back pressure sufficiently to allow high-pressure liquid chromatography.

A small drug company in a room

Soane and Caliper are both planning to screen large libraries of chemicals against drug targets for pharmaceutical companies. Constraining small molecules for the time needed to do cell-based assays is a challenge, but a Caliper scientist states this is "an engineering problem rather than a theoretical limitation." Simpler protein-based assays will start in the next few months, with a different compound sent into the Caliper system every few seconds. "You could assemble warehouses of equipment and get to that throughput, but it would cost too much," says Knapp.

Caliper does not plan on becoming a drug company, however. "We're pursuing more or less an Intel strategy — we're focusing on making the chips, not on becoming a diagnostics or pharmaceutical company," says Knapp.

The companies most interested in diagnostics are Micronics, Inc. (Redmond, Washington) and Cepheid (Santa Clara, California). The concerns in this area are somewhat different. "There is a lot of hype about handling picoliters of fluids," says Kurt Petersen, President of Cepheid. "In diagnostics that is not the point." Cepheid has used deep reactive ion etching to increase the depth of the channels and so the amount of material that can be tested for pathogens or biowarfare agents. Keeping the cost of the disposable chips low is particularly important in diagnostics, so plastics are the preferred material. "This is a traditional razor/razor blade technology," says Tom Schulte, Vice President of Research and Development at Micronics. "The razor blade must be made for a cost where we can make money." Micronics will release a prototype disposable cartridge in the next few months, with a final product launch in mid-2000. The diagnostic machine will cost ~$12,000, says Schulte, and the cartridges will cost less than $2 each. Blood in a syringe is injected directly into a cap at one end and moves into the credit-card-sized plastic device. The results, including a platelet count, red blood cell count, and hemoglobin levels, are all reported in 2.5 minutes.

Both companies must convince private medical insurers in the United States that centralized testing services can be distributed into doctors' offices. "The market for diagnostics is not limited simply by technology," says Knapp. "But if you look 1000 years from now, do you really think you will send a blood sample to Teterboro, New Jersey?"

The first test market will, however, probably be the research community. Church is anxious for the machines' release. "It's like a brand new piece of Intel hardware: you need to get it out there for people to write cool software," he says. "This is a blank sheet of paper."

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