Laboratory Focus

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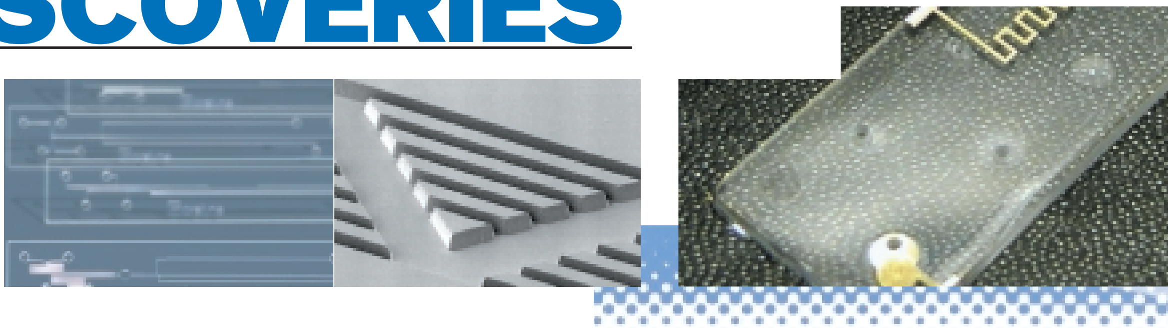
BIG DISCOVERIES WITH SMALL TOOLS



Left: Devices with T- and Y-intersections of channels for mixing or injection of reagents, channel meanders and open chambers for mixing or reaction of reagents, and straight channel lengths for electrophoretic separation of reagents and products.

Centre: A scanning electron microscope photograph of a quartz microfluidic mixing device made using reactive ion etching to form channel depths of 10 microns.

Right: A close-up of a bonded polymer microfluidic chip produced by Micralyne Inc. This chip has a serpentine heater with wire bonding pads.

Images courtesy of Micralyne Inc.

Existing and emerging microfabricated technologies are allowing radical improvements in instrumentation through miniaturization of mechanical components, which is driving significant innovation in various fields. These innovations have found their way into many laboratories, resulting in exciting new devices that are being used in drug discovery, genomics and proteomics, and in the development of novel new diagnostics. While nanotechnology has been receiving a lot of attention (and, in some cases, hype) over the last few years, it is microtechnology used in MEMS (micro-electro-mechanical systems) that is already being used in laboratories and industrial settings, and that will continue to be increasingly integrated into important life science applications.

WHAT ARE MEMS?

The two most commercially successful examples of MEMS devices in any marketplace to date are air bag accelerometers and ink-jet printer heads. MEMS devices that are used in life science applications, or "bioMEMS," are in earlier stages of finding their way into the marketplace, but have become increasingly important because they enable orders of magnitude in improvements in the size, performance and cost of key components within products. These improvements can miniaturize the drug-discovery process, accelerate the pace of discovery, and enable the development of assays to detect cellular and molecular phenomena in ways that have not previously been possible.

MEMS are produced using traditional semiconductor manufacturing technologies to fabricate 3-D mechanical components at an extremely small scale. To put this into perspective, devices are manufactured with features on the scale of microns (1,000 microns equal one millimetre). A MEMS device is usually a key component within a larger product, such as a biosensor within an imaging or diagnostic system or a microfluidic component for genetic analysis.

Each MEMS device will typically include components from one or more of the following three classes: a sensing component to detect changes in the system's environment (microfluidic devices are included here); an intelligent component (i.e., integrated circuit) that makes decisions based on the changes detected by the sensors; and microactuators (moving parts), by which the system changes its environment. A MEMS device may be constructed on different substrates and connected together (i.e., hybrid system), or all components of a system can be constructed on a single substrate (i.e., monolithic system).

HOW ARE THEY MADE?

MEMS devices are made on polymer, silicon, glass and/or quartz substrates. The latter three substrates are produced using techniques (described below) similar to those used to fabricate semiconductor chips.

Photolithography is the basic technique used to define the shape of the micromachined device. A mask with the desired pattern is produced — typically a chromium pattern on a glass plate. The substrate to be patterned is then coated with a polymer that is sensitive to ultraviolet light. This polymer is called a photoresist. Ultraviolet light is then shone through the mask onto the photoresist, transferring the pattern from the mask to the substrate. The photoresist is then developed, which removes it from the appropriate areas of the substrate. These open areas are then etched to the desired depth; the remaining photoresist protects the rest of the substrate. Finally, this remaining resist is removed, leaving the patterned wafer.

There are three basic techniques associated with MEMS micromachining. These are the deposition of thin films of materials (such as an oxide or noble metal), the removal of material (patterning) by wet chemical etchants, and the removal of material by dry etching techniques.

Wet etching is a blanket term that refers to the removal of material by immersion of the substrate in a liquid bath of the chemical

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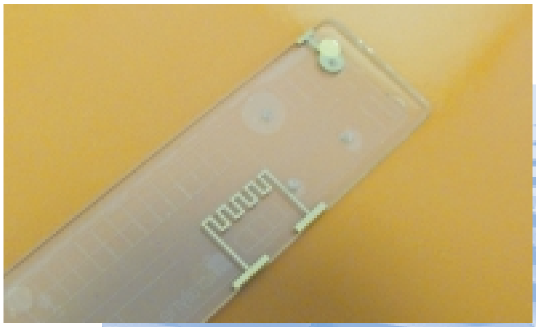
etchant. The most common form of dry etching for micromachining applications is reactive ion etching (RIE). In this case, high-energy ions impact the surface of the substrate, causing etching to occur. Deep trenches and pits (typically tens of microns, but ranging from less than one to hundreds of microns) of many shapes and with vertical walls can be etched in a variety of materials. These three techniques can be combined with various bonding protocols to produce complex multi-layer devices or to seal microfluidic channels.

Polymer MEMS use moulds fabricated using the techniques described above. These moulds are then used to produce multiple copies of the desired design by various replication techniques including casting, hot embossing and injection moulding. If desired, polymer MEMS devices can then undergo metallization and/or bonding (multiple layers are possible). A wide variety of polymers can be used, although traditionally the polymers are optically transparent (e.g., polymethylmethacrylate, polycarbonate and cyclic olefin copolymers).

APPLICATIONS FOR BIOMEMS

In drug-discovery applications, the term often heard today is “lab-on-a-chip,” which refers to devices utilizing microfluidics as the essential element. Microfluidic chips are miniaturized laboratories that use channels to manipulate the movement of fluids and gases on a small scale. This allows better measurement of certain reactions. Important benefits of this small scale include a huge reduction in the volume of expensive reagents required, faster reaction rates and analysis time, and significantly reduced cost. These chips are capable of performing such tasks as DNA and protein analysis and separation of cells, leading to quick and accurate diagnoses, improved treatments and faster development of drugs for a host of diseases, including cancer.



A bonded polymer microfluidic device detailing one of many possible metallization schemes. Wire bonding pads are possible on the surface (as shown) or on the edge of the device. **Image courtesy of Micralyne Inc.**

There are many advantages to be reaped by moving chemical analysis from conventional millimetre-sized fluidics to the 20-micrometre channel sizes found in microfluidic chips. Faster chemical and thermal diffusion, faster separations with higher resolution, lower sample consumption, integrated operations (injection, pre-column reaction, separation, post-column reaction and detection all occurring on the same chip) and portability are all advantages that have been realized in microfluidic devices.

Diagnostics is an area of increasing focus for bioMEMS. There is much activity directed toward the development of point-of-care (POC) diagnostic instruments that will take advantage of the power of BioMEMS for miniaturization and for increasingly sensitive detection with minimal sample volumes.

BioMEMS are now even finding their way into the body. There is increasing activity in the area of implantable MEMS for drug delivery and for *in vivo* biosensors. A number of laboratories and companies are working in this area and will undoubtedly have an impact on the way therapeutics are delivered and physiological environments are monitored in the years to come.

POLYMER MEMS

The growth in polymer MEMS has been driven by the high-volume, low-cost requirements inherent in the diagnostics market and, to a lesser extent, in the drug-discovery market. A single mould can produce hundreds of thousands of replica devices with very low cycle times, which can reduce the part price from hundreds of dollars to just a few dollars.

Until recently, polymer MEMS devices had been relatively simple microfluidic chips. Micralyne Inc. (Edmonton, AB) has been taking these simple devices and transforming them into more complex tools that include such components as heaters, sensors and electrodes. These integrated thin-film components change a static device into an active component that can easily interface with the macroscopic world.

While the use of polymers for the fabrication of MEMS devices might be precluded in applications in which stringent thermal or optical performance must be achieved, there are many applications in which polymer bioMEMS devices will become increasingly important. Hybrid devices can be created in those instances when cost reduction is critical but technical considerations preclude the option of having a totally polymeric device. In this instance, the material (i.e., glass, silicon or quartz) that is best suited for the optical or thermal conditions required can be used for fabrication of a sub-component, which can then be “hybridized” to a polymeric sub-component for which the optical or thermal conditions are not as rigorous.

CONCLUSION

Due to the significant impact MEMS can have on drug-discovery costs and timelines, it is very likely laboratory scientists will continue to increasingly see bioMEMS integrated into their lab instrumentation and systems for years to come. Advances in genomics, proteomics and pharmacogenomics help to support the favourable future outlook for the industry, and advances in diagnostics will accelerate this growth even further. Sophisticated new tools likely to take advantage of these areas include biochips, mass spectrometers, and biosensors used in detection and diagnostic applications. MEMS applications will no doubt lead to interesting breakthroughs in the development of “smart” laboratory devices and other types of equipment that rely on advanced sensors and minute precision.

Sandra Katz is vice-president of Marketing and Business Development, Biosystems, at Micralyne Inc. Micralyne is a pioneer and leader in the development and OEM (original equipment manufacturer) manufacturing of microfluidic and MEMS-based products. Micralyne has developed strategic relationships with companies that include Applied Biosystems Group (Foster City, CA), MDS Sciex (Concord, ON), JDS Uniphase Corp. (San Jose, CA), MicroCHIPS Inc. (Bedford, MA) and Li-Cor Inc. (Lincoln, NE). Micralyne’s micron-scale solutions are found in lab-on-a-chip devices for drug discovery, sensors in automobiles, optical switches for telecommunication networks, and commercial press equipment that print today’s most popular magazines. www.micralyne.com