Original Article

ISSN: 2349 - 4891

International
Journal of Recent Research and Applied Studies
(Multidisciplinary Open Access Refereed e-Journal)

A Novel Approach to Study on Lung Cancer Diagnosis using Halitosis Sensing System

C.Narayanan

Professor, Department of Biomedical Engineering, Dhanalakshmi Srinivasan Engineering College, Perambalur, Tamilnadu, India.

Received 06th July 2020, Accepted 05th August 2020

Abstract

Halitosis or bad breath is emitted due to metabolic changes in the body. It contains several Volatile Organic Compounds (VOCs) that are emitted due to various reasons and indicates early stage of a disease. Toluene is a biomarker, which represents indication of lung cancer in patients due to smoking. Our work is to develop a sensing system which can identify toluene concentration in human exhaled breath and thereby diagnose lung cancer at its early stage. The material used for developing this prototype is a toluene gas sensor connected to a microcontroller unit. The study involved 20 participant, among which (n=10) were smokers and (n=10) were non-smokers. The data was obtained by making those volunteers to blow on the sensor. The toluene concentration in normal atmosphere was obtained as 0.59 ppm. The range for toluene concentration obtained from normal people was 0.10-0.40 ppm whereas in case of smoking people it was greater than 0.40 ppm. The results obtained from the current study shows that an increase in toluene concentration was seen in case of smoking people than a normal healthy people.

Keywords: Lung Cancer, Halitosis, Sensing System.

Sensors

Sensors are used in everyday objects such as touch-sensitive elevator buttons (tactile sensor) and lamps which dim or brighten by touching the base, besides innumerable applications of which most people are never aware A sensor's sensitivity indicates how much the sensor's output changes when the input quantity being measured changes. For instance, if the mercury in a thermometer moves 1cm when the temperature changes by 1 °C, the sensitivity is 1 cm/°C (it is basically the slope dy/dx assuminga linear characteristic). Some sensors can also affect what they measure; for instance, a room temperature thermometer inserted into a hot cup of liquid cools the liquid while the liquid heats the thermometer. Sensors are usually designed to have a small effect on what is measured; making the sensor smaller often improves this and may introduce other advantages.

Gas Sensor

A gas sensor is a device which detects the presence or concentration of gases in the atmosphere. Based on the concentration of the gas the sensor produces a corresponding potential difference by changing the resistance of the material inside the sensor, which can be measured as output voltage Italy aiming to provide a low-cost and easy way for novices and professionals to create devices that interact with their environment using sensors and actuators, Common examples of such devices intended for beginner hobbyists include simple robots, thermostat and motion detectors.

Correspondence
C.Narayanan
E.Mail: ncnmce@yahoo.com

Cancer Diagnosis

Human body undergoes some process when some metabolic changes occur in the body. Among those processes halitosis is one of them. Volatile Organic Compounds (VOCs) found in the halitosis also known as bad breath can be related to, but not limited to stress, nutrition, and disease indication. Thus, VOCs in halitosis can be used as biomarkers for identifying a multitude of diseases at their early stage. Several practitioners, doctors, and other medical scientists were using these biomarkers to identify various diseases. Studies also indicate that one can identify diseases related to respiratory, digestive and kidney. Halitosis based diagnosis is a non-invasive method unlike other diagnostic techniques such as blood test, urine test or other test involving bodily fluids - this technique only takes breath samples for diagnosis. In this paper, we have investigated the relationship between bad breath and lung cancer in detail. Lung cancer starts by affecting the lymph nodes in the lungs and slowly spread to the chest and other regions. The risk of getting affected by lung cancer is more likely to the people who were smoking in large quantities or for a long time or both. The other factors which can cause lung cancer are exposure to toxic environment and hereditary. Lung cancer can classified into two types namely small cell lung cancer which can commonly seen in patients who were chain smokers and non small cell lung cancer which behave in similar ways to lung cancer. By using halitosis, lung cancer can be identified at an early stage by detecting the right VOCs such as acetone, HCHO & toluene . Among them, identifying toluene concentration can give more accurate result for lung cancer diagnosis. Toluene is an industrial solvent which can be used in paints, coatings, gasoline and etc. Toluene is also one of the chemical which can be found in cigarette smoke. Since toluene is water insoluble chemical, which can gets deposited in the lungs for a long duration of time. Increased toluene absorption in body can lead to dizziness, headache and nausea. It can also affect Central Nervous System (CNS) when exposed to higher concentrations. Since the toluene is insoluble, even trace amounts in cigarette smoke get deposited in the respiratory airway and can be significantly detectable in halitosis of a lung cancer patient. It is relatively favorable for medical practitioners to treat the patients at earlier stage of cancer but often, patients consults the practitioners at latter stage which will complicates the treatment process. The method of detecting the targeted VOCs from the halitosis can help in identifying the lung cancer patient at an early stage which in-turn facilitate the practitioners to start the treatment at earlier stages of cancer. Treatment at an early stage can increase the success rate of getting cured.

Non Invasive Method

Non-invasive technologies, more especially the nanosensor breath technologies which are portable, cheap to fabricate, highly sensitive and easy to use, have potential in lung cancer detection. A growth in the economy directly impacts the lifestyle of the people, and this is evident in the diet-related issues such as diabetes mellitus .Thus, there is a great potential need of using toluene as a biomarker for lung cancer, and detect it using non-invasive chemoresistive sensors. Human exhaled breath contains thousands of different volatile organic compounds (VOCs) derived from the body's metabolic processes. In patients with lung cancer, Halitosis based diagnosis is a non invasive method this technique take breath samples such as toluene or voc components as a biomarkers for detection of lung cancer which are then exhaled during respiration. Many studies have reported on non-invasive analysis of breath for detection of diseases using techniques such as gas chromatography with mass spectrometry (GC–MS), proton transfer reaction with mass spectrometry (PTR–MS) and many other sensitive techniques . Although these techniques are sensitive and reliable, they are not portable for detection.

Breath for Diagnosis

Human breath is mainly composed of oxygen, nitrogen, carbon dioxide, water and so on. The volatile organic compounds, described fully in the section below, are derived in the body or from the environment, and make up the rest of the breath .

Human breath has been used as a potential tool for the diagnosis and study of diseases. The human breath was first analyzed by Pauling in 1971 using gas chromatography and around 250 different gases were identified. Currently, scientists are able to detect more than 300 different volatile organic compounds and other particles in breath .

- Human breath analysis is also crucial for delivering non-invasive, real-time and rapid screening and diagnosis of complex diseases such as cancers and acute infections. Furthermore, it is not only non-invasive, but also has several advantages as compared to traditional diagnostic techniques, which include painless procedures and sampling that does not require skilled medical staff .
- The human breath contains several hundred VOCs with concentrations ranging from part-per-trillion (ppt) to part-per-million (ppm). The cellular and biochemical origin of many of these VOCs has not been detected.

VOC IN Breath

Volatile organic compounds (VOCs) are either subtracted from inspired air (by degradation and/or excretion in the body) or added to alveolar breath as results of metabolic processes . They exchange across the alveolar blood capillary membrane into exhaled breath .

There are many other sources of VOCs in human breath, including airway surfaces, inhaled room air, blood and peripheral tissues throughout the body. Some of these volatile organic compounds are the byproducts of biochemical reactions, whilst others might be produced for specific physiological roles such as cell-to-cell signalling.

There are several classes of VOCs that can be measured in the exhaled breath. These include saturated hydrocarbons, unsaturated hydrocarbons, and oxygen-containing, sulfur-containing and nitrogen-containing compounds .

The saturated hydrocarbons include pentane aldehydes and ethane, which are formed by the lipid peroxidation of fatty acid components of cell membranes triggered by reactive oxygen species, while the unsaturated hydrocarbons include isoprene, and are produced by the melavalic pathway of acetoacetate from lipolysis or lipid peroxidation. The oxygen-containing compounds, which include acetone are produced from decarboxylation of acetoacetate from lipolysis or lipid peroxidation .

The sulfur-containing compounds include ethyl mercaptane and dimethyl sulfide, and they are all produced from incomplete metabolism of methionine . Last but not least, the nitrogen-containing compounds are produced during liver impairment and uremia . So, analysis of VOCs in inspired air and alveolar breath is a useful research tool with crucial applications in clinical medicine . As already mentioned in the text, different VOCs rather than acetone for diabetes are used as the biomarkers for different diseases in medicine. We are going to outline how other researchers have been able to diagnose diseases such as cancer, liver disease, kidney failure and so on using human breath.

Phillips and coworkers' research on VOCs showed that 22 VOCs are breath markers of lung cancer . Methylated alkanes and selected alkanes have been shown to be able to distinguish lung cancer patients from healthy controls .The rule of the lung cancer breath diagnosis is to check if a 0 nmol/mol or ppbv, which was observed in 25 of the 52 liver cirrhosis patients. Furthermore, hydrogen sulfide and methyl mercaptane have also been reported as possible mediators. However, in vitro experiments showed that the free -SH group of methyl mercaptane reacts with blood, which results in an irreversible binding and oxidation. In contrast, dimethyl sulfide is a neutral, stable molecule that can be transported from blood into alveolar air and be expired .

Toluene Metabolism

Person's breath contains more than 1 of the 11 VOCs with a concentration that is higher than the breath diagnostic cut-off. If the peak area of the 11 VOCs is >200, the patient is considered as a lung cancer patient .

Liver disease is one of the most prominent extra-oral causes of bad breath. It was found that dimethyl sulfide, acetone, 2-pentanone and 2-butanone were significantly higher in alveolar air of liver disease patients . Impairment of the liver function increases the concentrations of these compounds, which have a characteristic smell of a rotten cabbage . Other researchers used gas chromatography to demonstrate that the levels of all sulfur-containing molecules were elevated in the breath of patients with cirrhosis, even outside liver coma . The characteristic sulfur odor could only be detected by the human nose, whereby physicians were sniffing the breath. The alveolar concentration of dimethyl sulfide is more than 3

Toluene is an exhaled volatile organic compound that has been used as a biomarker for lung cancer.

Various Technique used for Diagnosis

Monitoring of numerous volatile compounds in breath is a promising and expanding field. Techniques such as gas chromatography coupled to mass spectrometry (GC–MS), solid-phase microextraction (SPME), high-performance liquid chromatography (HPLC), selected ion flow tube mass spectrometry (SIFT–MS) and liquid chromatography-mass spectrometry (LC–MS) have provided highly selective analysis of VOCs in breath. Although the GC and other mentioned analytical methods are highly sensitive and selective for diagnosis of lung cancer, they are expensive and the issue of portability is particularly important considering that lung cancer should be monitored and diagnosed in real-time for daihealthcare purposes .

Block Diagram

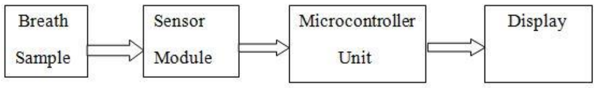

Fig 3.1: Schematic block diagram for the sensing system

The process of this paper is as follows

- The sensor module is connected to the microcontroller unit i.e. arduino with using base shield extension board.
- Once the sensor module is connected the code for identifying sensor resistance value in air (Ro) where typed and run in the arduino IDE so that the Rs value can be identified.
- This Rs value can be identified in normal atmosphere.
- Once the Rs value is identified generate another set of code so that we can identify the resistance value in the target gas like toluene.
- By referring the typical sensitivity curve from the datasheet of the sensor model we can calculate the concentration level of the target gas.

The concentration of the target gas can be obtained either by referring the typical sensitivity curve or by applying in the formula. The formula for obtaining concentration level of the target gas is as follows

ppm= 10^{[log(Rs/Ro)-b]/m}

where b= y intercept and m= slope of the line

b and m are obtained by calculating the slope and y intercept of the typical sensitivity curve of the target gas using straight line equation since the curve is in linear form. By uploading this formula in the code we can directly obtain the concentration of target gas without any further calculation.

Grove

Grove makes it easier to connect, experiment, and simplify the prototyping process. No jumpers or soldering required. We have developed more than 300 Grove modules, covering a wide range of applications that can fulfill a variety of needs. Not only are these open hardware, but we also have open source software.

Figure I. wsp 2110

The Arduino Shield usually has the same pin position as the Arduino development board and can be stacked and plugged into the Arduino to implement specific functions.

Technical details

Dimensions	69mm x53mm x23mm
Weight	G.W 40g
Battery	Exclude

Table 1. *Technical Dimension*

3.4.2 Parts List

Base Shield V2	1

ECCN/HTS

HSCODE	8543909000
USHSCODE	8473305100
UPC	841454111801
ROHS	1

Grove-Hcho Sensor

The Grove - HCHO Sensor is a semiconductor VOC gas sensor. Its design is based on WSP2110 whose conductivity changes with the concentration of VOC gas in air. Through the circuit, the conductivity can be converted to output signal that corresponding to the gas concentration. This sensor can detect the gas whose concentration is up to 1ppm. It's suitable for detecting formaldehyde, benzene, toluene and other volatile components. This product can be used to detect harmful gas in the home environment. Therefore, it's a good assistant for you to improve indoor environment quality of life.

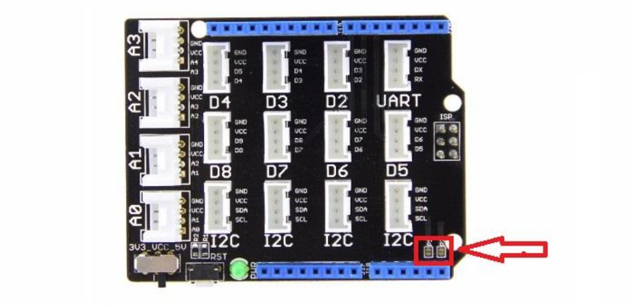

Figure II. Base Shield v2.1

Circuit Diagram

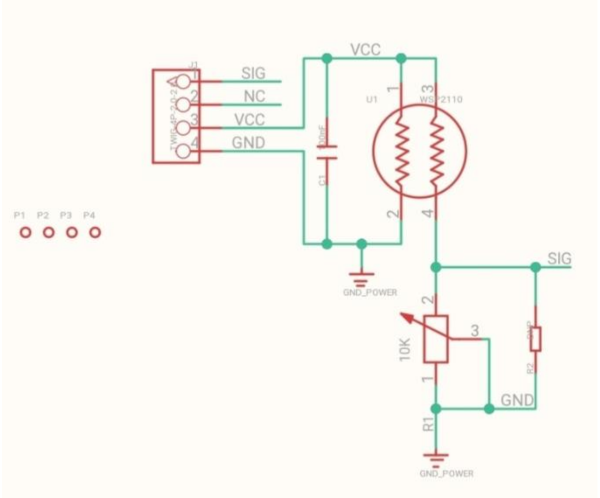

Figure III. WSP 2110 SENSOR CIRCUIT DIAGRAM

By using halitosis, lung cancer can be identified at an early stage by detecting the right VOCs such as acetone, HCHO & toluene . Among them, identifying toluene concentration can give more accurate result for lung cancer diagnosis. Toluene is an industrial solvent which can be used in paints, coatings, gasoline and etc. Toluene is also one of the chemical which can be found in cigarette smoke. Since toluene is water insoluble chemical, which can gets deposited in the lungs for a long duration of time.

- Increased toluene absorption in body can lead to dizziness, headache and nausea. It can also affect Central Nervous System (CNS) when exposed to higher concentrations. Since the toluene is insoluble, even trace amounts in cigarette smoke get deposited in the respiratory airway and can be significantly detectable in halitosis of a lung cancer patient [3].
- It is relatively favorable for medical practitioners to treat the patients at earlier stage of cancer but often, patients consults the practitioners at latter stage which will complicates the treatment process.
- The method of detecting the targeted VOCs from the halitosis can help in identifying the lung cancer patient at an early stage which in-turn

facilitate the practitioners to start the treatment at earlier stages of cancer. Treatment at an early stage can increase the success rate of getting cured.

The block diagram gives an overall workflow of the sensing system. The subjects are made to breathe over the sensor module where it is connected to the microcontroller unit so that the change in resistance can be given as output which can be shown in the display unit.

The sensor module is connected to the microcontroller unit (i.e. arduino) using base shield extension board. Once the sensor module is powered up, system is exposed to atmospheric air in order to record it as Reference Resistance (Ro). Later the system is exposed to target gas atmosphere and change in resistance (Rs) in proportion to target gas concentration is recorded. Microcontroller Unit accurately calculates the target gas concentration using the following equation

$$ppm = 10^{[\log(Rs/Ro)-b]/m}$$

Where b and m both are constants specific to detect toluene (i.e. target gas)

System calculated toluene concentration is now displayed in the output console.

Implemented Coding

Looking around, we find ourselves to be surrounded by various types of embedded system. Be it a digital camera or a mobile phone or a washing machine, all of them has some kind of processor functioning inside it. Associated with each processor is the embedded software. If hardware forms the body of an embedded system, embedded processor acts as the brain, and embedded software forms its soul. It is the embedded software which primarily governs the functioning of embedded systems.

During infancy years of microprocessor based systems, programs were developed using assemblers and fused into the EPROMs. LEDs, switches, etc. were used to check correct execution of the program. Some 'very fortunate' developers had In-circuit Simulators (ICEs).

Embedded C requires compilers to create files to be downloaded to the microcontrollers/ microprocessors where it needs to run.

Coding 1:

To find R0:

```
void setup()
{
Serial.begin(9600);
}
void loop()
{
int sensorValue=analogRead(A0);
float R0=(1023.0/sensorValue)-1;
Serial.print(&quot;R0 = &quot;);
Serial.println(R0);
delay(500);
}
```

Coding 2:

To find PPM of toluene:

```
#include &lt;math.h&gt;
#define Vc 4.95
//the number of R0 you detected just now
#define R0 34.28
void setup()
{
Serial.begin(9600);
}
void loop()
{
int sensorValue=analogRead(A0);
double Rs=(1023.0/sensorValue)-1;
Serial.print(&quot;Rs = &quot;);
Serial.println(Rs);
double ppm=pow(10.0,((log10(Rs/R0)+0.1119)/(-0.4329)));
Serial.print(&quot;Toluene ppm = &quot;);
Serial.println(ppm);
delay(1000);
}
ppm = 10 ^ ((log10(Rs/R0) + b) / m)
```

Result and Discussion

Subjects	Age (years)	Gender	Toluene concentration (in ppm)
1	24	Male	0.24
2	23	Male	0.18
3	22	Male	0.31
4	22	Female	0.16
5	22	Female	0.23
6	25	Male	0.26
7	30	Male	0.32
8	28	Female	0.28
9	27	Male	0.15
10	25	Male	0.30
Non-smoker (n=10)	24.8 ± 2.78	-	0.24 ± 0.06

Table 3. *Toluene concentration sampled from subjects without smoking habit*

Comparison Statement

Table 1 presents the result that was obtained from subjects without smoking habit and Table 2 from subjects with smoking habit. Toluene concentration in atmospheric air 0.59 ppm is recorded as reference. Breath samples from healthy individuals without smoking habit were collected at least 30 minutes after their last food intake in-order to avoid any errors in toluene concentration. The toluene concentration sampled from them falls between 0.1 to 0.4 ppm ranges. Breath samples were(sample A)

Subjects	Age (years)	Gender	Toluene concentration (ppm)
1	33	Male	0.42
2	37	Male	0.54
3	42	Male	0.58
4	29	Male	0.50
5	26	Male	0.44
6	30	Male	0.60
7	32	Male	0.66
8	40	Male	0.54
9	35	Male	0.51
10	28	Male	0.74
Smokers (n=10)	33.2 ± 5.27	-	0.55 ± 0.1

Table 4. *Toluene concentration sampled from subjects with smoking habit (smple B)*

Breath samples were collected from individuals with smoking habit after 30 minutes from taking their last puff of smoke in order to avoid excess concentration of toluene in the breath sample. The breath samples are collected from diverse group smokers that ranges from occasional to chain smokers and the toluene concentration sampled were always above 0.4 ppm

Conclusion

Toluene concentration in breath samples of non-smokers always falls below 0.4 ppm whereas on the other hand, the higher toluene concentration (i.e. always above 0.4 ppm) was seen in breath samples of smoking individuals. This indicates the toluene from cigarette smokes gets deposited in respiratory airway. This direct indication of toluene deposition in the airway reveals that they are at the risk of developing lung cancer. The sensing system developed by the proposed method could find significant differences in the toluene concentration of healthy and smoking subjects. Therefore, we suggest that the proposed idea could be used for lung cancer screening.

References

1. A.Zamini ,et al"Lung cancer detection using frequency-domain microwave imaging" ,International Electrical Electronic Engineering, 2014.
2. Albert Tangerman, Halitosis in medicine : a review. Department of Gastroenterology and Liver Diseases, University Medical Center Nijmegen, 6500 HB Nijmegen the Netherlands 2002.
3. Chris L. Whittle, Steven Fakharzadeh Jason Eades, and George Preti, Human Breath Odors and Their Use in Diagnosis, 2007.
4. Noah lee ,et al"Potential of Computer-Aided Diagnosis toImprove CT Lung Cancer Screening" ,International Electrical Electronic Engineering, 2013.
5. Ping chan,et al"Breath Analysis of Lung Cancer Patients Using anElectronic Nose Detection System" ,International Electrical Electronic Engineering, 2015.
6. Shannon Fischer, et al" Sniffing for Cancer : Nano Noses Hold Promise for Detecting Lung Cancer and Other Diseases" International Electrical Electronic Engineering, 2013.
7. Stephen lam ,et al" Sex and Smoking Status Effects on the Early Detection of Early Lung Cancer in High-Risk Smokers Using an Electronic Nose", International Electrical Electronic Engineering, 2017.
8. Tanthip Eama ,et at "Screening and discrimination of Hepatocellularcarcinoma patients by testing exhaled breath with smart devices using composite polymer/carbonnanotube gas sensors ",International Electrical Electronic Engineering, 2012.
9. Thomas pengo, et a l" Novel Automated Microscopy Platform forMultiresolution Multispectral Early Detectionof Lung Cancer Cells in Bronchoalveolar,International Electrical Electronic Engineering", 2017.
10. Wei Qiam ,et at"Fusion of Quantitative Image and GenomicBiomarkers to Improve Prognosis Assessmentof Early Stage Lung Cancer Patients" ,International Electrical Electronic Engineering, 2010.
11. Xiao Yao ,et al"SCT Promoter Methylation Is a HighlyDiscriminative Biomarker for Lungand Many Other Cancers" ,International Electrical Electronic Engineering, 2014.
12. Xing Chen ,et al"A Non-invasive Detection of Lung CancerCombined Virtual Gas Sensors Array with Imaging Recognition Technique" ,International Electrical Electronic Engineering, 2016.