PERSPECTIVE

Ubiquitous Sensors: When Will They Be Here?

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ABSTRACT Chemical and biological sensors are necessary for making continuous measurements in a variety of settings. A typical sensor comprises a molecular recognition element coupled to a transducer. Binding of the analyte to the recognition element leads to signal transduction. Many sensors employ an extrinsic label to indirectly signal the presence of the analyte. Label-free methods have the advantage that no exogenous reagents are required, making the sensor simple to implement. New label-free transduction methods should facilitate the wider application of sensors. Challenges remain with reproducibility, calibration, and manufacturability. Solving these problems will require an interdisciplinary collaboration between chemists, biologists, biochemists, and engineers. An article by Sailor and coworkers in this issue takes a significant step toward this goal. The availability of inexpensive sensors for wide-scale deployment will transform society in terms of health care as well as home and workplace monitoring.

See the accompanying Article by Alvarez *et al.* on p 3301.

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Published online October 27, 2009.
10.1021/nn901295n CCC: $40.75

Sensors and sensing have become an important and pervasive part of our society. Many papers published in fields as diverse as molecular recognition, nanotechnology, polymer chemistry, microfluidics, and molecular biology mention sensors as potential applications of the work. The present and future value of sensors is enormous. Sensors can measure components of our environment, our health, the performance of our automobiles, and the freshness and quality of our food. For example, oxygen sensors in all new automobiles enable continuous adjustment of the air–fuel mixture to optimize engine performance. The "Holy Grail" in diabetes management is to develop continuous glucose sensors to enable monitoring of an individual's blood glucose levels to allow him or her to adjust their food intake or to deliver insulin on an as-needed basis. A closed-loop system in which insulin pumps are actuated by the glucose sensor would provide diabetics with unprecedented control over their glucose levels and enable a more normal lifestyle.[1] Similarly, sensors for environmental contaminants would allow ventilation systems to recirculate air to minimize exposure to outside unhealthy air. These simple examples underscore the present value of sensors.

Sensors—Official and Unofficial Definitions. Sensors come in three flavors: physical sensors, chemical sensors, and biosensors. Physical sensors are familiar to most people in that they measure such parameters as temperature and pressure. Most chemists do not realize that chemical sensors have an official IUPAC definition:[2] "A chemical sensor is a device that transforms chemical information, ranging from concentration of a specific sample component to total compositional analysis, into an analytically useful signal." A typical chemical sensor contains a receptor that provides the requisite selectivity. Upon binding to the receptor, an analyte causes a response in a transducer. Most sensors operate on the basis of an optical, electrical, or mass change, referred to as the transduction mechanism. Selectivity can also be accomplished by a selective membrane that only allows the analyte of interest to pass through and can be as simple as a size-exclusion membrane. Biosensors are another chemical sensor type and also have an IUPAC definition:[3] "A biosensor is an integrated receptor–transducer device, which is capable of providing selective quantitative or semiquantitative analytical information using a biological recognition element." Many scientists think that making a measurement of a biological sample, such as Na^+ in blood, or measuring a biochemical, such as glucose, constitutes a biosensor. The discussions about such definitions have gone on for decades. Without getting any further into the debate, there are some other aspects of sensors that deserve mention. Unofficially, sensors traditionally have been defined as continuous measurement systems. Many scientists commonly confuse sensing with making a one-time measurement. Finally, sensors usually operate without the need for reagents or sample processing.

There are four aspects to making a measurement: sampling, sample processing, analysis, and data processing. Sensors combine all four of these aspects. Sampling occurs wherever the sensor is placed. Sample processing is typically eliminated because the sensor contains all the necessary components to provide specificity and selectivity. Analysis is accomplished by binding of the analyte to the sensor. Data processing is performed on the signal generated from the sensor.

In many cases, the sensor signal does not arise from the direct interaction of the analyte with the transducer but instead requires the analyte to contain a label that

can be detected. For example, optical sensors may exhibit changes in a fluorescent label in the presence of the analyte and electrical sensors by changes in an electrochemically active label. Sensing methods that employ labels, such as fluorescent dyes, quantum dots, and electroactive reagents, are common but are always indirect measures of the analyte of interest. In contrast, cantilever-based sensors operate by measuring the resonant frequency change that occurs upon binding.[4] This response of the cantilever to binding is a direct method and is label-free. The only species required to give a signal is the analyte. Such label-free methods are much less common but offer the most promise for ubiquitous sensing.

In work described in this issue of *ACS Nano*, Sailor and co-workers have now taken a significant step toward making label-free sensing practical.[5] The Sailor group has worked extensively with porous silicon, a versatile material that can be electrochemically etched with high precision. Since they first reported the principle,[6] the Sailor team has prepared numerous different porous silicon-based sensors with sensitivity to a diverse suite of various analytes including chemical vapors and proteins. Unfortunately, porous silicon is not easily prepared in most laboratories. More importantly, porous silicon forms an oxide layer of SiO_2, which is susceptible to degradation under most aqueous reaction conditions, the medium one wants to employ for important analyses, such as many clinical or environmental samples. In the present work, the group reports an optical label-free transduction system based on anodized aluminum that employs such interference-based sensing yet makes it both practical and accessible. Aluminum is known to form nanopores when it is anodized.[7] The resulting material

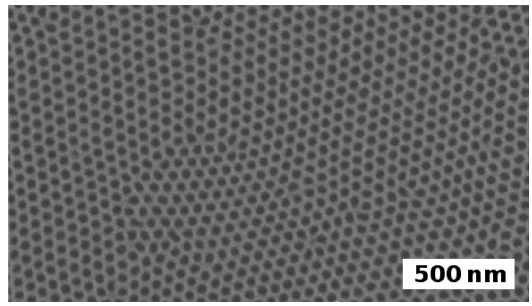

Figure 1. SEM image of nanoporous alumina etched at 25 V for 24 h in 0.3 M H_2SO_4. Reproduced from ref 8. Copyright 2008 American Chemical Society.

contains a highly regular pore structure (Figure 1). Anodized aluminum has been available for many years; it is cheaper, easier to prepare, and more stable than silicon.

The present work by Sailor and co-workers describes sensors prepared with 60 nm pores and 6 μm depths. The nanoporous material consequently has a high surface area. The anodized aluminum contains a surface layer of Al_2O_3, which is highly stable compared to the SiO_2 layer on the porous silicon used in previous studies. In addition, the anodization procedure is considerably simpler than the methods used to prepare porous silicon.

In both the porous silicon and porous aluminum sensors, the authors describe how they use Fabry−Perot interference to detect binding to the surface of the porous substrate. Essentially, when white light shines on a structured nanoporous surface, reflection from the surface creates an interference pattern. Any change in the thickness of the layer or the refractive index at the surface causes a shift in the interference pattern and the wavelength of the reflected light. Sailor and colleagues demonstrate the ability to modify the alumina surface with specific binding receptors for proteins and show that the sensors recognize only the analyte protein and do not respond to other proteins. Although the alumina surface is susceptible to acidic conditions, the authors rightly point out that it is stable in the neutral or slightly basic conditions typically encountered for bioassays such as proteins and nucleic acids.

Significant Issues and Challenges. There are still some significant issues and challenges that need to be addressed in the chemical and biosensing field. Nonspecific binding is a big one. Although Sailor and co-workers discuss nonspecific binding in their *ACS Nano* paper, they do so in the context of a limited set of control experiments.[5] Nonspecific binding of species that are not targeted by the binding reagent (*i.e.*, the receptor) gives a false positive signal. Such signals are notorious for limiting the specificity and sensitivity of many assays, including most commercial ones. Immunoassays are particularly susceptible to nonspecific binding as they are directed toward proteins contained in complex samples such as blood. These proteins stick to most surfaces, due to their charge, their large size, as well as the high concentrations of some proteins such as albumin. While surface modifications, such as modification with poly(ethylene glycol) (PEG) or bovine serum albumin (BSA), help prevent nonspecific binding to

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some extent, ultimately, the low levels of nonspecific protein binding provide a floor to the sensitivity that can be achieved with most affinity-binding schemes. In the Sailor paper in this issue, specificity of the sensor is a consequence of the receptor protein used,[5] but, in principle, the pore size of the nanoporous alumina could be employed to provide an additional level of specificity by excluding larger proteins from interfering. Such an approach may provide a simple general surface treatment to prevent some forms of nonspecific binding. In the meantime, nonspecific binding remains a serious problem that would benefit from a universal solution.

Another challenge is calibration. In the Sailor work, the authors show that the sensors are specific to the desired analyte,[5] but they do not discuss quantification. While for some analytical measurements it is sufficient simply to *identify* whether a substance is present or absent, or even if it is present at a particular level or threshold, it is often necessary to *quantify* the amount of material in a sample. For quantification, sensors need to be calibrated. Calibration is required because all sensors differ from one another due to variability in the manufacturing process; it is virtually impossible to make two sensors identically. Consequently, each sensor's signal needs to be calibrated with regard to analyte concentration, a tedious and time-consuming process. Moreover, sensors have a tendency to drift when they are stored or used, requiring regular periodic calibrations. Ideally, sensors would be calibrated intrinsically, either by a reproducible manufacturing process or by incorporating an internal signal against which the sample signal can be compared. The techniques such as those described by Sailor and co-workers for preparing nanostructured materials, particularly with the precision provided by the anodization procedure, bode well for reproducible sensors that may eventually be calibration-free.

Before sensors can reach their full potential, they must become simpler and much less obtrusive.

Reversibility of the sensing components is another challenge. Receptors must have an affinity for the analyte in the concentration range of interest but must be able to release and to rebind analyte molecules when the solution being analyzed changes. For high-sensitivity measurements, the sensor requires high-affinity receptors, which usually requires receptors with low OFF rates. Such low OFF rates make response times slow such that the sensors are measuring an average concentration over a long time period rather than making an instantaneous measurement.

Before sensors can reach their full potential, they must become simpler and much less obtrusive. Individuals do not want to know that they are constantly being interrogated and scanned nor do they want to take time out of their lives to perform analyses, even one so simple as a finger prick to obtain their glucose level. Until these conditions can be met, the use of sensors may be limited to the trained specialists that can operate them.

Recent Trends for Chemical Sensors. One major trend in modern analysis is to take a more holistic approach to measurement. For example, it is insufficient in most cases to analyze a sample for a single component; rather, it is important to determine a variety of analytes in order to provide a more comprehensive characterization of the sample of interest. High-density arrays have been developed to address the need to make measurements of hundreds to millions of analytes simultaneously.[9] For example, DNA microarrays are used for performing comprehensive genetic analyses, but since these arrays are used only once, they are not considered to be sensors. For most analyses, many analytes co-occur and it is the overall *pattern* of analyte concentrations that enables a sample to be fully described. In order to make multianalyte measurements, many different sensors are required, each with specificity toward its target analyte. This challenge is monumental, as with only a 1% cross-reactivity of each interfering analyte with a given sensor, the complexity of most samples (*e.g.*, blood) can create a complicated response pattern. Although modern pattern-recognition algorithms can process such data,[10] the sheer complexity of samples with hundreds of components makes the identification of each analyte an impossible task without sensors with exquisite specificity.

An additional challenge with multianalyte sensing using the porous aluminum approach is the need to create sensor arrays. Array preparation would be onerous as it would require one to be able to attach specific binding reagents to different regions of the porous aluminum and to collect and to distinguish signals from the many sensing regions simultaneously or at least sequentially, with a fast interrogation time for each sensing element in the array. Optical sensing arrays perhaps have the biggest advantage in this regard because of the ready availability of array detectors such as charge-coupled device (CCD) and complementary metal−oxide−semiconductor (CMOS) cameras; however, the optical signals must be intensity-based (or at least converted into an intensity-based format). Cantilever arrays and electrode arrays are more difficult to prepare with distinct specificities, and each sensing element must be capable of individual interrogation. Wiring such arrays, while possible, complicates the system.

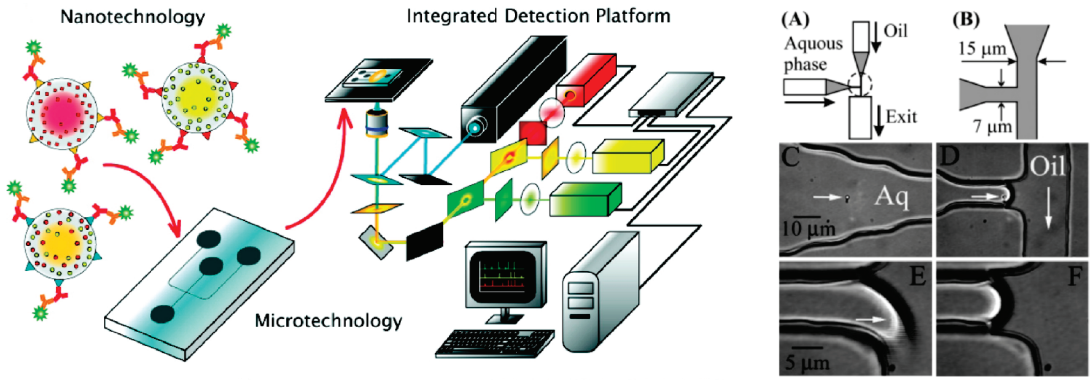

Figure 2. Left: A nanoparticle- and microfluidics-enabled diagnostic system for high-throughput, multiplexed biomarker detection. Reproduced from ref 13. Copyright 2007 American Chemical Society. Right: A microfluidic design used for the encapsulation of single micro- and nanoparticles into droplets. Reproduced from ref 11. Copyright 2005 American Chemical Society.

Another trend is with fully integrated sensing *systems*. As discussed above, sensors are designed to perform an analysis without the use of external reagents. Oftentimes, it is not possible to make a measurement without some type of sample processing. For example, if one wants to measure the intracellular protein concentration in a cell population, the cells must be lysed to make the proteins accessible. Simply inserting a sensor into a sample containing cells will not provide access to the proteins. Consequently, systems that enable sample preparation are desirable as a front-end capability. In particular, microfluidics technology is a powerful tool for preparing cells,[11] separating different cell types, isolating and amplifying DNA,[12] separating cell debris from soluble material, and separating proteins, nucleic acids, and small molecules from one another. The sophisticated capabilities provided by microfluidics, combined with integrated sensors downstream of the sample preparation features, suggest that lab-on-a-chip sensing systems will be available in the future (Figure 2).

Molecular recognition is a vibrant field that has a large impact on chemical sensing. The need to develop specific receptors for different analytes is a major challenge. There have been some remarkable efforts with molecular design of complex structures for small organic compounds,[14] ions,[15] peptides, and nucleic acids.[16] Such receptors need to be developed only once for each analyte, but there are potentially tens of thousands of substances that need to be measured, ensuring that molecular recognition will be a prolific field for a long time to come.

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Another trend of particular relevance to nanoscience and nanotechnology is the need to make measurements of extremely small volumes. For example, it is desirable to make measurements of single cells to understand cell-to-cell variability. A bacterial cell has a volume of several tens of femtoliters. An analyte concentration in the micromolar range (a high concentration) in such a small volume represents only a few thousand molecules. For the more typical nanomolar to picomolar concentrations of proteins in cells, only a few to a hundred molecules may be present. Stochastic processes in a cell could easily account for large differences in concentrations of such analytes between cells. Diluting such small volumes extends the measurement time because of mass-transport issues. Poisson sampling issues can also arise if such a small number of molecules is diluted into a larger volume; the absolute number of molecules in a given volume can be zero! The need for making measurements of such small volumes is a challenge to nanotechnologists. The present work by Sailor and coworkers is limited by the rather large size of the pores necessary to immobilize the receptor while still enabling analyte access to the pore.[5] This size scale is dictated by the transduction mechanism and is constrained to nanometer dimensions.

THE FUTURE OF CHEMICAL SENSING

Looking to the future, sensors will become pervasive. Sensor-laden buildings will enable constant monitoring of all aspects of the environment, including climate and air quality. Sensors will provide surveillance and protection against terrorist attacks of both chemical and biological agents. Such sensing

systems will be put in place first in airports, train stations, and public transportation systems, followed by all public and commercial buildings. Issues of sensor longevity and power will need to be solved before such systems can be implemented reliably.

People will have continuous and enhanced monitoring of their health through implanted sensors and sensors embedded in devices such as cell phones, watches, and even household fixtures. Japan already has a "smart toilet" available commercially that performs a glucose analysis on urine. With a more sophisticated suite of sensors installed, one can imagine that an individual's health could be monitored at least daily with no change in the individual's behavior or activities. In addition, data fusion and processing from the entire suite of sensors will enable continuous reporting of health status to both the individual and to the appropriate health care provider. If a deviant result occurs, the individual's physician will be informed electronically in order to schedule a follow up with the patient.

The field of chemical and biological sensing is an active one involving many different fields and technologies. There are certainly transduction schemes that have not even been contemplated but that will enable sensitive, specific, unobtrusive, and ubiquitous sensing in the future. Toward this end, Sailor and co-workers' work makes a lot of sense.

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