Update

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# Nanosensors: Evolution, not Revolution ... Yet

**Promising nanotechnology-enabled sensors, monitoring devices and analytical instruments continue to advance toward commercialization for diverse industrial, environmental, medical and military applications — but hurdles remain.**

Although they are invisible to the naked eye, engineered nanoscaled materials made from such common substances as metal oxides, polymers, ceramics, and novel carbon derivatives (*e.g.*, carbon nanotubes) demonstrate many desirable physical properties. For instance, compared to their macroscaled counterparts, nanomaterials may offer greater reactivity, optical absorption and catalytic efficiency; increased electrical conductivity, hardness, wear resistance, strength and flame retardancy; and improved barrier and magnetic properties.

These unique characteristics confer performance advantages in a wide range of applications. In recent years, nanotechnology-related advances have enabled the commercialization of precision chemical-mechanical polishing (CMP) slurries used in semiconductor manufacturing, as well as catalysts, advanced composite materials, ceramics, paints and coatings, cosmetics, sunscreens and other personal-care products. The healthcare field has benefited from a diverse array of diagnostic and therapeutic advances related to early-stage disease detection, improved drug delivery, and streamlined drug discovery.*

So it's no surprise that the research community has been hard at work to exploit the extraordinary surface-area-to-volume ratios and other unique properties of numerous nanostructures — including nanoparticles, carbon nanotubes, nanowires, nanoscaled thin films, semiconductor quantum dots, and nanocantilevers — to develop state-of-the-art nanosensors. Specifically, with their small size, light weight and large reactive surface area, such engineered nanostructures have been shown to improve — by orders of magnitude — the sensitivity, selectivity and response time of sensor technologies (thereby providing an advantage over slower, more costly, laboratory-based analytical methods), and to dramatically reduce the size, weight and power requirements of the resulting monitoring devices compared to conventional, macroscaled alternatives.

Today, numerous nano-enabled sensor designs are being pursued to improve industrial process monitoring and leak detection, environmental monitoring (air and water quality), food-quality surveillance, and medical diagnostics, and to enable the reliable, real-time detection of chemical, biological, radiological and nuclear hazards for military and anti-terrorism applications.

## Exploiting surface area

When familiar items are expressed in terms of nanometers, the unimaginably small dimensions of the nanorealm become more apparent. For instance, the page this article is printed on is about 100,000 nm thick, the average human hair is roughly 10,000 nm in diameter, most proteins have dimensions from 1 to 20 nm, a single gold atom is about 0.33 nm in diameter, and a single hydrogen atom has a diameter of 0.04 nm.

"To get an idea of the enormous surface area that comes from the downsizing, consider single-walled carbon nanotubes, which have a surface area of 1,600 m$^2$/g. Just 4 g of nanotubes has the same surface area as a football field," says Meyya Meyyappan, chief scientist for exploration technology at NASA Ames Research Center (Moffett Field, CA; www.ipt.arc.nasa.gov), who until last year was the director of the Center for Nanotechnology at NASA Ames. Nanoparticles of metal oxides and other conventional macroscaled materials are similarly well-endowed when it comes to extraordinary surface-area-to-volume ratio.

"Many types of sensors are dependent on sorption of the target analyte for detection, and sorption is dependent on surface area and surface chemistry," says Glen Fryxell, staff scientist at Pacific Northwest National Laboratory (PNNL; Richland, WA; www.pnl.gov). Making the sensor interface out of a nanoporous or nanocrystalline material "makes it possible to increase the surface area substantially (by multiple orders of magnitude), thereby potentially increasing the signal intensity that is possible from that sensor by a similar factor," he adds.

"Today, the chemical gas sensor market is largely dominated by macroscaled tin-oxide-based sensors and polymer-based sensors, yet neither is that great in terms of sensitivity, and the oxide-based sensors require operation at elevated temperatures (around 200°C)," says Meyyappan. By comparison, nanosensors that use nanoscaled particles of tin oxide, indium oxide, zinc oxide and other materials show

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* See also the author's article on the use of nano-related advances for improved cancer diagnosis and drug delivery, "Nanobiotechnology: Cancer's Newest Deadly Foe," *CEP*, Feb. 2006, pp. 43–47.

greater sensitivity, and they can be smaller, which has advantages in terms of simplicity of design and operation, reduced power consumption, and even room-temperature operation.

"Today's promising nanosensors have unprecedented sensitivity, but on their own, many 'unadorned' nanomaterials and nanostructures are rather poor on selectivity at this time," says Thomas Thundat, group leader and corporate fellow in the Nanoscale Science and Devices Group Biosciences Div. at Oak Ridge National Laboratory (ORNL; Oak Ridge, TN; www.ornl.gov). One of the challenges associated with using carbon nanotubes is that "they are not naturally selective for anything, so nanotube-based sensors invariably require some type of chemical engineering intervention," adds Meyyappan.

Investigators worldwide have made enormous strides toward functionalizing the nanotubes — by modifying their surface (*e.g.,* by adding a coating), or by doping atoms (such as palladium) into the nanotubes — to make them more selective to specific analytes. Similar efforts are underway to modify other types of nanoparticles. For example, the conductivity of quantum dots and the wavelength of the light they emit can be tuned by doping the dots with foreign atoms or by modifying optical excitation techniques or external electrical fields used to activate them.

## Multi-analyte sensor arrays

Most conventional chemical sensors are optimized for the detection of a single chemical species. By comparison, many nanosensor designs are able to not only detect the target chemical, but also to distinguish among multiple chemical species in a sample stream. This multiplexing capability offers a vast improvement for real-time chemical-exposure monitoring and disease identification.

"Nanosensors are able to detect multiple analytes at the same time because they allow an array of minute sensors — potentially in the hundreds or thousands — to be used within a single monitoring device," says Thundat. "By comparison, efforts to monitor numerous target gases using numerous standalone conventional sensors is a very bulky and costly approach."

To develop nanotube-based sensors that can effectively discriminate among target analytes and produce a unique signature upon exposure to a sample, many investigators are developing sensor chips that carry up to 32 different nanosensors on a single 1-cm by 1-cm chip. Each nanosensor is tuned for a specific chemical or biological agent — using a mix of nanowires or nanotubes that contain different chemical coatings or functional groups, or as a result of chemical and/or physical differences.

"Today, very powerful signal-processing and pattern-recognition algorithms are already available, so when you expose this nanosensor array to a single ambient sample, the device can generate a unique fingerprint that identifies the target molecules," explains Meyyappan (Figure 1).

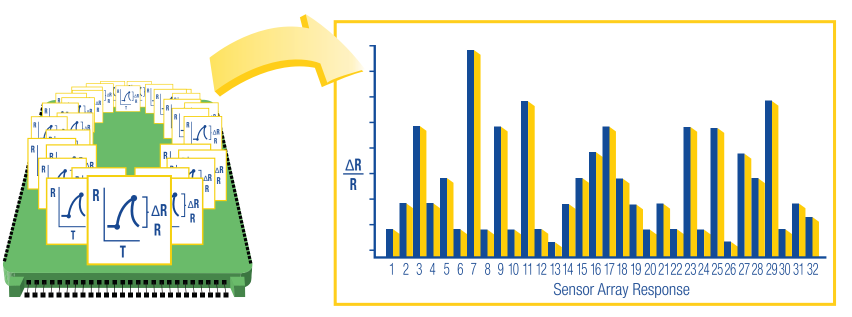
The availability of ultra-compact, low-power nanosensor-based monitoring devices is expected to eventually

### QUANTUM DOTS: A NANO-ODDITY

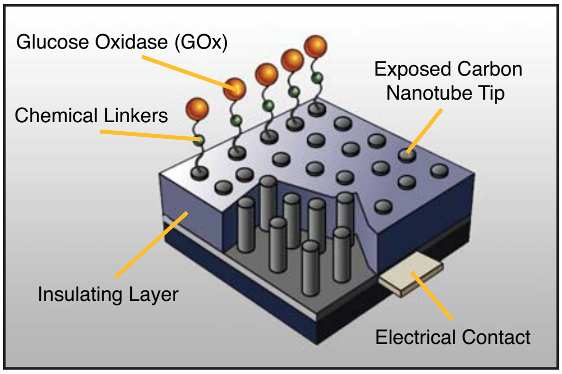
Over the past two decades, the evolution of fluorescent semiconductor nanocrystals known as quantum dots has helped to usher in a new era in laboratory and biomedical diagnostics. Quantum dots are small, tuneable semiconductor crystals with dimensions on the order of a few to a few hundred nanometers. They are typically made of cadmium selenide, cadmium sulfide, or cadmium telluride, but more recently other materials, such as the heavy-metal-free indium gallium phosphide (InGaP). Quantum dots typically have an inert polymer coating that both safeguards human cells from potential cadmium toxicity and facilitates the attachment of a variety of molecules to foster the preferential uptake by targeted cells during *in vivo* applications.

The defining characteristic of quantum dots is their ability to demonstrate different, custom-designed optical properties as a result of changes in shape, size and composition. For instance, simply by controlling their size, quantum dots can be made to emit light in different colors upon optical or electrical excitation. This allows them to be used to color-code and track different cell processes, thereby providing high-resolution cellular imaging, observation of individual molecules, and the ability to track different cancers or stages of cancer.

Quantum dots have generated considerable interest for optical biodetection. To date, work with quantum dots has largely focused on biomedical applications (*i.e.,* as labels for the detection of DNA and immunosensing of disease biomarkers, and to improve biomedical imaging), but their use is also being investigated for the real-time detection of biowarfare agents, says Yuehe Lin, staff scientist at PNNL.



■ Figure 1. A device that integrates a vast number of nanosensor elements, each functionalized for a different target analyte, together with sophisticated pattern-recognition software, can serve as a state-of-the-art "electronic nose" to monitor multiple analytes simultaneously. Source: Jing Li, NASA Ames.



■ Figure 2. This glucose sensor couples the reactivity of the glucose oxidase enzyme with the high conductivity of carbon nanotubes and the sensitivity of a vertically aligned nanoelectrode array. Source: PNNL.

open the door for the use of massively parallel sensor arrays. In such a system, hundreds, thousands or even millions of high-sensitivity nanoscale sensing elements would be widely distributed to simultaneously monitor a large number of chemical, biological and radiological analytes in a given application, with increased reliability, sensitivity, accuracy and selectivity.

Miniaturization brings other advantages, as well. For instance, the tiny devices address the weight considerations that are particularly important for military and airline applications. And the use of rugged, reliable, low-cost sensors allows for the long-term, unattended operation of maintenance-free sensor networks in harsh environments or remote locations.

Miniaturized nanosensors are also ideal for use in mobile or handheld (even disposable) monitoring devices for a host of applications — extending unprecedented detection capabilities to a personal level, to provide real-time monitoring for the presence of explosives or the potential exposure to chemical and biological warfare agents (such as anthrax and smallpox) or radiological hazards.

Opinions vary as to which nanosensor methodology, and which application, will emerge as the front-runner in the race for commercialization.

"The end user doesn't really care what's inside the sensor. They're just looking for unambiguous results from a monitoring device that can provide greater sensitivity, greater selectivity and absolute discrimination, low power consumption, compact design, and low capital and operating costs," says Meyyappan. "Once nanosensors become commercially viable, they'll open up a whole host of opportunities for chemical sensors, and they will be able to address the wide-open demand for improved chemical gas sensors that exists in the monitoring arena today."

"Today, a lot of companies are working to develop nanosensors for use in biomedical diagnostics, because there tends to be a more clearly defined path to market that makes it easier for investors to evaluate the technology, and more clear valuation metrics that make it easier to raise capital," says Michael Holman, research director for Lux Research (New York, NY; www.luxresearchinc.com). "Health-care-related and biomedical applications also tend to be less price-sensitive, so there's a perception that users will be willing to pay more for a premium testing mechanism that's quicker and more-sensitive than today's prevailing lab-based test methods, which are costly and time-consuming."

In contrast, Yuehe Lin, staff scientist at PNNL, predicts that small, multiplexed nanosensors that enable the fast, accurate detection of toxic chemical species (for industrial and environmental monitoring and to improve homeland security) will be the first to cross the commercialization threshold. "From a technical standpoint, detecting target analytes in air or water is not as complicated as working with biological samples such as blood," he says.

**Nanotube-based sensors: on the brink**

Carbon nanotubes have been the darling of the nanotechnology community since their discovery in 1990, thanks to their unique mechanical, electrical and other properties. For instance, in addition to their extraordinary surface area, they boast strength ranging from 20 to 100 times that of high-strength alloys and steel; exceptional resilience, with the ability to be straightened without damage after extreme bending; ultralight weight; tensile strength around 200 gigapascal; and stiffness five times that of steel.

With this remarkable suite of properties, and their ability to be chemically or biologically modified to make them more-sensitive to target molecules, nanotube-based sensors are regarded by many industry observers to be the most likely to make their way to widespread commercial availability.

"Because conductivity, capacitance, dielectric constants and other properties of carbon nanotubes change as vapors or gases are adsorbed, monitoring one of these properties forms the basis for sensing," explains NASA's Meyyappan. "The use of an array of sensors, combined with pattern-recognition algorithms, makes it possible to develop an 'electronic nose' type of sensor."

Lin and his coworkers at PNNL and Boston College have developed a novel nanotube-based glucose monitor (Figure 2) that can selectively detect glucose in the presence of other bioactive compounds. The device can potentially be used for the rapid and accurate detection of glucose levels in biological fluids for diabetic patients.

Lin's team fabricated the device's vertically oriented nanotube array by growing nanotubes directly on a patterned catalyst, and can adjust the density of the array by changing the density of the catalyst. Next, they attached glucose oxidase enzymes to the tips of the nanotubes, which were grown

through a chromium-coated material that acts as an electrode contact. The tips of the aligned carbon nanotubes protrude through an insulation layer, allowing them to come into contact with the sample.

"Glucose in the sample starts a catalytic reaction with the enzyme, the energy from which is conveyed through the nanoectrodes," says Lin, who was the principal investigator for this nanosnsor. "The stronger the signal, the higher the sugar level."

"Using this approach, nanoelectrode arrays consisting of millions of vertically aligned nanotubes, each acting as an individual electrode, have been fabricated using a non-lithographic method. This leads to fast response and higher signal-to-noise ratios (higher current density generated by the sensor)," he explains.

The array holds about one million nanotubes integrated on a microchip electrode that measures 5 mm by 5 mm. This sensor array has been integrated into a portable unit using PNNL-patented technology.

Another portable nanotube-based sensor that acts as an ultrasensitive approach for detecting exposure to lead has also been demonstrated at PNNL. "Because lead ions are soluble in biological fluids and can be concentrated on the tips of the nanotubes by electrodeposition, the sensor has been shown to accurately detect lead poisoning in three minutes or less," says Lin.

Meanwhile, NASA Ames "has successfully demonstrated a nanotube-based chemical sensor for detecting nitrogen dioxide, sulfur dioxide, ammonia, methane, acetone, benzene, toluene, formaldehyde, hydrogen peroxide, nitrotoluene and others," says Meyyappan. He notes that this technology is nearing commercialization, and is currently being transferred to industry through a licensing agreement with Nanoshield, Inc. (Palo Alto, CA).

An inherent advantage of the NASA nanosensor, according to Meyyappan, is that it uses non-aligned bulk nanotubes that are randomly applied and immobilized on the electrode surface using solution casting by ink jetting. "You don't have to grow aligned nanotubes on each substrate, so the diode is much simpler to fabricate," he says. "If you have to rely on electric fields or flowing fluids to align nanotubes during manufacturing, that could end up busting your budget, and your proposed sensor design will be dead on arrival. The same goes for three-terminal devices and other complex designs."

### Nanoscaled thin-film sensors

Thin-film nanosensors typically rely on a nanocrystalline or nanoporous sensing film, 100–500 Å thick, which interacts directly with the ambient environment that is being monitored. Such sensors operate by measuring changes in electrical conductance that occur when gases adsorb, desorb, and/or react at the surface of the semiconducting films. In recent years, a wide array of nanoscaled thin-film sensing materials — including various polymers, gold, platinum, diamond, titanium, and iridium oxide — have been successfully demonstrated.

"Nanoscaled thin films, particularly those comprised of polymers and certain oxides, are already being used to make a variety of sensors today," says PNNL's Fryxell, who notes that the lab is currently working with PANalytical (Almelo, The Netherlands; www.panalytical.com) to develop functionalized nanoporous thin films (FNTF) for enhanced x-ray fluorescence (XRF) analysis. He notes that the use of these thin films "allows heavy metals to be selectively preconcentrated for XRF analysis, thereby extending the limits of detection from the ppm level to the sub-ppb level." The prototype product is expected to be in commercial production sometime in 2009.

PNNL has also developed a promising electrochemical nanosensor based on a silica thin film whose nanopores have been functionalized with a thiol monolayer that selectively binds lead and other toxic heavy-metal ions from solutions (Figure 3). The silica thin film is synthesized using a surfactant-templating process, in which a silica sol-gel is first spin-coated onto the surface of a gold microelectrode. The cubic lattice — whose pores have a precise size (77 Å), structure and orientation — is formed when the sol-gel surfactant is removed by calcination, explains Fryxell.

Thiol functional groups are then immobilized onto the thin film through a self-assembly process, which "requires no additional additives or binders, and allows surface layers to be constructed in a manner that is highly reproducible. This is very important for any two-dimensional surface reaction to be successful," Lin points out. The thiol-functionalized thin film then acts as the electrode sensing layer for the detection of toxic heavy metals

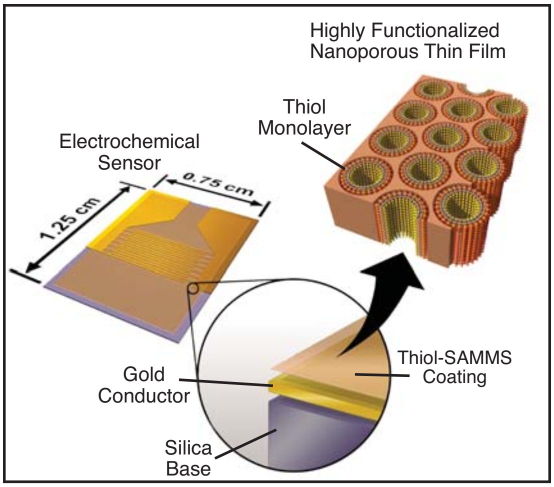


Figure 3. A two-step process is employed to make this nanoscaled lead sensor: First, a mesoporous silica film is deposited by spin-coating onto an electrode surface. Then, thiol functional groups are immobilized inside the film pores via self-assembly chemistry. Source: PNNL.

(such as lead, mercury, copper and cadmium) in contaminated water or biological samples, using adsorptive stripping voltammetry (AdSV) as the detection technique.

"Silica materials are becoming more-attractive electrode modifiers than zeolites due to their much larger pore openings, which improve diffusion and accessibility for larger analytes or liquid-phase sensing, where an analyte diffusion rate is much slower than in a gas phase," says Lin. "In this device, the binding affinity of lead to the thiol ligands performs the preconcentration step under an open circuit, without additional electrolytes."

He says that PNNL is looking for a commercial partner to bring this nanosensor to market. His colleague Lin adds that "by coating the nanomaterial surface with other functional groups, this sensor design can also be used to detect arsenic and uranium."

## Out on a limb

Another emerging category of nano-enabled sensors are based on microcantilevers and nanocantilevers — which look like tiny beams or diving boards with one surface coated with a chemical that will attract and bind the target molecule. When molecules of interest bind to them, these small structures deflect, and the deflections are either observed directly by laser light or correlated to detectable shifts in other physical properties of the beam, such as resonant vibration frequency.

Microcantilevers and nanocantilevers represent the simplest type of micro-electro-mechanical systems (MEMS) that can be machined and mass-produced using conventional techniques. "The MEMS fabrication infrastructure, largely based on photolithography and micromachining techniques that are similar to those used to integrate mechanical and electronic parts on the surface of a silicon chip, has become tremendously well-developed in the last 25 years," says Meyyappan of NASA Ames.

In recent years, such devices have been demonstrated by numerous investigators. Since arrays of microcantilevers can be arranged on a single chip, they may be useful for multi-target detection.

In one example, Thundat and his colleagues at ORNL are working to develop microcantilever sensors that can be used in handheld devices to detect explosives at airports and other locations, as a more readily accessible, lower-cost alternative to cumbersome mass spectrometers.

## Scaling the scaleup hurdles

While nanosensors have the potential to revolutionize the detection of toxic constituents in a range of applications, even the most-promising nanosensor breakthroughs face considerable technical hurdles before they can be cost-effectively mass-produced and expected to perform reliably under harsh, unpredictable real-world operating conditions. "Many of today's promising nanosensor concepts are well past their infancy, but most are not ready for prime time yet," says Thundat.

Among the many challenges is the need to perfect cost-effective, reproducible fabrication methods that can ensure the desired composition, structure and purity, lower the cost of the engineered nanomaterials, and increase production yields in order to drive down costs. "For some classes of nanomaterials and engineered nanostructures, scaleup of production remains a major issue," observes PNNL's Fryxell. However, many industry observers agree that — as is often the case with emerging technologies — once the technical details are worked out and commercial-scale production is made possible, economies of scale will eventually help to bring down the overall costs associated with these specialty materials.

Lin remarks that in the long run, material cost considerations may not be a major obstacle for nanosensor fabrication, because individual sensor arrays typically require such a tiny amount of the enabling nanomaterials. As an example, Meyyappan cites a NASA Ames nanotube-based gas sensor that is on the brink of commercialization, which "uses such a small amount of nanotubes that even if bulk nanotubes cost $1,000/g, just 1 g would be enough to produce a billion nanosensors."

Lin also points out that many of the prevailing procedures and protocols being investigated to functionalize the engineered nanostructures are complicated. Furthermore, he adds that the long-term stability of some nanosensors may be compromised by issues that could potentially arise between the inorganic nanostructures and biomolecules (such as enzymes or antibodies) attached to them.

"Chemical and biological sensing is a very complex process. A fully engineered monitoring system will require modules to collect the target molecules and bring them to the sensor, the nanosensor array to carry out detection, a mechanism to refresh and regenerate the nanosensor as needed, and data-management capabilities to communicate and display the information," explains Thundat of ORNL. "Integrating all of these aspects presents the next set of challenges."

Fryxell of PNNL add that "the integration of nanomaterials is further complicated by the need to connect them to the macro world."

Thundat says, "There are still many unanswered questions, but things are happening every day, and since every breakthrough helps us to answer more of these questions, it's a very exciting time to be working in this area."

Many industry observers agree that the question is not "if?" but "when?" these novel devices will start to become widely deployed in real-world applications. CEP