Toward Nanometer-Scale Sensing Systems:
Natural and Artificial Noses as Models for Ultra-Small, Ultra-Dense Sensing Systems

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Abstract

The development of highly sensitive, selective, reliable, and compact sensing systems to detect toxic chemical and biological agents is of great importance to national security. This paper examines the best such naturally occurring sensing system, the sense of smell or "olfaction," as well as artificial sensing systems built to emulate the nose. The goal is to combine lessons learned from natural and artificial olfaction with opportunities presented by advances in nanotechnology, in order to further the development of nose-like sensing systems integrated on the nanometer scale. The olfactory processes are reviewed here in some detail. Dense arrays of olfactory neurons, acting as ultra-small, non-specific sensors, use molecular recognition to perform highly parallel molecular sensing. The sensory signals so generated are identified by the brain using a spatio-temporal coding scheme. In this way the olfactory system recognizes, with great accuracy and sensitivity, a broad range of chemical stimuli. The principles of olfaction have been applied to developing artificial noses that are composed of arrays of cross-reactive gas sensors of various types. Artificial noses based upon conductivity-change devices, mass-change devices, and fluorescent optical fibers are reviewed here. The smallest artificial noses at this time are devices that incorporate micron-scale sensing elements and are comparable in size to a credit card. To more closely approximate the capabilities and compact size of the natural nose, it will be necessary to shrink the individual sensor size even farther, integrating nanometer-scale sensors into systems. Individual nanometer-scale devices, such as carbon nanotubes and nanowires, already have been demonstrated to function as gas sensors, and their applicability to nose-like sensing is discussed. At this point in time, however, no complete, nose-like nanometer-scale sensing system has been developed. This paper concludes by presenting for consideration a proposal for an electronic nose composed of nanowire sensors.

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1.0 INTRODUCTION

The purpose of this paper is to examine the sense of smell and how it works, with the goal of applying lessons learned from the operation of natural and artificial noses to the development of sensing systems integrated on the nanometer scale. Ensuring the security of the nation requires the development of fast, reliable, comprehensive, and compact sensing systems to provide early warning of attacks by terrorists using toxic chemical or biological agents. The sensing system with the best sensitivity, speed, and reliability is provided to us by nature in the nose and the sense of smell, or "olfaction." This natural sensing system has been imitated, over the past decades, by a variety of artificial nose-like sensing systems, but a wide gap still remains between the capabilities and sizes of artificial and natural noses. Advances over the past few years in building nanometer-scale devices, however, particularly the development of nanosensors, offer us the opportunity to make new progress towards closing this gap. Combining our understanding of olfaction with these recent developments in nanometer-scale devices and systems offers exciting new prospects for fielding sensors with truly nose-like sensitivity, accuracy, and reliability.

In this paper we will explore the physiological processes of the sense of smell, presenting new insights gained over the last few years through genetic research. We will examine how researchers have translated the model of the olfactory system into artificial noses using a variety of sensing mechanisms, looking specifically at examples of very small artificial noses. We will look also at recent developments in nanometer-scale sensors and discuss how these "nanosensors" might serve in artificial noses. Finally, we present a proposal for integrating nanometer-scale sensors into a nose-like sensing system.

The model for nanosensing employed in this work, the sense of smell, is the oldest of the senses, existing at a time when only primitive multi-celled creatures inhabited the oceans, without sight or hearing. Smell has been the primary sense for many animals, helping them navigate through their environment, directing them to food, finding them mates, and alerting them to danger. Even in humans, for whom vision and hearing have replaced smell as the primary sense, the nose remains a highly sensitive instrument. The olfactory system is also very small. The sensing region in the nose is the size of a large postage stamp, with individual sensing elements on the nanometer scale. These two aspects of the sense of smell, its remarkable effectiveness and its very compact size, are without parallel in any other natural or artificial sensing system. This makes olfaction an ideal model to guide research and development toward advanced ultra-dense nanosensing systems.

Although the basic physiological processes associated with smell have been known for some time [1], it is only recently that science has begun to understand the more detailed processes at the cellular and molecular level. As a result of a series of relatively recent remarkable discoveries [2-13], we now know that the olfactory system is a sensor system that uses molecular recognition and a combinatorial coding process to recognize a broad range of chemical stimuli. Within just the last five or six years, we have been afforded a detailed view of the olfactory processes from initial molecular recognition and transduction within a neuron [2,14,15], to transmission of the signal all the way to the brain [7,8,11,13,16]. The exploration of olfaction spans many disciplines and is being conducted by scientists from many fields, including biology [6,9,10], physiology [16], biochemistry [2,4,11], bioengineering [17], neuroscience [3,5,8], computer science [18], and mathematics [19].

The detailed insights gained in recent years into the sense of smell might be of mostly academic interest were it not for the new awareness, especially after the terrorist attacks in the Fall of 2001, of the grave threats that chemical and biological weapons pose to our national security. Since that date, increased attention has been focused on developing sensor systems for early detection and warning of toxic agents in the environment [20]. The need is for sensor systems that are at once highly sensitive to minute quantities of individual toxic gases or bio-agents, while at the same time capable of detecting and discriminating among a broad range of potentially harmful agents. Sensor size is also of importance, as it would be desirable for a chemical/biological sensing system to be small enough to be placed anywhere without interfering with other activities or the operation of other devices in which it might be embedded. Very small sensors would permit dense sensor placement which could provide populated areas with nearly ubiquitous air testing for toxic agents. Ideally, such a sensor system would be so small that it could be incorporated into everyday objects such as books or clothing, including, for example, a soldier's fatigues. A soldier could therefore have the protection of an effective sensing system every time he or she gets dressed! Such a sensing system also might be able to recognize humans by their unique odor, as dogs do, providing new capabilities for personal identification. To permit the design of truly nose-like sensor systems such as these, the need for an understanding of the processes of olfaction has gone beyond academic interest to being of fundamental practical importance.

Work on developing larger-scale "artificial noses" or "electronic noses," as they are commonly known, has been in progress since the early 1980s. (In artificial noses the sensing signal is generally transduced into an electrical signal, leading to the term "electronic noses.") Initial research focused directly on recreating human odor perception, such as making quality assessments in food, beer, wine, and perfumes. In the years since then, applications of electronic noses have greatly expanded to

include such tasks as monitoring air quality, testing for the presence of explosives and landmines, making medical diagnoses, and, in recent years, detecting toxic chemicals and biological agents. Artificial noses have used a variety of fundamental physico-chemical approaches to sensing. Among them are measurement of conductivity changes in metal oxides and polymers, frequency changes in piezoelectric materials, and color changes in fluorescent optical fibers.

Over the years advances have been made toward developing smaller, more effective artificial noses [21,22]. Today's electronic nose is much smaller than the gas chromatograph or mass spectrometer used in the past; sensor systems that once were desk-sized objects may now be hand-held devices. Although advances have been made in sensing capabilities, these remain relatively primitive when compared with those of the natural nose. Attempting to enhance these capabilities by more closely approximating natural olfaction, however, would result in significant growth in system size, even if today's smallest, micron-scale, sensing elements were used. The only way artificial noses can emulate the natural nose more closely, while at the same time becoming smaller, is to develop and apply nanometer-scale sensing. This will require integrating sensors which are only a few nanometers in dimension – i.e., on the molecular scale – into extended but still very small and very dense sensing systems. The application of recent advances in nanometer-scale devices to sensing systems promises the future deployment of highly sensitive, selective, reliable, and ultra-small sensing systems for early warning of chemical or biological weapons attacks. Research in developing nanometer-scale sensing systems, therefore, is of great importance to the national defense, and it is one of the areas of research being sponsored by the National Nanotechnology Initiative (NNI). In addition, the Defense Advanced Research Projects Agency (DARPA) has recently initiated a 5-year program called the MoleSensing Program, which has the goal of producing ultra-dense, ultra-small micron-scale sensing systems with the equivalent of 10^{11} sensors per square centimeter!

In subsequent sections of this report we examine the operational processes of the premier natural sensing system, the sense of smell, as well as those of existing electronic noses, in order to identify operational principles and lessons for developing artificial nanosensing systems. To that end, Section 2 of this report presents a review of current research into the physiology of the sense of smell. A brief overview of olfaction in mammals is followed by a more detailed look at the constituent parts of the olfactory system and the processes which take place in each component. This section concludes with a summary of "lessons learned" about the key operating principles of natural olfaction that seem to be of particular importance for the design of artificial nose-like nanosensing systems. Section 3 contains a survey of sensing systems which attempt to emulate olfaction using various sensing mechanisms. Of particular interest are the smallest electronic noses which could be identified in each category.

Although not yet incorporated into extended systems, individual nanosensors already exist, and Section 4 identifies some of the current research and development efforts in the area of nanometer-scale sensors. Finally, a discussion is presented in Section 5 on the suitability of individual nanometer-scale sensors for gas sensing systems, as well as a proposed design for an electronic nose with nanometer-scale sensing components.

2.0 THE PHYSIOLOGY OF THE SENSE OF SMELL

To make use of olfaction as a model for nanosensing systems we must understand its components and processes. We will explore these in some detail, but here we begin with a high-level description of what happens when odorant molecules, or what is perceived to be "smells," arrive at the nose.

The smell sensing process begins when an intake of air sends odorant molecules on a journey up the nasal passages and into the olfactory system. (See Figure 1.) At the top of the nasal passage the odorant encounters a small region, the epithelium, densely covered with millions of olfactory receptor (OR) neurons. These neurons perform the sensing function; when a receptor neuron is stimulated by interaction with an odorant molecule it generates an electrical signal. The pattern of stimulated receptor neurons effectively forms a "signature" by which an odorant may be identified.

The electrical signals generated by the receptor neurons are processed in several stages; the signals travel first to the olfactory bulb, located in the pre-brain, then to the olfactory cortex, and finally to other regions of the brain. Processing at all of these stages contributes to an analysis of the odorant's signature based upon the particular set of receptor neurons that have been stimulated. This analysis, along with comparisons with stored memories, results in final odor identification [5,23,24].

Research over the last twelve years has greatly expanded our insights into what happens at each of these stages of olfactory processing. The following subsections explore, in more detail, the current understanding of each of the components and processes of the olfactory system.
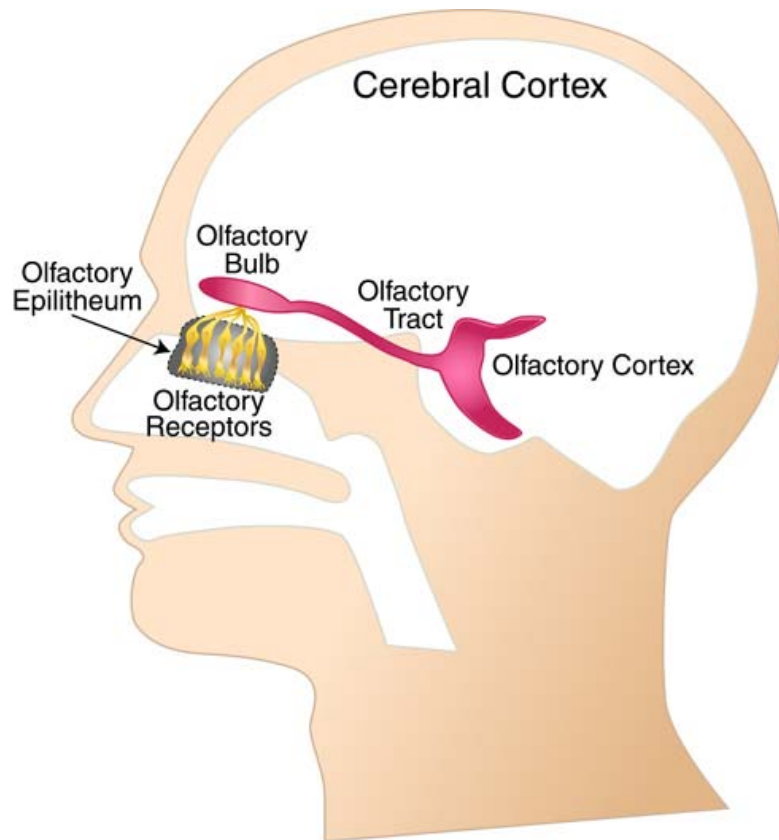
Figure 1. The Human Olfactory System

Odorant molecules make contact with the olfactory receptor neurons. The signals from those neurons are sent to the olfactory bulb for pre-processing, and then on to the olfactory cortex and other regions of the brain for further processing. See Figure 2 for a detailed view of the olfactory epithelium and the olfactory receptor neurons.

2.1 THE OLFACTORY EPITHELIUM

2.1.1 The Neurons of the Epithelium

The olfactory process begins in the olfactory epithelium, where the initial encounter with odorant molecules takes place. The epithelium, which in humans is about 4 cm^2, contains approximately 10 million neuron cells that are specific to the olfactory system. These olfactory receptor (OR) neurons, or simply "receptor neurons," host the receptor sites for odorant molecules. (See Figure 2.) The OR neurons are bipolar neurons with a cell body that is approximately 5 μm in width and that has specialized functional projections on each end. On one end, 10 to 30 hair-like cilia project from the epithelium into the mucus layer. The olfactory receptors, where odorant-receptor binding occurs, are located on the surface of the cilia. At the neuron's other end, an axon, a long, thin process about 0.2 μm in diameter, projects from the epithelium to the first signal processing center, the olfactory bulb [1,25].

Advances in the techniques of molecular genetics have been especially instrumental in revealing a number of the cellular and molecular mechanisms for olfaction in humans and other animals. Researchers have gained a range of insights into the operation of the olfactory neurons indirectly, by studying the genes which code for their receptors. In 1991, Linda Buck and Richard Axel at Columbia University, in a breakthrough discovery for which they won the 2004 Nobel Prize in physiology or medicine, identified the genes encoding the olfactory receptors [2]. In this study, Buck and Axel found that about 1000 mammalian genes encode 1000 different olfactory receptors, and a single gene may be expressed by thousands of receptor neurons [23]. Since the gene pool in mammals is comprised of approximately 35,000 genes, olfactory genes account for about 3% of the gene pool, making them the largest gene family in the genome [26].

Early in 2002, Xinmin Zhang and Stuart Firestein of Columbia University published the results of their study, using the Celera genome database, of the OR gene family in the mouse [10]. They found 1,296 mouse OR genes, of which about 20% were pseudogenes, or non-functioning genes. Thus there are approximately 1000 intact mouse OR genes, each encoding a different receptor. Doron Lancet and his team at the Weizmann Institute in Israel have been working on classifying human OR genes, and have found only 347 fully intact genes in the set of about 900 human OR genes [27]. Comparisons of the mouse and human gene repertoires indicate, however, that the human olfactory system covers much of the same "receptor space" as that of the mouse. That is, humans are able to perceive the same broad range of odorants,

but do not necessarily have the same capability for fine discrimination as does a mouse [10].

Each receptor neuron hosts many receptor sites on the surface of its cilia. For a time it was not known if receptors on a single receptor neuron could be of different types. In 1995, Buck and Axel were able to establish that every receptor neuron has only one type of receptor [23]. Each receptor neuron recognizes not just a single odorant, however, but a small range of odorants. In 1998, Firestein and his team demonstrated that each olfactory receptor responds to a restricted set of odorants which have similar molecular structures [3]. The set of odorants that are recognized by the receptor comprises its response profile. The Firestein study also provided additional support for the one neuron-one receptor-type hypothesis. It was found that forcing an increase in the number of receptor neurons expressing a particular gene led to an increase in sensitivity to odorants within the receptor's response profile, but not to other odorants.

The relationship between odorants and receptors is many to many. Just as one receptor neuron responds to a range of odorants with similar molecular structures, so a single odorant molecule can be sensed by a number of receptor neurons of different types. Integrating the information from the various receptor neurons which sense an odorant molecule helps identify that particular odorant. Even small changes in an odorant's molecular structure will cause a change in the set of receptors that bind with it. A change in odor concentration will also cause a change in the set of activated receptor neurons [5].

In addition to receptor neuron cells, the olfactory epithelium also contains stem cells and supporting cells. The role of the supporting cells is limited to the structural support of the epithelium and to contributing secretions to the mucus. The stem cells, also known as basal cells, are the source for new generations of olfactory neurons. Unlike most other neurons, olfactory neurons have a lifespan of 30 to 60 days before they are replaced by successor neurons. The stem cells undergo mitosis to generate new olfactory receptor neurons [1].

Olfactory receptor neurons with the same receptor type are scattered about the epithelium, but the scattering is not totally random. Separate experiments conducted by Axel [28,29] and by Buck [30,31], then at Harvard University, show that the olfactory epithelium is not monolithic, but can be divided into four distinct regions or zones. Each of the four zones hosts a different set of olfactory receptor types; receptors with similar amino acid structures tend to be clustered in the same zone [5,16]. Each receptor is randomly distributed across its zone. Therefore sensory information is divided into 4 subsets of data with individual receptor
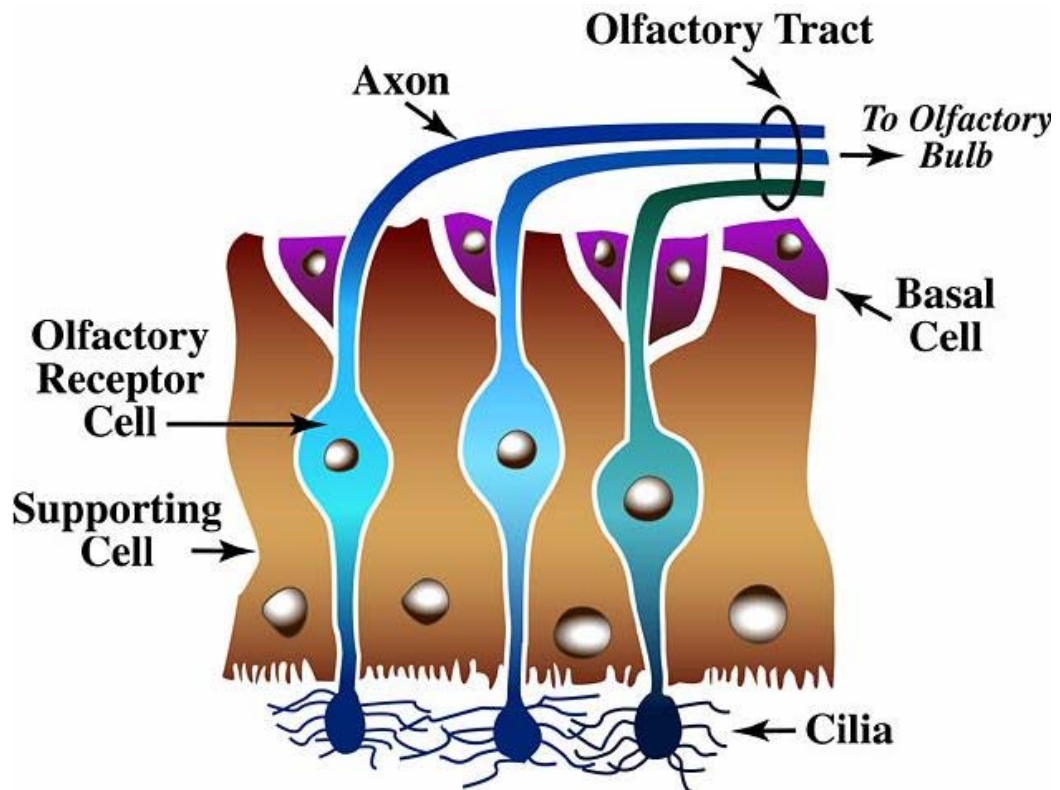
Figure 2. Inside the Olfactory Epithelium

Receptor sites for odorant molecules are found on the surface of the cilia. Odorant binding with receptors initiates neuronal firing, sending signals along the axons to the olfactory bulb

neurons highly distributed across about 25% of the epithelium.

2.1.2 Transduction

At the heart of the sensing process is the transduction of molecular recognition into an electrochemical signal which is sent to the brain. (See Figures 3 and 4.) Since the initial 1991 study by Buck and Axel, in which they identified both the olfactory receptor proteins and the genes which encode them, there has been much progress in understanding the molecular interactions which are responsible for transduction [2,14].

Incoming odorant molecules first dissolve in the mucus layer covering the epithelium, where they bind with small, water-soluble proteins. These odorant-binding proteins help transfer the odorant through the mucus layer to the odorant receptors, which are located on the surface of the cilia. The odorant receptors are membrane proteins called "7 transmembrane domain G-protein coupled receptors" (GPCRs) [23,24]. (They derive their name from passing through the neuron cell membrane seven times.) When an odorant molecule binds to a receptor, a G protein on the interior of the cilium, G_{olf}, is activated. The G_{olf} protein, in turn, activates the enzyme adenylyl cyclase (AC), which catalyzes the conversion of the intracellular molecule adenosine triphosphate (ATP) into the neurotransmitter cyclic adenosine monophosphate (cAMP). cAMP, which is called a "second messenger," now travels throughout the cell, binding with and thus opening cyclic nucleotide-gated (CNG) ion channels in the cell membrane. The open ion channels conduct positive ions, or "cations," such as Na^+ and Ca^{2+}, into the cell. In a resting state, the interior of the neuron is negatively charged with respect to the exterior; the voltage difference across the membrane is about –65 mV. As the cations flow into the cell, the local cell interior becomes less negative, or "depolarized." The threshold for signaling is reached when the voltage difference has decreased to about –45mV. At that point, an "action potential" is generated; the local depolarization causes the depolarization to threshold of adjacent resting membranes. In this way the action potential is propagated along the length of the axon into the olfactory bulb. There, the signal is transmitted to the secondary neurons for processing [1,25,32].

This process, from odorant binding to activation of the cAMP second messenger system to generation of an action potential, serves to amplify the signal created by one or a few odorant-receptor binding events. One bound receptor can activate tens of G_{olf} proteins. Each of the G_{olf} proteins activates an AC molecule, and each AC molecule can cause the production of 1000 molecules of cAMP per second. It takes three cAMP molecules to open a CNG channel, and once open, hundreds of thousands of ions can cross the channel into the cell. This amplification process can therefore result in a neuronal firing caused by a single molecular binding event [25]. (It should be noted, however, that a single neuronal firing may not be perceptible in the brain.) The second messenger system also serves to integrate binding events occurring within the same neuron over a short period of time. Thus, it acts as a "counter" for molecular binding events, and in this way provides a measure of odorant concentration [25].

A secondary amplification mechanism also operates to increase cell depolarization. The calcium ions entering the cell activate other ion channels which permit passage of negatively charged chloride ions, Cl^-, out of the cell. This egress of negatively charged ions from the cell serves to steepen the voltage gradient, and allows the neuron to reach its firing threshold sooner [25].

There is also a regulatory mechanism that works in conjunction with the second messenger system to enhance receptor sensitivity. This mechanism provides negative feedback to the ion channels. As the concentration of calcium within the cell increases, the calcium acts on the ion channels to desensitize them to cAMP, resulting in the requirement for a stronger odorant stimulus, and consequently more cAMP, to open the channels. This adaptation response allows continuous sensitivity to small changes over a broad range of concentrations [25].

2.2 THE OLFACTORY BULB

2.2.1 Signal Pre-Processing

Once molecular recognition has occurred and a receptor neuron has fired, its axon transmits this signal to the olfactory bulb (OB), the first olfactory processing center in the brain. As illustrated in Figure 5, the axons, bundled together in groups of 10-100, penetrate a thin bone, the cribiform plate, before entering the OB. There, the axons project onto the glomeruli, fibrous knots about 50-200 μm in diameter. A glomerulus is made up primarily of the bushy endings, called "dendrites," of the various neurons which meet there. Within the glomeruli, the axons of the olfactory receptor neurons form synapses with the dendrites of the secondary neurons, the mitral and tufted cells [1,16,25,32]. One of the functions of the OB, therefore, is to act as a relay station for signals going from the epithelium to the brain.

While receptor neurons of the same type are distributed randomly about a region of the epithelium, order emerges as the axons make their way to the olfactory bulb. Peter Mombaerts and Fan Wang, both then members of Axel's group at Columbia University, were able to use gene targeting to visualize axons projecting from the epithelium to the bulb. In separate studies, they showed that all neurons expressing a given receptor gene project their axons onto the same two

Figure 3. Sensory Transduction in the Sensory Neuron

Odorant binding with receptors starts a chain of chemical reactions inside the cell. These reactions cause the difference between interior and exterior cell voltages to reach a threshold value, which triggers neuronal firing.

This figure is reproduced with permission of Dr. Tim Jacobs of the University of Cardiff, from his website: "Olfaction: A Tutorial on the Sense of Smell," http://www.cf.ac.uk/biosi/staff/jacob/teaching/sensory/olfact1.html

Figure 4. Flow Chart of the Transduction Process

Figure 5. Inside the Olfactory Bulb

The electrical signals generated in the epithelium travel down the axons to the olfactory bulb. In the bulb, the axons make contact, within the glomeruli, with secondary neurons, which transmit the signal further into the brain.

glomeruli, symmetrically opposite each other on the two halves of the olfactory bulb [4,33]. This creates a fixed sensory map in the olfactory bulb for each set of stimulated receptor neurons, and thus for each odorant.

All neurons expressing a given receptor gene project to a single glomerulus, and they are the only ones projecting to that glomerulus. Kensaku Mori and fellow researchers at the University of Tokyo were able to show that each glomerulus receives input from only a single type of odorant receptor, and that each receptor binds with a limited range of odor molecules with similar molecular structures [16]. Therefore each glomerulus, as well as the mitral and tufted cells which send their dendrites to that glomerulus, is "tuned" to specific molecular features, and these features comprise the molecular receptive range for the glomerular cluster. As each glomerulus is stimulated, it "identifies" particular features of the odorant being sensed, and the pattern of activated glomeruli presents a composite picture of the odorant's characteristics [16].

There are about twice as many glomeruli as there are different types of receptor neurons. The mouse olfactory bulb, for example, contains approximately 900 types of receptor neur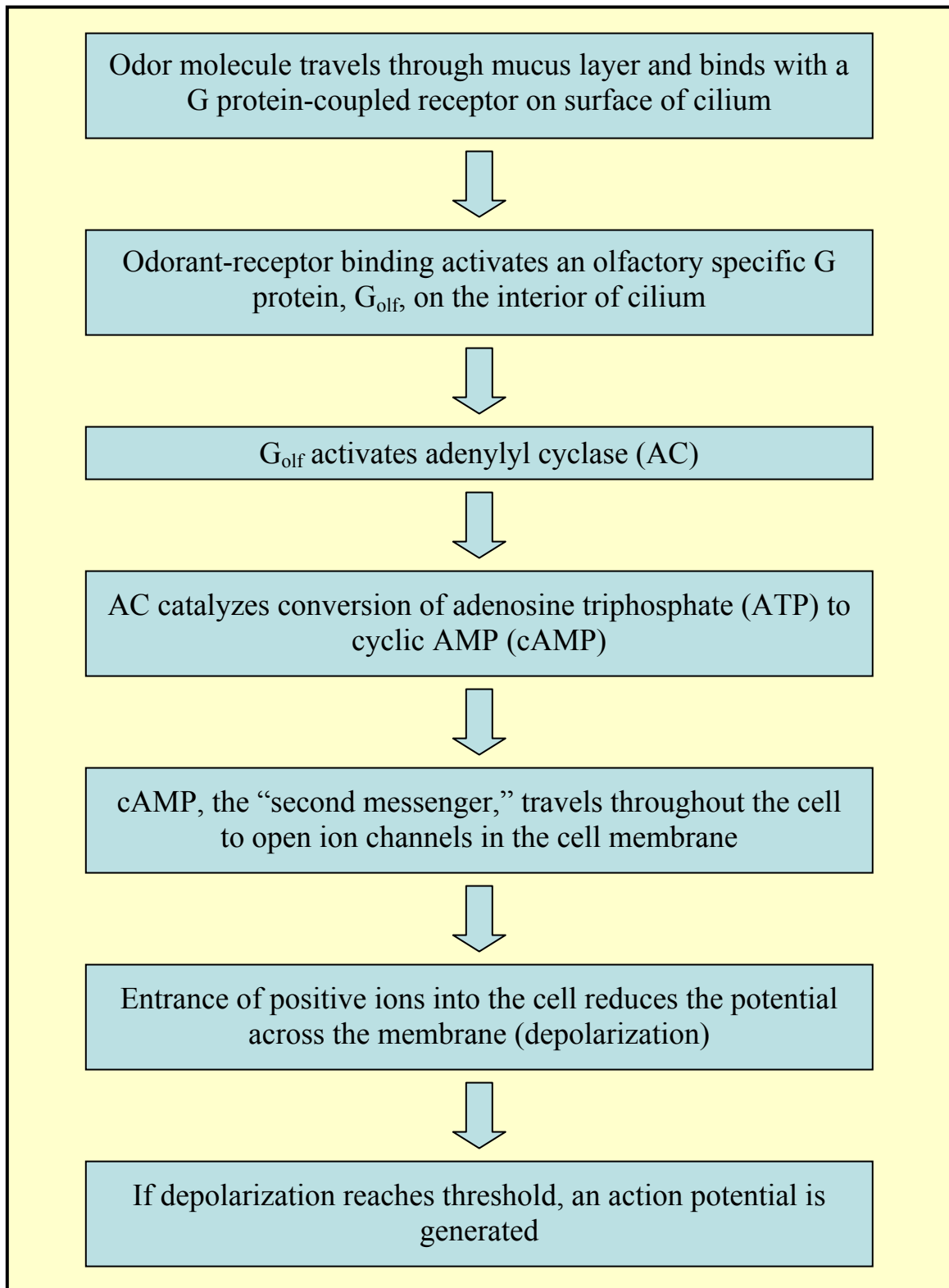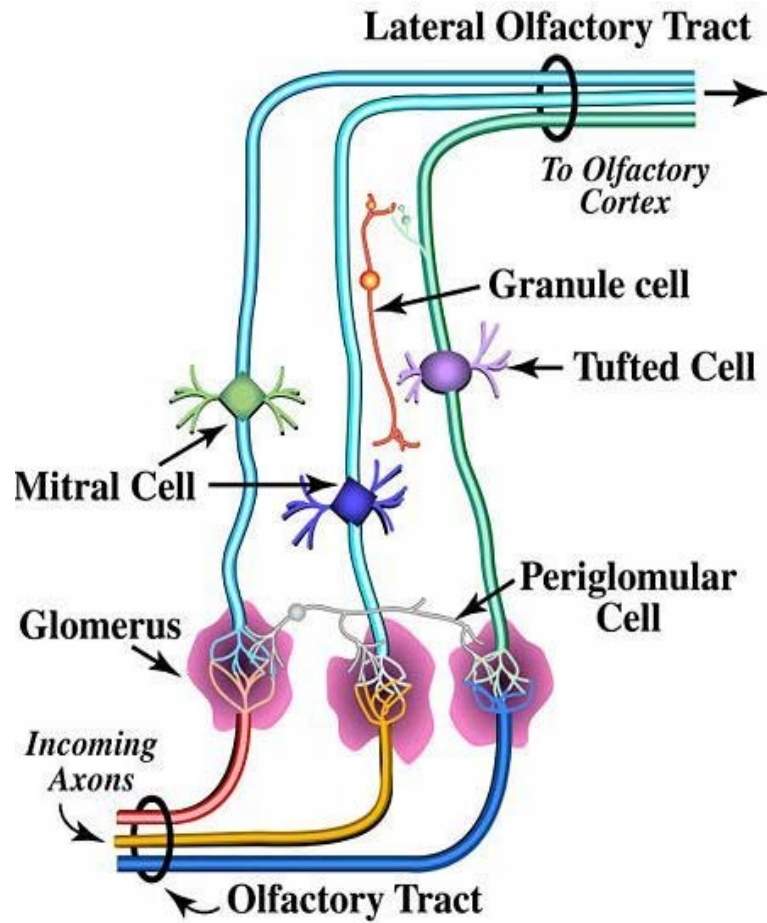ons and 1800 glomeruli [23]. There are thousands of neurons of each receptor type, and their axons all converge onto two glomeruli, each with only 5 - 25 mitral cells which receive and pass on the signal [25]. This high degree of signal convergence serves two functions; it amplifies sparse signals, increasing the sensitivity of the nose to low concentrations of odorants, and it increases the signal-to-noise ratio in a noisy odor environment.

Additional signal processing is also performed by the olfactory bulb's local neuronal circuitry. Periglomerular cells and granule cells form connections between the mitral and tufted cells of one glomerular module and those of neighboring modules [1]. The periglomular cells have short bushy dendrites whichspread throughout a glomerulus, and a short axon which extends to a radius of about 5 neighboring glomeruli. Granule cells are axonless and form interconnections between mitral and tufted cells. The functions of this local circuitry are less well known, but it does appear that they synchronize neuronal discharges from cells that belong to different glomerular modules, which may converge onto a single target neuron in the olfactory cortex [16,34]. The synchronized discharges may serve as a mechanism for combining signals, generated simultaneously or within a small time interval, from two different neurons in the olfactory bulb.

Different theories have been proposed about other functions of the interglomerular neurons. Mori and others have hypothesized that these neurons are responsible for lateral inhibition, a process in which neuronal activity in an individual cell is inhibited when neighboring cells are activated [16]. If the molecular receptive ranges of neighboring neurons are closely related, lateral inhibition would amplify local differences, the equivalent of edge enhancement in vision processing. This would serve to enhance the tuning specificity of individual neurons.

Gilles Laurent, at the California Institute of Technology (CalTech), challenges this interpretation, positing instead a systems oriented viewpoint [34]. Laurent proposes that lateral inhibition may serve to eliminate redundant information and possibly perform other data optimization, thus sharpening the tuning curves of the system as a whole rather than those of single neurons. Laurent points out that there is no convincing evidence that the position of a neuron is a factor in olfactory processing, as it is in vision, where light pixels close to dark ones may make an increase in contrast desirable. Instead, it is the identity of the neuron which is of importance. This calls into question the benefit to be gained by more strongly distinguishing the signal of a neuron from those of its close neighbors. Additional investigations into the processes of olfactory bulb local circuitry will be needed before its functions can be clearly established.

The olfactory neurons, unlike almost all other neurons, are short-lived. Individual neurons are replaced every 30 to 60 days, and the axons of replacement neurons must find the way to their respective glomerulus, one among thousands, on a daily basis [1,14,35]. In 1998, Axel and others speculated that finding the path to the right glomerulus was an inborn characteristic [4]. They hypothesized that the OR gene is not only expressed on the cilia, providing molecular binding sites, but may also be expressed on the axon, where it would serve to help guide the axon to its designated glomerulus. Additionally, the OR gene may need to be complemented by other guidance receptors in order to form a complete set of directions which takes the axon to its destination.

This hypothesis was verified in a 2001 study of the Drosophila (fruit fly) olfactory system by Liqun Luo at Stanford University [7]. Luo and his team demonstrated that the information which leads pairs of neurons to make the correct intersections, or synapses, appears to be part of their programming from birth. The axons of all neurons born with the same OR type found their way to the same glomerulus, no matter where in the epithelium they were located. The OR gene thus controls not only the type of receptor expressed on a neuron, but also the destination for that neuron's signals. This result, along with other recent research, suggests a high degree of genetic programming, or hardwiring, in the olfactory system [8].

2.2.2 Zones in the Olfactory Bulb

The zonal organization of the epithelium (discussed in Section 2.1.1) is carried forward to a corresponding zonal structure in the olfactory bulb; axons maintain zonal segregation as they project into the olfactory bulb [16].

Just as neurons with similar amino acid structures tend to be clustered in the same epithelial zone, glomeruli which have overlapping specificities also tend to be clustered in the same area within a bulb zone. Thus, the spatial arrangement of activated glomeruli creates a characteristic map in the olfactory bulb.

Recent studies also have shown that the positions of the glomeruli are fixed within a species; therefore all animals in a species will have the same brain activity pattern in response to a particular odorant [4]. Since each glomerulus receives input from a limited set of receptor neurons, and the positions of the glomeruli are topologically fixed, this generates in the olfactory bulb a two-dimensional map of stimulated receptors [8]. A "combinatorial" coding scheme for identification of odorants seems to be operational here; the particular combination of glomeruli and receptors that have been stimulated form an identification code, or signature, for that odorant.

It is important to recognize the distinction between the physical location and the "identity" of a glomerulus, as defined by its input receptor neuron type. In certain cases, physical location may be important. All animals use odor data to reveal their environment, and the speed with which that information is decoded may be of critical importance for survival. Thus, it may be that certain odors activate glomeruli whose location matters. For example, these glomeruli may provide greater speed in transmitting certain signals from the nose to the brain to reduce reaction times. In general, however, there is no data to show that the position of a glomerulus, as opposed to its identity, is of importance in the downstream processing of odor information. As Laurent points out, whether and how the brain makes use of receptor and glomerular position is still an open question [34].

2.2.3 Temporal Aspects of Signaling

The role of the timing of neuron signals in odorant identification has been the subject of numerous studies in recent years [9,16,34,36-46]. This temporal aspect of neuronal activity includes fast oscillatory synchronization of pulses as well as slow patterning, which occurs over hundreds of milliseconds. Information required for the identification of at least some odorants appears to be contained in the timing of these action potentials. In particular, it appears that the olfactory system uses synchronization and patterning of pulses in at least two ways: to determine odor concentration, and to separate constituents within a blend of odors [45].

The temporal aspects of olfaction have been of particular interest to Laurent, whose laboratory at CalTech has been a center of research in this area. In 1997, Laurent and his colleague Mark Stopfer demonstrated that synchronization was necessary for odor identification. Specifically, they found that induced desynchronization of signals impaired the ability of the olfactory system to discriminate between similar odors [39].

In studies of the olfactory system of the zebrafish, Laurent and his colleague Rainer Friedrich found that odorant stimulation is represented in the olfactory bulb by a pattern of activity across many mitral cells [9]. The mitral cell activity pattern for an odor thus changes continuously over the stimulus period. Laurent and Friedrich found that the slow temporal patterning in the zebrafish olfactory bulb reduced the similarity in patterns for related odors. Over time, this made each odor's representation in the olfactory bulb more specific, and served to "tune" the responding mitral cells as an ensemble rather than as individual neurons.

In 2000, Thomas Christensen and John Hildebrand of the University of Arizona were able to show, in a study of the moth olfactory system, that neuron firing synchrony depends strongly on contextual variables such as odor intensity and different pulsing patterns used to inject the odor stimulus into the olfactory system under study [42]. Their study also showed that the temporal behavior of the neurons for a blend of odors could not be predicted from the behaviors of the neurons for the constituent odors. This means that the reaction of the olfactory system to an odorant blend is not simply a "sum" of the reactions to the individual odor components.

Synchrony and timing of odor signaling is not as well understood as the functioning of the individual olfactory receptor neurons. Temporal aspects of odor processing are clearly important, but a better understanding of their function within the olfactory system awaits additional investigation. The following section presents the hypotheses of various researchers about how spatial (which refers to neuronal receptor type) and temporal processing, as currently understood, might contribute to odorant identification.

2.3 ODOR IDENTIFICATION

After the olfactory bulb, the next step in odor identification is signal processing within the olfactory cortex, which is in the brain. Here, the complexities of brain functioning make further explorations extremely difficult. Nonetheless, the understanding that has emerged most clearly is, as explained above, that the olfactory system makes use of a spatio-temporal coding system for odorant identification. Buck and her team at Harvard Medical School investigated the spatial aspects of the code, and in March 1999, Buck and Bettina Malnic were able to prove that different odorants are recognized by different combinations of olfactory receptors [5]. Even slight variations in the odorant or in its concentration changed the make-up of the set of receptors

which recognized the odorant. This finding demonstrated that the brain makes use of a combinatorial coding scheme, in which each odorant has an associated receptor code or signature.

In November 2001, Buck and Zhihua Zou were successful in marking the pathway of neurons all the way from the nose to the brain, and showed that there is predetermined order in the projection of neurons from bulb to cortex [8]. Zou, along with Lisa Horowitz, inserted a transneuronal tracer called barley lectin (BL) into two odor receptor genes, M5 and M50, expressed in two different zones in the olfactory epithelium. The BL marker is transferred across synapses to connecting neurons, labeling chains of connected neurons. This allows tracing of an entire neuronal route.

What Buck's team found was that marked neurons projected a route to one or two glomeruli symmetrically located on each side of the olfactory bulb, and from there to several clusters of neurons in the olfactory cortex. Signals from a particular receptor neuron cause the excitation of specific clusters of cortical neurons, demonstrating the existence of a stereotyped, or fixed, sensory map in the olfactory cortex. Furthermore, the neuron clusters in the cortex were not randomly distributed. The distribution pattern for a given receptor type was the same for all mice with the engineered M5 and M50 genes. This similarity in the cortical sensory map across a species also offers an explanation for commonality in odor perception; skunk odor is repellant to everyone, while most people enjoy the smell of lavender or roses.

The research of Buck et el. also yielded other significant results, including indications of both the divergence and convergence of signals into the cortex. It appears that signals from different receptor types first converge in the olfactory cortex. Initial signals from the epithelium to the olfactory bulb are segregated by receptor type. Neuronal projections from the bulb to the cortex do not maintain this segregation, however, since inputs from different olfactory receptors map onto partially overlapping neuronal clusters in the cortex. Individual cortical neurons seem to receive inputs from up to 50 different types of receptors. Since an odorant is recognized by a specific combination of receptor neurons, the convergence of signals from different receptors in the cortex may reflect the initial integration of the various signals which make up the "code" for that odorant.

The convergence of signals in the olfactory cortex leaves open the possibility that much information from individual neurons is lost. If this were the case, however, it would render useless the previously described careful segregation of signals by receptor type, and that would run counter to nature's tendency to maximize the efficiency of such highly evolved systems. The solution to this puzzle may lie in the second component of the coding scheme, which is temporal signaling. If we include neuronal timing, synchronization, and patterning of an ensemble of signals in the coding scheme, along with neuronal identity, then the coding scheme becomes capable of representations of complex information using far fewer neurons at higher processing levels than were required at lower levels.

Laurent and his colleagues at CalTech have conducted numerous studies on the timing patterns which emerge as olfactory signals are sent from the bulb to the brain [9,36-39,41,43]. As discussed previously, early in their investigations they demonstrated that the synchronization of signals was essential for fine odor identification [39]. They also demonstrated a convergence of signals in the cortex, as they found that information encoded in the timing of spikes across an assembly of neurons converges onto single neurons in the cortex [37]. From these findings, Laurent infers that the brain can "reconstruct" an odor from the information contained in the spike trains of this neural assembly.

A 2002 study of the insect (locust) olfactory system by Laurent and Perez-Orive confirmed again the convergence of signals in the cortex [43]. They showed that while signals in the antennal lobe (the equivalent of the olfactory bulb in mammals) were dense and seemingly redundant, they were sparse in the mushroom body (equivalent to the cortex) and carried by more selective neurons. There may be advantages to a sparser representation of odors, including a reduction in overlaps between individual odor representations, and simpler comparisons between stimulus-evoked patterns and stored memories.

In the systems viewpoint adopted by Laurent and others, olfactory processing is modeled by positioning the odorant within a coding space defined by the features of the odorants [38]. Odorants are mapped to a position in such an "odorant space" based on their spatio-temporal pattern of activated neurons. One round of processing performs "decorrelation," in which the overlap between representations of related odors is reduced. This is the equivalent of spreading out the representations within the odor space. A concurrent or closely following set of processing is responsible for "sparsening," or compression of the representations into only a few active neurons. The latter results in an increase in specificity for individual neuronal responses.

Final transmission of olfactory signals to the frontal cortex regions suggests the brain may perform parallel processing of olfactory inputs. The olfactory cortex is composed of several anatomically distinct areas which may have different functions. Buck and Zou found that the labeled neurons projected to clusters in most of these cortical areas [8]. Since each area in the olfactory cortex can transmit information to different frontal cortex regions, this suggests that information from the same olfactory neuron eventually may be transmitted to different regions of the cerebral cortex. The divergence

of signals in the cortex would allow the same input data to be organized and processed in several different ways, aiding in correct identification of the odorant.

In summary, the research just discussed suggests that the odor processing appears to rely initially on careful segregation of signals from individual neurons. Individual information streams are maintained for each neuron from the epithelium to the olfactory bulb. Additional "temporal" information, timing and synchrony of signals, appears to be generated within the bulb. This temporal information may be based upon the incoming "spatial" information, which conveys the identity of the particular combination of stimulated neurons. The additional temporal information appears to be incorporated into the data flow as the signals travel from the bulb to the olfactory cortex. Within the olfactory cortex, spatial data are compressed, as multiple signals from the bulb converge onto single neurons in the olfactory cortex. If information is not lost at this stage, it seems likely that temporal data now contain some of the information which would otherwise be lost in convergence of spatial data. Finally, information is sent from the olfactory cortex to many other regions of the brain, which appears to perform parallel processing to arrive at final odor identification. The high-level steps within the process of olfaction are summarized within the flow chart of olfactory processes, presented in Figure 6.

2.4 CHARACTERIZING ODOR SPACE

If we view olfactory identification as a representation of an odor within an odor space, and consider the odor space to be defined by a set of odorant features, the question remains what those features might be. The difficulty can be seen when olfaction is compared with the visual system or the auditory system. In vision, retinal cells are activated by light over a range of wavelengths. The wavelength of the incident light elicits a particular response in the photoreceptor. Similarly, audio receptors are activated by a range of sound frequencies. There is no similar continuum of physical descriptors which can be used to characterize odorants and their receptors [6,25,44].

One approach scientists have used to characterize the molecular receptive range of a receptor is pharmacological, based upon medicinal chemistry. Since each receptor binds with a small range of odorant molecules, one could establish the molecular characteristics that are common to that set of odorants. Stuart Firestein and Ricardo Arenada at Columbia University used this approach when they attempted to define the molecular range of a particular olfactory receptor known as the "I7" receptor [6]. They found an odorant molecule binding with the I7 receptor must have two specific characteristics: it must have an aldehyde

carbonyl, and it must be of length between 8 Å (one Å, or "angstrom," is 10^{-10} meters) with at least seven carbons in the backbone, and 12 Å with no more than eleven carbons in the backbone. They found odorants binding to I7 subject to very strict constraints on molecular structure at the carbonyl head of the molecule, while allowing a wide range of variations at the tail end. Extrapolating this result to other receptors would indicate that a receptor may be highly specific for a particular structural component, while being largely indiscriminate for other components of an odorant molecule. This provides us with a general model of receptor affinities: a narrow spectrum of specific characteristics combined with a wide tolerance band for other characteristics. The brain then integrates input from the receptor neurons to generate a representation of an odorant's molecular composition and structure. As higher-order centers of the brain integrate input from a number of receptor neurons, they would be able to distinguish a wide variety of odors, while at the same time they are able to discriminate among odors with only subtle differences [25].

2.5 KEY OPERATIONAL PRINCIPLES OF NATURAL OLFACTION

The olfactory system is a remarkably effective sensing system. With organs that have, in humans, dimensions of only a few centimeters, and using the nanometer-scale transduction process of molecular recognition, the olfactory system is able to recognize and distinguish, with great accuracy, many thousands of odorants. In the preceding subsections we have examined, in some detail, what is now known about the components and operations of the natural nose and sense of smell. Here we present a summary of that examination, and conclude by identifying what appear to be the major operational principles of natural olfaction that have import for the design of artificial analogs.

The model the olfactory system presents has three main components: the sample handling system, the sensing system, and the signal processor. Sample handling in the nose is performed by the physical nasal structure as it ensures an even airflow of odorant molecules across the epithelium, and then allows an influx of fresh air to perform a "wipe-clean" function, as molecules initially adsorbed to the surface are desorbed again. This clears the receptors, and thus resets the system [24].

The other two components of olfaction, sensing and signal processing, are not wholly separable. As discussed earlier in this report, information required for odorant identification is contained in assemblies of stimulated neurons and their interrelationships, rather than within a single neuron [34]. This means that the sensing function

An odorant molecule binds with a receptor protein within the olfactory epithelium

⬇

The binding event is transduced into an electrochemical signal (See the Transduction Flow Chart, Figure 4)

⬇

The combination of stimulated receptor types forms an identifying "signature" for the odorant; signals segregated by receptor type transmit the signature to the olfactory bulb

⬇

Within the Olfactory Bulb:
Signals from receptor neurons are relayed to secondary neurons Other intra-bulb processing occurs, possibly converting some spatial into temporal data

⬇

The processed signature is transmitted by the secondary neurons to the olfactory cortex, where the signals converge onto far fewer neurons

⬇

Odorant signature is transmitted to other regions of the cortex; this parallel processing includes signature comparison with stored memories
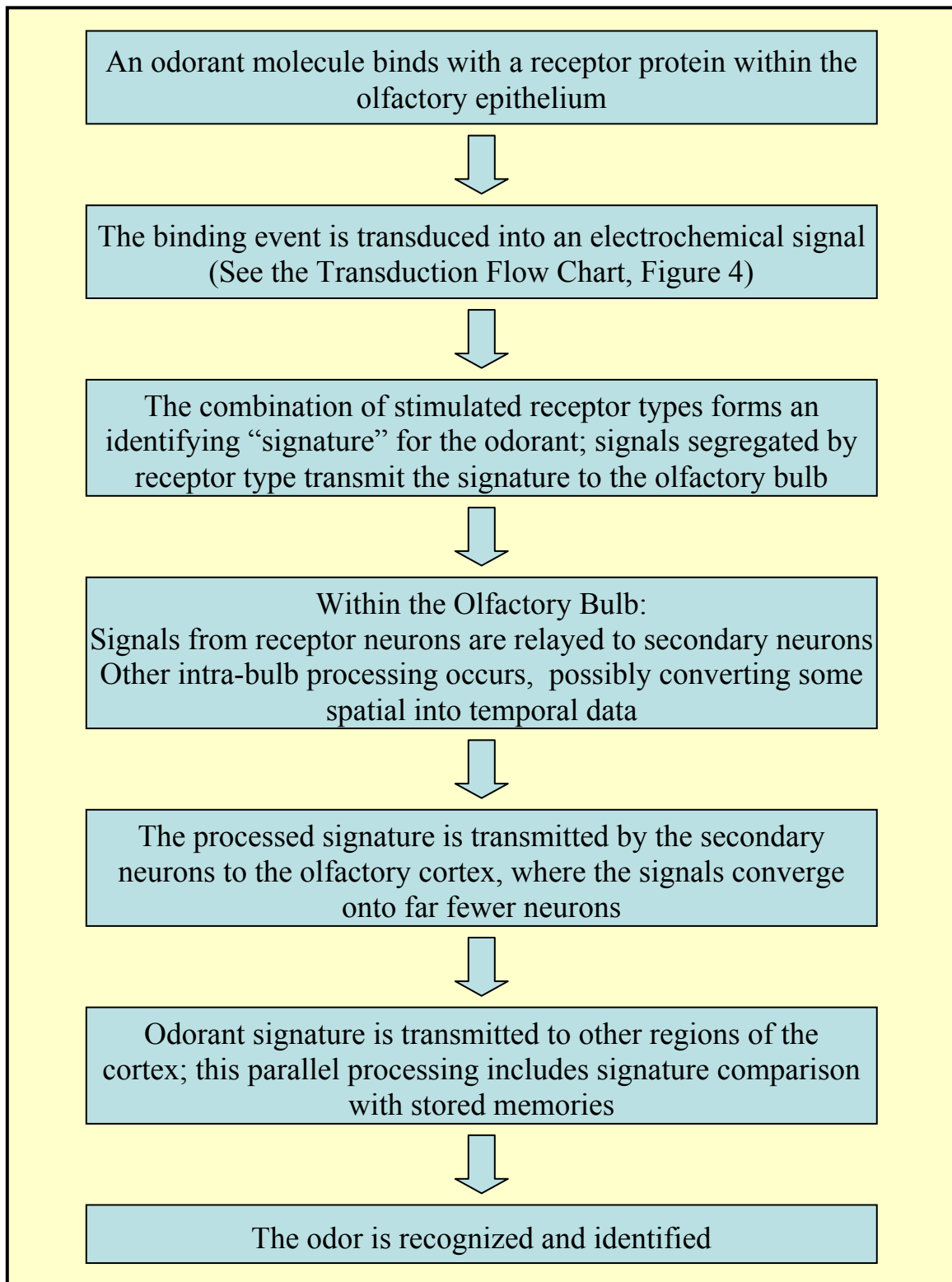
⬇

The odor is recognized and identified

Figure 6. Flow Chart of the Olfactory Processes

itself also provides initial signal processing, as, for example, in highly parallel neuronal sensing wherein the convergence of signals improves signal-to-noise ratios. In spite of this overlap it is possible to characterize broadly both the sensing and signal processing systems. The odorants arrive at the epithelium in an air flow, and are sensed, via molecular recognition, by a multitude of tiny neuronal sensors. Each neuron hosts many protein-receptors, all of the same type. The receptors bind with a limited range of odorant molecules that have similar molecular structures. In this way, each neuron acts as a sensor for a set of molecules that have one or more common molecular features. An incoming odorant will bind with a diverse set of neurons, each of which registers a particular feature of the odorant's molecular structure. Thus, the range of molecules to which a neuron is receptive will generally overlap with the ranges of many other, different, neurons. The sensing function of the epithelial neurons results, finally, in the activation of a set of neurons which provides an initial signature for that odorant.

Olfactory signal processing is highly complex, and not yet well understood. Researchers are in agreement, however, that data processing makes use of a spatio-temporal combinatorial system and also draws on stored memories in order to complete odorant identification. Signal processing begins with the sensing process, as an encounter with an odorant produces a spatial "map" of activated neurons in the epithelium. The neuronal signals then are projected into a corresponding map of activated glomeruli in the olfactory bulb. This glomerular map preserves the signature generated by the activated epithelial neurons. Further processing in the bulb and the cortex is not well understood, but it appears that intra-bulbar neurons may refine the signature received in the bulb through temporal (signal timing and synchrony) processing. In subsequent data transmission to the olfactory cortex, signals from different glomeruli, and hence from different neurons, are combined. Signal convergence in the olfactory cortex may serve as a step to providing the composite picture of the odorant required for identification.

Although the path of olfactory signals from epithelium to olfactory bulb to olfactory cortex has been identified, other areas of the brain also participate in olfactory signal processing [1]. Signals are sent from the olfactory bulb to several different areas of the olfactory cortex as well as to subcortical limbic structures, whose functions include memory processing. In addition, signals may be projected from one region of the olfactory cortex to another, from the olfactory cortex to the neocortex, and even from the olfactory cortex back to the olfactory bulb. The processing of these olfactory signals in various regions of the brain is not yet understood.

Thus, from our current knowledge of olfaction we can identify the following important features of the sense of smell, which appear to be among the most significant operating principles of olfaction:

- *Operation of vast numbers of very small, densely spaced, sensing neurons*

- *Sensing neurons which are non-specific sensors, in that each neuron is sensitive to a small range of odor molecules that have one (or a few) common structural features*

- *The sensing range of an individual neuron overlaps with those of other neurons; each neuron senses different features of a particular molecule*

- *Repetition of the same sensing neuron many thousands of times within the epithelium (sensing platform), serving to increase the likelihood of odorant binding with receptive neurons and amplifying sparse signals*

- *Odorant identification using, along with stored odor memories, a spatio-temporal combinatorial system, in which activated sensor-neurons provide a "signature" which can be used to identify the odor*

Although our knowledge of the sense of smell and its operations is far from complete, these features of the olfactory processes are likely to serve us well as we move on to consider artificial analogs of the nose and its sense of smell.

3.0 ELECTRONIC NOSES: CHEMICAL SENSING SYSTEMS

Now that we have completed a review of the operations of the natural nose, we will examine some of the diverse artificial chemical sensing systems which have been built in an attempt to imitate the nose. Artificial noses, usually known as "electronic noses," have been designed to sense and identify odorants, or volatile organic compounds, in ambient air. Electronic noses differ from other sensing systems in that they are meant to operate in the noisy sensory environment of open air rather than in the laboratory. Sensing the presence or absence of a particular substance within a controlled sample of air (or liquid) in a laboratory is a much simpler problem than detecting the presence of that substance in ambient air or water. Sensing elements that react to a particular chemical may react, as well, to many other substances with similar chemical structures. Thus, a single sensing element, viewed in isolation, is likely to produce many false positive readings, and may not correctly identify a particular chemical when it is part of a mixture. The sensing system of the natural nose, in

contrast, is not only highly sensitive, but it is capable also of remarkable discrimination among competing odors. Someone cooking dinner, for example, can smell the odors of the herbs and spices and oils of a simmering stew, but at the same time is able to isolate the odor associated with natural gas which warns of a gas leak. A wine connoisseur can pick up subtle differences in wines just by smelling them. Thus, the model provided by the natural nose is ideal for creating artificial sensing systems which operate effectively in the noisy natural environment.

Research on artificial noses is not new, but has been ongoing since the early 1980s [47]. Initial research efforts were geared toward artificial noses for use in the food and cosmetic industries, where they are still widely used to provide quality assessments in food production, flavor control, and quality grading of wines and beers. Electronic noses are used also in environmental monitoring for identification of toxic wastes, testing of ground water for hazardous chemicals, and monitoring of air quality and industrial emissions. Recently, progress has been made also in applications to health monitoring and medical diagnostics [48].

Electronic noses, as do natural noses, perform sample handling, sensing, and signal processing. The sample handling function provides an air-flow to the sensing elements, and, after sensing has occurred, must "wipe-clean" the sensing elements and bring them back to a known resting state. Some electronic noses may revert to a resting state simply by exposure to air, as the molecules initially adsorbed to the surface are desorbed again. Others may require exposure to a "washing gas" such as alcohol vapor, followed by a reference gas which drives the sensors back to their resting state [21].

Natural olfaction uses vast numbers of sensing neurons -- tiny, non-specific sensors -- to perform the sensing function. Thus, the olfactory sensing mechanism employs what can be considered to be a multitude of tiny gas sensors. The electronic noses reviewed here follow this model by using arrays of cross-reactive (non-specific) gas sensors. (Although there are also electronic noses using a single gas sensor, such as gas chromatography columns, only electronic noses using arrays of sensors will be considered here.) These electronic noses may be classified by sensor type, which results in the following major categories [21,49,50]:

- Electrochemical Sensors
  - Conductance-Based Sensors: Metal-oxide and Conducting Polymers
  - Potentiometric Sensors: Chemically sensitive field effect transistors (FETs)

- Mass-Change (Piezoelectric) Sensors
  - Quartz crystal microbalance (QCM)
  - Surface acoustic wave (SAW) devices

- Optical Sensors
  - Fluorescent optical fibers
  - Colorimetric

- Other Artificial Nose Systems

Table 1 presents a survey of electronic noses already developed or under development in each of the above-defined categories.

As described in Section 2, olfactory signal processing makes use of both spatial information (neuron type) as well as temporal information (timing and synchrony of signals). Today's electronic noses, in contrast, apply a simplified version of this data processing model, using only spatial information to make identifications. The type of sensor element that has been activated by an odorant, as well as the strength of its response, become inputs to the data model. Analysis methods commonly used include multivariate data analyses, such as principal component analysis (PCA) or discriminant function analysis (DFA), or a non-parametric method such as artificial neural networks (ANNs) [50]. Olfactory-like signal processing for electronic noses has been an area of interest to many researchers, both here and abroad, for several years [18,19,51-58].

A review of the literature was conducted to identify examples of electronic noses using each type of gas sensor, with particular attention to electronic noses whose size is on the micrometer or nanometer scale. The search was conducted primarily within the Journals and Proceedings of the Institute for Electrical and Electronics Engineers (IEEE), as found online in *IEEE Xplore* journal and conference paper repository, the journals of the American Chemical Society, *Science*, *Nature*, *Sensors and Actuators A* and *B*, other databases of scientific journals, the *Handbook of Machine Olfaction* [50], and on the wider Internet. It should be noted that the specific examples of electronic noses presented here are not an exhaustive list of all such sensing systems, but are representative of the smallest electronic noses found in each category.

Sensor Type	Description	Researcher/Developer
Conductance-Based Metal Oxide	Sixteen tin dioxide sensors on a 4x4 mm^2 chip, for sensing of all gases except nitrogen and the noble gases	Joachim Goschnick et al., Karlsruhe Research Center, Karlsruhe, Germany
Conductance-Based Metal Oxide	Ten tin dioxide sensors on a 1.1 x 1.2 cm^2 substrate; senses combustible and explosive gases	Dai-Sik Lee, Duk-Dong Lee, et al. Telecomm. Research Institute (ETRI) Taejon, Korea
Conductance-Based Carbon Black Composites	Research in carbon black composites for sensing explosives and chemical agents	Nathan Lewis, et al. California Institute of Technology Pasadena, California
Conductance-Based Carbon Black Composites	Commercial production of hand-held devices using carbon black-composite sensors; can be used for sensing chemical and biological weapons agents	Smiths Detection – Pasadena, Inc. (formerly Cyrano Sciences, Inc.) 73 N. Vinedo Avenue Pasadena, California 91107
Potentiometric - ChemFETs	Research toward development of a chemical sensing "nose on a chip"	Julian Gardner, University of Warwick Tim Pearce, University of Leicester Alister Hamilton, University of Edinburgh
Mass-change Surface Acoustic Wave	Array of eight cantilevers, each approximately 500μm x 100 μm x 1 μm, for gas sensing in ambient air and bio-sensing in solution	Christoph Gerber, et al. IBM Research Division Zurich Research Laboratory
Mass-change Surface Acoustic Wave	Array of cantilevers on a chip approximately 8 mm x 2 mm for biosensing in ambient air	William Hunt, et al. Georgia Institute of Technology
Mass-change Surface Acoustic Wave	Commercial production of hand-held devices using SAW sensors; used for chemical weapons agents and other toxic chemicals	Microsensor Systems Inc. 62 Corporate Court Bowling Green, KY 42103
Optical	Flourescent beads, each 3μm in diameter, in microwells on the tips of optical fibers; demonstrated for sensing of gases, including nitroaromatic compounds	David Walt et al. Tufts University Tim Pearce, University of Leicester
Optical	Optical fiber sensors demonstrated to detect TNT in landmines	John Kauer, Joel White Tufts University School of Medicine
Optical	Commercial production of bio-sensors in a BeadArray^{TM}, used for genotyping and gene expression profiling	Illumina. Inc. San Diego, California
Optical - Colorimetric	Color change in metalloporphyrins upon exposure to toxic gases	Neal Rakow, Kennth Suslick University of Illinois at Urbana-Champagne
Combination of Mass-change, Capacitive, and Calorimetric Sensors	Sensor system on a 7 mm x 7 mm chip, integrates 3 different gas sensors, a temperature sensor, plus microelectronic and micromechanical components; demonstrated to sense ethanol and toluene	A. Hierlemann et al. Physical Electronics Laboratory Swiss Federal Institute of Technology Zurich

Table 1. An Overview of Selected R&D into Electronic Noses

3.1 Electrochemical Sensors

Electrochemical sensors demonstrate detection and recognition of a chemical by a change in conductance, resistance, or electrical potential. There is little practical difference between sensors that measure conductance and those which measure its inverse, resistance, so these two sensor types will be discussed together as "Conductance-Based Sensors." Field effect transistors (FETs), such as metal oxide-semiconductor FETs (MOSFETs) and other chemically sensitive FETs (ChemFETs) are the most common chemical sensors that operate via measurement of change in the potential [21,49].

3.1.1 Conductance-Based Sensors

Conductance-based sensors were among the earliest sensor types developed by pioneer researchers in this field in the early 1980s [21]. In conductance-based sensors, an active material, which may be either a metal oxide or a conducting polymer, is deposited between two metal contacts, as in Figure 7. Binding of a target agent, a volatile organic compound, with the sensing platform causes a change in resistance between the metal contacts. This change in resistance is proportional to the concentration of the organic compound, and thus the sensor provides an indication of both presence and quantity of the target agent.

3.1.1.1 Metal Oxide Sensors

Metal oxide-based sensors use a variety of different oxides, most commonly tin, but also zinc, titanium, tungsten, or irridium, and they are usually doped with platinum or palladium. These sensors also require the incorporation of a resistive heating element, because they operate at temperatures between 200ºC and 400ºC. The sensing platform can be designed using different combinations of metal-oxide and dopant to respond to specific organic compounds. Once the sensor is built, the response selectivity can be adjusted further by changing the temperature. The sensitivity for metal oxide-based sensors ranges from 5 to 500 parts per million [21].

The high operating temperature of metal oxide sensors is their biggest drawback, because it adds a requirement for a heating element and contributes to heat dissipation problems as well. The baseline sensor response also tends to drift with time, and the sensors can be rendered useless by irreversible binding with sulfur compounds. These drawbacks are offset, however, by the relative ease and low cost of their manufacture. Thus, metal oxide sensors have been the most commonly used gas sensors.

Electronic nose research began with metal oxide sensors in the early 1980's [21], and since that time the sensing elements in these devices have been shrinking steadily down to the micron scale. Joachim Goschnick and a team from the Karlsruhe Research Center in Karlsruhe, Germany, have been working for several years on a metal oxide electronic nose they call the "KAMINA," which stands for "Karlsruhe Mikro-Nase" (Karlsruhe Micro-Nose). KAMINA, which is shown in Figure 8, is designed to monitor indoor air-quality by sensing gases such as formaldehyde, carbon monoxide, and ammonia [59-61]. KAMINA features 38 or 16 sensors in micro-arrays of dimensions of 10 x 11 mm^2 and 4 x 4 mm^2. A micro-array is produced by partitioning a monolithic tin dioxide (SnO_2) or tungsten trioxide (WO_3) layer with very narrow parallel electrode strips made of platinum. Differentiation between the individual segments in the array is caused by temperature gradients and by the difference in thickness, from 2 nm – 20 nm, of a gas-permeable silicon dioxide (SiO_2) membrane applied over the metal oxide layer. KAMINA was able to detect some gases, including carbon monoxide (CO), at less than 1 ppm. A KAMINA sensing system that can be used for smoke detection, air quality monitoring and detection of nearly all gases, is available commercially from SPECS Scientific Instruments, Inc. of Sarasota, Florida [60]. Earlier versions of KAMINA were about twice the size of a cell phone. The present version of KAMINA incorporates a sensing chip and all processing elements in a device approximately half the size of a credit card.

Another research effort is that at the Electronics and Telecommunications Research Institute (ETRI) in Taejon, Korea, where a team led by Dae-Sik Lee and Duk-Dong Lee built a tin dioxide sensor array to sense combustible and explosive gases such as methane, propane, butane, and CO [62]. The ETRI team enhanced the sensitivity of the SnO_2 used as the base material in the sensors by employing calcium (Ca) and platinum (Pt) catalysts to reduce the size of the SnO_2 grains to 8 nanometers, and thereby increased the overall surface area and reactivity. This material then was enhanced with 10 different additives, modifying the sensitivity spectrum of the base material to create 10 different sensors which were placed on a 1.1 x 1.2 cm^2 alumina substrate. The 10-element sensing array was used in combination with a neural network analyzer to classify the kind of gas detected, and a neuro-fuzzy network to determine gas concentration values. This sensing system accurately recognized target gases and determined continuous concentration levels, at target concentrations of several hundred to several thousand parts per million, with error rates of less than 5%.

Figure 7. A Conductive Sensing Device

Odorant molecules which bind with the active material cause a change in its conductivity. The metal-oxide sensing material operates at temperatures of 200° to 400°, and this sensor therefore requires a heating element.

This figure modified and reproduced with permission from Nagle, Gutierrez-Osuna, & Schiffman, "The How and Why of Electronic Noses," *IEEE Spectrum*, September 1998, p. 25.   © 1998 IEEE

Figure 8. The KAMINA Micronose

This micro-scale metal-oxide electronic nose has an array of either 38 or 16 sensing elements, each of which is approximately 1-2 square millimeters in size. A complete 16-element sensing chip is about 4 mm x 4 mm in size. The heating element on the reverse side of this chip is shown in the upper right corner.

Picture reproduced with permission of Dr. Joachim Goschnick, Karlsruhe Research Center, from Goschnick and Körber, "Condition Monitoring for Intelligent Household Appliances," Forschungszentrum Karlsruhe, Institut für Instrumentelle Analytik," 2002.

3.1.1.2 Conducting Polymers

Early versions of metal-oxide based sensors were built with macro-scale sensing arrays, and only more recently were they shrunk down to the micron scale. For conducting polymers to work, however, the sensor size *must* be on the micron scale. The two electrodes which experience the change in resistance are separated by a gap of only 10 to 20 μm, and the entire sensor surface area is less than 1 square millimeter [50]. Conducting polymer sensors have sensitivities of 0.1 to 100 ppm [21]. As with metal oxide arrays, varying the composition of individual sensors leads to a different sensitivity spectrum for each sensor.

Conducting polymer sensors operate at room temperature, so there is no need for heating elements; this makes for easier manufacturing. On the other hand, the fabrication process itself is more complex. The polymer bridges between the electrodes are formed in layers using a process called "electropolymerization," in which there is cycling of the voltage between the electrodes. The voltage sweeps act to deposit layers of polymer, and by varying the voltage sweep rate one can create a variety of different active materials, each engineered to sense a particular volatile organic compound (VOC). Unlike with metal-oxide sensors, however, the surface morphology of the conducting polymers is not predictable. As a result, the surface conductivity and, therefore, the sensing function is not entirely reproducible from batch to batch [21,49].

A number of naturally conducting polymers such as polypyrole and electroconducting conjugated polymers such as polyaniline, polythiophene, and polyacetate are used in electronic noses. All of these polymers are highly sensitive to gases and vapors, and experience a marked change in conductance upon the binding of the target analyte. It is also possible to make non-conducting materials such as silicon and polystyrene conductive by adding nanometer-sized particles of carbon called "carbon black" [50]. Unlike other nanomaterials, carbon black is very inexpensive and available in large quantities, which make polymer-carbon black composites attractive sensing elements.

The biggest operational drawback of conducting polymer is its high sensitivity to water vapor. This means that excess humidity can mask responses to VOCs. These sensors are also prone to drift over time, and in addition, they may encounter VOCs which penetrate the polymer base. Removing these VOCs from the polymer stretches out the recovery time, thus lengthening sensor cycle time [21].

The California Institute of Technology (CalTech) has been a center of research in the use of conducting polymers in microsensors for electronic noses. Chemist Nathan Lewis and his team members began their research in 1992 with the exploration of organic conducting polymers for use in nose-like sensors [63]. The drawback of the polyacetylenes they used originally was that, upon exposure to air, they lost their conductivity in only a few hours. Michael Freund, one of Lewis' postdocs, then experimented with polypyrrole, which did not deteriorate in the same way. Freund found that if he mixed different kinds of insulators into the polypyrrole, the resultant mixtures had different sensitivities to various solvents such as methanol, ethanol, acetone and benzene. Finally, Lewis and fellow chemist Robert Grubbs realized that they could achieve the same sensing effects by turning the process around and mixing conductors into insulating polymers. It turned out that carbon black particles function well as the conducting element, and Lewis continued his work building resistor arrays composed of insulating organic polymers into which carbon black conductors are dispersed. More recently, Lewis and his team members have designed these carbon black composite sensing arrays to detect explosives and chemical agents such as sarin and soman [64]. They have also used them in medical diagnostics, where they "smell" the air near a patient's head, called the "headspace," in order to diagnose certain illnesses without bodily contact [65].

This and other research on conductive polymers and carbon black composites has been applied successfully to commercial electronic noses by a company in Pasadena, California originally known as Cyrano Sciences, Inc. The company was acquired by Smiths Group PLC in March 2004, and is known now as Smiths Detection – Pasadena, Inc. This company markets a hand-held electronic nose, the *Cyranose® 320*, which houses a chip containing an array of 32 polymer carbon black composite sensors [66]. The *Cyranose® 320* can be customized for specific uses. The unit is "trained" by exposure to and measurement of vapors common to the client's application processes. The sensor activation patterns of vapors encountered in subsequent use are identified by comparison with signatures stored in a database of vapor patterns. The range of applications includes chemical detection, food production and process control. More recently, it has been extended to detection of chemical and biological weapons agents as well as medical diagnostics. Testing of the *Cyranose® 320* in applications to medical diagnostics showed that the device was able to identify, from headspace, several types of bacteria causing ear, nose, throat, and eye infections. It was even able to discriminate among subspecies of the same bacteria [48].

Smiths Detection – Pasadena also applies carbon black composite technology to produce customized products it terms NoseChips™, which are complete sensors on a dime-sized chip of less than 5 cm^3 in volume. NoseChips™ are made to order for specific sensing applications, and can be used as sensing nodes for facilities monitoring, for personal badge detectors, or incorporated into larger systems. NoseChips™ also can

be combined to form intelligent sensor networks for distributed monitoring of air quality in industrial settings or other large enclosed spaces [67].

Lewis and his team at CalTech continued their research into carbon black composites, and in 1998 they compared the performance of arrays of carbon black polymer composites, conducting organic polymers, and tin oxides in distinguishing among 19 solvent vapors [68]. Some of these solvents, such as methanol and benzene, had very different chemical properties, and others, such as *n*-pentane and *n*-heptane, were very similar. They found that the carbon black polymer composites significantly outperformed the tin oxide and the conducting organic polymers. In the Lewis study, carbon black-based systems proved best, on average, in pair-wise resolution of the 19 analytes tested. They also had the advantage of most accurately resolving the most difficult-to-resolve pairs of analytes. The performance of the carbon black composites in producing the largest mean statistical separation of response patterns for the analytes was approximately 5 times better than that of tin oxide and at least 8 times better than conducting organic polymers. The tin oxide detectors, however, displayed much faster response times. They consistently achieved steady-state responses in under 7 seconds. The carbon black composites and conducting organic polymers had longer and more varied response times, reaching steady-state responses in 20 to 200 seconds. The tin oxide array also displayed response magnitudes about 10 times greater than the carbon black composites and 15 times greater than conducting organic polymers.

At least for the particular analytes tested in Lewis's study, carbon black composites and metal oxides seem to outperform conducting organic polymers in resolution ability, speed, and response magnitude. Carbon black composites demonstrated better resolution than tin oxide for the analytes tested, while the situation was reversed for speed and response magnitude. The results of this study would seem to point toward the use of carbon black composites or metal oxides as conductance-based sensing elements. Choice of sensor material for an electronic nose might depend, to a certain extent, on a tradeoff between better resolving abilities or greater speed and response magnitude. Other factors such as operating temperature requirements, sensitivity to humidity, and cost and manufacturability, also must be considered.

This same study by Lewis et al. also attempted to identify an optimum number of sensors in the array. Previous discussion of this question centered around two main viewpoints. The first maintained that a fairly small number of sensing elements are needed to span odor space, and that the addition of more detectors adds to noise without significantly adding to classifying ability. The second, more closely following the paradigm of olfaction, held that one should incorporate as many sensors as possible. Doleman and Lewis found that their study supported the latter view; array performance increased as the number of different detectors increased. All three sensor types showed increasing resolving power with larger numbers of detectors, although there was a leveling off of performance as one approached the full complement of sensors.

3.1.2 Potentiometric Sensors

Field effect transistors (FETs) also can be used as sensors by making the gate sensitive to the presence of a gas [21]. Normally, a charge applied to a transistor gate opens the gate and allows current to flow. When the gate is modified by application of a sensing layer, incoming volatile organic compounds produce a reaction in the sensing layer. The reactants diffuse into the gate and cause the physical properties of the gate to change. The gate threshold voltage is altered, thus changing channel conductivity. Metal-oxide-semiconductor field effect transistors (MOSFETs), for example, may have their gates coated with a noble metal catalyst such as platinum, palladium, or iridium. More recently, conducting polymers such as polyaniline have also been used as the gate's sensing layer [49].

Potentiometric sensors have a natural advantage over conductivity-based sensors in that the magnitude of the signal they generate does not depend on the size of the sensing area [49]. They are transistors, and thus amplify small signals. This should make such chemical FETs (ChemFETs) good candidates for miniaturization. However, miniaturization of chemical sensors has not kept pace with that of conventional electronics; the size of today's transistor is now below 1 μm, and that of a ChemFET remains at approximately 5 μm, as it has been since the mid-1970's. This is because there are specialized requirements for chemical sensing arrays which are over and above those for conventional microelectronics. These requirements include thicker gate insulators which can withstand harsh chemicals. Gold or platinum must be used as conductors, because their inertness and electrochemical qualities make them preferable to the less expensive aluminum or polysilicon. One of the biggest drawbacks to micron-scale potentiometric sensing devices is that in order to measure a change in potential they require a reference component for comparison, analogous to the reference electrode in macroscopic potentiometric analytical devices [21]. A reference ChemFET would need to be shielded from exposure to the target gas. For an array of broadly sensitive ChemFETs, this adds the requirement for development of microchannels which conduct the target gas to the sensing ChemFETs, while preventing the reference ChemFETs and other chip electronics from being exposed to the target agent. This adds greatly to the complexity of device manufacture.

Among the groups attempting to develop an electronic nose using gas-sensitive FETs is a consortium of researchers at universities in Great Britain, where investigations into developing electronic noses first began [21]. Julian Gardner, a professor of engineering at the University of Warwick, is a pioneer in the field of electronic noses. He began his investigations in the early 1980's using metal oxide sensors. Later in the decade the Warwick team also began to use conducting polymers, and by 1993 they had developed an electronic nose for testing beer quality, using an array of 12 different conducting polymers [69].

More recently, Gardner has been collaborating with researchers at two other British universities, Tim Pearce at the University of Leicester and Alister Hamilton at the University of Edinburgh [70]. Their goal is to develop a neuromorphic analogue sensor on a very large scale integration (VLSI) chemical-sensing chip. This would be, in essence, a complete "nose on a chip." (See Figure 9.) The sensors being used are an array of polymer-gated FETs, each sensitive to different odors. They are to be combined with a diffusion microchannel for odor delivery to the FETs. The FET array will be combined with the signal processing components on a single chip that is approximately a square centimeter in size. The team is proposing to mimic the olfactory system much more closely than prior efforts have, in that the new system will model temporal as well as spatial processing. An encounter with a group of target molecules will cause trains of voltage spikes to be generated with a frequency proportional to the concentration of the molecules [71]. This attempt to emulate the temporal as well as the spatial aspects of olfactory processing is the only such research effort in electronic noses encountered by the author in the course of reviewing the literature for this report.

3.2 Mass-Change Sensors

Piezoelectric devices, which can be used to measure a variety of physical phenomena, are used in electronic noses to measure changes in mass [21]. Piezoelectric crystals have the interesting property that they naturally resonate under an applied voltage. The resonance frequency of a particular crystalline structure is dependent upon its mass. When the mass changes, the resonance frequency changes, and this frequency change can be used to report the presence of gases.

There are two types of piezoelectric devices used as sensors: quartz crystal microbalance (QCM) and surface acoustic-wave (SAW) devices. A QCM is a thin, polymer-coated resonating disk. Adsorption of gas molecules to the polymer coating increases the mass of the disk, thus changing the resonance frequency. QCM devices have been used by the military for several years to detect explosives and other hazardous compounds. They

can measure mass changes to an accuracy of 1 picogram (10^{-12} grams), which is the equivalent of sensing less than 0.01 ppm [21].

In surface acoustic wave (SAW) sensors, the waves travel primarily over the surface rather than throughout the device. A signal applied at an input transducer creates an acoustic wave which travels across the piezoelectric surface to an output transducer, having undergone a phase shift in that distance. The phase shift is due in part to the distance traversed, but also depends on the mass of the substrate. As gas molecules are adsorbed to the substrate its mass changes, and the frequency shift and phase shift in the traveling wave can be used to sense the presence of the molecules. Since they are planar, SAW sensors can be fabricated using microelectromechanical systems (MEMS) technology, and this makes their manufacture in large quantities relatively inexpensive [21]. A drawback is that SAW devices are very sensitive to temperature. A change in temperature also contributes to a change in resonance frequency, producing an ambiguous sensor response [72]. Another drawback is that as the SAW devices get smaller they get noisier. When SAW devices shrink, the surface-to-volume ratio increases, and this causes instabilities in the surface processes, which lead to degradation of the signal-to-noise ratio [21]. Reference sensors generally are included with a SAW sensing array so that temperature effects and noise can be subtracted from the sensor readings.

In 2003, a team from two German universities reported in the journal *IEEE Sensors* on the design and fabrication of a miniaturized QCM sensing system for liquids [73]. As of this time, however, QCM sensors still have not been miniaturized into arrays for gas sensing. Miniature SAW devices, on the other hand, have been the subject of several fruitful research efforts [72,74-78]. In the 14 April 2000 issue of the journal *Science*, Christoph Gerber, H.P. Lang, M.K. Baller, J. Fritz, and others at IBM Research Division, Zurich Research Laboratory, reported on the development of an electronic nose using a micromechanical cantilever array, in which each of eight cantilevers is coated with a different sensor layer [76]. This system is depicted in Figure 10. The individual cantilevers are 1 μm thick, 500 μm long, and 100 μm wide, with a pitch of 250 μm and a spring constant of 0.02 Nm^{-1}. Adsorption of a compound onto the cantilever results in a change of mass, causing a deflection of the cantilever. The amount of deflection is measured using an optical beam deflection technique. Alternatively, the cantilever array can be actuated by a piezoelectric drive controlled by a phase-locked loop (PLL) unit, in which case the mass change can be sensed by measuring changes in cantilever resonance frequency. Using this sensor in ambient air, the IBM team was able to demonstrate detection of various analytes, including ethenes, alcohols, natural flavors and water vapor [74,75].
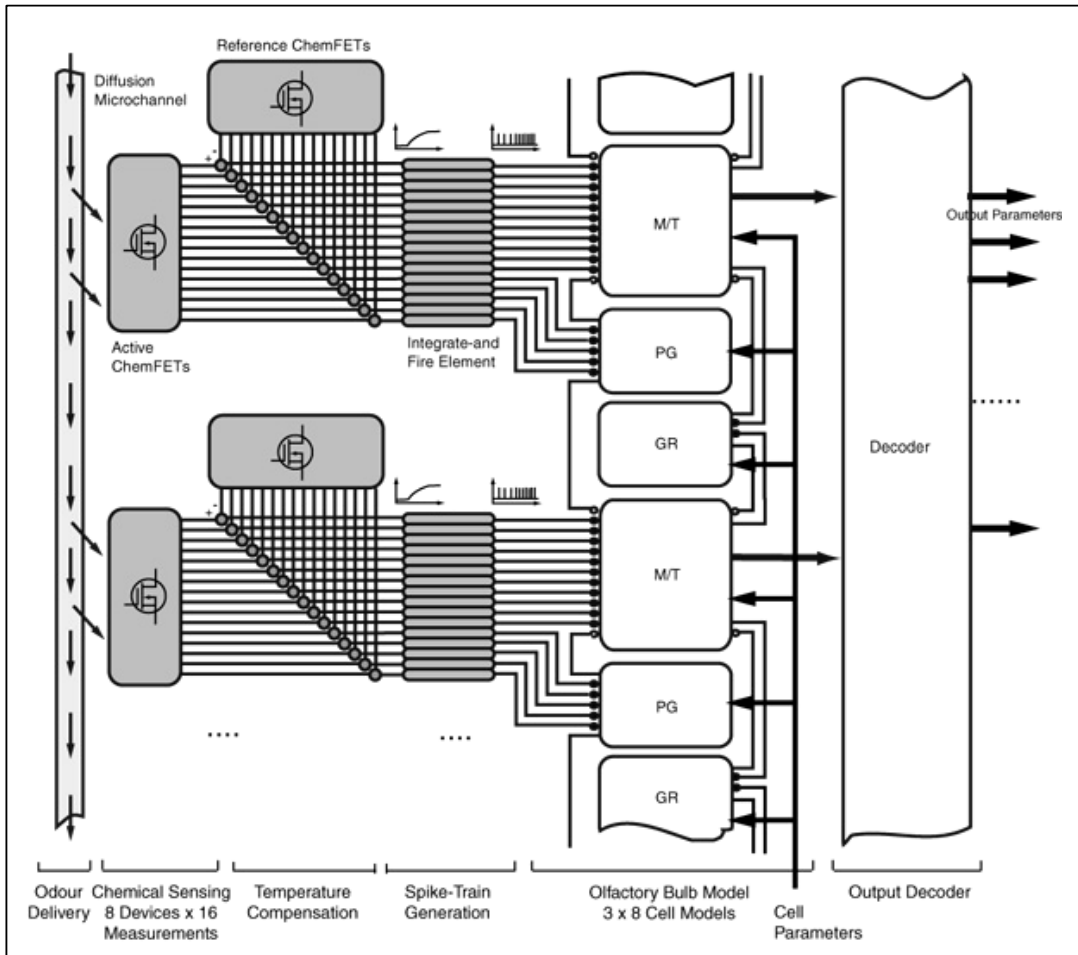
Figure 9. The Warwick/Leicester/Edinburgh Nose-on-a-Chip

A design for an electronic nose using ChemFET sensors. Both the sensing and the processing components are meant to mimic the components of the olfactory system.

This figure is reproduced with permission of Dr. Tim Pearce of the University of Leicester, from his website "Silicon Olfactory System Implementation," http://www.le.ac.uk/eg/tcp1/avlsi/
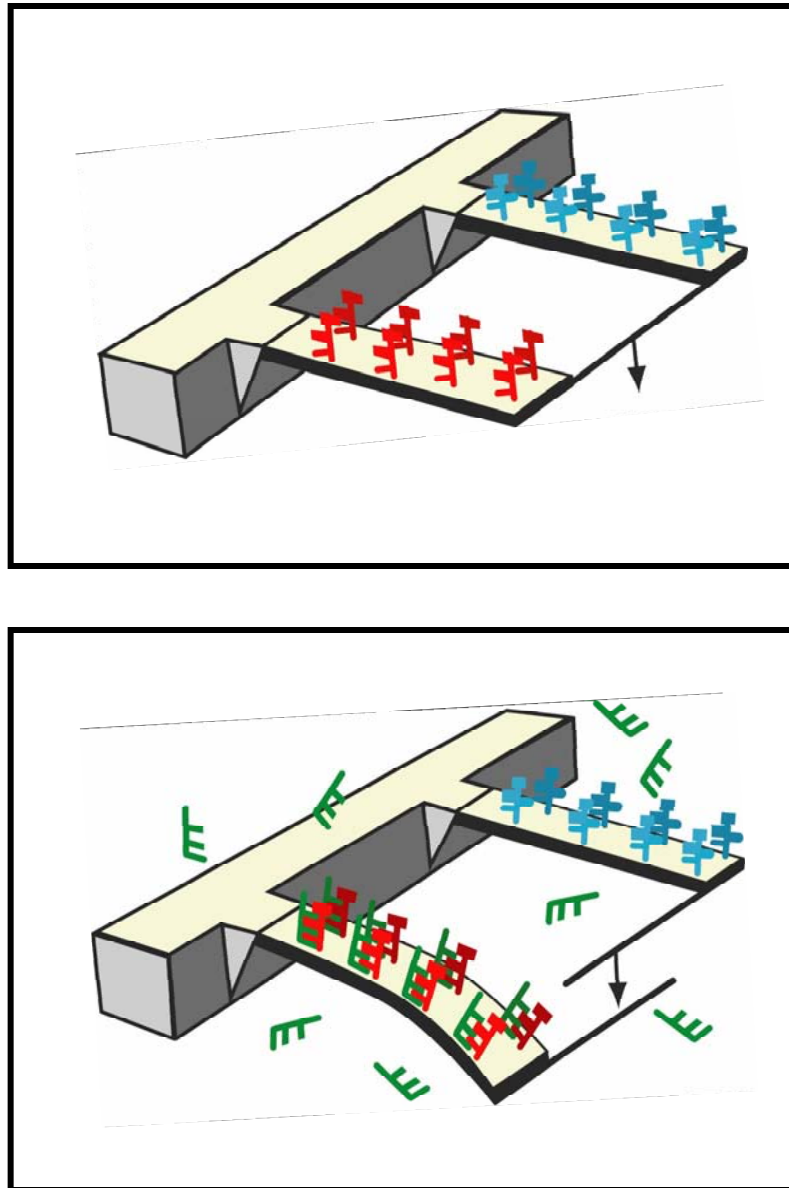
Figure 10. IBM's Cantilever Array

The micromechanical cantilevers in IBM's cantilever array are coated with a sensing layer. Adsorption of the mass associated with a target compound onto the cantilever can be detected by a change in cantilever deflection, or by a change in cantilever resonance frequency.

Picture reproduced with permission of Dr. Christoph Gerber, IBM Zürich Research Center, from the IBM Zürich Research Laboratory website, http://www.zurich.ibm.com/st/nanoscience/bio_DNA.html.

They also used the cantilever sensor in a liquid cell, where the cantilevers were functionalized with a range of different biomolecules. With that modification they were able to demonstrate detection of a single base pair difference between DNA strands [76].

Using gas sensors to recognize biomolecules can be difficult. This is because of the low vapor pressure of biomolecules, such as antibodies, and because they must be in an aqueous environment in order to maintain their structure and function [77]. In 2002, however, William Hunt, Desmond Stubbs, and Sang-Hun Lee at the Georgia Institute of Technology successfully demonstrated recognition of biomolecules in the vapor phase using an electronic nose with SAW sensors [77]. Using a layer of antibodies as the substrate, they were able to observe a baseline frequency shift when the analyte presented was the antigen for the immobilized antibody. To ensure that the frequency shift they were observing was, indeed, due to antibody/antigen binding, they performed an independent check using a confocal laser scanning microscope. With this instrument they were able to identify the locations of the attached analytes, verifying that the SAW gas sensor was observing molecular recognition. The size of the SAW chip used was 8.10 x 1.98 mm^2, with individual resonating electrodes 1.5 μm in width.

As was the case for metal oxide and carbon-black composite sensors, a hand-held device using SAW sensing elements is available commercially. Microsensor Systems Inc. of Bowling Green, Kentucky, has combined millimeter-scale SAW gas sensors with electrochemical cell sensors in their HAZMATCAD Plus™ chemical agent detector [79]. This device is 5.8 x 20.0 x 24.9 cm in size, and detects chemical weapons agents such as nerve, blood, and blister agents. Nerve agents can be identified at 0.04 – 0.14 ppm in 20 seconds when operating in fast mode, or at 0.01 – 0.03 ppm in 120 seconds in high sensitivity mode.

3.3 OPTICAL SENSORS

Optical fibers also can be used as the sensing elements in artificial sensors that simulate noses [21]. Optical fibers are composed of an inner ring, called the "core," and an outer ring, called the "cladding" [80]. A slightly higher refractive index in the core than in the cladding allows light to be transmitted for long distances through the fiber. These fibers can be turned into sensors by attaching sensing material either to the fiber's end, or by removing the cladding and coating the sides with it. The sensing materials used are polymers that contain chemically active fluorescent dyes. The presence of a target agent causes a change in the polarity of the fluorescent dyes, which, in turn, causes a shift in

wavelength. The sensor is read with a pulse of light from an external source; activated fluorescent dyes then emit light with a shift in emission spectrum [21]. The polymers react differently to different agents, and the resulting fluorescence changes over time create a pattern which acts as a signature for that agent.

For the past ten years David Walt and his team at Tufts University have been conducting leading research on optical fiber sensors. As early as 1996 they devised an artificial nose composed of 19 individual optical fibers [81]. Their sensor was able to identify components within mixtures, and also could characterize test compounds on the basis of chemical characteristics such as functional groups and relative molecular weight. Those fibers, at a diameter of 300 μm, were relatively large. By 1999, Walt's team had modified this approach by using as sensing elements thousands of spherical fluorescent beads, each only 3 μm in diameter [82]. In place of the larger, single-core fibers, they used optical image guides, 500 μm in diameter, which enclosed approximately 5000 closely packed optical fibers, each of diameter 3.5 μm. The microbeads were then distributed randomly into chemically etched microwells on the faces of the optical fibers. The beads, which were of three different types, were encoded so that once in place, each bead could be identified. The sensing system was "trained" to identify the sensor bead type at each location, and was then successfully used to detect the presence of four different vapors, methanol, dichloromethane, toluene, and acetone.

This approach, using large numbers of sensors of a few discrete classes, has several advantages. Since there is significant redundancy in microbeads across the array, combining the signals from same-type beads serves to amplify the signal and enhance the overall sensitivity of the array. Summing the responses from a number of microbeads also serves to improve signal-to-noise ratio, which is of particular importance when only low concentrations of a target agent are present. In addition, the random dispersal of microbeads obviates the need for the precise placement of sensing elements inherent in other manufacturing methods [82]. The downside of the random sensor placement is that effort is shifted from manufacturing to data processing, as each optical fiber sensor must be trained individually before use.

In a more recent effort, Walt's group at Tufts University and Pearce's group at the University of Leicester collaborated in testing an optical bead array with six different bead types, each replicated over 250 times [83]. This sensing platform was tested for its ability to discriminate between six different complex odors, including acetone, toluene, 1,3-dinitrotoluene (1,3-DNB), and three coffee types. The system was able to fully discriminate all analytes, achieving 100% correct classification at the highest relative concentration levels (e.g. 9000 ppm each of acetone and toluene and 0.9 ppm of 1,3-DNB), and better than 85% correct at the lower

concentration levels (e.g. 450 ppm each of acetone and toluene and 0.1 ppm 1,3-DNB).

Optical fiber-based artificial noses also hold promise for detecting explosives, particularly landmines. The toluene and 1,3-DNB compounds successfully detected by Walt and Pearce's optical fiber sensors are nitroaromatic compounds similar to low-level explosives. When dogs are used to hunt for landmines, they most likely smell DNT (dinitrotoluene), a byproduct of the explosive TNT (trinitrotoluene) in the landmine. Two other scientists at Tufts University, neuroscientists John Kauer and Joel White of the Tufts University School of Medicine, both active in studying natural and artificial olfaction, conducted a study in 2001 investigating the substitution of an optical fiber sensor for a dog's nose in detecting landmines [84]. Since a dog can detect 1 part per billion (ppb) or less of TNT, this is a difficult challenge. In a test conducted in a special chamber, the artificial nose was not yet that sensitive, detecting only 10 to 15 ppb. In a field test, the artificial nose was able to detect the presence of landmines but could not locate them very precisely. Kauer suggested this could have been due to interference from other odors in the environment. Other factors, such as wind or lateral diffusion of the odorant, also may have contributed to the failure to locate the source precisely. The problem of accurate sensing in a complex or interfering environment is one that will continue to challenge sensing systems of all types.

Tufts University has licensed its optical bead sensing technology to Illumina, a San Diego-based company founded in 1998 [85]. Illumina now builds biological sensors using BeadArray™ technology on two substrates. One of these, the Array Matrix, is composed of 96 arrays of fiber optic bundles. Each bundle consists of 50,000 individually etched fiber optic strands. Microbeads are deposited into the etched wells, which are 6 microns from center to center. The Array Matrix and the BeadChip, in which microbeads are assembled into etched wells in a slide-shaped device, are sold commercially for genotyping and gene expression profiling. (See Figure 11.) Illumina also is in partnership with Dow Chemical and Chevron on a project to develop chemical sensing systems using this technology. The oNose™, their optical electronic nose currently in development, will be a handheld device about the size of a calculator.

3.4 OTHER SENSORS

Most sensing mechanisms used in artificial noses fall into one of the three categories discussed above: electrochemical, mass-change, or optical fiber. A different optically based method is that of the "colorimetric" nose, created in 2000 by Neal Rakow and Kenneth Suslick at the University of Illinois at Urbana-Champagne [86]. Rakow and Suslick observed that many of the most toxic vapors are excellent ligands for metal ions, an area which had been little investigated in previous artificial nose research. They also observed that metalloporphyrins are good candidates for detection of metal-ligating agents, as they provide excellent binding sites and undergo large spectral shifts upon ligand binding. So they created a sensor array of metalloporphyrin dots deposited on a reverse phase silica surface, and then used a flat-bed scanner to obtain color images of the dots before and after exposure to an analyte. The color change in dots was measured by using a computer to subtract the pixels in the "before" image from the "after" image. The array response was then compared to a library of color "fingerprints" for identification of the analyte. Using this method, the researchers were able to identify, at below 2 ppm, a wide range of gases, including alcohols, amines, ethers, phosphines, phosphites, thioethers, thiols, arenes, halocarbons, and ketones. However, the operational requirement for a scanner would make it difficult, at least for the present, to make significant size reductions in the colorimetric sensor (e.g. down to the micron or nanometer scale).

Another effort by Baltes, Brand and their colleagues incorporates three different types of gas sensors plus a temperature sensor to create a sensing system on a chip [87]. The sensors used were mass-sensitive (a micro-machined cantilever), capacitive (differential signal between a polymer-coated sensing capacitor and a reference capacitor), and calorimetric. The calorimetric sensor works by detecting changes in enthalpy, or energy content per unit mass, upon adsorption or desorption of an analyte on a sensitive polymer film. Adsorption or desorption of molecules causes heat to be released or absorbed, which is recorded by an array of polysilicon/aluminum thermocouples. The temperature variations are translated into a voltage change. The temperature sensor was included to calibrate the sensors for detection of analyte concentration, since adsorption of volatile organic compounds on polymers is temperature dependent. These sensing elements, together with analog-to-digital converters and a digital bus interface for transmission of data to off-chip recording units, were integrated on a 7 mm x 7 mm chip, which then was used to detect the presence of ethanol and toluene. The three sensors displayed varying responses to the two analytes; ethanol caused a capacitance increase, for example, while toluene caused a capacitance decrease, and the cantilever responded more strongly to toluene than ethanol, because ethanol has a lower molecular mass. From these results it can be seen that future artificial noses need not be composed of sensors of only one type; an array of sensors of different types may broaden the spectrum of agents that are detectable.
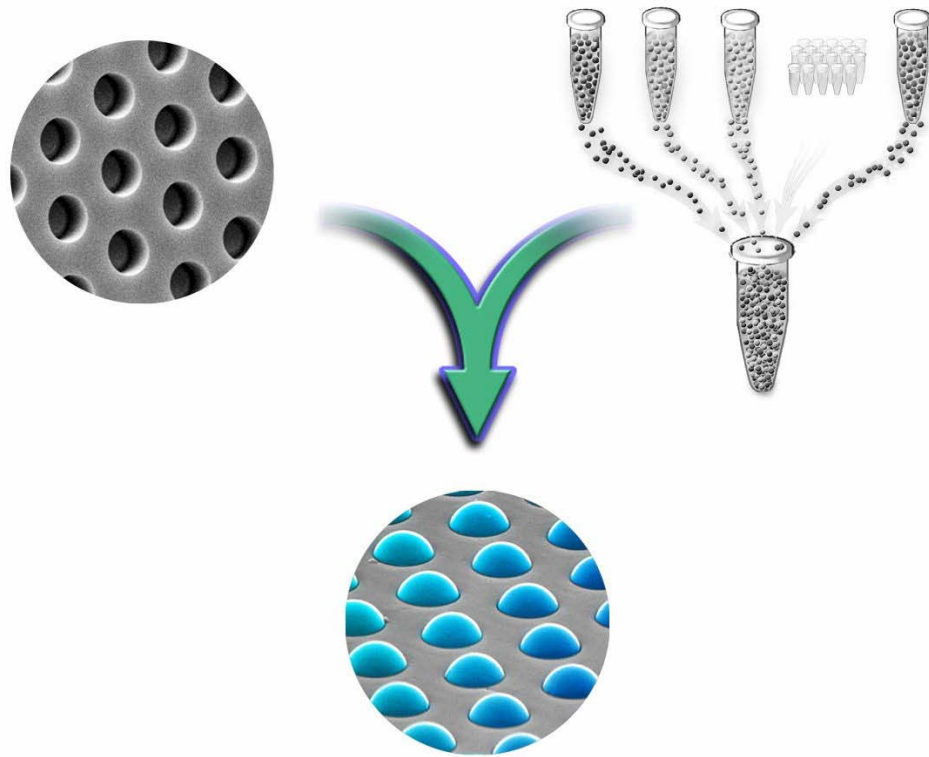
Figure 11. BeadArray™ Technology for Sensing by Illumina, Inc.

Illumina, Inc. randomly assembles microbeads coated with hundreds of thousands of copies of a single-stranded nucleotide sequence. Arrays are decoded before use to determine which bead type is in which location. Nucleotide binding with a matching nucleotide sequence causes a change in the polarity of fluorescent dyes in the microbeads.

This figure reproduced, with permission, from graphics supplied by Illumina, Inc.

3.5 NEXT STEPS IN ARTIFICIAL NOSES

As can be seen from the survey presented above, investigators and developers of artificial noses have attempted to follow the model of olfaction in devising sensor arrays with broadband sensing elements, using many different materials and sensing methods. Each sensor array element reacts differently to different target agents, both in absolute terms (activated/not activated) and in the degree of activation. Thus, these sensing arrays are designed to produce "signatures" for chemical agents in much the same way that activated olfactory neurons produce an odor's signature. The number of different sensing elements in artificial noses has not yet exceeded the two or three dozen of the KAMINA micronose [59], however, while the number of different sensing neurons in humans is at least an order of magnitude greater [27]. The total number of sensing array elements is also much smaller than the number of neurons in the epithelium; Walt's fiber-optic sensors have several thousand sensing elements (of only three different types) compared with several million epithelial neurons [1,82]. All of these artificial noses, therefore, fall short of emulating another characteristic of the olfactory system, which is that it contains millions of small, densely-spaced sensors in an area only several square centimeters in size.

To come close to matching the sensitivity, selectivity, and discriminatory abilities of natural noses, it will be necessary to increase the numbers and kinds of sensing elements in artificial noses. Even the individual microsensors used today, however, when replicated thousands of times, would result in sensing systems much larger than hand-held devices, let alone ultra-small sensing systems which could be incorporated into clothing. To make this leap down the size scale, we will need to use sensing elements that are themselves orders of magnitude smaller than the sensing elements in today's smallest artificial noses. This means that the sensing elements in artificial noses will have to be nanometer scale structures and devices. Research on individual nanometer-scale sensors is already underway. More recently, efforts to develop prototype *systems* of nanosensors have begun, as well [88-90]. The next section of this report presents a review of several research efforts to explore and develop nanometer-scale sensors, or "nanosensors."

4.0 NANOSENSORS

This section reviews research and development upon individual nanometer-scale sensors and towards entire artificial nose-like sensor systems integrated on the nanometer scale. In this consideration of nanosensors, we attempt to apply the lessons learned in the review of natural noses and nose-like microsensor systems that appeared in the foregoing sections of this paper. In reviewing the literature for very small artificial noses, it was possible to find examples of micron-scale sensing systems of all three major types (conductance-based, mass change, and optical), some already in commercial production. No operational artificial nose-like sensing *systems* of any type were found that are integrated on the nanometer-scale. Research and development is being conducted upon individual nanometer-scale sensors, however [91-109]. Investigations also are ongoing in chemical sensing using large numbers of nanometer-scale sensors in thin films, meshes, or in other ordered arrays [110-120], as well in the integration of nanosensing elements into microelectronic systems [121,122].

The results of several studies on the use of individual nanometer-scale devices as sensors are presented in the following sections. In particular, these discussions concern research on carbon nanotubes [91-93], nanowires [101,102], and other nanostructures [123] as nanosensing elements. An overview of the research efforts discussed below is presented in Table 2.

4.1 CARBON NANOTUBE SENSORS

Carbon nanotubes are ultra-small, ultra-strong, tubular molecules of pure carbon, which have unique electrical properties [124,125]. They can behave either as a semiconductor, a narrow bandgap semiconductor, or a metal, depending in large part on their chirality or "twist." The fact that they are conductors makes them good candidates for conductance-based sensing, and a number of investigations over the past few years have shown that both single-walled carbon nanotubes (SWNTs) [91-93,95,96,100] and multi-walled carbon nanotubes (MWNTs) [94,97-99] can be used as chemical sensors.

For example, a team led by Hongjie Dai at Stanford University has been investigating the use of carbon nanotubes as sensors. In 2000, Dai and Jing Kong showed that the electrical resistance of semiconducting SWNTs changes dramatically upon exposure to nitrous oxide (NO_2) or ammonia (NH_3) [91]. (See Figure 12.) Dai and Kong placed a SWNT approximately 1.8 nm in diameter and 3 μm in length between two metal electrodes, each consisting of a 20 nm-thick layer of nickel covered by a 60 nm layer of gold. Exposure to NH_3 caused a decrease in SWNT conductance by approximately two orders of magnitude, with a response time (the time required for the resistance to change by 1 order of magnitude) between 1 and 2 minutes for 1% NH_3, and about 10 minutes for 0.1% NH_3. An increase in SWNT conductance of approximately three orders of magnitude resulted from exposure to NO_2, with response times of about 2 to 10 seconds for 200 ppm, 0.5 to 1 minute for 20 ppm, and 5 minutes for 2 ppm.

Type	Description	Researcher/Institute
Carbon Nanotube	Semiconducting-SWNTs sense NH_3, NO_2 and H_2 by undergoing a conductance change	Hongjie Dai et al. Stanford University [91,93,125]
Carbon Nanotube	SWNTs show high sensitivity to exposure to oxygen or air, changing their electrical properties	A. Zettl et al., University of California at Berkeley [92]
Carbon Nanotube	MWNTs, which generate very high electric fields at their tips, are used in an array to form a miniature gas ionization sensor	Pulickel Ajayan et al., Rensselaer Polytechnic Institute [94]
Nanowire	Silicon nanowires in solution sense pH changes, presence of streptavidin and Ca2+, and antibiotin/biotin binding with conductance changes	Charles Lieber et al., Harvard University [101,126]
Nanowire	Tin oxide nanowires sense N_2 and CO with conductance changes	Martin Moskovits et al., University of California at Santa Barbara [102]
Nanobelt	Tin oxide nanobelts sense CO, NO_2 with a change in conductance	Zhong Wang et al. Georgia Institute of Technology G. Sberveglieri et al., The National Institute for the Physics of Matter, Brescia, Italy, and Università di Brescia [123,127]

SWNT = Single-Walled Carbon Nanotube
MWNT = Multiwalled Carbon Nanotube

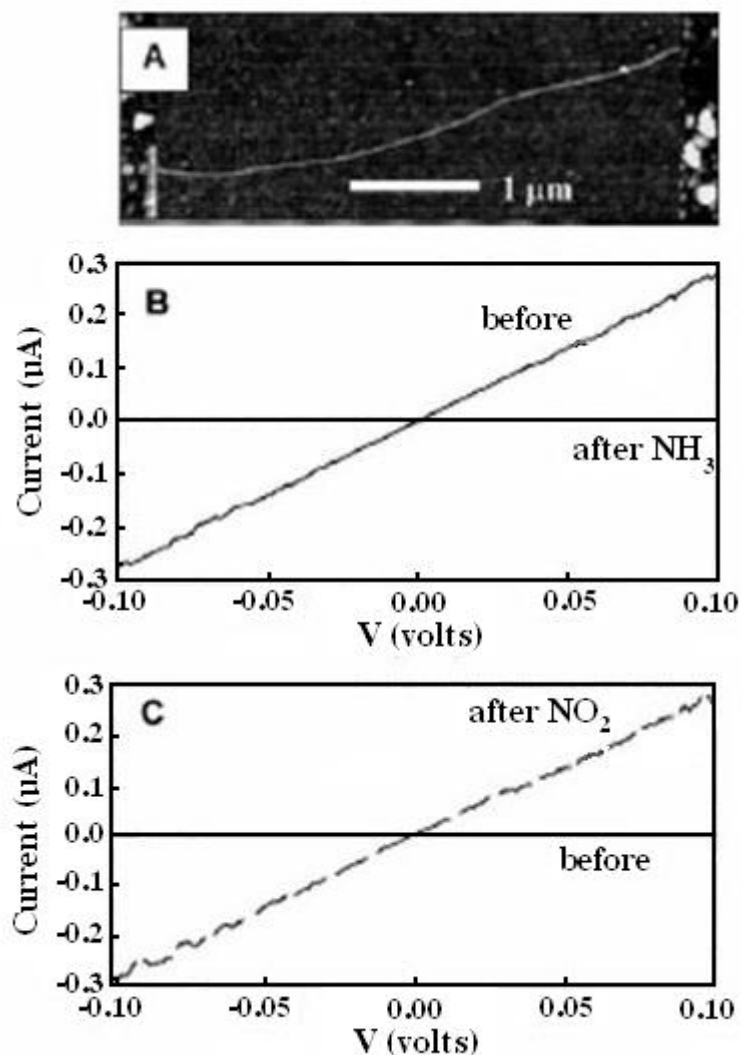**Table 2. An Overview of Selected Nanosensor Research and Development**

Figure 12. Single-Walled Carbon Nanotubes (SWNT) as Conductive Gas Sensors

Honjie Dai's group at Stanford University has demonstrated that individual semiconducting SWNTs, as seen in **(A)**, behave as sensors for the presence of nitrous oxide (NO_2) and ammonia (NH_3). SWNT exposure to NH_3 causes a decrease in conductance, as shown in **(B)**, while **(C)** shows increased conductance due to exposure to NO_2.

Reprinted with permission from Jing Kong, Hongjie Dai, et al., "Nanotube Molecular Wires as Chemical Sensors," *Science*, 28 January 2000, vol.287: p. 623. Copyright 2000 AAAS.

Carbon nanotubes also are highly sensitive to oxygen, however, which may have an impact on their application to sensing in ambient air [92]. Philip Collins and A. Zettl at the University of California at Berkeley found that exposure to oxygen, whether pure dry oxygen or air, caused an increase in conductance by 10% to 15%. They also found that the effects of oxygen exposure were increasingly irreversible with decreasing temperatures, and that once the SWNTs were exposed to oxygen, it was not possible to deoxygenate them without heating them in a high-vacuum environment to 110° to 150° C for several hours. Exposure to oxygen also changes other characteristics of the SWNTs, including electrical resistance, the local density of states, and their thermoelectric power ($\mu V/°K$). Such exposure can convert a semiconducting carbon nanotube into one that is metallic. Thus, the properties of a SWNT, including its conductance, are functions of its gas exposure history as well as its diameter and chirality.

The carbon nanotubes tested by the Stanford and UC Berkeley teams were unmodified SWNTs. Such carbon nanotubes, while sensitive to NO_2, NH_3 and oxygen, are not sensitive to many other target molecules such as hydrogen (H_2) and carbon monoxide (CO) [93]. Functionalizing the SWNTs, however, by decorating the sidewalls with desired molecular groups, can change the sensitivity of the SWNT for specific target gases. In 2001, Kong and Dai were able to create carbon nanotube hydrogen sensors by decorating SWNTs with palladium (Pd) nanoparticles [93]. Deposition of approximately 5Å of palladium over an entire SiO_2 substrate containing the SWNTs resulted in a thin, non-continuous layer of palladium deposited on the nanotubes. The gaps in the palladium layer ensured that the electrical conduction path in the modified SWNT was not through the palladium particles, but remained through the decorated SWNT. Exposure of the decorated nanotubes to a flow of air mixed with 400ppm H_2 then resulted in a decrease in conductance by approximately a factor of 2, with ready reversibility when the flow of hydrogen was stopped.The response time (i.e. the time during which half the resistance change occurred) was about 5 to 10 seconds, with approximately 400 seconds required for full recovery. Similar results were obtained with concentrations of 40 ppm and 4 ppm H_2. This experiment demonstrated that the functionalization of SWNTs can expand the spectrum of gases to which they are sensitive.

The experiments described above examined the effects of the interactions of different gases with the surfaces or sidewalls of carbon nanotubes. In contrast, Pulickel Ajayan's group at Rensselaer Polytechnic Institute (RPI) looked, instead, at reactions occurring at their ends [94]. In a 2003 study, Ajayan, Ashish Modi, and others found that multi-walled carbon nanotubes (MWNTs) could be used as gas ionization sensors. Ionization sensors work by identifying gases by their unique breakdown voltage, which is the electric field at which the gas is ionized. Ajayan and his team created an ionization sensor using an aluminum plate cathode, separated by 150 μm from the anode, which was a film of vertically aligned MWNTs on a SiO_2 substrate. The MWNTs were about 25 to 30 nm in diameter and 30 μm long, with a separation of 50 μm between nanotubes. The sharp tip of a MWNT generates a very high non-linear electric field, and the billions of MWNTs which compose the anode contribute to an increase in the electric field. This allows breakdown at voltages that are several times lower than those of traditional electrodes. Several gases were tested by releasing them, one at a time, into a high vacuum chamber containing the sensing device, and each gas exhibited a unique breakdown voltage. The breakdown voltage of air was observed to be 65% lower (346 V vs. 960 V) in the vicinity of the MWNT electrode than that required near conventional metal electrodes. Other gases tested showed similar results. In addition, the discharge current at ionization also increased approximately 6-fold. Since discharge current is proportional to analyte concentration, higher discharge currents allow detection of dilute concentrations and thus increase sensor sensitivity. Gases tested and successfully detected were helium, argon, nitrogen, oxygen, carbon dioxide, and ammonia, as well as air. Unlike other ionization sensors, which must be used with a gas chromatograph, this sensor can be used directly with gas mixtures. Lower voltage requirements also translate into lower power requirements. Thus, a sensor using this approach could be fairly compact. The present design requires millions of MWNTs spaced tens of micrometers apart, which results in a device size in the millimeter range; future designs may be able to provide further size reductions.

4.2 NANOWIRES AND OTHER NANOSTRUCTURES

Semiconducting "nanowires" have shown themselves to be particularly promising for applications as nanosensors and for the development of dense systems of such sensors [101,102,123,126-129]. Nanowires and other nanometer scale structures with promise for sensor applications have been synthesized from a number of materials, including zinc, tin, indium, cadmium, silicon, and polysiloles (silicon-polymer combinations). Two research efforts to develop and perfect nanowire sensors for gases and biological agents, plus an investigation into "nanobelt" sensors, are described below [101,102,123].

Early in 2001, Charles Lieber and his group at Harvard University demonstrated that semiconducting

nanowires can be assembled to build nanometer-scale electronic devices, including passive diodes, transistors, and inverter-like digital circuits [126]. They fabricated their devices and circuits from boron- and phosphorus-doped silicon "wires" approximately 20 nm in diameter. Subsequently, they tested the ability of these nanowires to perform four different sensing functions in aqueous solution [101]. They used boron-doped silicon nanowires (SiNWs) that were functionalized by different chemical substituents to make the SiNWs sensitive to four different target agents, and measured the conductance change upon exposure to the target analytes. Using amine- and oxide-functionalized SiNWs, Lieber's group observed constant conductance for a given pH, stepwise increases in conductance with discrete changes in pH from 2 to 9, and sensor reversibility for increasing or decreasing pH. (See Figure 13.) SiNWs modified with biotin were able to detect ligand-receptor binding of biotin-streptavidin with an increase in conductance. However, this process was not reversible. Lieber's group also tested the reversible binding of monoclonal antibiotin (m-antibiotin) with biotin, and found a well-defined drop in conductance upon introduction of m-antibiotin solution, and an increase to approximately the original conductance value upon addition of pure buffer solution. Finally, the team used SiNWs functionalized with calmodulin to detect Ca^{2+}. The decorated SiNWs displayed a drop in conductance upon encounter with a 25μM Ca^{2+} solution, and a conductance increase when a Ca^{2+}-free solution was introduced. Undecorated SiNWs did not react to the presence or absence of Ca^{2+}, indicating that the calmodulin was, for this purpose, an essential element of the nanowire detector.

Lieber's work showed that nanowires could behave as nanosensors for chemical and biological agents in solution. In 2003, Martin Moskovits and a team at the University of California at Santa Barbara demonstrated the applicability of nanowires to gas sensing, as they successfully used nanowires to detect the presence of CO and O_2 [102]. Moskovits' group measured the conductance change in individual tin (SnO_2) nanowires, each approximately 60 nm in diameter, connecting timonium/gold (Ti/Au) electrodes. The experiment was performed at operating temperatures between 120° C and 300° C. It was found that the nanowires were good conductors in the absence of oxygen, and they were converted into insulators in the presence of oxygen. Nanowires exposed to CO experienced an increase inconductance. The experimenters found that alternating pulses of N_2 + 10% O_2 and CO, delivered at approximately 10 minute intervals, caused a sequence of sharp conductance changes in the nanowires. (See Figure 14.) Response to CO was dependent on temperature and concentration, with larger conductance changes demonstrated at higher temperatures. Pulses of CO caused an increase in conductance that was linearly proportional to CO concentration, and pulses of oxygen decreased the conductance back to a baseline value for nanowires in an oxygen environment. The response time (time for full conductance change) upon exposure to CO was approximately 30 seconds.

Moskovits and his team point out that for bulk SnO_2 at 500 K, electron exchange between the surface states and the bulk takes place in a layer that is approximately 43 nm thick. This means that for a 60 nm diameter SnO_2 nanowire, the "surface layer" encompasses the entire structure. Thus, adsorption or desorption of analytes on the surface alters the bulk properties of the entire nanowire. This makes these SnO_2 nanowires conductance switches whose conductivity is determined entirely by reactions on their surfaces. Moskovits proposes that a large array of differently functionalized nanowires could be integrated to create a parallel sensing system similar to the olfactory system.

A different kind of nanostructure was synthesized in 2001 by a group at the Georgia Institute of Technology led by Zhong Wang [127]. These structures, called "nanobelts," are ultralong, ribbon-like nanostructures with a rectangular cross section. Typically, they are between 30 and 300 nm wide, with width-to-thickness ratios of 5 to 10, and lengths in the tens or hundreds of micrometers, sometimes extending to millimeters. Wang's team successfully synthesized nanobelts of semiconducting oxides of zinc (ZnO), tin (SnO_2), indium (In_2O_3), and cadmium (CdO). These were found to be pure, structurally uniform, single crystals that are relatively free of defects and dislocations. They concluded a 2001 report on their findings in *Science* by suggesting that the nanobelts could be used as nanosensors.

The following year, 2002, G. Sberveglieri and colleagues at the University of Brescia, in Brescia, Italy, in collaboration with Wang and his team, actually used tin nanobelts as sensors [123]. They built a sensing device by placing SnO_2 nanobelts atop a platinum interdigitated electrode structure on an alumina substrate. A platinum heater on the reverse side of the substrate kept the working temperature at 400° C. The nanobelts successfully registered the presence of carbon monoxide (CO), ethanol, and nitrogen dioxide (NO_2) by a significant change in conductance. The sensor response, defined as the ratio of the change in conductance to the initial conductance ($\Delta G/G$), was found to be +0.9 for CO, +41.6 for ethanol, and -15.5 for NO_2. Thus, tin dioxide nanobelts were shown to function as effective gas sensors.
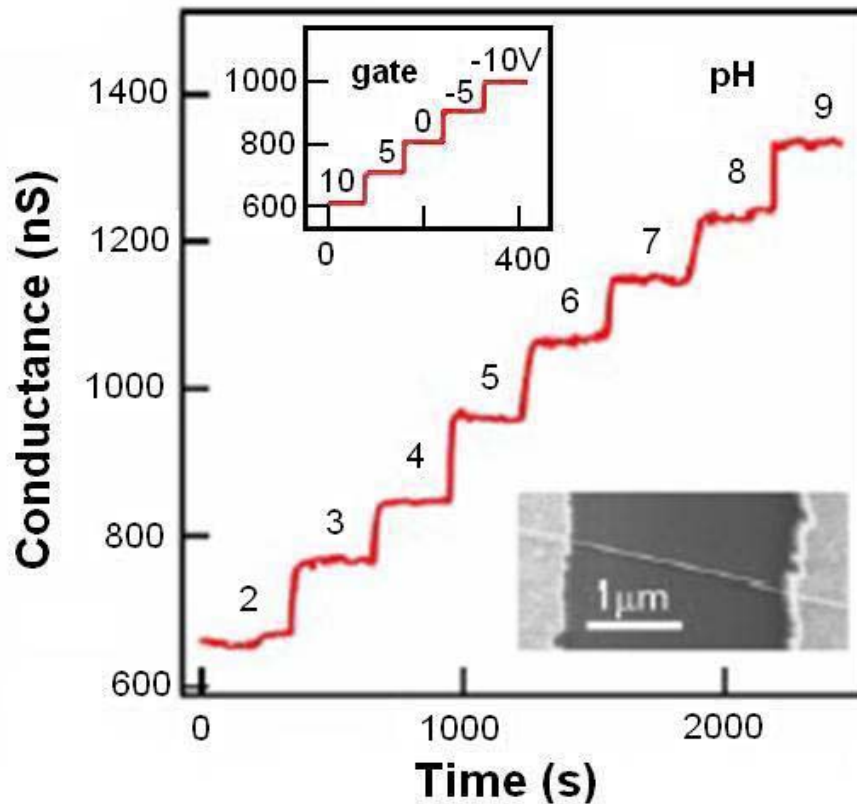
Figure 13. A Semiconducting Silicon Nanowire (SiNW) Sensor

Charles Lieber's group at Harvard University has demonstrated semiconducting silicon nanowires (SiNW) behave as conductance-based sensors in solution for pH levels, antigen-antibody binding, streptavidin, and Ca^{2+}. Shown here are stepwise increases in nanowire conductance with pH changes. The conductance change was also reversible with decreasing pH.

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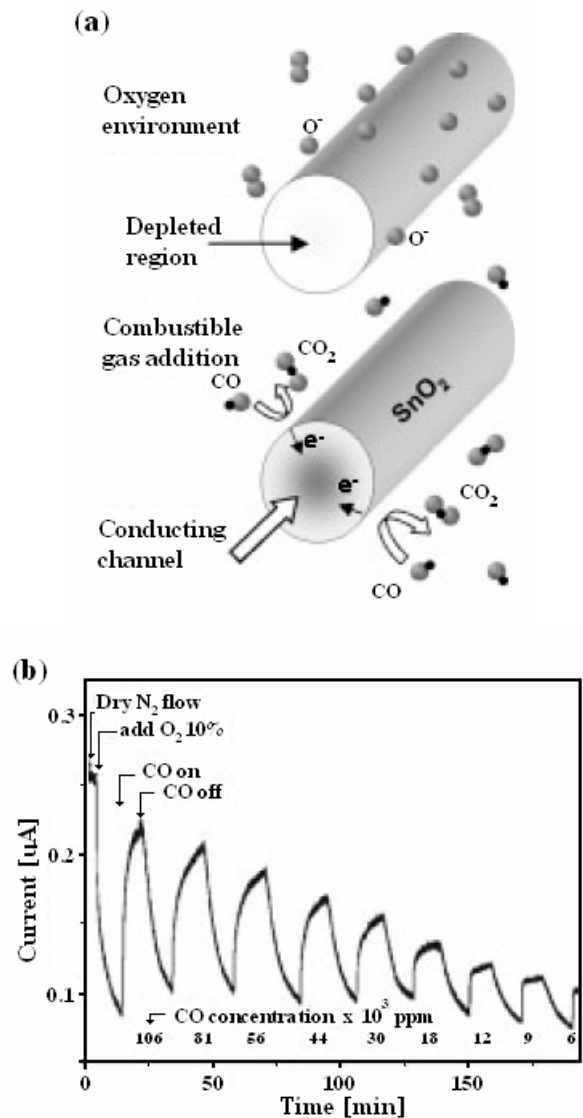
Figure 14. Tin Dioxide (SnO$_2$) Nanowires as Gas Sensors

Martin Moskovits and his group at the University of California at Santa Barbara demonstrated that SnO$_2$ nanowires behave as conductivity-based sensors for carbon monoxide (CO) and oxygen (O$_2$). Part (a) of the figure shows CO binding with oxygen at the surface of the nanowire, freeing electrons to form a conducting channel through the nanowire. Part (b) shows the effect upon nanowire conductance of exposure to alternating pulses of CO and O2, with CO concentration decreasing with successive pulses.

Reprinted with permission from Kolmakov, Moskovitz, et al., "Detection of CO and O$_2$ Using Tin Oxide Nanowire Sensors," *Advanced Materials*, 17 June 2003, Vol 15, No. 12: p. 999. Copyright 2003 WILEY-VCH Verlag GmbH & Co KGaA, Weinheim

5.0 DESIGNING A NANOMETER-SCALE NOSE-LIKE SENSING SYSTEM

As discussed earlier in this report, the development of artificial noses which truly emulate the remarkable sensing abilities of the natural nose will require the integration of many ultra-small, nanometer-scale sensors into systems. In the preceding section, we presented an overview of several different research efforts for developing individual nanosensors. This section will consider how one might use the information above to integrate a number of components to design a nanometer-scale nose-like sensing system. In order to do that, we will consider, in Section 5.1, the advantages and drawbacks of each of these devices – carbon nanotubes, nanowires and nanobelts – as candidate sensing elements in such an ultra-small electronic nose. Based on these considerations, we recommend that such a system be built using nanowires, as discussed below in Section 5.2.

5.1 CONSIDERATION OF NANOTUBES, NANOWIRES, AND NANOBELTS FOR ELECTRONIC NOSES

Carbon nanotubes, nanowires, and nanobelts all have high surface-to-volume ratios and all have been demonstrated to react to the presence of certain gases and other analytes with a change in conductance. Thus, each of these devices could conceivably be used as a nanosensing element within an electronic nose. The strengths and weaknesses of using these devices for this purpose are discussed below.

Carbon nanotubes show strong sensitivities to several gases, and can operate at room temperature. Using carbon nanotubes as sensors, however, presents several difficulties [101]. Large numbers of nanotubes with uniform, predictable characteristics would be required for building arrays of nanosensors. Using presently available techniques, carbon nanotubes always are synthesized in mixtures of metallic and semiconducting nanotubes. Often, the product mixture contains single- and double-wall nanotubes with a wide range of diameters and chiralities. Researchers have put forward different methods for separating nanotubes, including a recent proposal by Ralph Krupke and Frank Hennrich at the Karlsruhe Research Center [130], and another by a team at DuPont Central Research and Development [131]. The MITRE Corporation also has obtained a December 2003 patent for a method to perform bulk separation of SWNTs based on chirality [132,133]. At the present time, however, sorting and selecting carbon nanotubes of a specific kind remains difficult and time consuming.

Functionalizing or decorating carbon nanotubes also presents challenges. Dai's group successfully function-alized carbon nanotubes by depositing a layer of palladium on the SWNT. In general, however, flexible methods for the functionalization of carbon nanotubes are not easily available [101], because the long tubular surface of the molecule presents few ready binding sites for acceptor molecules. Finally, the strong, essentially irreversible, binding of carbon nanotubes to oxygen may change their characteristics. This raises questions about the predictability of their sensing behavior following prolonged exposure to ambient air.

Nanowires and nanobelts of tin oxide also have been demonstrated to be effective gas sensors, and both are considered together here as "nanowires." Individual metal and semiconducting nanowires can be fabricated predictably and uniformly, even in very large arrays, as was demonstrated in 2003 by James Heath and his group at CalTech [134]. The characteristics of nanowires can be fixed during the fabrication process by controlling the dopant types and concentrations. Thus, their sensing behavior is predictable [101]. In addition, the use of metal oxides and conducting polymers in electronic noses over several decades has resulted in some familiarity with chemical modifiers for metal and silicon oxide surfaces [50,101]. This existing body of knowledge provides a natural starting point for development of the sets of nanoscale sensors that are required for olfaction-like sensing: ultra-small sensors with broad, overlapping sensitivity spectra. The primary disadvantage of metal oxide nanowires is their requirement for high operating temperatures. For example, Moskovits' team measured response curves for their SnO_2 nanowires at 200°C to 280°C [102]. The need for a high temperature operating environment for tin oxide nanowires is similar to the requirement for metal oxide macro- or microsensors. This requirement has been met on the micron scale, as demonstrated by the KAMINA micronose and its micron- to millimeter-scale heating element [59]. It is possible that a heating element analogous to that employed in such a microsensor (see Section 3.1.1.1) could be implemented for a nanosensing system as well. Since the nanosensing system also will require close integration with a data processing system, a portion of the heat required for sensing might even be derived from the dissipation arising from an integrated nanoprocessor or nanomemory.

At present, the uniformity, predictable behavior, and well characterized materials interactions exhibited by nanowires offer clear advantages over carbon nanotubes when selecting building blocks for a nanosensing system. Metal and silicon nanowires also appear to share with larger metal oxide sensors a characteristic required for electronic noses: broad-based chemical sensing capability. The amazing sensing abilities of the mammalian nose are not due to highly specific sensing elements, but to vast numbers of semi-specific sensors, whose combined input leads to identification of the target agent. This feature of olfaction is one that has been successfully implemented in large-scale electronic noses, and should be emulated in nanometer-scale gas sensor

systems as well. Lewis, Walt, and others have pointed out that a system with "lock-and-key" sensing elements, each specific to only one target agent, would be very difficult to implement for chemical sensing in unknown environments [22]. Specific sensors work only when background and interfering agents can be controlled. In an unknown environment, such specific sensors are likely to respond to agents with molecular composition similar to that of the designated target. Binding with these similarly-structured molecules would result in a positive sensor reading even in the absence of the target agent. The resulting false positives would reduce greatly the reliability of the system.

From the discussion above, we conclude that nanowires appear at present to be the most reasonable choice for the sensing elements in a nose-like nanosensing system. Both Lieber at Harvard [101] and Moskowitz at UC Santa Barbara [102] have demonstrated that nanowires can behave as sensors. The experiments conducted by Lieber's group were conducted with silicon oxide nanowires in solution, and those by Moskovits' team were conducted with metal oxide nanowires in air. For the purpose of designing a nose-like gas sensing system to be used in ambient air, it seems reasonable to start with the metal oxide nanowires already demonstrated to work as gas sensors.

5.2 New Design for an Electronic Nose System Integrated on the Nanometer Scale

It is proposed, therefore, based on the considerations outlined in Section 5.1, that a nanometer-scale electronic nose might be built that uses, as sensing elements, nanowires composed of a platinum-doped SnO_2 core surrounded by a layer of SiO_2. Such a sensing element is shown in Figure 15. The SnO_2 nanowire core, 60 nm in diameter, is similar to the nanowires demonstrated to function as gas sensors by Moskovits [102]. Here we sketch out how such nanowires might be assembled to produce a nose-like sensing system.

In order to incorporate these nanowires into an electronic nose, it is necessary to differentiate them. Following the example of the sensing neurons, the range of sensitivity for a particular nanowire should overlap but not be identical to that of other nanowires. Goschnick and his Karlsruhe team have accomplished this differentiation in their KAMINA micronose by applying a layer of SiO_2 of graduated thickness over a segmented sheet of SnO_2 [59]. The variance in SiO_2 thickness from segment to segment is responsible for differences in the sensing range of each segment.

We will employ the same concept in the nose-like sensing system we propose here. This is illustrated in Figure 16. Individual SnO_2 nanowires will be coated with a layer of SiO_2; the thickness of the coating layer, between 2 nm and 20 nm, will vary from nanowire to nanowire. Thus, the sensing range of each nanowire will depend on the thickness of its SiO_2 coating. The differentiated nanowires will be integrated into a nose-like sensing system in which the nanowires function much like the individual segments of the KAMINA micronose. Therefore, this nanosensing system, in combination with a heating element and a data processor, could be expected to detect also the same range of agents detected by KAMINA. This includes most non-inert gases, particularly formaldehyde, carbon monoxide, benzene, ammonia, acrolein, and sulfur dioxide.

Functionalized nanowires of various diameters, arranged in parallel, would form a "memory array," with each array element reporting an encounter with a target agent by a change in conductance/resistance. The particular combination of nanowires reporting conductance changes would provide the target agent identification. Figure 16 is a sketch of such an electronic nose, composed of six individual nanometer-scale sensors in a 6x1 memory array.

6.0 SUMMARY

Recent explorations of the olfactory system have begun to fill in the blanks in our knowledge of the sense of smell and how it works. What was pure speculation in the middle of the last century has been transformed, especially over the past 13 years, into detailed insights about the functions and processes of the individual cell chemistry, neuronal interactions, and information processing that make olfaction work. Advances in genomics have allowed researchers to identify the genes responsible for the sense of smell, and this has led to broad new understandings of olfactory detection processes in the tissues and cells of the nose and brain. New technologies also have allowed researchers to follow the path of olfactory signals into the brain, providing exciting new insights into how the brain responds to olfactory stimulation. This expanded body of knowledge has presented us with a more complete picture of a natural sensing system which is broadband in its range of application while being remarkably sensitive to individual odorants. This new knowledge also presents us with a picture of an integrated system, in which the sensing function is performed by large ensembles of non-specific receptors, and information is processed in parallel and sequentially in several stages. It is a system that is remarkably successful in using sparse information to make precise identifications.

Although much progress has been made in creating artificial analogues to the olfactory system, electronic noses still fall short of duplicating the amazing abilities of the natural nose. In part, this is due to the fact that many questions still remain to be answered about how the nose
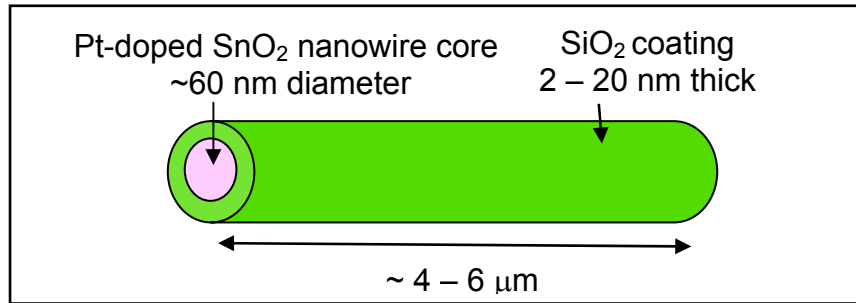
Figure 15. A Proposed Nanowire Sensing Element

This sensing element synthesizes the ideas of two researchers. The core consists of a 60 nm diameter platinum-doped SnO_2 nanowire, such as the nanowire sensors demonstrated by Moskovits et al. [102]. The SnO_2 wire core is coated with a layer of SiO_2 of uniform thickness. The SiO_2 layer will vary in thickness, from wire to wire, from a minimum of 2 nm to a maximum of 20 nm. Application of these SiO_2 layers is the method used by Goschnick et al. [59-61] to differentially sensitize SnO_2 to different chemicals.
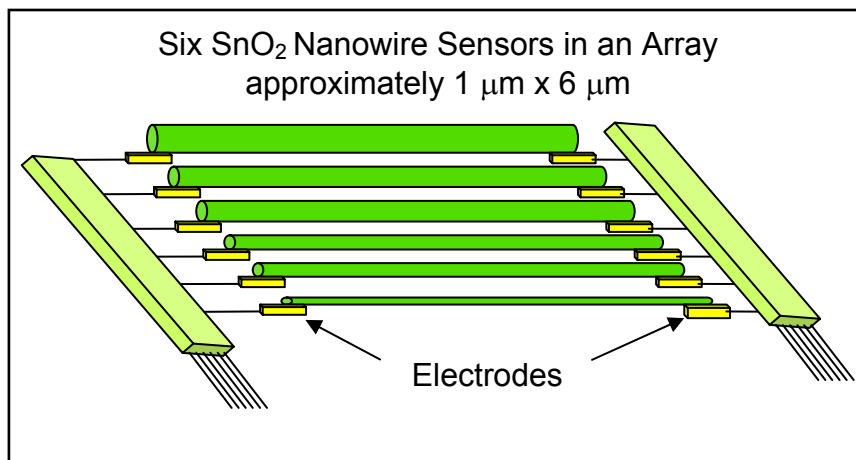

Figure 16. A Proposed Nanowire "Nose-Like" Sensing System

Each nanowire sensing element in this sensing system has a SnO_2 core covered with a layer of SiO_2, as in Figure 15 above. SiO_2 layer thicknesses of 2 nm to 18 nm result in sensing elements with diameters of 64 nm to 96 nm. As proposed in this paper, wires of different diameters would react to different chemicals such as formaldehyde, carbon monoxide, and ammonia.

works so well. However, the shortfalls in the performance of artificial noses also are due to the fact that what we do know about the functioning of the nose is not necessarily easy to emulate. Although we know that odorant identification utilizes a spatio-temporal combinatorial coding system, it is not yet clear how to characterize molecules by artificial means in such a way that the resulting code would permit identification of a wide range of toxic chemical or biological agents. In addition, present-day artificial noses make use of a variety of techniques for molecular recognition. However, these techniques cannot be made to work yet at the density of epithelial neurons or within the size constraints of the human olfactory system, let alone those of the far more sensitive rat or mouse nose.

It seems likely, though, that nanotechnology can make significant contributions to electronic noses and ultra-small gas sensing systems in terms of reduction in size and increase in sensor density. Nanometer-scale sensing devices such as carbon nanotubes and nanowires already have been demonstrated. Integration of these nanoscale sensors into sensing systems will be the next step. One proposal for integration of nanowire sensors into an electronic nose system is presented here. Researchers certainly will propose many more designs in coming years. For example, several investigative groups in the U.S. have begun development of nanosensor systems under the auspices of the Applications of Molecular Electronics R&D Program that was recently initiated by DARPA.

National security concerns since the terrorist attacks of September 11, 2001 have made the de-sign of small, fast, sensitive, broadband sensors for chemical and biological agents a matter of high importance and great urgency. Our growing knowledge of the olfactory processes and their translation into electronic noses provide much encouragement for this effort. Further research offers the potential for the development of the high performance, truly nose-like nanosensing systems we seek to build.

ACKNOWLEDGEMENTS

ACRONYMS

Å	angstrom (= 10^{-10} meters)
ANN	artificial neural network
ARDA	Advanced Research and Development Activity
ATP	adenosine triphosphate
cAMP	cyclic adenosine monophosphate
BL	barley lectin
ChemFET	chemically sensitive field effect transistor
cm	centimeter (= 10^{-2} meters)
CNG	cyclic nucleotide-gated
DARPA	Defense Advanced Research Projects Agency
DFA	discriminant function analysis
1,3-DNB	1,3-dinitrotoluene
DNT	dinitrotoluene
ETRI	Electronics and Telecommunications Research Institute, Korea
FET	field effect transistor
G	electrical conductance
G_{olf}	G protein specific to the olfactory system
IT	Information Technology
KAMINA	Karlsruhe Mikro-Nase (Karlsruhe [Research Center] Micro-Nose)
m	meter
MEMS	MicroElectroMechanical Systems
mm	millimeter (= 10^{-3} meters)
MOSFET	metal oxide-semiconductor field effect transistor
mV	millivolts
MWNT	multi-walled carbon nanotube
μm	micrometer (= 10^{-6} meters)
N	Newton

nm   nanometer (= 10^{-9} meters)

NNI   National Nanotechnology Initiative

OB   olfactory bulb

OR   olfactory receptor

PCA   principal component analysis

pH   hyprogen power, or the degree of acidity or alkalinity of a solution

PLL   phase-locked loop

ppb   parts per billion

ppm   parts per million

QCM   quartz crystal microbalance

RPI   Rensselaer Polytechnic Institute

SAW   surface acoustic wave

SiNW   silicon nanowire

SWNT   single-walled carbon nanotube

TNT   trinitrotoluene

V   volts

VLSI   very large scale integrated

VOC   volatile organic compound

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