Compatibility and Incompatibility of Chemical Sensors and Analytical Equipment with Micromachining.

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Abstract

During the past 25 years the commercialization of chemical sensors and instrumentation based on microfabrication failed to keep pace with earlier projections. In this presentation we will explore the causes that slowed down the development of micromachining to produce chemical sensors and analytical instruments and we will suggest the kinds of actions that can be taken to speed up the progress of applying micromachining tools.

Micromachining is emerging as a set of new manufacturing tools to solve specific industrial problems rather than as a monolithic new industry with generic solutions for every manufacturing problem. Based on some concrete examples we will show that, whereas mechanical sensor manufacture is moving towards more integration, embodied in increased reliance on surface micromachining, chemical and biosensors are moving away from integration toward hybrid technology. In the case of instrumentation there is a trend toward using laser machining and some early exploration of LIGA use.

Micromachining in the chemical and micro-instrumentation area has the stigma of a technology used in backrooms only. To change this it will be important to describe most new results as fine-tuning of micromachining skills rather than as the latest breakthrough in analytical instrumentation. A more thorough understanding of the application is needed to make it easier to decide upon the correct manufacturing technique.

Introduction

We are focusing this presentation on the microfabrication of chemical sensors and analytical instruments that promise to become successful market opportunities i.e. biomedical and some selected industrial applications. The commercialization of chemical sensors and instrumentation based on microfabrication over the last 25 years has not kept pace with earlier projections while progress in biosensors and analytical instrumentation, based almost exclusively on classical manufacturing techniques, has been significant. In the industrial arena, characterized by less aggressive R&D efforts, the progress in developing new sensors and equipment based on micromachining was even more restricted than in the biomedical arena.

Concurrent with the above developments the number of tools made available to fabricate small devices has grown dramatically. Some important techniques for chemical sensor and instrumentation construction are compared in Table 1. This presentation shows that in contrast to mechanical sensors where the excellent mechanical properties of single crystalline Si tend to favor Si technology, the choice of the optimum material and manufacturing technology for chemical sensors and micro-instrumentation is far less evident. We can point out the following trends. Whereas mechanical sensors (pressure, acceleration, temperature etc.) are moving toward more integration embodied in surface micromachining, chemical and biosensors are moving away from integration and toward hybrid technology. Where instrumentation is concerned there is a move toward using laser machining and some early exploration of LIGA use. In this presentation we want to explore what was lacking in the application of micromachining to chemical sensors and analytical instruments, what can be done to speed up the progress and how to correctly apply the manufacturing tools in Table 1.

Chemical Sensors in Table Top and Hand-Held Analytical Equipment

The progress enabling the development of small table top medical diagnostic instruments was mainly based on the development of solid-state stabilized reagents (over 30 dry reagent chemistries are available for detection of biological compounds) and to a minor extent on advances in thin-film technology [1]. It was anticipated that micromachining would play a more prominent role in the development of sensors for the smaller, next-generation, hand-held, portable diagnostic instruments. In reality, the micromachining and Si sensor content in the more advanced, hand-held, biomedical products has been surprisingly limited. We will describe a few representative examples of micromachined chemical sensors for such instruments.

Ion Selective Electrodes (ISE's).

In vitro - Some of the biggest hurdles in silicon based ISE development are the construction of a true on-board external reference electrode in the same plane as a FET device (Field Effect Transistor), a stable internal reference, a simple calibration scheme, incompatibility of sensor materials with Si processes, electrolyte shunting the electronics, high fabrication cost at low volumes and packaging [2]. Another reason for the slow commercialization of silicon-based ISE's is that the currently available chemical sensing technologies are proven and cost effective. After

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25 years of R&D, the ISFET (Ion Sensitive Field Effect Transistor) only has found some limited niche applications. Its research in the US seems at a standstill for now.

Most sensor experts have come to appreciate that for chemical sensors one should only implement on-board electronics if it is absolutely essential for the integrity of the signal. The extended gate field effect transistor (EGFET) device was conceived to avoid some of the problems associated with the leakage problems of an ISFET [3]. By depositing the ISE membranes a short distant away on conducting lines extending from the FET gates, encapsulation was made easier. This seemed like an elegant solution at the time. But i-STAT abandoned the EGFET approach and eliminated all on-board electronics. The Portable Clinical Analyzer from i-STAT uses Si only as a substrate for the chemical sensors and as a contacting base, clearly a more economical approach. The sensor electrodes, gels and membranes are all deposited with semiconductor type processes [4].

Another problem in the manufacture of Si chemical sensor arrays manifests itself in the decrease in manufacturing yield with increasing number of array elements. When depositing the sensor materials associated with the different array elements, each new layer added to the wafer reduces the yield of the finished product, especially since the materials involved are mostly non-standard. To increase the manufacturing yield dramatically, one would need to fabricate a different wafer with only one type of sensor, combining the individual sensors into an array, e.g. with pick and place techniques. This automatically would make the sensor array larger though and the Si approach would lose some of its attractiveness.

The success of i-STAT's product introduction [5] renewed the interest in making planar ISE's. Efforts by this author in collaboration with SENSORS 2000! at NASA and efforts at the Center for Emerging Cardiovascular Technologies (CECT)[6] focus on depositing ISE components on inexpensive non-Si substrates (ABS and Kapton respectively). At NASA we are comparing silkscreening and drop-delivery systems to deposit ISE membranes and hydrogels.

In vivo. Cost of disposable sensors for in-vivo use does not represent as big a concern as for in-vitro disposable sensors. It is estimated that a catheter based pH, CO_2 and O_2 sensor may cost up to $250.00 and would serve a market of well over $300 M a year in the U.S. alone [7] [8]. Unfortunately the warm, wet, saline in-vivo environment exemplifies perhaps the most severe environment in which silicon sensors might be used. Si based in-vivo chemical sensors are not commercially available today. Biocompatibility is the single most complex issue facing in-vivo sensor development. As biocompatibility is the main concern it should be addressed up front. In the following example we, at first, neglected to do just that. For 4 years ($6 M research fund) we attempted to develop an in-vivo pH, CO_2 and O_2 probe, the so-called RT-MECSS (i.e. the Micro Electronic Chemical Smart Sensor) shown in Fig. 1 [9]. The RT-MECSS attempted to put chemistry and electronics on separate planes while keeping the signal line as short as possible. This linear electrochemical array fitted inside a 20-gauge catheter (705 μm in diameter) without taking up so much space as to distort the pressure signal monitored with a pressure sensor outside the catheter. A classical (macro) reference electrode, making contact with the blood through the saline drip, was used for the pH signal while the CO_2 and O_2 had their internal reference electrodes. Results obtained in saline solutions were encouraging but funding for continued research stopped before serious biocompatibility efforts could be started. In order to avoid this type of situation we have launched an ambitious program where we are addressing the biocompatibility issue of a catheter based electrochemical sensor up front [10]. If biocompatibility results warrant such an endeavor, the RT-MECCS design will be put back into the catheter.

The catheter shown in Fig. 2 is used for those biocompatibility studies with animals. The internal dual lumen structure shown has a working and a reference chamber. The reference chamber has a hole contacting the external medium, and the working electrode chamber has a hole contacting the ion selective membrane (see also Fogt et al. [11]). The membrane for the pH ISE is based on PVC doped with tridodecylamine as the ionophore. The purpose of the external 'sleeve' shown in Fig. 2 is the incorporation of a reservoir for slow release of an anticoagulant such as Herudine or Heparin. The catheter is further interfaced with a 450 kHz amplitude-modulated (AM) implantable telemetry transmitter which incorporates a high impedance (> 10^{12} ohm) preamplifier and allows for nearly continuous measurement of pH and temperature at a distance of two feet from the animal. In-vivo and in-vitro telemetric pH data will be presented.

Immunosensors. Whereas for ISE devices and enzyme based sensors electrochemical techniques are preferred [2], optical techniques are more prevalent for immunosensing today. A comparison of optical and electrochemical immunosensors is presented in reference [12]. Two major issues facing any immunosensor are its inherent irreversibility and non-selective

protein binding. Almost all immunochemical reactions are irreversible given the large association constants (K_a) that are involved in an antigen-antibody binding reaction (typical K_a values range between 10^5 and 10^9 M^{-1}). The Ag-Ab association constants are composed of large forward (k_1) and small reverse (k_{-1}) rates. These kinetic parameters make antibodies very selective for the analyte of interest but also make them quite irreversible.

The best way to avoid non-specific binding effects in immunosensors is to make a reference as similar to the sensing surface as possible i.e. a reference that is subject to all the same non-specific protein binding phenomena as the sensor surface itself except for the antigen-antibody of interest. This enables the best possible correction for non-specific binding. An interesting way of implementing this idea is to create an optical grating pattern with the antigen-antibody binding modulation providing the grating structure. The reference in this grating is based upon the loss of antigenicity by UV radiation as observed by Panitz and Giaver [13]. They found that the antigenic sites on proteins are very sensitive to ultraviolet radiation in air. By using a photomask, alternating bands of antibodies can be inactivated by creating a biological diffraction grating. A CD-type He-Ne laser beam diffracts from the grating with an intensity related to the antigen concentration. This technology is being pursued by Idetek (1993) [14].

Barnard et al. [15] introduced an ingenious way to make an assay continuous. They used fluorescein-labeled antibody (F-Ab) and Texas Red-labeled immunoglobulin G antigen (TR-Ag) in a competitive immunoassay based on fluorescence energy transfer. To circumvent the inherent irreversibility of this assay Barnard et al. used a controlled-release delivery system capable of sustaining a constant release of fresh immunochemicals (similar to our approach to biocompatibility illustrated in Fig. 2). In cases where continuous monitoring is of major importance but response time is not very critical this technique seems very promising.

Examples of optical and electrochemical immunosensors developed by this author are shown respectively in Fig. 3 and 4. Our one-step electrochemical immunosensor combines the fundamentals of enzyme immunoassay, electrochemistry, and gel filtration [16]. To make the components as cheap as possible, thick film technology on a plastic substrate has been used. The detection limit of the FAD/apoglucose oxidase system used in the sensor in Fig. 3 is well below 10^{-10} M which is adequate for the analysis of a majority of analytes. A further challenge is to find reproducible ways of layering the different organic materials shown in Fig. 3. This challenge has little to do with Si micromachining but everything with learning how to stack and manipulate hydrogel materials.

Our optical immunosensor is based on Langmuir-Blodgett technology [12]. The difference in thickness of two adjacent steps as shown in Fig. 4 corresponds to a double layer of stearate (approximately 48 Å) and forms an interference based color gauge which sensitively tracks thickness increases. Steps can be built using etching techniques in inorganic materials with optimum refractive indices for maximum interference effect [17]. We experimented with both Si and glass substrates. This system can follow antigen-antibody binding in a simple and inexpensive way. Langmuir-Blodgett deposition is a difficult manufacturing proposition. More recently we found a better way: a substrate was pulled at a uniform rate from an etchant solution making a continuous optical wedge rather than a staircase type structure.

In general optical thin film immunosensors are quite amenable to IC type micromachining techniques (e.g. for protein patterning) but for electrochemical immunosensors hybrid approaches seem more appropriate.

Gas Sensors-Dry. Solid state gas sensors for industrial applications i.e. zirconia based oxygen sensors for the automotive, toxic and combustible gas sensors for the chemical and petrochemical industry and humidity sensors for the energy conservation market (e.g. all drying operations) constitute a sizable industrial market served by, with few exceptions, mediocre products [18]. With the automotive world as the driving force, significant efforts in using microfabricated gas sensors are under development. So far results have been disappointing.

We developed a planar zirconia oxygen sensor for automotive applications fabricated by using plasma-spray deposition [19],[20]. Although not exactly micromachining, the use of plasma spraying might enable the batch fabrication of such sensors at a cost below $2.00 rather than the current $12.00 and up. Controlling the plasma spray process to form the porosity gradient in the sensor is still a major challenge.

The use of a ceramic tube in a classical Taguchi sensor maximizes the utilization of the heater power, so that all power is used to heat the tin oxide. The tin-oxide paste is applied on the outside of the ceramic body over thick film resistance measuring pads and is sintered at high temperature. The sintering stabilizes the intergranular contact where the sensitivity of the gas sensor resides. The design is not suited for mass production as it involves excessive hand

labor. The problems with the thick film structure are mainly in the area of reproducibility: compressing and sintering a powder, the deposition of the catalyst, the use of binders and other ceramics (e.g. for filtering) are all very difficult to control. Application of IC techniques could improve the state of the art dramatically if one could make a thin semiconductor- oxide film (e.g. tin-oxide) with the same sensitivity as the thick film. Micromachining the heater elements would further improve reproducibility and the absolute power budget needed to heat the thin film. Such thermal efficiency and low power budget is obtained by thermally isolating the heater. It has proven to be very difficult to make a thin film as sensitive as the ceramic type thick films.

The use of the intergranular contact potential as the resistance-determining parameter is required for maximum sensitivity [2]. When making thin films, the films have to be thin enough so that extraction of electrons has a significant effect on the overall film resistance. Obviously thickness control becomes a key factor here. Another problem is that the resistance is not controlled by the bulk electron density, but by grain boundaries in the films. Again intergranular contact resistance is involved in determining the resistance of the film, and because oxygen cannot directly reach the intergranular contact (as it does in the powder case) it must diffuse in and out at the grain boundary. This makes for long time constants unless the grain boundaries are completely blocked.

Finally the currently available devices, already quite small and inexpensive, only will be replaced quickly by newer technology in terms of: reproducibility, cost, sensitivity, response time, concentration range, specificity, reversibility, stability and power consumption.

At this time the best course for future progress in the Taguchi sensor R&D area is to optimize sensitivity of thin film oxide semiconductors, use planar silicon devices (reproducibility and cost) and concentrate on implementing less power-consuming microheater elements. These devices will cost more than the planar ceramic devices but they will outperform them in terms of power needs and reproducibility. For the short term thick film planar devices on ceramic substrates are the best way to go.

Wet. We have attempted to make faster responding electrochemical gas sensors by innovative methods of exposing the triple points to gas media [21]. The intent was to make the liquid path through which the gas must diffuse to reach the triple point as short as possible or even do away with it completely. We believed it was possible to create gas sensors that combine some of the positive characteristics of both electrochemical and solid state gas sensors. The sensor we invented is the Back-cell™ [22] (Fig. 5). Two versions of the back cell sensors were investigated: sensors using a porous ceramic substrate and those based on a silicon substrate with micromachined pores. A thin layer of Nafion or a hydrogel was deposited over the metal electrodes on the front of the porous slab and the gas to be detected only was allowed to reach the sensing electrode from the back of the porous substrate. The details of the microfabrication procedure were explained elsewhere [21], [23].

The response of this sensor to a step change in oxygen concentration from 0 to 100 % exhibits a 90 % response time of 300 msec; this is extremely fast compared to other amperometric sensors (typical response time 30 to 90 seconds). Gas does not need to diffuse through a thick layer of electrolyte to reach the triple points where they react. In other words the triple point is almost dry (as water is involved in the reaction, gas probably still diffuses through a few monolayers of water to react at the metal). The recovery of the sensor back to baseline upon a step change in oxygen concentration from 100 % to 0 % is slightly slower than the initial response-400 msec.

For ease of manufacturing the ceramic approach is preferable. The major problem with the current device is water management. The fast response of the sensor gets lost when water fills the pores on the back of the metal electrodes.

Instrumentation

From the time a gas chromatograph, the size of a matchbox, was printed on the cover of the April issue of Scientific American in 1983 [24] (Terry and Angell built a first prototype between 1974 and 1975), there has been a continued effort to micromachine analytical instruments. Today there are only two commercially available 'micro-instruments' with some key components based on micromachining. The first is the gas chromatograph by MTI, looking significantly different than the device shown on the Scientific American cover (e.g. the column itself is not micromachined). Second are a class of instruments based on Molecular Devices' patented LAPS (Light-Addressable Potentiometric Sensor) technology [25]; a silicon based microphysiometer i.e. the Cytosensor: capable of measurement of the metabolism in living cells and the immuno assay; Threshold: for rapid quantitation of a variety of analytes at sub-femtomole levels. In the LAPS devices the Si

content is a minute contributor to the $80,000 dollar price tag but it is the most essential part (very much like the Si tips in AFM and STM). For most of the other micro-instrumentation listed the verdict on the wisdom of using Si micromachining is still out.

Gas Chromatography (Mini-GC).

The first integrated GC, consisting of a long separating column, a sample injection valve, and a thermal conductivity detector, all fabricated on a single silicon wafer, was developed at Stanford in 1974. MTI 's commercial Mini-GC based on that original work uses a classical capillary column but has retained all the other micromachined components.

Column diameter profile is an important issue not adequately addressed with micro-machining. The smoothness of the film coating on the inside of a capillary column is a function of the profile symmetry and is extremely important. Rectangular columns and columns made by joining two cylinder halves tend to accumulate coating on the corners or joints leading to a less perfect separation [26]. Analytes might spend a longer time in areas where the coating is thick compared to places where it is thin, leading to a broadening of peaks. As we will discuss in our lecture, miniature Joule-Thomson cryogenic refrigerators [27] and micro electrophoresis units [28] are not as sensitive to the column diameter profile but other problems are associated with these two instruments. Since traditional columns are perfectly adequate for the mini-GC, the focus has shifted to other problem arenas where micromachining could help. For example a GC only works properly if the volume of the injected gas is small compared to the volume of the column so that a miniature sample-injection valve needs to be build. Also the volumes between column and detector and valve and detector need to be minimized. Large dead volume in anaytical equipment leads to a high power budget and too slow response time. To accept a range of gas volatilities the injector column assembly needs to be heated uniformly. Fast heating and cooling rates are very important creating the following challenge for micromachinists i.e to add and remove heat locally, fast and uniformly (a requirement also for building the next generation of PCR units). In the Personal Chromatograph or PC [29] injector temperatures up to 220°C are possible and the chromatographic column assembly consists of a 3 meter 100 μm i.d. tubular column with an ultra low thermal mass column oven heater and RTD sensor in intimate contact with the column. Through efficient thermal management heating rates to 5°C per second over temperatures up to 230°C can be obtained. The controller maintains the carrier gas pressure at the head of the column by electronic pressure control using a fluistor (Redwood Microsystems) and manages flow of sample and carrier gas through the entire system by appropriate sequencing of flow control valves.

We are considering LIGA to integrate the column, heater and sensor of the PC in one simple monolithic structure.

Mini-Ion Mobility Spectrometer (Mini-IMS)

In an ion mobility instrument, ions, produced at atmospheric pressure in an ionization cell by a ^{63}Ni beta source, are accelerated in a drift chamber (uniform field of 150-250 V/cm), where they are separated according to their mobilities and detected as a current on a Faraday plate and plotted on a time axis in accordance to their time of arrival (see Fig. 6). About six years ago we set out to micromachine some critical components of an IMS instrument. Field uniformity, temperature and pressure, we recognized, could be controlled with miniature Si sensors. Our principal aim though was to substitute the ^{63}Ni ionization source with a less fragmenting ionization source (a "soft" field ionization technique (FI)), mainly creating parent ions (M^+) and thus simpler spectra for complex environmental gas mixtures. Considering the extreme electric fields required for FI, one might expect that under atmospheric pressure conditions, catastrophic electrical breakdown would occur. The idea for the new ionizer was based on the peculiar behavior of micro electrodes when operating at the left side of the Paschen curve. In Fig. 7, the Paschen curves, the sparking potential as a function of pd (where p is the pressure of the gas phase between the two electrodes and d the inter electrode distance) for a variety of gases are shown. Interestingly, with d small, the sparking potential goes up dramatically. This can be understood by recognizing that when the distance is too short to allow an electron avalanche to gather enough electrons, no spark between the two electrodes results. The minimum of the curve shown at atmospheric pressure in air is 6.4 μm.

An array of 10*10 microvolcanoes was fabricated with a typical throat opening of 1 μm. Given the small dimensions of the microvolcanoes, the intense electric fields required for field ionization can be produced with significantly lower voltages than macro FI sources. Referring back to the Paschen curve in Fig. 7, it is clear that the microvolcano sources should operate at atmospheric pressure with voltages up to several hundred volts and perhaps as high as a kilovolt. We have shown that these sources can indeed resist electrical breakdown at atmospheric pressure and produce

positive ions and usable current levels in a set-up as shown in Fig. 6 (we experimented with butane, toluene and pyridine). On the basis of these observations we believe that a strong possibility exists to make a working ion mobility spectrometer using an atmospheric field ionization source.

In a separate effort [30] we also have shown that negative ions can be formed at atmospheric pressure as well.

Discussion

There is no doubt that the chemical sensor and analytical instrument market constitutes a potentially larger market than mechanical sensors, not in the least because sensors here are often disposable and cost is usually less of an issue with analytical equipment. Despite the slow progress, the search to make sensors and instrumentation smaller, less expensive, faster, more sensitive etc. will continue.

From the above it is clear that in chemical sensors hybrid technology is becoming more important. Also for instrumentation and for many chemical sensors one micromachining tool does not represent a deus-ex-machina. All tools shown in Table 1 need to be considered. In many cases a better fundamental understanding of the application is needed before a manufacturing technique is decided upon. Often the influence of miniaturization on device performance can be studied independently from the manufacturing technique, e.g. by laser machining (fast turn around prototyping).

The following is a good definition for micomachining in the application field of mechanical devices. Microfabrication, micro-machining or micro-manufacturing comprises the use of a set of manufacturing tools mostly based on electronic integrated circuit (IC) manufacturing technologies, often enhanced or modified, to build devices such as sensors, actuators and other micro-components and microsystems. In the case of chemical sensors and microinstrumentation this definition must be expanded to include, in a wide variety of materials using parallel batch lithography as well as serial direct write and thick film (hybrid) techniques.

The direct write techniques may indeed become economically viable solutions for microsystem applications. Micromachining has matured around Si and Si processes, further development of sensors and actuators will require the adaptation of many different materials to the micromachining process and hybrid technology will actually become more important for the construction of chemical sensors. The need to incorporate new materials is especially urgent for progress in chemical sensors and biosensors.

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Table 1. Machining Tools.

	Surface μ		Wet Bulk μ	Dry Bulk μ (e.g. SCREAM*)	LIGA**	Laser	Hybrid
	Poly-Si	SOI					
Z-Height	< 10 μm	up to 100 μm	Single wafer : 600 μm	up to 100 μm	Up to 1 mm was reported	Very wide range	Less than 20 μm is difficult
X, Y-Shapes	Free	Free	Limited	Free	Free	Free	Free
IC Comp.	Good	Good	Poor	Good	Not demonstrated	Good	Not applicable
Materials	Poly-Si	SCS***	SCS	Free	Some choice	Free	Lot of choices
Maturity	Fair	New	Mature	New	New	Very new	Mature
Cost	Low	Fair	High	Fair	? (low with replication)	High	Low
Access	Good	Not yet	Good	Good	Poor	Fair	Good
Parallel (P)/ Serial (S)	P	P	P	P	P	S	P

* Single Crystal Released Etched and Metallized
** From the German acronym for lithography, electro deposition and molding.
*** Single Crystal Silicon

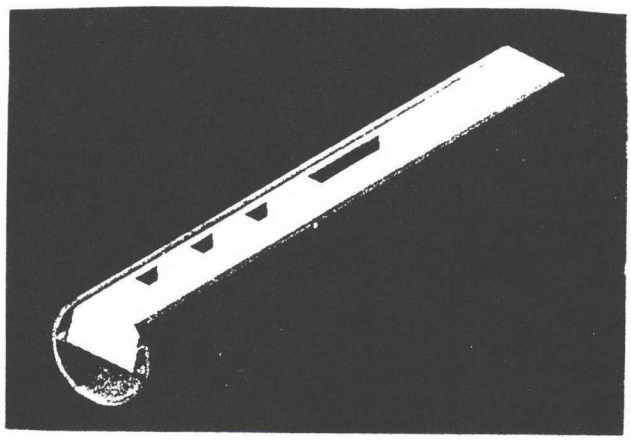
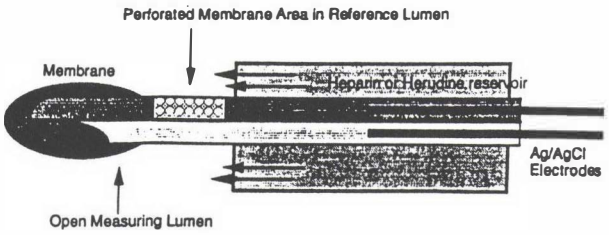


Figure 1. Array of electrochemical cells etched in Si to accomodate sensors for e.g. pH, O_2, CO_2 .



Total Maximum Diameter is < 1 mm.

Figure 2. PH sensitive catheter used for biocompatibility experiments (telemetric transmitter and receiver are not shown).

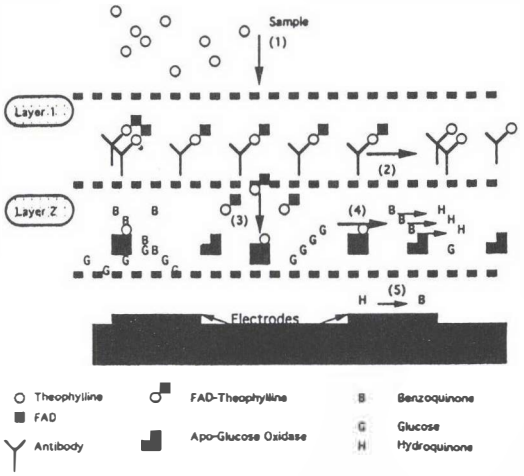


Figure 3. Layer configuration of the immunosensor using theophylline as example Reaction scheme: (1) Theophylline sample diffuses into 1st layer, (2) free theophylline displaces pre-bound FAD-theophilline conjugate, (3) FAD-theophilline diffuses into the second layer and activates Apo-Glucose Oxidase, (4) Benzoquinone consumed and Hydroquinone produced, (5) Hydroquinone isoxidized at the metal electrode leading to an increase in current.

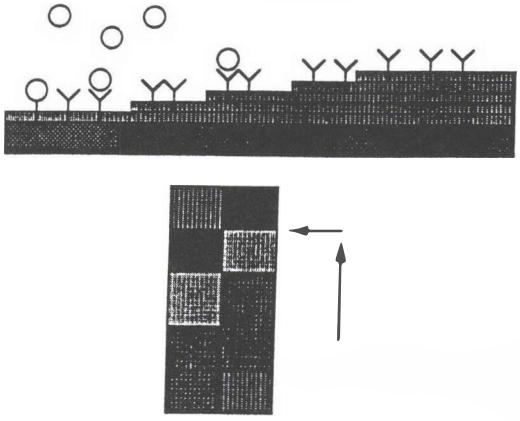


Figure 4. Interference based immuno sensors (staircase).

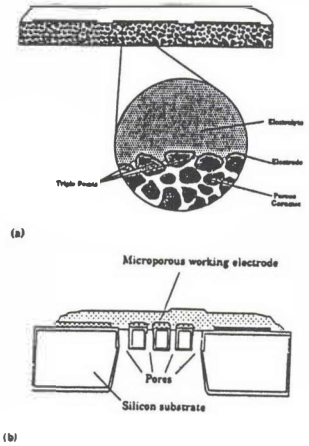


Figure 5. Backcell configurations :
(a) Back cell sensor in porous ceramic substrate;
(b) Back cell sensor with a silicon micromachined substrate.

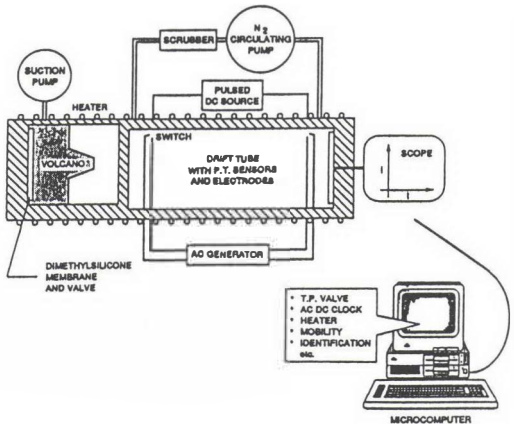


Figure 6. IMS set-up for testing of micro volcanoes.

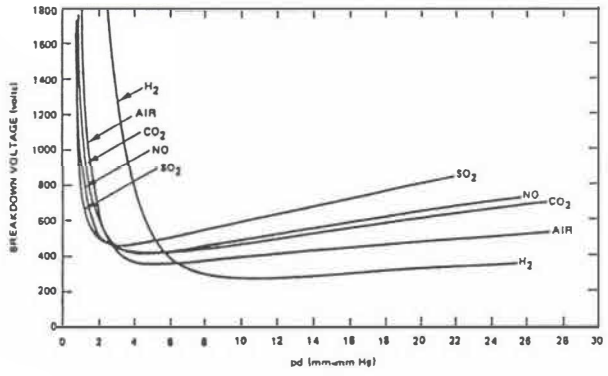


Figure 7. Paschen curves for various gases.