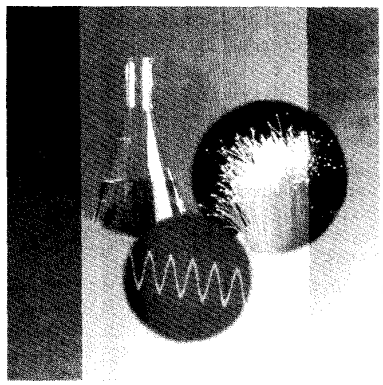

Biosensor Development at the University of Utah

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Interest in biosensors has increased rapidly in the past few years due to the many potential advantages of these devices, such as small size, speed of response, and specificity [1]. The term "biosensor" in the broad sense describes any device or apparatus which detects biological signals for the purpose of diagnosis, monitoring, imaging or sensing the state of the biological organism. This includes the more narrow definition—that of a biosensor as a continuous, reversible monitor of some physiological parameter. At the University of Utah, we are pursuing more than a dozen biosensor development projects which fit within the spectrum of these definitions. For example, the chemically sensitive field-effect transistor (CHEMFET) project is working toward perfecting a practical, miniaturized electrochemical sensor capable of measurements in biological fluids. On a larger scale, the silicon retina project is developing a combined photodetector/signal processing chip intended for eventual application as the smart detector for the visually disabled.

Recently, the biosensor field has entered a phase which stresses practicality, miniaturization and reliability [2]. Devices which have shown promise in the laboratory are being scrutinized from the viewpoint of price and performance and are being closely compared to existing techniques. To lower costs through quantity production savings, integrated circuit or integrated optics techniques are often adopted. These same trends are also seen in the projects under development at the University of Utah. In this article, we give three examples of biosensor developments at the University which are typical of the types of projects ongoing. First, we describe the silicon retina chip, part of the "Artificial Vision" project. A major advance in this device is the incorporation of three-dimensional architecture in the silicon wafer, seen to be critical to this kind of sensor, which requires complex interconnections between its parts. Next, we detail progress on making the CHEMFET sensors reliable and accurate in practical fluid environments; much of this effort has involved putting a protective layer over the nonsensing (nongate) portions of the device. Finally, we describe the development of an optical immunoassay chip utilizing a planar waveguide for fluorescent measurement of analytes such as hormones, viruses, or blood components. This device is intended to employ disposable sensor modules and be inexpensive enough for portable use in field hospitals, emergency rooms, and the like.

Silicon Retina

The Artificial Vision project at the University, headed by Richard Normann, is developing a silicon retina, a "smart" camera with signal processing circuitry modelled after the vertebrate retina. Its eventual application will be as a sensor input to an implanted cortical stimulation array for sightless persons. Conventional cameras do not model such functions as light adaptation and lateral inhibition found in the vertebrate retina, which are desirable in an artificial retina.

The human visual system, with light and dark adaptation, is able to make good judgements of relative light intensities over greater than a million fold range of light intensities (from twilight to a sunlit afternoon). Even though the basic dynamic range of the cone is only 2.5 log units, it can operate over more than 6 log units of range. This is possible because each cone contains its own automatic gain control mechanism that sets cone sensitivity to be appropriate for each level of ambient illumination [3, 4]. Thus, the cone has a 2.5 log unit dynamic range around each level of ambient illumination, and as the ambient illumination is increased to a new level, the dynamic range of the cone is shifted such that the cone is able to produce graded responses around the new ambient level.

In addition, the lateral inhibition in the human retina has mechanisms that augment spatial contrasts; e.g., uniform visual scenes tend to be "ignored" by the retina, while the edges or boundaries of objects are accentuated. This spatial filtering works so well that we are virtually unaware of its existence except under certain circumstances, associated with what we call illusions. The presence of Mach bands around dark/bright edges, where the dark region appears darker and the light region

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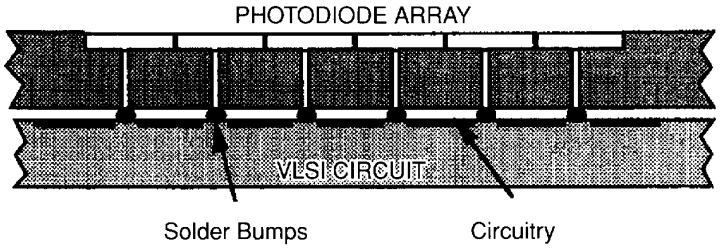
appears lighter near the boundary, is one such illusion.

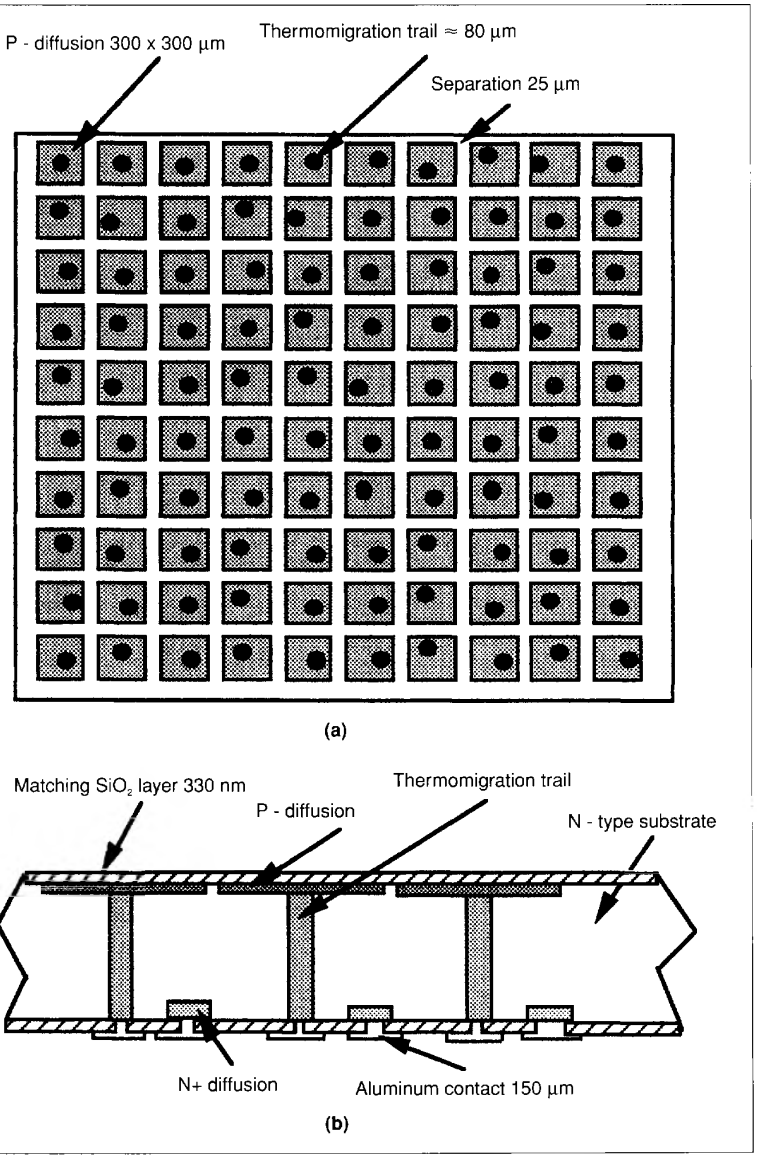
In the artificial retina, extensive signal processing circuitry is necessary to mimic such functions as real-time spatial filtering (lateral inhibition) and temporal filtering (light and dark adaptation) of optical signals from an array of high sensitivity photosensors. The required signal processing circuitry will be even more complex and occupy even more silicon area when additional retinal functions are implemented on these smart photosensing arrays. If these functions are to be realized using a two-dimensional (2-D) architecture, there will be an obvious trade-off between photosensor sensitivity and the complex signal processing circuitry. Intelligent photosensor chips using a 2-D architecture have been developed to perform some of the processing on the sensor chip and some of the digital signal processing off chip [5]. A foveated, retina-like sensor using CCD technology has also been developed [6].

Both approaches are novel; however, as the functionality and parallelism are increased it can be advantageous to use a three-dimensional (3-D) architecture, with sensors and signal processing circuitry fabricated on different planes in the structure. This eliminates the trade-off between sensitivity and circuitry complexity, since the sensors and the signal processing circuitry do not compete for the same silicon surface area. Such a 3-D silicon retina architecture with its retinal signal processing not only mimics some of the functions of the human retina but achieves this function using a laminar architecture similar to that of the retina. Figure 1 shows our current design. It is built with silicon wafers that are fabricated with through-wafer interconnects; the individual silicon wafers are connected using solder bump technology.

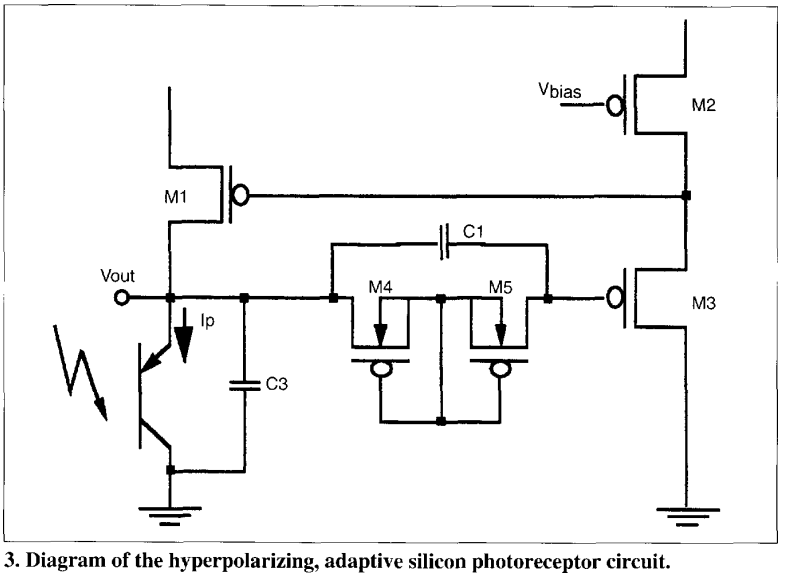
As a first step towards the creation of such a 3-D silicon retina, we have developed a 3-D architecture for a parallel processing photosensing array, a 10 x 10 array of photodiodes that fully occupy one surface of a silicon die [7], as shown in Fig. 2. The output of each sensor is transmitted directly through the silicon die to its rear surface where a 10 x 10 array of bonding pads has been formed. These bonding pads form the output structure of the photosensing array. We have also investigated the signal processing circuitry in a 3-D structure to model the light and dark adaptation of the vertebrate retina [8]. However, we have yet to implement the parallel processing photosensing array with the signal processing circuitry in a 3-D structure.



1. Three-dimensional photosensing array and silicon signal processing circuitry. The two wafers are connected using solder bump technology.



2. Three-dimensional architecture for a parallel processing photosensing array: (a) top view, (b) side view.



3. Diagram of the hyperpolarizing, adaptive silicon photoreceptor circuit.

Making the 3-D Photosensing Array Using Thermomigration

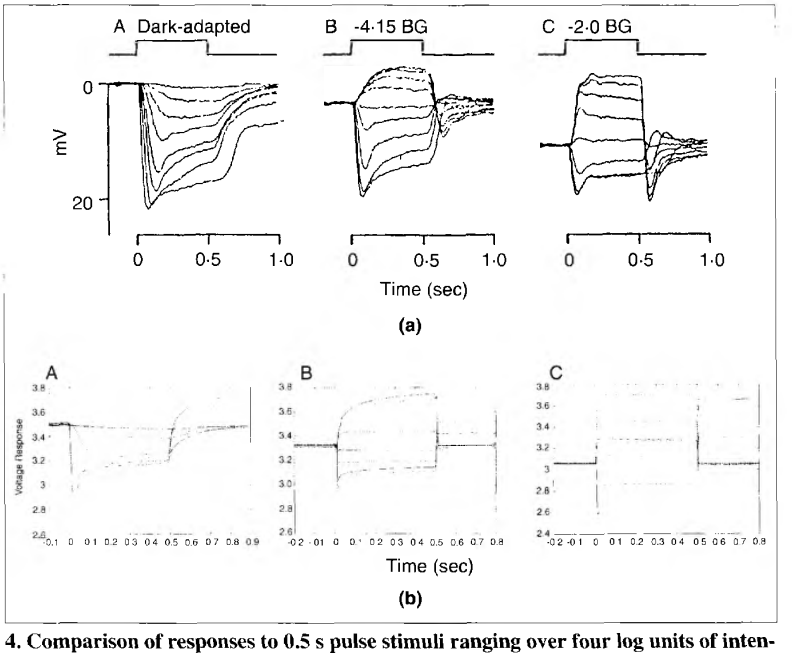
The photodiodes of the photosensing array shown in Fig. 2 are pn-junction silicon devices formed by boron diffusion into the n-type silicon substrate. Each of the one hundred photodiodes is 300 μm x 300 μm, separated from its neighboring photodiodes by 25 μm. The photosensitive side with the pn-junctions is referred to as the "front side" of the die.

The interconnects between the front side and the back side are thermomigrated trails made using the temperature gradient zone melting process (TGZMP) developed by Anthony and Cline [9, 10]. This is a high temperature process where a thermal gradient is produced across the silicon wafer, causing aluminum, deposited on the surface of the wafer, to migrate through the wafer as an Al-Si alloy droplet. As the droplet moves through the wafer, it leaves behind a highly conductive trail of p-doped silicon. Each thermomigration trail has an average diameter of 80 μm. Aluminum square pads, 150 μm on a side, make contact to the p-doped trails which emerge from the silicon die. Thus, the highly conductive p-type thermomigrated trails connect the photodiodes to the aluminum contacts on the back side of the die. An additional set of aluminum pads on the back side of the wafer make a low resistance ohmic contact to the n+-doped silicon substrate.

Silicon Retina Signal Processing Circuitry

There have been several developments of 2D analog VLSI silicon retinas [11-13]. All of these designs include spatial integration modelled after the lateral inhibitory mechanism in the vertebrate retina. However, only two attempts have been made to implement light and dark adaptation, one using digital signal processing [5] and one using analog VLSI circuitry [6]. We have focused our efforts on modeling adaptation, which results in high incremental sensitivity concurrent with a wide dynamic range. The photosensor we have fabricated is based upon the work of Mahowald [12] and is designed to emulate the light adaptation behavior of the vertebrate retinal cone photoreceptor. The circuit of the silicon photosensor is shown in Fig. 3 and consists of a total of five MOSFET transistors, two of them connected as a current conveyor [14]. The bidirectional path of the current conveyor has an extra RC-network to produce the light adaptive behavior. The resistor is formed by two back-to-back diode-connected MOSFET's with the gates tied to the transistor's body. I_p represents the current produced by the phototransduction element, a vertical pnp phototransistor with its collector connected to ground.

An example of the output from our adaptive photosensor is shown in Fig. 4 compared to the response from a turtle red cone photoreceptor. The response to a 0.5 second pulse of different intensities was measured for both detector systems after they were adapted to three different background intensities: -6.5, -4.15, and -2.0 log units, respectively. These data show three important similarities between the cones and the silicon photoreceptors: First, both were able to respond with graded responses to increments and decrements in intensity stimuli. Second, the operation



4. Comparison of responses to 0.5 s pulse stimuli ranging over four log units of intensities for: (a) turtle cone photoreceptors [4], and (b) the silicon photoreceptor. Each receptor system was adapted to: (A) -6.5, (B) -4.15 , and (C) -2.0 log units of background intensity. The data show that the silicon retina has a dynamic range of at least 5 log units of intensity.

point or mean level of operation, shifted without too much output voltage offset for different background intensities. Third, the operating ranges for each of the three background intensities were approximately the same for both phototsensors; the dynamic range of the silicon photoreceptor was about 4 log units and for the turtle cone 3 log units.

Future Work on the Silicon Retina

Before this 3-D architecture can be used in a silicon retina application, some important issues need further work. The first is an improvement in the yield of the photosensor array and overall 3-D structure. Because of the highly interconnective nature of the signal processing circuitry, an almost perfect yield of the photosensor inputs to the circuitry is necessary to demonstrate and use the 3-D architecture. Since the 3-D silicon retina architecture is a complex structure with many manufacturing steps, it may be hard to achieve a high yield in the overall system.

Also, the benefits accruing from a 3-D structure may not justify the added manufacturing complexity. However, the 3-D structure will prove more advantageous in highly parallel structures when benefits such as high S/N ratios, high structural density, and increased sensitivity outweigh the additional manufacturing cost.

Electrochemical FET Sensors

Chemically sensitive field-effect transistors (CHEMFETs) are now more than two decades old. Much of the pioneering work was done by Jiri Janata at the University of Utah. Several theoretical and practical papers have been published and this topic has been extensively reviewed [15,16].

One reason for CHEMFET popularity is the general trend towards miniaturization of chemical sensors. Another is that these devices are modern analogs of familiar ion selective electrodes and other time-tested potentiometric devices [17]. However, although in theory the CHEMFET devices offer a convenient, rugged and miniaturized alternative to conventional devices, there are still numerous technical fabrication problems that preclude their widespread use:

a) integrity of the solid state part of the device;

b) integrity of the final sensor package;

c) definition of the sensitive areas in multisensors;

d) adhesion of the selective membranes to the solid state substrates.

Some of these problems can be dealt with at the wafer level while others must be addressed at the individual device level. Obviously, from the point of view of the fabrication cost it is important to perform as many fabrication steps as possible at the wafer level. In our lab, we have addressed each of these problems. The following sections give a brief description of these technological steps, which are important to the performance and durability of the CHEMFET devices.

Integrity of the Silicon Nitride Layer

In solid state chemical sensors exposed to conducting liquids, integrity of the top passivation layer is of a paramount importance. Existence of small cracks in the top silicon nitride (Si_3N_4) film may not be particularly important in conventional device applications, but in CHEMFETs cracks and pinholes invariably downgrade input characteristics, introduce baseline instability and, ultimately, may lead to a catastrophic failure [18]. The formation of these imperfections severely decreases the yield of the microfabrication process, sometimes to as low as 30%.

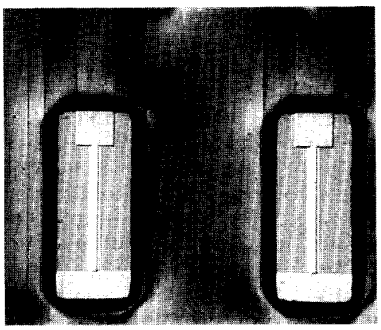
Amorphous silicon nitride films are generally deposited by a high temperature chemical vapor deposition (CVD) technique. Such films have high uniformity and a low processing cost [19,20], but are deposited on the substrate in a state of stress. As a result, the Si_3N_4 layers are sensitive to subsequent treatment such as annealing or wet etching. For example, the rate of cooling of Si_3N_4 from the deposition temperature has a major influence on the integrity of the film . We have found that application with a cooling rate of 1-2 C/min effectively increases the yield to over 90% [20].

Definition of the Sensitive Areas

One of the major difficulties encountered with chemical sensors is that the area housing the electrical circuit and the area of chemical sensitivity must be chemically isolated from each other. The former must be well protected from conducting liquids, while the latter must be exposed to the very same liquids. Moreover, the performance of multifunctional CHEMFETs is primarily determined by the properties of the chemically sensitive membranes, which must be deposited over separate but closely spaced gates of the FET. Those areas must be geometrically well defined and separated from each other. This process is accomplished at the wafer level [21] by patterning a thick insulating material in such a way that cylindrical openings (into which the chemically sensitive material is deposited) are created above individual gates. Materials used for the area definition have to be chemically inert in order to eliminate possible chemical interactions with the sensor material. Equally important is their good mechanical adhesion to the top passivation layer, usually Si_3N_4.

Historically, epoxy (a two-component mixture of Epon 825 and Jeffamine D-230) has been used in sensor encapsulation. The wells were formed by hand under a microscope, individually on every chip. In an effort to minimize labor-intensive encapsulation and as the first step towards automated fabrication, thick photosensitive materials were then introduced. Two materials have proven to be particularly suitable: (i) Vacrel™ (DuPont) polymer, originally developed for printed circuit board fabrication, and (ii) Selectilux™ (Ciba-Geigy) photosensitive polyimide. Vacrel provides good environmental protection to the underlying material. The lateral resolution that can be obtained with 100 μm-thick laminated Vacrel is between 125 and 150 μm. This material is used whenever a deep well (100 μm) is required. However, its operating temperature is limited to approximately 120 C.

When smaller well openings are needed, Selectilux HTR3-200 has been found superior. Openings as small as 55 %m can be patterned in a 60 μm-thick layer. The practical thickness limit is 70 μm for fully cured polyimide; thicker layers exhibit adhesion failure [22]. Also, polyimide can be used at elevated temperatures up to 350-400 C without observable deterioration. Figure 5 shows a dual-gate CHEMFET protected by a Selectilux layer.



5. Photograph of a dual-gate CHEMFET. The top encapsulation, which defines the chemically active areas on the chip, is a layer of 65 μm-thick photosensitive polyimide. The dimensions of the oval openings are approximately 230 x 600 μm.

Gross Encapsulation

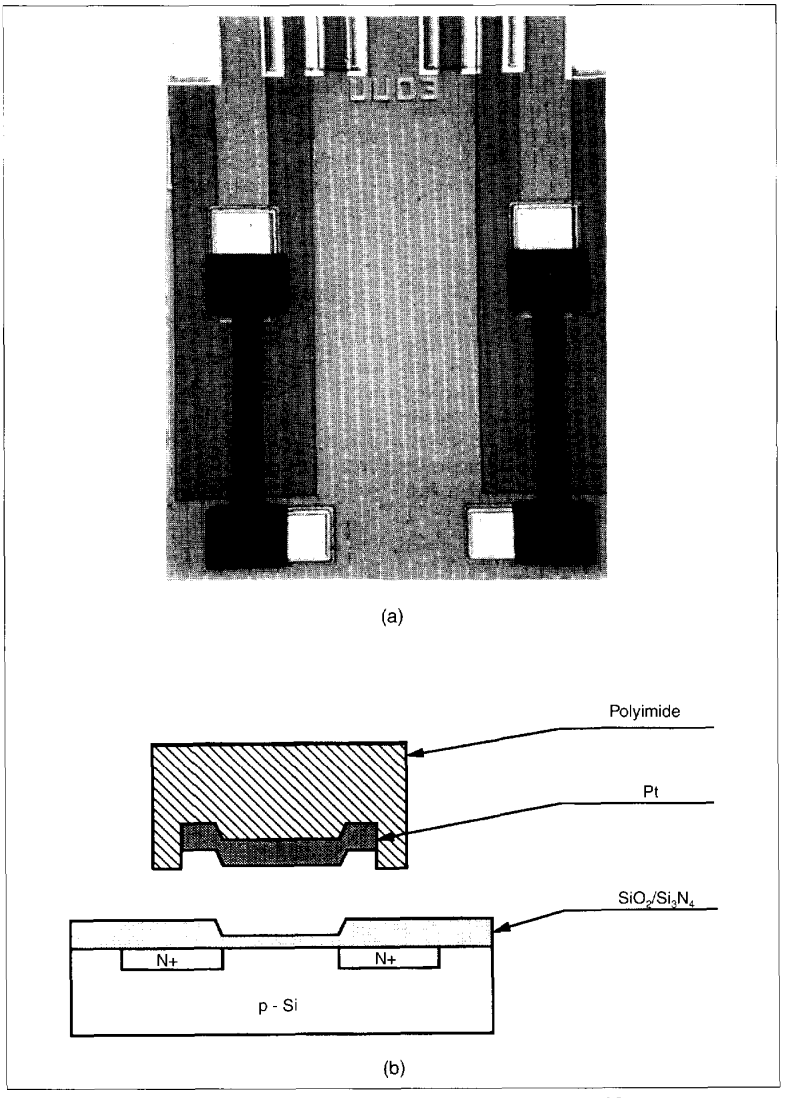
Areas that need to be protected on CHEMFETs are the bonding wires, the electrical contacts on the device, and the edges of the silicon chip. In order to ensure the sensor integrity, selection of the type of encapsulant material (including its adhesion to the defined regions of the substrate) is important. These factors determine the long-term stability of the finished devices. Manual procedures for encapsulation of sensors present many challenges. New encapsulation processes based on electrochemical deposition have the major advantage of being geometrically conformable, i.e., the layer follows minute details of the contours of the electroactive area. This is particularly important in fabrication of multisensors. A process where the electrochemically generated layer is poly(oxyphenylene) has been employed for encapsulation of a sensor package with a CHEMFET die attached to a mechanical support, such as TO5 standard transistor header or a catheter, with all the bonding contacts made of noble metals [23].

Multiple Sensing ISFETs

An improved procedure for preparation of multiple gate, ion sensitive, field-effect transistors (ISFETs) with polymeric membranes has been developed [24]. The process is based on the simple idea that most ion-selective membranes consist of a common matrix made of the polymer and plasticizer, and that the selectivity is imparted on the membrane by the presence of a low molecular weight ionophore [25]. Preparation of the selective material for an ISFET then proceeds in two steps: First, a blank membrane containing only the polymer and the plasticizer is applied to the encapsulated FET chip, enveloping the entire probe. In the second step, the low molecular weight electroactive components of the membrane (ionophores and/or other additives) are introduced by locally doping this blank membrane. The main benefit of this simple procedure is a continuous and therefore mechanically stable membrane, without electrical shunts between the membrane and the encapsulant. This approach alleviates, for the most part, the problem of adhesion of the membrane. However, in the future, the overall performance of the ISFET may benefit from specially formulated, well adhering membranes that have already been developed [26].

Alternative CHEMFET Sensor Technology

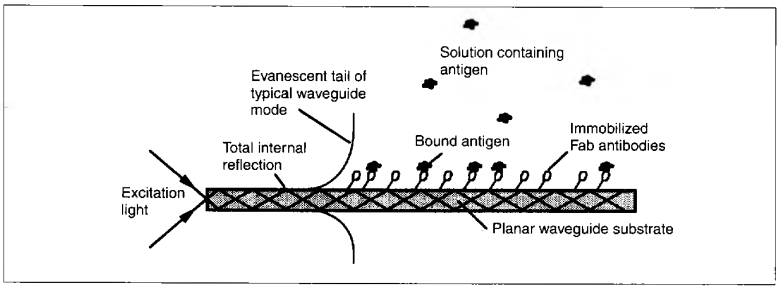
CHEMFET technology relies on the presence of a chemically sensitive membrane, which upon interacting with the species in solution or gas changes the gate potential of the FET. During the last few years, another type of sensor has been constructed and tested. This sensor, which does not require cumbersome membrane deposition steps, is based on modulation of the electron work function and is dedicated for gas applications (it is the microscopic equivalent to the so-called Kelvin probe or vibrating capacitor). The sensor is composed of of a field-effect transistor, in which the metal gate forms a suspended bridge that is separated from the solid insulator by a narrow gap [27]. A photograph and schematic diagram of this device are shown in Fig. 6. It can operate in an ambient gas or in a vacuum, and the active area of the probe can be locally heated [28].



6. Suspended-gate gas sensor: (a) Photograph of the suspended bridge structure. The dimensions of the suspended beam are approximately 80 x 440 μm. (b) Schematic diagram of the suspended beam cross section area.

There is no practical limit on the lifetime of bare CHEMFET chips. This is important from the point of view of fabrication and storage of the unfinished devices. The in-use lifetime of the CHEMFET depends on the type of chemically sensitive layer. It can be years for a bare silicon nitride pH ISFETs, or months for membrane ISFETs and days for Enzyme FETs (ENFETs). Lifetime data for various gas FETs are not yet available.

It is fair to say that some types of



7. Side view of fluorescence planar waveguide immunosensor. Light entering from the left is trapped inside the guide by total internal reflection, except for an evanescent portion which excites surface-bound fluorescence. The relative size of the antibodies and evanescent field compared to the waveguide thickness is exaggerated for clarity.

CHEMFETs, such as ISFETs, have reached the stage of possible commercial application. Others are still in the research and development phase but show every promise to play an important role in the future sensing domain. In our laboratory as well as in others, ISFETs have been prepared and tested that consistently perform as well or better than conventional ion selective electrodes in a variety of measuring applications. The remaining developments in the area of ISFETs are expected mainly in multi-gate ISFET probes with associated electronics on the same chip. A logical step would be application of advanced data processing techniques, such as chemometrics and neural networks. Automated packaging and membrane deposition techniques should drastically reduce the cost of manual operations in their sensor preparation.

Fluorescence Immunosensor Using a Planar Waveguide

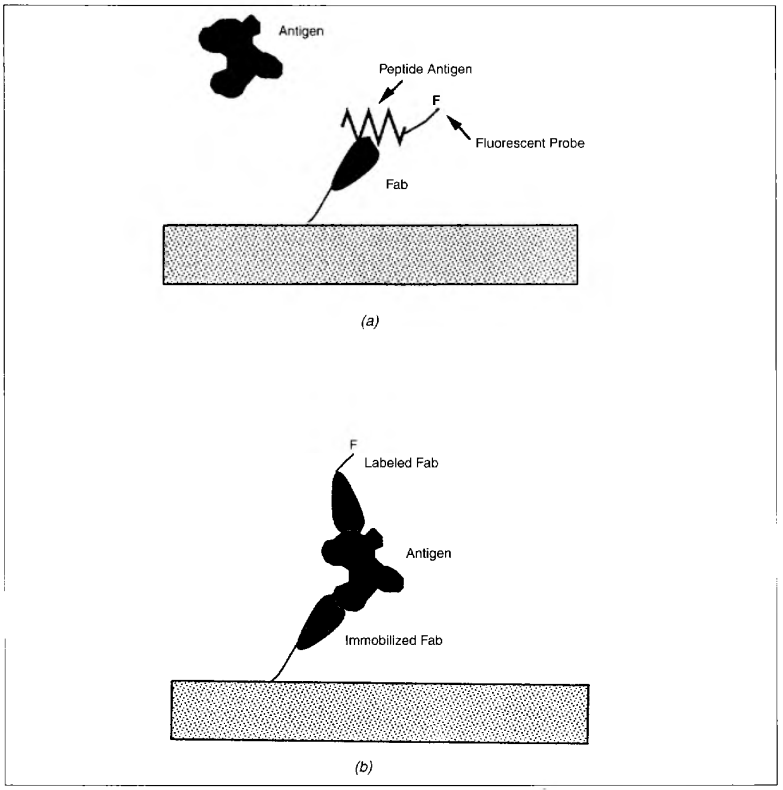
We have also been pursuing the development of a fluorescence immunosensor for medical diagnostics. This sensor is intended to be faster and more convenient to use at the site of patient care than the current clinical immunoassay instruments, which are typically batch machines located at remote central laboratories. The sensor has the following design features: sub-picomolar sensitivity for the analyte (such as the pregnancy hormone hCG), no wash steps (to reduce the requirement for highly trained operators), 5-10 minute measurement times, and small (about 0.1 ml) sample volumes. To achieve these goals, we have chosen a fluorescence immunoassay technique which uses a 1.0 mm-thick transparent planar waveguide surface as the substrate upon which analyte-specific antibodies are immobilized. The waveguide also provides the means for optically exciting the fluorescence in the bound species.

Figure 7 schematically shows the elements of the immunosensor module [29]. Excitation light from a laser (either argon ion or HeNe) is end-coupled into the planar substrate where it propagates by total internal reflection (TIR) down the length of the guide. Most of the light is contained within the substrate by TIR, but a certain portion penetrates in a nonradiating manner into the adjoining solution region, obeying an exponential decay profile. This evanescent tail extends only about 200 nm into the solution, but this is far enough to cover the layer of immobilized antibodies with its attached antigen, without penetrating appreciably into the bulk solution. This excites fluorescence of the bound species but does not excite any of the fluorescence of species in the bulk. Thus, a wash step to get rid of unbound bulk protein is avoided by the limited penetration of the excitation light from the surface of the waveguide substrate.

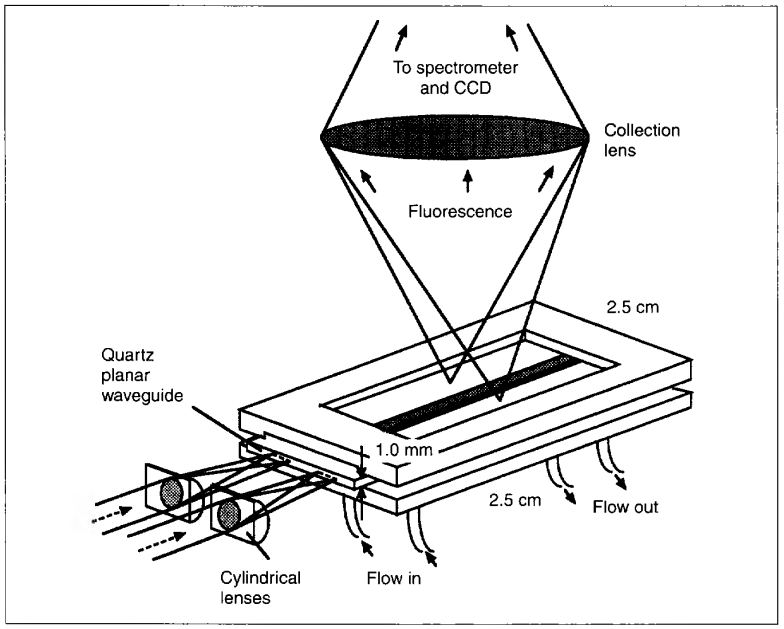
Competition and Sandwich Assays

As an example of the use of this technique for immunosensing, we have fabricated a sensor using a 1.0 mm x 2.5 cm x 2.5 cm waveguide of quartz. Anti-hCG antibodies in the form of Fab fragments were immobilized on the surface, either by avidin/biotin coupling chemistry or coupled to an intermediate hydrogel layer. Two different sensing schemes have been tried [30]:

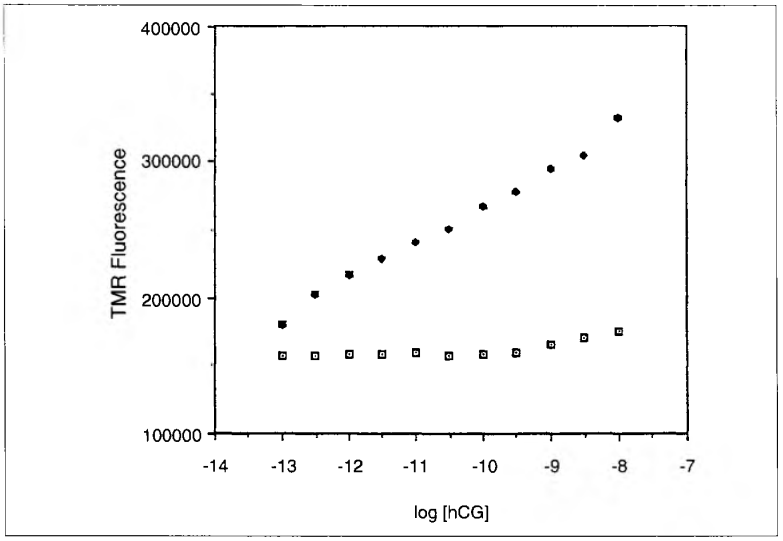
a) Competition Assay - In this configuration, shown diagramatically in Fig. 8a, a synthetic peptide antigen similar to the hCG antigen is labeled with the fluores-



8. Two different assay schemes: (a) competitive assay; (b) sandwich assay. The Fab portions of the antibodies are sufficient for binding purposes here.



9. Planar waveguide sensor in a two-channel flowcell with end coupling of two excitation beams. The emitted fluorescence is collected by a lens from the side.



10. Response of planar waveguide immunosensor to varying concentrations of the analyte hCG in the sandwich format. Upper curve is sample channel; lower curve is reference channel (no hCG). The reporter solution in both channels contains 10^{-8} M anti-hCG labeled with tetramethylrhodamine (TMR).

cent molecule rhodamine and is preloaded—before the introduction of the sample solution—onto the immobilized Fab antibody layer where it binds to a high degree with the antibodies. Then, upon introduction of the sample containing the unknown concentration of the analyte hCG, a certain number of these fluorescently labeled peptides are displaced from the antibodies by competition for the binding sites with the hCG. The amount displaced is proportional to the concentration of the hCG antigen; thus the fluorescence signal decreases with increasing concentration of hCG.

b) Sandwich Assay - Here a solution containing free "reporter" Fab antibodies to hCG labeled with rhodamine is mixed with the solution containing the unknown concentration of the antigen hCG. The scheme is shown in Fig. 8b. In the presence of the layer of Fab antibodies immobilized on the waveguide surface, complexes of immobilized antibody/analyte/labeled antibody are formed on the surface within the evanescent zone, and the amount of excited fluorescence then increases in response to an increase in the hCG concentration.

Optical Configuration and Results

Figure 9 shows a two-channel flow cell arrangement which is convenient for holding the waveguide while introducing two different solutions, such as the unknown sample and a calibration solution. The excitation beam from the laser is coupled by short focal length cylindrical lenses into the end of the waveguide. The fluorescence emitted from the surface layer is collected by a lens and focused to the entrance slit of a 1/4 meter grating spectrometer. The output slit of the spectrometer is replaced with a thermoelectrically cooled 512 x 512 pixel CCD camera. A 100 nm range of the emission spectrum can be captured at one time by the camera, with resolution of approximately 1 nm. The other dimension of the two-dimensional CCD image gives spatial information across the two channels.

In our experience with hCG measurements, the sandwich scheme gives a higher sensitivity than the competition technique, with detection levels approaching 0.1 picomolar. A typical response curve for the sandwich scheme is shown in Fig. 10 [29]. For this test, increasing concentrations of hCG were introduced into one of the two sensor channels after being mixed with a reporter solution of constant 10^{-8} Molar anti-hCG labeled with the fluorescent dye tetramethylrhodamine (TMR). The other channel was employed as a reference channel, with only 10^{-8} Molar reporter solution introduced (no hCG antigen). The excitation wavelength was 515 nm. After an incubation time of five minutes, the intensity of the fluorescence emission was measured from both channels. To get a representative value, the spectrum from each channel was integrated over a range of about 40 nm around the peak wavelength of 575 nm. The sample channel intensity is plotted on the upper curve in Fig. 10, while the reference intensity is plotted as the lower curve. As can be seen, the sample channel signal increases with analyte concentration. The reference signal, which is more or less constant, can be used to normalize the

sample intensity of compensate for varying laser power or for nonspecific binding.

The sandwich technique gives better sensitivity that the competition method, partly due to the fact that the fluorescent signal is increasing from a small background value rather than decreasing from a large beginning value, thus improving the optical signal-to-noise ratio. The sandwich design is therefore the prefered method when it can be used, which is with larger analyte molecules. With smaller analytes, there may not be enough surface area on a single analyte molecule to bind two antibodies in a sandwich, and the competition scheme must be used.

Future Work on the Waveguide Sensor

The waveguide sensor provides measurements in much shorter times (about 5 minutes) than traditional enzyme-based techniques (which typically require 30-60 minutes). The length of time needed for a reading is limited only by the incubation or binding time of the analyte to the antibodies. The planar geometry of the sensor also allows for multiple channels to be placed on one sensor module. This is convenient for doing calibrations and/or simultaneous measurements of multiple analytes.

In the next generation, the module will be made such that the solutions will be held by gravity in multiple wells next to the waveguide. The spectrometer/CCD camera arrangement will be replaced by a simple bandpass filter and photodiode array. The module will be inexpensive enough to be disposable and the overall instrument will be small and convenient enough for patient care sites such as emergency rooms or battlefields. Here, the measurements of interest will be blood components and infectious diseases.

Conclusions

The three examples of sensors described above give a small flavor of the biosensor work ongoing at the University of Utah. Although there are obvious differences between each of these three sensors in terms of their application areas, the parameters measured, and the technologies used, there are several simularities that are shared by many biosensor developments. These include the move toward smaller device sizes, inexpensive fabrication, large-scale manufacturing methods, and improved reliability in actual applications. The extent to which each of these sensors can meet those real-world requirements will largely determine their eventual commercial viability.

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