From Batch to Continuous Manufacturing of Microbiomedical Devices

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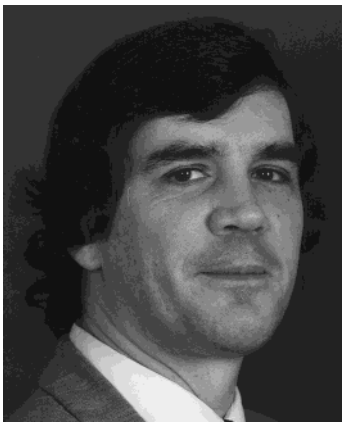

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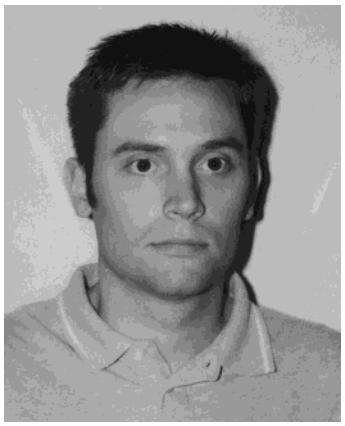

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I. Introduction

In this review, we demonstrate how manufacturing of miniaturized biosensors, fluidic platforms, drug delivery systems, and other microbiomedical devices is moving to non-silicon micromanufacturing techniques. Micromachining of mechanical and chemical devices and systems, in silicon, is contrasted with new manufacturing methodologies more appropriate for biomedical applications. The new methodologies are hybrid in nature and merge IC fabrication methods (e.g., lithography) with more traditional manufacturing (e.g., lamination, plastic molding, and electroplating). These hybrid methods may involve large sheets of materials or may even be continuous, i.e., the number of devices that can be produced per single substrate is larger than that for a silicon batch. The techniques are also modular rather than integrated and involve methods such as drop delivery, pick and place, laser drilling and cutting, and other methods borrowed from the IC packaging and PC board industries. These new processes will afford, for the first time, miniaturized sensors, fluidics, and other microbiomedical devices at a cost that will enable them to become pervasive in our daily lives. The greater modularity in combining different components and the wider choice of materials with the required properties (e.g., in terms of protein adsorption characteristics or optical transparency) will further accelerate the advent of many more innovative microbiomedical devices. In this paper, we discuss four important technology needs crucial to the realization of inexpensive disposable microbiomedical devices and then examine recent progress toward the manufacture of three microbiomedical devices: disposable biosensors, CD-based microfluidic platforms, and responsive drug delivery pills.

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II. Silicon in Micromachining

A. Silicon in Mechanical and Chemical Sensors

For over two decades silicon and IC fabrication have been promoted as the optimum choice of material and fabrication methodology for miniaturized chemical and mechanical sensors.[1,2] This was largely based on the success of silicon in IC fabrication in the electronics industry. The advantages of small, planar, and batch fabricated sensors over serially manufactured large sensors were obvious in terms of size and cost reduction. The integration of electronics with sensing functions and the possibility of redundancy and multifunctional arrays were seen as additional desirable features. In the case of mechanical devices such as temperature sensors, pressure sensors, accelerometers, and gyros, etc., such predicted advantages have largely been proven correct, leading to a small but fast growing MEMS (microelectromechanical systems) industry (currently about 1−2% of the total IC industry).[3] Although the market is often too fragmented to warrant a totally integrated approach, silicon is an excellent substrate if the mechanical properties of the substrate are important. Silicon exhibits several superior mechanical characteristics that make it an excellent engineering choice. Silicon does not exhibit plastic deformation or creep below 800 °C. Even with 10^8 cyclic loads, silicon does not fail. When silicon yields, it yields catastrophically rather than plastically (i.e., silicon is brittle). The Young's Modulus (E) of (111) silicon is 190 GPa versus 206−235 GPa for stainless steel. Silicon is almost as stiff as stainless steel. The yield strength of silicon is 2800−6800 MPa versus 35 MPa for aluminum and 1400 MPa for some steels. Silicon can withstand higher stresses without yielding. Silicon has a density (ρ) lower than aluminum but surpasses the yield strength of steel, making it possible to design lighter but stronger miniature mechanical sensors. All of these properties make silicon an excellent engineering material, and although it is brittle, it is a good option when low mechanical hysteresis is required. The superior mechanical properties of silicon are further illustrated in the stress−strain curves in Figure 1.

The high piezoresistivity of silicon combined with its excellent mechanical properties make it a superb material for the conversion of mechanical deformation into an electrical signal. The specific strength (σ_y/ρ) of silicon is better than most common engineering materials (see also Figure 1). Silicon is harder (Knoop = 850 kg/mm^2) than steel (Knoop = 820 kg/mm^2), almost as hard as quartz, and harder than most glasses. The piezoresistivity of silicon is high (>10 times higher than for metals) with a strain gauge factor as high as 90. The strain gauge factor is the relative resistance change divided by the applied strain (2 for a metal, 90 for silicon). The thermal expansion coefficient of silicon closely matches Pyrex glass, a material often used in combination with silicon. Figure 2 illustrates the basic geometry of a silicon membrane piezoresistive pressure sensor and piezoresistive cantilever accelerometer.

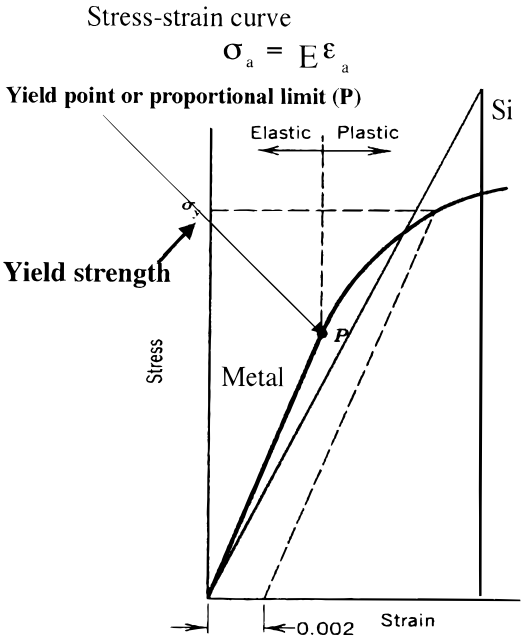

Figure 1. Stress−strain curve or elasticity curve of silicon and some mechanical properties of silicon.

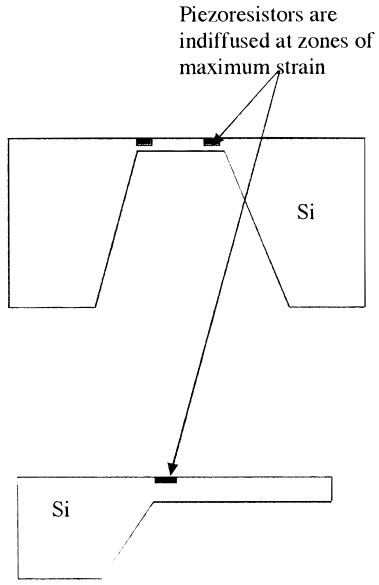

Figure 2. Silicon as a mechanical element in pressure sensors and accelerometers.

A good engineering guideline to determine if silicon is suitable for a given mechanical application is the following: there should be at least two benefits arising from the use of silicon over other substrates (aside from the possibility of integrating the electronics on the same substrate).[4] For example, in the case of a torsional micromirror used in a microscanner and based on SOI (silicon on insulator), as shown in Figure 3, the two benefits are excellent mirrorlike surface[5] and superior torsional behavior of the silicon mirror hinges.[6]

In microbiomedical applications, advantages of using silicon are often not as clear as in the case of mechanical sensors. In Table 1 a number of possible substrates such as silicon, quartz, plastics, glasses, etc., are listed. Important substrate features compared here are cost, packaging issues, fracture ten-

Table 1. Comparison of Substrate Properties[a]

		cost	pack-aging	frac-ture	metalli-zation	installed equipment base (access)	web	machinability (common methods)	dielectric constant	E GPa	thermal conductivity W/mK
single crystals	silicon	$	difficult	b,s	good	very large	no	very good	11.8	165	150
	quartz	$	easy	b,s	good	small	no	poor	4.4	87	7
	GaAs	$$$	difficult	b,f	good	small	no	poor	13.1	119	50
	sapphire	$$$	easy	b,s	good	small	no	poor	9.4	490	40
amorphous	fused silica	$−$$	easy	b,f	good	small	yes	poor	3.9	72	1.4
	plastic	c	very easy	t,s	poor	very large	yes	fair			
	paper/cardboard	c	easy	t,s	poor	very large	yes	fair			
	glass	c-$	easy	b,f	good	large	yes	poor	4.6	64	1.1
polycrystalline	alumina	cc−$$	easy	b,s	fair	fair	yes	poor	9.4	400	∼30
	aluminum	$	difficult	t,s	good	very large	yes	very good	77	∼240	

[a] b brittle, t tough, s strong, f fragile; $ = dollars, $$ = more dollars, $$$ = most dollars, c = cents, cc = more cents.

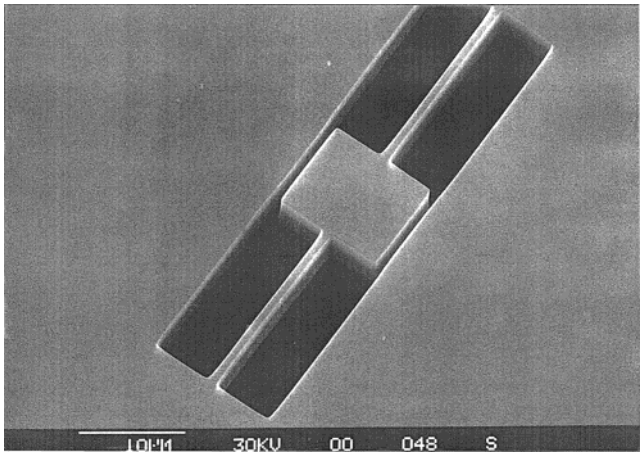

Figure 3. Torsional micromirror made from SOI (silicon on insulator). The excellent flatness and polished nature of the silicon surface together with the excellent torsional properties of silicon make this a good approach for building hinged micromirrors (Micromachined at TSDC, Menlo Park, CA, 1992).

dency, ease of metallization, the access to installed equipment to process the types of substrates, the availability of the substrates in large sheets or rolls (for manufacturing in very large batches or in a continuous mode), ease of machining, dielectric constant, the Young's modulus (stiffness), and thermal conductivity. Ceramic and glass substrates are more difficult to machine than silicon, and plastic substrates are not as readily amenable to metallization. Silicon has the highest material cost per unit area, but this cost can often be offset by the small feature sizes possible in a silicon implementation. Silicon, with or without passivating layers, due to its extreme flatness, relative low cost, and well-established coating procedures, is often the preferred substrate, especially for thin films. Much thin film deposition equipment is built to accommodate silicon wafers, and as other substrates are harder to accommodate, this lends silicon an advantage of convenience. There is also a greater flexibility in design and manufacturing with silicon technology compared to other substrates. In addition, although it is much more expensive than thick film hybrid manufacturing (green ceramic tape casting, screen printing, electroplating, lamination, doctor's blading), the initial capital equipment investment is not product specific. Once a first product is on line, next generation or new products will require changes in masks and process steps but not in the equipment itself. For large batches of electronic products, silicon becomes less expensive, but for smaller volumes, thick film hybrid technology is better.[1]

Disadvantages of using silicon are usually most pronounced with increasing device size, low production volumes, and when electronics do not need to be or cannot be incorporated on the same silicon substrate. The latter could be either for cost reasons, as in the case of disposables such as glucose sensors (target production cost about 10 cents), or for technological reasons, such as when the devices are to be immersed in conductive liquids (which short circuit or shunt the electronics). Another technological reason preventing integrated electronics could be if the devices are to be operated at temperatures above 150 °C (which tends to increase the junction currents too much).

The combination of active electronics with wet chemistry is especially challenging; besides the aforementioned shunting issue, there are several other reasons why silicon and thin film technology are not optimum for chemical sensor manufacture. The optimum thickness of hydrogels and membranes in chemical sensors is in the range of 20−100 μm. In this thickness range, thick film processes are more suitable for chemical sensor construction. Moreover, many chemical sensor materials, such as hydrogels (e.g., PolyHEMA (poly(2-hydroxyethyl methacrylate)) and agarose (for gel electrophoresis)) and ionophores (e.g., valinomycin) for ion-selective membranes, are incompatible with thin film IC processing as most are low-temperature materials or may contaminate the active electronic functions of the device (e.g., sodium would be detrimental to gate oxides). The very point of using silicon—its standardness—is forfeited in a chemical sensor environment.[1] An overwhelming determining factor for substrate choice is the final package of the device. A chemical sensor on an insulating substrate is, in general, easier to package than a chemical sensor on a piece of silicon with conductive edges in need of insulation. With sensors on a silicon substrate, a saw cuts each individual sensor, leaving unpassivated silicon sides exposed to the conductive electrolyte. Sensor packaging is so important for chemical sensors and systems that as a rule sensor and system design should start from

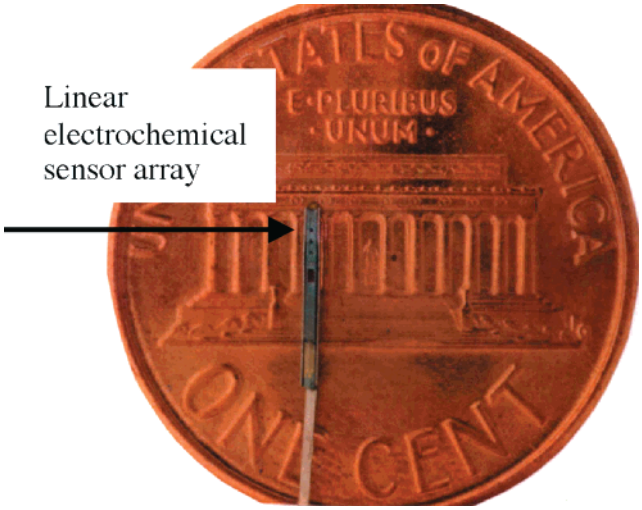

Figure 4. Micromachined linear electrochemical sensor array for in vivo pH, CO_2, and O_2 sensing.

the package rather than from the sensor or system itself. In this context, a substrate that is easier to package has a significant advantage. The latter is the most important reason recent chemical sensor developments in industry have retrenched from the move toward integration on silicon in the 1970s and early 1980s to thick film hybrid technologies on ceramic and plastic in the late 1980s and 1990s. In academic circles throughout the United States, chemical sensor integration with electronics continued until the late 1980s; in Europe and Japan such efforts continue.[7]

An application area where integration of electronics with chemical sensing functions is hard to avoid is in vivo applications such as the electrochemical pH, CO_2, and O_2 sensor array shown in Figure 4.[1,8,9] In the case of the in vivo electrochemical sensor in Figure 4, the probe body must be small enough to fit in a 750 μm diameter catheter and the resulting high impedance of the probe requires the electronics to be closely integrated to avoid noisy signals. For in vitro chemical sensor applications, on the other hand, size is less of a concern and the prospect of using a large sheet or even a web of substrate in a continuous manufacturing mode is an attractive option, especially for disposables. For most biosensors, one expects a cost less than that of a typical silicon sensor (10 cents for a glucose sensor vs $1 for a typical silicon sensor). From Table 1, no single-crystal materials qualify for sheet or web production modes, and as a consequence, it will remain difficult to make sensors in the 10 cents range based on silicon or other single-crystal materials.

B. Silicon in Biomedical Instrumentation

Chemical sensors, in large or small format, are much less reliable than mechanical sensors due to their direct contact with the chemical environment they probe and need more frequent recalibration. Chemical sensors are also less robust and often cost more than mechanical sensors. Therefore, progress in making chemical sensors more widely adapted has been hampered. Microinstrumentation, based on integrating miniaturized fluidic handling together with the required chemical sensors, has been proposed as a better approach to solve chemical and biological problems than chemical sensors alone. The resulting instrument justifies a somewhat higher cost than simply a disposable chemical sensor. Many shortcomings of chemical sensors will most probably be solved by enabling automatic calibration, separation of bound and unbound species, cleaning the detectors, filtering out unwanted compounds, and obviating the need for very selective chemical sensors. In addition to reduction in reagent volumes, the basic theory of hydrodynamics and diffusion predicts faster and more efficient chromatographic and electrophoretic separations in miniaturized biomedical and analytical equipment. With miniaturization, performance is expected to increase by exploiting the favorable scaling properties of some important instrument processes (for example, heating and cooling are faster while the effect of diffusion is reduced).[10] Micromachining might also allow co-fabrication of many interconnected functional instrument blocks. Tasks that are now performed in a series of conventional benchtop instruments could then be combined into one unit, reducing labor and risk of sample contamination. Since microinstruments could potentially be batch fabricated at low cost; they might be used only once and then thrown away to prevent sample contamination. Potential applications of microinstruments include disposable diagnostic kits for infectious agents, tests for chemical purity assurance, and instruments for biotechnology such as drug discovery.

Generic technical challenges in making a miniature biomedical instrument include sample introduction, valves, sample preparation, fluid propulsion through tiny conduits (including sample to be analyzed, reagents, wash and calibration fluids), mixing fluids when so desired and preventing mixing when they are to be kept separate, thermal management, detection of appropriate signals at a useful level, and most of all cost-effective manufacture.

Even before answering the technical questions of how to miniaturize an instrument with all these functions, one must decide how to partition all of these functions between disposable and permanent units of an instrument. In one extreme, one might envision a totally integrated option in which there are no boundaries between the disposable and the permanent instrument. More realistically, a hybrid construct may be considered in which the disposable unit would contain reagents and fluidics only while the permanent unit would contain power, fluid propulsion, heating, detection, and electronic functions.[1] For most microinstruments it indeed makes more sense to envision a disposable 'cassette' incorporating the specific reagents needed for a set of tests and a separate permanent reader instrument. An important design step, then, is to determine which functions to integrate within the disposable cassette and which to incorporate in the reader, i.e., how to partition the electrical and mechanical functions of the instrument and the disposable. The μ-TAS con-

Table 2. Machining Options for Fluidic Platforms and MicroBiomedical Instrumentation

technique	author's remarks
bulk micromachining (single-crystal silicon)	Silicon may be used as a substrate for an electroplated metal mold insert. Wet etching of the silicon is used to create the fine features metal mold insert. The latter method accommodates very sharp corners, very small features and very smooth surfaces (anisotropically etched silicon).
surface micromachining (polycrystalline silicon)	No use here, stiction is a problem and the technique is limited in terms of dynamic size range needed for fluidic conduits.
SOI (silicon on insulator)	See bulk micromachining.
traditional mechanical machining	Used for machining of metal mold inserts with dimensions >50−100 μm. Method is truly 3D. Not good for sharp corners or right angles. Surface quality is difficult to control.
LIGA	Ultimate in resolution, aspect ratio, surface smoothness. Often better than required for the application at hand. Perhaps best used to benchmark against the ultimate insert mold.
deep UV photoresist	Depending on the properties of the UV photoresist this method can be used directly to generate the fluidic platform or indirectly to electroplate a metal mold insert for molding a plastic with the desired properties. Used for dimensions that cannot be accessed by traditional machining (<50 μm). Higher resolution, good aspect ratios, sharp walls, any projected shape is possible.
deep RIE	Mostly optimized for silicon, a deep RIE machined silicon wafer can be used to electroplate a metal mold insert for reaction injection molding a plastic with the desired properties. Silicon walls are often rough.
electrodischarge machining (EDM), wire EDM (WEDM)	Making of mold inserts, truly 3D shapes, edges often too rough.
laser microablation	For making metal masters. Excellent resolution ($\sim$ 10 μm width and 10/1 aspect ratio) but thin recast layer makes for rough walls.
focused ion beam milling (FIBM)	Perhaps for an insert mold but usually much too slow.
continuous or large sheet machining and lamination	Method of choice.
AFM and STM	No use here. Much too slow.
plastic micromolding	Method of choice.

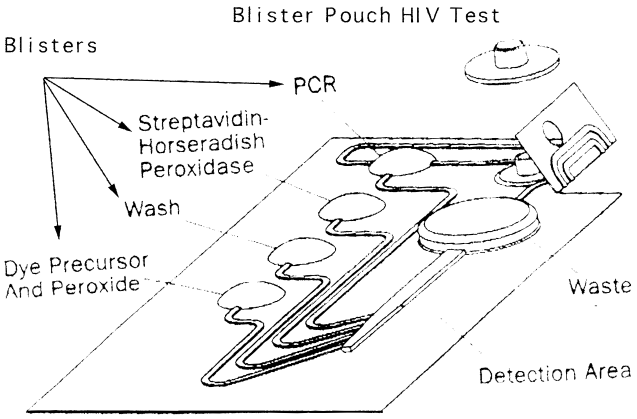

Figure 5. Blister pouch HIV test (Johnson & Johnson).[15] (Reprinted with permission from ref 15. Copyright 1993.)

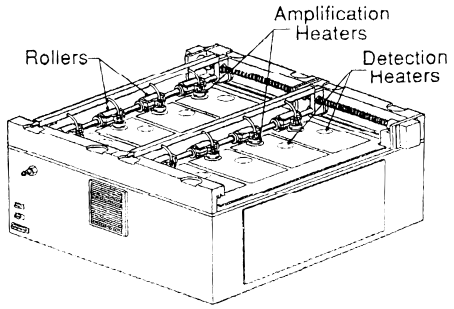

Figure 6. Eight blister pouches on reader instrument containing rollers for fluid propulsion, amplification heaters (for PCR), detection heaters, and optics (Johnson & Johnson).[15] (Reprinted with permission from ref 15. Copyright 1993.)

cept promotes the integration of all of the important chemical functions on one chip with the possibility of a separate reading instrument.[11−13]

In the case of an inexpensive disposable fluidic platform, e.g., for diagnostic purposes, the disposable should only have liquids and plastics. All electronics, heaters, detection, etc., should be part of the instrument. This is embodied in the HIV test shown in Figures 5 and 6.[15] In this case the disposable plastic pouch only contains liquids and plastic (Figure 5). A simple entry port in the pouch is provided for applying the blood sample. Small nips in the plastic channels act as valves that break when the rollers push fluid against them. The mechanics (rollers), heating sources (for PCR), detectors, etc., all reside within a fixed reader instrument (Figure 6). If the disposable is to be used in, say, drug discovery or responsive drug delivery, more components can be integrated with the fluidic platform, as the allowable cost for the disposable is higher. High throughput compound screening instruments will also typically have a more sophisticated connection between the fluidics and the outside world (e.g., a micropipetor).

In terms of machining options for microbiomedical equipment, there are a plethora of machining choices available as made clear in Table 2. In this table, the relative merits of different machining methods for making fluidic devices or microbiomedical instrumentation are listed. For the construction of most microinstrumentation, the building materials should be readily available and well characterized. Fabrication tools such as lamination, lithography using wet and dry films, electroplating, hot embossing, and reaction injection molding make it possible to choose the plastic material that fits the application at hand. For example, in the CD centrifuge platform substrate (discussed below), very specific protein adsorption behavior and optical characteristics are required. If the device were simply fabricated using a deep UV

polymer without the replication step, the desired properties may not be obtained.

C. Economic Considerations

The mechanical MEMS area has become quite an economic success yet remains at about 1−2% of the total IC industry in terms of total sales volume (the total IC industry was estimated at $200 billion/year in 1996).[3] The dollar evaluation in IPOs (initial public offering) for mechanical MEMS companies has been very modest (typically $5−45 million). In the case of Bio-MEMS, one deals with life-saving disposable diagnostic sensors, devices speeding up drug discovery, pills improving drug delivery, etc.; thus, the sales volume is expected to be significantly larger than that for mechanical MEMS. Early company acquisitions in this area tend to confirm this point, e.g., Affymax, a start-up in the drug discovery area, was bought by Glaxo for $600 million. In terms of the funding climate in Bio-MEMS, an important distinction needs to be made between diagnostic devices and drug discovery. It is very difficult to raise money for diagnostic equipment development, not only because many investors have already invested large amounts of money in that area with little return, but also due to the uncertainty in health care reimbursement. i-STAT, with its planar electrochemical sensor array for in vitro blood electrolyte and blood gas analysis, is one of the few survivors in the area of miniaturized diagnostics. i-STAT's manufacturing methods, after 10 years, still make it difficult to be profitable. This may be related to the manufacturing approach being silicon based and the design being integrated rather than modular. Moreover, disposable diagnostics are not necessarily perceived positively. One has to demonstrate a new diagnostic sensor/instrument 80% toward the finished product in order to attract investments. In the case of drug discovery, and to some degree in the case of drug delivery, investors are much more willing to take major risks at an early stage of the technology development. Consequently, most microfluidic companies are targeting drug discovery. Despite the investment climate, improvements in fluidics technologies may find early fruition in better diagnostic systems such as two-point sensor calibration, sensor cleaning devices, cell lysis, etc. We believe that after more significant progress is made in microfluidic platforms, there will also be a resurgence of interest in chemical and biological sensors and methods to manufacture them inexpensively.

To realize the economic potential in microbiomedical devices, one will need to develop the new micromachining tools described here and a generation of engineers will also be needed who are comfortable with chemical and biological issues as well as different types of micromanufacturing considerations.

III. Micromachining Technology Needs for Biomedical Applications

Four aspects of micromachining approaches have been identified, which need to be addressed for micromedical and microanalytical devices to be realized commercially.

A. Modular Approach to Manufacture

The variety of analytes and applications for biosensors and micromedical equipment is huge compared to that for mechanical sensors. Moreover, microbiomedical devices must often be disposable. These distinctions make for a large difference in manufacturing strategy between Bio-MEMS and mechanical MEMS, a fact exemplified in the amount of integration of electronics with the sensor/instrument, the types of materials used, and the processes for making arrays of sensors.

1. Separation of the Electronic Chip from the Sensor Chip

In IC technology, and with mechanical sensors, integration is the ultimate goal, while in Bio-MEMS, a modular approach is often preferred. Too much integration is a problem for the manufacturing yield of chemical and biological sensors and systems. Since it is crucial to subject the chip containing the active electronics to as few processing steps as possible, especially for processes involving nonstandard chemical sensor materials, implementing the electronics on a separate chip from the bioprobe(s) is clearly a better approach. Aside from materials incompatibility, another major problem associated with integration of electronics in chemical or biological sensors is leakage of conductive and corrosive liquids leading to shunting of the high-impedance electronics.[1]

2. Array Elements Fabricated on Separate Substrates

Even when there are no electronics on the chip and one only wants to fabricate an array of chemical sensors a modular approach is preferred. When the different sensor materials associated with the independent components of the array are deposited using batch semiconductor (thin film) techniques such as lift-off, each new layer added to the wafer may interfere with the chemical activity of the previously deposited layers, thus crippling the yield of the finished array. A critical consequence of the integrated array approach is that the largely nonstandard materials and their modes of deposition need to be reinvented for each new element added to the array. To increase the manufacturing yield dramatically, fabricate a different wafer with only one type of sensor and, after cutting out the individual sensors, combine them into an array with pick and place techniques. This modular approach enables the independent development of different chemistries for different analytes and obviates all fabrication compatibility issues. In a factory environment, this makes the fabrication of different panels on demand much easier. The above observation explains why i-STAT's disposable sensor cartridges for a seven-analyte analysis contain up to three separate silicon pieces rather than one as the product originally contained.[16] Figure 7 illustrates a modular approach in which sensors are built separately on individual wafers and put in a biomodule or fluidic platform. Figure 8 shows the ultimate goal, i.e., an array of sensors in a biomodule. The individual sensors in this

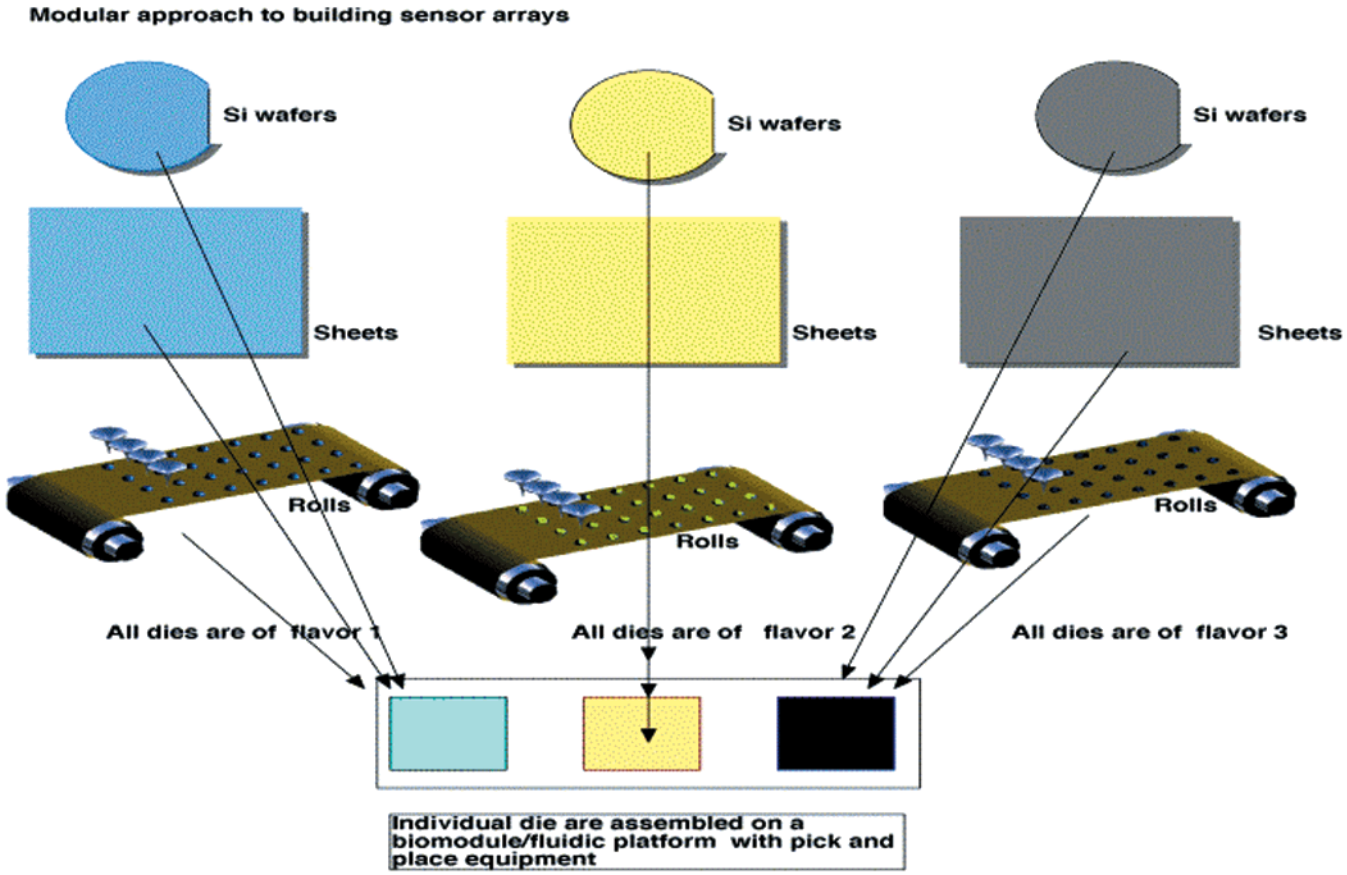

Figure 7. Modular approach to making a chemical sensor array. Wafers, sheets, or rolls of substrate with sensors of one type only are optimized separately to ensure optimum yield. They are then cut out and with pick and place equipment put into a biomodule/fluidic platform. Different sensor panels can be put together easily as there are no compatibility issues to deal with.

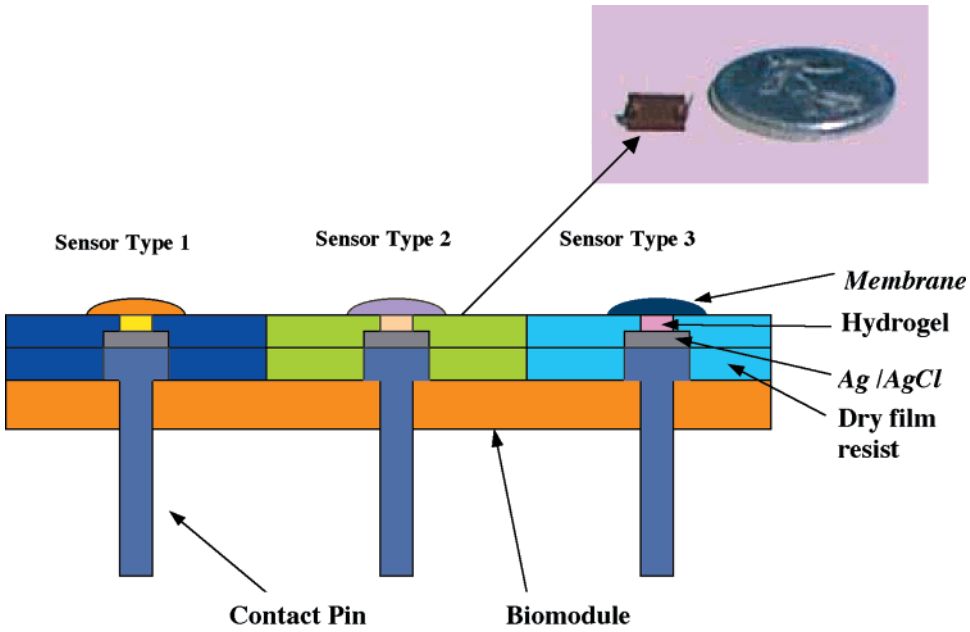

Figure 8. Individual biosensors are combined in a so-called biomodule with pick and place equipment.

biomodule are made on separate plastic substrates and put in a desired panel configuration by using pick and place equipment. Progress toward such a manufacturing process is illustrated further below with the manufacture of arrays of biosensors fabricated from negative photoresists (Figure 9).[17]

B. Moving beyond Batch Processing

In cases where silicon is only a substrate and does not play any role in the sensing mechanism itself, as is often the case in chemical sensor applications, advantages in using silicon are often not clear

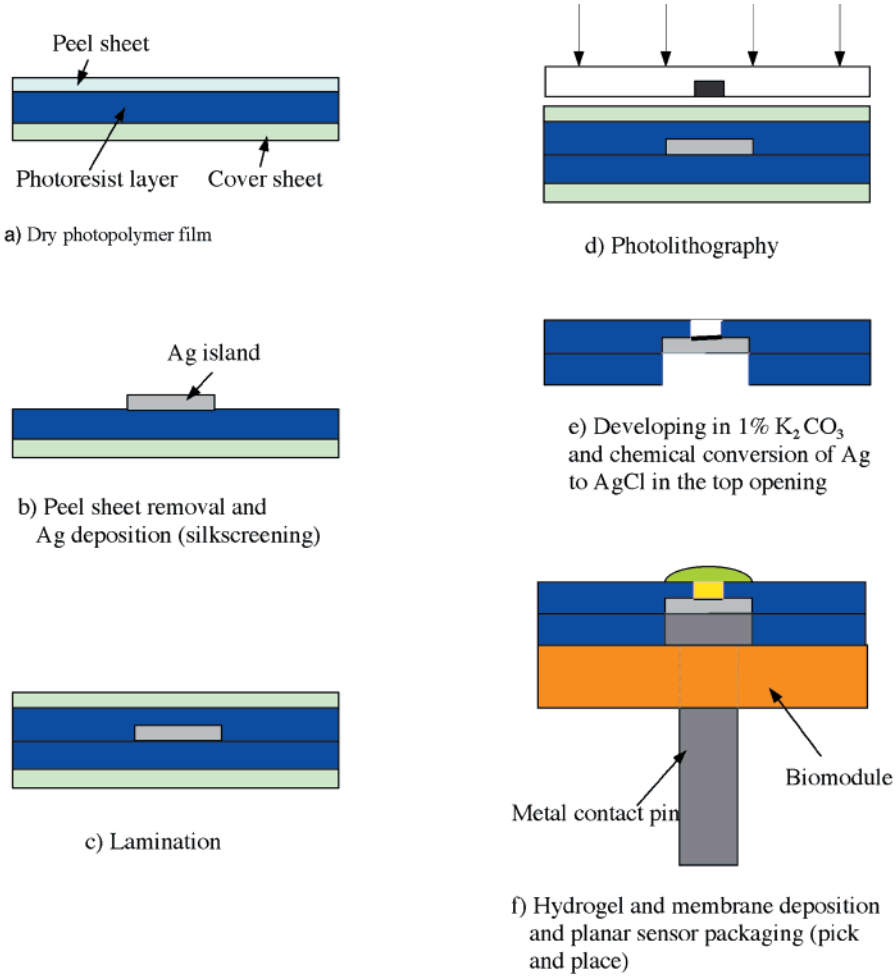

Figure 9. Schematic illustration of the procedure for fabrication of an individual array element.

because substrates such as plastic, cardboard, etc., are much less expensive. This argument and the discussion in section III.A clearly point to the need for a modular non-silicon approach in fabricating inexpensive disposable chemical and biological sensors and systems. Having addressed modularity and materials choice, the competing manufacturing processes must also be addressed. In microfabricating disposable biosensors, continuous manufacturing processes are used that yield less expensive devices than silicon batch processes. As an example, consider the mass production of amperometric glucose sensors where the cost per sensor target is 10 cents. Using a silicon batch approach, it will be very difficult to make a glucose sensor for less than $1 (or any disposable biosensor for that matter!). The current process to make glucose sensors involves such proven technology as a doctor's blade on a continuous moving web, making a 10 cents cost per sensor possible. The doctor's blade technology is a continuous fabrication method of products such as hydrogels or green ceramic tape on a moving substrate, typically another ceramic or polymer film. The doctor's blade apparatus is set up along a conveyor so the process may run continuously. The product (e.g., hydrogel or ceramic slurry) is continuously dispensed onto the moving substrate from a hopper or other appropriate plumbing. The substrate and dispensed product then move under the doctor's blade, an adjustable gate with a precisely controlled height. The purpose of the doctor's blade is to allow a known thickness of material to pass under the blade. In this way the thickness of the product is precisely regulated.[18,19] In the case of green ceramic tape casting, the substrate and bladed ceramic slurry are then moved through a precision oven for partial drying. The result is a flexible green ceramic tape of precise thickness that can be further machined before final drying and sintering. Thus, the challenge is to microfabricate devices on large plastic sheets or even moving webs, as shown in Figure 7. The process illustrated in Figure 7 allows for the fabrication of a sensor array composed of sensors that may otherwise have fabrication incompatibilities. Application incompatibilities such as calibration or cleaning may need to be addressed. This may be accomplished through the clever implementation of fluidics. Illustrated below is a disposable sensor manufacturing process that merges traditional machining options with IC-based manufacturing options and is more akin to packaging processes (e.g., drop delivery, pick and place, etc.) than to the front-end part of the IC industry (e.g., lift-off, integration, etc.).

A barrier to the successful introduction of biosensor systems to the point-of-care market has been the high cost of planar disposable biosensors.[1,16] The design demonstrated here involves only non-silicon materials and a modular manufacturing methodology based on a combination of thin and thick film technologies.

Table 3. Basic Properties of the Different Photoresist Materials

photoresist	XP SU-8	Pyralin PI2721 (photosensitive polyimide)	Pyralux PC1025 dry resist film	Riston 4600 dry resist film
resist tone	negative	negative	negative	negative
developer	PGMEA	DE6180	1% K_2Co_3	1% K_2CO_3
etching profile	vertical sidewall	undercut	vertical sidewall	vertical sidewall
smallest feature	2 μm	2 μm	20 μm	20 μm
compatibility with plastic substrate in developing	no (surface coating and back cover are needed)	no (surface coating and back cover are needed)	yes	yes
thickness of single layer	any thickness up to 1 mm	~20 μm	64 μm	30 μm
bonding to dry resist film	excellent	excellent	excellent	excellent
adhesion to substrate	excellent	excellent	excellent	good
uniformity	good	fair	excellent	excellent
flexibility	n/a	n/a	excellent	brittle
developing	vibration needed	vibration needed	washing needed	easy and quick
multicoating availability	yes	yes	multilayers by lamination	multilayers by lamination

The biosensors are electrochemical sensors that can be combined in so-called biomodules (see Figure 8) with pick and place equipment after they have been laser cut from their microfabricated sheets. These electrochemical planar sensors may be made on a variety of polymer substrates (Table 3).

The current preferred material embodiment of the individual array elements in the disposable electrochemical sensor array is Pyralux, a negative dry resist. The manufacturing procedure of an individual array element, i.e., for sensing potassium, is illustrated in Figure 9. Currently 5 in. × 5 in. sheets are used, but the Pyralux comes in rolls, so it will eventually be possible to make these types of sensors on a continuous base. An important simplification in the sensor manufacture is in the self-aligned step (Figure 9d). By exposing from the top through the photomask, both cavities in the photoresist bilayer are made at the same time. The top cavity results from the pattern on the mask, while the bottom cavity originates from the silk-screened Ag pattern, which acts as a mask for the lower part of the resist.[17] No expensive double-exposure system is required.

The above 'beyond batch' fabrication sequence is generic and applies equally well if optical sensor probes had been selected and will make it possible to fabricate biosensors in an affordable manner. This will lead to a wide variety of additional biomedical products currently impossible to fabricate using silicon technology.

C. Fabricating Devices in Polymers: Replication Methods and Photopatterning

Most microfluidic devices developed in the recent past used silicon, glass[20] (e.g., soda−lime glass), silicon/glass combinations, or quartz. For many fluidic applications[21−23] in microbiomedical devices, especially disposable ones, these are not the optimal materials in terms of cost, optical properties, biocompatibility, ruggedness, etc. Silicon, for example, is being abandoned because of cost considerations (microfluidic devices are large compared to ICs!), protein adhesion to the surface, and the fact that in contact with water silicon needs to be passivated. A passivation layer such as SiO_2 is often not adequate to hold the large fields required in electrokinetic applications.[24] In the case of electrokinetic devices, glass[25] has an advantage over silicon because of its favorable electrical properties and optical transparency but plastics have the cost advantage because their fabrication is usually based on replication methods.[26−30] Although more research is required to better understand and control their electrokinetic behavior, the use of thermoplastics (e.g., PMMA, poly(methyl methacrylate)[27]) and elastomers (e.g., PDMS, poly(dimethylsiloxane)[28]) in electrophoretic separation devices has been established. Materials selection is more complex than we have room to discuss here. We will only briefly highlight, as an example, one area where materials selection must be extremely carefully considered. Micromachined electrokinetic devices exploit both electro-osmosis and electrophoresis. Electro-osmosis facilitates sample motion toward the detector, and electrophoresis enables the separation of the species to be detected. The materials requirements are different for these two modes of operation. For electro-osmosis emphasis, materials that exhibit charged walls at the pH of interest (e.g., Si, SiO_2, glass) should be chosen. For emphasizing electrophoretic separation, the capillary walls should be passivated or materials with low surface charge should be selected (e.g., PMMA).[28]

Ultimately, what is needed is the capability to fabricate the widest range of new micromedical devices in inexpensive 3D plastic, metal, carbon, ceramic, and glass. This achievement will allow materials selection to be determined by the application rather than the methods of manufacture that are available. Direct machining of polymeric substrates (e.g., with laser ablation) does not produce the desired smooth surfaces that replication methods, such as hot embossing, injection molding, and casting from a machined metal master (diameter > 100 μm), achieve. For most microsystems, one wishes to work with widely available and well-characterized materials that are biocompatible and have favorable optical properties. For devices with smaller features, this will usually involve lithographically patterning thick layers of resists to create desired features, electroplating the patterned resists to form micrometal mold inserts, and then using the mold inserts in traditional molding processes. Once a reliable insert mold has been fabricated, it is possible to choose from many plastics, glasses, or ceramics for the application at hand.[32,33] Although there are substantial efforts on

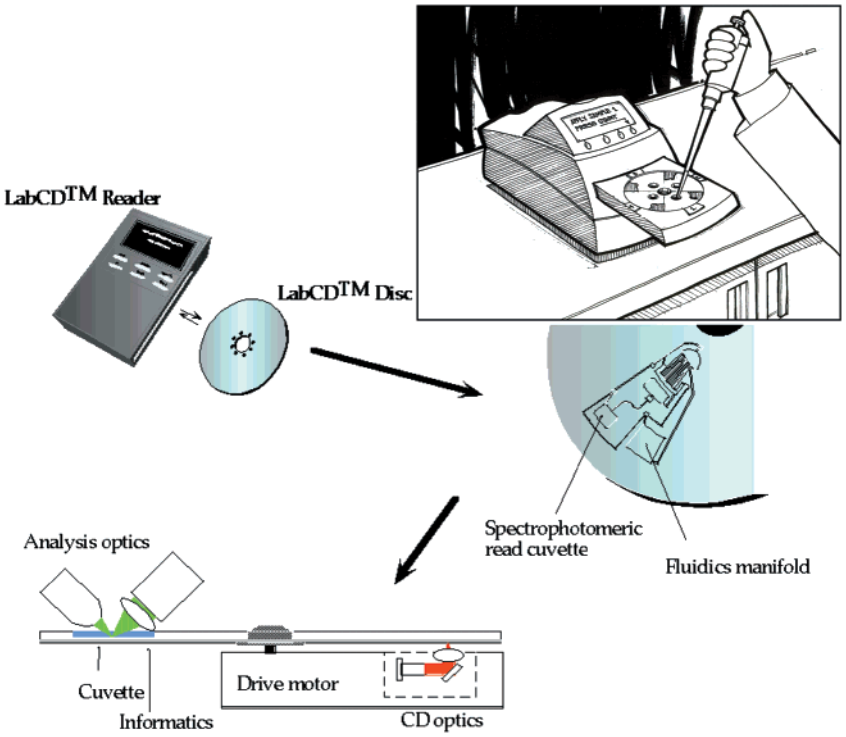

Figure 10. LabCD TM Instrument and disposable CD.[17,29] (Reprinted with permission from Gamera Bioscience.)

making the miniaturized metal mold inserts,[34,35] the ability of making miniaturized fluidic devices by plastic micromolding on a commercial scale is growing but is still relatively small in the United States. Ehrfeld et al. at IMM have been leading the way in plastic miniaturized fluidic devices by micromolding in Germany.[36,37] Molding against an electroformed master has been used in limited production runs of miniaturized capillary electrophoresis (CE) devices.[26] In addition to polymer injection molding, ceramic injection molding[38,39] and metal injection molding[40] are starting to gain importance.

Alternative approaches to producing devices in polymers (other than molding against an electroformed master) include molding against the patterned photoresist directly and using patterned photoresist itself as the fluidic structure (see Table 3). For example, the Whitesides group[29−31] has developed a rapid prototyping method that uses a laser-printed CAD drawing on a transparency as a photomask. A high aspect ratio photoresist such as SU-8 is then patterned and used as a mold for casting the final device in PDMS. This approach allows polymeric microfluidic systems to be fabricated rapidly and at low cost and has been used to develop a micro-CE device,[29] ultrahigh-density microwells,[30] and a method for patterning biological materials.[31] Although this method is useful as a research tool and in limited (100s) production runs, work needs to be done to make the mold more rugged for high-volume manufacture. PDMS and other plastics are incompatible with most organic solvents, which induce swelling. There can also be compatibility issues with samples that include absorption of hydrophobic samples and the sticking of proteins. These compatibility issues must be considered during the design and material selection of any microfluidic device.

In Table 3 we compare a wide variety of photoresists that have been studued with both to make fluidic devices directly and to make insert molds for casting polymeric replicas.

As an example of replication methodology, in collaboration with NASA, Madou et al. are developing an integrated, microanalytical system based on a centrifugal fluidic platform.[17] The LabCD platform consists of a plastic disk in which fluid propulsion is primarily controlled by the application of centrifugal force through a motor at the hub of the microfluidic disk (see Figure 10). The valves in this system are based on capillary action.[41] They have no moving parts and are actuated by fluid pressure resulting from increased rate of rotation. Applications for the LabCD are being developed in genomics and proteomics, and it is believed that this system will be useful in the life sciences, drug discovery, and molecular diagnostics.

Four approaches are being used to fabricate microfluidic structures for the LabCD. First, conventional CNC machining has been used to fabricate fluidic structures (>100 μm) quickly in order to rapidly develop prototype systems. Second, when higher volume production of a finalized design is needed, conventional injection molding with a metallic mold has been used. Third, rapid prototyping[29] has been used to create smaller (>20 μm) fluidic structures in PDMS. This method was used to develop a LabCD which can perform 96 enzymatic assays simultaneously. Molding against photoresist masters allows a wide range of sizes to be covered, from 5 μm to several millimeters, while maintaining a good aspect ratio throughout this range. Fourth, fluidic structures have been made directly in all of the various resist systems listed in Table 3. The use of two or more photoresists in combination has enabled

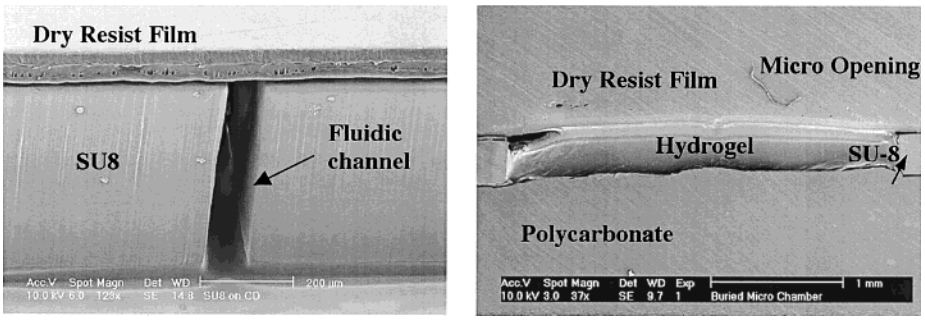

Figure 11. Buried SU-8 microchannel (a) and multilevel microchamber filled with hydrogel (b) (to be used as an on-board electochemical reference electrode.)

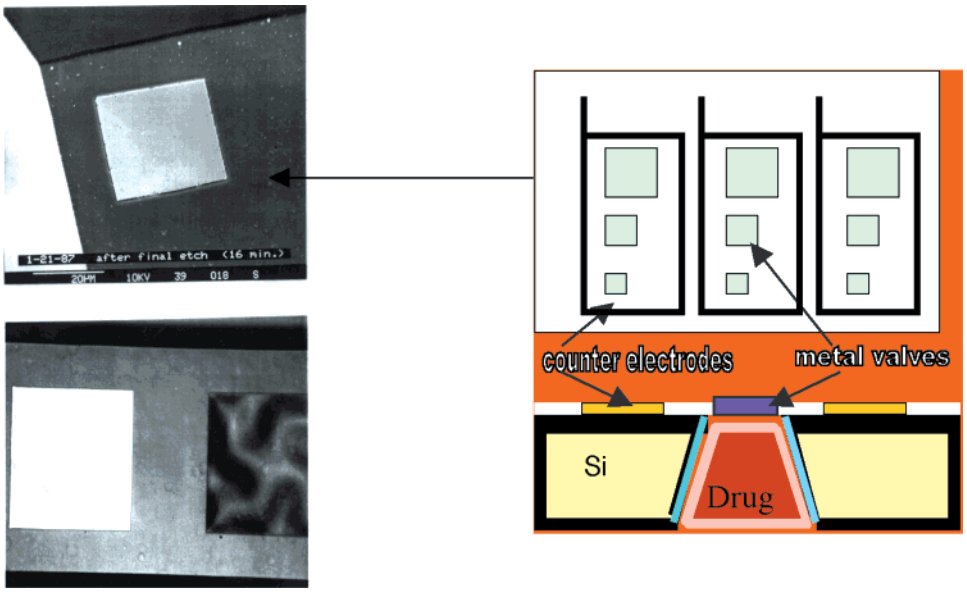

Figure 12. Metal electrodes are blasted open electrochemically by applying a small current between the metal valve and a counter electrode in a saline solution. By making arrays, the number of openings is selectable. The metal valve material may be Ag, Pt, Au, etc. In the SEM picture on the left, a Pt valve electrode (top) and a set of an Ag valve electrode and an IrO_x valve electrode (bottom) are shown.[43]

the fabrication of photopatternable multilayer microfluidic structures. For example, Madou et al. sealed photopatterned microchannels of SU-8 with sheets of the flexible photoresist, Pyralux, as shown in Figure 11a. Subsequent patterning of the Pyralux allows for the creation of more complex three-dimensional fluidic structures, as shown in Figure 11b.[17] The latter structure can be used, for example, to seal liquids or hydrogels such as for an on-board electrochemical reference electrode.

D. Valves in Microfluidic Systems

One of the most difficult aspects of developing a microfluidic system is the miniaturization of valves.[1] Valves with moving parts, such as diaphragm valves that are micromachined in silicon, are prone to malfunction through clogging. The best way to overcome this difficulty is to use valves with no moving parts. This approach has been used successfully in electrokinetic fluidic systems[13,20,26,27,29,42,43] and in a centrifugal platform[41] (see above). Simple, single-use valves such as bursting metal membranes or simple reversible polymeric valves to be used in disposable fluidic systems such as drug delivery are discussed below.

In 1992, Madou et al. discovered that they could put small amounts of drugs into micromachined chambers (say in silicon) and then electrochemically open a metal valve, releasing the drugs stored in those micromachined chambers. Different drugs could be released at different times, and by opening more "holes", the rate of drug delivery could be set.[44] The drug release valves in Figure 12 are for single-use only. The small current, applied between a counter electrode and the metal valve electrode, causes local electrolysis of water and leads to bursting of the thin metal barriers.

More recently, Madou et al. developed a smart valve for drug delivery that can be opened or closed many times, either electrochemically or chemically by using so-called "artificial muscle".[45,46] "Artificial muscle" refers to a chemomechanical actuator consisting of a blend of a hydrogel and an electronically conducting redox polymer like polyaniline (PANI), polypyrrole (PPY),[47] or their derivatives. The redox polymers, which form the 'electronic backbone' of the muscle, are sensitive to pH, applied potential, and chemical potential in their microenvironment. Hydrogels, which form the 'ionic body' of the muscle, provide a cross-linked network of hydrophilic homopolymers or copolymers and exhibit dramatic

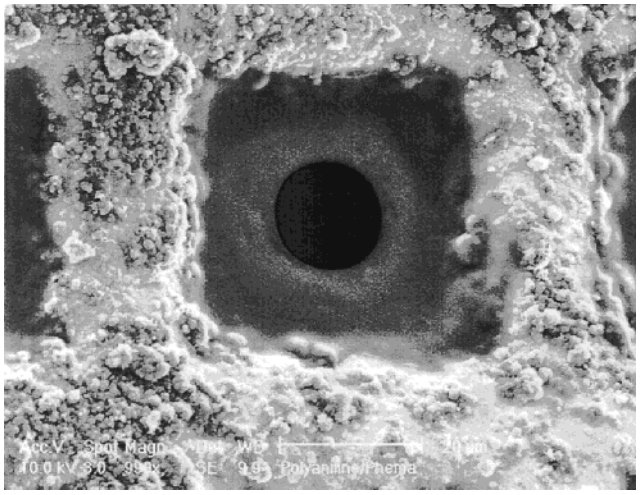

Figure 13. Artificial muscle in holes of a drug reservoir lining (TEM gold grid with holes of 38.5 × 38.5 μm each).[17,46]

effects of swelling and shrinking upon changing pH, solvent, temperature, electric field, or ambient light conditions. By making a blend, the impressive actuator properties of a hydrogel, i.e., very large swelling (e.g., 300% original size) and shrinking, are retained. Meanwhile, the redox polymer, which by itself does not swell or shrink that much (e.g., 20%), makes the swelling/shrinking process much faster and more controllable with a bias. Moreover, the incorporation of a redox polymer makes it feasible to deposit the artificial muscle material locally and selectively within a chosen microstructure.

Responsive controlled drug delivery is being examined using "artificial muscle" to open and close small holes in a drug reservoir lining (see Figure 13). The small holes are opened and closed either electrochemically or chemically. In preliminary work, the swelling and shrinking processes of the PANI/hydrogel system in response to electrochemical actuation was studied by monitoring the phenomenon with a compound microscope. In situ monitoring of the artificial muscle blend of PANI and PHEMA-PVP showed a significant change in the size of the opening when this blend was cycled between electrical potentials of −0.2 and +0.8V (SCE) in 0.5 M H_2SO_4, as indicated in Figure 14. The change in the longest length between the largest opening and the smallest opening is approximately 150%.[46] For comparison, real-time swelling and shrinking of PANI were also examined. Under identical experimental conditions, no significant change in the size of the opening was observed for PANI alone, as shown in Figure 15.

IV. Conclusion

Biomedical applications are broadening MEMS considerably in terms of materials and manufactur-

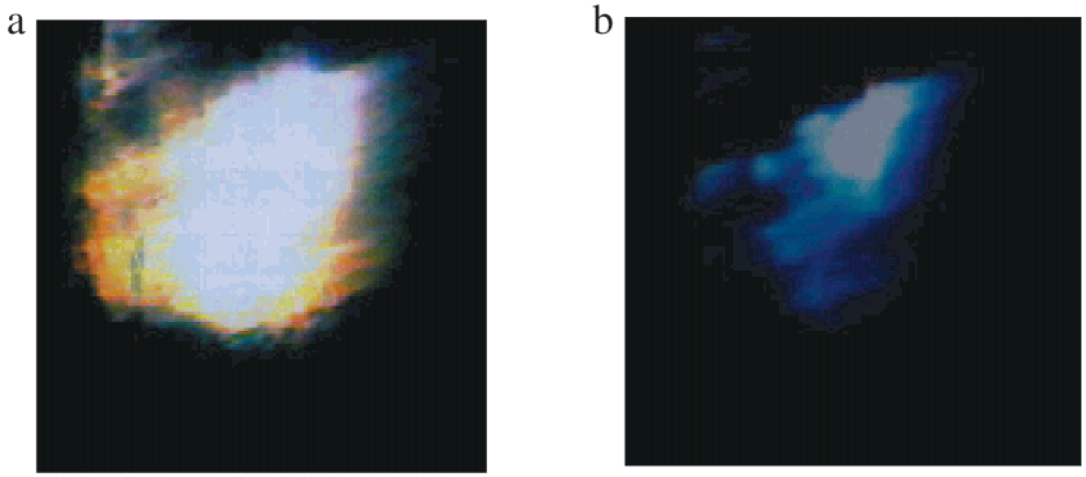

Figure 14. Artificial muscle blend in (a) shrunken (open) state at −0.2 V (SCE) and in (b) swollen (closed) state at +0.3 V (SCE).[17,46]

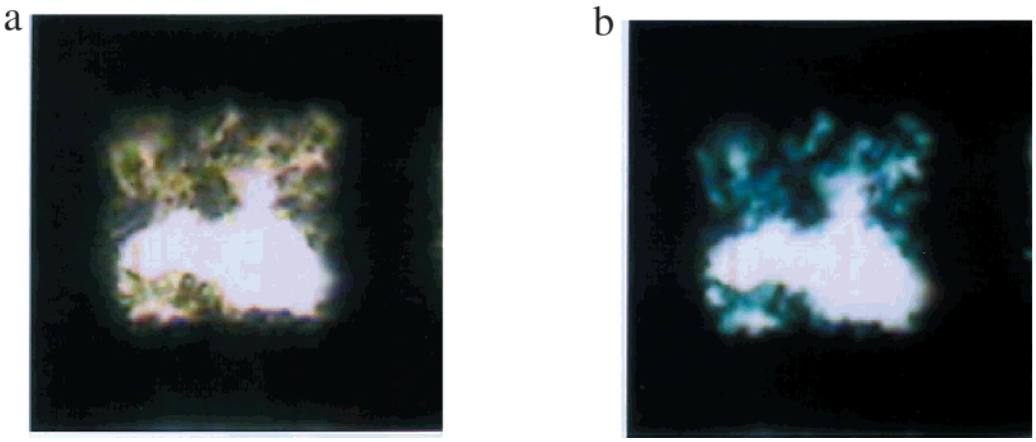

Figure 15. PANI at (a) −0.2 V (SCE) and at (b) +0.3 V (SCE). In this case, there is hardly any closing of the hole.[17,46]

ing options. Non-silicon, modular, and "beyond batch" techniques (pick and place, drop delivery, lamination, etc.) will become more and more important to realize inexpensive devices. By using micromachined mold inserts and plastic micromolding for prototyping and volume manufacturing, the attractive properties and relatively low cost of plastics can be exploited. The combination of redox polymers with hydrogel enables low-voltage actuation of valves and pumps in fluidic devices.

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