Electronic Nose: Current Status and Future Trends

Frank Röck, Nicolae Barsan, and Udo Weimar*

Institute of Physical and Theoretical Chemistry, University of Tübingen, Auf der Morgenstelle 15, 72076 Tübingen, Germany

Received August 23, 2007

Contents

1. Introduction

Dodd and Persaud introduced the idea of an electronic nose as a device to mimic the discrimination of the mammalian olfactory system for smells.[1] They used three different metal oxide gas sensors and identified several substances by the steady-state signals of these sensors. One of the initial hopes for work in this area was to instrumentally assess attribute descriptors such as fruity, grassy, earthy, malty, etc. reliably by the results of an electronic nose measurement.[2] In other words, capturing the "flavor fingerprint" [3] or "recognizing the odor". Even if one concentrates solely on the different sensitivity characteristics of technical sensors and biological receptors, it is not surprising that despite 25 years of research this is still not possible. The comparison between an electronic nose and a human nose is in the best case like the comparison of an eye of a bee with a human one.[4] It is blind for a part of the visible spectrum but sensitive for other wavelengths. For this reason only in well-defined cases the correlation between human odor impressions and electronic nose data makes sense. On the other side the evaluation of nonodorant volatiles, such as the detection of explosives, becomes reachable.[5,6] Therefore, the term "electronic nose" may be misleading and makes the uninformed reader believe in system capabilities comparable to those of the human nose. Attempts to avoid this term and to replace it (e.g., by "application-specific sensor system") have not taken root up to now, and in most of the current literature the term "electronic nose" is still used.

In recent years much work has been done to understand the principles of odorant receptors and the organization of the olfactory system.[7−9] On each olfactory receptor cell only one type of odorant receptor is located, which can detect a limited number of substances. For a complex odor, composed of multiple odorant molecules, several receptors are activated. The resulting receptor pattern determines our impression of the odor.

Keeping in mind the technical limitations of the electronic nose, we should define it as what it is: an attempt to mimic the principles of smelling that gives another view on the whole scene of volatiles compared to its biological inspiration. The sensor data are analyzed to extract features which can be evaluated as a whole to eliminate redundancy and to arrive at a description of the overall mix of volatiles and their intensity. Consequently, in addition to common sensor arrays, new technologies such as flash GC (gas chromatography) or MS (mass spectrometry) devices are also often referred to as electronic noses.

2. Technology

The term "electronic nose" is often associated with the detection of odors or the attempt to "smell" with a technical device, but as already mentioned, the electronic nose is more and at the same time less, because while it offers the capability to detect some important nonodorant gases, it is not adapted to substances of daily importance in mammalian life such as the scent of other animals, foodstuff, or spoilage. Nevertheless, there are strong drivers to apply it in the field of olfaction because alternatives either are not practicable or are too costly and time-consuming, e.g., human test panels.

One of the challenges of the practical application of electronic noses is that the gases of interest are part of a complex background, which may include water vapor, etc. Technical sensors may also be sensitive to these background gases, whereas, for example, humans have no receptors for water vapor; it is not relevant because it is everywhere in the ambient atmosphere. Similarly, we are not able to perceive carbon monoxide, as prior to the ability to deliberately control fire it made no evolutionary sense. This fact, namely, the relation between, on one hand, detectable and not detectable substances and, on the other hand, relevant and not relevant ones is the crucial point for every electronic

* To whom correspondence should be addressed. Phone: +49-7071-29-77634. Fax: +49-7071-29-5960. E-mail: upw@ipc.uni-tuebingen.de.

10.1021/cr068121q CCC: $71.00
Published on Web 01/19/2008

Frank Röck got his diploma in chemistry in 2003 with a work dealing with quality assessment of food packaging materials by using gas sensor arrays at the University of Tübingen. There, he is currently finishing his doctoral studies in which he is focusing on the application of chemical sensor systems to solving industrially relevant problems; his main approach is centred on the reduction of cross-interferences by employing various strategies. His contributions have been published in three papers in peer-reviewed journals and presented at nine international conferences.

Nicolae Barsan received his diploma in physics in 1982 from the Faculty of Physics of the Bucharest University and his Ph.D. in solid-state physics in 1993 from the Institute of Atomic Physics, Bucharest, Romania. He was a senior researcher at the Institute of Physics and Technnology of Materials, Bucharest, between 1984 and 1995. Since 1995 he has been a researcher at the Institute of Physical Chemistry of the University of Tübingen and actually is in charge of the developments in the field of metal oxide based gas sensors. He has published about 150 papers and contributions to international conferences.

nose application and should be explained in detail for the case of odor detection.

Gaseous substances can be either odorous or odorless (Figure 1). We refer here to both true gases and liquids in their vapor phase ("volatiles"). Concerning the technical detection of odors, one has to distinguish between trace components and concentrated gases.[10] In the ideal case, the high-concentration substances are responsible for the odor impression and the odorless components which are also present are negligible regarding the measurement results (case 1). Otherwise, the odorless background *interferes* with the measurement. We can then differentiate between three cases where interfering gases are present: If they are correlated with odorous substances, a limited odor measurement is possible as long as the relation between the concentrations is fixed (case 2). If this is not the case or the odorless gases mask the target compound, an odor measurement is excluded (case 3), unless the measurement system eliminates the effect of the interfering substances (case 4). The latter can be

Udo Weimar received his diploma in physics in 1989, his Ph.D. in chemistry in 1993, and his Habilitation in 2002 from the University of Tübingen. He is currently the head of the Gas Sensors Group at the University of Tübingen. His research interest focuses on chemical sensors as well as on multicomponent analysis and pattern recognition. He is the author of about 180 scientific papers and short notes. He is responsible for several European projects and for coordinating the Network of Excellence GOSPEL.

achieved by several approaches, which can be related to the configuration of the sensing unit of the electronic nose itself and the sample pretreatment techniques. For the existence of odorous trace components, again two cases should be considered: A limited odor measurement is possible if a correlation exists with substances which are present in higher concentrations, either odorant or odorless concomitant (background) gases (case 5). Otherwise, it is not possible to make a prediction about the odor impression of a sample because the sensitivity of the device to the responsible substances is just not high enough (case 6).

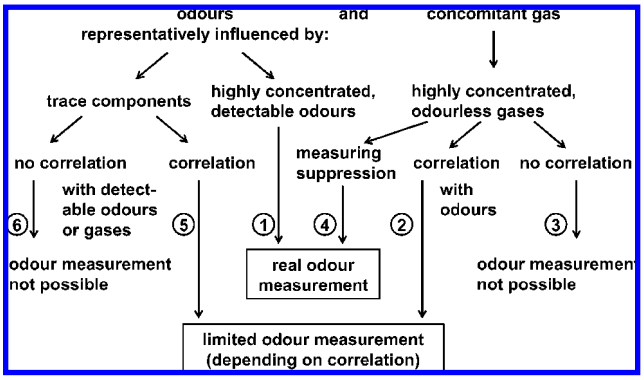

Figure 1. Schematic demonstrating the possible conditions for a reliable odor measurement. For target analytes not causing the human odor impression but which are of interest for other reasons the same flow diagram is applicable. Therefore, analytical background knowledge is important for the best adaptation of the system. Reprinted with permission from ref 10. Copyright 2003 Springer-Verlag.

2.1. Classical Electronic Noses Based on Chemical Gas Sensors

The classical electronic nose, consisting of an array of sensors, is still the most common approach, although new technologies have recently entered this field (Figure 2). There are two reasons for the continuing popularity of sensor arrays. As this is how the field began there is a wide body of experience gained by using them for a diverse set of applications, and the setup of a sensor-based electronic nose resembles most closely the biological model. Every part of

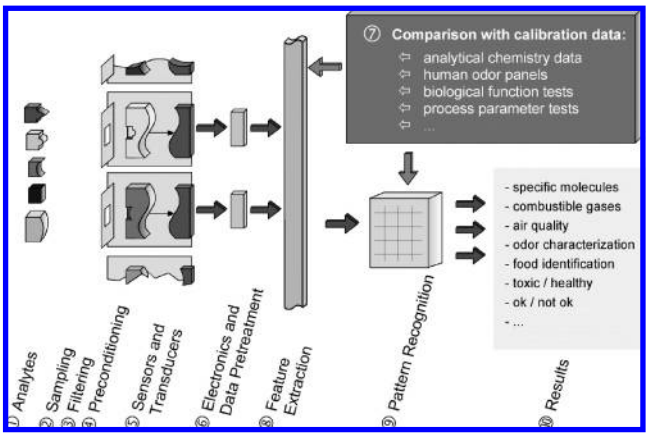

Figure 2. Schematic setup of a sensor system. Via sampling, filtering, and preconditioning the analytes are led to the sensing elements. These consist of a sensitive layer and a transducer to transform the chemical information into an electrical one. After the signal is recorded, data pretreatment, and feature extraction, pattern recognition evaluates the data using the calibration data. Reprinted from ref 11. Copyright 1998 American Chemical Society.

the mammalian nose has its technical equivalent. While all of the sensing technologies require a similar approach to data evaluation, the key feature of sensor arrays is their modularity. For the detection of gaseous substances, the counterparts of biological receptors are gas sensors, which, as with biological receptors, provide a certain multiplicity of detection by not being fully selective.

The information on the smell or identity of a sample can only be obtained by comparing the signals of several sensors or receptors. One of the main reasons why it has not been possible to make a one to one copy of the human nose is the high specificity of the human receptors. The technical realization is always a tightrope walk between high specificity and reversibility. High specificity demands irreversible interaction between the sensor and target gas. Even after a few million years of evolution, the human receptor cells have a lifetime of only a few weeks.[12] This demonstrates the high costs of smelling in nature and the challenges faced in technological development where the lifetime of sensors needs to be much longer.

The assortment of different sensor transducer principles is not to be disregarded, and for each sensor type, a variety of sensor specificity tuning possibilities is available.[13] For example, for metal oxide sensors different sensitive materials are used, different doping elements are available, different production processes to reach different morphologies of the sensing layer are applied, different electrodes are utilized, different filter layers are attached, and different operating temperatures are possible. Although the metal oxide (MOX) sensor can be considered as one of the standard sensors in the field of electronic noses, the same diversity is found for other transducer principles, be it surface or bulk acoustic wave (SAW, BAW) sensors, metal oxide field effect transistors (MOSFETs), or conducting polymer (CP) sensors.

It is important to note that even combining all types of available sensors there are limits to the useful dimensions of the array; instead of obtaining new information about the gaseous composition, increasing the array size amplifies the noise, e.g., by sensitivity toward unimportant information.

The best method to arrange a sensor-based electronic nose is not to use as many different sensors as available but to select them with an eye on the desired application and the knowledge of the analytical data. That is the only way to ensure that the substances which have to be detected are causing the signal. Early attempts at electronic noses took a "black box" approach to correlating sensor outputs with measurement parameters, blindly hoping that, despite changes in the measurement conditions, the correlation remained reliable. This approach can often be found in the literature and often works well for a limited sample collection or constrictive parameters. There are applications where such approaches can provide reasonable results, but one often faces the risk of focusing on the wrong parameters, such as the age of the test persons or their cigarette consumption instead of the intended lung cancer when analyzing exhaled samples.

2.2. New Approaches

It can be shown that by using sensors with different transducer principles the gain in useful information correlated with the increase of the sensor set can be further extended.[14,15] Sensors with different transducer principles will be selective for different classes of substances and can therefore often provide additional information. Hence, in recent years the original sensor types used for electronic noses were not only enhanced but complemented by other technologies introduced in this field. The range of electronic noses available today is not limited just to devices based on chemoresistors or gravimetric sensors but also includes those based on optical sensors or even systems without a modular setup such as mass spectrometers or flash gas chromatographs. Machine olfaction has benefited from scientific developments in other fields, ranging from optical technologies developed by the telecoms industry to the improvements in analytical chemistry. This trend has also narrowed the gap between the traditional electronic nose used as a black box and classical analytics which aims to quantify each single component of a given sample.

2.2.1. Optical Sensor Systems

Optical sensor systems resemble most closely classical sensor-array systems because the dimension of data output can be precisely defined and adapted.[16−18] Instead of having transduction principles based on electrical changes in resistance, potential, current, or frequency, the modulation of light properties is measured. In general, optical instruments are more complex but offer a variety of different measuring possibilities. The assortment of applicable technologies is high and ranges from diverse light sources over optical fibers to detectors such as photodiodes and CCD and CMOS cameras.[19] Therefore, different operation modes were developed and are deployed using changes in absorbance, fluorescence, optical layer thickness, and polarization.

The most direct method measures the absorbance of the analyte gas in a special frequency range. This method is applicable, for example, for carbon dioxide, but is too insensitive (within a justifiable technical effort) for other components in a lower concentration range. Therefore, in other cases, the interaction with a sensitive layer is utilized. The simplest approach is to use color-changing indicators, such as metalloporphyrins, and measure with an LED and a photodetector system their absorbance upon analyte gas exposure. Figure 3 shows how thin films of chemically responsive dyes are used as a colorimetric sensor array. Even more sensitive are the fluorescence methods; they work in a similar setup by detecting not the absorbance but the light emission at a lower wavelength. For reflectometric interfer-

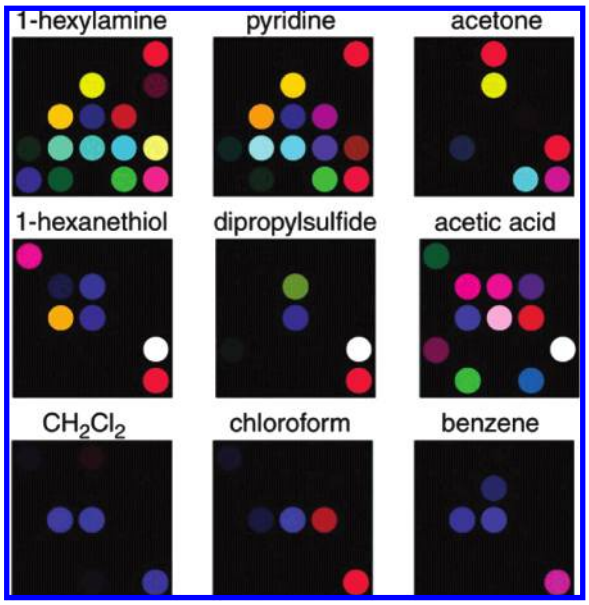

Figure 3. Thin films of chemically responsive dyes are used as a colorimetric sensor array. Multiple dyes change their colors depending on intermolecular interactions. By digital subtraction of each single pixel before and after exposure to the sample the difference map of the colorimetric array is obtained. The different colors are caused by the relative change in the red, green, and blue values of each dye and the brightness by its absolute change. Reprinted with permission from ref 17. Copyright 2004 Elsevier.

ence spectroscopy (RifS), the sensitive layers are similar to the polymer layers used for the gravimetric methods (QMB and SAW transducers). However, in this case the changes in the optical layer thickness and not the weight increase are taken as the sensor signal.

2.2.2. Mass Spectrometry

Combined with gas chromatographs, mass spectrometers are often applied for lab analytics or as stand-alone devices for the identification of pure chemicals. After ionization of the compounds through thermionic emitted electrons (electron ionization) or through interaction with reagent ions (chemical ionization), the molecule ions and their fragment ions are separated according to their mass-to-charge ratio (m/z). This takes place with an electric and/or magnetic field, and nowadays a variety of mass analyzers are established. To mention only a few of them, the sector instrument is the classical approach with tunable static fields, whereas the quadrupole mass analyzer consists of four parallel metal rods and filters the several ions by oscillating electrical fields. Finally, the ions collide at the electron multiplier, and the current is measured.

The disadvantage of all types of mass spectrometers is that their operation requires a vacuum, and therefore, they are not as convenient as the solid-state sensor arrays described previously; it also introduces additional costs. When used as electronic noses, the system is fed with the gaseous sample without previous separation—no chromatographical step. Each m/z ratio can be treated as a separate virtual sensor and analyzed by a pattern recognition algorithm.[3,20] Despite its higher technical complexity, this approach is, in general, not better suited for odor detection when compared to the classical electronic noses but has advantages for defined tasks. For example, the mass spectrometer has proved its ability of detecting peptides in a higher mass range and was used for mixtures of peptide pheromones.

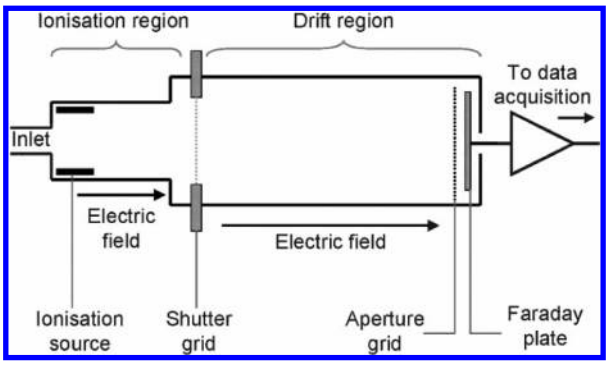

Figure 4. Schematic diagram of an ion mobility spectrometer. Ions are generated in an ionization region by electrospray or by a ^{63}Ni source. An ion shutter pulses the ions into the drift tube where they are accelerated by a uniform weak electric field toward a detector. Their progress is impeded by a number of collisions with the drift gas. Larger ions with greater collision cross sections experience more collisions. Therefore, the separation of ions of differing shape and size becomes possible. Reference 21—Reproduced by permission of The Royal Society of Chemistry.

2.2.3. Ion Mobility Spectrometry

The working principle of ion mobility spectrometry (IMS) is also the filtering of ions as in the case of mass spectrometry (Figure 4). In IMS this is more easily realized, because the aim is not to separate the target molecules exclusively by their differences in the mass/charge ratio, but also on the basis of their different mobilities. This means that, as well as their reduced mass and their charge, the different collision cross sections, determined by size and shape, has a direct influence on the separability of ions. Thereby, the collisions between the ions and the ambient air molecules is utilized, and the measurement can be performed under normal pressure.[21]

The most common agent for ionization is a radioactive β emitter such as ^{63}Ni or ^{241}Am. After a series of ion−molecule reactions, a sample molecule with a high proton affinity reacts in humid air under proton transfer to a positively charged ion. By doping the drift gas with NH_3 vapor, acetone, chlorinated solvents, or others, the selectivity can be modified. Substances with electron-capturing capabilities, such as halogenated compounds, can be detected by potential inversion as negative ions as well. Another often used alternative, for compounds with sufficiently low ionization potential, is UV photoionization. It is appropriate for selective measurements of molecules with an ionization potential of less than 8−12 eV.

After ionization of the air sample the ions are pulsed through a shutter into a drift tube, which is isolated from atmospheric air. The drift tube has a uniform weak electric field, which accelerates the ions along the tube. The movement is hindered by collisions, until the ions reach the detector at the end. Depending on the ion impact, a current is generated and measured over the time of flight. For a manageable and calibrated component amount this gives information about the identity and concentration. If the composition is too complex however, this often fails, because of ion−ion interaction or overlapping peaks. In this case, classical electronic nose data evaluation algorithms (adapted from spectroscopy)[22,23] can be applied to gain a maximum of information out of the measurements. Compared to mass spectrometry, the virtual sensor array is not given by discrete mass/charge relations, but by the signal integration over definable time intervals.

Figure 5. The selective hybrid microsystem consists of a zero grade air unit, a commercial minipump, a minivalve, a silicon micromachined packed GC column, and an MOX sensor as the detector. The analysis time of a certain mixture of volatiles depends on the type of stationary phase, gas flow rate, column length, and temperature of the GC column. Zampolli et al. have shown that within 15 min the complete separation of benzene, toluene, and *m*-xylene is possible. Reprinted with permission from ref 26. Copyright 2005 Elsevier. By the use of a temperature-controlled capillary column the separation time for microfabricated systems can be decreased.[27,28]

2.2.4. Gas Chromatography

Although it is possible to separate mixtures by using the properties of their ions in electrical or magnetic fields, the most established and widely used technique in analytical chemistry is to separate them by chromatographic methods. In the case of volatiles, gas−liquid chromatography and gas−solid chromatography are possible ways. The sample, transported by the mobile phase (gas), is directed over the stationary phase (liquid or solid) and interacts with it. Depending on physical and chemical properties, such as the boiling point, the polarity, H-bonding, polarizability, etc., the affinity of each single substance for the stationary phase is different. The partition behavior determines the retention time of the components and, consequently, the order of elution.

Because, compared to sophisticated analytical chemistry, the claim of electronic noses is to be simple and fast in use, GC entered in this field not in the conventional but in the fast or ultrafast mode. To increase the separation speed during analysis, different parameters have to be adapted. For gas−liquid chromatography this can be an increase of the carrier gas flow rate, an increase of the temperature-program heating rates, a reduction of the column length, a reduction of the column diameter, a reduction of the thickness of the stationary phase, and the use of a faster carrier gas. Depending on the sample, it is important to avoid using all possibilities at once, because this always results in a decrease of the resolution, the sample capacity, or both. It is also important to note that these optimizations increase the demands on the detector technology used in terms of sensitivity, speed, and dead volume.

To simplify the evaluation, the signal over defined time intervals is again integrated and treated as the sensor response of a virtual sensor array.[24,25] An example of an electronic nose using chromatography technology is shown in Figure 5.

2.2.5. Infrared Spectroscopy

Infrared (IR) spectroscopy can also be considered as an electronic nose.[29−31] In a range between 4000 and 200 cm^{-1}, molecular vibrations and higher energy levels are excited. Through characteristic absorption bands the type of chemical bonds can be determined, and pure chemicals can be identified by their unique fingerprint spectrum. The spectrum corresponding to mixtures is evaluated by classical electronic nose algorithms. For the detection of substances in the gas phase, two affordable methods for mobile devices are established. In photoacoustic infrared spectroscopy, a modulation of the intensity of an IR source causes a temperature variation and the resulting expansion and contraction of the gas will be measured as audible frequencies with a microphone. Alternatively, the absorbed energy of a narrow bandpass infrared beam is measured in filter-based infrared spectroscopy. Commercially available devices (e.g., MIRAN SapphIRe from Thermo Scientific) are mostly used for absolute measurements of concentration either in detection of a single species which has a unique absorbance wavelength or by analysis at multiple wavelengths for a known gas mixture. However, where the constiuents of the gas mixture are unknown, these instruments can also be combined with pattern recognition and used as an electronic nose. Despite confirmed feasibility,[29] the infrared-based nose has not become popular and commercially available devices such as the MIRAN SapphIRe from Thermo Scientific can rather be considered as portable analytic tools than as electronic noses.

2.2.6. Use of Substance-Class-Specific Sensors

The types of electronic noses discussed all have one characteristic in common in that they measure a set of features, subsequently analyzed by a fixed algorithm to compare samples in a qualitative or quantitative way without targeting the exact identification or concentration of the single compounds. Similarly to human olfaction, the outcome should only be to determine the sample's identity (orange or apple), to verify variations (compare batches), or to give a prediction on the differences between samples (e.g., intensity of odor correlating with spoilage). In this context, detailed analytical results of the composition are not wanted and often are not available. These facts are reflected in the setup used, where one does not aim to detect one specific substance with one sensor, but one aims to have a broad selectivity and afterward extract the wanted information by comparing the sensor signals. For MS, IMS, and especially GC noses, the number of detectable target molecules per virtual sensor is much more limited. Therefore, an MS nose can detect the presence of high molecular weight substances even without elaborate data evaluation, and a GC nose can differentiate easily between polar and nonpolar substances or between low- and high-volatility compounds, depending on the column used. To follow this line of thought, the next step is to include detectors which are able to detect only one substance/class of interest and not all of the compounds present as with MS and GC. This can either be a class-specific device such as a flame spectrophotometer, which only detects phosphorus-containing compounds, or a standalone device of broad selectivity, such as a thermal conductivity detector measuring nearly every composition change in an air sample. Strictly speaking, these are not independent electronic noses, but they can be integrated into one as a supplementary module providing additional information.

The flame photometry detector (FPD) is based on the decomposition of any organic compounds in a hydrogen flame. If phosphorus or sulfur is present, light of a specific

wavelength will be emitted. After the other wavelengths are masked out through filters, a photomultiplier detects the concentration of one of the elements. Because phosphorus and sulfur are present in classical nerve gases, this technology is often used in the military/security application field.

Another previously mentioned detector is the photoionization detector (PID). Without coupling it to an ion mobility spectrometer, it is also possible to use it as a stand-alone detector to measure all volatile organic compounds that have ionization potentials equal to or less than the energy of the UV radiation. For example, by using a 9.5 eV lamp, amines, benzene, and aromatic compounds are detectable. A 10.6 eV lamp additionally detects ammonia, ethanol, and acetone, whereas acetylene, formaldehyde, and methanol are only to be detected by using an 11.7 eV lamp.

Single gas detection of oxygen or toxic gases is typically performed by electrochemical cells (ECs). They are designed to detect one special gas, but despite their particular filter, electrodes, and electrolytes, they are often not completely specific. Behind a diffusion barrier the target gas is either oxidized or reduced and determines a current between the sensing and the counter electrode. This current is proportional to the target gas concentration. The third electrode, the reference electrode, has a stable potential and is used to eliminate interferences from side reactions and increase the selectivity of the electrochemical cell.

For a nonspecific determination of flammable compounds, flame ionization detectors (FIDs) are used. In a hydrogen−oxygen flame the compounds are burned in an electric field, and the increases of ions are detected as an electrical current. Because all organic compounds are detectable, flame ionization detectors are often used in gas chromatographs, but they are available as stand-alone devices as well.

2.3. Combined Technologies

The combination of different sensor or detection technologies comes along with an improvement of the selectivity range but determines at the same time an increase of the setup complexity and, accordingly, additional costs for the whole device. Thus, the combination of different technologies is only reasonable for the following two cases: first, for a special problem where a single technology does not achieve satisfactory results and, second, for an all-purpose electronic nose with a maximum of application possibilities. The ideal all-purpose electronic nose does not exist: however, systems that can be applied to more than one application field are available.

One example for the latter case is the electronic nose Prometheus produced by Alpha MOS. It combines a sensor array with a fingerprint mass spectrometer. The sensor array consists of 18 different sensors. These are arranged in three separate sensor chambers equipped with six different metal oxide sensors. If desired, the use of conducting polymers or quartz microbalances is also possible. The fingerprint mass spectrometer consists of an electron impact ionizer and a quadrupole mass filter. It can be operated in the single ion mode, or alternatively, the range between 1 and 200 amu will be scanned. The combination of these technologies causes both high selectivity through mass spectrometry and high sensitivity through the use of a sensor array. The system is more flexible in use compared to the individual parts and thereby appropriate for more applications.

Another hybrid system is the GDA 2 (Gas Detector Array 2) produced by AIRSENSE Analytics. It consists of an ion-mobility spectrometer with a ^{63}Ni ion source which can be used in the positive and negative modes, a photoionization detector with a 10.2 eV lamp, an electrochemical cell, and two metal oxide sensors. The manufacturer recommends this portable device for detection of hazardous gases and chemical warfare agents. Because a variety of different harmful agents, such as ammonia, benzene, carbon monoxide, chlorocyane, hydrogen cyanide, and phosgene, should be detectable, it is necessary to use sensors and detectors whose sensitivity and selectivity cover the whole range of potential substances and concentrations. This is assured by the use of different technologies.

3. Companies

The previous section described how sensing odors using an electronic nose is a significant technical challenge. Instead of attempting to reproduce human odor impression, most commercially available instruments nowadays have other application areas. The classification of odors is not in the fore, but the detection of any volatiles giving information about a characteristic of the sample is. The range of electronic noses on the market spans from military, security, and safety applications, food processing, and medical applications to use in the pharmaceutical industry, and even includes mass markets such as automotive applications or white goods. The border between classical analytical systems, electronic nose technology, and detectors for specific substance classes or even single compounds becomes more and more fuzzy. Some manufacturers call their devices “electronic noses”, whereas others avoid mentioning this term even if their product operates in a similar way. Table 1 gives an overview of electronic noses on the market according to the criteria above, listing their manufacturers and technology basis.

4. Application Areas

In the past two decades, the applicability of electronic noses has been tested in every imaginable field where odors or odorless volatiles and gases are thought to play a role.[32−35] A typical approach was to prove the ability of a given sensor array to discriminate a sample set in a desired manner (the black box approach). Consequently, researchers were frequently overly hasty in concluding that positive experimental results demonstrated success in the application. As a result one was considered to have reached the target and/or went ahead to the next challenge: the quantification of the sample property of interest. Taking the electronic nose as a black box, without having a feeling for the chemical processes going on and having no idea about the marker substances and interferents, one becomes critically dependent on the sample set. Accordingly, it is very important to be aware of the fact that one can sometimes have a limited or even a biased sample set, and as a consequence, the initial results can look much better than they are in reality. Typical examples have included the determination of the quality of complex food products, see section 4.1, such as coffee, tea, olive oil, or wine.[36] Under laboratory conditions for a strongly restricted set of samples, the correlations may succeed: nevertheless, no commercial breakthrough to industry took place. There are many reasons for this approach to fail; one key factor is often a mismatch between the detector sensitivity and the components responsible for the odor.[37] For an unrepresentative sample set there is a high risk of discovering bogus correlations with the consequence that for unknown

Table 1. Commercially Available Electronic Noses

manufacturer	no. of systems sold	model	technology
Agilent, http://www.chem.agilent.com/		4440A	quadrupole fingerprint mass spectrometry
AIRSENSE Analytics, http://www.airsense.com/	180	i-PEN	gas sensor array
		PEN3	gas sensor array
		GDA 2	IMS, PID, EC, 2 MOX sensors
Alpha MOS, http://www.alpha-mos.com/	500	FOX 2000	6 MOX sensors (or QMB/CP)
		FOX 3000	12 MOX sensors (or QMB/CP)
		FOX 4000	18 MOX sensors (or QMB/CP)
		Gemini	gas sensor array
		Kronos	quadrupole fingerprint mass spectrometry
		Heracles	2 capillary columns (1−3 m) and 2 FIDs
		RQ Box	EC, PID, MOX sensors
		Prometheus	MS and 18 MOX sensors
AltraSens, http://www.altrasens.de/		OdourVector	6 sensors
AppliedSensor, http://www.appliedsensor.com/	>100 000	Air Quality Module	2 MOX sensors
Chemsensing, http://www.chemsensing.com/			colorimetric array
CSIRO, http://www.csiro.au/		Cybernose	receptor-based array
Dr. Foedisch AG, http://www.foedisch.de/		OMD 98	2 × 6 sensors
		OMD 1.10	2 × 5 MOX sensors
Draeger, http://www.draeger-safety.com/		Multi-IMS	ion mobility spectrometry
		MSI150 Pro2i	ECs
Electronic Sensor Technology, http://www.estcal.com/		ZNose 4200	GC and SAW
		ZNose 4300	GC and SAW
		ZNose 7100	GC and SAW
Environics, http://www.environics.fi/	9000	M90-D1-C	ion mobility spectrometry
		ChemPro100	ion mobility spectrometry
Forschungszentrum Karlsruhe, http://www.fzk.de/		SAGAS	8 SAW sensors
Gerstel GmbH & Co. KG, http://www.gerstel.com/		QCS	3 MOX sensors
GSG Mess- und Analysengeräte, http://www.gsg-analytical.com/		MOSES II	modular gas sensor array
Illumina, http://www.illumina.com/		oNose	fluorescence sensors—bead array
Microsensor Systems Inc., http://microsensorsystems.com/		Hazmatcad	SAW
		Hazmatcad Plus	SAW array and EC
		Fuel Sniffer	SAW
		CW Sentry 3G	SAW and electrochemical sensor array
		SAW MiniCAD mk II	2 SAW array
		VaporLab	GC and EC
Owlstone Nanotech, Inc., http://www.owlstonenanotech.com/		Tourist	field asymmetric ion mass spectrometry
		Lonestar	field asymmetric ion mass spectrometry
Proengin, http://www.proengin.com/		AP2C	flame spectrophotometer
		TIMs detector	flame spectrophotometer
RaeSystemes, http://www.raesystems.com/		ChemRAE	ion mobility spectrometry
		UltraRAE	separation tube and PID
		Eagel monitor	GC and EC
		AreaRAE monitor	PID, 2 ECs, 1 catalytic bead sensor, O_2 sensor
		IAQRAE	PID, NIRD CO_2, EC, polymer-capacitated humidity sensor, thermistor, humidity−temperature sensor
RST-Rostock, http://www.rst-rostock.de/		FF2	6 MOX, *T*, humidity
		GFD1	6 MOX, *T*, humidity
Sacmi, http://www.sacmi.eu/		EOS 835	gas sensor array
		EOS Ambiente	gas sensor array
Scensive Technologies Ltd., http://www.scensive.com/	<100	Bloodhound ST214	14 conducting polymers
ScenTrak, http://www.cogniscentinc.com/			fluorescent dye
SMart Nose, http://smartnose.com/	250	SMart Nose 2000	quadrupole fingerprint mass spectrometry
Smith Group, http://www.smithsdetection.com/		Cyranose 320	gas sensor array
		IONSCAN SENTINEL II	ion mobility spectrometry
		CENTURION	ion mobility spectrometry
		GID-2A	ion mobility spectrometry
		GID-3	ion mobility spectrometry
		SABRE 4000	ion mobility spectrometry
		ADP 2000	ion mobility spectrometry
		CAM	ion mobility spectrometry
Sysca AG, http://www.sysca-ag.de/		Artinose	38 MOX sensors
Technobiochip, http://www.technobiochip.com/		LibraNOSE 2.1	8 QCM sensors

samples the model will fail. For example, the prediction of the ethanol percentage in the headspace of a wine sample by an electronic nose is easy to accomplish, while, on the contrary, even with elaborated analytical equipment it is not possible to entirely comprehend the quality of wine samples. For a chosen sample set, where the goal is to judge the quality of the wine or the grape variety of the samples by an electronic nose, the ethanol concentration may be fortuitously correlated with those characteristics.[38,39] This way we will obtain the right results by dealing with the wrong input data. Admitting that such obvious mistakes are actually avoided, for each application it is still possible to have other—

more often than not unknown—substances not related to the targeted sample characteristics but having a considerable impact on the (classification) result. The conclusion is that, to prove the applicability, analytical background information and/or lots of independent validation measurements are needed (in the ideal case both are to be used). Returning to the wine example, the validation should recognize that characteristics such as ethanol concentration, grape variety, vintage, wine region, or winery are not correlated by chance and outliers in prediction should be critically examined and compared to sample properties. In doing so it is always better to increase the sample set by using new independent samples instead of repetitions or mixtures of old ones to uncover unexpected correlations.

For historical reasons, the main research fields for electronic nose technologies are still related to those areas where the human olfaction system is relevant. During recent years many efforts were made in the field of foodstuff and beverages where, in addition to classification, time-dependent processes were investigated.[35,36,40] These include unwanted processes such as changes during storage or spoilage as well as the intended ripening or fermentation of particular products. The driver is that electronic noses are by far less expensive when compared to classical analytical systems such as GC/MS or the running costs for human sensory panels. For this reason, the aim has been to replace one or the other established methods or at least to complement them. Besides cost savings, electronic noses promised fast, round-the-clock operation, which, combined with an automated data evaluation, could at least for some applications replace humans.

In addition to the assessment of food, the human nose gives us further important information: It warns us about dangers such as fire or air pollutants and gives us indication of certain diseases such as diabetes or hepatic failure.[41−44] Consequently, there are also efforts to mimic this human ability with electronic noses.[35,45−49] Because of the different responses and sensitivities to the respective marker molecules, one needs to find which are the appropriate tasks for electronic noses. Therefore, current research also explores the field of marker molecules that are odorless for humans.

One further step is to improve on human capability and target instead that of macrosmatic mammals. Even if modern research shows that for some odorants the perception of humans and primates is comparable to that of canines and rodents,[50] the ability of the latter is superior in many fields. For instance, dogs are able to identify individuals by their scent, to track them, or to track down hidden narcotic drugs or explosives.[51,52] Recently, the capabilities of insects have been investigated, and the feasibility of using honeybees for land mine detection has been demonstrated.[53] However, dogs show behavioral variation depending on changes in their mood, and all animals are subject to fatigue. To decrease the complexity of execution, it would be desirable to have an artificial system with the same performance. For this reason, electronic noses are being investigated in the security field for the detection of hazardous substances and explosives.

Process control is also a promising application field. Independent of the character of the product, it is important to ensure it always has the same characteristics. Therefore, the application area ranges from control of industrial production lines as in the pharmaceutical industry and in the manufacture of food packaging to the control of composting processes. Besides the control of temperature, humidity, optical appearance, viscosity, etc., the electronic nose adds another dimension in observation and can help minimize the variability between batches.

4.1. Food and Beverage

Applications in this field include inspection of the nature and quality of ingredients, supervision of the manufacturing process, and, finally, everything related to shelf life. For instance, it is important to be able to distinguish between different quality classes of the same food, e.g., extravirgin olive oil, virgin olive oil, olive oil, and olive-pomace oil, to avoid fraud and to fulfill customer expectations. Equally important is knowledge of the ingredients of a product to protect the customer from low-quality raw material and/or to avoid breaking the law. For instance, in the European Union one has to make sure that cheese sold as "feta" is only made from goat and/or sheep milk without additions of cow milk to fulfill the protected designation of origin (PDO). To avoid a low-quality product and to reduce defects during the production process, it is desirable to detect irregularities at an early stage and to initiate remedial action as fast as possible. This includes individual adaptation of the treatment of biological raw materials related to their natural variability. Fermentation and roasting processes are examples where the conditions used have a direct influence on the taste and odor of the product and where sophisticated monitoring helps to increase the quality. Because degeneration processes cause off-odors, off-flavors, or in the worst case harmful substances, the detection of spoilage, no matter whether chemical, enzymatic, microbiological, or a combination of these, is an important task in itself and one which opens up the possibility of predicting shelf life.

The established methodologies to deal with this challenge are diverse and range from microbiological analysis to sensory test panels to classical analytical approaches. The information they provide is not all the time orthogonal. The question from the electronic nose point of view is which additional information can be obtained by using it and in which fields can it replace the established techniques. To get a feeling on what is feasible, one has to acquire knowledge about the substances detected by the human nose, by classical analytical detectors and by the electronic noses. For that reason, gas chromatography experiments are very helpful because they reduce the problem from the whole bouquet to the single substances. In aroma and odor analysis GC−olfactometry (GC−O) has been established for many years and helps to identify which volatiles are responsible for the respective odor impression (Figure 6). Direct comparison of GC−O results with GC/FID or GC/MS results gives information about which marker substances are detectable without a sensory test panel and about those for which the human nose is the only reliable detection method. This is important to know because measurements with foodstuff such as daidai peel oil,[55] green Mexican coffee,[54] grapefruit oil,[56] cooked asparagus,[57] cashew apple nectar,[58] tarhana,[59] or Croatian Rhine Riesling wine[60] have shown that sometimes there is a big discrepancy between substances detectable by the human nose and those detectable with commercial detectors and vice versa. One still needs to keep in mind that, despite this systematic approach, the rules governing the combination of individual chemical compounds in the global aroma of a product are not yet fully understood and

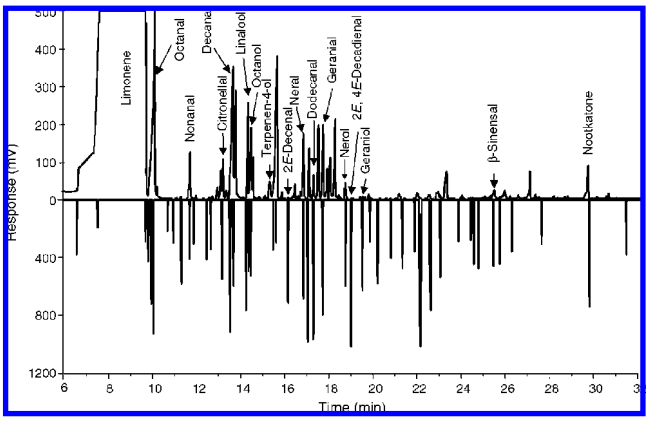

Figure 6. Comparison of a GC/FID chromatogram (top) with a time−intensity aromagram (bottom, inverted) of grapefruit oil. Some odorants have been identified by mass spectrometry. It is obvious that the human nose is sensitive to substances the flame ionization detector is not able to detect and vice versa. Reprinted with permission from ref 56. Copyright 2001 John Wiley & Sons, Limited.

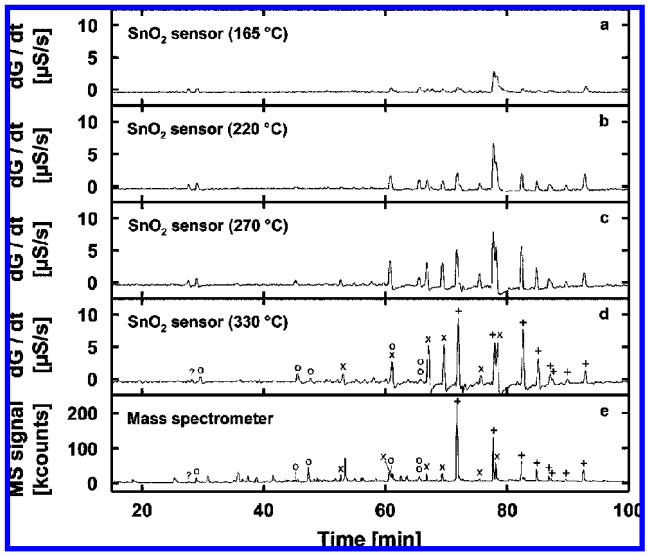

Figure 7. HRGC/SOMMSA (high-resolution gas chromatography/selective odorant measurement by a multisensor array) for sensor evaluation. In this example the sensitivity of a SnO_2 sensor at different temperatures (165, 220, 270, and 330 °C) to compounds out of beech wood smoke was tested. The output from the gas-chromatographic column is split in two to enable simultaneous measurements with a reference detector (mass spectrometer in this case) and the sensor array to identify relevant compounds. Reprinted with permission from ref 65. Copyright 2003 PCCP Owner Societies. With this approach the choice of adequate sensors/conditions is possible without costly experiments at the gas mixing system.[61−63]

the different methodologies allow us only to widen the limited view on the whole scenery. Nevertheless, chromatography has already been successfully used to ensure the appropriateness of chemical sensors to a given problem.[61−63] For example, this approach was used to prove the sensitivity of metal oxide sensors to food aroma during baking and roasting processes[64] (Figure 7). However, it is also applicable to other problems such as the detection of odorless volatiles or the selection of gas sensors.

A very promising application field for the electronic nose is its use in spoilage detection of foodstuffs. The fight against autolysis and against the growth of microorganisms is the main objective for food preservation and can be reached in

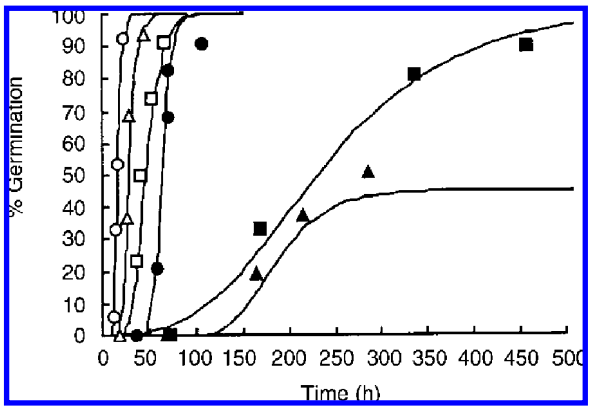

Figure 8. Effect of water activity on germination of one isolate of *Eurotium* spp. at 25 °C on flour wheat−sucrose agar. Water activity levels are (○) 0.90; (△) 0.875, (□) 0.85, (●) 0.825, (▲) 0.80, and (■) 0.775. It is shown that the temporal rates of germination depend strongly on the water activity. Reprinted with permission from ref 84. Copyright 1999 Blackwell Publishing.

different ways. The most popular approaches are pasteurization, refrigeration, removal of water, change in pH, the use of packaging under vacuum, the use of food additives, or a combination of these. In all cases, food deterioration cannot be prevented but only postponed. Therefore, the challenge is to detect spoilage at an early stage or, alternatively, to predict it.[66] The field is quite complex as both the nature and origin of the foodstuff and the preservation technique used influence the species of bacteria, fungi, or enzymes responsible for spoilage. Due to the variety of different substances that can be produced during spoilage, the biologically evolved human perception is still the best detection method for most applications of off-odor and off-taste detection. To use instrumental analysis, one has to be aware of the relevant substances for each sample type, but despite our knowledge of the formation of free radicals, influence of enzymes, different bacteria which are produced, yeast and mold strains, and their metabolism products, the experience with the electronic noses in detecting them is still at the beginning. First trials with red wine,[67] apples,[68] mandarins,[69] bakery products,[70−73] bread,[74] wheat,[75−77] Crescenza cheese,[78] beef,[79,80] poultry meat,[81] and milk[82,83] show that, in principle, differences caused by spoilage are detectable with an electronic nose. For instance, it was shown that it is possible to track the changes in the headspace of an individual food sample during storage. The critical point is the generalization and, closely connected to it, the question of the usability of the electronic nose results without first thoroughly exploring all applications' variables (different samples, different batches, long-term behavior, etc). Because foodstuff is very heterogeneous, there is no warranty that the results will be reproducible for a sample set varying in an unconsidered parameter. According to Abellana et al., the speed of fungal spoilage depends not only on temperature but also on the water activity in food (Figure 8).[84] For simplification, these variables are often kept constant to have a direct correlation between spoilage level and time. Keshri et al. showed that with a Bloodhound BH-114 electronic nose it is possible not only to detect spoilage but even to differentiate and classify the fungal species in the bread analogue.[74] However, the question of the validity of their results for different humidities, different corn varieties, variations in baking time, or various bread volume/surface ratios is still unanswered.

Fish spoilage is one of the best investigated deterioration processes with respect to an electronic nose. Knowledge ranges from the very basic post mortem biochemical processes in the fish to the specific volatiles produced and their relationship to the perceived odor. As the oxygen supply stops, the proteolytic mechanisms involved in disorganization of fish muscles are initiated, and hence, the muscles are tenderized.[85] The autolytic modifications start with an anaerobic degradation of the stored carbohydrate glycogen to lactic acid, and hence, the pH value drops from close to 7.4 to around 6. The muscle osmotic pressure increases, ATP (adenosine triphosphate) is hydrolyzed, and lipids are oxidized. TMAO (trimethylamine oxide) is reduced to TMA (trimethylamine), nitric oxide and reactive species of oxygen increase, and calcium ions are released into the cytosol. Finally, endogenous enzymes, especially calpains, cause proteolysis of muscle proteins and connective tissue as well as fat hydrolysis. The growth of microorganisms is now supported by the availability of catabolites[86] and is dependent on extrinsic and intrinsic factors. The main extrinsic factors are temperature and composition of the atmosphere, whereas the fish species is fundamental for the intrinsic factors. These include the poikilotherm nature of the fish, its aquatic environment, the post mortem pH of the flesh, and the concentration of nonprotein nitrogen and of TMAO. These variables not only determine the absolute microbiological growth but are relevant for the increase of each individual strain and consequently for the proliferation ratio between them. Therefore, for different fish species under different storage conditions (air, vacuum packed, CO_2 atmosphere) different spoilage organisms dominate, primarily, Vibrionaceae, *Shewanella putrefaciens*, *Pseudomonas* spp., *Photobacterium phosphoreum*, *Lactobacillus* spp., and *Carnobacterium* spp.[87] It is not surprising that the sensory descriptors for the metabolites produced by different microorganisms vary.[88] For instance, marine temperate-water fish have an offensive fishy, rotten, H_2S off-odor, whereas some tropical fish and freshwater fish stored in air can be described with a fruity, sulfydryl off-odor.[86] Regarding the volatile spoilage products, Malle et al. showed that the ratio between TVBN (total volatile basic nitrogen) and TMA (trimethylamine) can be used as a quality index for sea fish.[89] Because of its restricted precision and limited applicability, it should be only used as an orientating method.[90−92] In search of further spoilage markers, Duflos et al. identified 20 common volatiles from whiting, mackerel, and cod.[90] For these substances, the contribution to the entire smell of the fish is partially known.[93] It was shown that the characteristic spoilage compounds fluctuate significantly from one species to another. Furthermore, there are even quantitative and qualitative differences of volatiles between fish skin and fish muscle for the same species.[94] To conclude, much basic research in the field of fish spoilage has been carried out, and useful marker molecules detectable by an electronic nose are known; at the same time, one has to be aware that a lot of different factors influence the smell and the headspace composition of the stored fish (see section 5.1). For that reason the precision of prediction of the electronic nose will increase with the homogeneity of the sample. With these limitations, special attention has to be paid to the comparability of the training set and the real-life samples.

The suitability of different electronic noses has been evaluated for fish freshness applications, with transducing principles ranging from electronic noses with electrochemical gas sensors to metalloporphyrin-coated QMB, metal oxide sensors, conducting polymer sensors, computer screen photo-assisted based gas sensor arrays, and vapor-phase Fourier transform infrared spectroscopy. It is difficult to compare the different approaches because of the different conditions of the experiments. One exception is the work of Di Natale et al. where for the same sample set of cod fish fillets the commercially available electronic noses FreshSense (Element-Bodvaki)—consisting of five electrochemical sensors—and LibraNose (Technobiochip)—consisting of eight thickness shear mode resonators—have been tested.[95] Data evaluation was done by PLS-DA (partial least-square discriminant analysis), where both systems demonstrated sensitivity to the temporal variations of fish headspace. For the leave-one-out validation the misclassifications of storage times were 33% and 9%, respectively. It was possible to achieve a value of only 4% for the combined input data of both electronic noses. However, this is not surprising as PLS-DA is a supervised classification method, so the prediction should be improved by adding additional inputs. Furthermore, these values should not be seen as representative of general application because of possible flaws in the calibration method. In this work eight samples out of three batches were measured for each storage time, but to obtain a reliable prediction model for unknown samples, a segmented cross-validation instead of the leave-one-out method for the prediction of the freshness of fish would be desirable.[96,97] This is the requirement to ensure a correct classification of unknown batches not already comprised in the calibration data set. Otherwise, differences in new batches caused by, for example, different fishing grounds, the fishing season, the fat content in the flesh, or physical damages due to rough handling and bruising will not be taken into account.[98,99]

A very good study about the potential of electronic noses in this field was presented by Olafsdottir et al.[100] Using a fundamental approach, the chemical reason for the sensor response of an electronic nose consisting of four electrochemical gas sensors was identified. The experimental setup used included microbial analysis, determination of TVBN, pH measurements, GC/MS measurements, and GC−O measurements. Thereby, it was possible to determine the increase of the most abundant volatile spoilage compounds over time, including their standard deviations (Figure 9). In addition, the instrumental detectable compounds which influence the odor were identified, and their contribution (intensity, description) to the overall odor was evaluated. At the same time the work demonstrates the discrepancy between substances detectable by humans, the mass spectrometer, and the chemical sensors used and points out the danger that volatile compounds are often not detected until the products are overtly spoiled; the TMA concentration significantly increased in this example, but the electrochemical NH_3 sensor was not sensitive enough to contribute relevant information at an early stage of spoilage (Figure 10). In contrast, the CO sensor was suitable to detect incipient spoilage of the Styrofoam-packed chilled cod fillets because of its sensitivity to alcohols, aldehydes, and esters. This success has to be seen in the context of another publication of the authors. For haddock fillets they found that the absolute sensor response was higher.[101] This can be interpreted as a proof of the described complexity of spoilage and the need for individual calibration for each product (here fish species) and storage condition.

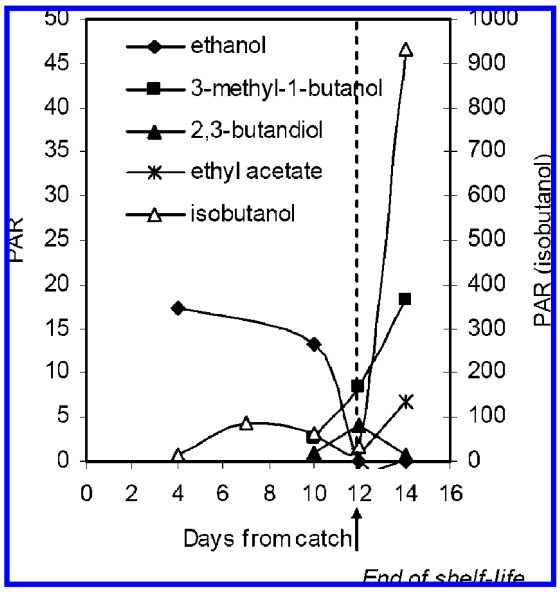

Figure 9. Headspace composition of cod fillets as a function of storage time (storage temperature of 0.5 °C).[100] A selection of components out of 25 substances quantified by GC/MS is shown. In addition to alcohols and esters, aldehydes, ketones, acetic acid/ and trimethylamine were detected. The time dependency for each analyte is different and has a high standard deviation (not shown). The signals from electrochemical gas sensors are presented in Figure 10. PAR = ratio between the peak area of the analyte and the peak area of the external standard. Reprinted from ref 100. Copyright 2005 American Chemical Society.

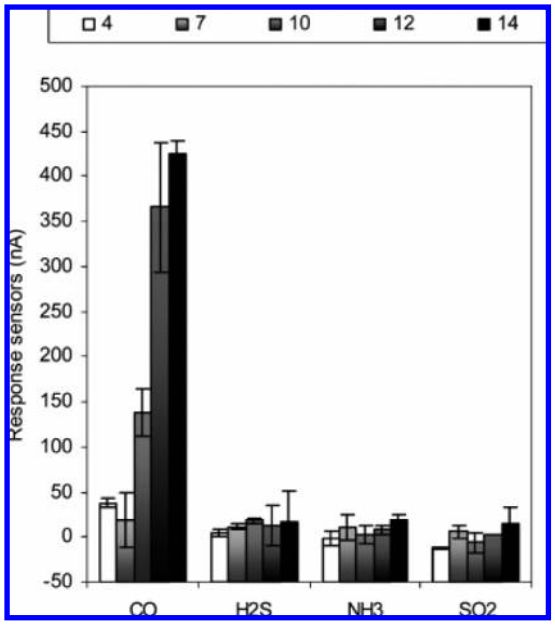

Figure 10. Response of the electrochemical gas sensors toward cod fillets during storage at 0.5 °C on days 4, 7, 10, 12, and 14. The CO sensor was most sensitive to changes during spoilage because of its sensitivity to alcohols, aldehydes, and esters (Figure 9). Although the trimethylamine concentration increased significantly at day 14, neither the NH_3 sensor nor the other ones contributed additional information. Reprinted from ref 100. Copyright 2005 American Chemical Society.

4.2. Environmental Monitoring

Environmental monitoring has become more and more important during the past few decades with increased awareness of the effects of pollution on human health and the quality of the environment. Electronic noses have been investigated for detection of toxic compounds in the ambient atmosphere, at the source (e.g., on industrial premises), and in the headspace of water.

In ambient air, toxic compounds are present at concentrations which will not have an immediate effect; nevertheless, the main components, namely, carbon monoxide, nitrogen oxides, sulfur oxides, volatile organic compounds, ammonia, ozone, and particulate matter, are a long-term danger for human health. For that reason, the regulating agencies introduced strict threshold values that have to be observed. This concerns, on one hand, the direct monitoring of emissions at the place where they occur and, on the other hand, monitoring of the concentration limits at the place where people are living and working. The thresholds are not limited only to substances which are known to cause physical damages, but also include compounds with unpleasant odor and, therefore, that reduce the quality of life. Until now, the detection and rating of emissions has been performed using traditional methods including olfactometry measurements realized by a human panel and identification and quantification by analytical instruments. The disadvantage of these techniques is that they are not appropriate for on-site real-time and continuous operation due to their high operating costs. The introduction of the electronic nose for this task is—depending on the target components—very challenging. In addition to very complex target mixtures and low detection thresholds, sampling is a major concern. Samples must be representative and independent of variable ambient conditions. Knowledge of spatial and time patterns of concentrations is important, particularly for air pollutants in urban areas where topography and meteorology create a complex pattern that has to be considered to place the electronic nose at the right positions.[102] Additionally, changes in temperature and humidity influence the measurement results. To deal with this interference, two methodologies are commonly used. One is sample pretreatment to obtain fixed experimental conditions, and the other is a parametric compensation by additional measuring of the variable parameters and calibration under, e.g., different humidity conditions.

From the practical point of view, one can distinguish between the following application areas: (1) the measurement of exhaust gas streams directly at the source of emission; (2) the measurement of ambient outdoor air to characterize broad area pollutant levels; (3) indoor measurements in vehicles, workplaces, and residential buildings;[103] (4) the analysis of the headspace over polluted water or contaminated land. This classification can give a first indication about the particularities of the experiments. However, for each single application the sensitivity of the electronic nose to the target substances as well as to potential interfering substances has to be known. This principle is independent of the task and should be applied for the determination of the level of harmful substances, the estimation of odor emissions, and the determination of the general "air quality". The only difference is the reference data set for calibration, which can be obtained by the approved analytical methods or by artificial mixtures of the critical components. An alternative approach is to try to differentiate between different samples without deeper background knowledge of the occurring substances. This provides an indication of the applicability of an electronic nose but cannot be seen as a proof-of-principle for real life conditions. Consequently, the usability of the gained information is strongly variable and ranges from the first steps toward a new application field

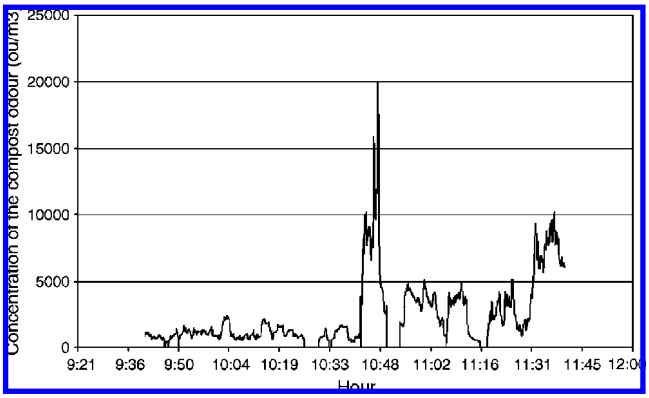

Figure 11. Time evolution of the odor concentration for compost emissions. This was directly calculated from the signal of one single sensor. The reliability of this procedure was surveyed by a sensor array combined with a PCA-based data evaluation. Thus, the presence of non-compost-related interfering gases was detected and taken into account (gap in the curve). These intervals were cut out. The peak at 10:48 can be explained by the turning of a compost row. Reprinted with permission from ref 125. Copyright 2006 Elsevier.

to well-developed prototypes for certain tasks. Using this limited approach, the electronic nose has already been tested for a wide range of applications: to determine odorous emissions from animal production facilities,[104] emissions of malodors produced through industrial factories[105] or waste disposal sites,[106] and emissions at the point of odor production from the decomposition process of kitchen and vegetable waste.[107] Applications where the odor impression does not come to the fore are the determination of single solvents or mixtures of them,[108] the identification of microorganisms such as bacteria and fungi,[109] the detection of leaking of refrigerant gas,[110] and the differentiation between automotive fuels.[111,112] Very practical examples are the detection of smoke compounds,[113] the control of automotive ventilation,[114,115] and the determination of indoor air quality.[116−119] For headspace measurement of water samples, both very specific and more general cases were considered. Examples of the former are the determination of residues of insecticides[120] and the amount of cyanobacteria[121] in drinkable water. Examples of the latter are the determination of water pollution[122] and sewage facility emissions[106] and the general assessment of wastewater samples.[123,124] Each application has its relevance, with some of them already further developed because of their extended impact and, consequently, their higher commercial prospects. Examples are the use of sensor arrays for comparing the in-cabin and outdoor air quality for cars for automatic flap-control systems, the use in failure-proof fire detection systems, and air quality control for ventilation on demand.

However, there are also emerging applications where the electronic nose has the potential to be established. One example is the use as a warning system to detect the emergence of odors from general waste. Nicolas et al. presented a simple approach to estimate the odor emission rate of a compost hall.[125] The sensor signal of a single Figaro metal oxide sensor (TGS822) was correlated with the odor concentration measured by olfactometry. In a straightforward way the calibration was directly used to predict the malodorness and the possible odor annoyance for the neighboring area (Figure 11). Knowing that volatiles and gases from other sources also cause a sensor response, Nicolas used a sensor array of six metal oxide sensors to determine time intervals when interferences occur. Using this approach, it is possible to find out when the odor predictions are reliable and when they are influenced, for example, by exhaust gases emitted from trucks or machinery or conversely when an odor-neutralizing product is sprayed in the hall. This is, of course, a simple but direct mode of operation which can be improved by compensating for temperature or humidity changes. It shows nevertheless in a clear way that a limited number of different sensors can deliver the desired information if the application characteristics are known. In a more elaborate way, Dickert et al. monitor the composting procedure with the long-term aim to ensure ideal transformation and avoid strong smells from a very early stage.[126] With six QCM (quartz crystal microbalance) resonators, coated with different molecularly imprinted polymers, they trace four key analytes, namely, water, 1-propanol, ethyl acetate, and limonene. The concentration pattern of the organic compounds showed strong similarities to GC/MS measurements. Thus, it is possible to determine the state and the advancement of the degradation process throughout its different phases to completion. These two studies represent the first steps on the way to solving the problem of odor monitoring in a robust way, already demonstrating the capability to provide information about odor generation and the process of composting under reproducible conditions. For general applicability, the system should be explored for changing ambient conditions. That means a repetition of the odor−sensor signal calibration curve for other waste compositions and the comparison of odor evaluation through the composting process with the concentration of the key markers.

4.3. Disease Diagnosis

Smell has been used to diagnose disease since ancient times and is directly linked to traditional medicine in different cultures. (“You can learn a lot just by smelling your patients with the unaided nose.” −Hippocrates, 430 B.C.) However, as modern diagnostic techniques provide more precise information with physical, chemical, and microbiological methods observation of odors fades into the background and is used only in some obvious cases as a disease indicator. The subjective odor perception of the physician is no longer required, although this ignores a lot of information on the health condition of the patients.[43] Hence, there is considerable interest in a reliable device that could use the released volatiles and gases for objective diagnosing of a multiplicity of infections, intoxications, or metabolic diseases. Over recent years laboratory tests and instrumental analysis have been used to increase our knowledge about marker substances, their origin, and their smell. Despite this progress, the standard analytical method, namely, gas chromatography, has not been accepted as an accredited diagnostic tool. Apart from the cost of the equipment, the main reason is the complexity of its use. Because of the measurement time and the need for qualified labor in its operation, it is used neither in diagnosis nor for health condition monitoring. Still, the introduction of an easy to use diagnostic device—based on an electronic nose—would open up new fields of application. Several publications and reviews on disease marker substances and their detection reflect the interest in that matter. Independent of the detection methodology used, one important issue is always the question of sampling. The skin, the sputum, the urine, the stool, or the breath can be disease-correlated odor sources. This diversity of detection sites makes a universal sampling system, compared to the ability

of the human nose, impossible. Therefore, already from the very beginning, one has to adapt the system for the particular needs and the specific disease.

Instead of direct measurements requiring complex sample strategies, one can consider the alternative of combining classical microorganism cultivation methods with subsequent analysis by an electronic nose. Of course, the analysis speed advantage for the whole procedure diminishes, but from the academic point of view, the resulting bacterium and fungus cultures are excellent objects to isolate the problem from interferences and, hence, are rewarding investigation subjects. In these in vitro experiments, the electronic nose has shown the ability to detect a variety of fungi and bacteria and, in some studies, to have even the ability to distinguish between them. Furthermore, the particular marker substances were identified by characterization of the gas phase above the microorganisms. Therefore, subsequent studies can fall back on sensors with the required selectivity. In this context the time dependency of incubation time and classification was checked for the in vitro experiments to obtain a reliable and, additionally, a fast classification. Another possibility to accelerate the identification of bacterial strains is to add biochemical precursors to the nutrient media for the liberation of specific odors through the pathogens.[127]

In clinical research the potential of electronic nose technology has already been tested for a variety of diseases. Swabs, sputum, serum, or urine samples were measured after a short incubation time or in some cases directly. The following list gives an overview on the most recent publications in this domain.

(1) Beginning with the identification of bacteria, Parry et al. were able to recognize β-hemolytic streptococci extracted from chronic venous leg ulcers.[128]

(2) The screening for bacterial vaginosis in vaginal swabs seems to be feasible.[129] Newer publications even give the impression that the reliability is comparable to that of present tests and show the possibility of controlling treatment of bacterial vaginosis by tracking the acetic acid concentration with a conducting polymer array.[130,131]

(3) Common bacterial pathogens of the upper respiratory tract were obtained from in vitro samples and successfully detected by a Cyranose 320 electronic nose.[132] The same device was able to identify and classify pathogens from 90 patients suffering from ear, nose, and throat infections with a correct classification of 88.2%.[133]

(4) In search of the causative agent of tuberculosis, Pavlou et al. was the first to demonstrate proof-of-principle for the detection of mycobacterium tuberculosis in human sputum after incubation with an enzymatic cocktail.[134] Furthermore, using the same Bloodhound 114 electronic nose, it was shown that one can distinguish between mycobacterium tuberculosis and other pathogens both in culture and in spiked sputum samples.[135] By means of untreated serum, Fend et al. succeeded in diagnosing the agent of tuberculosis in badgers and cows, *Mycobacterium bovis*, as early as 3 weeks after experimental infection.[136] They also used the Bloodhound 114 EN consisting of 14 conducting polymer sensors based on polyaniline.

(5) A further field of bacterial disease is urinary tract infections on which first studies have been undertaken to detect the specific volatile pattern.[137−139]

(6) The analysis of urine by electronic nose technology is also able to detect metabolic disease. Mohamed et al. has predicted type 2 diabetes successfully with accuracy up to 96%, depending on the data evaluation used.[140] Furthermore, in renal dysfunction the capacity to remove metabolic products from the blood is limited, and the resulting change in body odor can be detected by an electronic nose.[141] On the other hand, the volatile products which are accumulated exist as well in an increased concentration in the headspace of blood. Consequently, an electronic nose can be used for monitoring hemodialysis and to replace the established parameters based on urea concentration.[142]

In addition to the examples mentioned above, there are still other domains which are relatively unexplored. Examples are typhoid and yellow fever, where the skin has a smell resembling baked brown bread or a butcher's shop, respectively. The sweat of diphtheria patients smells sweet, and the odor of sweat after a rubella infection has been compared to freshly plucked feathers. Rancid-smelling stools can be an indication of shigellosis, and as the name suggests, in maple syrup urine disease the urine smells of burned sugar.[143]

A multiplicity of further diseases can be detected by the analysis of breath. For diabetes a sweet, fruity smell is typical, reminiscent of decomposing apples. Uremia patients have a fishy breath, and a feculent odor can be caused by an intestinal obstruction or an esophageal diverticulum. Hepatic failure is the reason for the liberation of mercaptans and dimethyl sulfide, which smell like musty fish or raw liver. The origin of a foul, putrid odor can be a lung abscess or an empyema but just as well an intranasal foreign body.[44] The main advantage of breath analysis, besides the detection of diseases directly related to the respiratory tract, is the fact that volatile organic compounds are mainly blood borne and the concentration of biologically relevant substances in exhaled breath closely reflects that in the arterial system. Therefore, breath is predestined for monitoring different processes in the body.[144] Apart from the odor impression of specific diseases, much about the biochemical processes and the formation of marker substances is already known.[145] In addition, direct sampling is possible without further time-consuming sample preparation; therefore, breath measurements are suitable for a straightforward and easily achievable diagnosis by the use of an electronic nose. This represents a noninvasive and easily repeatable test that is not disagreeable or embarrassing for the patient compared to blood or urine tests. In spite of the ease of the sampling procedure, special care has to be taken to take the measurements in a reproducible way. In principle, two elements should be considered: First, the different approaches of breath collection should distinguish between pure alveolar gas and the total volume of exhaled breath, which consists of a mixture of dead space air and alveolar air. Additionally, factors such as exhalation speed and ambient temperature have to be standardized.[146,147] Second, a correction for exogenous concomitants present in the inhaled ambient air should be carried out.[144,145] Without going deeper into the chemical pathway of substances appearing in human breath, examples for analysis done by an electronic nose are the following.

(1) The detection of the ethanol content of exhaled breath is the only example not directly connected to a disease,[148] but from the practical point of view, the quantification of acetone, which is the marker substance for ketoacidosis, can be solved in a similar approach. This is a possible way to screen for diabetes.[149,150]

(2) In contrast, the substance of interest for the detection of asthma is an inorganic gas, namely, nitric oxide.[151−153] By means of an electronic nose, patients with asthma can

be clearly discriminated from the control group, whereas the accuracy of classification of severity is less reliable.[154] Recently, a hand-held device was developed by Aerocrine, the NIOX MINO, which is able to determine the NO concentration in exhaled breath accurately.[155,156]

(3) Uremia can be reliably detected, whereas between patients with chronic renal insufficiency and chronic renal failure the correct classification is limited to 86.78%.[157]

(4) Examples for the detection of bacterial and/or fungal respiratory disease are chronic rhinosinusitis[158] and the very promising approach to identify ventilator-associated pneumonia in patients in surgical intensive care units.[159−161]

(5) The reason for halitosis is sulfur-containing gases of oral bacterium origin,[162] which is normally evaluated by an organoleptic test. Tanaca et al. and Nonaka et al. presented a clinical assessment of oral malodor by an electronic nose system.[163,164]

(6) Finally, several groups have undertaken efforts to detect lung cancer.[165−170]

To conclude, the possibilities for the application of the electronic nose in the medical field are very diverse as the different examples have shown. There is a need for preventive medical checkups to diagnose disease early, to speed up the healing process, to increase the rate of complete recovery, and consequently to save money for the health care system.[171] Despite the potential of the electronic nose in this field, for applicability one has to minimize the false positive rate and—even more important—the false negative rate. Because humans are a very heterogeneous sample set, one has to know the effect of most common variables on the classification. These can be additional diseases or changes in nutrition,[172,173] in medication,[174] or in the use of cosmetics. Furthermore, animal experiments suggest the existence of sex-dependent pheromones,[175,176] and behavioral studies show that individuals of different genetic backgrounds,[177−179] ages,[180] menstrual cycles,[181,182] or even emotions[183] are differentiable. This variability in sweat, urine, saliva,[178] or just breath[178,184] complicates the implementation of an electronic nose, in the first instance for diseases which are correlated with one of the odor-influencing factors mentioned. This problem should be illustrated in detail by the use of a concrete example. It is known that the breath of lung cancer patients has a defined odor and dogs can be trained to distinguish between the exhaled breath samples of sick and healthy test persons.[185] The metabolic pathway for the formation of several biomarkers has been clarified,[186] and volatile marker substances in the breath have been identified.[187,188] On the basis of chromatography and subsequently selection of the important peaks, a prediction of lung cancer had an accuracy comparable to that of screening chest CT.[189,190] Machado et al. used a Cyranose 320 electronic nose consisting of 32 polymer sensors.[168] The training set consisted of breath samples from 14 individuals with relatively advanced bronchogenic carcinoma and a control group of 45 individuals consisting of a combination of healthy persons and patients with other diseases. Support vector machine analysis was used to diagnose cancer in an independent validation group. The result was that 10 out of 14 cancer patients were classified correctly and 57 out of 62 individuals of the control group were correctly identified. Repetitions of the misclassified measurements (normally four) were in most cases misclassified again. In a letter to the editor, Phillips criticizes the fact that there is no evidence for the sensitivity of the sensors used to the biomarkers available.[191] Therefore, he suspects that there is a possibility that other substances may be responsible for the successful discrimination. One possibility may be compounds directly from tobacco smoke in lung cancer patients. In the study, the target group was also significantly older than the healthy control group. For that reason Phillips speculates that a higher amount of consumed cigarettes during lifetime may be an explanation for the observed results. This case study demonstrates the difficulties that have to be faced in the medical field to construct a robust prediction model. Risk factors, which are often linked to diseases, should not be wrongly treated as a calibration basis.

5. Research and Development Trends

After the initial euphoria engendered by the prospect of replicating biological olfaction, the limits of electronic nose technology were realized and linked primarily to the fundamental sensing components[192] and the sampling system. For the former, the problem is that, in contrast to nature, the information gained by adding additional sensors rapidly saturates. Therefore, the knowledge content provided by the sensor arrays currently used is far from the one delivered by the receptor cells of the olfactory epithelium. Consequently, an increase in selectivity (i.e., an increase in the number of sensors delivering useful new information) is necessary to enhance the capabilities of the electronic nose. On one hand, this is, of course, possible by the improvement of the individual sensors, which is not the main topic of this review. On the other hand, regarding the electronic nose as a complex system comprising a sampling system, the sensor array itself, the reference data set, and the data evaluation algorithms, there are other starting points for improvement. In this context, a higher sensitivity is often demanded to open up new application fields where trace components are the subject of interest. For instance, the human perception is usually sensitive to odor compounds down to the parts per billion range.[193] However, for some substances the detection threshold is even several orders of magnitude lower, as the example of 2,4,6-trichloroanisole shows[194] (the target compound for the cork taint in wine quality applications). This benchmark established by human perception is the target for an electronic nose;[39,195−199] additionally, it must show its ability when compared to analytical systems.[200,201] Besides this well-known application, the detection of explosives is of special interest in recent research and a further example of the need of highly sensitive systems. Because of the low vapor pressure of most explosive substances, the concentrations in the gas phase are in the same range as the previous example or even below.[202] Despite the advances in the sensor field based on different transducer principles[5] and a multiplicity of different preconcentration possibilities,[203,204] one has to point out once more that for real-life applications an increased sensitivity of the system can only be useful if sufficient selectivity is provided. Otherwise, the interferents will cover the target compounds. The established all-around electronic nose systems produced by different companies have finally found their place in basic research and for some particular applications in laboratories. When it comes to mass market applications, a highly optimized system for the specific operating conditions is necessary. This can be a flap-control system in the automotive area,[114,115] a fire detection system,[205] or a quality control device for food packaging[206]—all of which are either on or close to market.

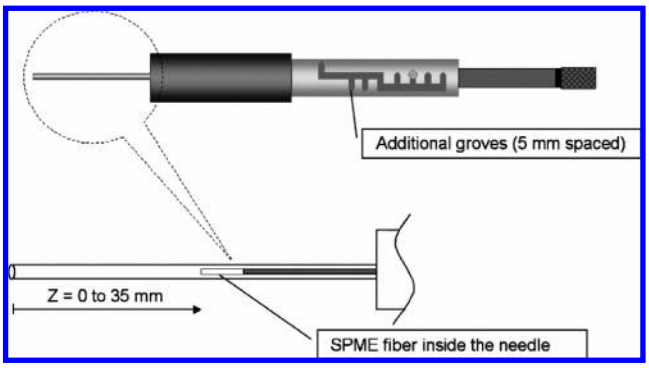

Figure 12. Schematic of an SPME fiber. To take a sample, the fiber is extended through the needle and exposed to the target analytes. After the volatiles have reached equilibrium between the fiber coating and the gaseous phase (or after a strongly defined time), the fiber is withdrawn into the needle. Desorption will take place in a heated inlet under a similar procedure. Reprinted with permission from ref 211. Copyright 2006 Elsevier.

5.1. Sample Handling

Sample preparation and sampling are error-prone steps and have to be well considered to achieve reliable results. This begins with a representative selection of samples, continues with their appropriate pretreatment, includes possible preconcentration and separation steps, and ends with a reproducible sample delivery procedure to the sensor array. Each of these steps can cause statistical as well as systematic errors, but besides these possible sources of error, the sample preparation opens up additional opportunities: It has the potential to dramatically increase the sensitivity of the whole system and, in addition, to remove the problems caused by background interferences. Because the original electronic noses concept was to move on from sophisticated analytical instruments and to create a simple and straightforward device, sophisticated sampling procedures were omitted. However, the need to solve ever-demanding applications has brought sample preparation techniques more and more in the focus in the past few years. The fact that samples can be solid, liquid, or gaseous and that their nature differs a lot makes it difficult to give a complete overview of the strategies used. For instance, aqueous samples can be stirred, heated, or salted out, or the pH can be varied to increase the concentration of volatiles in the headspace.[207] To make the system even more sensitive and not solely dependent on the direct vapor partitioning, a preconcentration step is inevitable.[208] The enrichment of the analytes can be divided into two major categories: active and passive air sampling.[203] In active sampling the gaseous sample is drawn through an adsorbent material. To measure the flow rate and the total volume, a flow meter is necessary for this approach. The advantage is that for a given sampling time lower concentrations can be monitored. In contrast, passive sampling is much simpler in implementation, and when a sample is taken, there is no need for additional technical equipment (Figure 12).[209] In this case, the analytes follow the concentration gradient according to Fick's first law to the sorbent. Therefore, the only driving forces are diffusion and the partition coefficient between the two phases. Each method has further advantages and disadvantages, and choosing one of them depends on the particular application.[210]

In combination with an electronic nose different preconcentration methods have been compared for some specific examples. Schaller et al. analyzed the ripening grades of Swiss Emmental cheese with the help of a mass-spectrometer-based electronic nose (SMart Nose).[212] The extraction methods used are static headspace extraction, purge-and-trap extraction with a mixture of Carbosieve SIII and Carbopack B60/80 as adsorbent materials, and solid-phase microextraction (SPME)[211] with a 65 μm CW/DVD-coated fiber.

The authors conclude that the static headspace measurement is useful for high levels of volatile compounds for which the two preconcentration methods do not bring an increase of sensitivity. However, both techniques extract approximately the same class of compounds with a higher mass-to-charge ratio. Because of better repeatability, usability, and concentrating ability, in direct comparison they favor the SPME technique to trap middle to high molecular masses. Ampuero et al. confirmed this finding for the classification of the botanical origin of unifloral honeys with the same electronic nose.[213] In this study static headspace measurement and solid-phase microextraction were performed under similar conditions. Instead of the classical purge-and-trap technique with continuous gas flow, they used inside-needle dynamic extraction (INDEx) as the active sampling procedure. Compared to SPME, this method has a higher mechanical robustness, needs half of the analysis time, and is simple.[213,214] However, SPME showed clearly a better extraction capacity for heavier volatiles with an $m/z > 110$. One has to note that the benefit of using preconcentration methods for sensor-based electronic noses is often not apparent from the sensor signal itself but becomes visible after data evaluation. Examples are the identification of lampante virgin olive oils,[215] the differentiation between apple varieties, the identification of the ripeness of pineapples, and the detection of an off-flavor in sugar with an SPME−SAW sensor array.[216] On the basis of a tin dioxide multisensor, Lozano et al. tested the ability of different SPME fiber coatings for wine discrimination.[217] Particularly for quantification tasks the influence of the coating thickness has to be considered as even low variations have a strong influence on the analyte response.[218,219] Therefore, a lack of interfiber comparability depending on the production process used can adulterate the results.

5.2. Filters and Analyte Gas Separation

The comparison between different extraction techniques has already shown that depending on the chosen approach the ratio of the detected compounds changes. This gives the potential to increase not only the sensitivity but also the selectivity to the target compounds of the system by a deliberate choice of sampling conditions. The obvious way is to adapt the polymer coating of the SPME fiber (Figure 13) or the Gerstel Twister, used for stir bar sorptive extraction (SBSE),[203,220] or to use an appropriate filling for the adsorbent tubes.

In addition, ingenious solutions can be found in the literature for the requirements of specific applications. The following examples show possible approaches and demonstrate that there are no clear boundaries between the separation techniques with or without simultaneous sample preconcentration.

(1) Villanueva et al. discriminated red wines, differing only in the variety of grape, by a system based on SPME and a metal oxide sensor array.[222] In a two-step desorption process, they first "dried" the polar absorbent fiber at low temperatures to eliminate the influence of water and ethanol.

(2) Instead of taking discrete temperature steps, Morris et al. desorbed the volatiles from a Tenax TA bed using a

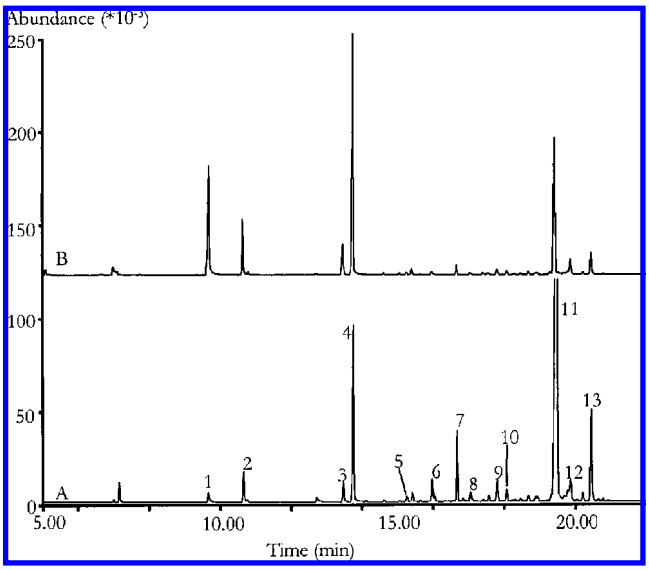

Figure 13. Chromatogram obtained from a single rose petal.[203] Sample preparation was carried out using SPME fibers with different coatings. In the lower trace PDMS (poly(dimethylsiloxane)) was used as the polymer, and in the upper trace PA (polyacrylate) was used. The choice of the fiber coating determines the composition of the detected substances. In this example the ratio between substance 4 and substance 11 is dramatically different. Reprinted with permission from ref 221. Copyright 2000 Wiley-VCH.

temperature program.[223] The bed had previously been exposed to the headspace of groundwater and to urban air. The temperature profile over time means that water is eluted first separately from the interesting volatiles. Instead of obtaining a steady-state sensor signal, a complex spectrum is created that contains information about the boiling point of the particular substances (elution time) and the functional type (peak width). A similar approach was previously used by Strathmann et al.[224]

(3) Ali et al. used a heated preconcentration tube as a dispersive element for a QCM array.[225] Water interferences were eliminated by using the different breakthrough times of water and toluene, the target substance.

(4) Investigating off-flavor detection in wine, Ragzzo-Sanchez et al. proposed back-flush gas chromatography to remove water and ethanol from the other volatiles.[198] Off-flavor-doped wines were discriminated by using FOX 4000 electronic nose data.

(5) The group at the University of Tübingen characterized packaging emissions with the help of four metal oxide gas sensors connected to a chromatographic column. For this purpose a very simple packed column was sufficient to separate water from the residual solvents and to determine the total amount of solvent in paper and paperboard in a reliable way (Figure 14).[206]

(6) The hardware of the zNose is a complete gas chromatograph with an SAW sensor as the detector. A similar approach was used by Zampolli et al. with a micromachined gas chromatographic column connected to a solid-state gas sensor (Figure 5).[116] In this case the use of a single sensor means that the convential 2D data evaluation approaches can be used.

(7) A further possibility to enhance selectivity was demonstrated using mass transport phenomena across a membrane.[226] Organophilic pervaporation can be used to discriminate wine model solutions in the presence of ethanol.

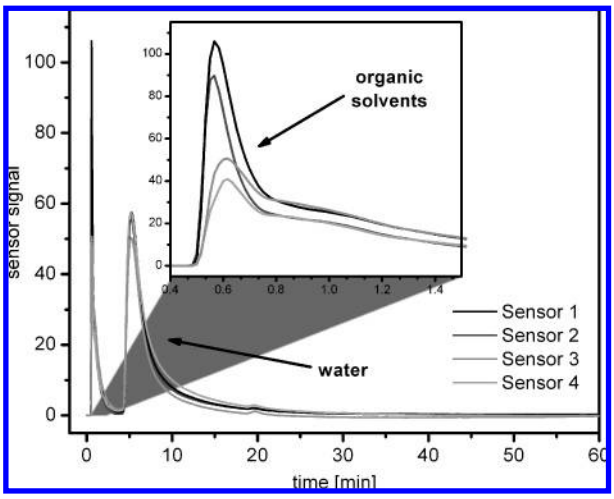

Figure 14. Determination of residual solvents from paper and paperboard packaging in the food industry.[206] Influences on the results of the variations of the high-humidity concentration have to be excluded. In the graph the separation of the organic solvents (first peak) from water (second peak) by means of a simple chromatographic approach is shown. Within the first minute the peak height of the residual solvents, consisting of ethanol, 2-propanol, 2-butanol, cyclohexanone, 1-ethoxy-2-propanol, and trace components, can be evaluated. Reprinted from ref 206. Copyright 2005 American Chemical Society.

After this pretreatment both conducting polymer-based sensors[227] and metal oxide sensors[228] are able to overcome the ethanol interference.

The examples presented demonstrate different strategies to eliminate interferences and enhance the electronic nose as a whole system. In contrast to sensor-based improvements of the selectivity, they all have the disadvantage of an increase in setup complexity and in analysis time, but the crucial point is that, in contrast to highly selective sensors, reversibility is a feature of most of these approaches. This has practical implications: when the system is being trained on calibration sets, these approaches do not suffer from instrumental drift as in the case of high-selectivity sensors. The stability of the system is preserved, and there is no need for drift correction in the subsequent data analysis. A direct comparison of the improvements and the additional costs brought by the different sampling strategies is difficult. Each application has its own requirements, and the sample preparation cannot be considered in isolation. In the examples shown, the information obtained often increases at the expense of additional time dependency. Therefore, an adapted data evaluation strategy is necessary to maximize the benefit gained.

5.3. Data Evaluation

Dodd and Persaud used the ratio of the steady-state sensor responses for data evaluation 25 years ago,[1] whereas in current research the data obtained are often so complex that they cannot be manually evaluated. Furthermore, data evaluation is not limited only to pattern recognition; it begins with the data acquisition step.[229] This includes the choice of the appropriate sensors, feature selection, scaling, and normalization. Finally, pattern recognition and classification techniques can be model free or model based and supervised or unsupervised. Each of these functions can be performed by a variety of different approaches which are more or less suitable for a specific application. Unfortunately, no general

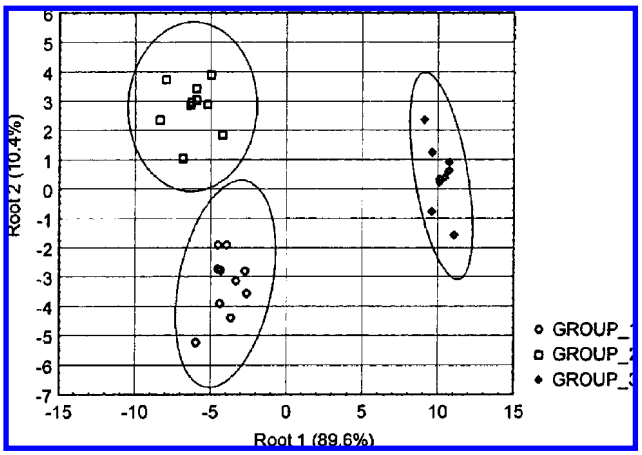

Figure 15. DFA of randomly generated data for a theoretical 24-sensor array. A total of 30 data points with a relative standard deviation of 7% were arranged into 3 groups of 10 data points. DFA discriminated them with a confidence interval (shown ellipses) of 95%. Reprinted with permission from ref 230. Copyright 2001 Elsevier.

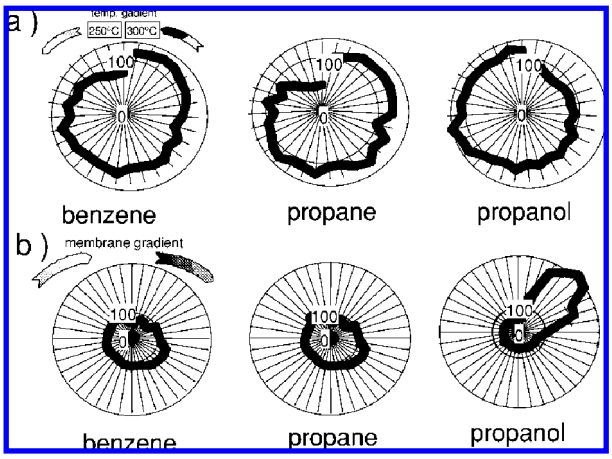

Figure 16. Measurement results of the gas sensor microarray KAMINA.[248] The array consists of a single monolithic metal oxide film separated into 38 segments by a parallel electrode structure. A temperature gradient (a) or a membrane thickness gradient (b) slightly changes the selectivity from segment to segment. The change of conductivity was normalized to the median (inner circle − 100), and the results are depicted as polar plots. As can be seen for both temperature (a) and membrane (b) gradients benzene and propane are difficult to discriminate even without considering the standard deviation. However, propanol can be readily distinguished by comparison of the first and last segments. Reprinted with permission from ref 248. Copyright 2001 Elsevier.

guidelines to determine the appropriate strategy exist. For this reason, in several publications these factors are a product of chance or, if they were done more systematically, a product of trial and error. In the latter case, however, the danger of overfitting and therefore false classification is high for operators lacking a deeper understanding of this field, as Goodner was able to demonstrate (see Figure 15).[230] Additionally, the lack of knowledge on which substances may be encountered hinders an adequate selection of the sensors and the training of the array to each possible analyte.

An overview of the analysis of data is given in the review of Scott et al.[231] Because of the need to have real experimental data, current research in this field is in most cases specific to the application and the electronic nose used. Therefore, there is a need to compare existing pattern recognition processes on the same data set,[232] to adapt and improve existing algorithms,[233−235] and to transfer data evaluation methods from other research areas.[236−238] The latter is especially important for the new types of electronic nose setups which produce additional time-dependent information.[236,237] However, in handling large amounts of data, it is important to consider redundancy. As these new techniques increase the dimensions of the data set the number of theoretical features becomes large, and hence, selection of the right features becomes challenging.[20] For electronic noses based on a sensor array these are principally transient sensor response,[239−241] temperature modulation of metal oxide sensors,[242−245] partial preseparation of the compounds,[206,223,225,246] or slight differences in the sensors caused by a gradient over temperature, doping concentration, sensitive layer thickness, or membrane thickness (compare Figure 16).[247,248]

Modern approaches may also have high-dimensional output data as well, for example, the mass-spectrometer-based Smart Nose with its high amount of mass-to-charge ratios, IMS with the time-dependent measurement,[120] or high-density optical sensor arrays.[249,250] However, for any given training set there exists an optimum number of features. In case it is too high, overfitting or computational ill-conditioning will take place and generalization will fail with the consequence of poor validation performance.[251] Therefore, a lot of work has been carried out recently to select the best features[251−256] or even the most appropriate sensors.[257,258] This is progress in the direction of having solid features and consequently reliable results from data evaluation instead of fitting the noise.[20]

6. Conclusion

Since the first attempts to identify a small number of single volatiles with the help of a set of unspecific gas sensors, much work has been carried out within the field of electronic noses. Today it is not only metal oxide sensors of varying selectivities which are available for this task, but also other transducers with electrochemical readouts such as conducting polymers, metal oxide field effect transistors, or amperometric sensors. Furthermore, gravimetric, thermal, and optical sensors which have a completely different transduction principle are also in use. On the basis of this variety of sensors, the electronic nose has proven that it is appropriate for a limited number of well-selected and -characterized applications. It is possible to classify bacteria, to monitor air quality on the space shuttle,[259] or to check the spoilage of foodstuff, to mention only a few successful examples.

Despite the success in some areas, the efforts to arrive at a universal device that can make fine discrimination of flavors, perfumes, and smells and eventually replace the human nose are disappointing. The initial hope was to approach the ability of human odor sensing by increasing the number of individual sensors. However, the reason for the nose's unequalled performance has turned out to be not only the high number of different human receptor cells, but their selectivity and their unsurpassed sensitivity for some analyte gases. Therefore, instead of creating redundant information by adding more similar sensors, current research efforts are targeting both these directions. Sensors with new sensitive layers are under development, for instance, based on DNA, molecular imprinted molecules, or even immobilized natural receptors (up to whole cells), which

promise to increase the sensitivity and importantly selectivity.[260−263] Moreover, considering the electronic nose as a whole system, there are other possibilities to reach both of these aims. On one hand, the increase in sensitivity can be realized by appropriate sample pretreatment and preconcentration techniques, whereras filters and separation units can be used to increase the selectivity and reduce interfering substances. These strategies are a further step in the evolution of the electronic nose by learning from nature and which should lead to an enlarged field of application areas. Going in this direction, the complexity of the whole system will be obviously increased, but learning from history this step is often inevitable to apply the electronic nose in the desired way. In spite of this divergence from the intended simplicity, the products obtained are still by far less expensive than analytical systems and have the potential for cost-engineering when adapted to one special task.

In addition to the classical sensor-array-based approach, electronic noses based on other technologies have become more and more common where, for example, mass and ion mobility spectrometers or flash gas chromatographs are used to detect the components of a gas mixture. Instead of the features given by a sensor array, in these cases, the detector arrays have a virtual character and the multiple features are provided by their specific *m*/*z* ratio, their time-of-flight, or their retention time. In spite of having another approach and thus providing a quite different input—a well-defined concentration profile—they are as equally unsuccessful in mimicking the sense of smell as their sensor-array counterparts. Neither the sensor-array approach nor instrumental analysis is by definition better. Their suitability for a specific application depends critically on the operating conditions and target species and should be considered on a case by case basis. Without a proper consideration of the problem there is a high risk of obtaining chemical fingerprints without a correlation with the relevant properties of the sample.

The electronic nose, in use today, replaces neither complex analytical equipment nor odor panels but supplements both of them. In comparison it might have several advantages regarding mobility, price (TCO), and ease of use. Therefore, it has the potential to enter our daily life far away from well-equipped chemical laboratories and skilled specialists. Keeping its limitations in mind and adapted for a special purpose, this will be the future for the electronic nose for as long as the ability to smelling odors rather than detecting volatiles is still far away over the rainbow.

7. References

(1) Persaud, K. C.; Dodd, G. *Nature* **1982**, *299*, 352.
(2) Walt, D. R. *Anal. Chem.* **2005**, *77*, 45a.
(3) Halova, J.; Strouf, O.; Zak, P.; Sochozova, A.; Uchida, N.; Yuzuri, T.; Sakakibara, K.; Hirota, M. *Quant. Struct.-Act. Relat.* **1998**, *17*, 37.
(4) Autrum, H.; Zwehl, V. *Z. Vgl. Physiol.* **1964**, *48*, 357.
(5) Singh, S. *J. Hazard. Mater.* **2007**, *144*, 15.
(6) Bunte, G.; Hurttlen, J.; Pontius, H.; Hartlieb, K.; Krause, H. *Anal. Chim. Acta* **2007**, *591*, 49.
(7) Firestein, S. *Nature* **2001**, *413*, 211.
(8) Buck, L. B. *Angew. Chem.* **2005**, *117*, 6283.
(9) Mombaerts, P. *Nat. Rev. Neurosci.* **2004**, *5*, 263.
(10) Boeker, P.; Hamacher, T.; Mannebeck, D.; Wimmer, P.; Horner, G. *Gefahrstoffe—Reinhalt. Luft* **2003**, *63*, 283.
(11) Mitrovics, J.; Ulmer, H.; Weimar, U.; Gopel, W. *Acc. Chem. Res.* **1998**, *31*, 307.
(12) Gaillard, I.; Rouquier, S.; Giorgi, D. *Cell. Mol. Life Sci.* **2004**, *61*, 456.
(13) James, D.; Scott, S. M.; Ali, Z.; O'Hare, W. T. *Microchim. Acta* **2005**, *149*, 1.
(14) Ulmer, H.; Mitrovics, J.; Noetzel, G.; Weimar, U.; Göpel, W. *Sens. Actuators, B* **1997**, *43*, 24.
(15) Pardo, M.; Kwong, L. G.; Sberveglieri, G.; Brubaker, K.; Schneider, J. F.; Penrose, W. R.; Stetter, J. R. *Sens. Actuators, B* **2005**, *106*, 136.
(16) Dickinson, T. A.; White, J.; Kauer, J. S.; Walt, D. R. *Nature* **1996**, *382*, 697.
(17) Suslick, K. S.; Rakow, N. A.; Sen, A. *Tetrahedron* **2004**, *60*, 11133.
(18) Suslick, K. S. *MRS Bull.* **2004**, *29*, 720.
(19) Filippini, D.; Lundstrom, I. *Appl. Phys. Lett.* **2002**, *81*, 3891.
(20) Hajek, P.; Havranek, T. *Mechanizing hypothesis formation mathematical foundations for general theory*; Springer-Verlag: Berlin, Heidelberg, New York, 1978.
(21) Creaser, C. S.; Griffiths, J. R.; Bramwell, C. J.; Noreen, S.; Hill, C. A.; Thomas, C. L. P. *Analyst* **2004**, *129*, 984.
(22) Massart, D. L.; Vandeginste, B. G. M.; Deming, S. N.; Michotte, Y.; Kaufman, L. *Chemometrics: A Textbook*; Elsevier: Amsterdam, 1988.
(23) Massart, D. L.; Vandeginste, B. G. M.; Buydens, L. M. C.; De Jong, S.; Lewi, P. J.; Smeyers-Verbeke, J. *Handbook of Chemometrics and Qualimetrics*; Elsevier: Amsterdam, 1998.
(24) Mielle, P.; Marquis, F. *Semin. Food Anal.* **1998**, *3*, 93.
(25) Staples, E. J. *Abstr. Pap.—Am. Chem. Soc.* **2000**, *219*, 236.
(26) Zampolli, S.; Elmi, I.; Sturmann, J.; Nicoletti, S.; Dori, L.; Cardinali, C. *Sens. Actuators, B* **2005**, *105*, 400.
(27) Lu, C. J.; Steinecker, W. H.; Tian, W. C.; Oborny, M. C.; Nichols, J. M.; Agah, M.; Potkay, J. A.; Chan, H. K. L.; Driscoll, J.; Sacks, R. D.; Wise, K. D.; Pang, S. W.; Zellers, E. T. *Lab Chip* **2005**, *5*, 1123.
(28) Kim, H.; Steinecker, W. H.; Reidy, S.; Lambertus, G. R.; Astle, A. A.; Najafi, K.; Zellers, E. T.; Bernal, L. P.; Washabaugh, P. D.; Wise, K. D. *TRANSDUCERS*; IEEE: Lyon, France, 2007; p 1505.
(29) van Kempen, T. A. T. G.; Powers, W. J.; Sutton, A. L. *J. Anim. Sci.* **2002**, *80*, 1524.
(30) Cozzolino, D.; Smyth, H. E.; Gishen, M. *J. Agric. Food Chem.* **2003**, *51*, 7703.
(31) Armenta, S.; Coelho, N. M. M.; Roda, R.; Garrigues, S.; de la Guardia, A. *Anal. Chim. Acta* **2006**, *580*, 216.
(32) Ampuero, S.; Bosset, J. O. *Sens. Actuators, B* **2003**, *94*, 1.
(33) Strike, D. J.; Meijerink, M. G. H.; Koudelka-Hep, M. *Fresenius' J. Anal. Chem.* **1999**, *364*, 499.
(34) Gardner, J. W.; Bartlett, P. N. *Sens. Actuators, B* **1994**, *18−19*, 211.
(35) Casalinuovo, I. A.; Di Pierro, D.; Coletta, M.; Di Francesco, P. *IEEE Sens. J.* **2006**, *6*, 1428.
(36) Capone, S.; Distante, C.; Francioso, L.; Presicce, D.; Taurino, A. M.; Siciliano, P.; Zuppa, M. *J. Argent. Chem. Soc.* **2005**, *93*, 123.
(37) Lacoste, F.; Bosque, F.; Raoux, R. *Ocl-Ol. Corps Gras Li.* **2001**, *8*, 78.
(38) Maciejewska, A.; Szczurek, A.; Kerenyi, Z. *Sens. Actuators, B* **2006**, *115*, 170.
(39) Ragazzo-Sanchez, J. A.; Chalier, P.; Chevalier, D.; Ghommidh, C. *Sens. Actuators, B* **2006**, *114*, 665.
(40) Deisingh, A. K.; Stone, D. C.; Thompson, M. *Int. J. Food Sci. Technol.* **2004**, *39*, 587.
(41) Liddell, K.; White, J. *Br. J. Dermatol.* **1975**, *92*, 215.
(42) Doty, R. L. *Chem. Senses* **1981**, *6*, 351.
(43) Fitzgerald, F. T.; Tierney, L. M. *West. J. Med.* **1982**, *137*, 169.
(44) Manolis, A. *Clin. Chem.* **1983**, *29*, 5.
(45) Persaud, K. C. *Int. J. Low. Extrem. Wounds* **2005**, *4*, 50.
(46) Pavlou, A. K.; Turner, A. P. F. *Clin. Chem. Lab. Med.* **2000**, *38*, 99.
(47) Turner, A. P. F.; Magan, N. *Nat. Rev. Microbiol.* **2004**, *2*, 161.
(48) Thaler, E. R.; Hanson, C. W. *Expert Rev. Med. Devices* **2005**, *2*, 559.
(49) Di Natale, C.; Pennazza, G.; Martinelli, E.; Santonico, M.; Macagnano, A.; Paolesse, R.; D'Amico, A. *J. Argent. Chem. Soc.* **2005**, *93*.
(50) Laska, M.; Seibt, A.; Weber, A. *Chem. Senses* **2000**, *25*, 47.
(51) Lorenzo, N.; Wan, T. L.; Harper, R. J.; Hsu, Y. L.; Chow, M.; Rose, S.; Furton, K. G. *Anal. Bioanal. Chem.* **2003**, *376*, 1212.
(52) Göth, A.; McLean, I. G.; Trevelyan, J. In *Mine Detection Dogs: Training, Operations and Odour Detection*; MacDonald, J., Lockwood, J. R., Eds.; GICHD: Geneva, 2003.
(53) Shaw, J. A.; Seldomridge, N. L.; Dunkle, D. L.; Nugent, P. W.; Spangler, L. H.; Bromenshenk, J. J.; Henderson, C. B.; Churnside, J. H.; Wilson, J. J. *Opt. Express* **2005**, *13*, 5853.
(54) Cantergiani, E.; Brevard, H.; Krebs, Y.; Feria-Morales, A.; Amado, R.; Yeretzian, C. *Eur. Food Res. Technol.* **2001**, *212*, 648.
(55) Song, H. S.; Sawamura, M.; Ito, T.; Ido, A.; Ukeda, H. *Flavour Fragrance J.* **2000**, *15*, 323.
(56) Lin, J. M.; Rouseff, R. L. *Flavour Fragrance J.* **2001**, *16*, 457.
(57) Ulrich, D.; Hoberg, E.; Bittner, T.; Engewald, W.; Meilchen, K. *Eur. Food Res. Technol.* **2001**, *213*, 200.

(58) Valim, M. F.; Rouseff, R. L.; Lin, J. M. *J. Agric. Food Chem.* **2003**, *51*, 1010.
(59) Gocmen, D.; Gurbuz, O.; Rouseff, R. L.; Smoot, J. M.; Dagdelen, A. F. *Eur. Food Res. Technol.* **2004**, *218*, 573.
(60) Komes, D.; Ulrich, D.; Lovric, T. *Eur. Food Res. Technol.* **2006**, *222*, 1.
(61) Barsan, N.; Ionescu, R. *Sens. Actuators, B* **1994**, *19*, 470.
(62) Hivert, B.; Hoummady, M.; Mielle, P.; Mauvais, G.; Henrioud, J. M.; Hauden, D. *Sens. Actuators, B* **1995**, *27*, 242.
(63) Mielle, P.; Marquis, F.; Trivier, V. In *Sensors and Microsystems*; Di Natale, C., D'Amico, A., Siciliano, P., Eds.; World Scientific: London, 2000.
(64) Hofmann, T.; Schieberle, P.; Krummel, C.; Freiling, A.; Bock, J.; Heinert, L.; Kohl, D. *Sens. Actuators, B* **1997**, *41*, 81.
(65) Eberheim, A.; Kohl, D.; Schieberle, P. *Phys. Chem. Chem. Phys.* **2003**, *5*, 5203.
(66) Dainty, R. H. *Int. J. Food Microbiol.* **1996**, *33*, 19.
(67) Cynkar, W.; Cozzolino, D.; Dambergs, B.; Janik, L.; Gishen, M. *Sens. Actuators, B* **2007**, *124*, 167.
(68) Karlshoj, K.; Nielsen, P. V.; Larsen, T. O. *J. Agric. Food Chem.* **2007**, *55*, 4289.
(69) Gomez, A. H.; Wang, J.; Hu, G. X.; Pereira, A. G. *Lebensm.-Wiss. -Technol.* **2007**, *40*, 681.
(70) Marin, S.; Vinaixa, M.; Brezmes, J.; Llobet, E.; Vilanova, X.; Correig, X.; Ramos, A. J.; Sanchis, V. *Int. J. Food Microbiol.* **2007**, *114*, 10.
(71) Needham, R.; Williams, J.; Beales, N.; Voysey, P.; Magan, N. *Sens. Actuators, B* **2005**, *106*, 20.
(72) Vinaixa, M.; Marin, S.; Brezmes, J.; Llobet, E.; Vilanova, X.; Correig, X.; Ramos, A.; Sanchis, V. *J. Agric. Food Chem.* **2004**, *52*, 6068.
(73) Needham, R.; Magan, N. *Aspects Appl. Biol.* **2003**, *68*, 217.
(74) Keshri, G.; Voysey, P.; Magan, N. *J. Appl. Microbiol.* **2002**, *92*, 165.
(75) Presicce, D. S.; Forleo, A.; Taurino, A. M.; Zuppa, M.; Siciliano, P.; Laddomada, B.; Logrieco, A.; Visconti, A. *Sens. Actuators, B* **2006**, *118*, 433.
(76) Tognon, G.; Campagnoli, A.; Pinotti, L.; Dell'Orto, V.; Cheli, F. *Vet. Res. Commun.* **2005**, *29*, 391.
(77) Costello, B. P. J. D.; Ewen, R. J.; Gunson, H.; Ratcliffe, N. M.; Sivanand, P. S.; Spencer-Phillips, P. T. N. *Meas. Sci. Technol.* **2003**, *14*, 397.
(78) Benedetti, S.; Sinelli, N.; Buratti, S.; Riva, M. *J. Dairy Sci.* **2005**, *88*, 3044.
(79) Panigrahi, S.; Balasubramanian, S.; Gu, H.; Logue, C. M.; Marchello, M. *Sens. Actuators, B* **2006**, *119*, 2.
(80) Blixt, Y.; Borch, E. *Int. J. Food Microbiol.* **1999**, *46*, 123.
(81) Rajamaki, T.; Alakomi, H. L.; Ritvanen, T.; Skytta, E. S.; Smolander, M.; Ahvenainen, R. *Food Control* **2006**, *17*, 5.
(82) Haugen, J. E.; Rudi, K.; Langsrud, S.; Bredholt, S. *Anal. Chim. Acta* **2006**, *565*, 10.
(83) Magan, N.; Pavlou, A.; Chrysanthakis, I. *Sens. Actuators, B* **2001**, *72*, 28.
(84) Abellana, M.; Benedi, J.; Sanchis, V.; Ramos, A. J. *J. Appl. Microbiol.* **1999**, *87*, 371.
(85) Delbarre-Ladrat, C.; Cheret, R.; Taylor, R.; Verrez-Bagnis, V. *Crit. Rev. Food Sci. Nutr.* **2006**, *46*, 409.
(86) Gram, L.; Huss, H. H. *Int. J. Food Microbiol.* **1996**, *33*, 121.
(87) Gram, L.; Dalgaard, P. *Curr. Opin. Biotechnol.* **2002**, *13*, 262.
(88) Joffraud, J. J.; Leroi, F.; Roy, C.; Berdague, J. L. *Int. J. Food Microbiol.* **2001**, *66*, 175.
(89) Malle, P.; Poumeyrol, M. *J. Food Prot.* **1989**, *52*, 419.
(90) Duflos, G.; Coin, V. M.; Cornu, M.; Antinelli, J. F.; Malle, P. *J. Sci. Food Agric.* **2006**, *86*, 600.
(91) Rodriguez-Jerez, J. J.; M. M.; H.-H.; Roig-Sagues, A. X. *Global quality assessment in Mediterranean aquaculture*; CIHEAM: Zaragoza, Spain, 2000.
(92) Ruiz-Capillas, C.; Gillyon, C. M.; Horner, W. F. A. *J. Food Biochem.* **2001**, *25*, 541.
(93) Jonsdottir, R.; Olafsdottir, G.; Martinsdottir, E.; Stefansson, G. *J. Agric. Food Chem.* **2004**, *52*, 6250.
(94) Mansur, M. A.; Bhadra, A.; Takamura, H.; Matoba, T. *Fish. Sci.* **2003**, *69*, 864.
(95) Di Natale, C.; Olafsdottir, G.; Einarsson, S.; Martinelli, E.; Paolesse, R.; D'Amico, A. *Sens. Actuators, B* **2001**, *77*, 572.
(96) Naes, T.; Isaksson, T.; Fearn, T.; Davies, T. *A user-friendly guide to multivariate calibration and classification*; NIR Publications: Chichester, U.K., 2002.
(97) Haddad, R.; Carmel, L.; Harel, D. *Sens. Actuators, B* **2007**, *120*, 467.
(98) Huss, H. H. *Quality and quality changes in fresh fish*; FAO: Rome, 1995.
(99) Shawyer, M.; Pizzali, A. F. M. *The use of ice on small fishing vessels*; FAO: Rome, 2003.
(100) Olafsdottir, G.; Jonsdottir, R.; Lauzon, H. L.; Luten, J.; Kristbergsson, K. *J. Agric. Food Chem.* **2005**, *53*, 10140.
(101) Olafsdottir, G. In *Rapid and on-line instrumentation for food quality assurance*; Tothill, I. E., Ed.; Woodhead Publishing: Cambridge, U.K., 2003.
(102) Gilbert, R. O. *Statistical Methods for Environmental Pollution Monitoring*; John Wiley & Sons: New York, 1987.
(103) Wight, G. D. *Fundamentals of air sampling*; CRC: Boca Raton, FL, 1994.
(104) Nimmermark, S. *Water Sci. Technol.* **2001**, *44*, 33.
(105) Di Francesco, F.; Lazzerini, B.; Marcelloni, F.; Pioggia, G. *Atmos. Environ.* **2001**, *35*, 1225.
(106) Micone, P. G.; Guy, C. *Sens. Actuators, B* **2007**, *120*, 628.
(107) Biey, E. M.; Verstraete, W. *Environ. Technol.* **1999**, *20*, 331.
(108) Zhou, H. Y.; Homer, M. L.; Shevade, A. V.; Ryan, M. A. *IEEE Sens. J.* **2006**, *6*, 1.
(109) Dutta, R.; Morgan, D.; Baker, N.; Gardner, J. W.; Hines, E. L. *Sens. Actuators, B* **2005**, *109*, 355.
(110) Delpha, C.; Lumbreras, M.; Siadat, M. *Sens. Actuators, B* **2004**, *98*, 46.
(111) Feldhoff, R.; Saby, C. A.; Bernadet, P. *Analyst* **1999**, *124*, 1167.
(112) Sobanski, T.; Szczurek, A.; Nitsch, K.; Licznerski, B. W.; Radwan, W. *Sens. Actuators, B* **2006**, *116*, 207.
(113) Kohl, D.; Eberheim, A.; Schieberle, P. *Thin Solid Films* **2005**, *490*, 1.
(114) Kalman, E. L.; Winquist, F.; Lofvendahl, A.; Rudell, B.; Wass, U. *Indoor Built Environ.* **2002**, *11*, 105.
(115) Blaschke, M.; Tille, T.; Robertson, P.; Mair, S.; Weimar, U.; Ulmer, H. *IEEE Sens. J.* **2006**, *6*, 1298.
(116) Zampolli, S.; Elmi, I.; Ahmed, F.; Passini, M.; Cardinali, G. C.; Nicoletti, S.; Dori, L. *Sens. Actuators, B* **2004**, *101*, 39.
(117) Kuske, M.; Romain, A. C.; Nicolas, J. *Build. Environ.* **2005**, *40*, 824.
(118) Ryan, M. A.; Shevade, A. V.; Zhou, H.; Homer, M. L. *MRS Bull.* **2004**, *29*, 714.
(119) Willers, H.; de Gijsel, P.; Ogink, N.; D'Amico, A.; Martinelli, E.; Di Natale, C.; van Ras, N.; van der Waarde, J. *Water Sci. Technol.* **2004**, *50*, 93.
(120) Tuovinen, K.; Kolehmainen, M.; Paakkanen, H. *Anal. Chim. Acta* **2001**, *429*, 257.
(121) Bastos, A. C.; Magan, N. *Sens. Actuators, B* **2006**, *116*, 151.
(122) Goschnick, J.; Koronczi, I.; Frietsch, M.; Kiselev, I. *Sens. Actuators, B* **2005**, *106*, 182.
(123) Stuetz, R. M. *Water Sci. Technol.* **2004**, *49*, 137.
(124) Bourgeois, W.; Gardey, G.; Servieres, M.; Stuetz, R. M. *Sens. Actuators, B* **2003**, *91*, 109.
(125) Nicolas, J.; Romain, A. C.; Ledent, C. *Sens. Actuators, B* **2006**, *116*, 95.
(126) Dickert, F. L.; Lieberzeit, P. A.; Achatz, P.; Palfinger, C.; Fassnauer, M.; Schmid, E.; Werther, W.; Horner, G. *Analyst* **2004**, *129*, 432.
(127) Pavlou, A.; Turner, A. P. F.; Magan, N. *Lett. Appl. Microbiol.* **2002**, *35*, 366.
(128) Parry, A. D.; Chadwick, P. R.; Simon, D.; Oppenheim, B.; McCollum, C. N. *J. Wound Care* **1995**, *4*, 404.
(129) Chandiok, S.; Crawley, B. A.; Oppenheim, B. A.; Chadwick, P. R.; Higgins, S.; Persaud, K. C. *J. Clin. Pathol.* **1997**, *50*, 790.
(130) Hay, P.; Tummon, A.; Ogunfile, M.; Adebiyi, A.; Adefowora, A. *Int. J. Stand. Aids* **2003**, *14*, 114.
(131) Chaudry, A. N.; Travers, P. J.; Yuenger, J.; Colletta, L.; Evans, P.; Zenilman, J. M.; Tummon, A. *J. Clin. Microbiol.* **2004**, *42*, 5170.
(132) Lai, S. Y.; Deffenderfer, O. F.; Hanson, W.; Phillips, M. P.; Thaler, E. R. *Laryngoscope* **2002**, *112*, 975.
(133) Shykhon, M. E.; Morgan, D. W.; Dutta, R.; Hines, E. L.; Gardner, J. W. *J. Laryngol. Otol.* **2004**, *118*, 706.
(134) Pavlou, A. K.; Magan, N.; Jones, J. M.; Brown, J.; Klatser, P.; Turner, A. R. *Biosens. Bioelectron.* **2004**, *20*, 538.
(135) Fend, R.; Kolk, A. H. J.; Bessant, C.; Buijtels, P.; Klatser, P. R.; Woodman, A. C. *J. Clin. Microbiol.* **2006**, *44*, 2039.
(136) Fend, R.; Geddes, R.; Lesellier, S.; Vordermeier, H. M.; Corner, L. A. L.; Gormley, E.; Costello, E.; Hewinson, R. G.; Marlin, D. J.; Woodman, A. C.; Chambers, M. A. *J. Clin. Microbiol.* **2005**, *43*, 1745.
(137) Aathithan, S.; Plant, J. C.; Chaudry, A. N.; French, G. L. *J. Clin. Microbiol.* **2001**, *39*, 2590.
(138) Pavlou, A. K.; Magan, N.; McNulty, C.; Jones, J. M.; Sharp, D.; Brown, J.; Turner, A. P. F. *Biosens. Bioelectron.* **2002**, *17*, 893.
(139) Kodogiannis, V.; Wadge, E. *Int. J. Neural Syst.* **2005**, *15*, 363.
(140) Mohamed, E. I.; Linder, R.; Periello, G.; Di Daniele, N.; Pöppl, S. J.; De Lorenzo, A. *Diabetes, Nutr. Metab.* **2002**, *15*, 215.
(141) Voss, A.; Baier, V.; Reisch, R.; von Roda, K.; Elsner, P.; Ahlers, H.; Stein, G. *Ann. Biomed. Eng.* **2005**, *33*.
(142) Fend, R.; Bessant, C.; Williams, A. J.; Woodman, A. C. *Biosens. Bioelectron.* **2004**, *19*, 1581.
(143) Podebrad, F.; Heil, M.; Reichert, S.; Mosandl, A.; Sewell, A. C.; Bohles, H. *J. Inherited Metab. Dis.* **1999**, *22*, 107.

(144) Cao, W. Q.; Duan, Y. X. *Crit. Rev. Anal. Chem.* **2007**, *37*, 3.
(145) Miekisch, W.; Schubert, J. K.; Noeldge-Schomburg, G. F. E. *Clin. Chim. Acta* **2004**, *347*, 25.
(146) Jones, A. W. *Acta Physiol. Scand.* **1982**, *114*, 407.
(147) Schoknecht, G.; Fleck, K.; Kophamel, B. *Blutalkohol* **1990**, *27*, 83.
(148) Paulsson, N. J. P.; Winquist, F. *Forensic Sci. Int.* **1999**, *105*, 95.
(149) Ping, W.; Yi, T.; Haibao, X.; Farong, S. *Biosens. Bioelectron.* **1997**, *12*, 1031.
(150) Yu, J. B.; Byun, H. G.; So, M. S.; Huh, J. S. *Sens. Actuators, B* **2005**, *108*, 305.
(151) Bates, C. A.; Silkoff, P. E. *J. Allergy Clin. Immunol.* **2003**, *111*, 256.
(152) Smith, A. D.; Cowan, J. O.; Filsell, S.; McLachlan, C.; Monti-Sheehan, G.; Jackson, P.; Taylor, D. R. *Am. J. Respir. Crit. Care Med.* **2004**, *169*, 473.
(153) Smith, A. D.; Cowan, J. O.; Brassett, K. P.; Herbison, G. P.; Taylor, D. R. *N. Engl. J. Med.* **2005**, *352*, 2163.
(154) Dragonieri, S.; Le Cessie, S.; Mertens, B. J. A.; Schot, R.; Assink, C. J.; Gauw, S. A.; Bel, E. H.; Sterk, P. J. *Proceedings of the American Thoracic Society*, San Francisco, 2007.
(155) Alving, K.; Janson, C.; Nordvall, L. *Respir. Res.* **2006**, *7*.
(156) Gill, M.; Graff, G. R.; Adler, A. J.; Dweik, R. A. *J. Asthma* **2006**, *43*, 731.
(157) Lin, Y. J.; Guo, H. R.; Chang, Y. H.; Kao, M. T.; Wang, H. H.; Hong, R. I. *Sens. Actuators, B* **2001**, *76*, 177.
(158) Mohamed, E. I.; Bruno, E.; Linder, R.; Alessandrin, M.; Di Girolamo, A.; Pöppl, S. J.; Puija, A.; De Lorenzo, A. *An. Otorrinolaringol. Ibero. Am.* **2003**, *30*, 447.
(159) Hockstein, N. G.; Thaler, E. R.; Torigian, D.; Miller, W. T.; Deffenderfer, O.; Hanson, C. W. *Laryngoscope* **2004**, *114*, 1701.
(160) Hockstein, N. G.; Thaler, E. R.; Lin, Y. Q.; Lee, D. D.; Hanson, C. W. *Ann. Otol., Rhinol., Laryngol.* **2005**, *114*, 504.
(161) Hanson, C. W.; Thaler, E. R. *Anesthesiology* **2005**, *102*, 63.
(162) Suarez, F. L.; Furne, J. K.; Springfield, J.; Levitt, M. D. *J. Dent. Res.* **2000**, *79*, 1773.
(163) Tanaka, M.; Anguri, H.; Nonaka, A.; Kataoka, K.; Nagata, H.; Kita, J.; Shizukuishi, S. *J. Dent. Res.* **2004**, *83*, 317.
(164) Nonaka, A.; Tanaka, M.; Anguri, H.; Nagata, H.; Kita, J.; Shizukuishi, S. *Oral Dis.* **2005**, *11*, 35.
(165) Di Natale, C.; Macagnano, A.; Martinelli, E.; Paolesse, R.; D'Arcangelo, G.; Roscioni, C.; Finazzi-Agro, A.; D'Amico, A. *Biosens. Bioelectron.* **2003**, *18*, 1209.
(166) Yu, H.; Xu, L.; Cao, M.; Chen, X.; Wang, P.; Jiao, J.; Wang, Y. *IEEE Sens. J.* **2003**, *2*, 1333.
(167) Chen, X.; Cao, M. F.; Li, Y.; Hu, W. J.; Wang, P.; Ying, K. J.; Pan, H. M. *Meas. Sci. Technol.* **2005**, *16*, 1535.
(168) Machado, R. F.; Laskowski, D.; Deffenderfer, O.; Burch, T.; Zheng, S.; Mazzone, P. J.; Mekhail, T.; Jennings, C.; Stoller, J. K.; Pyle, J.; Duncan, J.; Dweik, R. A.; Erzurum, S. C. *Am. J. Respir. Crit. Care Med.* **2005**, *171*, 1286.
(169) Mazzone, P. J.; Hammel, J.; Dweik, R.; Na, J.; Czich, C.; Daniel, Laskowski, D.; Mekhail, T. *Thorax* **2007**, *62*, 565.
(170) Neustein, M. E. M.Sc. Thesis, Drexel University, 2005.
(171) Humphrey, L. L.; Teutsch, S.; Johnson, M. *Ann. Intern. Med.* **2004**, *140*, 740.
(172) Hauser, G. J.; Chitayat, D.; Berns, L.; D.; B. a.; Muhlbauer, B. *Eur. J. Pediatr.* **1985**, *144*, 403.
(173) Mennella, J. A.; Beauchamp, G. K. *J. Pediatr.* **1991**, *88*, 737.
(174) Singh, P. B.; Herbert, J.; Roser, B.; Arnott, L.; Tucker, K.; Brown, R. E. *J. Chem. Ecol.* **1990**, *16*, 1667.
(175) Novotny, M.; Schwende, F. J.; Wiesler, D.; Jorgenson, J. W.; Carmack, M. *Experientia* **1984**, *40*, 217.
(176) Wyatt, T. D. *Pheromones and animal behaviour: communication by smell and taste*; Cambridge University Press: Cambridge, U.K., 2003.
(177) Thomas, L. *Proceedings of the 4th International Convocation on Immunology*, Buffalo, NY; S. Karger: Basel, 1975; p 2.
(178) Penn, D. J.; Oberzaucher, E.; Grammer, K.; Fischer, G.; Soini, H. A.; Wiesler, D.; Novotny, M. V.; Dixon, S. J.; Xu, Y.; Brereton, R. G. *J. R. Soc. Interface* **2007**, *4*, 331.
(179) Ables, E. M.; Kay, L. M.; Mateo, J. M. *Physiol. Behav.* **2007**, *90*, 726.
(180) Osada, K.; Yamazaki, K.; Curran, M.; Bard, J.; Smith, B. P. C.; Beauchamp, G. K. *Proc. R. Soc. London, B* **2003**, *270*, 929.
(181) Singh, D.; Bronstad, P. M. *Proc. R. Soc. London, B* **2001**, *268*, 797.
(182) Havlicek, J.; Dvorakova, R.; Bartos, L.; Flegr, J. *Ethology* **2006**, *112*, 81.
(183) Ackerl, K.; Atzmueller, M.; Grammer, K. *Neuroendocrinol. Lett.* **2002**, *23*, 79.
(184) Phillips, M.; Herrera, J.; Krishnan, S.; Zain, M.; Greenberg, J.; Cataneo, R. N. *J. Chromatogr., B* **1999**, *729*, 75.
(185) McCulloch, M.; Jezierski, T.; Broffman, M.; Hubbard, A.; Turner, K.; Janecki, T. *Integr. Cancer Ther.* **2006**, *5*, 30.
(186) Hilbe, W.; Dirnhofer, S.; Greil, R.; Woll, E. *Eur. J. Cancer Prev.* **2004**, *13*, 425.
(187) Gordon, S. M.; Szidon, J. P.; Krotoszynski, B. K.; Gibbons, R. D.; O'Neill, H. J. *Clin. Chem.* **1985**, *31*, 1278.
(188) Phillips, M.; Gleeson, K.; Hughes, J. M. B.; Greenberg, J.; Cataneo, R. N.; Baker, L.; McVay, W. P. *Lancet* **1999**, *353*, 1930.
(189) Phillips, M.; Cataneo, R. N.; Cummin, A. R. C.; Gagliardi, A. J.; Gleeson, K.; Greenberg, J.; Maxfield, R. A.; Rom, W. N. *Chest* **2003**, *123*, 2115.
(190) Phillips, M.; Altorki, N.; Austin, J. H. M.; Cameron, R. B.; Cataneo, R. N.; Greenberg, J.; Rom, W. N.; Schmitt, P. *Cancer Biomarkers* **2007**, *3*, 95.
(191) Phillips, M. *Am. J. Respir. Crit. Care Med.* **2005**, *172*, 1060.
(192) Stetter, J. R.; Penrose, W. R. *Sens. Update* **2002**, *10*, 189.
(193) Cometto-Muniz, J. E.; Cain, W. S.; Abraham, M. H. *Exp. Brain Res.* **1998**, *118*, 180.
(194) Prescott, J.; Norris, L.; Kunst, M.; Kim, S. *Food Qual. Prefer.* **2005**, *16*, 345.
(195) Marti, M. P.; Boque, R.; Riu, M.; Busto, O.; Guasch, J. *Anal. Bioanal. Chem.* **2003**, *376*, 497.
(196) Marti, M. P.; Boque, R.; Busto, O.; Guasch, J. *TrAC, Trends Anal. Chem.* **2005**, *24*, 57.
(197) Santos, J. P.; Lozano, J.; Aleixandre, A.; Sayago, I.; Fernandez, M. J.; Ares, L.; Gutierrez, J.; Horrillo, M. C. *Sens. Actuators, B* **2004**, *103*, 98.
(198) Ragazzo-Sanchez, J. A.; Chalier, P.; Ghommidh, C. *Sens. Actuators, B* **2005**, *106*, 253.
(199) Marti, M. P.; Pino, J.; Boque, R.; Busto, O.; Guasch, J. *Anal. Bioanal. Chem.* **2005**, *382*, 440.
(200) Buser, H.-R. *J. Agric. Food Chem.* **1982**, *30*, 359.
(201) Rapp, A. *Nahrung* **1998**, *42*, 351.
(202) Dionne, B. C.; Rounbehler, D. P.; Achter, E. K.; Hobbs, J. R.; Fine, D. H. *J. Energ. Mater.* **1986**, *4*, 447.
(203) Baltussen, E.; Cramers, C. A.; Sandra, P. J. F. *Anal. Bioanal. Chem.* **2002**, *373*, 3.
(204) Namiesnik, J.; Zabiegala, B.; Kot-Wasik, A.; Partyka, M.; Wasik, A. *Anal. Bioanal. Chem.* **2005**, *381*, 279.
(205) Scorsone, E.; Pisanelli, A. M.; Persaud, K. C. *Sens. Actuators, B* **2006**, *116*, 55.
(206) Röck, F.; Gurlo, A.; Weimar, U. *Anal. Chem.* **2005**, *77*, 2762.
(207) Friant, S. L.; Suffet, I. H. *Anal. Chem.* **1979**, *51*, 2167.
(208) Landy, P.; Mielle, P.; Ray, J. L. *Proceedings of ISOEN*, Rome, Italy; Aracne: Rome, 2002; p 19.
(209) Seethapathy, S.; Gorecki, T.; Li, X. *J. Chromatogr., A*, in press.
(210) Batterman, S.; Metts, T.; Kalliokoski, P.; Barnett, E. *J. Environ. Monit.* **2002**, *4*, 361.
(211) Ouyang, G.; Pawliszyn, J. *TrAC, Trends Anal. Chem.* **2006**, *25*, 692.
(212) Schaller, E.; Zenhausern, S.; Zesiger, T.; Bosset, J. O.; Escher, F. *Analusis* **2000**, *28*, 743.
(213) Ampuero, S.; Bogdanov, S.; Bosset, J. O. *Eur. Food Res. Technol.* **2004**, *218*, 198.
(214) Bosset, J. O.; Pillonel, L.; Altieri, D.; Tabacchi, R. *Mitt. Lebensmittelunters. Hyg.* **2004**, *95*, 85.
(215) Garcia-Gonzalez, D. L.; Barie, N.; Rapp, M.; Aparicio, R. *J. Agric. Food Chem.* **2004**, *52*, 7475.
(216) Barie, N.; Bucking, M.; Rapp, M. *Sens. Actuators, B* **2006**, *114*, 482.
(217) Lozano, J.; Santos, J. P.; Gutierrez, J.; Horrillo, M. C. *IEEE Sens. J.* **2005**, 1339.
(218) Shirey, R. *TheReporter USA*; Supelco: Bellefonte, PA, 2004; Vol. 22.4.
(219) Paschke, A.; Popp, P. *J. Chromatogr., A* **2004**, *1025*, 11.
(220) Baltussen, E.; Sandra, P.; David, F.; Cramers, C. *J. Microcolumn Sep.* **1999**, *11*, 737.
(221) Vercammen, J.; Sandra, P.; Baltussen, E.; Sandra, T.; David, F. *HRC, J. High Resolut. Chromatogr.* **2000**, *23*, 547.
(222) Villanueva, S.; Vegas, A.; Fernandez-Escudero, J. A.; Iniguez, M.; Rodriguez-Mendez, M. L.; de Saja, J. A. *Sens. Actuators, B* **2006**, *120*, 278.
(223) Morris, L.; Caruana, D. J.; Williams, D. E. *Meas. Sci. Technol.* **2002**, *13*, 603.
(224) Strathmann, S.; Hahn, S.; Weimar, U. *Proceedings of ISOEN*, Washington, DC; The Electrochemical Society: Pennington, NJ, 2001; p 1087.
(225) Ali, Z.; James, D.; O'Hare, W. T.; Rowell, F. J.; Scott, S. M. *J. Therm. Anal. Calorim.* **2003**, *71*, 163.
(226) Schafer, T.; Vital, J.; Crespo, J. G. *J. Membr. Sci.* **2004**, *241*, 197.
(227) Pinheiro, C.; Schafer, T.; Crespo, J. G. *Anal. Chem.* **2005**, *77*, 4927.
(228) Schafer, T.; Serrano-Santos, M. B.; Rocchi, S.; Fuoco, R. *Anal. Bioanal. Chem.* **2006**, *384*, 860.
(229) http://www.crisp-dm.org/.
(230) Goodner, K. L.; Dreher, J. G.; Rouseff, R. L. *Sens. Actuators, B* **2001**, *80*, 261.
(231) Scott, S. M.; James, D.; Ali, Z. *Microchim. Acta* **2006**, *156*, 183.

(232) Ciosek, P.; Wroblewski, W. *Sens. Actuators, B* **2006**, *114*, 85.
(233) Wang, M.; Perera, A.; Gutierrez-Osuna, R. *IEEE Sens. J.* **2004**, *2*, 591.
(234) Raman, B.; Sun, P. A.; Gutierrez-Galvez, A.; Gutierrez-Osuna, R. *IEEE Trans. Neural Network* **2006**, *17*, 1015.
(235) Raman, B.; Yamanaka, T.; Gutierrez-Osuna, R. *Sens. Actuators, B* **2006**, *119*, 547.
(236) Skov, T.; Bro, R. *Sens. Actuators, B* **2005**, *106*, 719.
(237) Bro, R. *Crit. Rev. Anal. Chem.* **2006**, *36*, 279.
(238) Gutierrez-Galvez, A.; Gutierrez-Osuna, R. *Sens. Actuators, B* **2006**, *116*, 29.
(239) Gutierrez-Osuna, R.; Nagle, H. T.; Schiffman, S. S. *Sens. Actuators, B* **1999**, *61*, 170.
(240) Snopok, B. A.; Kruglenko, I. V. *Thin Solid Films* **2002**, *418*, 21.
(241) Zhang, W. M.; Hu, J. S.; Song, W. G.; Wan, L. J. *Sens. Actuators, B* **2007**, *123*, 454.
(242) Hiranaka, Y.; Abe, T.; Murata, H. *Sens. Actuators, B* **1992**, *9*, 177.
(243) Lee, A. P.; Reedy, B. J. *Sens. Actuators, B* **1999**, *60*, 35.
(244) Burresi, A.; Fort, A.; Rocchi, S.; Serrano, B.; Ulivieri, N.; Vignoli, V. *Sens. Actuators, B* **2005**, *106*, 40.
(245) Heilig, A.; Barsan, N.; Weimar, U.; Schweizer-Berberich, M.; Gardner, J. W.; Gopel, W. *Sens. Actuators, B* **1997**, *43*, 45.
(246) Mielle, P.; Souchaud, M.; Landy, P.; Guichard, E. *Sens. Actuators, B* **2006**, *116*, 161.
(247) Althainz, P.; Goschnick, J.; Ehrmann, S.; Ache, H. J. *Sens. Actuators, B* **1996**, *33*, 72.
(248) Goschnick, J. *Microelectron. Eng.* **2001**, *57*−*8*, 693.
(249) White, J.; Kauer, J. S.; Dickinson, T. A.; Walt, D. R. *Anal. Chem.* **1996**, *68*, 2191.
(250) Michael, K. L.; Taylor, L. C.; Schultz, S. L.; Walt, D. R. *Anal. Chem.* **1998**, *70*, 1242.
(251) Perera, A.; Yamanaka, T.; Gutierrez-Galvez, A.; Raman, B.; Gutierrez-Osuna, R. *Sens. Actuators, B* **2006**, *116*, 17.
(252) Pardo, M.; Sberveglieri, G. *Sens. Actuators, B* **2007**, *123*, 437.
(253) Gualdron, O.; Llobet, E.; Brezmes, J.; Vilanova, X.; Correig, X. *IEEE Sens. J.* **2004**, *2*, 892.
(254) Gualdron, O.; Llobet, E.; Brezmes, J.; Vilanova, X.; Correig, X. *Sens. Actuators, B* **2006**, *114*, 522.
(255) Llobet, E.; Gualdron, O.; Brezmes, J.; Vilanova, X.; Correig, X. *IEEE Sens. J.* **2005**.
(256) Llobet, E.; Gualdron, O.; Vinaixa, M.; El-Barbri, N.; Brezmes, J.; Vilanova, X.; Bouchikhi, B.; Gomez, R.; Carrasco, J. A.; Correig, X. *Chemom. Intell. Lab. Syst.* **2007**, *85*, 253.
(257) Gardner, J. W.; Boilot, P.; Hines, E. L. *Sens. Actuators, B* **2005**, *106*, 114.
(258) Ballabio, D.; Cosio, M. S.; Mannino, S.; Todeschini, R. *Anal. Chim. Acta* **2006**, *578*, 170.
(259) Ryan, M. A.; Zhou, H. Y.; Buehler, M. G.; Manatt, K. S.; Mowrey, V. S.; Jackson, S. R.; Kisor, A. K.; Shevade, A. V.; Homer, M. L. *IEEE Sens. J.* **2004**, *4*, 337.
(260) Shirokova, E.; Schmiedeberg, K.; Bedner, P.; Niessen, H.; Willecke, K.; Raguse, J. D.; Meyerhof, W.; Krautwurst, D. *J. Biol. Chem.* **2005**, *280*, 11807.
(261) Vidic, J. M.; Grosclaude, J.; Persuy, M. A.; Aioun, J.; Salesse, R.; Pajot-Augy, E. *Lab Chip* **2006**, *6*, 1026.
(262) Liu, Q. J.; Cai, H.; Xu, Y.; Li, Y.; Li, R.; Wang, P. *Biosens. Bioelectron.* **2006**, *22*, 318.
(263) Schoning, M. J.; Poghossian, A. *Electroanalysis* **2006**, *18*, 1893.

CR068121Q