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Research Article

NON INAVSIVE BIOSENSOR FOR DIABETES MONITORING

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ABSTRACT

Objective: A method and apparatus to detect blood glucose non-invasively by measuring the vapor exhaled by humans, which usually consisting of numerous volatile organic compounds (*e.g*. acetone, ethanol, isoprene) generated in the liver, mainly from the oxidation of fatty acids, which further are exported to peripheral tissues.

Method: The proposed measurement system is based on the concentration of the gases present in exhaled breath Detection is completely non-invasive and non-contact type based on metal oxide gas sensors. The developed device will provide non-invasive diagnosis, monitoring of pathological processes and assessment of pharmacological response.

Results: The proposed method could perfectly detect traces of Volatile organic compounds (VOC's), when introduced with the fraction of millilitre of gas (sample)

Conclusion: The present sensor grid is suitable to produce results on some fraction of milliliter quantity of gas. Such compound when detected for the case of diabetes and asthma will indicate the presence of disease. Since we didn't had any opportunity to conduct a test on human being. It is presumed that the system will work satisfactorily for detection of such diseases in non-invasive manner.

Keywords: Volatile organic compound, Diabetes, Metal oxide biosensors, Non-invasive Sensors, Diagnosis, Pharmacological response.

INTRODUCTION

Todaydiabetes is one of the main causes of renal failure in developed as well as developing countries. Diabetes results in many other diseases like visual impairment and blindness. The risk of other diseases in diabetic patent is three times higher as compared to normal person. Diabetes is metabolic disease in which a patient has high blood sugar. This high blood sugar is due to less production of insulin by the body or due to the cells which do not respond to the insulin that is produced by the body. There are mainly three types of diabetes.Type I due to the less production of insulin by the body. The patient requires the injected insulin. Type II is due to a condition in which cells are fail to respond insulin properly. Type III occurs when a pregnant women having high blood glucose level without a previous diagnosis of diabetes.

Insulin deficiency causes the body to metabolize triglycerides and muscle instead of glucose for energy. Serum levels of glycerol and free fatty acids (FFAs) rise because of unrestrained lipolysis, as does alanine because of muscle catabolism. Glycerol and alanine provide substrate for hepatic gluconeogenesis, which is stimulated by the excess of glucagon that accompanies insulin deficiency. Glucagon also stimulates mitochondrial conversion of FFAs into ketones. Insulin normally blocks ketogenesis by inhibiting the transport of FFA derivatives into the mitochondrial matrix, but ketogenesis proceeds in the absence of insulin. The major keto acids produced, acetoacetic acid and β-hydroxybutyric acid, which are strong organic acids that create metabolic acidosis. Acetone derived from the metabolism of acetoacetic acid accumulates in serum and is slowly disposed of by respiration.

The vapor exhaled by humans contains numerous volatile organic compounds (*e.g*. acetone, ethanol, isoprene).1Keton (*β*-hydroxybutyrate, acetoacetate and acetone) are generated in the liver, mainly from the oxidation of fatty acids, and are exported to peripheral tissues, such as the brain, heart, kidney and skeletal muscle for use as energy fuels. [1,3] Acetone is mainly generated from decarboxylation of acetoacetate. Production of acetone is known to increase with diabetic ketoacidosis [4,5] fasting [5,6] and exercise. [7, 8] Since plasmaacetoneconcentrationis significantly related to breath acetone, breath acetone is potentially useful as an indicator of ketosis [9].There are various methods available for the diagnosis of diabetes. These areFasting plasma glucose (FPG) test,Oral glucose tolerance test (OGTT), Random plasma glucose test etc. A limitation of the method is the variability due to the effects of various factors including medications, time of day, and differences in technique and equipment.

Considering fact and limitation of diabetes diagnose methods a novel method of diagnosis is proposed which is free from all the above mentioned limitations. This proposed work is used to diagnose the CVDs (cardiovascular diseases, diabetes, cancers and chronic respiratory diseases) noninvasively. The invention of electronic noses made it possible, for the first time, to produce application-specific instruments that fulfill the needs of clinical requirements for routine use. Electronic-nose devices offers many potential uses and advantages for numerous biomedical applications as a result of a wide range of different operating principles associated with various e-nose instrument types and designs. The major strengths of e-nose devices are their versatile capabilities afforded by the potential abilities of developers to produce low-cost tools for particular applications with customized instrument designs with specific use-requirements, the high variety of individual sensors available for selection (from large sensor libraries) in designing instrument sensor arrays for specific applications, and the wide diversity of useful medical information that can be derived from aroma measurements and analyses of air samples obtained directly from human tissues, biopsies, or cultures. Some of the most important and useful applications of electronic-nose that offer to the healthcare and biomedical fields. Most biomedical e-nose applications have involved the use of MOS sensor arrays containing a variable number of sensors. The utilization of MOS sensors is somewhat surprising given that metal-oxide semiconductor sensors generally must operate at high temperatures and require high power consumption for detection.

A method for measurement system based on the concentration of the gases present in exhaled breath is proposed. This method is perfectly non-invasive and non-contact type. The regular methods

for diabetes diagnosis are costly as the gluco-stripe is very costly and cannot be reused by the patient. Moreover the cost of measurement is very high and significant time is required to diagnose the result.

A system which works on the breath out concentration is therefore proposed. As we know that human beings inhale oxygen and exhale carbon dioxide, but with this carbon dioxide so many other VOC's are also exhaled. When a patient is suffering from diabetes, exhale increased amount of acetone along with carbon dioxide. So this system requires a gas sensors array to diagnose diabetes.

According to the proposed block diagram initially a gas sample is taken in a closed chamber where a sensor array is present. Due to the presence of gas there is some variation in the output of the sensor. The output of these sensors is in the form of voltage or resistance (V or Ω). Then the data is saved in tabular form where the behavior of sensor is specified. After that Artificial Neural Network is used as a tool to identify the gas.

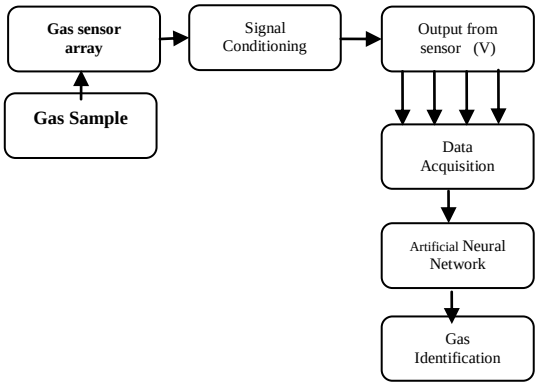

Fig.1: It shows the Block diagram of the sensor setup

Literature Review

Literature survey is an indispensable job of any research work. Some papers are found of direct concern with the work. Brief reviews of all these papers have been presented here.

K.Rajeswari*et al.* [10] investigated the variation in preliminary inquiry information obtained from patients of a diabetic and research center using fuzzy relation based model.. The proposed model is an attempt to closely replicate a physician's insight of symptom-disease associations and his approximate-reasoning for conclusion. The algorithm is evaluated on a dataset of 600 cases. The study is on people approaching diabetician with either past history of diabetes or new case with symptoms of diabetes. Some cases are Normal patients without diabetics. The required parameters are estimated by interviewing patients. Later the parameters are modelled using a fuzzy approach and after normalization classified by Artificial neural networks as 'Close to Type 2 diabetic' or not. This result may indicate the effectiveness of proposed algorithm to optimally model the diagnostic process for small or large datasets; especially, due to its computational simplicity. Further studies on a variety of datasets in different population is required to establish such utility. It is proved that the method as it models the realistic or linguistic way of the patient is proven to be highly efficient with good accuracy. Further, as it works on the real-time dataset, it can assist the diabetolgist as a support for classification and further analysis. The features collected in stage 1 are not enough to classify Type 2 diabetes patient from others. Further stages are required to be analysed for further improvement.

Chris SJ Probert*et al*. [11] proposed that the assessment of disease activity in various conditions may be performed using a range of different techniques. These include the use of non-invasive tests, such as acute phase inflammatory markers and simple radiological techniques, to more advanced invasive and complex modalities. Over the past two decades the analysis of volatile organic compounds (VOCs) in biological specimens has attracted a considerable amount of clinical interest. The investigation of VOCs, using a variety of analytical techniques, has shown a significant correlation between the pattern and concentration of VOCs and the occurrence of various diseases. This provides a potentially non-invasive means of diagnosis, monitoring of pathological processes and assessment of pharmacological response. It may be rapid, simple and acceptable to patients. In this paper we review the medical literature and research efforts that have been carried out over the past decades, and try to summarize the clinical implications of VOC analysis of various biological emanations including stool, breath and blood samples and their correlation with gastrointestinal and liver diseases

DongminGuo*et al*. [12] proposed that certain gases in the breath are known to be indicators of the presence of diseases and clinical conditions. These gases have been identified as biomarkers using equipment's such as gas chromatography (GC) and electronic nose (e-nose). GC is very accurate but is expensive, time consuming, and non-portable. E-nose has the advantages of low-cost and easy operation, but is not particular for analyzing breath odor and hence has a limited application in diseases diagnosis. This article proposes a novel system that is special for breath analysis. We selected chemical sensors that are sensitive to the biomarkers and compositions in human breath, developed the system, and introduced the odor signal preprocessing and classification method. To evaluate the system performance, we captured breath samples from healthy persons and patients known to be afflicted with diabetes, renal disease, and airway inflammation respectively and conducted experiments on medical treatment evaluation and disease identification. The results show that the system is not only able to distinguish between breath samples from subjects suffering from various diseases or conditions (diabetes, renal disease, and airway inflammation) and breath samples from healthy subjects, but in the case of renal failure is also helpful in evaluating the efficacy of hemodialysis (treatment for renal failure).

Ping *et al.* [13] developed a self-made MOS e-nose for the diagnosis of diabetes. Their analyses were performed by a prototype with thin-film sensors coated with SnO_2, having high selectivity for acetone, the most important chemical marker detected in the exhaled breath of diabetic patients.

In a more recent study, Guo*et al.* [14] classified subjects with renal failure before and after hemodialysis using breath samples captured and analyzed with an electronic-nose gas sensor. They successfully applied a similar MOS e-nose prototype system to distinguish between 14 healthy and 18 diabetic subjects suffering from diabetes, renal disease and airway inflammation based on analyses of breath odor. Cluster analysis indicated that diabetic and non-diabetic subjects sampled before a meal were diagnosed correctly, whereas some controls were mistaken for diabetics due to the rise in acetone concentration associated with hunger. One hour after a meal, 100% of diabetics were discriminated from non-diabetics using the e-nose breath tests.

M. Corradi*et al*. [15] showed that the change in glucose metabolism is one of the processes resulting in specific patterns of exhaled VOCs in diabetic patient some of them are breath acetone & ethanol. The breath acetone is increases during diabetes and it is a reliable indicator of circulating ketone bodies. According to M. Corradi, ethanol is not directly produced by any mammalian cellular biochemical pathway, may increase in exhale breath because of alcoholic fermentation of an excessive overload of carbohydrate-rich food, in conjunction with overgrowth of intestinal bacteria and subsequent movement from the gut into the portal circulation. It was also reported that the integrated analysis of breath ethanol and acetone both of which are associated with glucose metabolism, correlated with changes in serum glucose level. A multiple regression analysis of glucose, ethanol and acetone was used to estimate glucose profile which correlated with measured glucose value with an average individual correlation coefficient of 0.70 and not lower than 0.41 in any subject.

MATERIALS & METHODS

As we know that aroma sensor technology is useful in biomedical, by using a sensor array different disease were diagnose such as asthma, diabetes (blood sugar), tuberculosis, lung cancer, breast cancer etc. The objective of this experiment is to determine diabetes and Asthma by non-invasive method that is by using E- nose.

Our test chamber is a cylindrical box which contains the PCB (Printed Circuit Board) where we fixed six different types of gas sensors these are TGS 822, TGS 825, TGS 816, TGS 2620, TGS 2610, TGS 2611(Figaro Engineering Inc.). The system encompasses one input for inlet air coming from an air compressor which has been used to clean the box and the gas sensors after each test. One output is used for the exhaust air. The inner dimensions of the cylindrical box are 13.3 cm length and 17cm diameter while the effective volume is 3020.05 cm^3. The amount of volatile compounds needed to create the desired concentration in the sensor chamber (our cylindrical box) was introduced in the liquid phase using a syringe. Since temperature, pressure and volume were known, the liquid needed to create the desired concentration of volatile species inside the box could be calculated using the ideal gas theory.

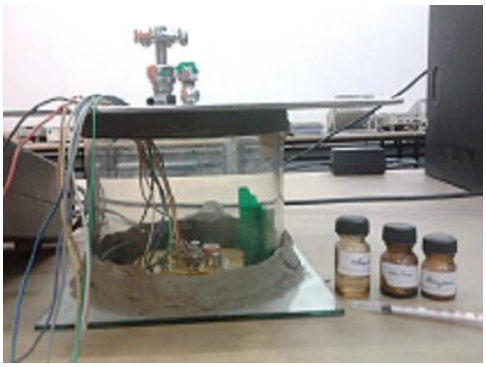

Fig.2: It shows the test chamber

To achieve high recognition rates, several sensors with different selectivity patterns are used and pattern recognition techniques must be coupled with the sensor array.

Metal oxide sensors are one of the most popular technological choices for sensor arrays, due to their high sensitivity [16]. Their main disadvantage is a lack of selectivity. The working principle of these sensors is based on the variation of their conductivity in the presence of oxidizing and reducing gases. The magnitude of the response depends on the nature and concentration of the gas, and on the type of metal oxide [17].

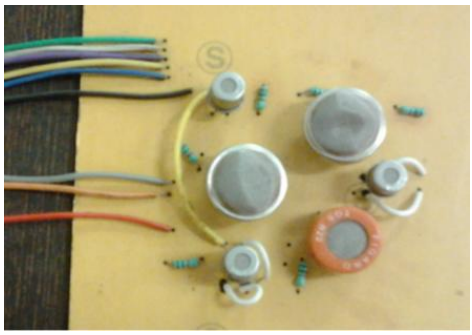

Fig.3: It shows the basic sensor array

The basic measuring circuit for TGS 825, TGS 816 & TGS 822 is shown in figure 3.

The basic measuring circuit for TGS 2610, TGS 2611& TGS 2620 is shown in figure 3.

That the test chamber contains a sensor array, connected to supply voltage of 3.65V and the heater wire with 5V supply. Supply should be given by the help of triple power supply i.e. Triple Power supply, HM5040 by Scientific. A syringe of 1 ml was used for injecting the test volatile compounds. We take acetone as an example for calculating the ppm (parts-per-million) for each compound. Acetone has a molecular weight MW = 58.08 g/mol and density ρ = 0.791 g/cm^3. The volume of the box was 2614.85 cm^3, therefore, for example, to get 100 ppm inside the box we used 0.3 cm^3 of acetone (shown in table 1). The density of acetone is [29]

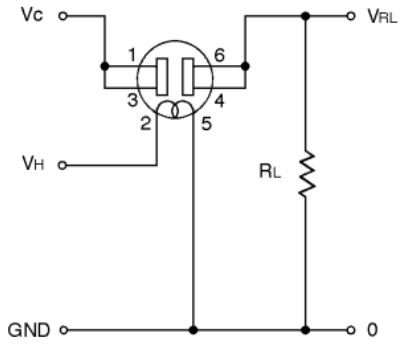

Fig.4: It shows the measurement circuit for sensor

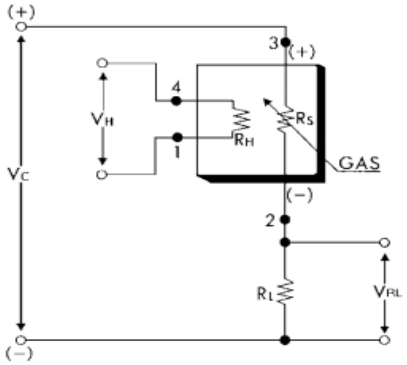

Fig.5: It shows the system measurement circuit

Table 1. It shows the Analyte concentration vs. analyte volume

Table 1: Analyte concentration vs. analyte volume

Analyte concentration (ppm)	Volume of pure analyte (cm^3)
10	0.03
50	0.15
100	0.30
200	0.60
400	1.20
800	2.40
1000	3.00
2000	6.00

$$\partial = \frac{P \times MW}{R \times T}$$

Where:

∂ = the density of the gas of Methanol in g/L,

P = the Standard Atmospheric Pressure (in atm) is used as a reference for gas densities and volumes (equal 1 atm),

MW = Molecular Weight in g/mol,

R = universal gas constant in atm/mol.K (equal 0.0821 atm/mol.K),

T = temperature in Kelvin (TK = TC + 273.15).

As a result we get ∂ = 2.36 g/L

Mass= v_{gas}* ∂ = v_{liquid} * ρ

wherev_{gas} is the volume occupied by the gas of acetone which is equal to 0.3*10^{-3} l, ∂ is the density of the gas of acetone as calculated before, ρ is the constant density of acetone, therefore;

v_{liquid} = (v_{gas} x ∂) / ρ;

v_{liquid}= (0.3 * 10^{-3} * 2.36) / 0.791,

the volume (v_{liquid}) is 0.895 *10^{-6} l which provides 100 ppm of acetone. This means that if we want to get 100 ppm of methanol we must put 0.895 µL of liquid acetone in the box by using the syringe. Table 2 shows different concentrations of acetone (in ppm) at different quantities (in µL).

Table 2. It shows the Acetone quantity vs. Acetone concentration.

Acetone quantity(µL)	Acetone concentration (ppm)
0.089	10
0.447	50
0.895	100
1.790	200
3.580	400
7.160	800
8.950	1000
17.901	2000

In this experiment we use 1 ml, 2ml & 3ml of acetone. Firstly take the readings at ambient air i.e. without inserting any chemical in the chamber. After taking these reading from all the sensors of sensor array then insert 1 ml acetone in the chamber by the help of1 ml syringe and then take the reading with the help of multimeter. Here Fluke 112 (Fluke Corporation, Made in USA) is used for taking readings. After taking reading with 1ml of acetone the whole chamber was disconnected from the supply voltage and removed the upper cover of the test chamber to clean the chamber. After 3- 4hr the glass chamber was cleaned by towel and then rearrange the arrangement for the next chemical i.e. 2ml acetone. The whole process was repeated for 3ml acetone.

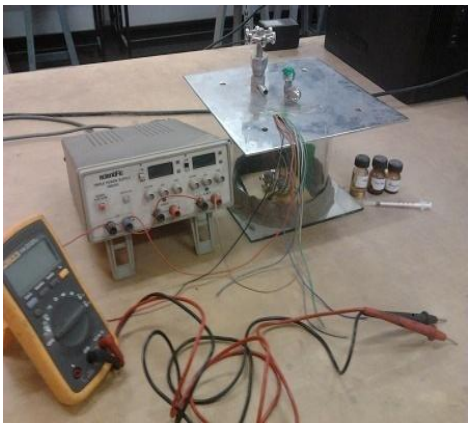

Fig.6: It shows the Data Acquisitionsystem

RESULTS & DISCUSSIONS

After takingreadings at different concentration of acetone, the mean and standard deviation of these values were calculated.

In these graphs six sensors, TGS 2611, TGS 2620, TGS output which indicates acetone having 2.652ml 822, TGS 2610, TGS 816 & TGS 825 were taken and concentration which is near by the 3 ml concentration. All represented as 1, 2, 3, 4, 5 & 6 respectively.

After the tabulation of all the data, ANN (artificial neural network) tool in MATLAB was used to identify the gas and their concentration.

Table 6. Shows that the first sample of unknown gas is acetone of 3ml after testing the data set we get the output which indicate acetone having 2.652ml concentration which is nearer to the 3 ml concentration. All other data also shows the nearby value

Table3: Mean &Standard Deviation of all the sensors output at acetone 1 ml (volts)

Mean/SD	TGS 2611	TGS 2620	TGS 822	TGS 2610	TGS 816	TGS 825
Mean	4.003636	4.640364	3.229364	0.099545	0.097636	3.422091
SD	0.542385	0.58469	0.092517	0.004845	0.003695	0.065485

Table 4: Mean &Standard Deviation of all the sensors output at acetone 2 ml (volts)

Mean/SD	TGS 2611	TGS 2620	TGS 822	TGS 2610	TGS 816	TGS 825
Mean	3.918333	4.681667	3.198333	0.097333	0.0945	3.478167
SD	0.045816	0.015069	0.018758	0.00575	0.000837	0.005776

Table 5: Mean &Standard Deviation of all the sensors output at acetone 2 ml (volts)

Mean/SD	TGS 2611	TGS 2620	TGS 822	TGS 2610	TGS 816	TGS 825
Mean	4.128833	4.355667	3.1595	0.206	0.167	3.479833
SD	0.060519	0.155418	0.019583	0.043179	0.024487	0.011444

Table 6: Mean &Standard Deviation of all the sensors output at acetone 2 ml (volts)

Sensors	TGS 2611	TGS 2620	TGS 822	TGS 2610	TGS 816	TGS 825			
Samples	**(in V)**	**(in V)**	**(in V)**	**(in V)**	**(in V)**	**(in V)**	**Name of gas**	**Conc. (ml).**	**Remark**
Sample 1 (Acetone, 3ml.)	4.4900	4.6050	3.3410	0.1020	0.1010	3.3370	Acetone	2.652	Correct

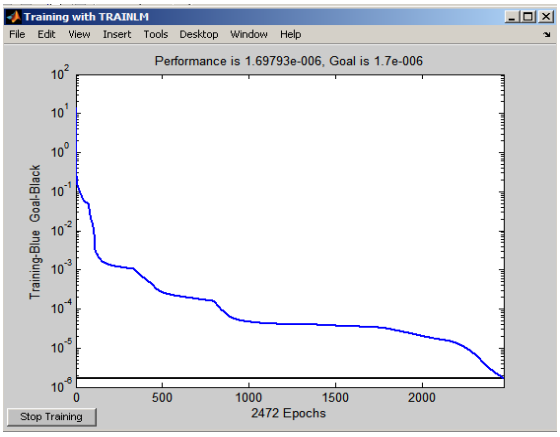

Fig.8: Training curve for Neural Network Model for the verification of gas

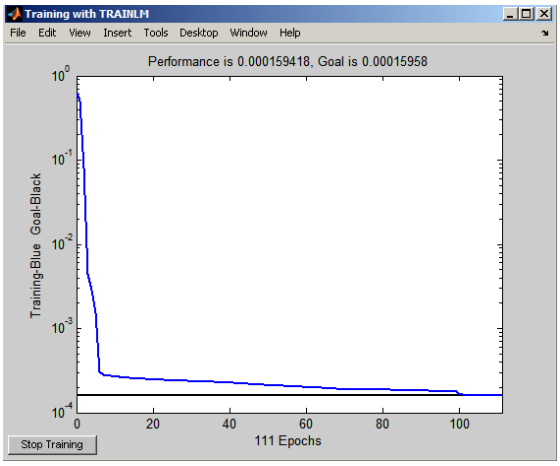

Fig.9: Training curve for Neural Network Model for the concentration of gas

CONCLUSION

On the basis of results and observation the existing experimental set up and applied

ANN tool can detect traces of VOC. Such compound when detected for the case of diabetes and asthma will indicate the presence of disease. Since we have no opportunity to conduct a test on human being. It is presumed that the system will work satisfactorily for detection of such diseases in non-invasive manner. The present sensor grid is suitable to produce results of some fraction of milliliter quantity of gas. Some other tools like PCA, Fuzzy logic, minimum difference method can also be applied for processing.

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