15

Future Applications of Electronic-Nose Technologies in Healthcare and Biomedicine

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1. Introduction

The development and utilization of many new electronic-nose (e-nose) applications in the healthcare and biomedical fields have continued to rapidly accelerate over the past 20 years. Innovative e-nose technologies are providing unique solutions to a diversity of complex problems in biomedicine that are now coming to fruition. A wide range of electronic-nose instrument types, based on different operating principles and mechanisms, has facilitated the creation of different types and categories of medical applications that take advantage of the unique strengths and advantages of specific sensor types and sensor arrays of different individual instruments. Electronic-nose applications have been developed for a wide range of healthcare sectors including diagnostics, immunology, pathology, patient recovery, pharmacology, physical therapy, physiology, preventative medicine, remote healthcare, and wound and graft healing. E-nose biomedical applications range from biochemical testing, blood compatibility, disease diagnoses, drug purity, monitoring metabolic levels, organ dysfunction, and telemedicine. This review summarizes some of the key technological developments of electronic-nose technologies, arising from past and recent biomedical research, and identifies a variety of future e-nose applications currently under development which have great potential to advance the effectiveness and efficiency of biomedical treatments and healthcare services for many years. A concise synthesis of the major electronic-nose technologies developed for healthcare and medical applications since the 1980s is provided along with a detailed assessment and analysis of future potential advances in electronic aroma detection (EAD) technologies that will provide effective solutions to newly-emerging problems in the healthcare industry. These new e-nose solutions will provide greatly improved quality controls for healthcare decisions and diagnoses as well as badly needed final confirmations of appropriate patient treatments. The purpose of this chapter is to provide some detailed insights into current and future e-nose applications that will yield a variety of new solutions to detection-related tasks and difficult problems in the fields of healthcare and biomedicine. The uses of electronic-noses for quality control (QC) and quality assurance (QA) issues, associated with numerous diagnostic-testing activities conducted within the medical field, also are discussed.

2. History of Electronic-nose developments for biomedical applications

Use of the olfactory sense (of smell) as an indicator of disease probably originated with Hippocrates around 400 BC. Observations that unusual human odors or aromas provided

some indication of human ailments caused early medical practitioners to recognize that the presence of human diseases changed the odor of bodily excretions that could be used to diagnose certain common diseases.

2.1 Early use of aroma-detection in evaluating health conditions

Medical doctors have utilized the sense of smell to facilitate determinations of the physical state and general health of their patients for centuries. The application of smell as useful sensory clues used by physicians to identify the causes of human ailments resulted in the development of qualitatively descriptive odors (or aromas) and specialized terms used to describe and identify odors associated with specific human diseases and physiological disorders. Some descriptive aromas found to be associated with some common human diseases are presented in Table 1. The use of olfactory information provided valuable additional information for physicians in assessing patient conditions and formulating accurate diagnoses before modern analytical equipment and chemical-detection devices became available for this purpose. Notice that in some cases the same term, such as "amine-like" for bacterial vaginosis and bladder infections, occasionally was used to describe common

Disease / Disorder	Body source	Descriptive aroma	References
Anaerobic infection	Skin, sweat	Rotten apples	Pavlou & Turner, 2000
Bacterial vaginosis	Vaginal fluid	Amine-like	Pavlou & Turner, 2000
Bladder infection	Urine	Amine-like	Pavlou & Turner, 2000
Congestive heart failure	Heart	Dimethyl sulfide	Smith, 1982
Fetor hepaticus	Breath	Newly-mown clover	Hayden, 1980
Gout	Skin	Gouty odor	Liddell, 1976
Hyperaminoaciduria	Infant skin	Dried malt or hops	Liddell, 1976
Hypermethioninemia	Infant breath	Sweet, fruity, fishy	Liddell, 1976; Hayden, 1980
Isovaleric acidemia	Skin, breath	Sweaty, cheesy	Hayden, 1980; Pavlou & Turner, 2000
Ketoacidosis	Breath	Acetone-like	Hayden, 1980
Liver failure	Breath	Musty fish, feculent	Hayden, 1980; Smith, 1982
Maple syrup disease	Sweat, urine	Maple syrup	Liddell, 1976; Pavlou & Turner, 2000
Pseudomonas infection	Skin, sweat	Grape	Pavlou & Turner, 2000
Scrofula	Body	Stale beer	Liddell, 1976
Smallpox	Skin	Pox stench	Liddell, 1976
Trimethylaminuria	Skin, urine	Fishy	Pavlou & Turner, 2000
Typhoid	Skin	Freshly-baked bread	Liddell, 1976; Hayden, 1980
Uremia	Breath	Fishy, ammonia	Hayden, 1980
Yellow fever	Skin	Butcher's shop	Liddell, 1976; Hayden, 1980

Table 1. Descriptive aromas previously used for diagnosing human diseases

odors associated with completely different diseases. This occurred because different diseases can result in the production of very similar compounds even though the mechanism of disease is quite different. In other cases such as for use of the term "fishy" for hypermethioninemia and uremia, both of these diseases cause the buildup of similar or identical compounds in the blood due to similar physiological processes that are often referred to as in-born genetic or metabolic diseases resulting from the absence of certain enzymes or the failure of certain organs. Many other metabolic diseases caused by genetic enzyme deficiencies are associated with various distinctive odors due to the accumulation of undecomposed metabolites in the body.

Some descriptive aromas, such as maple syrup and pox stench, are so diagnostic that the aroma was named after the specific disease referred to by name. Other diagnostic terms for descriptive aromas include fetor hepaticus, diabetic breath, and uremic breath which have been included in common medical vocabulary and continue to be used to some extent even in contemporary vernacular. Once modern analytical instrumentation became available in the twentieth century, the actual volatile compounds responsible for these characteristic smells began to be identified. Probably the first such identification was done by Linus Pauling, the noted chemist who was able to freeze out and identify some of the volatiles in urine using cold traps, followed by gas chromatography (Pauling et al., 1971). Many other discoveries of VOCs associated with specific human smells related to particular diseases followed in subsequent years leading up to the identification of diagnostic bioindicators of disease. These compounds are highly correlated with the presence of specific diseases in the body as discussed in the following section.

2.2 Discovery of bioindicators of disease

The discovery and recognition of particular volatile organic compounds (VOCs), released from various diseased human body parts or fluids derived from these tissues, have been found to be associated with specific human diseases through the use of specialized modern analytical instruments. These instruments have included such analytical machines as gas chromatographs working in tandem with mass spectrometers (GC-MS) and other such technical instruments used in analytical chemistry. The results of intense chemical analyses from numerous research studies have been the identification of many volatile biomarkers of disease and their associated chemical structures. The identification of unique molecular markers (volatile metabolites) associated with particular diseases has become an extremely effective and powerful tool for the early detection of diseased tissues and infectious agents in the human body. For example, the analysis of patients' breath odors has had a long history of application for the detection of various human diseases, not only respiratory diseases. Even though the human breath contains hundreds of volatile organic compounds at low concentrations, relatively few (less than fifty) of these are detected in the majority of healthy humans under normal physiological conditions (Phillips et al., 1999a). However, a much smaller number of aberrant VOCs are often found only in patients when disease is present somewhere in their bodies. Thus, the association of specific volatile metabolites, released within the expired human breath of patients, not only provides indicators of particular diseases, but also reflect the overall physiological state as an indication of general health and a useful index of disease (Jacoby, 2004). These volatile markers of disease often are released several hours to several days before outwardly-noticeable physical symptoms of illness appear and thus provide early indicators of disease or physiological disorders. New molecular markers that are indicators of specific diseases, both infectious and

noninfectious, are being increasingly revealed by new scientific research. Some examples of these volatile molecular biomarkers (or bioindicators) of disease and physiological disorders, reported hitherto by various researchers, are summarized in Table 2.

Disease / Disorder	Volatile chemical biomarkers	References
Allograft rejection	Carbonyl sulfide	Studer et al., 2001
Breast cancer	C4-C20 alkanes	Phillips et al., 2003b
Cholera	p-menth-1-en-8-ol, dimethyl disulphide	Garner et al., 2009
Chronic hepatitis	Methyl-mercaptan, dimethyl sulfide	Kaji et al., 1978
Cirrhosis	Dimethyl sulfide, mercaptans	Chen et al., 1970
Cystic fibrosis	Leukotriene B4, interleukin-6, carbonyl sulfide, alkanes	Carpagnano et al., 2003; Phillips et al., 2004
Diabetes	Acetone, ethanol, methyl nitrate	Rooth & Ostenson, 1966; Crofford et al., 1997; Ping et al. 1997; Novak et al., 2007
Halitosis	Methanethiol, Hydrogen sulfide, methyl mercaptan, dimethyl sulfide	Kaizu, 1976; Van den Velde et al., 2009
Hepatic encephalopathy	3-methylbutanal	Goldberg, 1981
Histidinemia	2-imidazolepyruvic acid, 2-imidazolelactic acid, 2-imidazoleacetic acid	Bondy & Rosenberg, 1980
Liver cancer	Hexanal, 1-octen-3-ol, octane	Xue et al., 2008
Lung cancer	Alkanes, ketones, specific aromatic hydrocarbons (benzene derivatives)	Manolis, 1983; Gordon et al., 1985; Preti et al., 1988; Phillips et al., 1999b, 2003a
Maple syrup disease	2-oxoisocaproic acid	Bondy & Rosenberg, 1980
Necrotizing enterocolitis	2-Ethyl-1-hexanol	De Lacy Costello et al., 2008
Oxidative stress	8-isoprostane	Montuschi et al., 1999
Periodontal disease	Pyridine, picolines	Kostelc et al., 1981
Phenylketonuria	Phenylpyruvic acid, phenyllactic acid, phenylacetic acid	Bondy & Rosenberg, 1980
Schizophrenia	Pentane, carbon disulfide	Smith & Sines, 1960; Smith et al., 1969; Phillips et al., 1993
Tyrosinemia	p-hydroxyphenylpyruvic acid	Bondy & Rosenberg, 1980
Trimethylaminuria	Trimethylamine	Pavlou & Turner, 2000
Uremia	Dimethylamine, trimethylamine	Simenhoff et al., 1977

Table 2. Molecular biomarker VOCs of specific human diseases and disorders

Analysis of expired human breath is considered particularly valuable because it can be monitored noninvasively (without causing physical damage to patients), yet provide information about the chemical and physiological state of the entire body. The reason that information about the physical health of the entire body is possible by the analysis of expired breath is because most volatile metabolites of infectious agents of disease, or those produced from abnormal tissues, are eventually eliminated from the body through the lungs, often soon after being formed within diseased tissues. Alternatively, other less volatile abnormal metabolites are eliminated through the urine which may be similarly analyzed using aroma-sensing instruments such as electronic noses.

Cao and Duan (2006) summarized some of the advantages and disadvantages of breath analysis for clinical practice and diagnosis. They found breath tests were noninvasive, easily repeated, and caused less discomfort and embarrassment to patients than blood and urine tests. Breath samples closely reflected arterial concentrations and provided much less complicated mixtures than serum or urine analyses and more direct information on respiratory function than by other means. They listed limitations of breath testing for clinical practice to include the lack of standardization of analytical methods, the high water content of breath samples affecting detection, relatively expensive costs compared to simple chemical tests (but much less time-consuming for results), and the lack of well-established links between breath VOCs and certain kinds of diseases. Biomarkers in chronic obstructive pulmonary disease (COPD) also may be useful in aiding diagnosis, monitoring exacerbations, evaluating effects of drugs, and defining specific phenotypes of disease (Borrill et al., 2008).

Frey & Suki (2008) found risk assessments, disease progression, and control of asthma and COPD required multidimensional fluctuation analysis of the dynamics of lung-function parameters that needed to be quantified and monitoring via precise biomarkers of these diseases using instruments capable of direct, electronic monitoring of these biomarkers.

The importance of the use of biomarkers for the detection of disease has become so prominent that Bentham Science, a leading international publisher of high quality scientific journals, decided to launch a new journal called *Recent Patents on Biomarkers* in January 2011 to publish reviews and research articles written by experts on recent patents and research relating to biomarkers in basic and applied, medical, environmental, and pharmaceutical research, and including patent biomarker applications, clinical development, and molecular diagnostics.

3. Current e-nose technologies utilized in healthcare and biomedicine

Electronic-noses are ideal instruments for biomedical uses because of their versatility, low-cost, rapid output of results, capabilities of continuous operation (for physiological-monitoring purposes), and the wide range of VOCs and other cellular chemical constituents that may be analyzed. The potential for miniaturization of electronic-nose devices also is great due to their microcircuitry and microsensor components. Some key ways in which e-noses have been particularly useful in various sectors of the healthcare industry are discussed in the following sections.

3.1 Electronic-nose technology types and applications

A variety of different types of e-noses, based on different working principles, have been used for biomedical tasks including conductive polymers (CP), metal-oxide semiconductor (MOS), quartz crystal microbalance (QCM), and surface acoustic waves (SAW) among

others. Each e-nose technology has different advantages, disadvantages, and limitations that largely determine what types of medical applications that individual e-nose sensor types are best suited for in practical clinical settings.

3.2 Point-of-care medicine

Point-of-care testing (POCT) may be defined as diagnostic testing at or near the site of patient care (Kost, 2002). The objective of POCT is to bring the test conveniently and immediately to the patient. The POCT approach to diagnostic testing increases the likelihood that the patient will receive the results and treatment in a timely manner. POCT is accomplished through the use of transportable, portable, and handheld instruments and test kits. The use of cheaper, smaller, faster, and smarter POCT devices, such as e-noses, has increased the use of POCT approaches by making diagnostic tests more cost-effective for many diseases.

3.3 Working e-nose applications in current medical practice

E-noses in general have the advantages of providing patient laboratory results much faster than standard cultures or wet chemistry tests and the capability of providing early detections of diseases before symptoms appear. These characteristics have been compelling reasons for the development of e-nose systems for clinical medicine. Some recent uses of electronic noses in hospitals and universities around the world are presented in Table 3.

The development of new e-nose applications for POC treatments will no doubt continue to increase as the breadth of existing e-nose systems is expanded with new capabilities and practical e-nose uses are discovered and implemented through more extensive empirical testing. This work will require extensive trials in hospitals and clinics as well as in the field (for portable units) to determine the range of multiple tasks that individual e-nose systems can perform for various types of detection and diagnostic testing needs. The cooperation of many levels of healthcare professions working in cooperation with e-nose manufacturers, clinical technicians and medical research scientists will be required to accomplish these tasks. This effort is quite a challenge in many situations because of the limited time available to physicians for testing new experimental equipment.

3.3.1 Health monitoring

Continuous monitoring of the physiological states of patients is essential to determine the current physiological condition of patients and whether treatment and recovery is progressing favorably. For example, the continuous monitoring of serum glucose levels, particularly with the aid of sophisticated algorithms, provides a means of generating alerts when glucose concentration exceeds the normal high and low threshold ranges (Sparacino et al., 2010). Monitoring exhaled VOC biomarkers of endogenous metabolic processes using electronic noses is an ideal means of detecting altered metabolic pathways resulting from diseases such as diabetes. The use of e-nose sensors for continuous glucose monitoring requires accurate calibration, filtering of data to enhance the signal-to-noise ratio, and effective predictions of future glucose concentration in order to generate alerts with minimal risk of causing false alarms or missing entirely the occurrence of life-risking events. Electronic-nose devices also might be used to facilitate the study of transcriptional gene regulation of glucose sensors in pancreatic β-cells and liver by monitoring changes in breath volatiles (primarily ethanol, acetone, and methyl nitrate) associated with hyperglycemia in type 2 diabetes patients (Bae et al., 2010; Lee et al., 2009).

Country	Hospital, University or Research Facility	E-nose utilized	Application	References
USA	University of Pennsylvania	Experimental model	Distinguish cerebrospinal fluid	Thaler et al., 2000
USA	Merck Research Laboratories	Fox 4000	Flavor analysis for drug formulation	Zhu et al., 2004
United Kingdom	Birmingham Heartlands Hospital	Cyranose 320	Identify *Staphalococcus*	Dutta et al., 2005
Germany	University of Applied Sciences	DE 101	Detect renal dysfunction	Voss et al., 2005
USA	Cleveland Clinic	unspecified	Diagnose lung cancer	Erzurum et al., 2005
Belgium	University of Antwerp	PEN 2	Clinical diagnoses of bacteria	Moens et al., 2006
United Kingdom	South Manchester University Hospital	experimental model	Burn and wound infection types	Persaud, 2006
USA	University of Pennsylvania	unspecified	Diagnosis of diseases via breath	Anthes, 2008
USA	California Institute of Technology	JPL ENose	Detect & differentiate brain cancers	Kateb et al., 2009
Australia	Prince Charles Hospital	unspecified	Detect chronic lung disease	Dent, 2010
Netherlands	Amsterdam Academic Medical Center	Cyranose 320	Discriminate inflammation airway diseases	Lazar et al., 2010
Italy	Catholic University	experimental model	Asthma detection	Montuschi, 2010
Tanzania	National Institute of Medical Research	Bloodhound EN	Diagnosis of Tuberculosis	Kolk et al., 2010
United Kingdom	Gloucestershire Royal Hospital	NST 3320	Diagnosis of ventilator-associated pneumonia	Humphreys et al., 2011

Table 3. Electronic-nose uses in hospitals and universities around the world

Monitoring inorganic anions and cations in the body are equally important for maintaining proper electrolyte levels and water balance in tissues. Thus, routine clinical assays of electrolyte levels (such as chloride, sodium, and potassium) in biological samples like serum, blood, plasma, and urine provide useful information about the proper functioning of organ systems and regulatory hormones of patients receiving treatments. Assessing urinary chloride concentration helps in the diagnostic evaluation of metabolic alkalosis and other physiological conditions caused by improper osmotic pressure, water imbalances within extracellular spaces, and acid-base imbalance. The Microcontroller P89C668 is an instrument that measures urinary chloride concentration to determine body electrolyte levels based on a mercuric thiocyanate colorimetric principle (Vasumathi & Neelamegam, 2010). This instrument works by measuring color intensity of a colored complex formed between chloride ions and mercuric thiocyanate which is proportional to the chloride concentration in the sample. Colorimetric e-noses operate similarly by measuring changes in absorbance caused by color changes resulting from interactions of the target analyte with an organic dye.

3.3.2 Infection and disease detection

Electronic-nose systems probably were first tested for disease detection in the biomedical field through the discrimination of pathogenic microbes in pure cultures (Gardner et al., 1998). Microbial identification is an integral part of infectious disease diagnosis and the subsequent determination of proper treatments as a consequence of the wide range of disease mechanisms associated with pathogenesis generated by various microbial agents. Dutta et al. (2002) used a portable Cyranose 320 e-nose, consisting of 32 polymer carbon black composite sensors, to identify six bacterial species responsible for eye infections. The bacteria were cultured at various concentrations in a saline solution and the VOCs from the headspace were analyzed using linear PCA and other data-clustering algorithms. The Self Organizing Map (SOM) network provided an accuracy of 96% for bacterial classification, but the Radial basis function network (RBF) allowed identifications with up to 98% accuracy. Most laboratory-grade instruments such as the Cyranose 320 are now being replaced with simpler and cheaper e-noses that are easier to use by trained clinical technicians. Many new types of experimental e-noses, based on different operating principles, currently are being tested for numerous healthcare applications.

Microbial biosensors are being employed increasingly to detect human diseases. These sensors, like e-noses, consist of a transducer that converts biochemical signals into a quantifiable electronic response, but instead of utilizing electronic sensors, the transducer is used in conjunction with either viable or unviable microbial cells. A variety of different transducers may be used such as acoustic, electrochemical, electric, or optical types. D'Souza (2001) did an early review of applications of microbial biosensors and gave some advantages and limitations of various types. Biosensors will be discussed in greater detail in section 4.2.1.

3.3.3 Detecting exposure to toxins and hazardous chemicals

Food safety and exposure to toxic substances in the environment has become of greater concern to man in the world today as a result of the acceleration and increasing frequency of bioterrorism and the growing susceptibility of world crops to toxic sprays and disease due to the planting of crop monocultures and the application of agricultural chemicals from the

air. Toxic volatile solvents also are found in the air within certain areas of hospitals despite the filtering of air. All of these opportunities for incidental human exposures to toxic substances necessitate the monitoring of food supplies and ambient air to assure that levels of harmful substances are below damaging levels. The occurrence of various toxins in food is potentially very harmful to human health. Sensor technologies such as electronic noses have been recognized as possible useful tools for determinations of the geographical origin of food products, now quite important for the identification of food lots that have become contaminated by toxins or other harmful substances in order to remove these specific food sources from grocery shelves (Luykx & van Ruth, 2008). Other examples include the occurrence of mycotoxins, toxic secondary metabolites (e.g. aflatoxin and ochratoxin A) produced by fungi such as *Aspergillus* and *Fusarium* species that commonly grow on agricultural products in the field or in storage (Huang et al., 2006). Cheli et al. (2009) very effectively utilized the PEN2 e-nose with principal component analysis (PCA) to detect the presence of aflatoxin in maize samples at a high level of confidence. This method was potentially useful for screening maize food lots for aflatoxin contamination prior to marketing.

Mujahid et al. (2010) used cholesteric liquid crystals (CLCs) as sensitive coatings on acoustic devices such as QCM e-noses for the detection of organic solvent vapors of both polar and non-polar compounds by the frequency shift of analyte samples. They were able to gain mechanical stability by combining CLCs with imprinted polymers. This e-nose application would be useful for detection of pharmaceutical preparations requiring solvent extraction or delivery, and for detection of potential patient exposures to hazardous chemical solvents in the hospital environment.

3.4 Quality control

There are many potential uses for e-nose instruments in quality control (QC) applications in medicine. These machines can be used to quickly double check diagnoses to help assure that patients are receiving the correct and precise treatments prescribed by physicians. Another possible related application is the e-nose evaluation of food quality and control measures to assure that food contaminants and toxins, that can adversely affect food safety and human health, are not present. Improved QC has been accomplished through use of specialized algorithms that increase analyte discriminations and confirm the results.

3.4.1 Electronic-nose algorithms

The efficiency with which electronic-nose systems are able to identify and discriminate VOCs associated with analyte mixtures largely depends on the effectiveness of discriminating algorithms used during headspace analysis. Pattern-recognition algorithms are heavily used for integrating signal outputs of sensor arrays and comparing such outputs to patterns of known analyte standards held in recognition reference libraries. This discrimination process is very similar to those used in GC-MS analyses that use reference libraries. New gas-recognition algorithms have provided a means of improving the effectiveness, robustness, and accuracy of gas detection and identification for the medical industry.

Flitti et al. (2008) developed a gas-recognition algorithm for an on-chip Complementary Metal-Oxide Semiconductor (CMOS) tin-oxide (SnO_2) gas sensor array that operates at high temperature (typically 300°C) with the advantages of cost effectiveness and high sensitivity

to various gases, but the disadvantages of low selectivity, high sensitivity to humidity, nonlinearities of sensor-response, and drift in signal output. Many pattern-recognition algorithms have attempted to correct for low selectivity of sensors, yet most do not address the problem of drift which was largely corrected according to experimental results in this study, indicating that more than 98% correct recognition was obtained using this robust method. Polat and Güneş (2006) proposed a decision-tree classifier system using fuzzy weighted preprocessing methods for the diagnosis of erythemato-squamous diseases. They used twelve clinical-evaluation criteria and twenty-two histopathological features in the diagnostic analysis. Similar fuzzy-reasoning methods have been used in e-nose algorithms to discriminate sensor-array patterns produced from headspace volatiles. Thus, many different types of diagnostic information may be used in these decision-tree classifiers. Seising (2006) created a similar model using fuzzy reasoning to address the phenomenon of vagueness in a physician's style of thinking concerning reasoning used to make clinical diagnoses.

3.4.2 Drug development, purity, and delivery

Spin-offs of electronic-nose technologies similar to conductive polymer (CP) e-noses, but with single sensors instead of an array, are being developed to work in aqueous solutions for the detection of drugs and other chemicals used in pharmaceutical preparations. Manganese (III) porphyrins are particularly useful for the construction of polymeric membranes. Vlascici et al. (2010) developed ion-selective electrode sensors composed of two types of manganese (III) porphorins, high molecular weight polyvinyl chloride (PVC) and sol-gel, for the determination of diclofenac in pharmaceutical preparations by direct potentiometry. Diclofenac is a nonsteroidal drug used in the treatment of ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis due to its antipyretic, anti-inflammatory and analgesic properties. Their best results were obtained with PVC membrane plasticized with dioctylphtalate and incorporated with sodium tetraphenylborate as a lipophilic anionic additive. Electrode response to diclofenac was linear in the concentration range of 3×10^{-6} to 1×10^{-2} M and in good agreement with a High Pressure Liquid Chromagraphy (HPLC) reference method.

Continuous glucose monitoring systems (CGM) may soon offer the possibility of continuous dynamic assessment and control of daily fluctuations in blood glucose concentration for diabetes treatment. The emergence of a new generation of open-loop and closed-loop subcutaneous insulin-infusion devices that are controlled by continuous glucose-monitoring sensors will soon make glycemic control and insulin treatment more reliable (Torres et al., 2010). New smart machines are on the horizon to simplify diurnal treatments, allowing diabetics to be less attentive to their daily insulin needs.

4. Future potential medical applications of electronic noses

The potential applications of electronic-nose devices in the healthcare and biomedical industries will continue to expand with greater research and in-hospital testing as new ways of using these chemical-detection machines are discovered, and the breadth of capabilities widened, particularly in the area of coordinated uses in combination with other medical devices. The combined uses of e-noses with other electronic medical instruments will facilitate the development and availability of improved real-time information of patient conditions, leading to even more effective decisions and treatments by physicians in

hospitals and POCT clinics. The future potential of combining the capabilities of e-nose devices with other types of detection technologies are examined here in light of new technological discoveries in chemical sensor-detection that are currently emerging.

4.1 Emerging e-nose biomedical developments

Electronic noses have even greater potential synergistic capabilities when used cooperatively in combination with many other electronic medical devices. The potential advantages of combining their use are enormous considering the possible permutations of combinations in which these analytical devices may be combined for cooperative tasks. Sometimes these advantages are so useful that e-noses are often combined with other technologies to produce compound e-nose instruments. Both theoretical and practical aspects of these conceptual instrument mergers are discussed in greater detail in section 4.3.

4.2 E-nose uses in cooperative combination with other electronic devices

Synergistic applications of e-nose technologies, used in combination with other medical devices, are receiving increasing attention in the healthcare industry because these instrument-combinations are viewed as ways of achieving greater cooperative effectiveness in improving clinical services to patients. Complimentary information obtained in this way leads to better diagnoses and prognoses. The ultimate results of synergistic uses of instrument combinations are better, more detailed and quality information for medical decisions and thus more effective treatments leading to faster patient recoveries.

One key area where electronic noses are effectively used in combination with other medical instruments is in the application of e-nose information on various physiological conditions of patients toward more effective treatments for particular ailments. E-nose information may be used to confirm the physiological states or functions in patients that are identified in pre-scanning and preliminary assessments of patient conditions during initial examinations. Medical infrared thermography (MIT) is a non-invasive, non-radiating thermal imaging method used to analyze physiological functions based on localized thermal abnormalities characterized by increases or decreases in skin temperature. MIT involves detection of infrared radiation usually related to variations in blood flow that affect skin temperature. Reduced muscular activity or degeneration leads to dermal hyperthermia whereas inflammation causes a hyperthermic pattern. Use of a MIT detection tool has been particularly useful in sports medicine for pre-screening athletes for injuries or muscular inflammation and degeneration (Hildebrandt et al., 2010). E-noses also might be used in combination with wearable motion-sensing sensor technologies for confirming physiological activities after monitoring mobility-related activities in individuals with chronic disease conditions (Allet et al., 2010). Electronic-noses could be used in combination with drug-delivery devices to monitor physiological responses and provide feedback to these devices during or following the administration of drugs. The feedback would then adjust the rate of drug-delivery to ease physiological stress of adverse reactions and thus regulate release rates of drug payloads and resorption rates (Anglin et al., 2008). Similar systems are possible using fiber-optic sensors such as the Sencil system for continuous monitoring of glucose (Liao et al., 2010). Other potential applications include uses in combination with associated cerebrospinal fluid (CSF) tests for analysis and monitoring of specific CSF constituents associated with specific diseases (Di Terlizzi & Platt, 2009), and in combination with the Liver Disease Quality of Life (LDQOL) instrument for liver transplantation evaluation in ambulatory adults with advance, chronic lung disease (Gralnek, 2000).

4.2.1 Biosensors

Biosensors are analytical devices that combine a biological-sensing element with a chemical or physical transducer to quantitatively and selectively detect the presence of specific compounds in a given external environment (Vo-Dinh and Cullum, 2000). Chaubey and Malhotra (2002) summarized the commercialization and applications of four different types of mediated biosensors based on the type of transducer used to convert the physico-chemical change in the selected biologically-active material, resulting from interactions with the analyte to produce the output signal. Biosensor technologies previously have been divided into optical, calorimetric, piezoelectric, and electrochemical biosensors. Optical sensors as based on the measurement of light absorbed or emitted from a biochemical reaction and guided with optical fibers into the sensor. Calorimetric biosensors detect the analyte by the heat released from the biochemical reaction of the analyte with a suitable enzyme. Piezoelectric biosensors operate by generating electrical dipoles through the subjection of anisotropic natural crystals to mechanical stress. The adsorption of an analyte to the sensing crystal increases the mass of the crystal which alters its frequency of oscillation that is recorded in the instrument output. QMB e-nose sensors essentially operate by this same principle. Electrochemical (EC) biosensors measure the generation or consumption of electrons during a bio-interaction process. EC biosensors are the most commonly used class of biosensors and are further subdivided into amperometric, conductometric, and potentiometric sensor types depending on the electrochemical property to be measured by the detector system. Specific EC biosensors such as the Ion selective electrodes (ISE), ion selective field effect transistors (ISFET), and pH electrodes usually measure the oxidation of specific substrates to produce an oxidized product. Two mediated biosensors were previously commercialized early on in biosensor development, including the lactate analyzer (LA 640) in 1976 and a glucose analyzer in 1987. The LAPS (light addressable potentiometric sensor) optical biosensor was commercialized in 1993.

New types of biosensor technologies have been tested and developed recently. For example, Thanyani et al. (2008) examined an affinity biosensor technology to detect antibodies to mycolic acid in tuberculosis patients. Mycolic acids are useful detection targets for tuberculosis because each *Mycobacterium* species produces unique types of mycolic acids in chemical structure and in association with specific liposomes. Komaitis et al. (2010) developed a fully-automated flow-injection bioluminescent biosensor for the assessment of water toxicity, particularly heavy metal toxicity. Kumar & Kumar (2008) analyzed a DNA biosensor for selective detection of target genes responsible for diseases using DNA hybridization with a specific probe. PCR-free DNA biochips are emerging new tools in the field of diagnosis because of the greater advantages of electrochemical biosensors due to the electrochemical behavior of labels associated with hybridization.

There are several notable recent reviews on the development of biosensor applications within the biomedical field. Yoo & Lee (2010) recently reviewed the present status and use of glucose biosensors in the management of diabetes in clinical practice. Dzyadevych et al. (2008) discussed the advantages and disadvantages of amperometric enzyme biosensors for medical diagnostics and other potential healthcare applications. Gomila et al. (2006) described some advances in the development of methods and techniques for the production, mobilization, electrical characterization, and development of olfactory nanobiosensors.

Implantable short-term and long-term biosensors offer utility for a plethora of clinical applications, particularly in the areas of point-of-care medicine, intensive care, and surgery (Guiseppi-Elie, 2010). Biosensors provide invaluable real-time data on the metabolic and

physiological status of patients that are required by clinicians and physicians to make medically-important, informed decisions that impact the short- and long-term outcome of patients. These devices potentially could save countless lives in the emergency room or in triage on the battle field where patient mortality is high due to trama-induced hemorrhaging and rapid decisions concerning patient status are essential to provide immediate care to individuals based on their current condition.

4.2.2 BioMEMS and MIP sensors

Biological Micro-Electro-Mechanical Systems (BioMEMS), also known as BioChips, are micro- or nano-scale devices that detect biochemical entities by either mechanical, electrical, or optical means. Mechanical BioMEMS use cantilever sensors on a chip that operate in either stress-sensing or mass-sensing mode. In stress-mode sensing, biochemical reactions cause changes in surface free energy resulting in stress and bending of the cantilever. In mass-mode sensing, the cantilever is excited mechanically so that it vibrates as a certain resonant frequency. A change in mass due to adsorption of chemical species on the sensor is detected by shifts in the resonant frequency. BioMEMS have a wide variety of important biomedical applications including the processing, delivery, manipulation, analysis, and construction of biological and chemical entities (Bashir, 2004). Some important major areas of research and applications range from diagnostic detections (e.g. DNA and protein micro-assays), micro-fluidics, and tissue engineering to surface modification, drug preparation and delivery, cell lysing, mixing, separation, implantable monitoring and sensing. Diagnostics probably represents the largest segment of applications because a very large number of BioMEM devices have been developed for diagnostic applications. Diagnostic detections of pathogenic viruses, bacteria, and fungi as well as small molecular components produced by these microbes may be detected. The advantages of using micro- and nano-scale detection technologies are greater portability through miniaturization, higher sensitivity, reduced reagent volumes with lower associated costs, and perhaps most useful is reduced time to results due to smaller volumes and higher effective concentrations (Bashir, 2004). Aponte et al. (2006) summarized the potential uses of BioMEMS devises to detect the presence of molecular markers in body fluids as indicators of immune system responses. The reviewed research focused on candidate biomarkers that could be useful for in-flight monitoring of astronaut immune status using MEMS and Nano-Electro-Mechanical System (NEMS) devices. They found cytokine levels were significantly affected by space flight conditions. Cytokines are chemical messengers directly related to immune responses and various diseases. They are classified as chemokines, colony-stimulating factors, growth factors, interleukins, interferons, lymphokines, stress proteins, and tumor necrosis factors (Stvrtinova et al., 1995).

Molecular Imprinted Polymer (MIP) microsensors utilize polymeric materials for the recognition of particular chemical substances that are complementary to a specific receptor cavity. MIP materials usually consist of a copolymerized monomer matrix cross-linked to a template molecule that creates a receptor cavity complimentary to the template molecule when the template is removed from the polymer matrix (Tokonami et al., 2009). These nanostructured MIP objects may be used to develop micro-and nano-sized sensors or sensor arrays for chemical sensing and detection. The small size of MIP materials provides the advantages of faster equilibrium with the analyte, increased number of accessible complementary cavities per material weight, and enhanced catalytic activity of the sensor surface. Large-scale sensor array systems utilizing MIP sensors are capable of handling large

sample throughput as high density detection for primarily biochemically-related substances such as enzymes, antibodies, and DNA (Tokonami et al., 2009).

4.2.3 Electroconductive hydrogels

Electroconductive hydrogels (ECH) are composite biomaterials made of polymeric blends that combine conductive electroactive polymers (CEPs) with highly hydrated hydrogels. They bring together the redox-switching and electrical properties of conductive electroactive polymers (CEPs) with the small-molecule transport and compatibility of cross-linked hyrogels (Guiseppi-Elie, 2010). CEPs are incorporated into biosensors for the detection of chemical species (e.g., antigens, drug metabolites, enzyme substrates, neurotransmitters, and ssDNA fragments) of medical importance. Biosensors based on CEPs operate either with electrochemical, gravimetric, or optical detectors. They are used for measurements of constituents in low-volume samples with continuous-flow systems and fast response times, high sensitivities, and detection limits in the ΦM range for enzyme substrates, and even lower detection ranges for DNA fragments. CEPs do have some serious limitations including slow switching speeds in bio-electronic applications, formation of reactive species due to over-oxidation, and time-temperature drift. ECH-based sensors are a new class of devices with potential for *in vivo* biocompatibility in human-implantable biosensors, low voltage actuation for electrically-stimulated drug release devices, and with low interfacial impedances suitable for neural prosthetic devices such as deep-brain stimulation electrodes (Guiseppi-Elie, 2010). ECH characteristics of soft elastic nature, low interfacial tension, and high swelling capacity results in low tissue irrigation and high permeability to low molecular weight drugs and metabolites (Li et al., 2004). These characteristics have allowed hydrogels to be used in biosensors, catheters, contact lenses, wound dressings, and tourniquets. Hydrogels can be designed to possess hydration characteristics and mechanical properties similar to that of human tissue. Thus, uses of ECH as a biorecognition membrane layer in biosensors has extended potential applications to clinically important biomedical diagnoses (using analyte-specific enzymes), neural prosthetic and recording devices (NDPs and NRDs), electro-stimulated drug-release devices (ESDRDs) and implantable electrochemical biosensors. A hydrogel synthesized from a poly(HEMA)-based hydrogel and poly(aniline was fashioned into a biosensor (by incorporation into recombinant cytochrome P450-2D6) that was responsive to the drug fluoxetine, the active ingredient in Prozac (Iwuoha et al., 2004). These polymeric materials provide a non-cytotoxic interface between the biosensor device and native living tissue or cell culture medium (Fonner et al., 2008).

Gawel et al. (2010) reviewed the various principles involved in the design of biospecific hydrogels acting through various molecular mechanisms to transduce the recognition of label-free analytes. The range of different responsive characteristics displayed by hydrogels include changes in equilibrium swelling volume in response to various changes in solution parameters such as solvent pH, ionic strength, temperature, electrical fields, and presence of surfactants.

4.2.4 Porous polymers and resins

Porous polymers and resins provide applications as enantio-selective catalysts, artificial antibodies, and sensors in electro-optical and micro-electronic devices. Unlike inorganic porous gels such as silica gel carriers, porous polymers have unique properties such as

flexibility, ductility, and capability to incorporate a wide range of organic functional groups useful for biotechnical and biomedical sensor applications (Hentze & Antonietti, 2002). Initial applications of porous polymers have included uses as insulators and ion exchange resins, employed in the field of column chromatography for separation and purification of organic compounds. Applications of porous polymers have now been extended into sensor development. Some potential pharmaceutical applications of template porous polymer gels are in the development of controlled drug-delivery devices, drug-monitoring devices, and for biological receptor mimetics. These materials have become particularly useful as active components in optical sensors.

4.3 Compound electronic-nose devices

E-nose hybrid devices are created by combining e-nose technologies with other types of sensors into one instrument. This is different from instrument systems such as GC-MS or HPLC-MS instruments used in tandem. In an e-nose hybrid device, different sensor types are found within the same instrument not in separate instruments combined in tandem. There are a number of different combined-technology commercial e-noses available with various types of e-nose sensors combined with other sensor types. The e-nose components of such compound-sensor devices usually contain MOS, SAW, QMB, or CB electronic-nose sensors with different combinations of electron capture (EC), ion mobility spectrometer (IMS), photoionization (PI), mass spectrometer (MS), oxygen (O_2), carbon dioxide (CO_2), and humidity sensors. The sensing range and capabilities of these compound e-noses are considerably greater, but also generally more expensive than typical e-nose devices alone. The efficacy and justification of expense depends on the particular combination of sensing needs that are required for specific medical applications.

Other possibilities exist for integrating e-nose components with DNA probes within a microarray. One such possibility might be the integration of the CombiMatrix microarray system with 12,544 electrodes in which multiplexed CMOS microarray DNA probes are on individual electrodes coated with electro-polymerized polypyrrole (PPY) that is a common material used in many conductive polymers e-noses (Maurer et al., 2010). The possibility of combining PPY sensors for detecting DNA as well as other similar sensors for VOCs within the same instrument is theoretically possible. Lorenzelli et al. (2005) have integrated a MOS detector with a microcapillary GC silicon-based system for clinical diagnostics and other biomedical applications. Initial planned future work are to test this biosensor-based e-nose micro-GC system for determining and monitoring hamovanillic acid (HVA) and vanillylmandelic acid (VMA) catecholamine metabolite concentrations, end-products of dopamine and norepinephrine metabolism, in urine samples as well as for oncological (cancer) diagnoses.

5. Conclusions

Many research and development (R&D) feasibility studies have demonstrated the effectiveness of electronic-nose technologies for detection-type applications in many diverse areas of the healthcare and biomedical industries. Electronic noses have proven to be very competent and effective in discriminating between VOCs and other cellular biochemical constituents, showing great potential for improving and speeding up detections for a myriad of applications. Most of this feasibility work has been done with expensive laboratory-grade instruments designed to allow maximum discriminations and sample-

sensitivity for rigorous scientific testing. Consequently, a number of major problems have resulted from attempts by commercial e-noses manufacturers to use laboratory-grade instruments for practical clinical POCT applications. Laboratory-grade instruments generally are too expensive, too complicated for operation by industry technicians, require extensive training (for operation, maintenance, and data-interpretation), and are too versatile in terms of numbers and permutations of control settings that are possible (adjustable) which complicates repeatability (precision and accuracy) within the normal range needed for diagnostic testing. All of these problems have contributed to the failure of applying laboratory-grade e-nose instruments to practical applications. The common mistake and practice of skipping the additional needed steps of customizing e-noses (in both design and operation) for specific biomedical applications has been costly, causing some potential end-users to lose faith in e-nose technologies, and has resulted in the business failures of some e-nose instrument manufacturers as a result of marketing instruments that are not simplified, adapted, and customized to the specific uses required by healthcare professionals.

Now, the electronic-nose industry is at the stage where lessons of design and manufacture have been learned and the path forward has shifted to designing e-noses that are smaller, less expensive, more application-specific (specialized), easier to use by operators, and produce results that are easily interpreted by the user due to limited data outputs. The only final steps left to be completed today for e-nose development for practical uses in many modern-day applications are largely limited to efficacy testing to determine such things as the range and breadth of applications of individual instruments, procedural uses that are possible in combination with other medical instruments or diagnostic tests, quality control between individual instruments (calibration concerns), and developing specialized aroma libraries, software and algorithms for specific medical applications. Once these tasks are completed, use of electronic noses should accelerate in diagnostic laboratories and POCT clinics, replacing many conventional time-consuming methods and instruments used in diagnostics and providing fast, reliable information useful for speeding up effective patient care with the most appropriate treatments.

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