ISSN: 2277-3754
ISO 9001:2008 Certified
International Journal of Engineering and Innovative Technology (IJEIT)
Volume 3, Issue 8, February 2014

Advances in electronic nose technology for clinical applications

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Abstract— ***Many diseases and intoxications are accompanied by characteristic odors, and their recognition can provide diagnostic clues, guide the laboratory evaluation, and affect the choice of immediate therapy. An electronic nose is a device that identifies the specific components of an odor and analyzes its chemical makeup to identify it. A wide range of electronic-nose instrument types, based on different operating principles and mechanisms, have provided solutions and applications to a wide variety of complex clinical problems. These devices have a clear potential to be a non-invasive, simple and rapid but above all accurate early detection screening tool. The purposes of this review are to present a comprehensive analysis of recent research findings and developments of electronic-nose sensor technologies and to identify current and future potential e-nose applications in clinical diagnosis. The review includes examples of diseases producing characteristic odor and recent contribution for disease detection. The results suggest the possibility of using the technology in medical diagnostic.***

Index Terms—**clinical applications, conducting polymers, electronic nose, gas sensor, odor detection.**

I. INTRODUCTION

Advances in aroma-sensor technology, electronics, biochemistry and artificial intelligence has made it possible to develop devices capable of measuring and characterizing volatile organic compounds (VOCs) released from a multitude of sources for numerous applications. These devices, known as electronic noses, were engineered to mimic the mammalian olfactory system within an instrument designed to obtain repeatable measurements, allowing identifications and classifications of VOC mixtures while eliminating operator fatigue [1]-[4]. This technology mimics the human olfaction system by producing a composite response unique to each odorant. The system comprises a sensor array that detects the odour and transduces the chemical vapors of a sample mixture into electrical signals. These electrical signals from individual sensors are collectively assembled and integrated to produce a distinct digital response pattern. Identification and classification of a sample mixture is accomplished through recognition of this unique odor signature or odor fingerprint of collective sensor responses. The identity of a simple or complex mixture represented by this unique odor signature pattern is determined without having to separate the mixture into its individual components prior to or during analysis[1],[5],[6]. The process of recognition starts after the sensor signals have been stored for processing. Data processing can be split into four sequential stages: signal preprocessing, dimensionality reduction, prediction and validation. Signal preprocessing focuses on compensating for sensor drift, extracting descriptive parameters from the sensor array response and preparing the feature vector for further processing. The dimensionality reduction stage aims at reducing the initial feature vector dimensionality as the data is highly correlated. In prediction stage, pattern-recognition techniques are utilized for data classification into class labels [7]. The final stage, validation, selects models and parameter settings and estimates the true error rates for a trained model.

Electronic-nose devices offer many potential uses and advantages for numerous clinical applications because of its ability to be a non- invasive, simple, rapid and accurate early diagnostic tool. Electronic noses have been developed for detecting volatile compounds from the human body for clinical diagnosis, such as rapid detection of tuberculosis (TB), airway inflammation and urinary tract infections (UTI)[8].

This paper aims to describe the application of electronic noses in clinical diagnosis. The working principles and types of electronic noses are discussed and the most relevant contributions in disease diagnoses are presented afterwards. Finally, some interesting remarks concerning the challenges and future trends of electronic noses in medical application are mentioned.

II. E-NOSE FOR CLINICAL APPLICATIONS

Electronic-noses are most suitable for clinical uses because of their versatility, low cost, rapid output of results, real time physiological monitoring, and the wide range of VOCs and other cellular chemical constituents that may be analyzed. Many devices have been developed based on different working principles and have advantages, disadvantages and limitations. These features of electronic noses type determine what types of medical applications that individual e-nose sensor types are best suited for in practical clinical setting [9]-[12]. Details of electronic noses used for clinical tasks are discussed below.

A. Metal-oxide semiconductor (MOS)

Semiconductor sensors are inexpensive to produce, easy to miniaturize, rugged, reliable and can be designed to operate over a range of conditions including high temperatures [13]. Metal oxides such as SnO_2, ZnO, Fe_2O_3, and WO_3 are intrinsically n-type semiconductors while CuO, NiO and CoO are p type semiconductors.[14] At temperatures of 200–500 ^{o}C, these oxides respond to specific gases and changes their conductivity when gas sample passes on it and gets adsorbed on the surface [13],[15]-[18]. They exhibit sensitivity towards both oxidizing and reducing gases by a variation of their electrical properties. Different composition of metal oxide gas sensors has sensitivity towards specific target gases. Also the adsorption of gas sample on the surface of MOS vary depending on the operating temperature of the sensor. Tin dioxide (SnO_2) is the most widely used MOS gas sensor. Drawbacks of these sensors are that they have detection limit in the range of ppm levels and exhibit relatively poor selectivity for gases [14]. Additives or dopants, which are added as an impurity to MOS material, provide flexibility and potential to apply MOS sensors to new gases, conditions, and systems. Some of the commercially available MOS gas sensors are manufactured by New Cosmos Electric Co. Ltd and Figaro Engineering Inc. (Japan). Table 1 shows typical gas sensors with their operating temperature using MOS.

Table I: Typical gas sensors and their target gases

Material (Dopants)	Operating temp(^oC)	Detecting gases	Ref
ZnO(Al)	200	H_2, NH_3	[20]-[21]
ZnO	300	CO	[22]
ZnO	450	CCl_2F_4, $CHClF_2$	[23]
ZnO	200	Dimethylamine (DMA)	[24]
WO_3(Pt)	300	N_2H_4, NH_3, H_2S	[25]
WO_3	500	CO, CH_4, SO_2	[26]
CuO	250	H_2, CO	[27]
SnO_2	300	H_2, ethanol	[28],[29]
SnO_2	400	CO	[30]
SnO_2(Pt, Pd, Au)	400	C_6H_6,CO	[30]
MoO_3	500	NH_3	[31]

B. Organic Conductive polymer

The potential uses for organic polymers for gas sensing application have since been multiplied due to their ease of processing, good environmental stability and wide range of electrical properties[32]. They exhibit a change in conductance when they are exposed to reducible or oxidizable gases, which adsorb and desorb from the polymer. The most commonly applied polymers for gas-sensing applications have been polypyrrole, polyaniline, polythiophene, and polyacetylene. Studies showed that gas sensors fabricated of polypyrrole respond to a wide range of organic vapors such as methanol, ethanol and ethyl acetate[33]-[35]. The gas sensing application of organic CPs on the response to reactive gases such as ammonia and hydrogen sulfide is also reported [36],[37]. Organic CP is a potentially useful material for applications in odor-sensing and e-nose applications with an advantage of having a wide range of materials available, sensitivity of less than 20 ppm and better stability.

III. E-NOSES FOR DISEASES DETECTION

Components of exhaled breath, which constitute the bulk of the exhaled breath volume are nitrogen, oxygen(%), water(%), and carbon dioxide(%). Others are mostly volatile organic compounds (VOCs) with their concentration is in ppm and ppb level. More than 3,500 different VOCs are identified and the list is continuously growing. Different sets of compounds or biomarkers account for the individual smell that characterizes a given subject and can be associated with pathologic metabolisms specific to different disease states. By examining the biomarkers in exhaled breath, detection of diseases can be possible[38]. Table II shows the list of diseases that can be detected using biomarkers.

The VOC profiles are assessed by an electronic nose, which is a system making use of MOS and organic CP sensors that are sensitive to these biomarkers. The sensors sense the sample and accordingly form a kind of breath signature that is typically associated with a given disease or condition. The breath signature is then sent to the computer for signal processing and pattern recognition.

Studies have been done to determine whether exhaled breath analysis using an e-nose correlates with pneumonia condition. The results show good correlation with clinical diagnosis and provide new potential for diagnostic analysis. Distinguishing patients with infection pneumonia and patients who have been treated have also been reported [67],[68].

The technology has been used to assess the VOC profile to identify patients with lung cancer [69]–[71]. In another study, exhaled breath of 101 persons, of which 58 as normal and 43 suffering from different types of lung cancer were examined using MOS gas sensors. The result showed an accuracy of 92.6%, a sensitivity of 95.3% and a specificity of 90.5% [72]. The results indicate that electronic nose can be a valid implementation of lung cancer diagnostic technique. Use of conducting polymer array to identify and discriminate between 14 bronchogenic carcinoma patients and 45 healthy controls is also reported [73]. An electronic nose (Cyranose 320), which uses conducting polymer array can distinguish diseased breath print from healthy controls with accuracy of 84.6% [74].

The technology has potential to be applied to identification of patients with COPD, asthma, and Tuberculosis. As seen in research work, it can differentiate between tuberculosis patients and healthy controls with a sensitivity of 76.5% and specificity of 87.2% [75]. Asthma has a unique molecular profile in exhaled breath that can be identified by electronic nose and can be used as a detection tool. The researchers are able to distinguish the exhaled breath of patients with asthma from healthy subjects with 90% accuracy [54].

MOS gas sensor using MoO_3 nanoparticles material, which is highly specific to ammonia gas, is used for renal disease detection in exhaled breath [31]. In another study, commercial MOS gas sensors are used to sample exhaled breath of controls and renal failure patient. The results have sensitivity of 83.96% and specificity of 86.14%. The same author showed sensitivity of 86.97% and specificity of 87.57% for distinguishing diabetic patient from controls[76]. Recently, a novel method to detect neurodegenerative disease

ISSN: 2277-3754
ISO 9001:2008 Certified
International Journal of Engineering and Innovative Technology (IJEIT)
Volume 3, Issue 8, February 2014

such as Alzheimer's disease and Parkinson's disease based on breath testing is studied. The organically functionalized carbon nanotubes and gold nanoparticles are used to fabricate the electronic nose. The result distinguished Alzheimer Disease from healthy subjects, Parkinson's Disease from healthy subjects, and Alzheimer Disease from Parkinson 's disease subjects, with a classification accuracy of 85, 78 and 84%, respectively [77].

Table II. Diseases associated with biomarker

Disorder	Biomarker	Ref
Diabetes mellitus	Acetone, ethanol, methyl nitrate	[39],[40],[41]
Lung cancer	benzene,1,1-oxybis-, 1,1-biphenyl,2,2-diethyl, furan,2,5-dimethyl	[42],[43],[44]
Uremia, kidney	Ammonia	[45]
Liver disease	carbonyl sulphide, carbon disulphide, isoprene	[46],[47],[48]
Tuberculosis	naphthalene,1-methyl-, 3-heptanone, methylcyclododecane	[49]
asthma	Pentane, ethane, 8-isoprostane nitric oxide, cysteinylleukotrienes, prostaglandin	[50]-[57]
COPD	NO, H_2O_2, aldehydes, 8-isoprostane, nitrotyrosine, Leukotriene B4, cytokines	[58]-[63]
rheumatoid arthritis	pentane	[64]
cystic fibrosis	ethane, propane, pentane	[65]
Breast cancer	alkanes, ketones, halogenated hydrocarbon, aldehydes, and esters	[66]

IV. CONCLUSION

In this review, we have described the types of electronic nose that are applicable to clinical applications. Applications of the technology for clinical purposes in recent years are discussed. Due to development in sensing techniques of electronic noses, potential for exhaled breath assays is possible taking advantage of real time, accurate, non invasive and fast detection system which allows earlier detections of diseases. Exhaled breath analysis is an attractive procedure for electronic noses to predict disease because it is cost effective and simple in operation.

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ISSN: 2277-3754
ISO 9001:2008 Certified
International Journal of Engineering and Innovative Technology (IJEIT)
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Engineering, Pune..Currently working on the above research, he has previously worked on Artificial Neural Networks for disease detection.