

UNDERSTANDING CHEMICAL SENSORS AND CHEMICAL SENSOR ARRAYS (ELECTRONIC NOSES): PAST, PRESENT, AND FUTURE.

By Joseph R. Stetter, William R. Penrose

Dedicated to the memory of my friend and colleague Wolfgang Göpel who died in June 1999 in the prime of his career.

Intelligence, intensity, depth, vision,
Marked your science call.
Passion, grit, and oft unappreciated wit,
Brought new knowledge to all.

ABSTRACT

The use of sensor arrays, embodied in electronic noses, to characterize complex samples is an active and dynamic expression of research in chemical sensors. In this review, we emphasize sensors, instrumentation, and applications aspects of electronic nose technology. In addition, we have added to the existing historical description of electronic nose development, projected likely directions into the future, and evaluated research needs that are a prerequisite to eventual success of electronic nose technology.

KEYWORDS

Sensor arrays, electronic nose, artificial olfaction, analytical chemistry

UNDERSTANDING CHEMICAL SENSORS AND CHEMICAL SENSOR ARRAYS: PAST, PRESENT, AND FUTURE.

By Joseph R. Stetter and William R. Penrose

Written in tribute to and in memory of our good friend and colleague Wolfgang Göpel who dedicated a part of his precious life to sensors, chemical sensor arrays and electronic noses.

1. INTRODUCTION

The field of chemical sensors has expanded dramatically in the past twenty-some years. The first International Meeting on Chemical Sensors [IMCS] in 1983 in Fukuoka, Japan [1] was the one at which I first met Wolfgang Göpel. He had just returned to Germany to head the Institute for Physical and Theoretical Chemistry in Tübingen. The International Meeting on Chemical Sensors (IMCS) has been held eight times, as has the "Transducers" series of conferences, since 1983. These conferences were the result of the international interest in the topic generated at an earlier Material Research Society technical session in 1980. Recent conferences on chemical sensors can be found on the websites of many technical organizations [2].

A major enthusiast and a leader in the explosive growth of the chemical sensor field was the late Wolfgang Göpel (1945-1999), scientist, friend and colleague. His efforts encompassed the tireless pursuit of better chemical and physical sensors as well as a more complete understanding of the science behind a broad range of sensors. It is in this tradition of sensor science, that this perspective and update is presented, with a special focus on gas sensors and the special properties of sensor arrays, including those applications often known as "electronic noses". We will describe current capabilities and some recent publications in a historical context in an attempt to make useful comments about future capabilities and trends. This review will discuss sensor arrays or electronic noses from the point of view of the sensors, analytical chemistry, and recent applications including the successes of artificial olfaction. Also, we will provide interpretive comments concerning the origin of unique sensing capabilities and the debunking of popular myths that have arisen about the electronic nose technology. The biology of olfaction and pattern recognition has been covered in depth by two recent, excellent reviews, and will not be covered in any depth here. The focus of this review is to summarize current understanding in new and meaningful ways that are complementary and not redundant to earlier issues of Sensors Update.

The scientific world of chemical sensors includes those that operate in gases, liquids, and solids. While arrays of gas sensors are known as "electronic noses", arrays of liquid sensors are becoming known as "electronic tongues". Sensing in each phase presents different technical challenges, but chemical sensors in all phases share some common characteristics. The following discussion centers mainly around gas sensors, but will often apply to all classes of chemical sensors. Although a discussion of sensor arrays is the main purpose of this paper, a discussion of individual sensors with a focus on those most frequently found in arrays is presented. The understanding of sensor principles and metrics is essential to the understanding of the performance of the resulting sensor arrays.

Chemistry, quality control, and process applications in the food industry have so far been the most common applications of sensor array technology. Many foods give strong signals on chemical sensors, compared with other sample types. Moreover, the great complexity of odors and flavors, as well as their subjective nature, frequently defeats conventional analytical methods. The potential for rapid analysis at lower cost has also made electronic nose technology attractive

to the food industry. In our laboratory, coffee, tea, cooking oils, cheeses, and beer have been used for student projects because they provide fine distinctions and good sensor responses [3].

2. THE LITERATURE ON CHEMICAL SENSOR ARRAYS AND ELECTRONIC NOSES.

The literature on chemical sensors, sensor arrays, and electronic noses has been regularly reviewed in *Sensors Update*. There has been a steady and rapid increase in the rate of appearance of references to electronic noses. From January 1994 to June 2001, there are over 360 returns on the keywords "electronic nose(s)", "artificial olfaction", or "sensor array(s)" from the Current Contents database ("sensor array" returns were filtered to exclude optical imaging and similar physical sensor arrays). A crude classification of these terms is shown in Table I. Many of these have been selected for inclusion in the bibliography for this manuscript.

***TABLE I NEAR HERE

Not surprisingly, much of the effort over the past eight years has been in the selection of gas sensors and instrument design. The novelty of the field has attracted a burst of development. Since sensor array instruments are not difficult to build, it is not surprising that many alternative designs and sensor selections are published each year.

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Major reviews on sensor arrays and electronic noses have appeared in the present series. Volume 2 of *Sensors Update* contained a review emphasizing pattern recognition [4], while a complementary article in Volume 3 addressed primarily the biology of olfaction [5]. We will not revisit these subjects, but will emphasize progress in sensors, sensor arrays, and electronic noses since the 1991 review by Vaihinger and Göpel [6] in the foundation volumes of this series.

Other reviews have appeared from time to time, with increasing frequency. As we have discovered ourselves in the preparation of this review, the field is rapidly becoming too large to cover comprehensively in a single contribution, and so most recent reviews have emphasized one or another aspect of the technology. In a recent *Chemical Reviews*, the properties of sensor arrays were covered by Albert et al. [7], while Jurs et al. [8] surveyed the literature on pattern classification algorithms. General reviews, that might be used as a first introduction to the field, are already becoming quite dated, although still useful. We would suggest the papers by Dickinson et al. [9] and Nagle et al. [10]. A textbook entitled "*Electronic Noses*" was recently published by Gardner and Bartlett [11], although it emphasizes chemical sensors with only relatively brief mention of sensor arrays and electronic noses. Excellent explanations and expositions on the electronic nose and sensor arrays can be reached at several academic institutions through the NOSE website [12].

The term "electronic nose" came into more common use after it appeared in the title of a major monograph on the electronic nose, edited by Gardner and Bartlett [13], which resulted from a 1991 NATO-sponsored meeting convened in Reykjavik, Iceland. To avoid the pejorative

connotation of the term "electronic nose", some authors prefer the term "artificial olfaction", while others prefer the more formal (if ambiguous) "chemical sensor arrays". Another multi-authored review, edited by Kress-Rogers [14], emphasized biomedical applications of electronic noses, along with biosensors.

Electronic noses have been the subject of at least one symposium series. A loose organization of researchers, first assembled by the French company Alpha MOS, has sponsored an annual International Symposium on Olfaction and the Electronic Nose. Even though the conference no longer has an institutional base, it held its eighth consecutive symposium in March 2001 in Washington, DC, under the aegis of The Electrochemical Society [15]. Some of the more recent meetings of this group have also resulted in published proceedings volumes [16].

Because the electronic nose paradigm has not yet been sanctified by the passage of long periods of time, considerable ingenuity continues to be invested in exploration of unique designs. Walt's group at Tufts University (Amherst, MA) has explored the optical behavior of polymer beads with different surface chemistry, coated with a solvatochromic fluorescent dye [17]. A large number of different bead types are mixed together. They are attached to the ends of optical fibers, where each may be individually interrogated with a light pulse. Because of the method in which the beads and fibers are assembled, the assignment of "sensors" (the sensitive polymer beads) to data channels (individual fibers) is random. A neural network is used to create an association between each sample type and the pattern of responses. In a real sense, this device resembles the structure and ontogeny of the mammalian olfactory sense more than many other realizations of electronic nose technology. The approach has been given the trade name of BeadArray and is being commercialized by Illumina, Inc. (San Diego, CA). A unique hint at the future can be gained by examination of the result of an experiment that would place several of these optical arrays inside a physical model of a dog's nose. This experiment would produce data that consisted of arrays of array data separated in space and time with some chemical filtration [i.e. changes] in between. This is very much like the mammalian olfactory system and should produce enhanced results with the additional information content.

Another unique variation on the electronic nose is the colorimetric sensor array recently proposed by Rakow and Suslick [18] for identifying solvent vapors. These authors noted that most odorous compounds have at least some Lewis base activity, and would bind to the central atom of a tetraphenylmetalporphyrin, changing its color in a unique way. The authors spot a series of different metalloporphyrins onto a silica substrate in a stereotyped pattern and expose it to various solvent vapors. Each vapor produced a unique pattern of colors. Such an "electronic nose" is not necessarily electronic, and does not even require an instrument! The authors, however, have proposed a CCD-camera to reduce the array colors to digital form for processing by automatic means.

3. CHEMICAL SENSORS AS RELATED TO ANALYTICAL CHEMISTRY AND ARRAYS.

To understand chemical sensor arrays, one should first understand chemical sensors and how their information is developed. The specific properties of each chemical sensor used in the array provide the chemical dimensionality to the array data and hence determine its sensing capability. Just as different human noses are different among people and their ages, sensors are also differently selective and sensitive. Some sensors respond to volatile organics and others to permanent gases. The wide range of chemical sensors now available is at least in part the reason for the evolution of arrays and electronic noses and, more recently, electronic tongues.

For the remaining sections, we will define a "class" of chemical sensors as one operating on a common transducer platform. Sensors using the DC resistance of a heated metal-oxide semiconductor (whether "Taguchi" SnO₂ sensors or higher temperature Ga₂O₃ sensors) would then be members of the same class, electrochemical sensors, and the subclass of impedance-based sensors. Sensors within a class with distinct properties can be referred to as "types." Thus, the differently doped SnO₂ sensors, made to have different selectivities for hydrogen, methane, and carbon monoxide, are "types" within the "class" of electrochemical-impedance sensors and are often called heated metal-oxide semiconductor or MOX sensors. While the nomenclature of "classes" and "types" is not standard or established in the literature yet, we will use it here to add clarity to the discussion of sensors and arrays.

Further, for the sake of this discussion, we can define four distinct kinds of problems each demanding a different analytical perspective as described in Table II. Of course any instrument can be used for any problem it solves. Infrared (IR) spectrometers have been used for the relatively simple online CO measurement for a long time. But the above comments point to typical analytical devices and instruments used to solve the analytical problem at hand. While it has been the goal for many years to obtain a sensor to detect trace explosives like TNT (a Type A problem), it would be difficult to imagine a single sensor capable of complex mixture analysis. Even high resolution IR spectrometers require additional help, including experienced human operators, in order to arrive at useful answer.

***TABLE II NEAR HERE

There are basically three types of "sensors" or tiny self-contained analytical systems that can perform chemical analysis:

(Type 1) Chemical Sensors and Bio-Sensors that measure quantity or quality of a substance because of its chemical reaction with the sensor interface, while the extent of this reaction is converted (transduced) to a measurable electrical signal by communication of the interface with a physical transducer.

(Type 2) Micro-Instruments that measure molecular properties, like small IR spectrometers. These are typically physical sensors that measure a molecular property. Chemists call this molecular spectroscopy and it can be done with electromagnetic (NMR, IR, UV, Xray), thermal (TGA, DTA, thermal conductivity), electronic (Auger), mechanical (sonic), or many other forms of energy interacting with the molecule. We extract molecular information from measuring the change in the physical energy that was caused when the energy interacted with the molecule. These sensors have been called physico-chemical sensors but this distinction is superfluous. An example of such a sensor is the nondispersive infrared sensor commonly used to measure carbon dioxide in ambient or exhaled air; some such commercial sensors are less than 25 cm³ in size and the latest research has given us microfabricated versions [19].

(Type 3) Micro-Total Analytical Systems (u-TAS), as they have become known, that are small analytical systems incorporating sampling, separation, mixing, transporting, detecting and all types of such analytical processes. They are generally made by silicon lithography, plastic molding, or imprinting methods [19].

While these definitions are somewhat arbitrary, they serve a useful purpose here so that we can discuss the field of sensors in an organized manner. As far as a customer or application is

concerned, a definition of chemical sensor could be “anything that goes into the small box and solves the analytical problem as long as the chemical analysis is correct.” But when we develop or discuss technology, the utility of the definition is proved by the increase in understanding and communication it provides. A more complex and comprehensive definition of a chemical sensor is given in Table III.

TABLE III NEAR HERE

The chemical sensor, as Wolfgang and I knew, is “a small self-contained integrated system of parts, that, as the result of a chemical interaction or process (i.e. a reaction) between the analyte and the device, transforms chemical or biochemical information of a quantitative or qualitative type into an analytically useful signal.” This is a type 1 device and all three types are compared in Figure 1. Conceptually, every chemical sensor consists of two domains: the physical transducer and the chemical interface layer or receptor domain (Figure 1a). At the chemical interface, the analyte interacts chemically with a surface or coating or catalyst that is part of the device and produces a change in physical/chemical properties. These changes are measured by the transducer domain, which monitors this change and generates a proportionally related electrical signal. Sometimes these domains are intermixed and the same, sometimes not. Sensors are frequently classified and named by their transduction method, e.g., conductimetry; potentiometry; amperometry; gravimetry, which includes SAW (surface acoustic wave) and QMB (quartz crystal microbalance) transduction; optical (fiber optic, spectrometric, and refractometric); metal oxide semiconductor or “MOX” (heated metal oxide chemiresistive); conductive polymer chemiresistive; polymer composite chemiresistive; or capacitive. Alternately, they may be named according to their structure, as in MOS (metal-oxide-semiconductor) or MIS (metal insulator semiconductor) sensors. A third name is derived from the chemical reaction such as “sorption” sensors or “catalytic” sensors.

FIGURE 1 NEAR HERE

The schematic of a chemical sensor, Figure 1a, is compared to a micro-instrument illustrated in Figure 1b and a μ -TAS in Figure 1c. Not included in the sensors here are the sampling systems or inlets, the housings, and the readout that is necessary to get an analytically meaningful result. These parts are often backward integrated into the sensor device as far as possible to meet simplicity, performance, or cost objectives. The physical sensor, Fig. 1b, sends out and receives a form of energy that interacts with the analyte molecule and, most distinctly, has no chemical interface that, per the above definition, is a required part of the chemical sensor. In the physical sensor for chemical analysis category are measurements of thermal conductivity (thermal sensor), infrared absorption (optical sensors), paramagnetism (usually for oxygen), NMR, etc. The analytical chemist calls this molecular spectroscopy when electromagnetic energy is involved and we could call this micro- or nano-molecular spectroscopy to differentiate it from the larger instrumentation found in the laboratory.

In the μ -TAS group illustrated in figure 1c, the portable GC or “lab on a chip” is illustrated. Also, we could include in this group the MS on a chip because it contains an inlet, ionization chamber, accelerator, mass filter, and ion detector in a vacuum and represents a process for molecule or atom isolation and subsequent detection. This approach integrates as many analytical processes as are required to solve the problem at hand.

Note well that the chemical or bio-sensor has a reactive interface. Every chemical reaction is characterized by an equilibrium constant with its attendant thermodynamic characteristics that can be used to understand the sensor. Note also that the interface is changed during sensing, i.e. it is

stoichiometrically a different material before and after analyte exposure! This is in stark contrast to the physical sensor or microinstrument as defined above.

Figure 2 illustrates one way to represent the categories of chemical sensors arranged by their physical principle, i.e., the physical sensor that transduces the signal. In this manner we see reactions at the interface that are catalytic or absorptive in all classes of sensors. For discussion purposes, it is also useful to organize chemical sensors by the type of chemical reaction that occurs at the interface. In Table IV we illustrate this rarely taken approach in the sensor literature. Each reaction is characterized by a different type of chemical reaction, an equilibrium constant, and attendant kinetic parameters. These chemical parameters will determine to a large extent the observed sensor performance and provide an explanation for the observed sensor selectivity and sensitivity.

FIGURE 2 NEAR HERE

TABLE IV NEAR HERE

Each of these chemical reactions can be used on virtually any transducer platform. For example, I have heard many times and read many proposals for sensor development where the proposer says that a sensor will be built for a gas, perhaps CO, on a platform, perhaps optical, and “all that is needed” is the right coating to make the sensor work. The next logical step seems to be to test a thousand polymer coatings for this purpose, but never the proposed chemical reaction that will be used to achieve the selectivity and sensitivity. It is a simple matter to understand that the polymer coating is not a very promising approach for CO, because it works by partitioning, an equilibrium reaction of the analyte between the mobile (or gas) and stationary (or liquid) phases. The amount of analyte that is absorbed into the stationary phase – the polymer in this case – is governed by this equilibrium constant. If no gas partitions into the surface coating, no change can be induced that will be detected by the platform. Typical GC phases attract gases by intermolecular or condensation forces, which are very weak in permanent gases like CO. This is the reason QMB and SAW devices that use a polymer coating have very low sensitivity to CO.

Logic would dictate the use of a chemical interface that was designed to take advantage of the special properties of CO. Since CO strongly adsorbs to certain metals and is oxidizable even at very low concentrations, the selection of a metal-based coating such as a metalloporphyrin, or an oxidation as the chemical interface is more promising. In fact, catalytic combustion on a metal oxide semiconductor, or an electrocatalytic oxidation, such as occurs in the amperometric CO sensor, are the favored reactions for common CO sensors. So consideration of the reaction type is extremely useful when trying to predict sensor characteristics while consideration of the transducer platform is less useful for this purpose.

When we categorize the chemical sensors by the chemical reaction of the chemical interface, it can make them easier to understand. Understanding makes it possible to avoid mistakes. Suppose, for example, we are searching for a sensor that will measure benzene in the presence of another aromatic hydrocarbon, such as naphthalene. Using a carbon sorbent operating with a physisorption reaction is not a promising approach. The intermolecular forces that are responsible for physisorption of aromatic compounds to carbon are going to be similar for all aromatics, and they will be stronger for polyaromatic compounds than for benzene. It is not reasonable to promise to develop a surface that will detect benzene to the exclusion of naphthalene or other aromatics using partition coefficients alone. The carbon coating will always adsorb more naphthalene than benzene at any temperature or pressure. This is a qualitative statement of the thermodynamics of gas adsorption, from which we can derive that physisorption forces are

similar to condensation. There will be no high sensitivity physisorption unless the substrate is cooled to at or below the boiling point of the analyte. It also explains why on sorption sensors, naphthalene is more "sensitively" determined because at any given gas pressure, more naphthalene than benzene will be condensed. This is not to say that it is impossible to selectively detect benzene in the presence of naphthalene, but it must be done by some selective interaction beyond simple surface adsorption, perhaps by molecular size. Molecular sieves, polymer imprinting, or some specific chemical reaction are better choices for the choice of a detection mechanism.

Further, selectivity is only achieved if the reaction is selective among the sample constituents. That is, an acid coating on the surface will detect all volatile bases. The relative sensitivities to bases will be determined by the relative strength of the acid-base equilibrium constants.

Sensitivity is also a function of temperature. The temperature response of amperometric sensors is a function of the temperature behavior of several electrode processes with different parameters, which are exponential, but may oppose or enhance one another. Sensor response, therefore, may increase or decrease with temperature, but perhaps not in a predictable way. It is for such reasons that many amperometric sensors are designed with a pinhole to limit the analyte entry into the sensor. In this way, the response is limited by a single, predictable physical process such as diffusion, which varies with \sqrt{T} .

In summary, to understand the origins of the performance characteristics like sensitivity, selectivity, response time, and stability, we examine the type of chemical reaction and its relevant thermodynamics and kinetics. Of course this can be an oversimplification if the sensor device is limited by the transducer platform or physical housing. But when studying and reporting results with sensors, testing and experimentation should clearly address the limiting factors be they the chemical interface, the physical system, or the transducer.

With this guidance, one can identify and resolve some of the myths about sensors, and better direct the development of sensor systems for any given application. In the latter discussion, we illustrate these principles considering that all E-noses are not created equal. Some are biased toward the detection of vapors and some permanent gases, some operated over a broad range of concentrations and others over a narrower window. It also becomes clear why heterogeneous arrays can perform many analytical tasks better than a homogenous array. The heterogeneous array is capable of responding to more classes and types of compounds in the sample, over a broader range, and can produce a larger information output.

Finally, we summarize some of the observations we can make about chemical sensors by collecting their common properties. Most often chemical sensors do not necessarily measure a simple physical property. A simple illustration is the response of a QMB polymer coating to a given analyte vapor, say benzene, at high and low relative humidity. Because of the presence of water vapor, we are no longer measuring the simple partitioning of benzene into the coating but the partitioning in coatings in different hydration states. Moreover, the interactions of water or matrix with the coating and benzene with the coating are interdependent. The coating may also change stiffness in response to analyte, water vapor, or other interfering compounds, which also affects the QMB response. Piezoelectric gravimetric sensors response not just to the mass loadings, but also to the shear modulus, or stiffness, of the coating. The final observed response will be the summed output of several reactions and several physical/chemical property changes that have occurred in the systems because of the interfacial reactions. These may or may not be linearly additive.

4. SENSOR ARRAYS AND ELECTRONIC NOSES

4.1 Properties of Chemical Sensor Arrays and Electronic Noses

A chemical sensor array once required little definition. It was merely a collection of sensors, with the only restrictions being that the sensors were all exposed to the same or nearly the same sample, and the responses were interpreted together. Exercise of the imagination in developing new electronic nose modes and embellishments has since complicated the definition. Often, it is necessary to specify the order of the sensors in the array, because some sensors act upon the sample and change it. An example of this is metal-oxide (MOX) sensors, which efficiently oxidize the sample and change the response of other, downstream sensors. The sensors may be of the same or mixed classes, and each will exhibit the features, advantages, limitations, and problems of its respective class. These arrays are termed homogeneous and heterogeneous arrays, respectively. Some of the classes of chemical sensors that have been used in arrays are listed in Table V.

TABLE V NEAR HERE

An additional complication in defining a sensor array is the emergence of the term *virtual sensor*. A virtual sensor refers to a large number of distinct responses gathered from a single or smaller number of physical sensors. An example is the use of the mass spectrometer as a sensor, in which a single physical detector (a photomultiplier) is used to gather hundreds of distinct m/e responses, any of which can be isolated and treated as a separate sensor response. Other examples of virtual sensors are sample fractions eluted from a gas chromatograph column, selected wavelengths from an infrared spectrometer, and the early use of programmed sample preprocessing to obtain multiple pattern elements from single electrochemical sensors in a sensor array [20,21].

The important feature of the sensor array lies in the collected responses of its constituent sensors. We are in the habit of calling the ordered array of sensor responses a "pattern", because at this stage of description we are beginning to enter the territory of pattern recognition or pattern classification, and we should properly adopt the terminology of this field. The patterns of sensor responses are uniquely determined by each sample. In the simplest interpretation, we can plot the sensor response patterns as histograms. For sufficiently different chemicals, these can usually be distinguished by eye (Figure 3).

FIGURE 3 NEAR HERE

The sensor array is one of three defining components of an "electronic nose" (Figure 3). Although there is no universally-accepted definition of an electronic nose, it is in all cases a gas sensor array packaged for use in practical analytical problems. The use of the term "electronic nose" became more common after the monograph by Gardner and Barlett [13], although nowhere in that collective volume does any author venture a definition of the term. Gardner and Bartlett [22] finally proposed a definition that may stand the test of time. They described the electronic nose as...

"...an instrument, which comprises an array of electronic chemical sensors with partial specificity and an appropriate pattern-recognition system, capable of recognizing simple or complex odours."

We would interpret the term instrument to include the sampling system and "partial specificity" as referring to the broad, differential selectivity that is observed in most reactive chemical

sensors, such as metal-oxide or electrochemical. Some authors, including some of those who are deliberately attempting to model the olfactory system, continue to scrupulously avoid the “electronic nose” terminology [23,24]. In fact, it is probably too soon to place a restrictive definition on the electronic nose concept. At this time, a great deal of imagination is being devoted to ways of deriving real-time, multidimensional patterns from vapor samples. The configuration that will prove most general and useful, and which may eventually be called “the” electronic nose, may very well be still awaiting discovery.

After the sensor array, the second defining component of an electronic nose is the pattern classifier. This is a means of extracting information from the collected sensor array patterns by comparing or associating them. In practice, this means associating a pattern from an unknown sample with a set of patterns from known standards to determine the closest match, for the purpose of identification.

The sampling system is usually sufficiently important that it is listed as the third essential component of an electronic nose. The sampling system assures that samples are supplied to the sensor array in a reproducible way, and conditioned if necessary to adjust concentration, temperature, water vapor concentration, etc. Some sampling systems also provide for automated measurement of a series of samples, although this is not a defining requirement.

4.2 History of the Electronic Nose

It seems that the electronic nose has had independent origins, in Europe, Asia, and North America. The European effort originated in attempts to mimic the mammalian olfactory system [25]; the North American genealogy had its roots in directed development of field portable identification and quantitation of toxic vapors [26], and the Asian effort to engineering solutions to specific odor detection systems [27]. These separate efforts are detailed in the remainder of this Subsection.

To our knowledge, the first attempt to use sensor arrays to emulate and understand mammalian olfaction was carried out by Persaud and Dodd [25], at the University of Manchester Institute of Science and Technology. Their purpose was to model the current conception of the mammalian olfactory system by demonstrating that a few sensors could discriminate among a larger number of odorants. They constructed an array of three metal-oxide gas sensors, which they used to discriminate among twenty odorous substances, including essential oils and pure volatile chemicals. Pattern classification was performed by visual comparison of ratios of sensor responses. A decade later, their discovery took the form of the AromaScan®, a commercial "electronic nose" instrument [28,29,30].

In 1980, in North America, a group led by the author started building an analytical instrument based on a chemical gas sensor array [20, 31, 32, 33]. At the time, our goal was to build a portable instrument for the U.S. Coast Guard. This organization needed a portable instrument that would rapidly identify and measure volatile chemical vapors in emergency situations, such as hazardous material spills. Rather than adopting one of the conventional approaches to chemical analysis, such as gas chromatography or infrared spectrometry, we elected to examine the differential responses of an heterogeneous array of chemical sensors. We considered electrochemical, infrared, MOX, catalytic, photoionization, and other candidate sensors. Ultimately, the prototype used only four electrochemical sensors. Since many common chemicals, such as hexane, do not react on electrochemical sensors, a heated catalytic filament in the sample stream converted electrochemically inactive compounds to reactive ones [20]. By varying the temperature of the filament, different patterns were obtained from the four sensors

(Figure 4). This catalytic conversion of the sample was reproducible over wide ranges of concentration and relative humidity, provided the filament temperature and sample flow rate were tightly controlled. Different patterns were obtained from the sensors by operating the filament at a different temperature. By operating the filament at four temperatures from 600°C to 950°C, the number of sensors was effectively increased from four to 16. We would say now that the instrument had four physical sensors and 16 virtual sensors. A relatively straightforward application of the "k-nearest-neighbor" pattern classification algorithm was used to compare the resulting patterns and to automatically identify unknown vapors. We demonstrated that this tiny heterogeneous sensor array could be packaged in a camera bag and accurately identify and quantify over thirty compounds. We estimated that well over one hundred compounds was possible [26,31,34]. This work resulted in the first engineered, packaged, fully functional field-tested instrument that included both the gas sensor array and pattern classifier. A commercial version was offered for sale in 1985 by Transducer Research, Inc. (Naperville, IL). The instrument was recently reconstructed in our laboratory and dubbed the "ILLI-Nose" (for Illinois). It still rivals modern instruments in selectivity and detection limits.

FIGURE 4 NEAR HERE

In the course of this work, we sometimes informally used the term "electronic nose". Now that we know more of the operation of Nature's noses, the term is no longer a joke. We can see that there are direct and meaningful parallels between the structure of the natural and artificial noses (Figure 5). The human nose, for instance, has olfactory sensor cells, each with a receptor protein that interacts with a range of volatile odorant molecules. There are estimated to be 100 million receptor cells, but only 100-200 different types of receptors [35, 36]. The brain learns to recognize the *pattern* of signals associated with certain odors, rather than the response of individual, highly selective cells.

In Asia, scientists were also beginning to foresee the potential of sensor arrays. In 1984, Iwanaga et al. [37] proposed an instrument employing an array of metal-oxide semiconductor sensors, but suggested using simultaneous equations to compute the relative concentrations of gases in a sample. In order for this approach to work, all the gases present in the sample would have to be known. (Clifford [38, 39] patented a similar idea in North America in 1985.) This approach does not use pattern recognition and is suitable only for certain industrial processes where all the analyte gases are known. This severely limits the use of the array in uncontrolled situations, i.e., most of the proposed uses of the e-nose in food science, medicine, and industry. More complex data interpretation was needed [26].

The work on chemical sensor arrays therefore proceeded on three continents in the 1980s. Ehara et al. [40] suggested an array of microfabricated metal-oxide semiconductor sensors, but relied on visual comparison of the signals for comparison of samples. In 1986, Ballantine et al. [41] used an array of four SAW sensors to generate patterns, and found structure-activity correlations among a series of substances, including selected chemical warfare agents. Importantly, they employed pattern-recognition methods to treat the array signals. This pattern recognition work was emphasized by Rose et al. [21, 42]. With a sampling system consisting of an organic sorbent preconcentrator and a short GC column, the SAW array was embodied in an instrument that was ultimately offered for sale [43].

About the same time as Persaud and Dodd's work resulted in the commercial AromaScan, we independently addressed the power of sensor arrays to work with ill-defined samples such as odors and flavors. We successfully used our original electrochemical sensor array instrument, with an improved sampling system and neural network pattern recognizer, to classify odors from

samples of sound and spoiled grain for the U.S. Department of Agriculture [44]. The final device was nearly as reliable as trained human inspectors at classifying grain samples as "good", "sour", or "musty". The electronic nose was about 83-96% in agreement with the human inspectors, depending on the sample type. According to data supplied with the samples, the human inspectors only agreed with one another at the same rate of 93%.

The explosion of interest in sensor array technology, especially in Europe, led to the international conference in Iceland [13]. We are humbled by the large number of scientific and engineering groups throughout the world who have made contributions to this development of the electronic nose technology (see reviews cited). All of us in the e-nose field are sincerely indebted to the great volumes of scientific and engineering work in tiny chemical sensors, computer algorithms for pattern classification, low power portable microcomputer systems, and our understanding of the olfactory process. Without these advances, the e-nose would never have become a reality for any of us.

4.3 Sensor Array Configurations in Electronic Noses

Like the mammalian olfactory system, the electronic nose uses a holistic approach to distinguish aromas. It does not separate or attempt to identify the individual chemicals responsible for the pattern. The electronic nose works equally well on pure compounds or on undefined samples such as flavors, aromas, and other complex odors. Conventional reductionist analytical methods often become less reliable as sample complexity increases. Our work on grain odors, for example, was preceded by a three-year effort by the USDA to use GC-MS to distinguish grain quality. The author of the final report on this study stated, after analysis of more than 300 samples, that "no relationship between the chemical composition and the odor could be found" [45]. Other authors have had similar problems correlating the results of detailed chemical analysis with organoleptic responses [46, 47].

Although conventional analytical instruments become less effective as sample complexity increases, the electronic nose retains its ability to discriminate closely related samples. It has found applications in the food and cosmetics industry, and there are other potential applications everywhere in industry. A particularly potent example is coffee, where the simplest electronic noses can make fine distinctions between blends [48]. Vintners have been able to identify wines by provenance as well as vintage [49, 50]. This distinguishing power can be thought of as an outcome of the chemical imaging character of the array that has been estimated to be able to represent more than 10^{21} different dimensions with even a simple array [51]. This view of the sensor system and its dimensions is a unique consequence of the complexity and selectivity of chemical and biochemical reactions.

Because the electronic nose is not yet a fixed configuration like a gas chromatograph or a mass spectrometer, much imagination has gone into its design. In this section, we will review the following topics:

- The standard or "homogeneous" sensor array.
- Virtual sensor arrays.
- Heterogenous (mixed-class) sensor arrays.

4.3.1 The Homogeneous Sensor Array

The majority of electronic noses, commercial and otherwise, use sensors of the same class, but generally of different types within a class. Figaro Engineering, Inc., lists more than 25 tin oxide

sensors in its product line, making a large variety of arrays possible for just this one class. A recent example is the array of 12 tin oxide sensors employed by Romain et al. [52] to discriminate environmental odors. Sensors may be operated under different conditions to alter their selectivities. Tin oxide sensors, for example, can be heated to different temperatures. There are fewer basic types of electrochemical sensors than of tin oxide sensors, but their selectivity can be modified further by altering the working electrode potential.

4.3.2 Virtual Sensor Arrays

A virtual sensor array consists of a small number of sensors, perhaps only one, which is manipulated to contribute many quasi-independent elements to the output pattern. In our original sensor array instrument, for example, four amperometric sensors were made to yield sixteen signals by pretreating the sample over a hot filament at four temperatures [20]. The response of alcohols, which have a strong natural response on amperometric sensors, decreases as the filament temperature is increased. Presumably, the alcohol is oxidized to less reactive substances. Most other organic compounds, such as ketones and alkanes, show increasing responses as temperature increases. Mielle and Marquis [53] recently used a tin oxide sensor operated at seven different temperatures on the same sample to generate quasi-independent pattern elements. Sensitivity to aldehydes was highest at low or intermediate temperatures, and sensitivity to alcohols was highest at the higher temperatures. Strathmann et al. [54] used sample adsorption followed by programmed thermal desorption to preconcentrate sample vapors for the Moses e-nose. They discovered that they were also able to derive extra pattern elements from desorption at stepped temperatures, greatly increasing the selectivity as well as the sensitivity of the Moses instrument.

Since pattern classifiers are blind to the physical source of their data, some electronic nose designers have devised even more radical ways of extracting independent pattern elements. Agilent Technologies (formerly Hewlett-Packard) has developed an electronic nose based on a mass spectrometer. Individual m/e peaks, or total ion current integrated over selected mass ranges, have been used to generate the patterns [55]. Another designer uses a single SAW sensor as the detector for a gas chromatographic column. The heights of selected peaks serve as the pattern data [56]. Company literature advertises “500 sensors”, referring to the elution intervals. This is not really new, since chemists have looked for structure-activity relationships in gas chromatograph data for 30 years. Optical spectra, especially in the analytical region of the infrared, have also been used historically to identify compounds; recent technology has involved pattern classification algorithms [57].

Data derived from mass spectrometry or gas chromatography is still subject to the same “MOSES principle” restrictions as data from discrete sensors (see the next section). Data sources, whether discrete sensors, or a region of a mass spectrum, that do not contribute to the identification of the sample, will still add noise. Accordingly, the selection of data sources must be optimized for every application.

4.3.3 Heterogeneous (Mixed-Class) Sensor Arrays.

Developers of electronic noses have experimented with arrays of different sizes. The most direct way to improve the data would seem to be to increase the number of sensors of the same class, i.e., using 20 sensors instead of four. However, this approach meets rapidly diminishing returns. Stetter et al. [21] demonstrated strong correlations among data in different data array elements from their virtual electrochemical sensor array, presumably because treatment of the sample vapor with the heated catalyst filament did not produce entirely independent data. Similar

interdependence might be expected with any array where all sensors belong to the same class. A statistical approach illustrates that a small array of 6 sensors is all that is required to differentiate up to 100 different patterns/compounds when found alone or in mixtures of up to four of the compounds that constitute the data base [34]. However, an assumption restricting the response of each pattern to 5 of the 6 sensors had to be made. This illustrates the importance of “off” or no response data in such array systems.

In 1998, Göpel and colleagues demonstrated that if sensors from several classes are used to form the array, the discriminating power is greatly increased [58]. His prototype instrument contained eight MOX sensors, eight QMB sensors, and eight calorimetric sensors, arranged in separate and interchangeable modules. They demonstrated greatly increased discrimination between olive oils of different provenance. They were also able to observe the development of rancidity in olive oil samples over time, which is due to the auto-oxidative formation of short-chain aldehydes. As a result of these experiments, the authors enunciated the so-called "MOSES principle" (where the acronym refers to "MOdular SEnsor System", after the modular design of the instrument):

- As array sizes increase, each additional type of sensor of the same class contributes less information, because sensors within a class are rarely orthogonal. However, each additional sensor contributes the same amount of noise. Therefore, there is an optimum array size.
- The use of different sensor classes, which respond to different physical or chemical properties of the analytes, allows larger numbers of sensors to be used, while still contributing information to the data set.

This approach is not so obscure that it has not occurred to others independently. The sensor array patent of Stetter et al. [33] included a claim covering sensors of mixed classes. Commercial electronic noses made by Alpha MOS (Toulouse), EEV Ltd. (Chelmsford, U.K.), Nordic Sensor Technologies AB (Linköping, Sweden), and RST Rostock Raumfahrt und Umweltschatz GmbH (Rostock, Germany), and Lennartz Electronic GmbH (Tübingen, Germany) later used sensors of mixed type [59].

4.4 Sampling Systems for Electronic Noses

A sampling system should deliver a vapor sample to a sensor array in a reproducible way. Its purpose is to reduce sample-to-sample variation that may result from differences in humidity, temperature, concentration, etc., as well as to preprocess the sample in any way that increases the quality of output data. To date, little research has been carried out on optimized sampling systems, even though some authors have demonstrated dramatic increases in performance of sensor arrays [60].

The most obvious use of a sampling system is to concentrate the vapors, in order to improve the sensitivity of the sensors. This approach was pioneered by Grate et al. [43] in a four-SAW sensor device which was optimized for chemical warfare agents. It was later commercialized for hydrocarbon measurement by H. Wohltjen at Microsensor Systems Inc. A short tube of organic sorbent (Tenax) was used to absorb vapors from the air. These were desorbed using a heater and passed through a short gas chromatography column to the sensor array. Similar preconcentrator approaches have been used by other authors [54].

Samples often contain substances that are common to all, and, although the sensors are dominated by them, they do not contribute to discrimination. In bacterial cultures, for example, the common substance is water. In beer and wine, water and alcohol will be present in all samples in much larger quantity than any other constituent. We have successfully used Nafion tubing and

anhydrous sodium sulfate to selectively remove water, alcohol, and some other hydrophilic vapors from samples [61]. Although sensor signals, on average, are reduced by a factor of ten or more, the removal of the dominant constituents greatly improves selectivity. Another type of sampling system [60] allowed TNT adsorbed to silica sand to be detected and discriminated from structurally similar compounds by vaporization of a sample from a tiny beaker, using a hot platinum filament. A second filament was located downstream to combust the sample to electrochemically reactive compounds, probably nitrogen oxides and carbon monoxide.

4.5 Signal Processing and Pattern Classifiers for Electronic Noses

Research into pattern classifiers has been perhaps the most aggressively-pursued aspect of electronic nose research. A large body of previous research on pattern classification and recognition has been drafted into the quest to extract the maximum information from the chemical data produced by the sensors. We cannot discount the glamor of artificial intelligence methodology, which attracts research effort at the expense of mundane hardware development. Even US funding agencies will readily fund development of insubstantial mathematical tools rather than support the development of new instruments and sensors.

Nevertheless, two of the chief problems hindering e-nose applications are not being actively addressed. One of these problems is *detection limit*, the ability to detect small amounts of an analyte in a typically responsive matrix. The second problem is the detection of analytes in a *variable matrix*, for example, the detection of the characteristic odors of disease on the breath. Human breath can vary in composition with factors that have nothing to do with disease states, such as diet, smoking history, cultural background, and nutritional state [62], and so there must be some scatter among normal individuals which may complicate the task of disease detection. In principle, the notion of isolating a known class (the disease pattern) from a variable background should be solvable to the same degree as isolating a variable class from a constant background. In either case, we expect some loss in sensitivity, but perhaps not to a degree that would interfere with the power of disease detection. The reason it is not yet solved is because the method for pulling a pattern from the matrix in which the response patterns are most probably related is akin to the brain recognizing that THE CAT can be written “T__ E C__ T”. We can read it, especially if it is given in context, but a computer has trouble with or without context. We need to understand how to generate the data that are truly independent and understand the ways or algorithms that allow us to pull the meaning from the data to solve this problem. I am not saying it is impossible, but I am saying that no one has succeeded yet in solving the two problems of sensitivity and/or selectivity.

Many pattern classifiers have been examined for use in electronic noses. Decision-surface methods are directly applicable to arrays of arbitrary data. In our first explorations of sensor array technology, we used the k-nearest neighbor (KNN) method [63], which is intuitively understood by people with a minimal mathematical background. It proved to be surprisingly powerful. Years later, we compared its performance directly to a back-propagation artificial neural network (ANN) [44]. Both methods were equivalent in their ability to classify unknown grain samples. However, when either random or systematic error was added to real data, the ANN proved to be much more robust. The rate of successful classification by KNN decreased twice as quickly with increasing error as the ANN method. Moreover, we determined empirically that periodic full calibration was not needed as often with ANN. Partial calibration by known samples related to the unknowns was found to be sufficient.

By far the most popular method of pattern classification in today's electronic noses is principal components analysis (PCA). PCA is primarily a method of reducing the dimensionality of data.

An n-sensor array produces n-dimensional data, which cannot be plotted on simple graph paper if $n > 3$. By extracting principal components, most of the systematic variance is typically gathered into two or three dimensions, readily plotted and giving an appearance of comprehensibility. On the other hand, reduction in dimensionality must necessarily result in some loss of information. It nevertheless remains popular, if only because it has the distinctive feature of producing attractive plots that clearly display grouping of replicate samples, and the relative affinity of different samples to one another. These plots have strong presentation, not to mention marketing, appeal; alternate, and more powerful, pattern classifiers do not produce such visually appealing output.

If any lesson has been learned from the use of PCA, it is that one must take care with the questions that one asks of a dataset with any statistical treatment. A data set that we gathered from bacterial headspace gases for different periods of growth can be used to understand the most common misuse or error in the application of PCA methods [60]. The data set consists of two bacterial species; separate cultures were grown for 0, 0.5, 1, 2, 3, and 6 hours. If PCA is applied to the entire data set in an attempt to separate all the classes at once, the 2 hour class can be separated from the 1 hour class. That is, growth can be detected at 2 hours. If, however, only a portion of the data set is selected, say, the blanks, the 0.5 hr and 1 hr cultures can readily be discriminated, even by PCA. In the first instance, we are implicitly demanding that the statistical method, which draws mutually perpendicular axis along the dimensions of maximum variance, separate all the classes at once when reduced to the two dimensions. In the second case, we are asking a much less complex question of our data set: can the 0, 0.5, and 1 hour samples be separated from one another?

In other words, it is important to be clear about *the question that is being asked of the pattern classification method*. In the first instance, we attempt to separate all the classes at once, first, because it makes a nice illustration for a publication or presentation, and second, because we have not realized that we were even phrasing a question! In the second instance, we have thought about the question that we wanted to ask in the first place: *How early in bacterial growth can we detect differences in the headspace gas?* Accordingly, we pruned the data set to deliberately look at only the relevant data. The rotation of the axes that is used to separate classes in PCA is no longer constrained by the presence of unimportant data. The lesson to be learned from this illustration is that, when you are viewing one of the myriad PCA plots generated for the E-nose data, this representation is only valid and representative for the data set under consideration! No extrapolation to unknowns, and no extrapolation to subsets, can be made! Each extrapolation must be validated, and the accuracy and precision of the extrapolation measured by a valid statistical technique.

Although many arcane advances have been made in the improvement of pattern classification, this subject is outside the scope of this review. We will limit our comments to two promising approaches:

Llobet et al. [64] proposed a pattern classification approach called ‘fuzzy ARTMAP’, which is able to update its training while not losing its previous training. Using samples of increasing complexity (pure alcohol, coffee, and breath from ketotic cows), the fuzzy ARTMAP method substantially outperformed a conventional back-propagation neural network. The cow’s breath samples were taken in a barn, obviously under widely variable environmental conditions. This study of the fuzzy ARTMAP approach is one of the few that has identified and directly addressed the variable matrix problem.

An additional nagging problem that is being attacked by signal processing development has been the problem of calibration. All chemical sensors exhibit drift over time. Much of this is

systematic and so can be predicted at least in part. Although drift is basically a hardware problem, there is no likelihood of solving this problem in the short term, and so some workers have turned to mathematical treatments to deal with it. Holmberg et al. [65] have developed methods to predict future calibration from past drift behavior. Of course, the continuing effort to develop sensors that do not drift or that have drift compensation [66] continues to be welcome since these decrease the reliance on algorithms which cannot entirely compensate for bad data.

5. DEBUNKING MYTHS ABOUT THE E-NOSE.

This section is presented to stimulate scientific and technical discussions. There are some clarifications required because words and terms can sometimes have ambiguous meanings and sometimes because there is genuine scientific controversy. But truth is found through open dialog and often disagreement is necessary to inspire progress. We sincerely hope that this section leads to better understanding of the E-nose and more rapid progress in its development and application. We apologize to those who do not hold these myths to be self-evident, and we realize that these are in some manner the humble constructs of the authors in order to structure discussion. However, many of these myths are in fact dearly held by potential users of the technology and may serve to warn the uninitiated who are just entering this field of research.

5.1 Myth 1. The E-nose is a “better” solution to analytical problems.

The analytical capability of the “electronic nose” has been greatly oversold, and as a result the technology has suffered damage to its credibility in certain applications that has taken years to overcome. Some entrepreneurs and researchers have still not learned the lesson, and continue to tout the E-nose as the final and only solution to virtually every analysis problem. Of the four major classes of analytical problem (Table II), the E-nose is only suited for selected subsets of these applications. The analytical problem, at least with today’s level of E-Nose sophistication, may often be better performed with another analytical instrument like a GC, IR, UV, electrochemical sensor, or GC/MS. The user still deserves the best available solution to their problem and often it will not be the E-nose.

The fact is, the e-nose is not better than conventional techniques like GC or GC/MS, but rather it is *different*. An example would be the detection of the rancidity in olive oil, for which we know the molecular cause, i.e. the accumulation of C5 and C6 aldehydes over time with exposure to air. After a modestly difficult workup, these aldehydes can be measured directly using GC or GC/MS. Rancid olive can also be discriminated from fresh by the enose using the headspace above a stored sample. The sample workup is nonexistent, but you do not get information on precisely what you are measuring. You are only aware that the oil has a pattern that is associated with patterns of rancid oils, and is different from those of fresh oils. For many applications, this is sufficient. Moreover, it is a simpler and less expensive method than GC/MS.

Interestingly, as samples get more complex, and endpoints become less definable in a molecular sense, conventional methods lose their power, but the enose retains its ability to discriminate differences between samples. In a one year study [44], discrimination of grain samples according to the USDA categories of 'good', 'sour', 'musty', and 'COFO' (Commercially Objectionable Foreign Odor—a catchall) with fidelity approaching that of an expert human panel was achieved with an E-nose. A prior study using GC/MS, lasting at least three years, had failed to find correlates between organoleptic scores and specific compounds observed in grain samples by GC/MS [45].

Coffee provides an example of an E-nose application that is appropriate to the method. The flavor and odor of coffee are composed of upwards of 640 volatile compounds [13]. Relatively minor changes in components (not necessarily major components, either) result in detectable changes in flavor and odor, according to no discernable pattern. Coffee, on the other hand, is a particularly good subject for e-nose analysis, and is capable of making fine distinctions among coffee varieties and blends [47].

During the sixties and seventies, a substantial effort had been spent using GC, GC/MS, and pyrolysis-GC to discriminate among bacteria. It was largely successful, as far as it went, but the complexity of the methods and the continuing need for expert involvement made the methods unfeasible except where no alternatives existed (as in food chemistry), and the methodology has been largely abandoned. The E-nose provides the potential to do bacterial analysis in foods and infectious disease diagnosis with a simplified 'black box' approach which is more amenable to automation, portability, minimal training, and very low cost. A worthwhile goal indeed is our long-term dream to produce a portable breath tester for tuberculosis, which is cheap enough, rugged enough, and simple enough to be used throughout the world, with less reliance on the cold chain or central laboratories [67].

5.2 Myth 2. The E-nose senses or determines “odor” and works like the human nose.

E-nose devices respond to the chemicals to which the sensors respond. The concept of odor is a human one and so human receptors/sensors respond sometimes to totally different compounds than the e-nose sensors. The human sensor responses together with the complex human brain form the substance of a true “odor.” By its nature, the e-nose most probably is not responding to the same group of compounds as the nose and, in fact, different human noses most assuredly produce different response patterns and are not the same. In this case, the tremendous flexibility of the brain still categorizes/learns the different patterns. However, the E-nose response pattern for the odor and its matrix may also be distinct from all other patterns of the odors and their matrices under consideration. In this case, the E-nose, with its pattern classifier, can “tell” one “odor” from another in the data set of odors. In this way, it can be called an odor classifier but should not be confused with identifying a “human odor” except in enlightened circumstances.

Does the E-nose work like the human nose? In some ways this is of course true and we can see this from the introduction, definition, the above discussion of the EN. But the sensors differ in critical ways. The nasal receptors typically amplify the sensor signals chemically in a manner much unlike current electronically amplified chemical sensors. For example, a single analyte molecule might un-block a channel in a membrane and release 10^5 or more ions. This makes the relative intensities in the nasal receptor patterns extremely large. We need to develop sensors that can chemically amplify (as well as electronically amplify) sensor signals. Perhaps neural nets and fuzzy logic methods of pattern recognition, which begin to simulate reinforcement of differences, are more effective in E-noses for this very reason [44, 64]. While we can learn from nature, we must be prepared to improve upon it, just like the microscope improves upon our eyes when viewing small images and the telescope improves our grasp of far away images. As the eye is not a spectrometer and can be fooled, so too can the nose be fooled. Our new E-noses must be more robust analytical instruments if they are to be deployed widespread.

5.3 Myth 3. More sensors in the array are “better.”

Are more sensors better? The debate continues, although most parties are now in agreement that there is an optimum number of sensors for each application, although that number, and the choice of sensors may differ greatly from one application to another. Some smaller arrays appear to have

as much or more capability than large arrays and the theoretical limit of selectivity has not been reached. At least one manufacturer of electronic noses has recognized this. Cyrano Sciences Inc. sells its Cyranose 320 with 32 polymer composite sensors. Specially developed software that isolates those sensors that contribute to the discrimination of samples for each application. These are typically just 8 sensors, although the selected sensors differ by application.

Several observations may be made. There is a clear benefit to more sensors if they are completely and perfectly redundant. The theoretical sensitivity of an optical array of completely redundant sensors has been shown to increase as the sq root of the number of sensors as expected from simple gaussian error theory [17]. A second observation is that too many sensors that are not exactly the same but are also not independently responsive or orthogonal can add noise but no new signal information and actually reduce the differentiating power of an array [21, 58]. A third observation is that the potential information content of an array of signals is quite large even for a small array [51, 68, 69]. A fourth observation involves the increased information content of heterogenous arrays, i.e. arrays made with different classes of sensor, as opposed to arrays made from sensors of a single class [58]. This is a direct result of the increased orthogonality of the data from different classes of sensors. At this stage of development of e-nose technology, the selection of the optimum sensor array is still an empirical science.

5.4 Myth 4. All the sensors in the array need to be “partially sensitive.”

Many arrays use sensor that respond to virtually every substance and these seem to work in the E-nose and so, therefor, it might be true that this is needed. For sure, the information content is directly related to the different sensitivities to the same compounds or differential selectivity of the sensors in the array. There is a general assumption that the human nose works because of the relative signals from the receptors. We can agree with all of this. This leads some to conclude that an array of partially sensitive chemical sensors is the only way to make an E-nose. I disagree with this statement without clarification. Just like the eye sees different wavelengths by relative responses of rods and cones, the nose smells by differential responses. But this is not the entire story because the eye can easily be fooled into believing that blue + yellow is the same as green. However, a spectrometer cannot be fooled this way because it immediately knows if the light is green or a mix of blue and yellow wavelengths. Why? Because the spectrometer is measuring a more fundamental property, the wavelength, and not a group of relative reactions on partially sensitive sensors! This analogy must be true of the nose also. So, admitting that there is a lot to be learned from the nature of the human nose, do we really want a human nose or do we want an instrument that is less ambiguous? I think the goal is the latter. So what are the differences we need and what must we do to get there?

The statements has been made that the E-Nose requires a group of “partially-selective” sensors and they should “**all**” be partially on for each compound in the gas stream. While this may be sufficient for some applications, this is not at all a general requirement but a myth. In fact, arrays that have some “off” channels should theoretically be better. And, in fact, the human nose probably gets as much information from the receptors that are not on as from the receptor that are on. Calculations illustrate that, using a statistical approach, the minimum number of sensors required to sort any one of 100 compounds into its components of up to a four component admixtures was only 6 gas sensors. In this data set, each analyte had a response on only 5 of the 6 sensors [34] and one had to assume one channel was “off” to get the statistical scheme to work..

A second reason the array of partially sensitive chemical sensors is incomplete is because we have seen that digital data can improve pattern classification [34]. In this case, intelligence about

the signal was used to reduce the number of possibilities in the library, i.e. choose from among a smaller set of possibilities. Consider the receptors in the human nose that amplify the signal up to 10^5 times [70]. This has the effect of making the data nearly digital. This receptor response has the effect of emphasizing certain receptors well beyond the noise and it would be as if we knew beforehand certain important sensors and in our software we could weight them heavily before interpretation. It seems we can do this with chemical sensors if principles are chosen that are radically different and heterogeneous. Responses that are “extremely” sensitive to one or a few compounds greatly improves discrimination power for arrays. Such performance may only come from heterogeneous arrays, e.g. an electrochemical sensor will respond to ppb levels of NO, but a QMB will not (it is ‘off’), whereas the electrochemical sensor is not responsive to benzene and the QMB can see ppm levels of benzene. Again the empirical observation that heterogeneous arrays fare better in applications supports this discussion.

Our third observation on this point follows from the above. The Human nose has receptors that are partially responding but it seems to me that some of them are totally non-responsive to a given stimulus. The power of the mammalian nose, especially that of the dog, is legendary. Thus, we could predict that the most powerful arrays would be smaller, heterogeneous, and contain some on/off channels, channels with orders of magnitude differences in relative sensitivities.

5.5 Myth 5. It is easy to calibrate an E-nose and extrapolate to unknowns.

No one may seriously believe this, but a more pertinent question may be: can calibration can be extrapolated to situations involving unknowns? This is true for any well-developed and validated analytical method, but not many of these exist today for the E-nose technology. Analytical method validation is a specific and thorough process [71]. This step must proceed with caution and is the most difficult part of the application of the EN to any real world problem. Simply put, the issue is that multidimensional sensory data has interferences, drift, and noise that are also multidimensional and adequate methods to handle this situation are not yet easily validated for many applications!

The rules for pattern classification are simply: 1) the pattern of responses must be statistically related to the endpoint, 2) the answer must be able to be adequately represented by the set of responses, 3) a relationship can be discovered by applying the chosen algorithm to the data, and 4) the relationship can be validly extrapolated to additional situations and unknowns. It is up to the E-nose method developer to prove statistically that his endpoint (flavor or odor) is statistically related to the pattern achieved by the sensors. Further, statistical methods strictly apply only to the data set under consideration unless you can also “prove” a relationship to unknown data as we have discussed above for the PCA plots (Figure 6).

Having burst the bubble here for some potential users, it is justified to be skeptical of E-nose results. However, can statistically valid relationships been found for difficult analyte/matrix data sets? The answer is a resounding yes. The power of the sensor array to represent feature space is apparently immense and estimate at more than 10^{21} features [34]. But the analyst must perform sufficient tests on calibration sets and unknown sets to understand that they are related and can be represented using the pattern classifier of choice.

6. ELECTRONIC NOSE APPLICATIONS

As recently as 1998 it was noted [9] that the majority of publications on electronic noses were in the area of research, with only a few (pardon the term) “real-world” applications beginning to appear. Our survey of the e-nose literature, done in February 2000 and again in July 2001,

showed a massive increase in the development of applications for the technology. In particular, applications in food technology dominate these.

Sensor array and electronic nose methods have immediate appeal to technologists who must cope with subjective responses of clients and customers to undefined samples. Foods, beverages, cosmetics, packaging materials, consumer polymers, and even wastewaters, all have organoleptic restrictions and requirements. Two approaches have been conventionally used to characterize such samples. Subjective analysis by panels of trained persons is the most common approach. Brute-force analysis, in an attempt to isolate the compound(s) responsible for taste and odor, is the other. The Water Department in the City of Chicago, for example, specifically searches for 2-methylborneol and geosmin in drinking water at specific times of year, because these are known to be the cause of the 'earthy' or musty taste of water during algal blooms in Lake Michigan. Electronic noses provide a third, and complementary, approach to characterization. Like taste and odor panels, they are especially useful for comparing samples, rather than relating them to a cause understood at the molecular level.

6.1 Food Applications

The food industry has spent considerable effort over the years to reduce flavors and odors from an art to a science, with limited success. Many foodstuffs produce volatiles in the concentration ranges of 1 to 1000 ppm which are appropriate to typical chemical sensors. Not surprisingly, therefore, applications to food have been reviewed regularly since the inception of the electronic nose concept. In 1992, Dodd et al. [72] reviewed some of the potential applications of electronic noses, foreshadowing a large amount of work over the next decade. The subject has since been reviewed by Göpel [73], Kress-Rogers [14], Schaller et al. [46], Krings and Berger [74], Giese [75], and Stephan et al. [76].

Electronic noses have been used for meat, grains, coffee, beer, mushrooms, cheese, sugar, fish, fruits, juices, alcoholic beverages, and packaging materials. Frequently, these reports refer to home-made or early commercial electronic noses such as the Aromascan. Homogeneous arrays with reduced resolving power are usually used. Yet these devices are often capable of the discrimination demanded by the application. Table VI lists several references according to the foodstuff examined. Many of these applications are concerned with the detection or confirmation of bacterial spoilage, especially in meat and stored grain. Such studies have sometimes been paired with the study of microorganisms recovered from spoiled meat [77, 78].

TABLE VI NEAR HERE

A recurring theme in much of the research on food is the correlation of subjective sensory responses, electronic nose responses, and conventional reductionist analysis by gas chromatography or GC-MS. Arnold and Senter [79] were able to detect ten alcohols, from C-2 to C-14, an aldehyde, and indole from the headspace of bacteria cultured from processed poultry. In another study, Siegmund and Pfannhauser [80] studied cooked poultry as it became rancid during chilled storage, presumably through nonbacterial spoilage.

Foods, because of their great variety, give us insight into the power of the electronic nose. Some odours are chemically simple. The rancid flavor of old olive oil is due to the accumulation of normal aldehydes [81]. Apples represent a more complex sample. Nakamura et al. [82] cites the flavor of apples as being due to a mixture of nine organic compounds. Commercial artificial apple flavoring is a mixture of these nine compounds. By comparing e-nose results on these mixtures,

an optimal sensor array for characterizing apple flavor was selected. Apples also show differences according to variety, integrity, and ripeness [53].

Coffee represents the other end of the spectrum of complexity. The subject of intense experimentation due to its value and complex chemistry, the flavor and odor of this beverage are due to at least 640 volatile compounds [72]. Over 120 of these compounds can be unambiguously identified at one time in a single analysis after extraction by SPME and gas chromatography [83]. Much more protracted analysis is needed to determine most of the compounds that actually contribute to flavor and odor. Relatively minor changes in this complex mixture can be readily detected by the senses.

6.2 Bacteriological

Bacteriologists have long known that many species of bacteria can be identified by their odors [84]. Historically, much of practical bacterial taxonomy has depended on the unique metabolic characteristics of each species of microorganisms. No organism completely oxidizes all its food to carbon dioxide, and it is safe to say that every species of animal has a metabolically determined baseline emission of waste. Since many metabolic products are volatile, it is not surprising that bacterial cultures are good subjects for electronic nose evaluation. Early research in headspace analysis of cultures and medical specimens has been used to identify the microorganisms involved [85, 86, 87]. Several authors have demonstrated that bacterial species can almost always be discriminated by even simple electronic noses [88, 89, 90, 91, 92].

For practical medical applications, however, detection limit has always been an important issue. McEntegart et al. [61] demonstrated that *E. coli* in a culture medium was not detected until cell concentrations had exceeded 10^8 /mL.

6.3 Medical

The medical field offers great potential for the application of electronic noses. In essence, the human body processes nonvolatile, mainly macromolecular foods into volatile products. Both the normal functioning of the body, and aberrations of that functioning, should be detectable on e-noses. There is a ready market for diagnostic methods that are noninvasive and inexpensive; the e-nose offers both advantages. The medical potential has been addressed recently in an excellent review by Pavlou and Turner [93].

Breath tests, in particular, hold special promise, because of the ease with which samples can be taken. Some research has indicated that the organic volatiles found in human breath do not vary greatly among individuals. Kratoszynski et al. [62] measured over 100 volatile compounds in the breath of healthy people selected across bounds of gender, race, and socioeconomic status. Three compounds, acetone, isoprene, and acetonitrile, made up 50% of the total mass of exhaled organics. Each organic compound varied within an order of magnitude among individuals. These results imply that the variation in matrix between individuals will not be very great. Similar studies have been done by Jansson and Larsson [94] Phillips et al. [95].

Some of the suggested applications are:

- Detection of urinary tract infections from urine headspace gas.
- Breath test for cancer
- Breath tests for respiratory infections (staphylococcus, bacterial pneumonia, tuberculosis, etc.)
- Breath tests for various forms of poisoning

- Breath and urine tests for metabolic disorders, including solid and humoral tumors and diabetes
- Melanomas, which have been detected by trained dogs using odor (news item)
- Wound infections
- Neonatal complications, such as jaundice, where even such simple diagnostic methods as blood sampling are invasive

Di Natale [96] has recently reported discrimination among patients with lung cancer, nondiseased controls, and lung cancer patients after surgery. Solid tumors are often poorly vascularized and have a metabolism adapted to rapid growth rather than static function. The combination of necrotic or anaerobic tissue and rapid metabolism would be expected to generate volatiles. The Greeks knew cancer as “the stinking disease”, which suggests that other types of cancer will also respond to diagnosis and monitoring by e-nose.

Because of the ease with which bacteria can be detected and discriminated from one another, one would also expect that infections would be easily detected against the background of normal metabolism. Besides volatiles produced by the bacteria themselves, local tissue inflammation and damage caused by the infection would also produce volatile substances. One researcher has reported the detection of bacterial pneumonia, albeit in intubated (i.e., seriously ill) patients [97]. Urinary tract infections have been observed to cause compositional changes in the headspace gas above urine specimens [86, 98, 99].

6.4 Environment and Safety

Analytical chemistry in safety and environment usually involves the detection and measurement of pure chemicals such as toxic gases or solvents. Although electronic noses have been used to measure or identify pure chemicals, these instruments are rarely the best approach, compared with such conventional techniques as gas chromatography or photoionization. There are distinct areas, however, where the special properties of the e-nose are helpful.

Rose-Pehrsson et al. [100] have been developing a fire detector for naval and space use that fuses the outputs of many sensors, both physical and chemical. In space, combustion has special characteristics due to the absence of gravity. Flames are often invisible, and carbon monoxide concentrations can increase very rapidly, since fumes do not escape from the fire by convection. Hence, it is in the interest of the designer to use as many modes of detection as possible, including ultraviolet and acoustic sensors, as well as carbon monoxide and other gas sensors, in a fire detection system.

E-noses have also been used in the characterization of wastewater. Rather than detailed analysis, wastewater is often characterized by comprehensive methods with endpoints that are as difficult to justify as the e-nose array. BOD, or biological oxygen demand, measures the consumption of oxygen by organisms in a sample of water over a fixed time period. Since the composition of such waters can be complex, in certain cases a sensor array pattern can substitute for analysis for several different parameters. Singh et al. [101] used an e-nose to monitor water quality. Later, Fenner and Steutz [102] used the technique to monitor waste treatment.

7. THE FUTURE OF SENSOR ARRAYS AND ELECTRONIC NOSES

It is always dangerous to predict the future, but it is often the way we challenge ourselves with the most difficult goals. The development of the electronic nose is still in its early stages. Many instruments have been rushed to market with insufficiently developed sampling systems and especially with sensors that are inappropriate for the task. Elaborate sampling and data-processing systems are typically used to attempt to compensate for the effects of temperature, humidity, memory effects, and low sensitivity. But even the most powerful pattern classifiers cannot operate with low-quality sensor data. Any new technology must overcome a barrier of suspicion, but the modest performance of the early commercial electronic noses has raised the barrier still further. One critic has already, if prematurely, dismissed the electronic nose in print as "a thing of the past" [103] and another has more accurately reported, "...the long-term performance of electronic noses has not lived up to expectations..." [104]. Each of the three components of the electronic nose is subject to improvement, to achieve improved sensitivity with minimum impact on selectivity.

Where do we go from here? It is clear that the E-nose has made much progress and come a long way. But, there is yet much to do. Our human nose is elegant but not foolproof. It still has more redundancy and self-amplified sensors and is better at most things than an E-nose. This is proven by the existence of the olfactory panels that have not been replaced by the E-nose. However, the sensor array does not fatigue as easily, can be placed in hazardous atmospheres, is less costly and can travel easily into outer space. It also holds the promise of being much cheaper, smaller and easier to use and maintain than a mass spectrometer. Students have build e-noses for us from spare parts found in the laboratory. When this simplicity is combined with the power of the sensor array, the e-nose warrants the attention it is getting.

If the issues of calibration, extrapolation to unknown data sets, and stability of sensors and patterns can not be improved, the E-nose will never achieve its rightful place in the arsenal of analytical tools. On the other hand, progress on these technical problems offers the promise to revolutionize analytical chemistry in the field. It ill boost the applications of chemical sensors and micro-instrumentation many-fold.

Where will these improvements lie? Certainly, at least in part in improved chemical sensors. We continue to observe improvements in drift correction [66]. Such on-board automated compensation, now routine for physical sensors, will become more routine for chemical sensors and spur more applications. Further, chemical sensors will more mimic nature in being self-amplifying and regenerating, perhaps by incorporating biological components and mechanisms. Chemical sensors will be tuned to measure such fundamental chemical parameters as solubility and binding constants, making them more like physical sensors that do not simply measure color but rather wavelength of light. Another area of improvement will be in the array itself with compensation for patterns and additional sensor heterogeneity. Arrays may become heterogeneous in sensor class and type as well as in integration into u-TAS, with the addition of sampling and separation systems. We can envision data from arrays of arrays that are spatially and temporally separated like the human nose to be an improvement. And, of course, pattern classification must be improved. A tiny bird, whose brain contains the smallest amount of gray matter, can recognize a mouse a 1000 feet away in milliseconds, against any background (matrix) while flying, yet the most powerful of our PCs struggle with elementary pattern recognition. We require novel approaches to these algorithms and stacked and/or sequential application of specialized algorithms seem appropriate here by the above analogy.

We hope that these discussions and citation do not offend anyone because of their less than

comprehensive nature. One always makes choices in these matters and the responsibility lies with the authors for this manuscript. However, we hope this is a contribution to those in and allied to this field of work.

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Table I. Classification of primary and review papers citing the terms “electronic nose(s)”, “artificial olfaction”, or “sensor array(s)” for the time periods 1994-1999 and January 2000 - June 2001. Classification was by inspection of titles and keywords. Since many different types of physical property sensors, such as imaging devices, are referenced under “sensor arrays”, only those papers referring to chemical sensors are included in this listing.

Category	Number of papers	
	1994-1999	2000-2001 (18 months)
Sensors and hardware design	50	46
Pattern classification and theory	25	16
Applications – food, agriculture	65	36
Applications – medical	6	9
Applications – bacteriology	5	8
Relationship to biological olfaction	5	6
General, reviews, miscellaneous	50	40
Total	206	161

Table II. Four generic kinds of analytical problems

Type A: A single component in a complex matrix, for example, CO in air or Fe in iron ore. The matrix (that portion of the sample that is not the target of the analysis) may be consistent or highly variable. A special subset of this class is trace analysis – the needle in the haystack problem. This is the class of analysis that single sensors often target. The carbon monoxide sensor is one of the two or three most common chemical sensors in commerce.

Type B: The major components of a mixture – Air consists of five important components, nitrogen, oxygen, carbon dioxide, water vapor, and argon. Such analysis can be carried out by gas chromatography or in part by infrared analysis or by oxygen and relative humidity sensors.

Type C: Complex mixtures – There are 640 characterized components in the headspace gas above coffee. Extensive sample preparation and complex instrumentation and training is generally required for this type of task.

Type D: Determination of a subjective, collective, or arbitrary endpoint. Examples of such endpoints include lower explosive limits or lower flammable limits, toxic concentrations, and assessments of quality of a raw material such as grain, or of a finished product such as a food for sale. One may not be able to provide a specific and complete molecular explanation of the endpoint or the endpoint may not refer to a specific molecule or set of molecules and their concentrations. This class of analytical problem is addressed directly by the human or electronic nose and/or tongue as well as a select few sensors (e.g., the combustible gas sensor).

Table III. Properties typically associated with chemical sensors.

They all have:

a sensitive layer that is in chemical contact with the analyte gas.

a change in the chemistry of the sensitive layer; i.e. it is not the same after exposure as before exposure to the analyte because a stoichiometric change has occurred [a reaction].

no moving parts in this mechanism

They all respond to the presence of a chemical with an electrical output and this means the sensitive layer is on a platform that allows transduction or coupling of the sensitive layer changes to a transducer that relates the change to electrical signals.

They are physically small.

They operate in real time, controlled by thermodynamic and kinetics of a chemical reaction - although the readout may be temporal [notwithstanding physical limitations due to design].

They do not necessarily measure a single or simple physical or chemical property.

They are typically less expensive and more convenient than an equivalent instrument for the same chemical measurements.

Table IV. Possible reactions at the chemical interface.

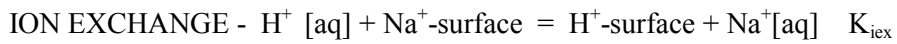
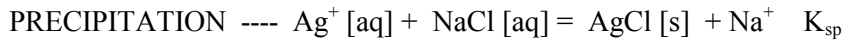
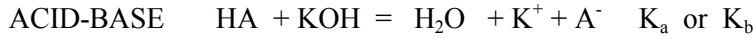
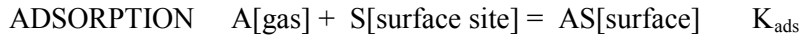


Table V. Chemical sensors used in arrays and e-noses. Internet links to these companies can be found at the NOSE web site [2].

Transduction Mode (Chemical Interface)	Comments
Conductimetric (conductive polymer)	Earliest commercial e-nose (Aromascan); easily made by electrodeposition (moisture, temperature, history-sensitive)
Conductimetric (metal oxide semi-conductor)	Used in largest number of e-noses (moisture and history-sensitive) WMA Airsense Electronic Nose Fox n000 (Alpha MOS) NST 3200 series (AppliedSensor (was: Nordic Sensor, MoTech) FreshSense (Element, Ltd.) Moses (Lennartz Electronic)
Mechanical (sorpitive polymer, quartz microbalance)	Better linearity than above sensors Libranose (University of Rome “Tor Vergata”) Moses (Lennartz Electronic)
Mechanical (sorpitive polymer, SAW sensor)	VaporLab (Microsensor Systems, Inc.) The Electronic Nose: combined with short-column GC (Electronic Sensor Technology)
Electrochemical (amperometric gas sensor)	Linear sensor response allows normalization of patterns for concentration independence Moses Electronic Nose (Lennartz Electronic) CPS-100 (Transducer Research, Inc.)
Electrochemical, Potentiometric ion-selective sensor	Electronic tongue
Conductimetric Polymer composite sensors	Cyranose 320 (Cyranose Sciences, Inc.)
Conductimetric, ChemFET	NST 3200 series (AppliedSensor (was: Nordic Sensor, MoTech)
Mass spectrometer	HP 4440A (Agilent Technologies) Prometheus, Kronos (Alpha MOS)
Optical, fluorescent sorpitive beads on fiber	BeadArray (Illumina, Inc., San Diego)

optics

Table VI. References to electronic nose classification of foodstuff.

Class of Food		Reference
Fruit	Apples	82, 105, 106
	pears	107
	juices	53
	juices, processing history	108
	identifying unknown	109
Milk	off-flavors	104
	spoilage	89, 92
Cooking oils	rancidity	81
	oxidation	110, 111
Grain	quality	44, 112
	cereals	113
Meat	general	114
	beef	78, 115
	fish	116
	chicken	79, 80
Beverages	coffee	13, 101
	wine	49
	beer	117
Prepared foods	mayonnaise	54

CAPTIONS TO FIGURES

Figure 1. Three categories of miniature analytical devices. (a) Chemical sensor, where a chemical reaction is linked to a transduction mechanism. (b) Micro-instrument, in which an external field or energy source is used to nondestructively measure a physical property such as optical absorption. (c) Micro-total analytical system, which carries out a multistep analytical procedure, and generally incorporates a sensor or a micro-instrument as the detection device.

Figure 2. Organization of chemical sensors by class (transduction mechanism).

Figure 3. Fundamental structure of an electronic nose, including a sampling system, and array of sensors, and a pattern classifier. Also shown are typical array responses for different pure chemicals.

Figure 4. The “ILLI-Nose”, designed by the authors, which uses four electrochemical sensors and a catalytic converter to generate 16 virtual sensors.

Figure 5. Functional comparison of the mammalian olfactory system and the electronic nose.

Figure 6 (a) Analysis of headspace gases of *Enterobacter aerogenes* cultures. All data are included. Growth at two hours can be discriminated from 1 hour and earlier data, but no growth can be seen at one hour. Data from eight metal oxide and four electrochemical sensors are included.

Figure 6 (b) Analysis of the same data set as Figure 6 (a), except that only data from 0.5 hour and 1 hour are included.

Figure 1.

Three Approaches to Chemical Analysis with Sensors

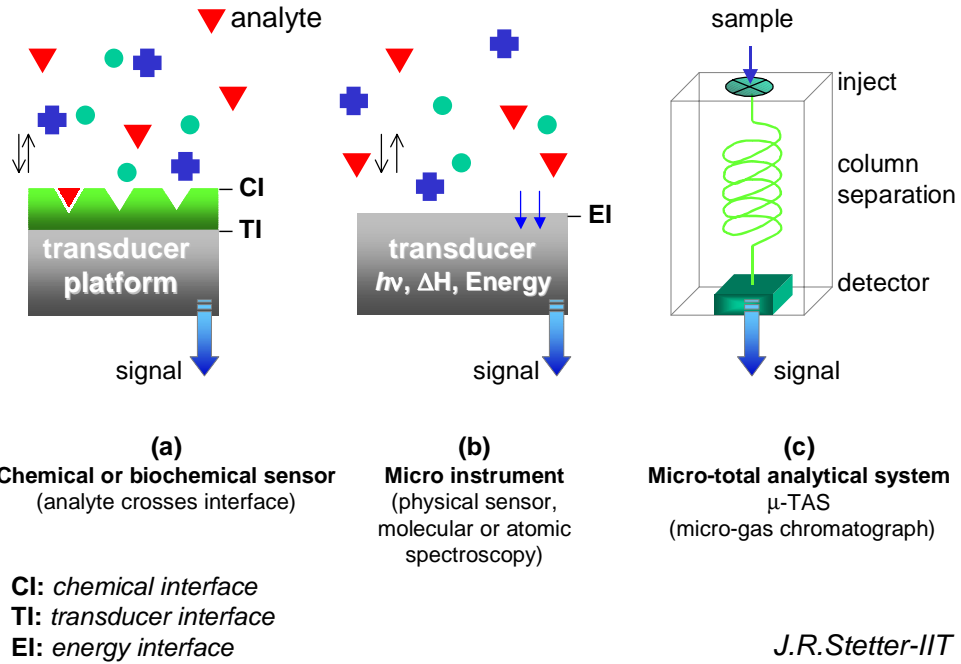
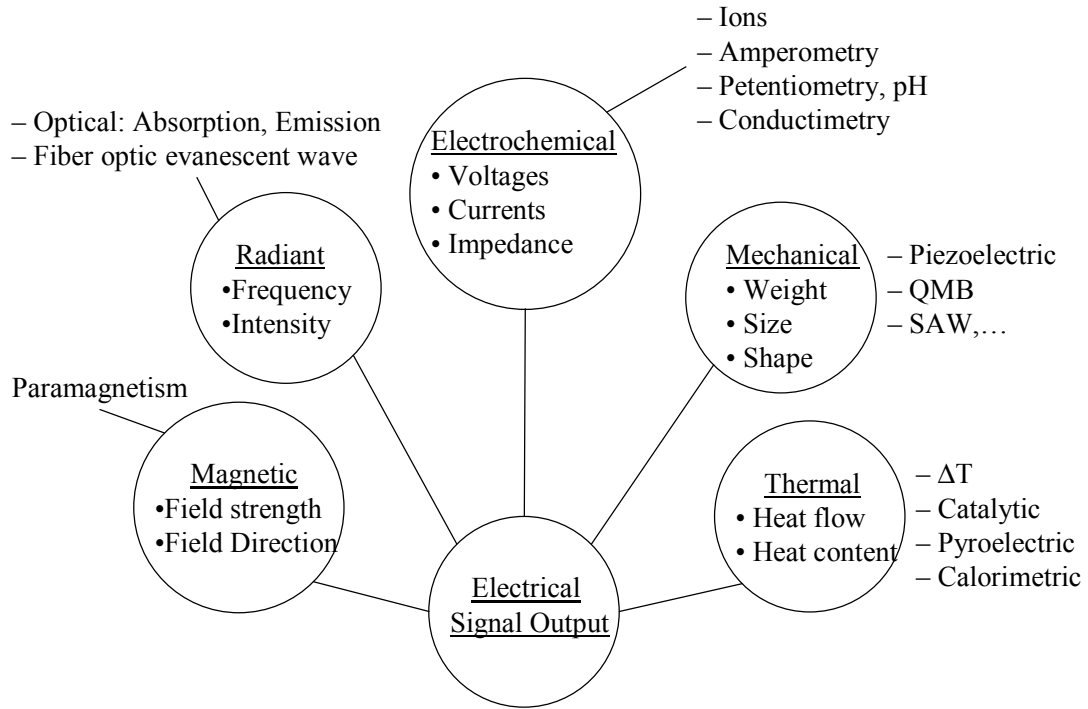


Figure 2.



Chemical Sensors by Class with Some Transducer Platforms

Figure 3.

Fundamental Structure of An Electronic Nose

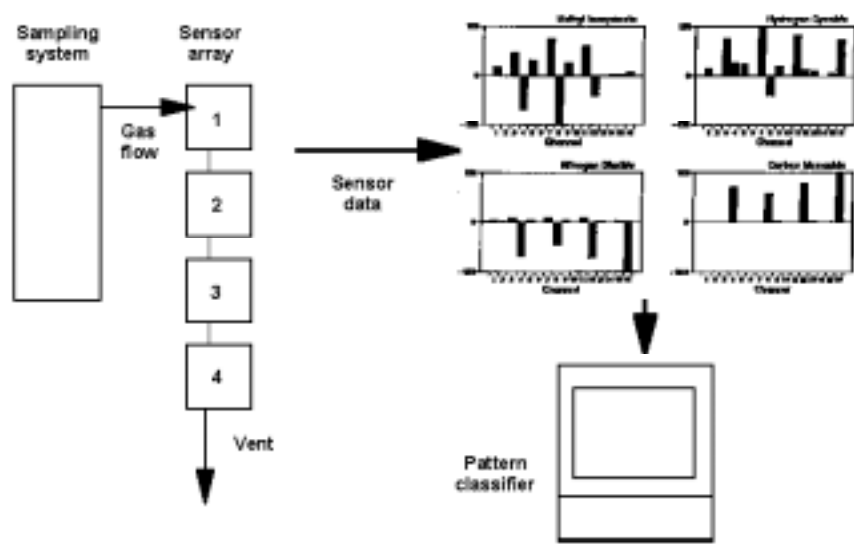
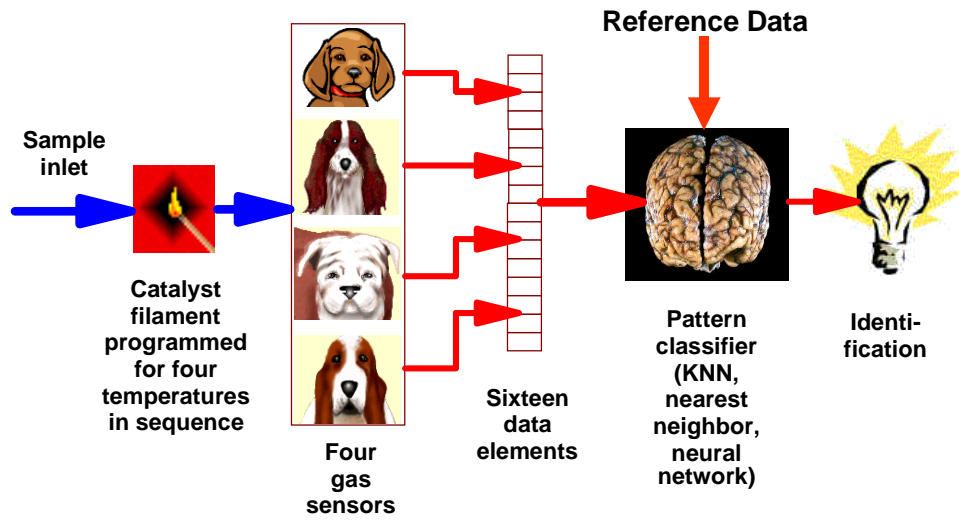


Figure 4.

Operation of the "ILLI-Nose"



Four sensors x four temperatures = 16 "virtual sensors"

Figure 5.

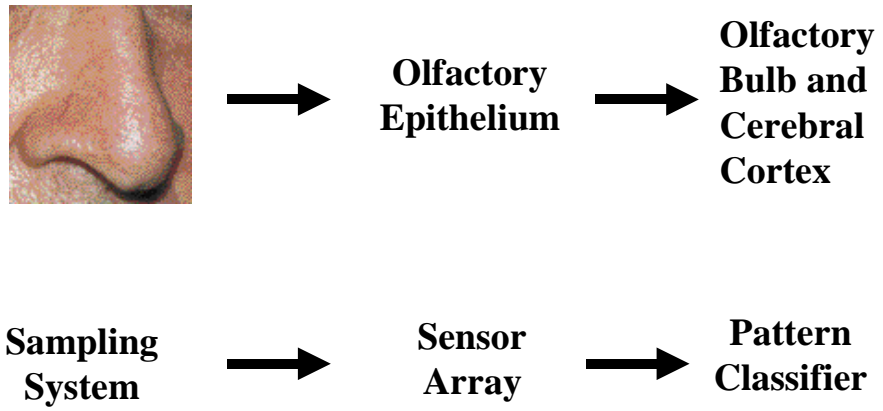


Figure 6a.

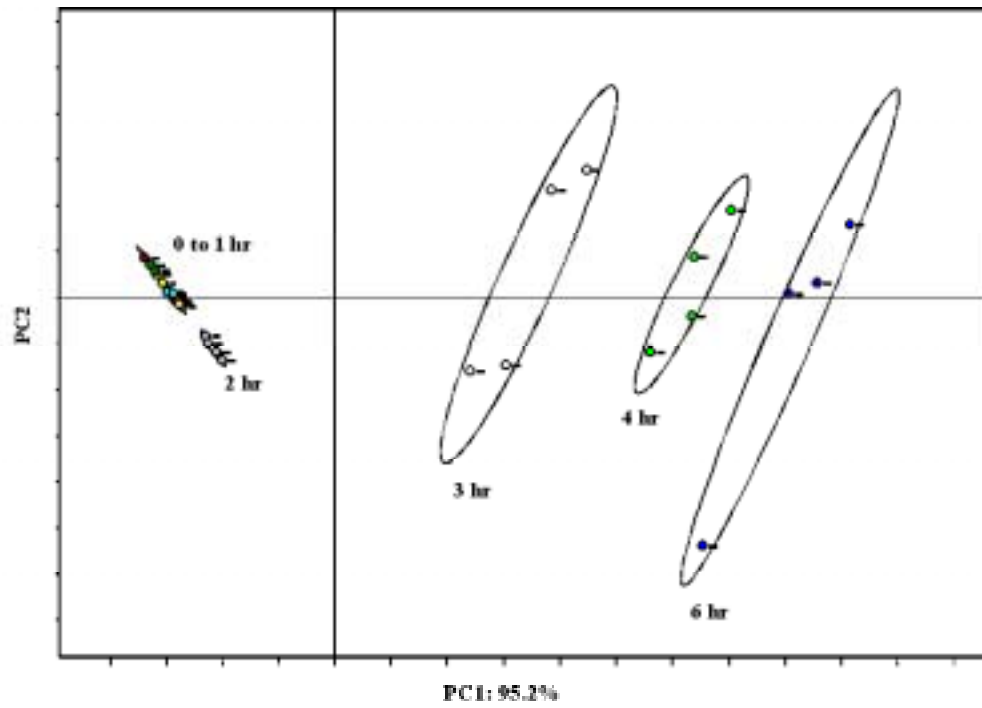


Figure 6b.

