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DynamicSilicon

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The Investor's Guide to Breakthrough Micro Devices

MEMS and the Electronic Nose

I step out of my car and head for the weekend farmers' market, a couple of blocks away near a small park. My cell phone emits a characteristic beep that isn't a call. It is a message *from* the cell phone. I pull it out and read the display. "Allergy warning: spore levels above threshold two blocks ahead." My phone knows where I am; it knows the direction I'm headed, so it checks the database maintained by the park's environmental sensors against my allergies. Silently thanking the park's sensors and Internet-accessible database, I change plans. That's the way it might work in a few years. Today I know I have a problem when my eyes start to water, but then it's too late.

Terrorists—as if Mother Nature's arsenal wasn't enough! There's immediate interest in detecting and preventing attacks by terrorists armed with anthrax and smallpox. Of course, anthrax and smallpox aren't the only possible agents. There are two types of agents: biological agents (bacteria and viruses) and chemical agents (toxins). Biological agents have DNA or RNA; toxins do not. This implies different detection methods. Tests for biological agents don't always look directly for the agent. A test might detect chemical byproducts of the bacteria's metabolism.

According to Western counter-proliferation agencies, 23 bacteria, 43 viruses, and 14 toxins are potential threats (*IEEE Spectrum*, October 2001). In addition to the identified threats, 24 nations are known to possess or are developing biological agents. New agents can show up any time. There's a lot to test for; and tests must track new developments—implying a delay in building and fielding detectors.

I've been enthusiastically describing Moore's law advances in semiconductor electronics and in microelectromechanical systems (MEMS). I've been saying that MEMS will be the sensors and actuators for a new generation of electronic devices. Couldn't we build an "electronic nose" that sniffs for harmful particles, and warns us? We could. The electronic nose for a building could be installed in the air-handling system. It could detect suspicious agents in the air and shut down the ventilation system until the agent is analyzed further. Electronic noses can detect chemical agents directly and can detect biological agents by the chemical byproducts of their metabolism. As the technology gets cheaper, it could be integrated into today's common smoke detector. There's progress in electronic noses, but the problem is a tough one.

For light and sound, sensing is straightforward. Light has frequency and intensity, so does sound. The energy in these signals is readily converted into electrical signals either by our senses or by electronic sensors. The same is true for pressure and for temperature. There's something that can be measured and quantified; light, sound, pressure, motion, and temperature have units and standards. For smells and tastes, it's different. Smell and taste are subjective; there are no units and no standards. There's no individual characteristic to measure and to convert. Further, there's an incredible variety of background "noise" that comes with any sample.

Biological agents

An unknown bacterium lurked in the water that supplied the air conditioner's cooling towers. The cooling towers and the hotel's air-handling system turned the water (with the nasty bacteria) into a deadly aerosol and delivered it throughout the hotel. Within two days, people fell ill. The bacteria struck 221; 34 died. It struck an American Legion convention celebrating the country's bicentennial, in July, 1976, at

In This Issue:

Vol. 1, No. 12
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the Bellevue-Stratford Hotel in Philadelphia. The event set off a panic that included speculation about a communist (or even a pharmaceutical company) plot against the legionnaires. President Ford, thinking it was an outbreak of the swine flu—then raging in Asia—signed the National Swine Flu Immunization Program of 1976. Swine flu was soon eliminated as the cause, but it would be months before the cause was identified. This lethal pneumonia, which became known as "Legionnaire's Disease," was caused by a bacterium isolated in January, 1977 and was named *Legionella pneumophila*. The outbreak prompted changes in cleaning and inspection procedures for air conditioning systems throughout the world. That hasn't been enough. In England, in 1985, a second large outbreak struck 101 people, killing 28. There have been at least four other outbreaks.

It's been twenty-five years since the first outbreak. The subsequent outbreaks show that we're as vulnerable to *L. pneumophila*—and to other airborne pathogens (organisms that cause disease) and toxins—as we were in 1976.

How about capturing an air sample and doing a chemical analysis? The air is so full of particles (dust, spores, pollen, organic and inorganic chemicals, DNA fragments, bacteria, viruses, etc.) that we should find it amazing that we can see through it (unless we live in L.A., where we're grateful *when* we can see through it). Separating all the stuff that isn't harmful is a daunting task. Chemical analysis might be the way to detect toxins, but to chemical analysis, a harmless bacterium or virus looks the same as its lethal cousin (same chemical composition, but different genetic codes). The way to detect pathogens is to analyze their DNA.

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DNA analysis entails three steps: preparing the sample, amplifying what you're looking for, and detecting it (*Dynamic Silicon*, Vol. I, No. 9). Sample preparation extracts, purifies, and concentrates nucleic acids. The sample contains a variety of DNA. The amplification step uses a recipe called polymerase chain reaction (PCR). PCR exploits DNA's ability to copy itself. Add polymerase—an enzyme—to the sample and add reagents that supply DNA building blocks (nucleotides). Add a few million copies of a "primer" tagged with a fluorescent molecule. The primer is a short nucleotide sequence that complements, and will therefore "anneal" to, only the target DNA. The primer is the "fingerprint" for the particular DNA you seek. Thermally cycling the mixture causes the DNA in the sample to "denature" (split into complementary strands). The long DNA strands combine with the short primers. The short primers extend (in one direction) to complement the attached DNA strand—growing a new fingerprint. The mix may contain several primers, each with a different fluorescent tag. DNA that complements any primer will be amplified by the cycling, leaving all other DNA at its original concentration. The detection step washes unused primers from the sample; shining light on the residue causes any fluorescent molecules to respond with their characteristic light—signaling the presence of the target DNA.

DNA analysis that employs the PCR process identifies DNA for which there are primers in the test equipment. A PCR-based tester with a primer for Legionnaire's Disease won't detect anthrax. A tester equipped to amplify all known biological agents would not detect a new agent (unless it was so closely related to a known agent that the same primer worked for both).

Cepheid's PCR on a chip. I have written about DNA analysis and about Cepheid (CPHD, www.cepheid.com) before (*Dynamic Silicon*, Inaugural Issue and Vol. I, No. 9). Cepheid builds DNA analysis systems. Cepheid's systems put PCR amplification on a chip. This MEMS technology was developed at Lawrence Livermore National Laboratories by Dr. M. Allen Northrup and it is licensed exclusively to Cepheid. Cepheid's current products, the Smart Cycler and the Smart Cycler TD, automate the amplification and detection phases of biological-agent analysis. The Smart Cycler is a desktop system that sells for $27,500; the Smart Cycler TD is transportable and sells for $33,500. The small reaction chamber, isolated from the surrounding silicon for efficiency, together with the small sample size speeds PCR's thermal cycling by a factor of ten over macro-scale PCR cycles. The sample

spends less time at transition temperatures, so fewer undesirable chemical reactions contaminate the sample.

Cepheid's disposable cartridge includes optics blocks that mate its PCR chip with laser diodes and detectors in the base system. Each cartridge contains four optical channels for real-time monitoring of the fluorescence-based detection. The cartridge mates with one of up to sixteen I-Core modules in the bench-top Smart Cycler system. Each I-Core module contains microprocessor-controlled circuitry for PCR cycling and for optical detection. Each Smart Cycler could look for as many as sixty-four different DNA strands (four per cartridge and sixteen cartridges per system). Up to eight Smart Cycler systems run from a Windows PC that independently controls and monitors each I-Core module. The difficulty with this is that the sample preparation step still needs a lab technician.

Cepheid's next system, GeneXpert, is in the prototype stage now and will be in production in 2003. The GeneXpert adds sample preparation, so all three steps in DNA analysis are automated inside a single cartridge. Like the Smart Cycler TD, the GeneXpert will be portable. GeneXpert simplifies sample handling and speeds analysis.

Cepheid is a Dynamic Silicon company for the MEMS PCR, microfluidic, and sample-preparation components in its Smart Cycler and GeneXpert systems. The MEMS components in these systems improve the speed and accuracy of DNA analysis and they reduce sample sizes and waste products, which makes the process cheaper and safer. Late last month Cepheid announced that the Centers for Disease Control and Prevention (CDC) have validated Smart Cycler-based test kits for several biological threat agents. CDC supplies test reagents to the Laboratory Response Network, a network of more than 80 state, local, and military laboratories.

Chemical agents

According to a 1998 U.S. Department of State estimate, there are 60 to 70 million land mines buried throughout the world. Mines (and unexploded ordnance) are a problem in 93 countries. Each year, the Red Cross estimates, mines kill or maim more than 25,000 people. Half the victims are children. Mines render huge tracts of land unusable in countries with economies that depend on agriculture. The estimates vary but buried mines are an urgent problem. The problem is that mines are effective. Mines are as cheap as $3, they can be placed quickly, they don't have to be trained or fed, they never sleep, and they work for as long as 50 years. Finding and disarming mines is slow and expensive. A UNICEF report (*Impact of Armed Conflict on Children*) puts the cost of removing a mine at $1,000.

Finding a mine is not as simple as sweeping the area with a metal detector like those used by treasure-hunters at the beach. Cheap plastic mines may contain less metal than a paperclip, or no metal at all. Dogs, whose general-purpose olfactory sensors are hundreds of times more sensitive than ours, can be trained to identify the "decomposition products" of the explosives in plastic land mines. Such decomposition products are referred to as volatile organic compounds (VOCs). Dogs can detect the unique chemical signature of the VOCs released by the mine's explosives. Humans have a few million olfactory sensors; dogs, depending on the breed, have a few *billion*.

The Defense Advanced Research Projects Agency (DARPA) Dog's Nose Program sponsored projects in mine detection. Two projects building electronic noses for mine detection, and at least partly sponsored by DARPA, illustrate different sensor strategies. Both projects use fluorescent polymers for the sensor.

The "Fido" mine detector from Nomadics, Inc., built in collaboration with researchers from M.I.T. and from Oklahoma State University, uses a fluorescent polymer chain to detect minute concentrations (parts per trillion) of specific VOCs from TNT and related explosives. The sensor's thin film of complex polymer chains normally fluoresces. Capturing a target molecule quenches an entire chain's fluorescence, amplifying the molecule's presence, making a sensor that is sensitive. Nomadics believes that its chain-connected polymer receptors amplify the fluorescent quenching by factors of 100 to 1,000 over the response of conventional isolated polymer receptors. Specially designed receptors in the polymer chains interact only with specific target molecules, making the sensor selective. In a field test with two experienced dog teams (one trained to detect explosives in mine fields and one trained to detect explosives in other situations), Fido did as well as or better than the dogs.

Professor John Kauer and Dr. Joel White of Tufts University Medical School built a land-mine detector with an array of thirty-two broadly reactive fluorescent-polymer sensors. Polymers in the Tufts detector are normally dark, but fluoresce when a molecule is captured. Unlike Fido from Nomadics, with sensors that are narrowly selective, the general-purpose sensors in the Tufts design mean that the detector's signal-processing algorithms must be trained to recognize the VOCs from the land mines' explosives. In initial tests, Fido was about 100 times more sensitive than the Tufts detector, illustrating a potential advantage of selective sensors over

general-purpose sensors. Modifications to the detector's optics, electronics, and airflow have brought its sensitivity on a par with the least-capable dogs (parts per billion), probably bringing it within a factor of 10 of the best dogs or of Fido's sensitivity.

Your sense of smell

What's in a fragrance? Molecules. The molecules we smell are VOCs. Humans, using an organ of a few million individual sensors—the *olfactory epithelium*—the size of a postage stamp, can distinguish about 10,000 smells. The olfactory epithelium is in the roof of the nasal cavity. Organic sensors in the olfactory epithelium capture molecules, setting off a chain of events that results in a signal propagating into the brain by way of a neural network. The olfactory system is three subsystems: sample collection and preparation (bony plates in the air passages that create turbulent airflow across the olfactory epithelium and proteins that capture candidate molecules and convey them to the sensors), detection (sensors selectively capture organic molecules), and processing (the neural network and the brain). The olfactory epithelium has sensors that respond differently to different molecules. The sensors are "broadly" selective (they capture organic molecules with molecular weights below about 300). You don't, for example, have a sensor for benzene. A sensor for benzene would be "narrowly" selective. Your nose is a collection of sensors that are not all the same; they have differing affinity for molecules. Your brain interprets patterns of response to VOCs across its array of sensors. The human nose is a general-purpose VOC detector; your neural network and your brain together "fingerprint" each smell. You have *learned* the smells you know and you can learn new ones. If your olfactory sensors were narrowly selective, you couldn't learn new smells.

Nose on a chip

Cyrano Sciences purchases what are called non-conducting commercial (off-the-shelf) polymers and manufactures NoseChip sensors. These polymers are cheap and are readily available. Cyrano Sciences mixes each polymer homogeneously with carbon black. (Carbon black is a mixture of partially burned hydrocarbons. It is an essential ingredient in tires and it is also used in pigments, dyes, and inks.) Since carbon black is a conductor and the polymers are non-conductors, the electrical resistance of their homogeneous mixture depends on how much carbon black is mixed with the polymer. This polymer/carbon-black mixture for the NoseChip is based on the work of Professor Nathan Lewis in the Division of Chemistry and Chemical Engineering at Caltech. Cyrano Sciences has licensed the technology from Caltech.

Cyrano's NoseChip has thirty-two sensors. Each sensor is a pair of electrical contacts, bridged by a layer of the polymer and carbon-black mixture. A different polymer bridges each of the thirty-two pairs of contacts. The thickness of the polymer determines how long it takes for VOCs to reach equilibrium as they stick to or diffuse into the polymer; thicker coatings produce slower responses. Polymer bridges on the current NoseChip are about 1 micron thick, giving it a response time of from less than 0.1 seconds to more than 100 seconds, depending on the VOC and upon the characteristics of the polymer. Future chips will probably use thinner coatings since the diffusion time increases as the square of the thickness. (A coating twice as thick responds four times slower.) Reducing polymer thickness to 0.1 micron should enable real-time response.

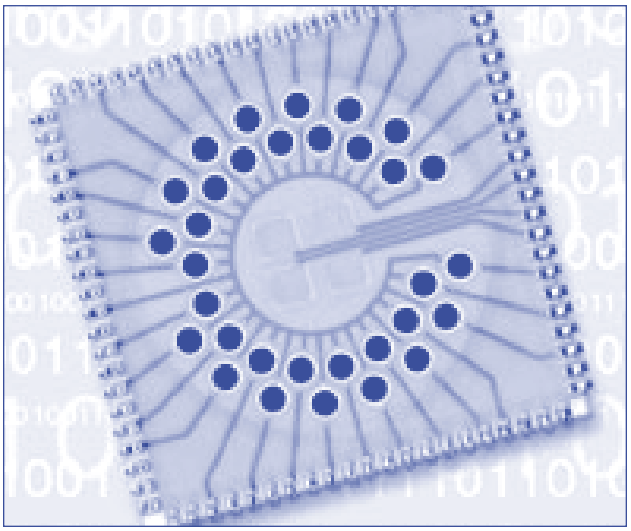

Fig. 1. The NoseChip from Cyrano Sciences has thirty-two different polymer sensors on a single chip.

The polymer at each sensor site sorbs VOCs to an extent that depends on the molecule and upon the structure of the polymer. As the polymer sorbs molecules, it expands, like a sponge soaking up water. As the polymer expands, distances between carbon-black molecules increase, which increases the electrical resistance between the contacts. Measuring the change in resistance is easy. Each of the thirty-two sensors responds to a broad range of VOCs, but, for a particular molecule, the response of each sensor differs from the others. This is important because it creates a "fingerprint" across the sensors for a particular molecule. Each molecule elicits a different combination of responses.

Fig. 2 simulates outputs for three different VOCs on a twelve-sensor chip. On the left is simulated raw data; on the right I used Excel's "radar chart" for each VOC to

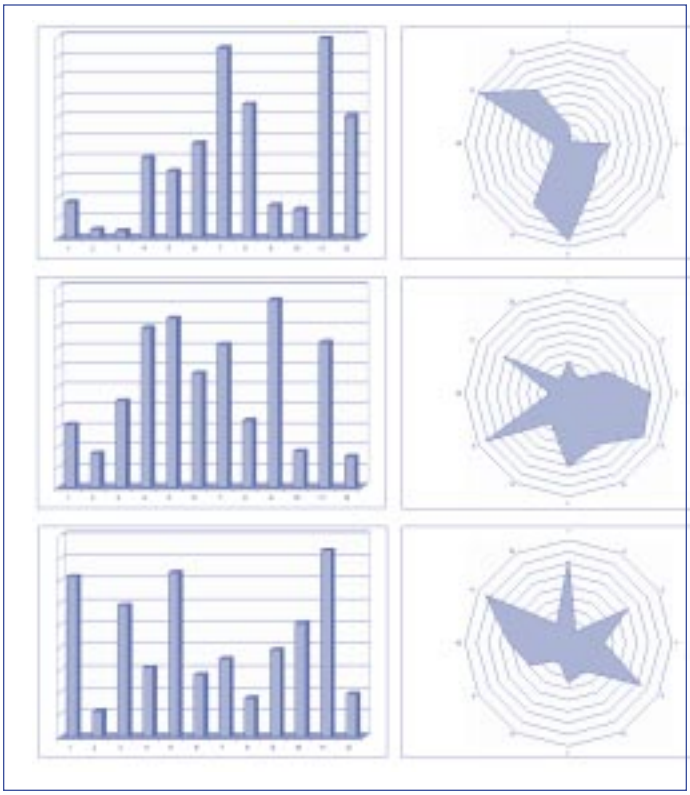

Fig. 2. Comparison of individual-sensor data and group "fingerprints" from simulating the response to three volatile organic compounds (VOCs) for an electronic nose with twelve broadly selective sensors.

show each chemical's unique fingerprint. Sensors one through twelve get thirty degrees of the plot each. The amplitude of the response is the distance from the center. Electronic noses convert collected data to visual images to exploit our natural pattern-recognition ability.

Sorption, which includes both absorption (diffusing into) and adsorption (sticking to), of VOCs by the polymer is reversible. The same sensor can be used at least tens of thousands of times. However, the insulating polymers and the carbon black are both cheap and easily available and the sensor is a simple array of wires and contacts, so the sensor is cheap enough to throw out after only one use.

"Biogenic amines" are useful indicators of freshness in meats, cheeses, and fermented foods. The human olfactory epithelium is particularly sensitive to biogenic amines. A promising improvement in the NoseChip would increase its sensitivity to biogenic amines. Besides the ability to discern the freshness of foods, the NoseChip would more nearly mimic our sense of smell. This would aid understanding and characterizing our sense of smell. Dr. Lewis's research group at Caltech has already reported success in experiments with conducting organic polymers. Conducting polymers amplify changes in electrical resistance in a way similar to the fluorescence change in the polymers used in the Fido land-mine detector. That is, the effect of a single molecule ripples through a long polymer chain.

Integrating electronics and signal processing with the sensors could produce detectors cheap enough to be suitable for packaging with foods. A simple product-freshness indicator might, for example, be built into a milk carton or into (disposable) packaging for meat. Future versions of the NoseChip might be integrated into kitchen appliances such as refrigerators or microwave ovens. Cheap electronic noses might sit in pantries and on cupboard shelves to monitor food quality.

The electronic nose

Cyranose. Cyrano Sciences believes the market for sensory and vapor analysis is $8 billion. Capturing a healthy share of that market is the incentive behind its electronic nose. Cyrano Sciences thinks it has a good answer and I agree. Its handheld, battery-powered electronic nose, the Cyranose 320, is about the size of a two-way radio and sells for $8,000.

The element that looks like an antenna is the unit's "snout." It also has a purge inlet and an exhaust port. Placing the snout near a sample and pressing the "run" button starts a programmed sequence. This sequence, including air reference, vapor sampling, sensor measurement, and signal processing, takes about a minute. The Cyranose can connect to a PC through its RS-232 port or through its USB port to store data or to load new signal-processing information. It is a general-purpose VOC detector that mimics the human nose. It combines Cyrano's NoseChip sensor with on-board signal-processing. It doesn't require special preparation of the sample.

The Cyranose doesn't know what it is analyzing; it has to be "trained." Suppose that you want to sort coffee beans by five countries of origin. You train Cyranose on ten samples from each of the five countries. *Cyranose* selects the signal-processing algorithm that best separates the samples by country of origin. When a trained unit tests new samples, it classifies each sample by country. This is a qualitative, not quantitative, process. If you want to sort lubricants, you can use the same unit with the same NoseChip, but it will have to be trained with ten samples of each lubricant. In these examples, a particular country and a particular lubricant, such as transmission fluid, are "classes." Sorting coffee beans is one "method" and sorting lubricants is another method. The Cyranose 320 can store five methods with up to six classes for each.

Storing only five methods (types of smells) seems restrictive, but any number of methods could be stored on a PC for transfer to the Cyranose. The limit of six classes

Fig. 3. Cyranose 320 electronic nose from Cyrano Sciences.

(pronouncements) per method also seems restrictive. It is a problem if you want to discriminate among large sets such as soft drinks or jelly beans or flower seeds. But there is a huge range of applications for which the two classes are "this is OK" and "this is not good." The Cyranose can be trained to discriminate good from bad gasoline or to distinguish pure from contaminated diesel fuel. Similar tests could screen meats, fruits, fish, vegetables, wines, and dairy products. The Cyranose could be a leak detector at a chemical plant or refinery.

In a clinical trial at Children's Hospital Los Angeles (sponsored by Cyrano Sciences), the Cyranose aids diagnosis of upper respiratory infections. In a role similar to law enforcement's Breathalyzer, the Cyranose attempts to detect VOCs that are byproducts of infectious diseases. This method shortens diagnosis, which can be particularly critical in some diseases. Quick diagnosis by the Cyranose could lower costs by reducing incidents of cautionary hospitalization that might otherwise be required for biopsy, tissue culture, and analysis.

Cyrano Sciences wants to be "the dominant provider of smell-detection hardware," beginning with the Cyranose 320 and the NoseChip. It also wants to build the leading database and to set the standard for digital storage formats for scents. Cyrano's "smellprints," similar to the "radar chart" images of fig. 2, exploit our visual pattern-recognition ability in the service of scent discrimination.

Cyrano Sciences is a Dynamic Silicon company for its Cyranose 320 and for its NoseChip. Both are potentially low-cost products, and both should be widely adopted once Cyrano Sciences prices them for market proliferation. Cyranose is a good instrument for scent decisions common in everyday situations. It works in the presence of background interference (particles, humidity, organic compounds, etc.), and it is relatively insensitive to temperature. Cyranose is lightning fast when compared to laboratory analysis procedures, but it'll take a minute or so and it won't give quantitative results. Its thirty-two sensors aren't going to match the human's millions or the dog's billions. But it's a start; it's programmed and it's technology, so it's adaptive, it's flexible, and it'll get better.

zNose. EST (Electronic Sensor Technology) builds a gas chromatograph (GC) analyzer, the "4100 Fast GC Analyzer." This analyzer is as fast as ten seconds, gives quantitative results, has sensitivity to parts per trillion, and identifies as many as 500 unknowns in a single sample. EST calls its product the "zNose." EST's web page (www.estcal.com) says it's an electronic nose. It isn't trying to mimic nature's combination of general-purpose sensors and signal processing, so it isn't really an electronic *nose*. In fact, it uses only a single sensor. EST's spec sheet for the 4100 is subtitled "Portable Handheld Gas Chromatograph." That's a stretch too; there's a handheld component about the size of a large iron, that's tethered to a nerd-sized-briefcase main unit. What it does have, however, is performance validation by the U.S. Environmental Protection Agency for environmental monitoring of VOCs in water and for PCBs in soil and by the White House Office of National Drug Control Policy for detecting controlled drugs. Government agencies can purchase EST's 4100 through the General Services Administration (GSA).

It's fast, it's sensitive, and it gives quantitative results for lots of unknowns. About half of the magic is in the gas chromatograph and half is in the sensor. Here's how it works. The EST 4100 captures and concentrates a sample. Next, in a process similar to electrophoresis (*Dynamic Silicon*, Vol. I, No. 9), the sample mixes with helium and passes down a long specially coated tube. This is the gas chromatograph. The sample's constituents travel down the tube at different rates and emerge from the end of the tube at different times (time slots). Upon exiting, particles in the sample condense onto a detector and then evaporate. The detector, together with the unit's electronics, detects not only whether there are particles in a particular time slot, but also the total mass.

The detector is a "surface acoustic wave" (SAW) sensor. The SAW is an uncoated, high-quality 500-MHz quartz-crystal resonator bonded to a heating and cooling element. As particles condense on the surface of the crystal, the resonant frequency decreases according to how much mass is added to the crystal's surface, just as adding a coating to a guitar string would lower its pitch. The heating and cooling element holds the detector at a constant temperature; adjusting the temperature controls sensitivity. The time slots contribute selectivity and the sensor contributes sensitivity. The sensor is uncoated to speed the response. A polymer

coating would lower the quality factor (Q) of the resonator, could be degraded by accumulated contamination, and it would slow evaporation of the particles. Particles condense and evaporate from this sensor within 20 milliseconds. Twenty milliseconds means 500 time slots fit into 10 seconds. The combination of the gas chromatograph and one SAW sensor behaves like a system with 500 narrowly selective sensors. The analysis phase is 10 to 60 seconds. Counting purging with helium, sampling, sample concentration, and the GC/SAW analysis phase, the minimum system cycle is 30 seconds. The helium bottle that comes with the unit is good for about 300 samples.

Like the Cyranose, the EST system enlists the operator's pattern-recognition ability by creating a visual image of the analysis. EST calls the image, which is similar to the "radar charts" of fig. 2, a "VaporPrint."

Other noses

The web site (http://nose.uia.ac.be) for the Network on artificial Olfactory SEnsing (NOSE) is dedicated to the exchange of information on the development of electronic noses. Though NOSE is primarily a European organization, it has a review page showing worldwide artificial-nose research and the commercial availability of electronic-nose products. The site lists eighteen companies, including Agilent Technologies, Alpha MOS, AppliedSensor, Marconi Applied Technologies, and SMart Nose, under a "commercial availability" heading. It also lists twenty-eight universities doing electronic-nose research, though many U.S. universities that do have projects are unlisted.

A word about tongues

You can recognize 10,000 smells, but your tongue knows only four tastes: sweet, sour, bitter, and salty (there's uncertainty over whether MSG should be added as the fifth taste). Most of what you "taste" in food comes from its aroma. There's quite a difference between the olfactory epithelium and the tongue, but they are both chemical detectors. The most significant difference is that the nose works with gases and the tongue works with liquids. I've covered a few projects for electronic noses; there are also projects to make electronic tongues. Cepheid's Smart Cycler is an electronic tongue of sorts. It might make a nice partner for a cheap electronic nose, monitoring an industrial air system. The electronic nose could sniff the air frequently; if its sensors say "not OK" it triggers the slower, more expensive, detailed analysis of the Smart Cycler. The system simply captures an air sample and circulates it in a closed chamber with a spray mist that precipitates particles from the air into a liquid for analysis by the Smart Cycler.

Lessons

There's good reason to try to prevent biological attacks, but public concern (aided by media attention), seems disproportionately high. Celebrities get anthrax vaccinations, for example, but not flu shots. Yet flu and pneumonia kill more than 65,000 people per year. Septicemia (what's that?) kills more than 30,000 each year, but there's no national movement for detecting and preventing the spread of these microorganisms. Shouldn't I be more interested in a septicemia or flu detector than an anthrax detector? Death rates from these biological agents give rise to neither panic nor demand for protection.

Government agencies buy sophisticated biological and chemical analysis systems for public health monitoring and for diagnosis. The military pays a premium for battlefield-ready systems that can test remotely and quickly for a variety of biological and chemical threats. If there's any good news created by the threat of chemical and biological weapons it is this: the technological advances underwritten in the name of detection and prevention of these threats will benefit us more directly than the same money put into developing the next-generation guided-missile cruiser or heavy tank.

Industrial markets for electronic noses are developing now, with food processing leading the way. With more narrowly focused problems to solve, entrepreneurs cost-reduce flexible, premium systems adapting them to commercial applications. Consumer markets will soon follow.

My background is electrical engineering, specifically computers and logic design. The more I learn about molecular biology, the more optimistic I become about applications that exploit the cross-fertilization of biology and information science. What a great time to be watching technology! We are at the stage where *silicon processes approach the dimensions of biological structures*. Not only can the tools that we have developed for technology, such as the atomic-force microscope and the scanning-tunneling microscope, help us to understand biological structures, but we can begin to *co-opt* Mother Nature's remarkably economical and efficient solutions to solve our problems. Our semiconductor processing equipment lets us build systems that interact *directly with biological systems at a molecular level.*

Nick Tredennick and Brion Shimamoto
December 17, 2001

Dynamic Silicon Companies

The world will split into the tethered fibersphere (computing, access ports, data transport, and storage) and the mobile devices that collect and consume data. Dynamic logic and MEMS will emerge as important application enablers to mobile devices and to devices plugged into the power grid. We add to this list those companies whose products best position them for growth in the environment of our projections. We do not consider the financial position of the company in the market. Since dynamic logic and MEMS are just emerging, some companies on this list are startups.

Company (Symbol)	Technology Leadership	Reference Date	Reference Price	11/30/01 Price	52-Week Range	Market Cap.
Altera (ALTR)	General Programmable Logic Devices (PLDs)	12/29/00	26.31	22.76	14.66 - 34.68	8.8B
Analog Devices (ADI)	RF Analog Devices, MEMS, DSPs	12/29/00	51.19	42.50	29.00 - 64.00	15.4B
ARC Cores (ARK**)	Configurable Microprocessors	12/29/00	£3.34	£0.58	£0.25 - 3.51	£108M
ARM Limited (ARMHY***)	Microprocessor and System-On-A-Chip Cores	11/26/01	16.59	16.27	8.39 - 26.82	5.4B
Calient (none*)	Photonic Switches	3/31/01				
Celoxica (none*)	DKI Development Suite	5/31/01				
Cepheid, Inc. (CPHD)	MEMS and Microfluidic Technology	12/17/01	4.73		1.48 - 11.48	125.8M
Chartered Semiconductor (CHRT)	CMOS Semiconductor Foundry	7/31/01	26.55	21.80	16.06 - 40.50	3.0B
Coventor (none*)	MEMS IP and Development Systems	7/31/01				
Cypress (CY)	MEMS Foundry, Dynamic Logic	12/29/00	19.69	23.02	13.72 - 29.25	2.8B
Cyrano Sciences, Inc. (none*)	MEMS Sensors	12/17/01				
QuickSilver Technology, Inc. (none*)	Dynamic Logic for Mobile Devices	12/29/00				
SiRF (none*)	Silicon for Wireless RF, GPS	12/29/00				
Taiwan Semiconductor (TSM†)	CMOS Semiconductor Foundry	5/31/01	14.18††	15.93	8.39- 19.02	53.6B
Tensilica (none*)	Design Environment Licensing for Configurable Soft Core Processors	5/31/01				
Transmeta (TMTA)	Microprocessor Instruction Sets	12/29/00	23.50	2.70	1.17 - 39.87	364M
Triscend (none*)	Configurable Microcontrollers (Peripherals)	2/28/01				
United Microelectronics (UMC†)	CMOS Semiconductor Foundry	5/31/01	10.16	7.79	4.25 - 10.86	17.8B
Wind River Systems (WIND)	Embedded Operating Systems	7/31/01	14.32	17.20	9.71 - 45.86	1.3B
Xilinx (XLNX)	General Programmable Logic Devices (PLDs)	2/28/01	38.88	36.11	19.52 - 59.25	12.1B

† Also listed on the Taiwan Stock Exchange
†† TSM reported a stock split on 6/29/01. The Reference Price has been adjusted for the split.
* Pre-IPO startup companies.
** ARK is currently traded on the London Stock Exchange
*** ARM is traded on the London Stock Exchange (ARM) and on NASDAQ (ARMHY)

NOTE: This list of Dynamic Silicon companies is not a model portfolio. It is a list of technologies in the Dynamic Silicon paradigm and of companies that lead in their application. Companies appear on this list only for their technology leadership, without consideration of their current share price or the appropriate timing of an investment decision. The presence of a company on the list is not a recommendation to buy shares at the current price. Reference Price is the company's closing share price on the Reference Date, the day the company was added to the table, typically the last trading day of the month prior to publication. The authors and other Gilder Publishing, LLC staff may hold positions in some or all of the companies listed or discussed in the issue.

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