Recent Advancements and Future Prospects on E-Nose Sensors Technology and Machine Learning Approaches for Non-Invasive Diabetes Diagnosis: A Review

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(Methodological Review)

***Abstract*—Diabetes mellitus, commonly measured through an invasive process which although is accurate, has manifold drawbacks especially when multiple reading are required at regular intervals. Accordingly, there is a need to develop a dependable non-invasive diabetes detection technique. Recent studies have observed that other human serums such as tears, saliva, urine and breath indicate the presence of glucose in them. These parameters open quite a few ways for non-invasive blood glucose level prediction. The analysis of a persons breath poses as a good non-invasive technique to monitor the glucose levels. It is seen that in breath, there are many bio-markers and monitoring the levels of these bio-markers indicate the possibility of various chronic diseases. Among these bio-markers, acetone a volatile organic compound found in breath has shown a good correlation to the glucose levels present in blood. Therefore, by evaluating the acetone levels in breath samples it is possible to monitor diabetes non-invasively. This paper reviews the various approaches and sensory techniques used to monitor diabetes though human breath samples.**

***Index Terms*—Non-invasive, diabetes, biosensors, biomarkers, breath, acetone levels.**

I. Introduction

MONITORING Elevated glucose levels in blood for a extended duration of time leads to a metabolic disorder called diabetes. Diabetes is characterized by insulin insufficiency. This can be either due to the body's inability to secrete enough insulin (Type 1 Diabetes) or the inability to use the insulin produced for the metabolic process (Type 2 Diabetes). Such impaired metabolism results in build up of glucose in the body thus leading to elevated Blood Glucose Levels (BGL). This chronic disease if left unattended creates associated problems of the the heart (cardiovascuar diseases), eyes (retinopathy pigmentation), legs (resulting in amputation), kidneys, stroke and such other complications. Currently diabetes has no cure, yet regular monitoring and maintaining blood glucose levels ensures control over adverse effects and complications associated with this disease. The Fig. 1 shows the growth of the diabetic population over the years. According to reports of the World Health Organization, the worldwide diabetic population has increased from 108 million to 422 million over the last 30 years. Among these, nearly half are yet to be diagnosed with this disorder. It is estimated that nearly 642 million shall be affected by diabetes by 2040. Studies also show that the predominance of diabetes among adults has risen from 4.7% to 8.5%. Out of this diabetic population it has been observed that nearly 50 million are Indians making India the diabetic capital of the world. These statistical studies suggest that is a dire need to control such alarming rate of increase in diabetic population worldwide.

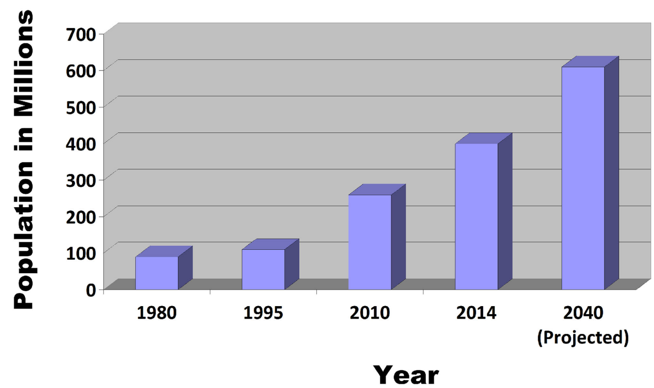

Fig. 1. Growth in diabetic population.

Presently the golden standard for measuring the glucose levels in blood includes a technique of drawing blood from the forefinger. This invasive diagnostic technique of blood glucose level prediction is highly accurate for the detection of diabetes, however this technique involves a lot of drawbacks such as, it is a painful process, it is inconvenient when multiple reading are required in a day, it involves continuously puncturing the

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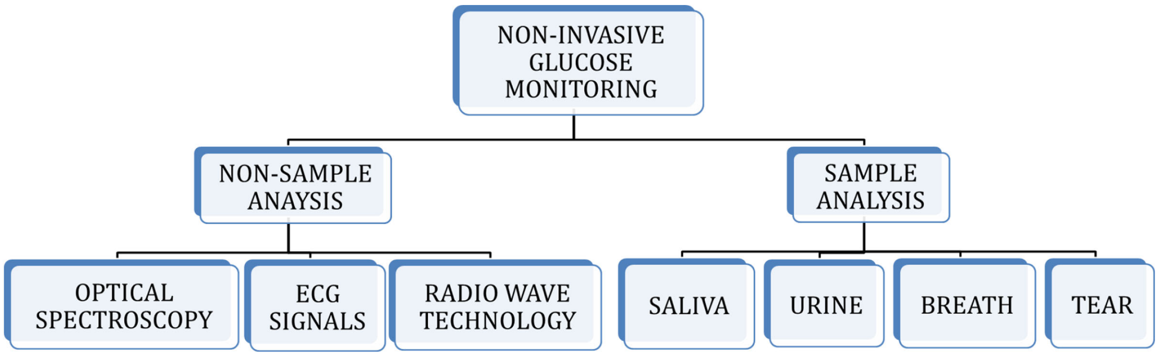

Fig. 2. Classification of non-invasive continuous BGL monitoring.

skin, it has a potential risk of spreading infectious diseases like Hepatitis and HIV, and also the wounds in a diabetic patient don't heal fast. Considering the disadvantages research for a non invasive diabetes detection system has been an area of research for a long time. Many new techniques have been developed, such as optical based sensors which do not need the extraction of blood for the measurement of glucose have been developed for diabetes detection earlier. These techniques involve the interaction of optical beam with the glucose within the body. These techniques make use of near-infrared light (wavelength between 600–2300 nm) which can penetrate into the tissue or fluid. The absorption and scattering of the light rays depends on the structure of the tissue as well as its chemical components which includes glucose. By measuring the optical parameters which include polarization, intensity, or wavelength of the optical signal the glucose concentration can be predicted. This technique although has merits for continuous glucose monitoring, it has a lot of drawbacks as it affects the ratio of body fluids in the tissues due to blood circulation, metabolic activities, creates body temperature shift and requires medications. Also changes in tissue texture, vasculature and changes due to ageing can affect the stability of the sensor in the long run. Millimeter-Wave/Terahertz Spectroscopy have also been studied for the detection of acetone concentrations [1]. Recent researches show evidence of trace content of glucose in human serums which includes tears, saliva, sweat, urine and breath [2]–[6]. These concentrations open quite a few alternatives for blood glucose level prediction. It is found that tears contain about 0.1–0.6 mM [7] glucose, urine contains 2.78–5.5 mM [8] glucose, sweat contains 0.277–1.11 mM [6], [9] glucose and saliva has about 0.008–0.21 mM glucose concentrations [10]. While in breath a Volatile Organic Compounds(VOC), acetone, has show a good relation to blood glucose levels and about 21–0.5 ppm [11] acetone contraction is detected. The classification of different non-invasive BGl techniques are shown in Fig. 2.

On reviewing the suitability of human serums, it has been observed that the biological fluids in urine have been extensively analyzed in clinical investigations. However the drawback of this process is that it requires some pre-treatment techniques as a result of low concentration of target analytes in urine. Also the incapability of the present instrumentation restricts the selectivity and also the sensitivity of measuring the glucose concentrations. Although blood and urine are the frequently used diagnostic human serum in clinical applications, the other serums such as saliva, sweat, tears, and breath also offer some characteristic advantages and researches are analyzing the possibility of these body fluids for diagnostics purposes. Saliva shows an advantage of ease in collection without the need for trained personals or specific equipments. This technique is cost-effective especially for screening vast populations [12]. However in case of glucose detection the range of salivary glucose is in trace quantities thus there is a need for highly advanced spectrophotometry to calculate the amount of these concentrations. Human sweat is another easy to access body fluid which can be used for glucose detection [5], [13]. The working of the glucowatch exploits this technique. Some of the limitations of this technique include a lag of about 20-mins in-between the extraction of the sweat and the calculation of the glucose, the system is inaccurate in detecting hypoglycemia and hyperglycemia and also causes rash under the skin [14]. Investigations have proposed that glucose concentrations in tear fluid as an alternative for blood and hence considerable research have focused on finding different methods to determine the glucose concentrations from tears. However the challenges faced include a requirement of techniques that to have very high sensitivity as well as a very low detection limit. Also another difficult task posed it the ability of the sensor to measure very small volume within a short time duration. Among these serums breath has gained popularity and has posed as a good alternative as a non-invasive technique of diabetes prediction. The human breath samples contain a large concentration of volatile organic compounds [15], [16]. Recent researches show that these chemical compounds act as good bio-markers for the detection of various chronic diseases [15] such as cancer (which includes colorectal, breast and lung) [17], [18], airway inflammations [19], [20], helicobacter pylori infection and recently diabetes. This paper focuses on breath analysis as a viable means of detecting diabetes.

II. Conventional Breath Analysis Techniques for Diabetes Detection

Human breath expels thousands of molecules into the air which comprises of inorganic gases such as NO, CO_2 and CO; volatile organic compounds such as isoprene, ethane, acetone and pentane; and other non-volatile gases. The detailed

TABLE I
VARIATION OF ACETONE CONCENTRATIONS

Diabetic State	Range
Healthy	0.22 to 0.80 ppm
Type 2 Diabetic	1.76 to 3.73 ppm
Type 1 Diabetic	As high as 21 ppm

examination of their concentrations can detail a diverse signature of physiological process that occurred in the body. Such analysis provide information on the health status of the body at present state as well as provide information related to future possible threats. One such VOCs called acetone, also referred as 2-propanone, is a ketone body present in exhaled breath [21]–[25]. During diabetes, the lack of insulin secretion or the inability of the body to breath down the body sugars, leads to a corresponding increase of glucose by the liver. Also the above condition leads to the human body going to the state of ketosis when it is required to break down body fat or sugar for energy. Thus this creates elevated ketone levels in the body. These ketones are excreted from the body though the breath in the form of acetone compounds [26].

Most initial studies have indicated that the elevated breath acetone concentrations elevate with respect to the increase in the blood glucose levels. Table I shows the variational range of the acetone levels for diabetic and healthy subject. It can be infered from the table that the concentrations of acetone in breath has a good linear correlation to blood glucose levels [27], [28]. These threshold ranges show that there is a good classification for the breath samples as Healthy, Type 2 and Type 1. Consequently the acetone levels in the breath samples can be related to the diagnosis and monitoring of diabetes [29]. Initially studies on acetone concentrations in breath were conducted by complex and expensive techniques such as Gas Chromatography-Mass Spectroscopy [30], Selected Ion Flow Tube-Mass Spectroscopy and Cavity Ring-dawn Spectroscopy. Crofford *et al.* [31] carried experimental studies on diabetic patients using GC-MS systems, in the year 1977, to measure the acetone concentrations and find the correlation of these to blood glucose levels. Wang C *et al.*, developed a breathe analyzer based on the principles of the cavity ringdown spectroscopy technique and calculated a range of 0.80 to 3.97 ppmv acetone in type 1 diabetic subjects which was higher than the mean concentration of acetone about 0.49 ppmv in the breath samples of healthy patients [32]. SIFT-MS technique was also used to measure the acetone levels in the breath of eight type 1 diabetes subjects and the authors showed a linear decline of the acetone levels with respect to the blood glucose concentration [33]. Compared to the above mentioned techniques the e-nose technique is seen to have more advantages. In this section the different mechanisms used in detecting acetone concentration are reviewed. Table II gives a brief outline highlighting the gas detection techniques.

A. Gas Chromatography Mass Spectroscopy

Gas chromatography Mass Spectroscopy is one of the traditional and most accurate technique used for gas concentration detection. The gases are detected based on the concept that different molecules in a gaseous mixture possess different chemical properties and hence their relative affinity to a stationary phase varies [34]. Through this concept the molecules of the gaseous mixture are separated and the concentrations of the chemical under analysis can be calculated. The capillary tube of the chromatography is utilized to separates gaseous mixtures into individual components while mass spectroscopy is used to identify the individually separated gas components. This system utilizes two phases which include the mobile phase and the stationary phase which are both placed inside a column. The mobile phase is a carrier gas which usually comprises of an inert gas while the stationary phase interacts with the gaseous compounds that are being analysed. Based on the mass-to-charge ratio, the molecules are separated into ionized fragments in the mass spectrometer thus identifying the components. The Figure 3 outlines the process of gas chromatography mass spectroscopy. This technique has been widely used in the earlier stages of identifying acetone as biomarkers for diabetes. In [21], the authors initially collect breath samples and through GC-MS establish the correlation between acetone gas concentrations and the blood glucose levels. The technique has also been adapted by other authors for detecting acetone in breath samples. It has been found that these concentrations could be one of the indicators for diabetes. Although this technique of detection shows high performance in terms of sensitivity and selectivity to acetone gas molecules when compared to the other detection mechanisms, it is not commercially viable. This is due to the fact that this mechanism utilities bulky and expensive equipment, the portability of the system is very low, the system works on complex mechanism and hence there is a need for specialized technicians, and this technique cannot be used for real-time applications.

B. Selected Ion Flow Tube

The SIFT mass spectrometric method is used to detect trace concentrations of gas by chemical ionisation of the volatile compounds. In this technique the positive precursor ions (H_3O^+, O_2^+ and NO^+) are selected and then are injected into a flowing carrier gas for a defined time period. In the microwave discharge source the precursor ions are formed and are selected according to their mass-to-charge ratio by a mass filter. These ions are then injected into the flow tube with helium carrier gas. These ions travel with the process of convection within the flow tube. The neutral analyte molecules of a sample vapor enter the flow tube with the aid of a heated sampling tube and meet the precursor ions. This may lead to chemical ionisation of the molecules based on their chemical properties such as ionisation energy or proton affinity. The new ion product flows into the mass spectrometer chamber which contains a second mass filter and an electron multiplier detector. This process is schematically explained in Fig. 4.

This gas quantification technique was first developed in the 1970's [35]. SIFT-MS technique has been widely used for quantification of trace levels of gases in human breath (Brian M Ross). The technique has shown good accuracy and has been applied in real time applications [36]. The advantage of this

TABLE II
COMPARISON OF GAS DETECTION TECHNIQUES

Ref.	Technique	Highlights	Challenges
[34]	Gas chromatography - mass spectroscopy (GC/MS)	Separates volatile organic components due to the variation in the chemical properties between these molecules in their gaseous mixture and their relative affinity for the stationary phase of the column. This procedure is highly accurate and shows high sensitivity and selectivity in the glucose monitoring.	High cost, Low portability, Complex usage, Practice cannot be done in real time analysis
[35]	Selected Ion Flow Tube - mass spectroscopy (SIFT-MS)	It is a form of mass spectroscopy where chemical ionization reactions are used to quantify volatile organic compounds. Detection of the VOCs can be done in real time and the accuracy of detection is found to be high.	High cost, Low portability, Complex usage.
[23]	Cavity Ring -down Spectroscopy	This is an optical spectroscopic technique which measures the concentration of volatile organic compound bases on the amount of absorbed or scattered light. The technique is highly sensitivity and it can be performed in real time analysis	Need for calibration procedure.
[39]	E- Nose or Electronic-nose	This is a sensing technology that uses an array of chemical sensors that detect and recognize the volatile organic compounds due to their chemical properties. These technique inexpensive, portable, and have a fast response time. Real time analysis of the compounds is possible	High temperature operations, Sensors are sensitive to humidity

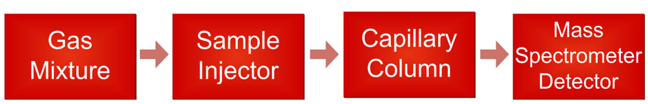

Fig. 3. Gas chromatography mass spectroscopy.

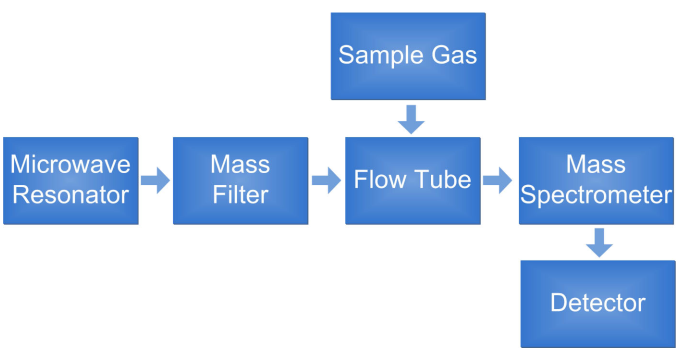

Fig. 4. Selected ion flow tube-mass spectroscopy.

method of acetone detection is that this process can be done in real time with high accuracy. Unlike the previous techniques used (GC-MS), this technique has a faster response time hence this technique can analyse samples in a real time environment. There is also no sample separation required. The high cost and complex usage of this technique renders this method unsuitable for commercial use. Also the detection mechanism involves a complicated technique which again makes it cumbersome to be preferred for clinical applications.

C. Cavity Ring-Down Spectroscopy

This spectroscopic technique measures the gas concentrations through the optical spectroscopic method. The structure of the device consists a laser source, a gas cell with reflecting mirrors, a sample introduction, a oscillator and a data processing unit. The optical cavity gets illuminated by the laser source and the two highly reflective mirrors. The intensity builds within the cavity as the result of the constructive interference once the laser attains its resonance with the cavity mode. The laser source is then switched off in order to allow the measurement of the exponentially decaying light intensity leaking from the cavity. When the acetone gas concentrations are introduced into the cavity, the amount of light decreases faster. Finally the setup measures the duration of time taken for the light to decay from its initial intensity. Thus the concentration of the absorbed acetone gas in the cavity is calculated based on this ringdown time. The rapid response time and high sensitivity of this spectroscopic method makes it attractive for acetone gas concentration measurement. However the need for high calibrations and specialized staff are some of the main disadvantages of this technique. Chuji Wang et al, have used the cavity ring down spectroscopic method to correlate the acetone concentrations to the blood glucose levels and glycohemoglobin A1C in diabetic patients [37]. Similar attempts have been made by the authors Meixiu Sun et al for type 2 diabetes [38]. Fig. 5 structure of the technique.

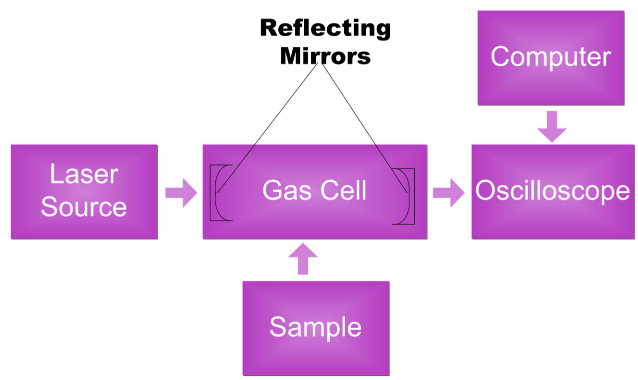

Fig. 5. Cavity ring-down spectroscopy.

D. E-Nose Sensors

All previously mentioned techniques have a lot of disadvantages especially when a user-friendly, portable device is needed for the detection of acetone levels from breath. To overcome these drawbacks the E-nose sensing technology are used to identify exclusive components through chemical means using simple mechanisms [39]. The technique employs a group of

TABLE III
OVERVIEW OF THE SENSOR TECHNOLOGY

Paper	Sensing Technique	Operating Temperature	Response Time	Longitivity	Reproducibility	Detection limit	Drawback	Power Consumed
[40]	Electrochemical	37 ^{o}C	3-5min	1-2 years	Good	0.2-10ppm	Interference of acetadehyde gas	~1.2 μW
[49]	Acoustic	150 ^{o}C	20-30 mins	<2years	Moderate	90.29 mg/dl and 443.2 mg/dl	Interference of moisture in breath	148 mW
[50]	Conducting Polymers	~30-55 ^{o}C	5min	3-4 years	Good	1-10ppm	Long recovery time	150mW
[51]	Metal Oxide Semiconductors	300-900 ^{o}C	3-4min	3-4 years	Poor	>0.5 ppm	Presence of moisture and temperature affects the performance.	833mW
[52]	Carbon Nanotubes	100-400 ^{o}C	~500sec	1-2 years	Good	0.5–5 ppm	Presence of moisture affects the sensitivity.	<30 mW
[53]	Microwave	20–40 ^{o}C	~5min	3-4 years	Good	0-265pp	Interference of other gases in breath.	~20mW
[54]	CMOS-MEMS	25-100 ^{o}C	7-8min	<2years	Good	0.05 -5 ppm	Frequency drift is observed and sensitivity is less.	~400mW
[55]	Photo-ionized Detector (PID)	20 to 60 ^{o}C	<10sec	1-2 years	Poor	0-1500ppm	The sensor shows non-linear response to high concentrations.	90mW

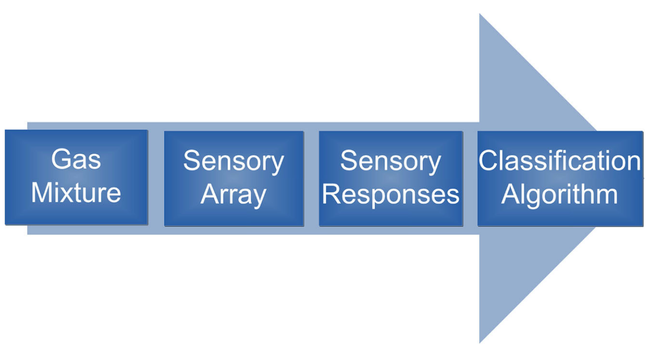

Fig. 6. E-nose.

chemical sensors which are sensitive to the analyte and hence detects the presence of the gas component under study. The e-nose sensor mimics the human nose in order to identify gases based on their chemical properties. The system consists of the sample delivery unit, the gas detection unit and the computational unit. Initially, the gases are injected to the detection system under constant operating conditions in the sample delivery unit. The e-nose gas sensor array is embedded within the detection unit and these sensors undergo some change in their electrical properties based on the presence of the analyte under study. Finally, the computational unit makes use of pattern recognition algorithms in order to identify the specific component under observation and quantify the gas concentration under study. Some of the commonly used sensors are metal-oxide semiconductors, conducting polymers, acoustic sensors (cantilever, quartz crystal sensors) and CMOS based MEMS sensors. Some of the advantages of this detection technique include low cost, portability, fast response time and this technique can be used in real-time applications. However, the influence of other gases and humidity in the detection process pose a big challenge. The Figure 6 explains the systems descriptions.

III. REVIEW ON BIOSENSING TECHNIQUES USED FOR DIABETES DETECTION

In the last decade, research has been concentrating on developing various sensors for the e-nose technique. The main focus of these researches is to achieve better accuracy and cost effectiveness. This section review the principles of the various sensor technologies used and their effectiveness in detecting acetone gas concentrations. Some of the commonly used sensors are reviewed below. Table III shows the overview of the sensor technologies used.

A. Electrochemical Biosensors

These biosensors measure the concentration of target biomolecule through electrochemical reactions which produce a current or potential. In general these sensors are classified as amperometric, conductometric, impedimetric and potentiometric sensors. These sensors are widely used to dectect actone concentations from breath samples. Authors Landini B.E. and Bravard S.T. used enzymatic electrochemical sensors that couple's acetone to hydrogen peroxide formation [40]. The generated hydrogen peroxide is detected chronoamperometrically The acetone concentration in breath is related to the electrochemical current that is produced due to the generation of the hydrogen peroxide. Kun-Wei Kao, *et al.* used a gas sensor made of Indium Nitride (InN) of 10 nm thickness [41]. The hydrogen atoms present on the acetone molecules react with oxygen atoms that are per absorbed in the sensing system. This effectively increases the conductivity of InN by reducing the effects of surface depletion. Tulus Ikhsan Nasution,et al. fabricated a thin film of chitosan-based acetone sensor using an electrochemical deposition method [42]. When the acetone molecule is absorbed into the chitosan body the sensors electrical conductivity is enhanced.

B. Metal Oxide Semiconductors (MOS)

MOS sensors work with the principle that when the gas molecule enters the sensing area there shall be a change in the electric field as these molecules shall be either positively or negatively charged [43]. The charged particles cause a change in the electrical properties such as the conductivity of the sensor. These changes are measured and the gas concentrations are quantified and interpreted by using computational systems. Through literature it is observed that these sensors are one of the most frequently used gas sensors for the detection of VOCs. These sensors are also employed in various studies to detect and quantify small concentrations of acetone samples.

Some of the metal oxides which have been used for detecting acetone include tin dioxide (SnO_2),zinc peroxide (ZnO), gallium dioxide (GeO_2), indium tin oxide (ITO), tungsten trioxide (WO_3), and titanium dioxide (TiO_2). Shoou-Jinn Chang et al, had found that the conductance of the ZnO nano-wires increases in the presence of acetone vapours and when gold (Au) particles are absorbed on their surface it increases the sensitivity of the sensor. These sensors where able to detect about 200 ppm acetone vapour concentrations at 300^0 C with 82% response time. Also SnO_2 nano-wires have shown a high rate of absorption of acetone molecules. Researches also prove that doping these metal oxide semi-conductors with other metals increases their sensitivity. The authors Giovanni Neri et al, developed a Platinum (Pt) doped Indium Oxide (InO) metal oxide semiconductor sensing device. It was observed that the Doping Pt enhanced the response of the sensor over a wide range of temperatures and improved the recovery time of the Indium Oxide based sensor. It could also be noted that WO_3 shows a good absorption of trace quantities of acetone molecules. Researches have also shown that dope metal oxide semiconductors with other chemicals can enhance the sensitivity or observation rate. Chang *et al.*, had observed that acetone vapors have high sensitivity to ZnO with Gold (Au) particles absorbed on its surface [44]. Also the authors Righettoni *et al.* enhanced the thermal stability of $\eta - WO_3$ nano particles by doping Silicon (Si) particles and hence enhanced the detection of acetone in the range of parts per billion [45]. It can be reviewed that the limitation of these sensors is that they tend to get influenced by other volatile organic compounds present in breath samples thus effectively reducing their accuracy of detection. Another limitation is that when the concentration of acetone gas is reduced to a few parts per million the sensitivity of these sensors is found to decrease.

C. Complementary Metal Oxide Semiconductor (CMOS) MEMS Biosensors

This technique has improved characteristics in fabricating Micro-electromechanical system and hence has been employed in many applications in gas sensing systems [46]. Some of the advantages of the CMOS MEMS sensors are that these sensors have shown high sensitivity, have low cost of fabrication, low consumption of power and also enhanced the signal to noise characteristics. These attractive characteristics are mainly attributed to the devices ability to integrate circuit parts with transducers. The device mainly comprises of a sensitive material to detect the gas, a heating element and some electrodes. These sensors mainly employ capacitive based sensing techniques. This technique works on the principle that the sensors capacitance varies based on the amount of gas absorbed on the sensitive material. The change in capacitance properties have been used to calculate the concentrations of gas in breath samples. However the influences of other volatile organic compounds pose as one of the biggest challenges in this sensing technique.

D. Conducting Polymers Biosensors

Organic polymers which posses semiconductor properties are defined as conducting polymers. Since the early 1980s polymers such as polypyrrole (PPy), polyaniline (Pani) and polythiophene (PTh) have been used in various gas sensing systems [47]. It is found that the intrinsic conductivity of these material changes when it absorbs gases such as H_2S, LPG, NH_3 and other gases. When the target analyte comes in contact with the polymer it is observed that there is a change in its electrical resistance. These sensing technique is found to be susceptible to variations in humidity. This in turn affects the baseline structure of the sensing technique [48]. One of the most significant advantage of this form of gas detection is that these conducting polymers are able to detect the target gas at room temperature. Other advantages include that they are simpler to synthesize and thus very cost effective.

E. Piezoelectric Biosensors

The adsorption of target analyte onto the surface of the sensitive layer leads to change in mass on the sensor surface. This produces a change in the resonant frequency of the crystal. One of the most commonly used piezoelectric sensors for gas sensing is the Quartz Crystal Micro-balance.Quartz Crystal Microbalance, is a piezoelectric mass sensor which works on the principle that when any mass is loaded or deposited on the QCM sensor there is a shift in the resonant frequency [56]. These sensors have been widely used to detect and quantitatively analyze liquid or gas molecules. Due to the sensors ability to monitor the target analytes in real time, they have found applications in the field of bio-medicine, food processing, environmental and clinical analyses. These sensors have been previously used under vacuum, in gaseous and recently in liquid environments. These sensors have been used to measure mass ranging from a few micrograms to fractions of a nanogram.

It has been observed that when the sensor is applied with an alternating electrical field which is perpendicular to its surface, a shear deformation called the Thickness Shear Mode (TSM) is observed [57], [58]. This thickness shear mode produces shear stresses inside the quartz crystal when a voltage is applied across the AT-cut crystal. When the QCM sensor is in this state of deformation, the initial resonant frequency decreases when small masses are deposited on crystal. These sensors show better performance when compared to the other e-nose based sensors due to the fact that frequency measurements can be calibrated to high precision thus enabling the sensors to measure and detect even trace quantities of gas or liquid concentrations.

F. Quartz Crystal Micro-Balance Sensor for the Detection of Acetone

One of the main challenges faced by the e-nose sensors is to accurately detect trace quantities of the acetone molecule in real-time. Also as there is a high demand for a portable device there is a need for a sensory device that can be hand-held. Among the reviewed sensors the Quartz Crystal Micro-balance sensor can be used as a possible solution. These sensors are piezoelectric sensor of the dimension of few millimetre range which works on the principle that the sensor experiences a the variation in its resonant frequency when there is a change in the surface mass. The steps given below explain the basic operation of the QCM sensor,

- Initially the gas mixture is passed through a concentrator at room temperature.
- All the valves of the sensory device is turned off.
- Next the heater is turned on till a temperature of 150^0C is attained.
- Once the required temperature is obtained, the sensors are cleaned by passing dry air through them.
- Finally the gas mixture collected is then passed to the sensors.

Typically quartz crystals operate within the frequency range of 5MHz to 20MHz. In order to increase the sensitivity of the QCM sensor, a high resonant frequency of operation is required. These frequency ranges are designed according to the thickness of the quartz plank. So it is observed that the thinner the device, the higher the resonant frequency. However one drawback is that as the quartz plank tends to become thinner, the crystals become more fragile making them unsuitable for regular use. Hence a resonant frequency of about 10MHz is optimal while designing the QCM sensor. These sensors have been widely used to detect and quantitatively analyze liquid or gas molecules. Due to the sensors ability to monitor the target analytes in real time, they have found applications in the field of bio-medicine, food processing, environmental and clinical analyses. These sensors have been previously used under vacuum, in gaseous and recently in liquid environments. These sensors have been used to measure mass ranging from a few micrograms to fractions of a nanogram.

One of the key reasons why these sensors show better performance is due to the fact that the frequency measurements can be calibrated to a high precision hence they have the ability to detect even trace quantities of gas or liquid concentrations. Another main attraction is that the sensitivity of the sensor can be controlled by coating these sensors with chemical layers specifically sensitive to acetone. Layers such as tin oxide SnO_2, zinc oxide ZnO, indium oxide In_2O_3 and tungsten oxide WO_3 are popularly used for sensitive layers and are highly sensitive to acetone. Tungsten trioxide has a good affinity to acetone gas molecules [59]. Studies conducted by Righettoni *et al.* have shown that Si-doped WO_3 shows promising results in detecting acetone gas from the breath [60]. Li *et al.* have used WO_3 hollow-sphere which has shown highly sensitive to acetone gas concentration [61]. Choi *et al.* have reported that loading Rh (Rhodium) to the WO_3 hollow spheres increases the selectivity to acetone vapors. It was also observed that the effect of humidity was also decreased by loading Rh to the hollow spheres. Wang *et al.* have reported that Cr (Chromium)-doped WO_3 has higher sensitivity to acetone as against NO_2 (Nitrogen Dioxide) , H_2 (Hydrogen) and other influencing VOCs [62].

IV. Review on Pattern Recognition Algorithms Used for Diabetes Detection

In the above section, on surveying the different detection techniques it is seen that the E-nose technique shows promising advantages viable for clinical applications. These technique combines the sensory unit and data processing machine learning algorithms. In this section various machine learning algorithms are reviewed and analysed.

Machine learning is a branch of computer science which enables the computer to learn and act without explicit programming. These algorithms are identified as being supervised or unsupervised. In supervised learning there is a requirement to teach the machines the desired output for a given set of input data. In form of learning there is a necessity for these algorithms to provide a feedback regarding the efficiency of the predicted outcomes during the stage of training. During the stage of testing, the algorithm predicts the outcome of new sets of data based on what was learned during training. A more complex processing is adopted by the unsupervised learning systems. In these algorithms the desired outcome are not available during the training phase. These algorithms are required to inspect and search for patterns from the input data and consequently adjust the program actions accordingly. Pattern recognition, a part of machine learning, deals with recognizing a set of patterns and recurrences in a collection of data so as to group them into different classes. These algorithms classify the data set by optimizing mathematical operations. The main aim of these algorithms is to derive the most likely outcome by taking into account their statistical variations.

The process of data classification and prediction employed two main algorithms. Feature extraction and Classification algorithms are the two most common data processing strategies in machine learning approaches. These algorithms have been used widely in detection systems to identify bio-markers in breath samples. The limitations of this traditional approach includes glitches which mainly includes as large computational cost. Also another glitch includes the lack of optimal feature selection. These snags reduce the overall efficiency when applied on real time signals. Deep learning algorithms are found to significantly reduce these limitations by adopting an unsupervised learning technique which combines both the feature extraction and classification techniques. Hence this technique helps improve the classifier's performance further. So as to improve the classifiers performance we have applied the concept of deep learning by modifying the convolution neural network for one dimensional breath signals. This section explains the concept of the proposed one dimensional CNN algorithm along with the details of the system implementation. Furthermore in our work the performance of the modified algorithm has been evaluated.

Previous studies have employed pattern recognition techniques to quantitatively analyze the concentration levels of various volatile organic compounds from breath samples [63]. These techniques have concentrated on optimizing the detection of many diseases by employing various feature extraction and classification techniques. This analysis initially begins by extracting optimal feature from the raw analog signals optioned from the gas sensors. The obtained feature sets are further analyzed with the help of appropriate classifiers. In such analysis it can be observed that in order to extract robust information from the gas signals adequate selection of feature extraction technique is essential. This optimization helps improve the efficiency of the classifier thus increasing the accuracy of the detection system. Some of the feature extraction methods used in prior studies include principal component analysis (PCA) [64], linear discriminant analysis (LDA) [65] and statistical features (standard deviation, mean and variance) [66]. While techniques such as decision tree [67], knearest neighborhood [68], artificial neural networks [69], perceptron [70], support vector machine [71] and other models are some of the classifiers used in literature. The above mentioned techniques have also been found effective in the detection of diabetes. The authors Ke Yan *et al.*, used the combination of principle component analysis algorithm and support vector machines to extract features and classify the breath samples respectively [51]. The authors Yan and Zhang have used transient features (derivative, magnitude, difference, time and integral) from the breath samples and the support vector regression algorithms for the detection diabetes [25]. A radial basis functional neural network were used to classify variations in frequencies of the signals by the authors, Hamdi Melih, *et al.* [49]. Prior literature suggests that selection of apt features for the given data set as well as choosing the appropriate classification technique help enhance the accuracy of the detection systems. Yet there are no reports of formulation of standardized optimal algorithms. Manual or hand-crafted selection of features used in these researches have yielded adequate performance in respect to the data set considered in these studies however the techniques may not be able to concede optimal performance in another thus limiting the generalization abilities of such techniques. Another notable drawback of these studies include the fact of increased computational cost and time due to the number of algrithms involved in the classification of the data samples. Hence these methods are rendered sub-optimal when used for real time detection applications. Recent advancements in machine learning has shown the deep learning algorithms can effectively address these issues mentioned above. Deep learning CNN approach has gained popularity in pattern recognition techniques [72], [73]. Such algorithms have been previously used and accepted for 2-D image recognition, video analysis, speech and language processing. These algorithms previously used for images have now been adopted for 1-D signal data and they have exhibited promising results [74].

Deep learning neural networks extracts features from a raw signal through algorithms that transform the input one dimensional signals through multiple processing layers. Various deep learning architectures have been realized such as the deep belief networks and recursive neural network [75]–[77]. The most popular pattern recognition technique among these algorithms includes the Convolution Neural Network (CNN) [78], [79]. The Fig. 7 shows the comparative analysis of the performance of the different data processing techniques. While the Fig. 8 compares the execution time of all the algorithms. One of the main drawback of the CNN architecture is that it uses the multi-layer perceptron algorithm. This algorithm faces problems of overfitting and hence the support vector machine helps to overcome this drawback [80].

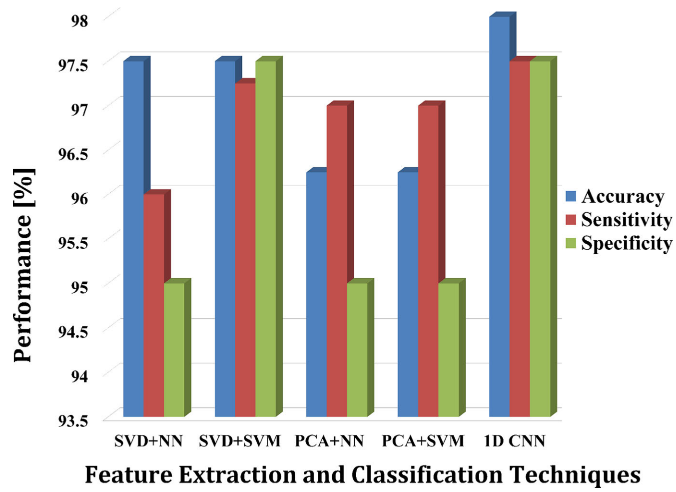

Fig. 7. Performance evaluation of the various classifier techniques.

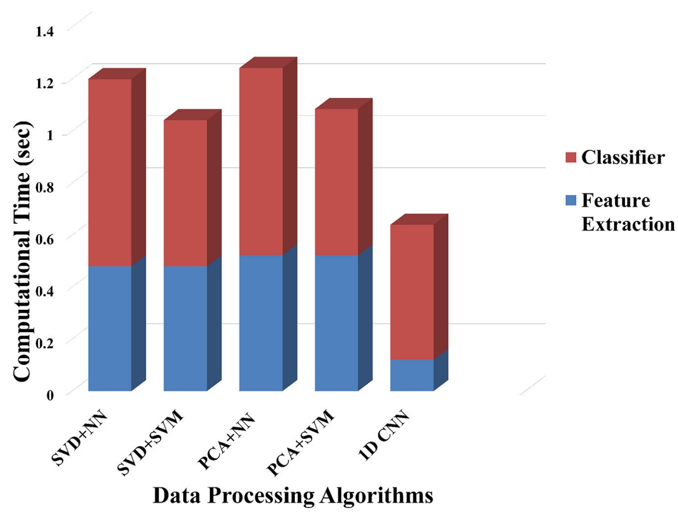

Fig. 8. Evaluation of the computational time of classifying algorithm.

V. Discussion

The meteoric rise of diabetes in the world has resulted in endless researches concentrating on developing effective techniques which helps diagnosis and and treat this disease. Today, the most accepted diagnosis procedure comprises of an invasive technique to diagnose this disease. As the demand for non-invasive techniques grow due to the shortcomings of the invasive approach, the current research on diabetes focuses on developing accurate non-invasive devices to predict diabetes. Some of the recent prototypes include the glucowatch, the near-infrared LED glucose sensor, the smart contact lens and the saliva glucose biosensor. Although these prototypes have made much progress and have achieved commendable performance, they still present a variety of impediments. These include interferences in the sensitivity of the sensor due to influences of other fluids present which have similar characteristics as glucose, need for high levels of calibrations, time lag in the sensors performance, sample collection issues and side effects such as allergic skin reactions. Among the techniques explored, breath analysis for diagnosis of this chronic disease has gained popularity. Over the last decade, there has been an exponential growth in the development of portable e-nose based breath-analyser to detect acetone molecules. This technique incorporates the use an array of chemical sensors and machine learning algorithms to detect diabetes. Various sensors and sensing techniques have been used in detecting the concentration levels of bio-markers in a breath. Sensors such as metal oxide semiconductors, conducting polymers, acoustic sensor and CMOS MEMS sensors have been widely used in developing the breathanalyzer. Unfortunately, these sensors face certain challenges which impede their success in commercial usage. One of the key issues these sensors face is the influence of other volatile organic compounds and humidity present in the breath. Also, when the concentration of acetone gas is reduced to a few parts per million, especially for a type 2 diabetic, the sensitivity of these sensors reduces.

Most recent researches are focusing on using other techniques such as the piezo-electric and MEMS based sensors to overcome the aforementioned drawbacks. Among these sensors, the Quartz Crystal microbalance has provided optimistic results. The principle of operation of this sensor is that when trace quantities of gas molecules deposit on the surface of these crystals there is a change in its resonant frequency. An attractive feature of this sensor is that the selectivity of the sensor can be controlled by coating them with different sensitive layers making the sensor extremely versatile in mass detection. These sensors show better performance when compared to the other e-nose sensors due to the fact that frequency measurements can be calibrated to high precision thus enabling the sensors to measure and detect even trace quantities of gas or liquid concentrations. In our analysis in [81], we have modelled a QCM sensor which can detect trace quantities of acetone in breath samples. The sensors use tungsten trioxide WO_3 as a sensitive layer for determining the level of acetone concentration. The proposed work has shown enhanced efficiency in performance.

Prior studies conducted on improving the e-nose technology has not only focused on improving the sensory system but also improve the performance of the machine learning algorithms used to predict the presence of the disease. Feature extraction and classification algorithms are the two most common data processing strategies in machine learning approaches. Principal Component Analysis (PCA) [75], [82], Linear Discriminant Analysis (LDA) [83], Spatial and Temporal features [84] are some of the commonly used feature extraction techniques while algorithms such as decision tree [85], k-nearest neighborhood [86], artificial neural networks [87], perceptron [70], support vector machine [88] are some of the commonly used classifiers. The limitations of these traditional approaches include glitches such as large computational cost and lack of optimal feature selection. These snags reduce the overall efficiency when applied on real time signals. Deep learning algorithms are found to significantly reduce these limitations by adopting an unsupervised learning technique which combines both the feature extraction and classification techniques [74], [89]. In our works [90] and [91], we have modified the two dimensional deep learning convolution neural networks for the feature extraction and classification of real time breath signal and successfully overcome the challenges posed by the traditional approach. Although these algorithm have shown promising results, they still face challenges such as overfitting. Therefore, enhancing the sensors performance as well as modifying the deep learning algorithms for data classification shall help develop a feasible non-invasive diabetes monitoring system.

VI. Future Prospectives

Development of non-invasive diabetes diagnostic techniques in an economical and clinically viable way is essential to control the rapid progression of this chronic disease. As mentioned in the sections above, diabetes accounts for one of the most important issues concerning global health today. Breath analysis as a non-invasive technique has demonstrated great capabilities for diagnosing this disease. On surveying the various gas analysis technology, the e-nose technique is the potential diagnostic tool for clinical diagnosis of the disease. Even though various approaches for breath based non-invasive diabetes monitoring are proposed and developed there are certain obstacles that halt its successful implementation. The following are some future research directions that can address these issues.

A. External Influences on the Sensors Performance

The e-nose technique, as mentioned in the previous sections, incorporate an array of gas sensors which measures concentration levels of bio-marker under study. Although the technique shows promising results it can be noted that the performance of this diagnostic technique gets the influenced due to the humidity in breath. The sensors accuracy can get affected when the humidity levels in the breath are high. Also the heating elements used for the sensors operation have shown to effect the performance of the sensors to detect the concentration levels of these bio-markers. Incorporating de-humidifiers and development of heat compensation techniques can serve as a promising approach to overcome all the above mentioned drawbacks.

B. Patient Centered Approach

Patient centered approch in diabetes monitoring plays a significant factor as the clinical outcome of blood glucose levels are highly influenced by the individual behaviour of the patient. This approach includes individualized predictive models and interactive models among patient and health care professionals. Despite various attempts to develop various patient centered approaches in diabetes management, there are still challenges to successfully implement these approaches in clinical practice. These barriers include the lack of regular connectivity to health care professionals, absence of good management systems and frameworks. Owing to the advancements in Internet of Things, such health care systems can provide global connectivity among patients and expertise. These advancements can also help personalise diabetes monitoring for better control and management of the disease.

C. Advanced Data Processing Algorithms

The e-nose technique usually comprises for two main component, the first being the sensory unit and the next is the data processing unit which comprises of machine learning algorithms to predict and classify the outcome. Some commonly used feature extraction and classification techniques includes Principal Component Analysis (PCA), Linear Discriminant Analysis (LDA), decision tree, artificial neural networks, perceptron, support vector machine. These traditional algorithms have a lot of merits, however they pose a challenge while applied in real-time systems. These challenges include selection of a proper feature extraction technique, less computational time, and more robust detection system. One solution to overcome such challenges include employing deep learning algorithms. However these this algorithms still face problems of overfitting. Hence advancements in predictive models are required for the enhancement for the performance of the e-nose technology.

VII. Conclusion

A survey on the different detection techniques and sensor technologies to predict diabetes through breath has been studied. It is seen that technique such as Gas chromatography Mass spectroscopy and Selected Ion Flow Mass Spectroscopy gives good accuracy. However these technique cannot be portable hence they can are not viable for clinical applications. The E-nose technique overcome the drawback of the other, but the cross sensitivity to other gases present in breath can decrease the sensitivity of the device. Among the sensor technologies used, MOSFET is the most commonly used sensor for the calculation of acetone. QCM and CMOS MEMS show better results compare to the MOSFET sensor unit. In conclusion it is seen that breath analysis proves as a good non-invasive diabetes prediction system. There is a need to improve the accuracy of acetone level prediction and make this form of diabetes protection portable.

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