SENSOR SENSITIVITY TRAINING

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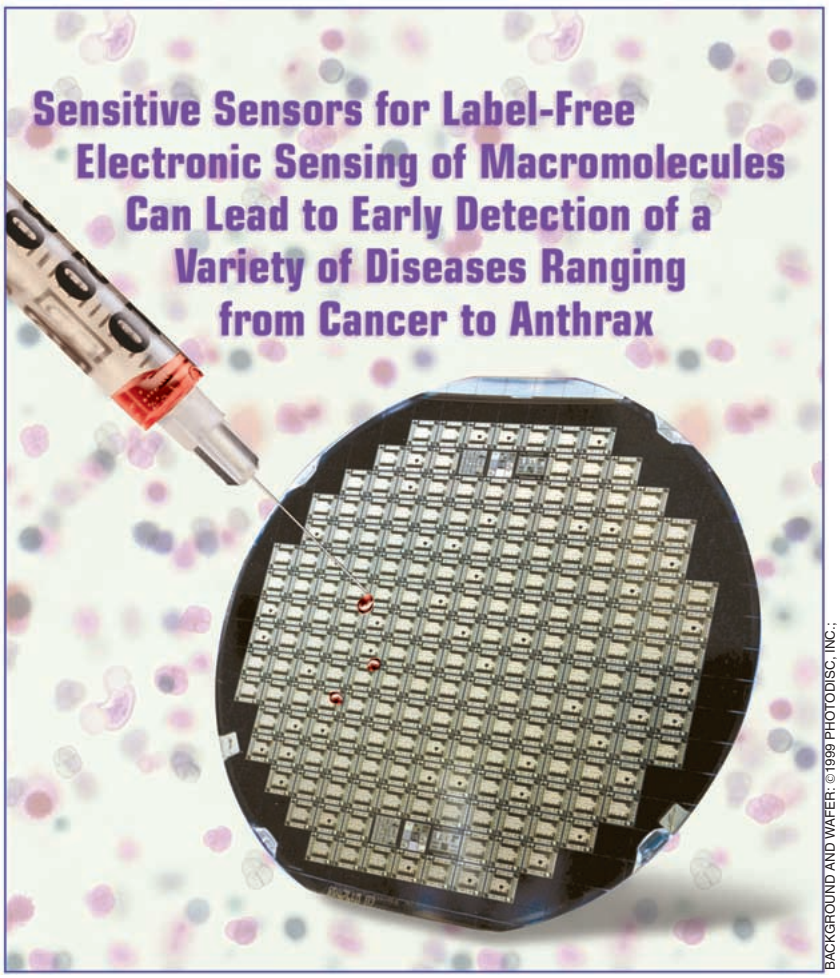


The union between biologists, physical scientists, and engineers has yielded accelerated output in all three of these areas for some time. New approaches to instrumentation [1], as well as new ideas in disease detection [2], [3], have been put forward and proven as a result of interdisciplinary teaming. The general public has been helped by new concepts in drug discovery—a field greatly benefitted by high-speed computation.

Biological macromolecules (i.e., proteins (including toxins, hormones, antibodies, enzymes and those on surfaces and/or within cells, bacteria, and viruses), DNA, and RNA) are central to biological processes. Their presence and state of flux (i.e., concentration and/or structural change versus time) provide important signatures of disease and threat exposure. Detecting specific biological macromolecules in vivo or from samples derived from untreated body fluids or an environment is a challenging but worthwhile endeavor. Relevant concentrations of biological macromolecules are often low (often femtomolar), and they exist in complex media containing many other macromolecules, some of which may interfere with detection. In addition it is desirable to detect multiple macromolecules simultaneously to ensure a high confidence level in disease diagnosis or threat assessment and to determine their progression [2].

In this article, we review recent progress in the area of biological macromolecular sensors and we present several research activities aimed at achieving such a device. Here we distinguish sensors from assays—the former describing devices capable of continuous monitoring and real-time detection, the latter describing devices and techniques for analysis of a single sample. We give examples of both types of detector below. We conclude by focusing on a specific device we are developing in our laboratory, based upon imparting molecular recognition to a

field-effect transistor as an example of current development strategies in the field.

We acknowledge that there is a considerable amount of recent interest in "biomimetic" sensing [4], [5]. Much can be learned from biology, particularly in the area of robust system design. Of course, detailed study of the biological systems probed is necessary to determine the appropriate analytical target. However, biological systems do not offer the speed of recognition and the ability to interface with electronic systems (such as computers) that we would like in an ideal sensing system. Emphasis here is on new approaches to those advances that are not "biomimetic."

As a result of this chaotic situation, the ideal sensor must be capable of employing the most sophisticated signal processing tools currently available.

The "Ideal" Macromolecular Detector

The ideal sensor must be "sensitive." That is, it must have a low detection threshold for small quantities of the analyte (the macromolecule sensed) present in the medium we are investigating. It must have a dynamic range sufficient to detect all the levels of analyte we expect to encounter. The ideal detector must be specific; i.e., it must be able to discern one macromolecule from another in the presence of many "interfering" chemical species (ions, small free radicals, etc.) As the sample population is large (potentially a fair fraction of the human race) it must be possible to build large numbers of reliable detectors cheaply and easily.

In addition to these considerations, which hold for most sensors manufactured today, there are other considerations resulting from the unique nature of the sample population. The dangers of the false negative are obvious. But we must also take care to avoid the "tragedy of the false positive." Assume we are sampling a population of a large city, about 10 million people. Even if our detection accuracy is one ten-thousandths of a percent (one false positive in a million) we will still have about ten false positives in the city. While this seems reasonable on the surface, the situation appears in a new light when we consider that there are ten human beings who may face invasive procedures, or even chemotherapy and radical surgeries, as a result of medical testing.

This has implications in the design of the ideal detector. In particular, arrays of many detectors allow us to do multiple checks on a given reading. Also, it would be desirable to include cross checking in the sensing array. That is, we'd like to have sensors in a single array targeting different recognition features on a single analyte molecule.

Also, the biological medium is one of the most changeable media addressed by sensor technology. The sensor sits in an ionic bath whose species concentration varies significantly over time frames ranging from seconds to minutes *independent of the time-fluctuation of the analyte.* The ambient is similar to that of a gas-phase plasma and every surface in it becomes coated with a "double layer," whose dimensions respond to the bias potential of the surface and to the local constitution of the ambient solution. This is a challenge indeed!

As a result of this chaotic situation, the ideal sensor must be capable of employing the most sophisticated signal processing tools currently available. Among these are:

- correlated sampling approaches: these include the "double-correlated" approaches achieved in the time domain and spatially correlated approaches such as differential sensing
- repeated tests for a given analyte: simple "voting" approaches are one example, in which multiple sensors target the same analyte and decisions are made based on the collective "vote" of the output from all the sensors
- cross checking: this requires us to employ sensors that trigger on different aspects of the same macromolecule. For example, one sensor might key into the presence of a specific chemical functional group specific to the target analyte, and another sensor might seek a second (or third) feature of the same analyte. From these different sensed aspects of a given molecule, a "decision space" statistical analysis may proceed. An excellent review of this type of analysis, as applied to biological sampling, was given by Jurs, et. al. [7]
- time-domain analysis: the rate of migration of a molecule to the sensing surface is an indicator of the type of molecule it is.

Another consideration in this type of sensing relates to the transduction pathway. Generally, the presence of the detection target must be manifested as an electronic signal to be recognized by a computer system. If the presence of the macromolecule triggered this electronic signal directly, this would be a "single step" transduction process. In bio-sensing, however, the molecule may be ligated to a surface or reacted with another species to create a precipitate or surface-bound film for weight analysis. The "paradigm" multistep process is the attachment of a fluorophor and subsequent fluorescents via a laser excitation process. The rule here is just this: *make the transduction path as short as possible.* Each added step in the path adds an uncorrelated noise process to the sensed signal.

Along these lines, we observe that the ideal array should be capable of label-free detection. That is, the sensor should be capable of detecting its targets without modification to these targets (i.e., the addition of labels). Labeling chemistry generally precludes in vivo operation. We cannot modify biologically important molecules in the body—it would destroy their important functions and the modification process may poison the animal

probed. Additionally, labeling requires time and adherence to rigid protocols. This prevents the rapid response necessary in assessing germ or chemical warfare threats.

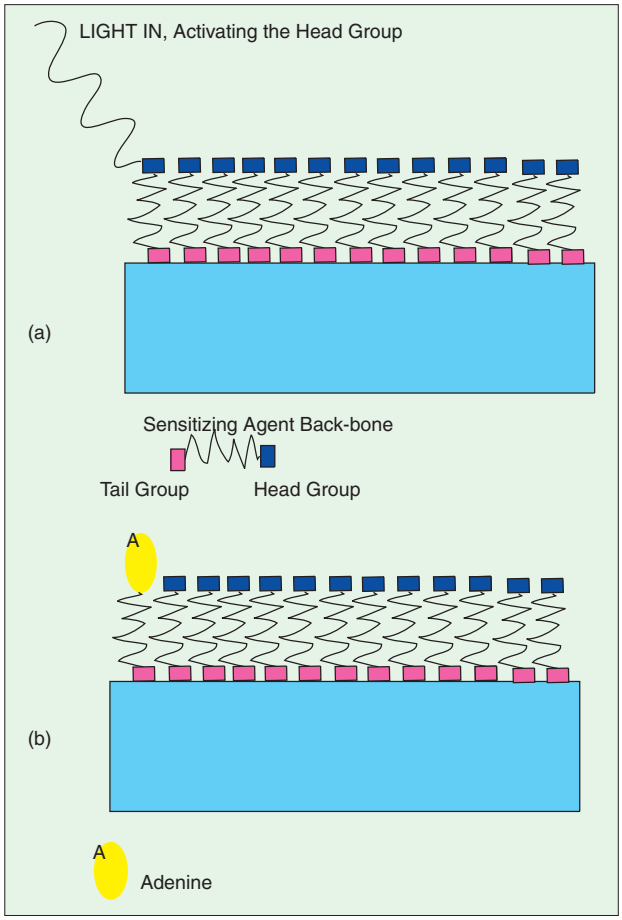
Given these considerations, we can evaluate many detector schemes. Now let us turn to some specific examples.

Examples of Macromolecular Detection Schemes

Many excellent reviews exist describing an enormous number of sensors employed in macromolecular research. In particular, *Chemical Reviews* recently published an outstanding volume [9], which covers the basics of sensor design and chemistry as well as statistical analytic techniques. The examples cited below stress new developments that have come to prominence since then.

Gene Chips Assay Detectors

One of the most visible of these new designs is the so-called "gene chips," produced by Affymetrix [8]. A primer is applied to a glass slide that is locally photo-activated using (more or less) standard photolithographic procedures. This process is illustrated in Figure 1. Here we see the primer as it appears on the substrate (a). For DNA, where each element is selected from one of four amino acids, an array of any size and complexity can be formed by $4 \times N$ masking steps (where N is the maximum chain length.)

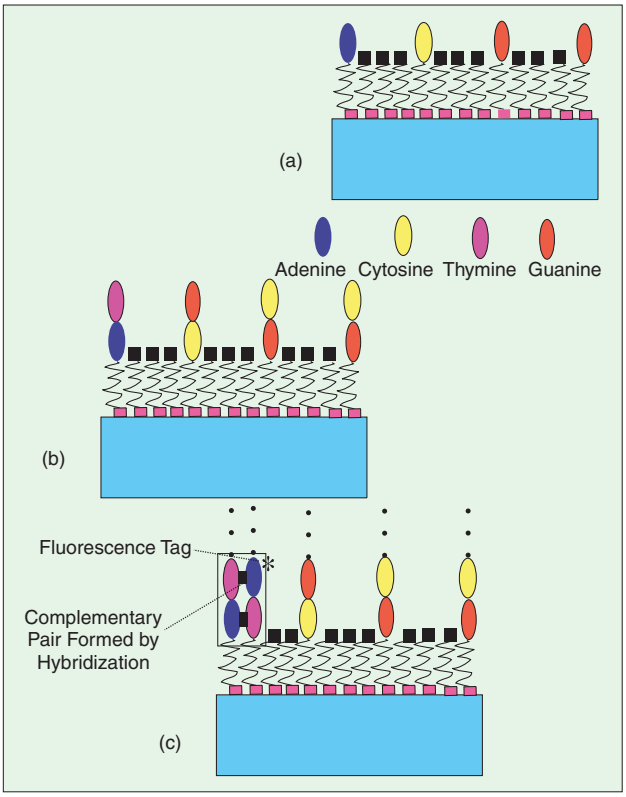


1. Surface bonding of an amino acid in the affymetrix approach. (a) Light striking the primer head group, allowing for deprotection of the underlying primer strand. (b) Surface attachment of an amino acid by the deprotected SAM strand.

This process can be repeated using photolithographic masking. Selective regions of the chip surface are lithographically photoactivated, allowing for attachment of a variety of amino acids across the chip. This is shown in Figure 2(a).

After the first layer is put in place, the photolithographic process can also be used to build up stacks of amino acids, as shown in Figure 2(b). At each step, selective photoactivation is required to initiate a new attachment process. When viewed along a given sequence stacked perpendicular to the substrate, it appears that we have arrays of DNA strands. These strands can bind fluorescence-tagged target molecules through hybridization.

Each array element can be addressed by laser beam. If the fluorescence-tagged analyte is present, and if it binds to the previously tethered strand, we can identify the hybridized molecule by its fluorescence signature. Slightly mismatched DNA strands



2. Building up a complementary DNA strand in the Affymetrix approach. (a) Light striking head groups across the chip allows for selective attachments of amino acids across the surface of the chip. (b) Buildup of strands across the chip require selective photo-activation of the underlying amino group to enable attachment of new amino groups like "adding beads to a string." (c) Exposure of the resulting strands to solution containing fluorescent-tagged complementary DNA strands leads to immobilization of the tagged complement through hybridization at a well defined detection site. The presence of the complement drawn out of solution is ascertained by laser addressing the sample surface at the detection site and observation of characteristic fluorescence.

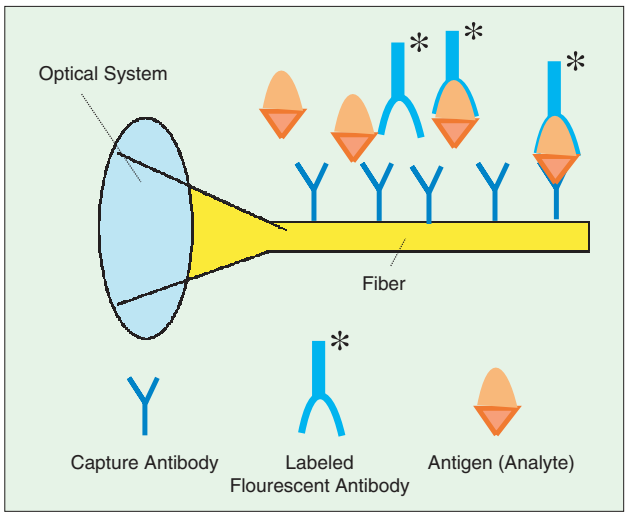
have a greater probability of escaping attachment and would yield lower fluorescence signals.

> The idea of using an FET as an integral part of a chemical sensor has many attractions.

"Lock-and-Key" and Sandwich Assays

A biologically derived macromolecule can be immobilized on a surface as a receptor to bind a specific target macromolecule from a sample solution. Such macromolecular "lock and key" recognition is a feature of biology long exploited for biological assays [17]. Examples of receptor/target pairs include antibodies that bind proteins, viruses, bacteria, and single-strand DNA (ssDNA) that bind (hybridize) complementary ssDNA or proteins, described above.

A number of transduction methods are used to indicate target binding. Prevalent are those utilizing reagents composed of a secondary receptor labeled with a fluorescent, phosphorescent, enzymatic, magnetic, or radio isotopic probe [18]. Following exposure to a sample fluid for analysis, the sensor surface is exposed to a solution containing a reagent that binds to the immobilized receptor-bound target macromolecule to form an immobilized receptor/target/(secondary receptor-probe) complex [19]. Measurement of probe signal is then used to determine target binding. Alternatively, an immobilized receptor/(target analog)/(secondary receptor-probe) complex is formed on the sensor surface prior to sample exposure in which the analog macromolecule is bound by both receptors with lower affinity than the target macromolecule. Displacement of analog by target macromolecule results in decreased probe signal [20]. The key attribute of such "sandwich" reagent-based detection is that it requires two recognition events to signal detection, providing a high degree of confidence. The key limitation of reagent-based detection is manipulation of the reagent, which hinders continuous real-time application, field application, and autonomous monitoring.



3. The RAPTOR detector channel: fiber optic and immunoassay. The final configuration of the bound analyte is shown as the tethered structure on the far right.

A classic example of the "sandwich" assay approach is the RAPTOR sensor, developed by Dr. Ligler and her group at the Naval Research Laboratory [11]. Here, antibodies keyed to capture a single antigen (the analyte) are fixed to an optical fiber. The solution containing the analyte and a fluorescent-tagged antibody is passed over the fiber. The analyte may be bound, either by the capture antibody or by the fluorescent antibody in solution. In any event, a "sandwich" of the capture antibody, antibody, and fluorescent antibody is bound to the fiber surface. This is shown in Figure 3. A limited number of parallel channels are possible, allowing for multi-analyte sensing or for cross checking.

Another prevalent transduction method is the labeling of a class of macromolecules within a sample (such as all ssDNA or all proteins) prior to analysis and utilizing surface immobilized receptors to bind only those of interest. The key attribute of this detection strategy is that it is amenable to high-density arrays, allowing for detection of thousands of target macromolecules simultaneously. This is not possible with sandwich detection strategies because they would require thousands of probe-labeled secondary receptors. The key disadvantage of this detection strategy is the sample labeling, which presents the same limitations as the reagent-based strategies above.

Surface ligation chemistry has been applied to surface acoustic wave (SAW) devices and to quartz crystal microbalances (QCMs) [12], [13]. These are examples of transduction methods. In both cases, the surface of the device is treated to bind a target analyte. For the case of the SAW device [10], attachment of the analyte changes the resonance frequency of a Rayleigh surface acoustic wave that propagates on the surface of a piezoelectric crystal. It is possible to measure the shift in frequency directly by propagating the wave through a sensitized region of surface and through a closely spaced control. The two propagating waves (one in the reference and one in the control) can be mixed, and the interference pulse rate counted and the frequency shift determined.

While the detection scheme associated with the SAW is "label free," the signal transduction path is lengthened by the fact that the "mechanical" resonance shift of the crystal must be further transduced to an electrical signal to achieve detection.

The quartz crystal of the QCM is similarly sensitized to bind a given target analyte. In this case, though, the added mass changes the mechanical resonance frequency of the crystal. This shift in resonance is detected and related to the amount of analyte attached. The details of the operation of the QCM, and the equations determining the mass-dependent frequency shift (the Sauerbrey equations), are discussed by Chopra [14].

Nanotechnology Applications

Recent approaches have made use of advances in "nanotechnology." Nanoclusters—balls containing small numbers of

atoms—have a specific color or they may be colorless before exposure to an attaching medium. On attachment, the clusters assume a characteristic color and are suitable for use as a fluorophor (as in the sandwich assay). These clusters are not bleachable and hold up well under extremes of illumination.

As nanotechnology is an emerging field, it is interesting to speculate on possible future applications. As we are manipulating structure on an atom-by-atom, bond-by-bond basis, we might anticipate "quantum" changes in the physical properties of a system. These quantum changes are discontinuous and the clusters of atoms that are modified by the macromolecular attachment processes are easily distinguished optically or electrically from unmodified counterparts.

For example, surface attachment of the target analyte to a nanocluster may affect a dramatic color shift resulting from the change in the electronic density of states that may accompany a single binding event. This is a "quantum mechanical" effect, not simply the result of multiple interference effects within the composite structure of the ball. Thus, the color change can be likened to the turning of a grain on a piece of photographic film. Here, a single event causes a physical change that is far from the precise point of incidence of the photon strike. A kind of chemical amplification is occurring, as illustrated in Figure 4. While this effect has not been fully exploited in practice, it is interesting to speculate its possible use in the future.

Advances In FET-Based Detectors

The FET as a Detector of Chemical Species

CHEMFETs (CHEMical sensing field effect transistors) are well known in chemical sensing literature [16]. A number of chemistries have been employed in conjunction with this device. Early activity centered around placement of chelating resins over the gate insulators of these devices. The charge build-up from chelated ions would cause easily detected threshold shifts in the FET sensors. In the examples presented here, a thin film containing immobilized enzymes exposed to a solution for analysis acts as a gate biased by potential of the solution. If the enzyme catalyzes reaction of a target molecule resulting in change in local pH (i.e., generation or consumption of a proton), a resulting change in local solution potential is detected by a change in transistor current-voltage behavior. CHEMFETS have never achieved widespread use. They offer a limited number of targets (enzyme substrates) that provide the necessary change in solution potential. In addition, the ionic component of the electrolyte bath surrounding the sensor is both rich and variable. This gives rise to a noisy sensor and a recognition event that is very difficult to distinguish from background. Use of enhancement mode (normally off) FETs is also a problem, because ionic charging may make it impossible to turn on the device before electrolysis of the bath occurs. In spite of this, the idea of using an FET as an integral part of a chemical sensor has many attractions.

The FET is an active element capable of developing circuit gain. It is known for its high input impedance, which makes it suitable for preamplifier application. Depletion-mode devices ("normally on" transistors) are just as useful as the enhancement-mode CHEMFETs. This solves the "turn-on" problem mentioned above. The FET is small, easily mass produced, and directly integrable in electronic systems. Large numbers of these devices can be packed into small areas (think of gigabit memories!). This enables the types of signal processing described in the last section.

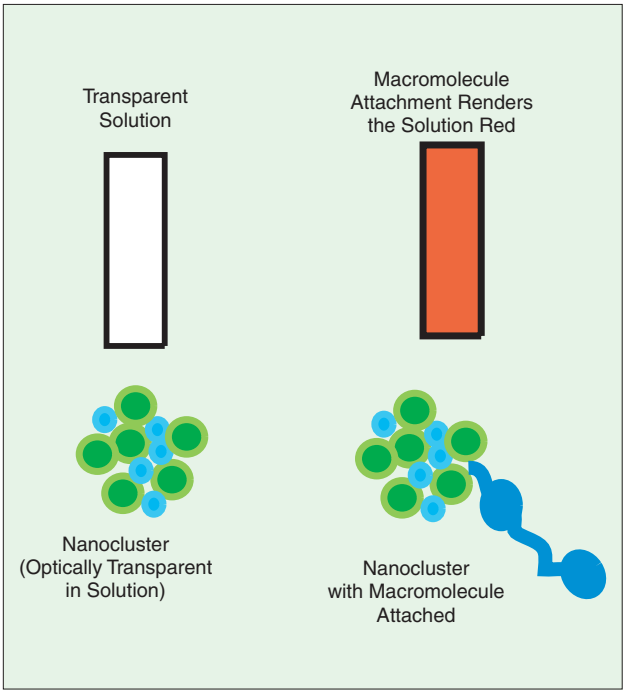
The FET has an added advantage: it can discriminate between charge and the thickness of a deposited film. To see this, consider the basic equation of saturated (depletion-mode) FET operation:

$$I_{ds} = \frac{1}{2}\mu C_{ins}\frac{W}{L}\left(V_{th}^2 - V_{gs}^2\right). \tag{1}$$

The device threshold voltage V_{th} depends on gate charge and on the thickness of the gate insulator C_{ins}, as shown in the expression below:

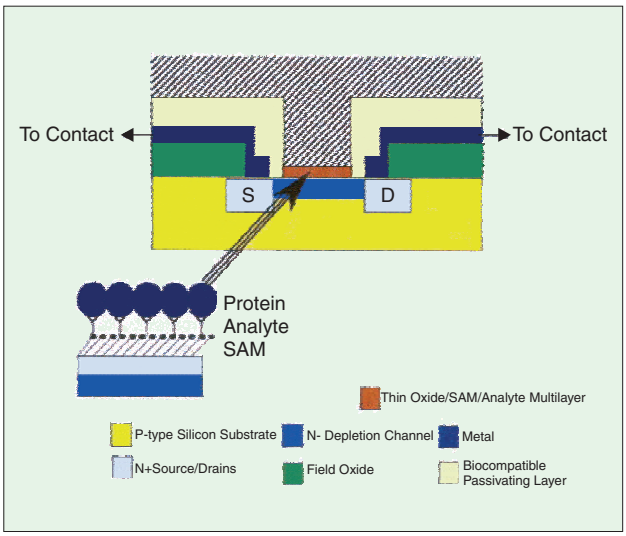
$$V_{th} = \frac{1}{C_{ins}}(qN_d x_d + Q_{ins}). \tag{2}$$

Here, q is the charge on the electron, C_{ins} is the insulator capacitance per unit area, N_d is the doping density of the buried layer, Q_{ins} is the *charge per unit area* in the gate insulator, μ is the channel charge mobility, V_{gs} is the voltage drop between the gate and the source, and W and L are the width and length of the channel. For the gateless operation envisioned, increase in insulator thickness above the active silicon channel decreases C_{ins}. Mobility (μ) is also influenced by charge but as a second-order effect. All of these parameters can be extracted with good precision from experimentally obtained current-voltage characterization (such as those shown in Figure 7).

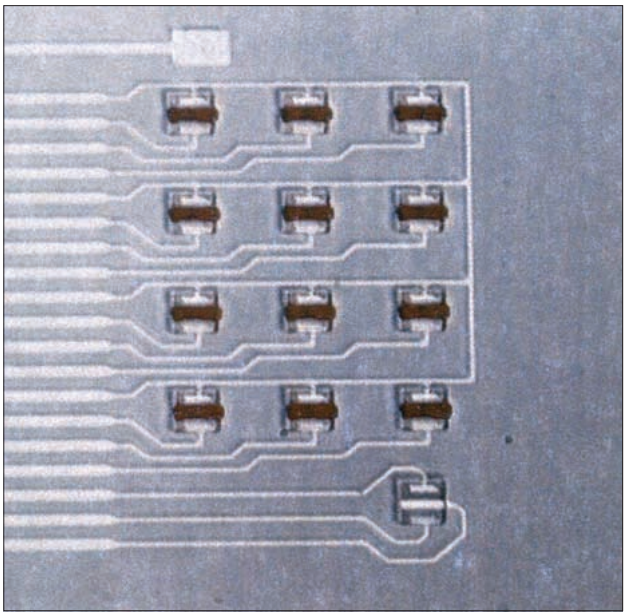


4. Attachment of a single macromolecule renders color to a solution containing nanoclusters.

The ability to extract both parameters (threshold and gate capacitance) is a major advantage over standard "CHEMFETs." In these devices, the materials used to immobilize the analyte were too thick to fully exploit the capacitance signal effectively. In addition, advances in SAM technology have replaced chelating resins as materials of choice for "lock-and-key" sensor technologies reviewed above. These SAMs can be locally applied, and different head groups can be applied to different sensors in an array through "microspotting" machines available today. Thus, multi-analyte arrays are possible.



5. Cross section of the gateless-FET macromolecule sensor. Note the use of the depletion-mode FET and the positioning of the SAM.



6. Micrograph of an FET cluster, the basic design unit repeated throughout a wafer. Note the 12 sensors with discrete drain and common source, one reference device (lower right), and substrate contact. The reference electrode is in the upper left-hand corner. Fine lines are 5 µm wide; sensor grid pitch is 80 × 75 µm.

Device Implementation

We have implemented an array of SAM-treated, gateless FETs. The basic idea of the design is shown in Figure 5.

As these devices may be as small as microns on a side (or smaller), the ability to pack large numbers together for high-density array sensors, or for differential sampling and voting techniques, is obvious. A view of a completed device array is shown in Figure 6.

For this structure, the starting material was a p-type <100> Si wafer. The channel region was 6 µm × 30 µm (L x W) and phosphorous (P) implanted at 60 keV to a dose of 6×10^{11} cm^{-2}. The source and drain contacts were formed by a P implant at 80 keV to an area density of 10^{15} cm^{-2}. Adjacent body contacts were formed by boron (B) implantation at 80 keV to 10^{15} cm^{-2}. A 63 nm thermal oxide layer was followed by a 30 nm LPCVD Si_3N_4 layer (thicknesses determined by ellipsometry). Following a Cr/Au contact metallization, a 600 nm APCVD oxide layer was formed over all. Our present configuration uses 288 devices per chip arranged in six groups (or cells) of four on a 6.5 mm pitch. Each device has a separate and independent drain contact. There is also one gated test structure adjacent to every dozen sensors. Finally, we have included a gold reference electrode in each cell to establish the solution potential.

Detection Protocols

At this time, all immobilization procedures we have used have relied on the facile attachment of thiol (-SH) ligands to Au by means of molecular self-assembly. To accomplish this, a patterned photoresist layer defined the active sensing region for a thin (< 10 nm) PdAu layer sputter deposited onto the wafer and subsequently lifted off in acetone. This step is process critical. It is clearly necessary to have enough gold to attach the thiol. However, if the gold is too thick, it will act as a conductor and inhibit device response. An ultimate aid in deciding the gold thickness is through in-situ monitors of film conductivity.

We describe two experiments here. One is aimed at detection of protein; the other is aimed at DNA detection. Some "notes" on future macromolecular protocols are also presented here.

Chemistries for Experiment I (Protein Experiment). All the devices were exposed to a dilute 1-dodecane thiol ($C_{12}H_{25}HS$) solution in ethanol overnight to form an inert nonreactive surface. This was rinsed with de-ionized (DI) water and dried. 16 devices were exposed to 1 µg/ml streptavidin solution in phosphate buffered saline (PBS) overnight to allow for absorption of the protein to the alkane surface. Four devices were exposed only to PBS as a control. Measurements were taken with the devices under PBS buffer.

Chemistries for Experiment II (DNA Experiment). All the devices were exposed to a 1 µM single-stranded thiolated DNA (a 15-base strand) solution in 0.5 Molar K_2HPO_4/0.5 M KH_2PO_4 buffer for one hour. (DNA sequence: HS-(CH_2)6-5'-GGC-ACT-GCC-TCA-CAA-3'). They were rinsed with a 10 mM Tris, 1 mM EDTA buffer solution. A third of the devices were exposed to 1 fM complementary DNA (5'-TTG-TGA-GGC-ACT- GCC-3'), a third were exposed to 1 fM mismatch DNA (5'- TTG-TGA-GAC-ACT-GCC-3'), and

a third to just the hybridization buffer (1 M NaCl, 10 mM Tris, 1 mM EDTA). Then they were rinsed with 10 mM Tris, 1 mM EDTA buffer solution. Testing occurred with the devices under 10 mM Tris, 1 mM EDTA buffer solution.

An important distinction between this device and its predecessors is its ability to sense capacitance and threshold voltage as separate quantities simultaneously.

Details of the protocol employed. Before use, a plexiglass fluid cell was fastened to the wafer to confine a phosphate buffer solution (PBS) to each cell, allowing independent testing and dosing. An on-chip gold counter electrode was used to establish the solution potential. Testing used a Keithley 617 electrometer to establish the source drain bias and measure the source drain current, and a second Keithley 617 electrometer was used to establish the gate (counter electrode) bias. The devices were demultiplexed into the electrometer in a Keithley 7002 matrix switcher and 7012 4×10 matrix cards. The experiment was controlled by custom software on a laboratory computer over an IEEE 488.2 bus.

An important distinction between this device and its predecessors is its ability to sense capacitance and threshold voltage as separate quantities simultaneously. In order to estimate the V_{th} and C_{ox} parameters used in (1) from our measurements of I_{DS} before and after exposure to ss-DNA solutions or null solutions, we applied a nonlinear Marquardt-Levenberg parameter optimization algorithm [21] to minimize the following functional form:

$$\chi^2 = \sum_i (y_i - y(x_i))^2 / \sigma_i^2, \tag{3}$$

where $y(x_i)$ are the individual values of I_{ds}, as given by (1), and our N repeated measurements of instantaneous current are used to calculate a mean y_i and sample standard deviation:

$$\sigma_i = \frac{\sum_{j=1}^{N} (y_{ij} - y_i)}{N}. \tag{4}$$

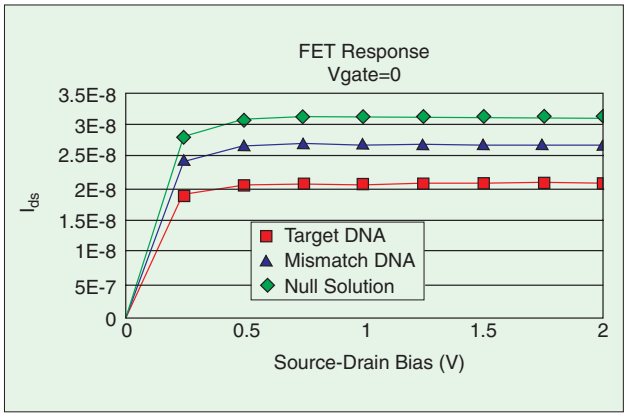
After correcting for a slight error in the voltage source applied across the transistor source and drain, we found satisfactory results by setting V_{gs} equal to 0 (as established), assuming no change in V_{th} due to exposure to the test solution, and allowing only C_{ox} to vary. While χ^2 was (slightly) improved by allowing V_{th} to vary as well, fixing C_{ox} and optimizing only V_{th} gave a relatively poor χ^2. This strongly suggests that our observations can be well modeled by assuming only effects due to displacement rather than charge state at the gate surface/liquid interface.

Results

Typical current voltage (IV) traces are shown in Figure 7. These curves were obtained after the sensor was soaked in control solution (no DNA), a solution containing a mismatched DNA, and a solution containing target DNA. Attachment times were less than a minute (time to saturate).

The traces shown were taken over a time period of 30 seconds under computer control. These traces indicate low-frequency noise was small. Over time, the plots did exhibit some drift, probably due to ionic charging of the gate insulator. For example, if the drain is set at 0.5 V, the drain current will drift on the order of 20% over a period of 45 minutes. In addition, there was a similar variation of response ongoing from device to device at time zero. This is due to minimal passivation above the active channel and the lack of a gate above the active channel to prevent ion impingment. Please note that these results come from "raw data." No signal processing has been done. In spite of this, the FET traces are stable for these devices over short periods of time.

The degree of variability (sample to sample and over time) did necessitate a statistical treatment of the data [22]. The sign test was used to ascertain the confidence level of detecting the targeted DNA. In the sign test, the "null hypothesis" is that a given sample lot exposed to the analyte will be randomly distributed about a mean over all samples (targets and controls). This would indicate an insensitive detector. The statistical marker used here was the parameter-extracted insulator capacitance. The preponderance of analyte-exposed samples are above this mean, suggests that we have achieved detection. By assuming a Poisson distribution of sampled events, we can assume a "confidence" level to the violation of the null hypothesis. For the analysis performed below, "n" is the total number of samples employed in the analysis.



7. Current-voltage response curves for devices exposed to mismatched DNA, matched DNA and buffer. There was little noise in the measurement in all cases. The mismatched DNA showed slight response (which proved not to be significant). The matched DNA showed clear response. The drain-source current is on the y-axis. The source-drain bias is on the x-axis.

The overall experimental results are summarized as follows.

- We detected 1 fM 15-mer single-strand DNA with a confidence level of 92%, as ascertained by the sign test described above ($n = 14$). Sample volume was 30 μL.
- We observed transient transistor response upon addition of single-strand DNA solution with time constant of 4 s (not device limited).
- We detected 1 mg/ml streptavidin with 95% confidence ($n = 17$) in 30 μL sample solutions.
- The same analyses were performed using transistor threshold as the statistical parameter. Using this parameter, the null hypothesis could not be eliminated with roughly 50% confidence. Thus, the device did not respond to surface charging induced by the analyte attachment.

Conclusions

This article has reviewed the basic principles of a number of emerging macromolecular sensor technologies. These sensors can be used in the area of biological warfare threat mitigation and as tools in disease diagnosis. The emphasis is on newer technologies, which make use of a variety of physical principles. These range from "catastrophic" changes in the electron density of states on attachment of a single macromolecule (the nanocluster detector), to exploitation of capacitance change of a surface in solution (the capacitance-sensing CHEMFET).

We focused on the capacitance-sensing CHEMFET as it could meet all the requirements of an ideal sensor for biological studies. It could be made cheaply and in large numbers. It has already shown itself capable of determination of femto-molar concentrations of analyte in small sample volumes (30 μL was the sample volume used here). Small, handheld systems are possible. All of this could lead to rapid, widespread deployment. For example, diagnostics could be accomplished in dental offices during the course of a normal check up. The analyte targets could be present in saliva. These same sensors could be used to give real-time readout of information on potential releases of toxic gases, environmental toxins, or germ warfare agents.

While these devices all show great promise, testing for field use is difficult and involves a considerable statistical database. Issues of false positives and false negatives occurring in large population studies are truly daunting. Challenges appear in the development of specific attachment chemistries, basic signal processing, noise floor reduction, and device design.

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