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BREATHE ANALYSIS FOR DETECTION AND PREVENTION OF CHRONICRESPIRATORY DISEASES AND BRONCHIAL ASTHMA

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ABSTRACT

This paper deals with the role of breath analysis in prediction of chronic and lung related diseases. Every time when we exhale air there are some volatile organic compounds (VOCs) and non-volatile organic compounds also came out with the air. That VOCs are used for prediction of diseases. When these VOCs came in contact with sensors it generates a bio-marks, with the help of that bio-marks we can easily predict information about diseases. There are different methods used for this like as ion mobility spectrometry, different types of electric noses, canine detection etc. you will get much detailed information related to these things in this paper. Here you also get a summarized view of their advantages, disadvantages and about their applications at different stages. This paper is completely based on their past uses, present uses and also about their future scope.

KEYWORDS: Respiratory Diseases, Lung Cancer, Exhaled Breathe & Vocs.

INTRODUCTION

Since earlier times, human's breadth is used for detection of many diseases. Such as uncontrolled diabetes was associated with a sweet and detected by acetone odour, liver failure produced a fish like smell and renal or kidney failure was identified by urine like smell. Dogs were also trained to detect lung cancer and breast cancer in subjects with various stages of disease with almost hundred percent accuracy, merely by smelling the subject's breadth. These observations suggest that there must be and identification or Bio-marks of exhaled breadth that are potentially useful for diagnosis of diseases [1,3,5]. Scientist have done many studies aiming to characterise these Bio-marks over the last 40-45 years. Firstly, in 1971 a scientist named pauling et al using a gas chromatograph(GC), measured 250 different compounds in human breath samples. Since after then another scientist named Philips measured 1,259 compounds in normal in 1997 and over 3,000 compounds in 1999.[4,5] The compounds which were found in exhaled breath were very useful in detection of disease symptoms.

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So from then they get motivated towards development of devices which can accumulate all the samples and gather all the information about that diseases through their Bio-marks. There are many compounds which comes out with exhaled air are classified as follows:-

- Inorganic compounds:- it consists of compounds like carbon dioxide, oxygen, nitric oxide etc.
- Non-volatile compounds:- these category consist of compounds like isoprostanes, cytokines, leukotrienes and hydrogen peroxide.
- Volatile organic compounds (VOCs) which are further classified into different classes like saturated hydrocarbons(ethane pentane, aldehydes) unsaturated hydrocarbons (isoprene),
  Oxygen containing (acetone), sulphur containing (ethyl-mercaptane, di-methylsulphide) and nitrogen containing (dimethylamine, ammonia). The most commonly identified VOCs are isoprane, acetone, ethanol, methanol, other alcohols and alkanes.

The VOCs present in the exhaled air works as a bio-marks for detection of chronic respiratory diseases and many diseases related to lungs. VOCs are endogenous that are produced by body as an end product eg:- isoprene ,an unsaturated hydrocarbon formed along the mevalonic acid pathway of cholesterol synthesis ,acetone an oxygen containing compound produced from glucose metabolism etc. VOCs are also component of exogenous contaminants from the external environment that have been inhaled and absorbed through the lungs or skins.[6,7]

There were many techniques and devices generated for detection of VOCs analysis they are as follows:-

GC and mass spectromy (GC-MS):- Because of the low concentration of VOCs(parts per billion) in exhaled breadth, a sensitive and highly accurate GCs and mass spectrometers have been utilized. But this technique have many limitations which are as follows:-

- Expensive.
- Difficulty of use.
- Highly experienced analysts need to operate them.

So they switched for inexpensive devices and technologies. These include ion mobility spectrometers and electronic nose instruments such as the cyranose 320, the quartz microbalance, colorimeters and gold particle nanosensor.

ION MOBILITY SPECTROMETRY

The working principle behind IMS system is a 550MBq^{63} Ni bita radiation ionising source(Ni), which breakdown analytes, came out with exhaled air into ions. The ions separated and travel down a chamber at speeds according to their related sizes mass and geometry and hits a farady plate at the end of the spectrum which works like a fingerprint for the exhaled breadth. In 2009, westhoff et al. was able to discriminate between 32 patients with lung cancer and 54 healthy subjects including both non-smokers and smokers in the group with 100% accuracy.[7,8,9,10]

Further with an advancement in technology a device were produced named **electronic nose.** It was portable array type device, which is used to detect and identify chemicals in gaseous samples. They are specially designed to respond to the mix of compounds in the sample rather than identify individual compounds. The principle behind the devices is that the VOCs adsorb onto a sensor produce a change in conductivity, colour or oscillation of a crystal. Output comes out from the process which is

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usually a pattern representing the mix of VOCs.[11,12]This devices uses different sensors or analyser for detection or identifications of chemicals in gaseous samples. Some of them are as follows:-

QUARTZ MICROBALANCE

It is an 8 sensor array of oscillatory quartz crystals coated with varied metalloporphyrins to which VOCs adsorb and change the mass of sensors and their oscillation frequency. That change in oscillation frequency is recorded for each sensor. This material (quartz microbalance) was used by di-natale et al. to demonstrate a 90.3% accuracy in discriminating between subjects with lung cancer (n=42) healthy volunteers (n=18) and post-surgery lung cancer patients (n=9) .all the cases related to lung cancer were correctly identified.[12] **Cyranose 320:-** it is a portable analyser with in carbon black polymer composite chemiresistors in an array format. These polymer matrix adsorbs VOCs in exhaled breadth to varying degrees and produce a differential response across the array. The combined results from the sensors produce a sample "smell print". In 2008 dragonieri et al. found that,it is possible to use the cyranose 320 to distinguish patients with lung cancer with accuracy of 85% and healthy control subjects.[13,14]

COLORIMETRY

This type of analyser has dots soaked with chemically sensitive compounds eg: metalloporphyrins on a cartridge. Each and every dot is sensitive to a broad range of VOCs but all having different varying sensitivity. Due to adsorption of VOCs to the dots causes them to change colour. The cartridges are scanned before and after exposure of the sample and the change in colour of the spots is measured and connected to a number. **Gold particle nanosensor:-** it was developed by peng et al. it is a nanaosensor array with 14 gold nanoparticle electrodes overlaid with a mixture of compounds including dodecanethiol, 4-methoxy-toluenethiol, hexanethiol, 11-mercapto-1-undecanol, decanethiol, octade-canethiol, tert-dodecanethiol, 1-butanethiol, 2-ethyl-hexanethiol, 3-methyl-1-butanethiol, 2-mercaptobenzoxazole, 11-mercapto-1-undecanol, 2-mercapto-benzyl alcohol, and 3-methyl-1-butanethiol. When these sensors are exposed to a breadth sample, they undergo a reversible change in resistance and are analysed using principle component and cluster analysis.In addition of these techniques they used method of **canine detection** in which dogs are used to detect different types of cancers by their smell. It was first described in 1989 by Williams, who reported the case of patient's in which dog showing interest in one mole but not others. The first public research revealed that trained dogs were able to detect bladder cancer by smelling urine samples. Dogs were successful in 22 out of 54 case which is about 41% compared with 14% expected by chance. The benefits of these techniques are these are simple and inexpensive as compared to others.[14,15,16] One another method which is used for the detection of chronic respiratory diseases and lung cancer are **EBC analysis**. EBC stands for Exhaled Breadth Condensate. It consists of approximately 99% water vapour as well as a small fraction of respiratory airway lining fluid droplets. EBC collection is simple and safe. The EBC can be collected by the subject breathing through a tube inserted in either a metal tube cooled to 0 degrees(r tube) or through a condenser (eco-screen). They breadth tidally for 10-20 minutes through the system and at the end of the time the condensate is collected and analysed.[20,21]

LITERATURE SURVEY

Respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD), are affectinga huge percentage of the world's

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population with mortality rates exceeding those of lung cancer and breast cancer combined. The major challenge is the number of patients who are incorrectly diagnosed. To address this, scientists developed an expert diagnostic system that can differentiate among patients with asthma, COPD or a normal lung function based on measurements of lung function and information about patient's symptoms [1]. According to global burden of disease (GBD) report in year 2010 that COPD was the third leading cause of death, accounting for approximate 2% of total adult deaths and it will increased to more than 30% in the upcoming 4,5 years. Approximately 1.5 lakh adults aged 40 years or older die due to COPD each year only in Europe [2]. In addition the cost of treatment of these diseases estimated to amount near about 141 billion Euro annually which is really a matter of concern. As the current available tools are not always fulfilling needs there is an increasing interest in non-invasive measurement of exhaled VOCs to improve the diagnosis and management of pulmonary diseases, current research mainly focused on profiles of VOCs rather than on individual compounds [3]. So there is a great need to increase the understanding of unique and common disease mechanisms and risk factors, which can either be natural or anthroprogenic environmental determinants. It influenced scientist to develop a device which can easily detect these disease at early stages and provide a better treatment on time and help in saving many lives [4]. Study shows that fingerprinting of exhaled air by electric-nose can easily distinguish between patients who is suffering from COPD and asthma. Furthermore electric-nose differentiate these patients from asymptotic smoking and non-smoking control subjects. Repeated measurements confirmed this distinction. This clearly shows that VOCs profiles in the exhaled breadth can differ between two inflammatory diseases [5].Indian scientists are currently working to detect early pulmonary diseases with a hand held battery-powered sensor with an electric nose technology because current devices are not so much reliable and cheaper with having accurate report. They are working on porphyry in based sensor for the exhaled breadth test in search of important surrogate markers in initial phases of microbial activity and observations after newer antibiotics. The best thing about this technique is it is non-invasive and cheap and provides instant result, so it increase people satisfaction and save time [6]. There are many techniques which are already available like GC-MS, canine detection but they are time taking and not available at the bed site. Thus, new innovative approaches are needed to help cope with this kind of disease [7]. Electric nose, Ion Mobility Spectrometry, EBC analysis is result of that which provide much better result as compared to previous used technique in lesser time with more accuracy and at lower cost and help in providing better diagnosis and saving many lives.

WORKING PRINCIPLE

The working of breath analyser consists of many steps, there are different components present here for different purposes , they all together make a complete setup of breath analyser, which will be used for breath analysis and provide an actual information about diseases. Firstly people have to exhale his/her breadth through a cavity having pipe like structure for collection of samples. This will be possible due to present of array of sensors at primary stages which changes that exhaled air components into form of electronic signals for further process. The Volatile Organic Compounds (VOCs) sensors we are using here is **Adafruit BME360.** This little sensor contains temperature**,** humidity**,** barometric pressure and VOC **gas** sensing capabilities. After that electronic signals reaches at microcontroller (**MSP EXP430FR6989**), which helps in including

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on-board emulation for programming, debugging and energy measurements. **MSP EXP430FR6989** works like a Launchpad development kitis an easy-to-use Evaluation Module (EVM) for the MSP40FR6989 microcontroller (MCU). It contains everything needed to start developing on the ultra-low-power **MSP430FRx FRAM** microcontroller platform.1st stage of user input is provided here and after processing the output generated at this stage will pass to next stage where a **CC3220** device is present which is used to run all Wi-Fi and Internet logical layers. This ROM-based subsystem includes an 802.11b/g/n radio, baseband, and MAC with a powerful crypto engine for fast, secure internet connections with 256-bit encryption. After that next stage comes where wi-fi router are present which will provide internet or network access, and allowing users to share a connection across multiple devices and computers. There after a mini computer is present there named as Beagle bone Black which have almost all the feature a general computer have. 2nd stage of user input are provided there and all the data will stored in database and uploaded to cloud with the help of Artificial Intelligence (AI), after processing of data and comparison of that data with the data already present in database an end result get ready which will be send on people phone, in which almost all the information related to his/her breath will present.

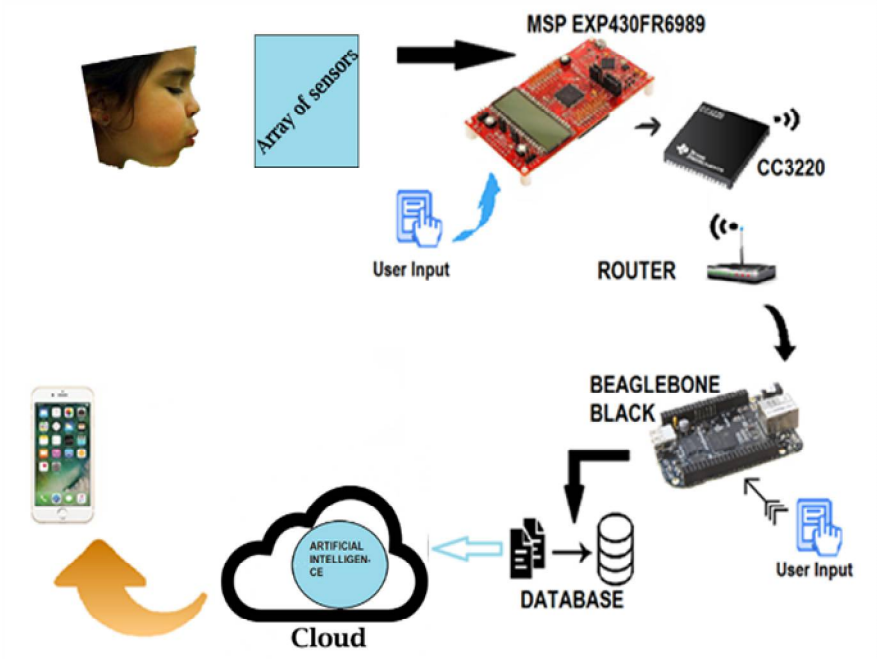

Figure 1.Working of Breathe Analyser

ADVANTAGES AND DISADVANTAGES

1. The main advantages of these breath analysis by different methods is we can easily detect chronic disease like coughing, lung cancer as well as many diseases by their VOCs in primary stages and easily diagonise these problems and prevent many people from death which occurs due to these diseases.
2. It will be much cheaper as compared to other breath analysing devices.
3. It can be used easily by an individual and helps in getting information about the conditions of their lungs just by sitting at home.
4. There is no need for going to hospitals and medical centres for diagnosing as our device can detect any sort of abnormality at an early stage and will thus systematically

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help in diagnosing any sort of disease which might prove fatal at a later stage if unchecked.

5. By all these facilities it helps in reducing the no of deaths caused due to respiratory diseases.
6. It will be non-invasive, easily repeated, and does not have the discomfort or embarrassment associated with blood and urine tests.
7. It will provides direct information on respiratory function that is not obtainable by other means.
8. It can dynamically real-time monitor the decay of volatile toxic substances in the body.

In addition to many advantages there are lots of disadvantages also present in this process.

1. Due to lack of recommended guidelines in the sampling of exhaled breath it is very much difficult to analyse them. These methods vary from place to place period to period, such as the method varies generally according to inhaled air whether it is filtered or not, due to this final analysing varies, time period is also a crucial factor each technique used their own time of tidal breathing prior to collect breath samples. Different methods are used for analysing and at last due to all these variations stastical analysis also varies.
2. Another critical issue is the high water content of breath samples, which may affect pre concentration, separation, and detection of single compounds. This is especially true for mechanically ventilated patients if active humidifiers are used in the respiratory circuit.
3. Compared with the simple chemical tests widely used in serum and urine analysis, instruments for breath analysis are expensive. At present, the most commonly used method, GC-MS, requires bulky instrumentation, is time-consuming, and needs skilled operators.
4. The lack of established links between breath substances and disease is also a problem. Take ethane for example. Ethane is produced as a result of lipid peroxidation, but ethane in breath could also be derived from environmental sources; another source of ethane in breath could be bacteria in the gastrointestinal tract. So I cannot, in all conscience, say that all the ethane in your breath is produced by lipid peroxidation. You don't know the complete origin of it. Therefore, in some case, the breath test is not a conclusive diagnostic tool but can be used as a part of a range of diagnostics.

FUTURE SCOPE

This Device will started a revolution specially in country like India where almost 7% population is suffering from respiratory diseases. With the coming of these devices in market the diagnosis cost decreases to very low, which can be affordable to most of the people. With the increase in pollution day by day climate also changes due to which respiratory diseases also increases, it will works like an important Instrument to fight against these problems. With many advantages it will help in reducing numbers of death and increase standard of living of people in village as well as in cities. It also help government to reduce the expenses on big machines, even a small clinics can afford it and provide better treatment. As we are going to use Artificial Intelligence (AI) in this device it will become smarter with passage of time. Every time it will collect different types of information regarding different diseases through their bio-marks and make a database in computer and after some time it has sufficient data to deal with and next time if it will find any match to data which was collected earlier it can provide much better or accurate

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result. Another benefits of using Artificial intelligence (AI) will be that it can differentiate between different diseases in much better and advanced way. Almost seventeen to twenty different types of diseases can be predicted through these devices.

CONCLUSION

Historically, canine detection of lung cancer was reported to be highly sensitive and specific but it still requires further validation and replication in larger trials to establish its accuracy. Studies examining exhaled breath using GC and mass spectrometers have identified individual chemical compounds associated with lung cancer and confirmed that there is not one VOC but rather a combination of VOCs that are either increased or decreased in concentration. These techniques have limited applicability in the clinical setting because of their expense, difficulty of use, and the need for highly experienced analysts to operate and interpret the results. Electronic noses and related instruments are simpler, cheaper and easier to use, facilitating their utilization in the clinical setting. These instruments employ different technologies to identify VOC patterns. No combination of the instruments, methodologies or statistical analysis has yet been shown to reliably predict which patients in at risk. There will obviously need to be some consensus regarding the most appropriate instruments, collection techniques and statistical methods to optimise the accuracy of the identification. So we are going to make this device which are much better and efficient as compared to previous method which are already in use. Our breath analysing device is very much simple to use, and at a time it also report people about their health with comparison from that database which are already present in computer. For these things person doesn't need to visit doctor and cost of diagnosis reduces.

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