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doi:10.15199/48.2021.03.23

MOX based E- Nose for Non-Invasive Biomedical Applications

***Abstract**. The non-invasive method to diagnosis any disease is an attractive topic of research due to its rapid, cost effective, convenient and efficient technique. The Health status of a patient can be directly known by examined of volatile organic compound (VOC) of a patient, and this VOC can be studied by an electronic nose (e-nose). E- Nose can be easily detect different types of diseases such as lung cancer, diabetics, by analyzing the exhaled breath of a patient. In the proposed work, a brief overview has been provided about different techniques used to develop the E-nose. The importance of Low temperature co-fired ceramics (LTCC) based breath analyzer and future objectives has discussed.*

*Streszczenie. EW artykule przedstawiono koncepcję wykorzystania analizatora zapachów tzw. E-nosa do wykrywania chorób na podstaiw badania wydychanego powietrza. Przedstawiono różne techniki analizy. Szczególną uwagę poświecono czujnikowi typu LTCC. (**Wykorzystanie analizy wydychango powietrza do wykrywania chorób**).*

Keywords: LTCC, volatile organic compound, Biomarker, sensor, metal oxide MOX sensor.
Słowa kluczowe: sztuczny nos – E-nos, analiza wydychango powitrza

Introduction

In the modern world, the different types of devices and equipment have been used to diagnosis human diseases [1]. Therefore, health care technology becomes the focal point of the researcher, which is an interesting research topic in biomedical engineering. Breathe odours becoming a convenient and efficient technique. Due to its extensive advantages over urine analysis and blood testing, it shows considerable thinking for researchers. It has low complexity than other tests and responsible to complete analysis of all the compounds present. It provides detail about respiratory functions with low complexity. Breath analysis can be applied to detect disease through the detection of VOC produced by the human breath such as ammonia, acetone, nitric oxide, ethanol, carbon dioxide, etc. These VOCs have different concentrations for different types of compounds for a healthy human breath and a sick human breath. For example, if concentration of acetone and ethanol vapors is high in breath which indicates metabolic products is more in the bloodstream, which leads obesity in a patient. Similarly if ammonia vapor found in the breath of patients which is a product of protein and nucleic metabolism which indicates that patients have renal diseases [2]. Therefore, analysis of different exhaled VOCs is helpful in detection of various diseases [3]. Breath analysis shows a potential tool for non-invasive, real-time illnesses diagnostics, metabolic status monitoring, and drug monitoring [4]. It is probably for early detection of an early stage of lung cancer, liver diseases, asthma, diabetes, etc [5, 6]. The breath test over conventional laboratory tests is non-invasive, safe, and painless. The breath analysis system developed using an electronic nose (e-nose) is rapid, inexpensive, more flexible than a urine analysis, and more comfortable than a blood analysis. The figure 1 indicates some major diseases which are related with concentration of different VOCs.

The analysis of breath can be done by an Electronic nose (E-nose). An Electronic nose (E-nose) is used to discriminate a mixture of odor which can be replaceable of complex biological olfactory systems to smell different type of odorant mixture and concentration of the mixture. It has been used widely for environmental contamination detection (air quality, hazardous gas detection), food quality detection, exhaled breath analysis, etc. It can be used to detect drugs [7]. Electronic noses are arrays of different types of sensors. They can be used to sense different types of gases which posses as biomarker to indicate various diseases.

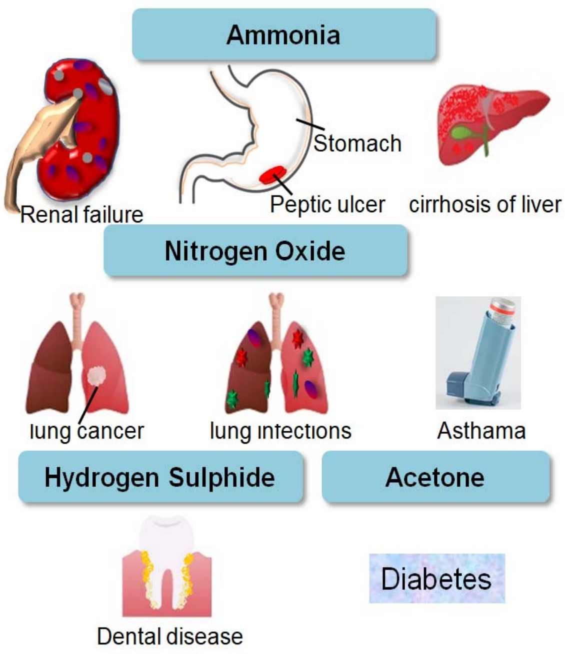


Fig. 1. VOCs with its related diseases

Various diseases with related exhaled breath

Diabetes: Acetone is a fat burning product and its increase in blood leads to diabetes. The acetone concentration for a healthy person is varied between 0.3 and 1 ppm while increment in concentration from 1.5 ppm to 3.7 ppm leads to diabetic patients [8-10].

Chronic kidney disease: The kidney disease can be identified through NH3 breathing. The concentration of NH3 for healthy person is ~400 to ~1800 ppb while for chronic kidney disease it has been~800 to ~15000 ppb [11].

Blood cholesterol: Isoprene is used to detect the blood cholesterol. The breath analyze developed by Park et al. [12] based on gas chromatography principle. He proposed a ZnO quantum dot (QD) sensor which is helpful in separation of isoprene from mixture of gases then produced electrical signal. The breath analyzer identifies isoprene in the range of 0.40 to 6.2 ppm within 83 s, with high selectivity and sensitivity to trace isoprene in human breath.

Lung cancer: Phillips et. al. (2003) [13] detects lung Cancer through VOCs such as butane; 3-methyl tridecane; 4-methyl octane; 3-methyl hexane; 5-methyl decane. Similarly Chen et. al. (2003) [14] has detected lung cancer using -hexene; hexanol; isoprene; benzene; styrene; decane; undecane; 1 propyl benzene;methyl cyclopentane.

Techniques used for detection

There are various techniques used to develop a breath analyser. Some important techniques are Gas chromatography, Selected ion flow tube-mass spectroscopy, Cavity ring down spectroscopy and E-nose.

Gas Chromatography (GC):

It is widely used method in breath analyser. The basic principle Gas Chromatography is a breath sample is transported in chromatographic column with inert gases such as helium or N_2. The separation of compounds in GC column is performed through boiling points and polarity of the VOCs. Flame ionization detection, mass spectrometry, and ion mobility spectrometry are different methods used in detection for GC. Mass spectrometry is widely used with gas chromatography, called GCMS and the combination was helpful in detecting around 3,000 VOCs with low concentrations.

The Gas chromatography is mainly used for diabities patients beacuse of it high accuracy and sensitive for glucose diagnosis [15]. The drawback of mention technique is sophisticated in use, unportable and expensive.

Selected ion flow tube-mass spectroscopy:

The Selected ion flow tube-mass spectroscopy [16,17] has real time analysis. It is also unportable and expensive with complicated circuitry.

Cavity ringdown specctroscopy:

Cavity ringdown specctroscopy (CRDS) is a technique based on optical spectroscopic. Its working is based on the absorption and scattering of light through the samples [18]. During sample storage and transportation, it suffer from sampling seriously because of loss, decomposition, absorption and reaction of VOCs in breath. The Schematic of CRDS is depicted in figure 2.

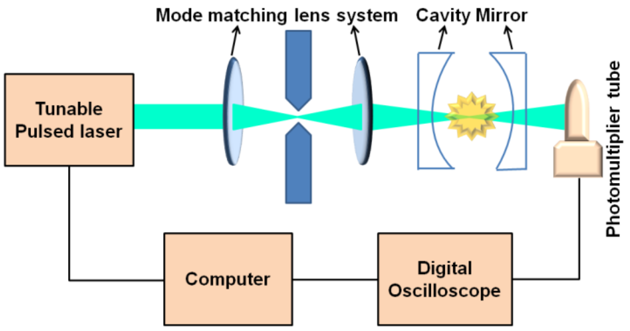


Fig. 2. Schematic of CRDS

It is highly responding and sensitive technique but it require high calibration for better results, unporatble and expensive [19].

Metaloxide semiconductor based breath analyser:

It is an advanced technique to develop E-nose which is easy to use, portable and highly sensitive. It has arrays of sensors which reacts with definite VOCs. This method is works like a clone of human nose. This technique is portable, easy to handling, high responsive, real time analysis and less costly. The E-nose has been developed mainly using metal oxide based sensor technology.

The metal oxide works on the intraction of gas molecules may be positive or negative charged. The charged molecules converted into electrical properties. connected to the signal conditioning unit. This signal condition unit consists of some active and passive elements. Generally, it will use an operational amplifier, and sensors resistance will be used as a feedback resistor of an operational amplifier. As the Exhaled breath sensor resistance changes, the output voltage also changes, and this output from op-amp will be changed. With the help of multiplexers, all the data from the different sensors can be obtained. This data will be fed into the data acquisition unit. The data acquisition unit will be connected to the PC and the software will analyze the data and give the desired output. Data acquisition software has built-in PCA and SVM algorithms by which data can be easily analyzed.

The E-nose is mainly developed using various metaloxide semiconductor. Commonly used gas sensing materials are Tin Oxide (SnO_2), Tungsten Oxide (WO_3), Copper oxide (CuO), Iron oxide (Fe_2O_3), etc. These oxides are characterized by sensitivity and responce times, but the main disadvantage is its high operating temperature (250 °C to 500 °C) [20,21]. When a volatile organic compound comes in contact with MOX sensing layer. It isolated into charged ions due to which variation takes palce in resistance of sensing film. The change in resistance is depends on the morphology and temperature provide to sensing film.

The different oxides works on different temperature and this temperature will be achived from micro-hoplate. The primary objective is to design low power consumption micro hotplate arrays with a temperature controller. Due to high temperature requirement, MOX sensors need high power consumption, which is an important limitation. To overcome this limitation, diffrerent techniques are used for the development of stable tempearture micro-hotplates.

Microelectromechanical system (MEMS):

The MEMS based micro-hotplates consumes low power and miniturize in size. Due to lot of fabrication processes such as wafer cleaning, oxidation in furnace, eatiching, spin coating etc. Its fabrication is costly and complex. The thermal conductivity is also high (150 W/mK) due to which it shows unstability at high temperatures.

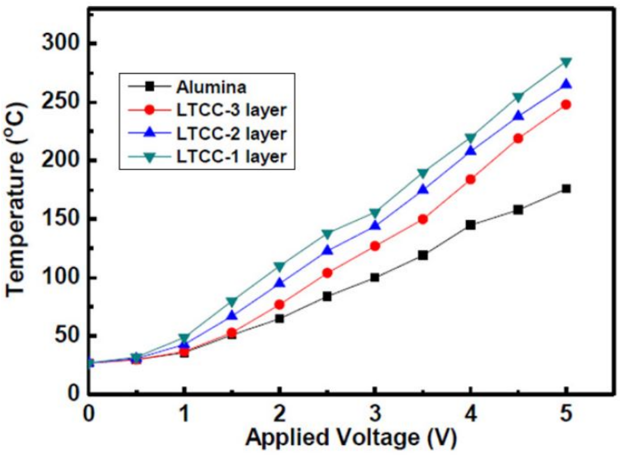
Alumina based micro-hotplate:

Thick film technology is used to produce various types of electronic components using the screen printing method. It is also used to produce different types of sensors for gas sensing and chemical application. These sensors have excellent sensing performance and compact design. In the thick film, sensor material generally printed on electrodes, and this electrode printed on a substrate. These thick film sensors considerably cheaper than thin film technology.
Its thermal conductivity is 28 W/mK, and stable on high temperature but it consumes high power and structuring is very typical on alumina substrate.

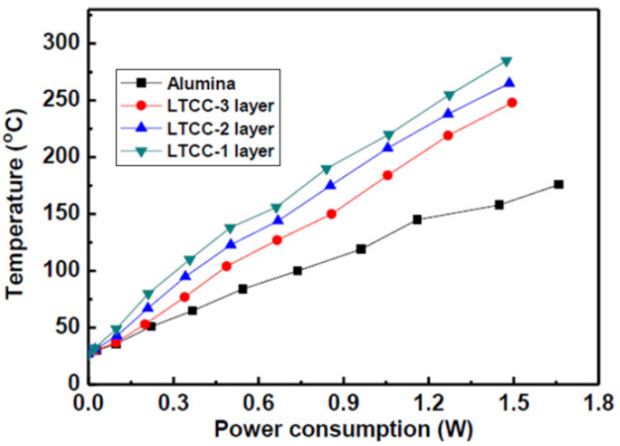
LTCC based micro-hotplate:

Low temperature cofired ceramic(LTCC) technique used to fabricate gas sensors and useful technology for circuit and package fabrication. These sensors have excellent performance because of its electrical characteristics and thick film pastes compatibility. It uses a multi-layer fabrication process and possible to manufacture 3D structures [24]. This technology is very attractive due to their packaging as they have the capability to prepare channels, cavities, diaphragms, passive component integration, etc [25]. This technology used in a wide range of applications such as gas sensors, fluid mixers, bandpass filters, strip antenna, etc. LTCC technology offers a lot of advantages that can be utilized in the production of various kinds of electronic noses in one module [24,26]. LTCC technology also enables the fabrication of three-dimensional (3D) structures which is especially desirable in the case of electronic nose applications and micro-fluidics applications.

The comparision of LTCC and alumina micro-heaters has been indicated by kulhari *L et. al. 2019* as shown in figure 3. Here characterization has been performed for same structure of alumina and LTCC substrate with differ ent thicknesses of LTCC substrate and analysed that LTCC consumes low power in comparision to alumina.



(a)



(b)

Fig.3 (a) Tem (˚C) vs applied voltage (V) & (b) Tem (˚C) vs power consumption (W) of LTCC/alumina micro-heaters [27]

The micoheaters developed using LTCC substrate are miniturize in size. The LTCC based micro-heaters has been sucessfully demonstrated for gas sensor applications [28-30].

Conclusion:

Developed micro hotplate arrays will be Characterized and compared with the simulated results. Characterization would involve various analytical tests to extract information related to the surface morphology, temperature distribution, and current-carrying mechanisms of the micro-hotplate. This would provide a feedback loop to fabricate better and improved micro- hotplate. The exhaled breath sensing material such as Tin(IV) Oxide (SnO_2), Copper (II) oxide (CuO), Zinc oxide (ZnO), Titanium dioxide (TiO_2), Indium (III) oxide (In_2O_3), and Iron (III) oxide (Fe_2O_3), etc shall be deposited by different methods such as thick film paste formation, sol-gel technology, and thin-film coating. The main purpose is to develop a fast and scientific determination of volatile organic compounds in the exhaled breath for real-time measurements and low costs. The developed biomarker will focuses to provide proper information on disease or asthma, diabetes, and lung cancer or the effects of treatment.

The LTCC-based MOX sensors are better E-nose for VOCs. The LTCC based E- Nose can be easily detect different types of diseases such as lung cancer, diabetics, by analyzing the exhaled breath of a patient. It will be a portable device with long life and provede stable output.

Acknowledgments

The authors would like to thanks Universiti Teknikal Malaysia(UTeM) Melaka and AMITY University Rajasthan for providing all the supportive information and material for the work. We would also like to thank the Faculty of Electronics and Computer Engineering of UTeM and acknowledge their support. Lastly, thanks to all the referees, the lecturer who has helped to complete this paper.

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