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ELECTRONIC NOSE FOR DETECTING LUNG CANCER

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Abstract - ***"When a person arises in the morning, think of what precious privilege it is to be alive-to breathe the fresh air."Lungs, one of the most vital organ in our body. The growth of extra cells on lungs leads to lung cancer, most lethal cancer. Till today there is no cost effective method introduced to detect lung cancer. Volatile biomarkers opened a new door to solve this problem. By detecting the volatile biomarkers from headspace of cancer can be analyzed from the exhaled air we breathe. This can be detected directly or indirectly. Direct method is via biomarkers from exhaled breathe. Indirect method means by using a non - invasive novel device. This device is named as "Artificial Electronic Nose". This device uses cross selective and sensitive sensor arrays to detect lung cancer biomarkers. Biomarkers or bio-indicators play an important role in detection of lung cancer [4]. They are volatile organic compounds released from the diseased from the organs. The volatile chemical biomarkers for lung cancer are alkenes, ketones, specific aromatic hydrocarbons (benzene derivatives). Expired breathe analysis is most valuable because it can provide many information about the physical parameters and its abnormal variations. This method is non – invasive, comfort, and can be repeated many times. Also it provides more direct information respiratory function than other means. Electronic nose can be classified as an ideal device owing to its versatility, cost effectiveness, rapid output and size. The main working principle for e – nose are Conductive Polymer (C P), Metal – Oxide Semiconductor (MOS), Quartz Crystal Microbalance (QCM) and Surface Acoustic Waves (SAW)***

Key words: *Electronic nose, diagnose lung cancer, diffusion method, fast responsive, non- invasive, highly sensitive, nano sized device*

I. INTRODUCTION

"Smoking is hateful to the nose, harmful to the brain and dangerous to the lungs"

Human nose is an inevitable part of human body it helps to feel the odor of the food, perfumes, and flowers and to respire. Smokers are increasing worldwide without any limits. Smoking leads to lung cancer. Lung cancer also known as carcinoma of the lung or pulmonary carcinoma. In lung cancer there is an uncontrolled growth of cells and tissues in lungs. Lung cancer will affect not only the smokers, but also to those people who are living around them. Many people die due to the lung cancer. This is because; it is diagnosed in an advanced stage. Early diagnosis of lung cancer can save millions of death occurring in world wide. The method used for diagnosing lung cancer is Computed tomography, Bronchoscope, Biopsy and Pulmonary puncture. C.T Scan also known as X-Ray computed tomography. The C.T Scan is a long process, costly, and cannot be diagnosed easily. So a new device has been introduced called electronic nose which helps to diagnose lung cancer.

Electronic nose is also called as e-nose. It works by detecting the volatile biomarkers. If this volatile biomarkers are present in the body, it shows an increased genetic risk of occurring lung cancer in that patient. The air breathe out by the diseased persons contains carbon dioxide, carbon monoxide, nitrous oxide and other volatile

organic compound. By detecting the presence of Volatile organic compound (VOC) we can understand the chance of lung cancer in that patient. The electronic nose can identify the presence of VOC by an array of coated sensors, for example silicon chip which can detect VOC. The electronic nose consists of a sensor which converts the non-electrical signal to an electrical signal. The non electrical signal entering the electronic nose is the exhaled gases by human. If the presence of hazardous gases which can lead to lung cancer is present in the person's body, the electronic nose produces an alarm. There by knowing the threat of lung cancer [9].

Once it is diagnosed, it can be treated even before it spreads the entire body and can be treated as early as possible. Thereby we can save millions of people worldwide. In this paper, we are discussing about the development of the electronic nose, how electronic nose detects lung cancer and a survey on people having lung cancer.

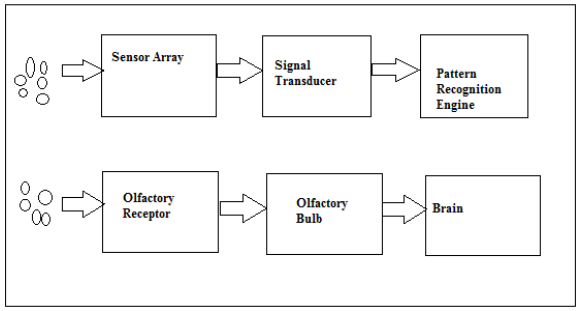


Fig.1: Image showing comparison between working of Mammal olfactory and electronic nose

II. LITERATURE SURVEY

The way of detecting diseases by means of olfactory sense was first originated with Hippocrates around 400 BC [7]. Early studies shows that dogs have the ability to detect cancer by sniffing the affected person's exhaled breathe. Similarly e – nose can easily detect aroma. Initially, the human sputum was poured on hot coals to generate a particular smell. From that particular smell they detect the human ailments. The olfactory diagnosis was developed long before the germ theory of diseases. Before the outbreak of e – nose, chest radiograph was performed to detect lung cancer and help to reveal consolidation, atelectasis, and pleural effution. Another technology is CT imaging, but it fail for early detection and cost. Brochioscopy was another method. Since the late 1990's, various prototypes were suggested to compare the features and characteristics of sensors. Now days, the demand for electronic nose is increasing substantially and become unanimous. Sensors are the main part in electronic nose Different types of sensors has been used in e – nose. Each one has different properties. It consists of a sensor array to provide output. Other analytical instruments like Electron Capture Detectors (ECD), Flame Ionization Detector (FID), Flame Photometry Detector (FPD), and Mass Spectrometers were not considered as e – noses. The main reason for this is, it do not provide a collective data output from the array of sensors. Applied Sensor Company has sold around 100,000 of their e- noses in past 10 years. More than 20 years ago scientist Gordon and O Neil suggested the relation between exhaled breathe containing VOC and lung cancer detection [2]. Many researches and analysis were done with lung cancer positive and negative patients and identified around 20 VOCs that have remarkable role in lung cancer detection (biomarkers). The entry of e – nose in medical field is by detecting the diseases by segregating pathogenic microorganisms. They also unveiled its ability distinguish variety of bacteria and fungi from human body. Electronic nose helped to identify severe lung cancer and discriminate between 14 bronchiogenic carcinoma. This device is based on 32 polymer composite sensor arrays. The output from this sensor is processed by filtering and baseline correction and then analyzed. The remarkable feature of e – nose is its 71.4% sensitivity and 91.9% specificity for early diagnosis. It can detect both lung cancer and related disorders.

III. PROPOSED METHOD

A. SNAPSHOT ON LUNG CANCER

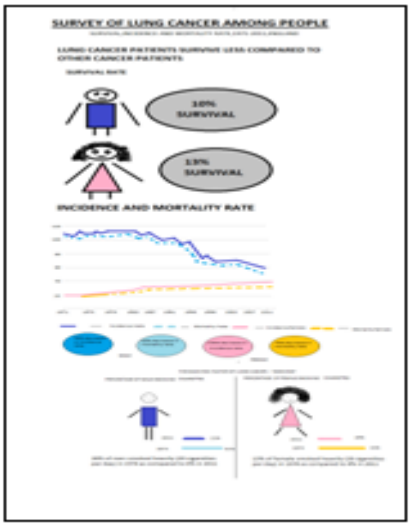
Lung cancer is a silent killer, was an unknown fact before the outbreak of smoking. Initially, the percentage of lung cancer patients as a total is very minute. But as the bad habits of man arise drastically, the percentage of LC also rises to its peak level [3]. Lung cancer can be classified based on their histology. Lung cancers are raised from epithelial cells.

The classification of lung cancer can be performed by studying the characteristics of cells under a microscope. Lung cancer can be primarily classified into two as non small – cell lung carcinoma and small – cell lung carcinoma [17]. NSCLC can be further classified as Adeno carcinoma, squamous cell carcinoma, and large carcinoma. Around half of the lung cancers are adeno carcinoma, originate in peripheral tissue. Lung cancer can be also affected by females who never have the habit of smoking. This is a subtype of adeno carcinoma, named as brochio alveolar carcinoma. Small – cell lung cancer contains a clump of neuro secretory granules. They spread at a faster rate in a un-controllable manner even in the early stage. This is mainly associated with smoking.

Adeno carcinoma	>40%
Squamous cell carcinoma	30%
Large cell carcinoma	9%

Combination of lung cancer subtypes causes dreadful cancers namely glandular tumors, carcinoid tumors and undifferentiated tumor. The main reason for wide outbreak of lung cancer is metastasis. Lung is a sponge like organ, so it can be easily disturbed [16]. The cancers affecting various parts of the body can spread to this soft organ meant for respiration. For e.g.: Metastatic Breast Cancer - cancer that spread from breast to lungs [21].

B. SURVEY ON LUNG CANCER



The figure shows the incidence, mortality and survival rate among the people in England from the year 1971 to 2011 as per the national statistics survey. From this survey, it is understood that those who are suffering from lung cancer the survival capacity for them is very less when compared to other patients who are affected with other types of cancer. The male patients who are affected with lung cancer will have a 10% chance of surviving and it is low when compared to female patient's survival. Female with lung cancer will survive a bit more than male patients that are 13 percent. The rate of occurring lung cancer in male is decreasing from 1971 to 2011 as per the graph. While female incidence rate of occurring lung cancer is increasing from 1971 to 2011 at a rate of 105 percent. Men death rate is also decreasing as the rate of occurrence of lung cancer in them is also low. It is decreasing at a rate of about 55 percent. As women, being affected with lung cancer is increasing; their death rate is also increasing at a rate of 76 percent. From this it is understood that women is more prone to lung cancer [14].

The main cause of lung cancer is smoking. In 1974, about 51 percent of males smoked. At that time, female smoking rate is 41 percent. In 2011, a male smoking rate is 21 percent, while female smoking rate is 19 percent. About 26 percent of the males smoked heavily, that is 20 cigarettes per day in 1974. Now it is reduced to 6 percent. 13 percent of women smoked heavily, that is also same as males 20 cigarettes per day in 1974 and it is reduced to 4 percent in 2011. So a need for cure for this hazard ling cancer should be founded. To treat it properly we need to diagnose it as early as possible. Thus the electric nose has been found with this purpose.

C. IMPORTANCE OF AN ELECTRONIC NOSE

The success of modern medicine depend on how fast a disease is being diagnosed, this paved a way for electronic nose. It helps to detect severe lung diseases. One of the deadly diseases among the long list is Malignant Mesothelioma (MM), a very rare tumor, difficult to diagnose in primary stages. But if it is treated early, can be cured for sure[15]. Here, the vital features of e- nose come into play by using CPA (Carbon Polymer Array) to recognize specific breathe pattern an odour. It detects not only malignant but also benign tumors. Asbestos is the main villain for Malignant Mesothelioma. Death rate due to MM is 15,000 – 20,000 per year. The techniques that have been used for decades are inaccurate, and difficult to manage. So, for early diagnosis a new technology is essential. Most of the diagnosis were done by sucking blood, from urine etc. scientist are racing to avoid these

invasive methods of diagnosis. E – nose has the capability to monitor the metabolites released by microbes from the diseased part. The traditional devices that we have being using can be replaced by e – nose because of the demerits of conventional devices like high cost, high complexity, and slow result.

D. PRINCIPLE OF OPERATION OF ELECTRONIC NOSE

Electronic nose is used to copy the human nose. It consists of an array of sensors that can identify and react to odors. The various methods used to grab the odor molecules into the e-nose are diffusion method, headspace sampling bubblers or pre-concentrators. It is sensed by the sensors and the transducers convert the non electrical quantity to electrical quantity for example conductivity. The sensors used are sensitive only to the VOC. Thereby it can detect VOC very faster. Usually while using sensors noises can occur. These noises can be eliminated by methods such as differential, relative and fractional. To eliminate the unnecessary noises any of these three methods can be used.

1. **Differential**

$$Y_s(t) = (X_s(t) + \mathcal{C}_A) - (X_s(0) + \mathcal{C}_A)$$

$$Y_s(t) = x_s(t) - X_s(0)$$

$Y_s(t)$ – Baseline manipulated response.

$X_s(t)$ – Sensor response, $X_s(0)$ – Baseline.

2. **Relative**

$$Y_s(t) = [X_s(t)(1 + \mathcal{C}_m)] / [X_s(0)(1 + \mathcal{C}_m)]$$

$$Y_s(t) = X_s(t) / X_s(0)$$

$\mathcal{C}_m$ - Multiplication drift.
$Y_s(t)$ – Dimensionless response.

3. **Fractional**

$$Y_s(t) = [X_s(t) - x_s(0)] / X_s(0)$$

E. DIFFERENCE BETWEEN HUMAN NOSE AND ARTIFICIAL NOSE

HUMAN NOSE	ELECTRONIC NOSE
More complex	Less complex
Contains thousands of receptors	Sensors are present
It can differentiate millions of odors	It can differentiate only particular odors.
It cannot detect any disease.	It can detect diseases.
The odor which is recognized is send to brain.	The odor which is identified is send to a portable PC

F. WORKING OF AN ELECTRONIC NOSE

Electronic nose which is fast responsive, non- invasive, highly sensitive, nano sized device to detect lung cancer. The important thing in an electronic nose is the sensor. The sensor detects the volatile organic compound released during breathing. Example:-Array of SAW sensors, Array of silicon. The VOC's present in the patients breathe is carried by the nitrogen. It happens because nitrogen has an affinity towards VOC [19]. The nitrogen is injected into the capillary column of the person. This is used in some e-nose only. When the VOC removes out of the column, they get adsorbed alternatively on the sensor. The electrical signals which are obtained from this are given for data recording, data transmission, data storage and data processing. The image of the signal thus produced. From these signals, we can identify the person with lung cancer by looking at the peak in the graph

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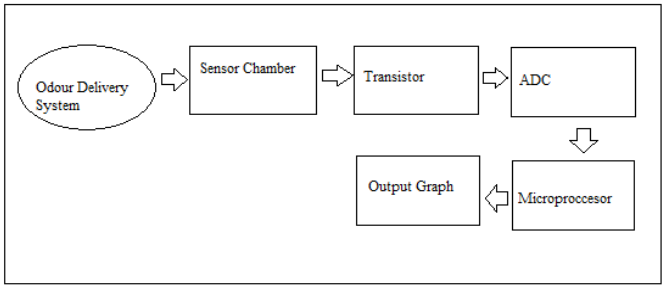


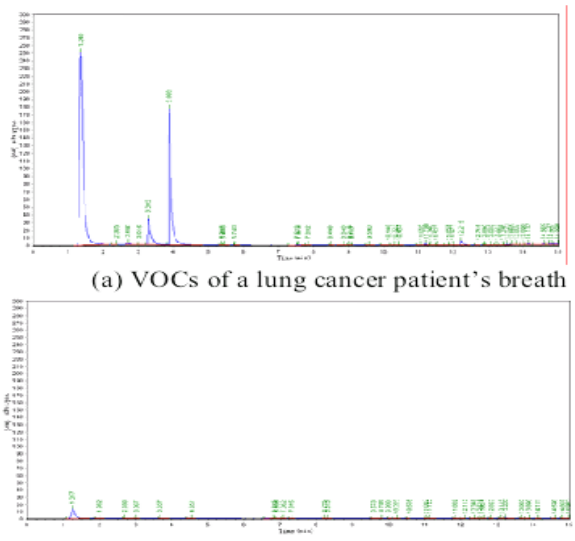
G. BASIC INSTRUMENTATION SET UP FOR ELECTRONIC NOSE

The basic components for explaining the working of e – nose are:

The odor delivery system, this is mainly employed to transfer volatile organic compounds /molecules from system to array of sensor system. Sensor chamber were all the sensors placed. This chamber is kept in an ambient atmosphere, having specific physical parameters (e.g.: temperature, humidity, pressure). Ambient atmosphere is created in order to avoid the adsorption or distraction of aroma molecules [12]. Transistor, the aroma molecule that are obtaining from the source is in the form of chemical signal. An electronic transistor helps to convert the chemical signal into electrical signal. Since the bio-signal (chemical signal from the source) are very small so it should be boosted with the help of an amplifier and further signal conditioning is performed. An Analog to Digital Converter (ADC) is attached along with the signal conditioning unit because the signals from source is analog and it is needed to convert into digital form, the form that the computer can understand easily. Microprocessor, the main function of this unit is to read the digital output from analog to digital converter and output is displayed, then the classification, analysis are performed. Basic constrain of an e – nose is, it should contain an efficient sensor array system that have the same ability of human nose. Manual headspace sampling is one of the simplest aroma delivery system. The materials that generate aroma are housed in a closed chamber and permit to form headspace. The volatile organic compounds are removed from the vessel by means of sucking instrument for e.g. syringe and then injected to the sensor chamber and then further conditioning is done.

H. OUTPUT OF ELECTRONIC NOSE

The person's breath should be collected in a bag. The bag we used to collect the air exhaled is called as toddler bag. Care should be taken that while collecting the breath flowers, or room sprays should not be used in the room. The whole room should be under constant temperature and humidity. By showing the air collected in the toddler bag to the e-nose, it produces a waveform which shows the amount of VOC in the person. The graph is plotted on a voltage – time axis. Voltage is taken on the Y- axis and time is taken on the X- axis. The amplitude of the VOC show whether the person is having chance for being affected with lung cancer[20]. Those persons who are having risk of being affected with lung cancer have a high peak voltage in graph than the healthy person.



(a) VOCs of a lung cancer patient's breath

(b) VOCs of a health person's breath

Fig. 3 Comparative data between a patient and a health person detected by GC

There are about four different lung cancer cells. They are squamous cell carcinoma, Gland cell carcinoma, non – small cell carcinoma and bronchial alveolus carcinoma. The graph has different peak voltage with respect to different cancer cells. Squamous cell carcinoma is having a high peak voltage followed by non – small cell carcinoma. It is followed by gland cell carcinoma. Among these four types, the one with very less peak is bronchial alveolus carcinoma.

From these graphs we came to a conclusion that each carcinoma has each VOC peak. There by we can easily recognize the patient is affected by which of the four different types of carcinoma.

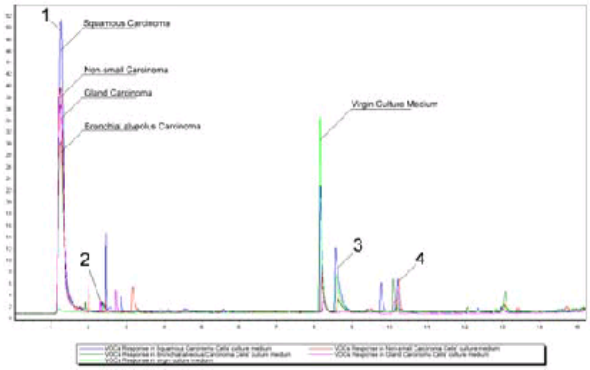


Fig.5 Four different Lung cancer cells' metabolic products (VOCs) contrasted with a blank control in the microenvironment in vitro

I. TECHNOLOGY IN SENSORS

We are using an array of sensors in electronic nose. Lots of varieties of sensors can be used in electronic nose[10]. It includes SAW sensors, silicon chip sensor, conducting polymer sensor, Metal oxide sensor, Optical sensor, and piezoelectric sensor. The main quality the sensor should posses are it should be sensitive to the volatile organic compound, It should give accurate output. It should not react to other odors, Low price, precise measurement, Noise should be less, Signal to noise ratio should be less [1].

Conducting polymers sensor: - Most used sensor in electronic nose is conducting polymer sensor. It is been using from 1980's. Polypyrrole polythiophene and their derivatives are various conducting polymers [11].

Metal oxide sensors: - It works on the principle of variation in conductance of oxide when actions between gas are takes place. The change is directly proportional to the concentration of the gas [13]. This metal oxide sensors are further classified as n type and p type. Its classified on the basis of its reaction to gases. n type reacts to reducing gases and p type reacts to oxidizing gases.

Optical sensors:-They are sensors which help to sense using light. Its thickness is 2 mm. It is coated with a fluorescent dye .The sensitivity of this sensor depends on the type of fluorescent dye used.

Piezoelectric sensors:-Piezoelectric is a property which says where a anisotropic crystal is subjected to mechanical stress it generates electric dipoles. It was proposed by Curie brothers. A piezoelectric substrate is placed on another substrate with transmitting and receiving centre acts as another device called SAW(surface acoustical wave)[6]. Piezoelectric sensors sub classified into 2 types. They are surface acoustic wave (SAW) and quartz crystal microbalance (BAW). It is classified on the basis of gas sensing. This device is based on the principle that when gas is adsorbed there is a change in mass of piezoelectric crystal which results in change in resonant frequency on exposing to a vapor [5].

J. TYPES OF SENSORS AND ITS CHARACTERISTICS

Sl. No	Sensor	Principle	Sensitivity	Merits	Demerits
1	Metal oxide Field Effect Sensor (MOSFET)		**(0.5-50) ppm**	Small size, cost effective.	Baseline drift, less sensitivity
2	Acoustic sensors	Piezo-electricity	**1.0ng mass change**	High sensitivity	Complex circuit
3	Conducting Polymer Sensor(CP)	conductivity	**(0.1-100) ppm**	Sensitive to VOC	Sensitive to temperature Humidity and less life time.
4	Metal Oxide Semiconducting sensor	conductivity	**(5-500) ppm**	High sensitivity, rapid response	High power consumption
5	Calorimetric method	calorimetry	**(10-100) ppm**	Highly stable	Catalyst poisoning

ADVANTAGES OS ELECTRONIC NOSE

- Highly versatile
- Low cost
- Easily available
- Rapid output results should be produced.
- Capabilities of continuous operation
- Early analyzing VOC over a wide range
- Available in miniature size
- Less error
- Early diagnosis of lung cancer
- Portable
- Cost effective
- Painless
- Non-invasive

DISADVANTAGES OF ELECTRONIC NOSE

- Easily affected by temperature and humidity
- Causes sensor drift.
- Catalyst poisoning of sensors
- Some materials are highly sensitive to ammonia and carbon dioxide.

CONCLUSION

Electronic nose is a non invasive, diagnostic device which is used to diagnose lung cancer as early as possible. This device is affordable for common people. Electronic nose is a vast developing technology not only for the detection of lung cancer but for all kinds of cancers and disorders that affect human body. The versatile feature of e – nose is due to specialized sensor array, inevitable unit in e – nose.

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