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Microtechnology for Instrumentation
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ABSTRACT
For the last two decades, the majority of research and development at LLNL in microtechnology has focused on photonics devices and bulk micromachining, including micro-electro-mechanical systems (MEMS) and associated areas. For the last ten years, we have used these capabilities to address our analytical instrumentation needs. Just as the integrated circuits in the 1960’s enabled the fabrication of portable electronics, MEMS and miniature photonics have enabled the fabrication of analytical instruments that are either higher performance, smaller, more portable, or are combinations of these. Examples of these are our portable thermal cyclers for DNA analysis, our hand-held gas chromatograph, our flow-stream-waveguide-based flow cytometer, and our etched-microchannel electrophoresis systems. This presentation will describe these and some related developments.

Key Words: Microtechnology, Instrumentation, PCR, flow cytometry, gas chromatography, DNA sequencing, microchannel, Human Genome Project.

1. MICROTECHNOLOGY
In the late 1960s, LLNL scientists and engineers began making miniature devices and structures for high-speed diagnostic equipment required for nuclear tests. Because commercial instrumentation was not able to perform as needed, the LLNL engineers fabricated components and systems to their own specifications for high-speed switches, high-speed integrated circuits, and radiation detectors. By the early 1980s, LLNL was fabricating thin-film membranes for use as x-ray windows in low-energy x-ray experiments, as x-ray filters, as debris shields for the Extreme Ultraviolet Lithography Program, and as targets for high-energy electron experiments in which x rays are generated. These passive microstructures have been applied to dozens of projects, including as diagnostic devices for LLNL’s Nova laser experiments. This early work in microelectronics, photonics, and microstructures at LLNL has grown into the Center for Microtechnology. Our Microfabrication normally involves silicon and silicon compounds for microstructures and micro-electro-mechanical systems (MEMS) applications, gallium arsenide for photonics applications, and lithium niobate for electro-optic applications, such as phase and amplitude modulators.

We began building photonic networks (made up of optical fibers, waveguides, amplifiers, receivers, wavelength selection elements, and modulators) using all-manual assembly methods. Because of the sub-μm alignment tolerances, the standard manual process was extremely time consuming and therefore expensive. In 1994, Mike Pocha, et al., won an R&D 100 Award for the development of a silicon "microbench" that reduces the time needed to align and connect the optical fiber in photonic components. The team's technique (Figure 1) provides just enough heat to melt the microdrops of solder needed to make the connection, allowing a rapid manual alignment and connection of the fiber to a laser diode or a lithium niobate modulator in less than five minutes and reducing the cost for this work by 90%.
An application of photonics technology, ultrascale computing, requires the cooperative action of thousands of microprocessors sharing tremendous volumes of data. This data sharing demands a communication "fabric" of very high bandwidth and low latency (short time delay) to enable the microprocessors to function efficiently. Optical fibers are an ideal medium provided that the optical signals are sufficiently amplified to cover the many receiver nodes. Erbium-doped fiber amplifiers are bulky and expensive, and conventional semiconductor optical amplifiers produce too much crosstalk at transmission rates above 1 gigabit per second. A team of LLNL scientists and engineers developed a low-cost, crosstalk-free semiconductor optical amplifier (Figure 2), using molecular beam epitaxy and chemically assisted ion-beam etching to make the device structures. The team won a 1996 R&D 100 Award for their device.

Figure 1. Photograph of the silicon-based miniature optical workbench, showing a fiber optic pig-tailed to a diode laser.

Figure 2. Photograph of a crosstalk-free semiconductor optical amplifier, pig-tailed to an optical fiber. See text. A dime is shown for scale.
2. INSTRUMENTATION

In 1991, we began to build analytical instrumentation, using components that were built with microfabrication techniques. One of the first applications was for the Human Genome Project, which has the goal of determining the nucleic-acid sequence (approximately 3 billion base pairs of adenine, thymine, guanine, and cystosine) of the human genome and finding all of the genes this sequence expresses. Here, we saw that the need for instrumentation capable of very-high-throughput sequencing could be addressed using parallel microfabrication processes. We began by building electrophoresis plates with etched microchannels in silicon and quickly moved to etching microchannels in plates of low-fluorescence glass. We etch the tapered wells for sample loading into a separate plate and then fusion bond the plates together with careful alignment, as shown in Figure 2.

![Figure 2](image)

Figure 2. Photomicrograph of the sample loading wells from an etched-channel electrophoresis plate. The smaller, almost-rectangular etched channels for electrophoresis are seen at the bottom of each opening. See text.

We have built plates, 7.5 centimeters wide and 55 centimeters long, with up to 400 parallel electrophoresis channels and the latest version of our sequencing instrument with this size plate is shown in Figure 4. Although this machine is still ramping up in its use with 100-channel plates, we expect to see more than two million bases of raw sequence per day being read out of one 400-channel plate.
3. PORTABLE INSTRUMENTATION

Supporting the Laboratory's bioscience research program and its nonproliferation efforts, the Laboratory has developed two instruments that facilitate biological analysis in the field, allowing real-time detection and identification. Because some samples cannot survive transport from the field to a remote laboratory, field analysis is often the only solution.

Flow cytometry is a powerful diagnostic tool used to characterize and categorize biological cells and/or their contents, such as DNA. It is used by laboratories throughout the world for blood typing and for testing for a wide variety of diseases and viruses, including HIV. The cells or DNA flow in single file in solution through one or more beams of laser light. The scattered light provides information about the cells or DNA. Instead of using a microscope lens or an externally positioned optical fiber as a detector, our system uses the flow stream itself as a waveguide (FSW) for the laser light, capturing the light and transmitting it to an optical detector. Several systems built around this principle were described recently. Figure 5 shows a FSW system which we took to the Joint Field Trials III, held in Fall 1996, at Dugway, Utah. This flow cytometer performed extremely well detecting the four simulated biological warfare agents. The LLNL flow cytometer detected 87% of all the unknowns with a false positive rate of just 0.4%.

An LLNL team, in collaboration with scientists from Roche Molecular Systems, Inc., developed a portable DNA analyzer that is small enough to fit in a briefcase. (Figure 6). This unit, the world's
first battery-powered, real-time portable DNA analyzer, moves analysis out of the laboratory for the first time. The heart of the PCR instrument is the thermal-cycling element, fabricated from etched silicon chips, bonded together, with thin-film, doped polysilicon heaters\(^7\). This allows very efficient use of the battery power - typically an average power less than one watt for heating and cooling a single chamber. Even with an LED and photodiodes for real-time monitoring of the PCR reaction, the average power consumption is less than 2 watts for this chamber. The control software automatically calls positives, typically in 30 minutes or less on this instrument.

Figure 6. Photograph of the briefcase-sized, real-time, battery-powered PCR instrument.

Gas chromatography is a proven method for identifying gaseous or volatile liquid species, with detection sensitivities as high as parts per billion. Conventional gas chromatographs, however, are several cubic feet in size and typically take about 20 minutes to analyze a gas sample. Conrad Yu is leading a team on a miniature, portable, low-power gas chromatograph. Our mini unit works faster, often requiring just one minute to complete an analysis, and would be very useful to carry into an area where an on-the-spot analysis is needed. We have developed a micromachined, silicon sample injector about the size of a little fingernail. We have also reduced the size of the chromatograph’s column where the various elements in the sample are separated before being directed to the detector. The column has been reduced from 100 in\(^3\) for a laboratory-sized unit to a coil etched on a silicon wafer. A circular column 100-\(\mu\)m wide and several meters long is etched on two silicon wafers that are bonded together (see Figure 7). The entire instrument occupies about 20 in\(^3\). Data collected using the silicon separation column is shown in Figure 8.

Figure 7. Photograph of one half of the gas chromatography column, etched into a silicon wafer.
Figure 8. Photograph of the data collected when a sample of N₂, O₂, Ar, CO₂, ethyl and propyl alcohol was run through a GC column, made by fusion bonding the wafer pictured in Figure 7 with its mirror image.

4. MICROACTUATORS AND MEMS

There are numerous applications for microtechnology that require self-powered, moving parts. This includes valves and pumps, but also other tools.

Microvalves are a key element in portable instrumentation that requires the transport of gases or liquids. Figure 9 shows a simple design, wherein an electrode is sandwiched between two polyimide films with different coefficients of thermal expansion. (Polyimide is a flexible plastic material.) For sealing gas flow, the delivery of less than 1 mW of power causes the "cantilever" to clamp down, sealing an etched hole beneath it.

Figure 9. Photomicrograph of a microfabricated valve. See text.

A more advanced tool is a self-powered microgripper on the end of a guide wire. The intent, here, is for the gripper to be positioned remotely, through a catheter. Developed by a team led by Abraham Lee, such a silicon microgripper, shown in Figure 10, is 1 by 0.2 by 0.4 mm. For this tool, the microactuator is a thin-film shape-memory alloy (SMA) of nickel-titanium-copper. At low
temperatures, SMAs are easily deformed, but when heated, they recover their original shape. This reversible transformation forms the basis for shape-memory actuators. Through the thin wire connected to the microgripper, an electrical current of 0.1 mA activates the actuator, deflecting each arm up to 55 μm and returning the gripper to its undeformed (open) position. As it cools, the gripper will open again.

Figure 10. Photomicrograph of a self-powered silicon gripper. See text.

5. THE FUTURE

Nationally and internationally, the scientists and engineers practicing microtechnology are using their devices and instruments to build more complex or autonomous systems for laboratory and field use. Because human-portable systems are clearly more desirable when lighter and smaller, microtechnology is an enabling capability, producing performance in a portable instrument that is often directly comparable to larger, traditional units. Since floor space can be a valuable commodity, the ability to miniaturize and integrate multiple functions will even drive microtechnology into non-portable applications, as well."

6. ACKNOWLEDGMENTS

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7. REFERENCES


