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Research Article

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Novel Technology for Non-invasive Extraction and Determination of Blood Glucose Levels

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Abstract Diabetes is a disease in which the body cannot properly process insulin and as such, glucose is not converted into energy required for cell function, growth, and regeneration. Continued diabetic management through monitoring, insulin injections and healthy lifestyle choices is essential to avoid long-term complications, such as blindness, kidney failure and nerve damage. There are several inhibitors to effective blood glucose level self-monitoring as associated with traditional methods involving direct blood extraction and self-interpretation of results, primarily associated with lack of motivation, commitment and perceived negative self-image. This paper proposes a novel technology for non-invasive extraction and monitoring of glucose levels through automated analysis of samples taken from the human breath. This paper discusses the approach, hardware development and calibration, in addition to supporting software, for successful acetone extraction and mapping to blood glucose level, for the purposes of non-invasive diabetic management.

Keywords Diabetes, Blood Glucose Monitoring, Acetone Extraction, Sensor Development, Decision Support

Introduction

Glucose is a vital form of fuel enabling cells in the body to function effectively. Diabetes is a disease in which the body is not able to properly utilize glucose as a form of energy. Where blood glucose is not properly regulated such as with medication, it may reach dangerously high levels and cause complications by slowly damaging the cells within the pancreas, preventing the production of insulin. At this stage a person is hyperglycemic and because of sustained levels of hyperglycemia, organs may become permanently damaged [1]. This may result in irreversible conditions such as kidney disease, stroke, heart attack, loss of vision, a weakened immune system, poor blood circulation to the feet and inability of wounds to efficiently heal [1]. Constant monitoring and management of blood glucose is essential for patients with diabetes to avoid organ failure [2, 5-8], both in type I and type II diabetes.

Physical symptoms of the diabetes may include an increased hunger, thirst, unexpected weight loss, frequent urination, blurred vision, irritability, numbness or tingling in the extremities, frequent infections in the skin, gum or bladder, slow wound healing, or extreme and unexplained fatigue [3]. Chemical symptoms typically require a more invasive and analytical investigation [3, 5], involving direct measurement of blood glucose level most commonly from the blood. The latter is essential for self-regulation of blood glucose with self-administration of insulin via an injection, for type I and a subset of type II, or an oral agent to assist the pancreas in the production of insulin and facilitate the body's processing efficiency of the insulin, for a subset of type II [5, 6, 8].

Irrespective of type, diabetics must actively engage in consistent monitoring and control of their blood glucose level, and make healthy lifestyle choices such as exercise, avoiding drinking and smoking, and healthy weight management [3, 5, 6, 9]. While existing techniques such as the finger-prick extraction of blood enable direct

blood glucose measurement, user motivation for ongoing self-administration of diabetic monitoring and management using such invasive solutions is lacking, with inconsistent user commitment [3, 7]. Further, non-invasive approaches as reviewed in [10] do not enable accurate measurement of blood glucose nor do offer lifestyle management decision support based on the result. Individual requirements for administration of medication for glucose regulation or intake vary depending on degree of mobility, physical condition, chemical requirements and health status [3], however current techniques for monitoring blood glucose do not discriminate for customized needs.

Requirements for blood glucose level depend on the individual; each diabetic varies in the amount of rise or fall of blood glucose over time, in their exercise degree and severity, and in how quickly they burn calories during exertion as well as at rest [3, 5]. There is a need for both a dynamic as well as a customized solution for monitoring and classification of blood glucose levels, in addition to determination of alternative methods for monitoring blood glucose levels without direct extraction of a blood sample, and classification of this into a category, based on the measurement and intended degree of physical activity. To achieve non-invasive determination of blood glucose level, an approach that extracts acetone from the human breath for mapping to a blood glucose level without blood sampling is proposed.

Novel hardware and supporting software development enables acetone to be successfully extracted from the human breath. Algorithm development has enabled this measurement to be mapped to a blood glucose level. Section 2.0 introduces the method associated with extraction of acetone from the human breath. Section 3.0 presents the mapping of acetone to blood glucose levels. Hardware design including architecture, and development of the sensor technology and associated hardware components are presented in section 4.0, for the extraction of acetone. Component and system results are presented and discussed in Section 5.0 Section 6.0 concludes with novel contributions of the work and extensions for future research.

Materials and Method

System Design: Acetone Extraction from Breath

To date, more than 1,000 compounds have been identified in exhaled human breath [2]. Their concentrations range from ppb to ppt levels [2]. Approximately 35 of the identified compounds in the exhaled breath have been established as biomarkers for particular diseases and metabolic disorders [2]. Acetone is one of the chemicals that is present in the human breath. Further, research results have indicated a positive correlation between measurements of ketone β-hydroxybutyrate (β-HB) in the blood and acetone concentrations extracted from human breath [4].

A system has been designed to extract acetone from the human breath and map it to a blood glucose level. As an initial stage, the diabetic subject blows into the apparatus and waits for device initialization. During this time, chemicals in the breath travel through a set of sensors which lie inside the device chamber, the latter comprising an isolated tube with sensor placement in a triangular configuration to prevent interference of the temperature sensor due to dissipation of heat from the same sensors.

To retrieve accurate concentration measurements, other environmental parameters are measured by the sensors and this information is sent to the microcontroller via Pulse Width Modulation for optimum gas extraction results. Analog data input from the sensor to the microcontroller and correct sensor calibration results in acetone concentration measurement. The microcontroller implements thresholding on data values, it processes and passes information through a comparator function where the information is analyzed every 100 ms.

Cross analysis is then performed whereby validated data is cross-referenced with historical diabetic measurements, to create a relationship between exhaled acetone concentration levels and measured diabetic blood glucose. Classification then occurs as stored values are placed into categories based on the patient's acetone level and corresponding blood glucose range. The microcontroller verifies each result by performing 4 re-tests and analyzing subsequent changes. The results are passed through an averaging function where an average of all test results are calculated and placed back into the comparator function for final verification.

The final results of testing are displayed to the patient through an LCD screen; the screen displays chamber temperature, chamber humidity, acetone concentration and classification category. If the patient is classified to be in a critical condition, the LCD screen displays emergency instructions for the patient's discretion.

A dedicated function enables the microcontroller to override and return only one instruction pertaining to emergency management during critical conditions. Emergency management of this nature is for a manual blood glucose check and to seek immediate medical attention. The microcontroller overrides all other functions to increase processing speed so that the patient is notified within minimal time, with an objective to prevent extreme hypoglycemia from occurring.

Hardware Design: Sensor Calibration, Calculation of Acetone Concentration

Extraction of acetone from the other biomarkers in the human breath is achieved by utilizing the Figaro TGS 822 gas sensor. The TGS822 enables detection of organic solvent vapors and in this application is effective in elimination of 27 unwanted gases from the biomarker spectra. The sensor processes gaseous content based on properties of chemical resistivity and using this detection strategy is sensitive to eight organic gases: methane, carbon monoxide, isobutane, n-hexane, benzene, ethanol and acetone, of which only ethanol and acetone are normally present in the human breath. Ethanol is not directly produced by any known mammalian cellular biochemical pathway. It may, however, be present in exhaled gas mixtures due to alcohol consumption. Acetone is a ketone body derived from oxidation of non-esterified fatty acids and is normally produced by humans in baseline conditions with very little circadian fluctuations. Its production is known to increase with high-fat ketogenic diets and in diabetic ketoacidosis.

Sensitivity characteristics of the TGS822 are shown in Figure 1; gas concentration versus sensor resistance ratio. The sensor resistance ratio is determined as the ratio of sensor resistance of the eight organic gases shown for various concentrations, R_s, to the sensor resistance in 300ppm of ethanol, R_0. The relationship of load resistance, R_L and sensor resistance, R_s can be defined by the voltage divider formula (Equation 1). Since the sensor detects the gas by a chemical reaction that takes place when the gas comes in contact with the sensor, the electrical resistance in the sensor decreases when it comes in contact with the monitored gas. This change in resistance is used to calculate the gas concentration.

$$R_s = ((V_c - V_{out}) / V_{out}) \times R_L \quad (1)$$

The relationship of sensor resistance, R_s, to gas concentration (in ppm) may be determined by considering the scaling factor of R_s/R_0 for different gas concentrations. From Fig. 1, the resistance of the sensor in air, $R_{s(air)}$ is R_0 multiplied by a factor of 19. R_{sair} is measured at 78kΩ±0.07%, giving R_0 value 4.105 kΩ. This value for R_0 can be multiplied with a scaling factor to then give R_s. Gas concentration is then determined by a formula that relates resistance to gas concentration. Scaling factors of acetone are computed and tabulated in Table 1 using this relationship. Tabulated results include the resistance of the sensor at different concentrations of acetone (in ppm).

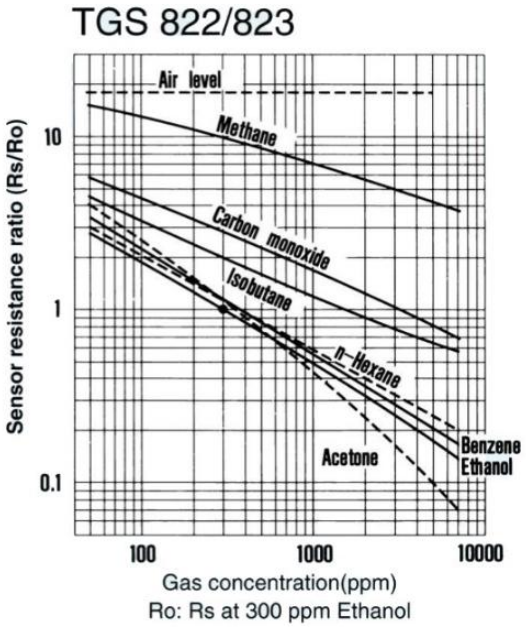

Figure 1: Characteristics of the TGS822 Sensor: Gas Concentration versus Sensor Resistance Ratio

Table 1

Acetone Concentration (ppm)	Scaling Factor	Sensor Resistance $R_S=R_0$* Scaling Factor R_0 = 4105,263157
0	19	78000
10	15	61578.947
10	10	41052.632
20	9	36947.368
20	7	28736.842
30	6	24631.579
30	5.7	23400
40	4.7	19294.737
50	4	16421.053
60	3.5	14368.421
70	3.2	13136.842
80	3	12315.789
90	2.7	11084.211
100	2.5	10263.158
150	2	8210.526
200	1.6	6568.421
300	1.2	4926.316
400	0.9	3694.737
500	0.75	3078.947
600	0.67	2750.526
700	0.58	2381.053
800	0.52	2134.737
900	0.47	1929.474
1000	0.4	1642.105
2000	0.2	821.053
3000	0.15	615.790
4000	0.1	410.526

Establishing a Relationship between Acetone Concentration and Output Voltage

The sensor is wired to a DC supply, V_c, of 5 Volts and connected to a 10K load resistor, R_L. The sensor produces an output voltage of a step-change of 5/1023 = 0.0048volts. The relationship between the acetone concentration and voltage can then be reasonably approximated through the application of the following functions (Table 2), for conversion of voltage to acetone concentration depending on resistor range.

Table 2

R < 3. 6kΩ	3.6 kΩ < R < 50 kΩ
Log PPM = (log10(sensor Resistance/ R0) – 0.9768) + 2.4906	Log PPM = (log10(temp Resistance/ R0) - 2.6) + 2.7
PPM = pow (10, log PPM)	PPM = pow (10, log PPM)

System Architecture: Hardware

An overall hardware component connectivity design is shown in Figure 3. All four modules are connected to a microcontroller, with display shown on a 5V LCD screen. The humidity and temperature sensors enable calculation of temperature and humidity of the participant's breath and their subsequent elimination from the overall gas mixture. The Figaro TGS22 electro-chemical gas sensor is sensitive to several gases; its calibration and programming (refer Section 2.2) renders it sensitive to acetone concentrations only for this application. The TGS22 sensor operates similarly to a resistor; the higher the gas concentration, the lower the resistance. The sensor configuration (refer Figure 4.) comprises pin connections for: Circuit (input) Voltage (V_C), Heater Voltage (V_H), Voltage across the Load Resistor (V_{RL}), 0V, Ground; power to the internal heater are connected across pins 2 and 5, and the remaining pins enable connections to the resistors. When the sensor is connected in

the application the output across the load resistor (V_{RL}) increases as the sensor's internal resistance (R_S) decreases, depending on the gas concentration.

The LM7805L voltage regulator ensures that the power dissipated to all sensors does not exceed 5V to prevent permanent damages to the sensors. The microcontroller utilized in this application is the Arduino Uno, offering features of high performance with low power consumption. The configuration of the Arduino Uno is shown in Figure 3. schematic. The DHT11 Temperature sensor is used with a power supply range of 3.5V to 5V, supply current 0.3mA. Other supporting hardware includes a 9V battery, battery charging unit, 10K resistors, a mouthpiece which is used by the participant to output breath into the chamber for gas collection and processing.

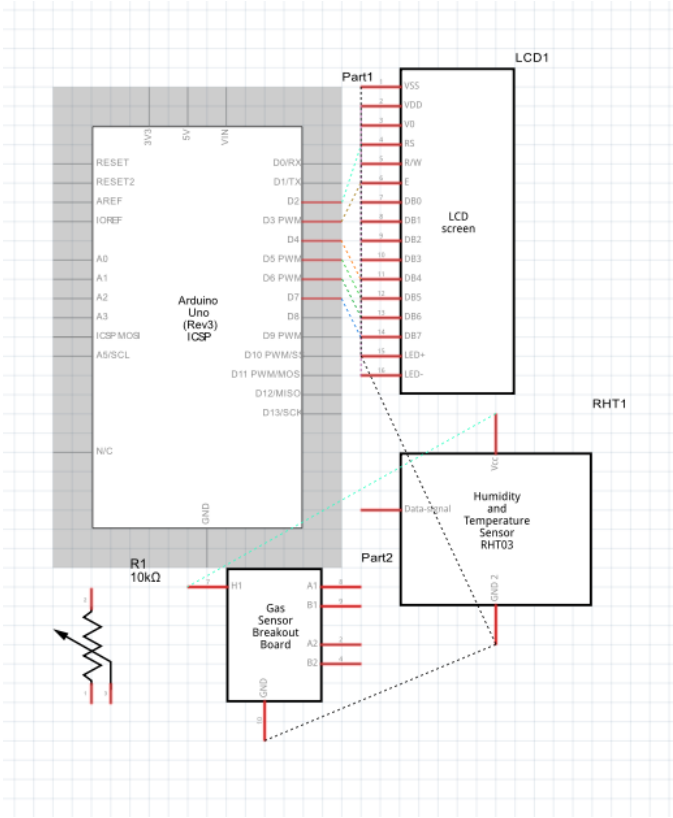

Figure 3: Overview of System Hardware Components

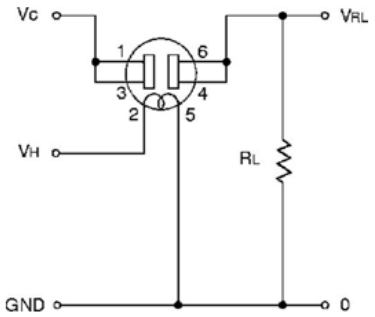

Figure 4: Figaro TGS822 Sensor Schematic

Results and Discussion

Relationship between Acetone Concentration and Output Voltage

Results from calculations of voltage to acetone concentration conversions are compared against measured acetone levels; these are shown in Figure 5. The blue colored points indicate the measured acetone levels and the orange indicates the calculated PPM. The functions are programmed on the microcontroller to translate output voltage into acetone concentration. Ketone levels are represented commonly in mmol/L so a conversion from ppm to mmol/L is required at this stage of the process, with a molar mass of acetone at 58.08.

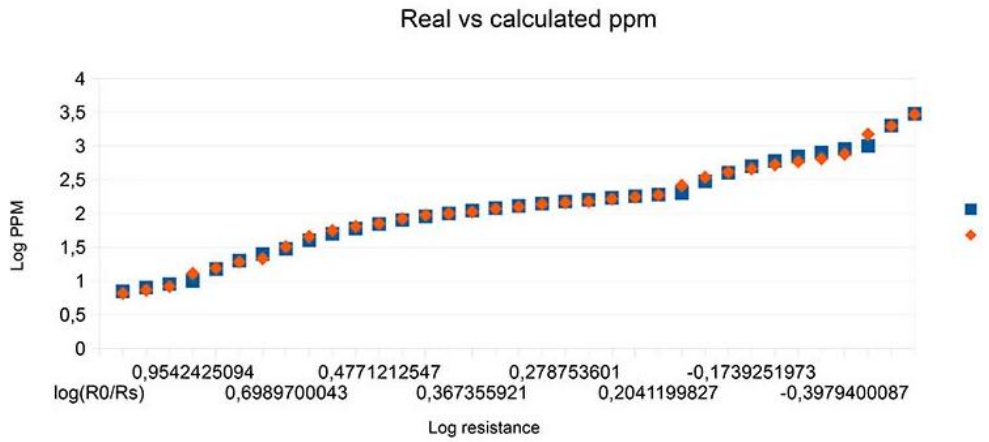

Figure 5: Measured (orange) versus Calculated (blue) Acetone Levels

Hardware Calibration and Results

Hardware testing involves component configuration and connectivity, real-time testing with appropriate chemical input and required user input, and sensor sensitivity adjustments. Successful sensitivity settings and extracted acetone levels are then combined with results from user-driven input (such as exercise type selection), in conjunction with customized Decision Support System software to provide an overall classification.

The system undergoes two phases before it is considered as stable for use. For stabilization of the TGS822 sensor, an algorithm has been developed that intakes sensor values every sampling period and passes them to a comparator function where they are compared with previously captured values; the function checks if the readings vary in less than 5 steps over a period of 20 seconds. Once this condition is met the sensor is considered stable, otherwise the sequence is repeated: the counter is restarted and the stability test is repeated.

The LCD will display the current humidity and temperature as well as the sensor counter captured by variable 'i' when exposed to the human breath. The second row on the LCD displays the maximum and minimum sensor values which are updated with respect to time during reading of the sensor voltage level. If the sensor is considered stable and reaches its optimum stability level, it is then ready take breath measurements from the user for acetone analysis.

After the system stability criterion has been met, the user is prompted to blow into the mouthpiece to start the acetone analysis test. Sampling rate is set at 5ms. Currently, information displayed to the user after breath sampling are sensor readings of temperature, humidity and resistance, in addition to the final acetone concentration.

When the blood sugar runs high for an extended period of time, the body turns to fat reserves in order to get the energy it needs. The byproduct of this process is ketones, which show up in the blood and urine. Ketone test strips help determine the level of ketones in either urine or blood. The test strips look for acetoacetic acid in the urine. The acid reacts with a chemical nitroprusside and produces a color. The color is matched to a reference chart that comes packaged along with the test strips.

The relationship between voltage and acetone concentration as outlined in the previous section (Method) is tested experimentally against data obtained by Urinalysis with the aid of Ketone Test strips and Blood Glucose readings. Samples of participant urine are collected at dedicated times throughout the day and tested for ketones using the test strips. In addition, blood sugar levels of the participant are measured over the same period. The urine sample is collected into a container and the test strip dipped into the sample for one second; after 15 seconds the test strip changes color based on ketone concentration in the urine. Figure 6 is a ketone color change reference chart typically provided with the test strips. Following the test, the color on the strip is compared to this reference chart to provide ketone concentration information. This test was conducted 40 times over a duration of 30 days. Results are displayed against measurements from the sensor-based hardware system described previously, for the same duration of time (refer Figure 7).

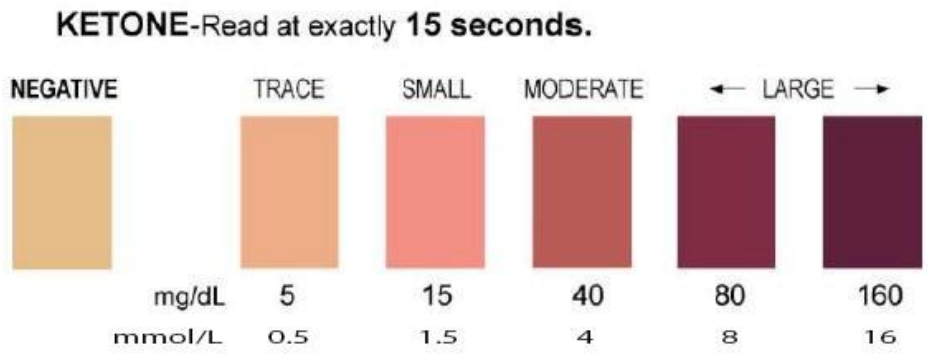

Figure 6: Ketone Reference Chart for Urine Ketone Strip Testing

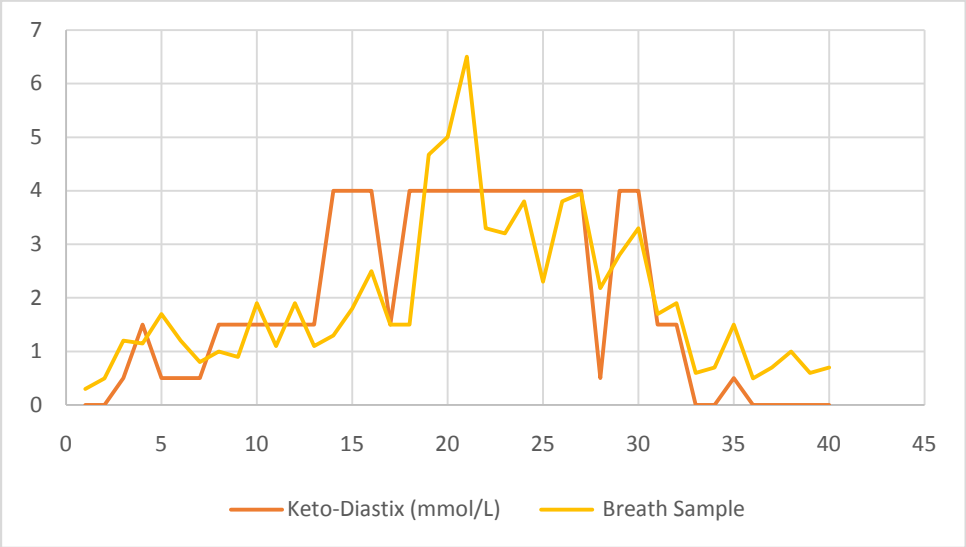

Figure 7: Exhaled Acetone Level in Keto-Diastix Urine Sample (orange) and Breath Sample (yellow)

During the experimentation, readings from the hardware system were taken immediately after the urine test and documented. The red line indicates results from the urine ketone strip test and the orange line represents results of acetone level from the breath sample. The graph shows a mainly positive correlation between ketone levels in urine and acetone levels in the breath. At some measurements, notably measurements 18 to 23, there is a notable variation between the exhaled acetone and Keto-Diastix value however since the ketone strip tests provides ranges (bands) of levels, the difference is not considered extreme.

Results of blood glucose levels extracted directly through blood sampling over the same period are shown in Figure 8 with hardware system values for a variety of sensor readings. Figure 8(a) shows the variation in concentration of blood glucose levels, as taken invasively through blood extraction, of a diabetic type 1 patient over time. Figures 8(b) to 8(f) reveal variation in different parameters during an independent non-invasive monitoring of blood glucose test using breath samples of the same patient over the same time span, of: (b) voltage readings, (c) resistance (d), pressure levels (e) humidity, and (f) temperature. For all tests, breath samples were taken immediately after blood sampling, within a 15 second interval.

Results from Figure 7 show a negative correlation between glucose levels and resistance. There are instances where the participant did not blow into the mouthpiece correctly, as shown where glucose level is high, yet voltage levels are low; this is due to considerably low pressure, humidity and temperature due to inaccurate use. The information obtained from the non-invasive hardware system for acetone extraction from human breath is passed to an Intelligent Decision Support System for final classification into danger band level dependent on the user's lifestyle and exercise expectations.

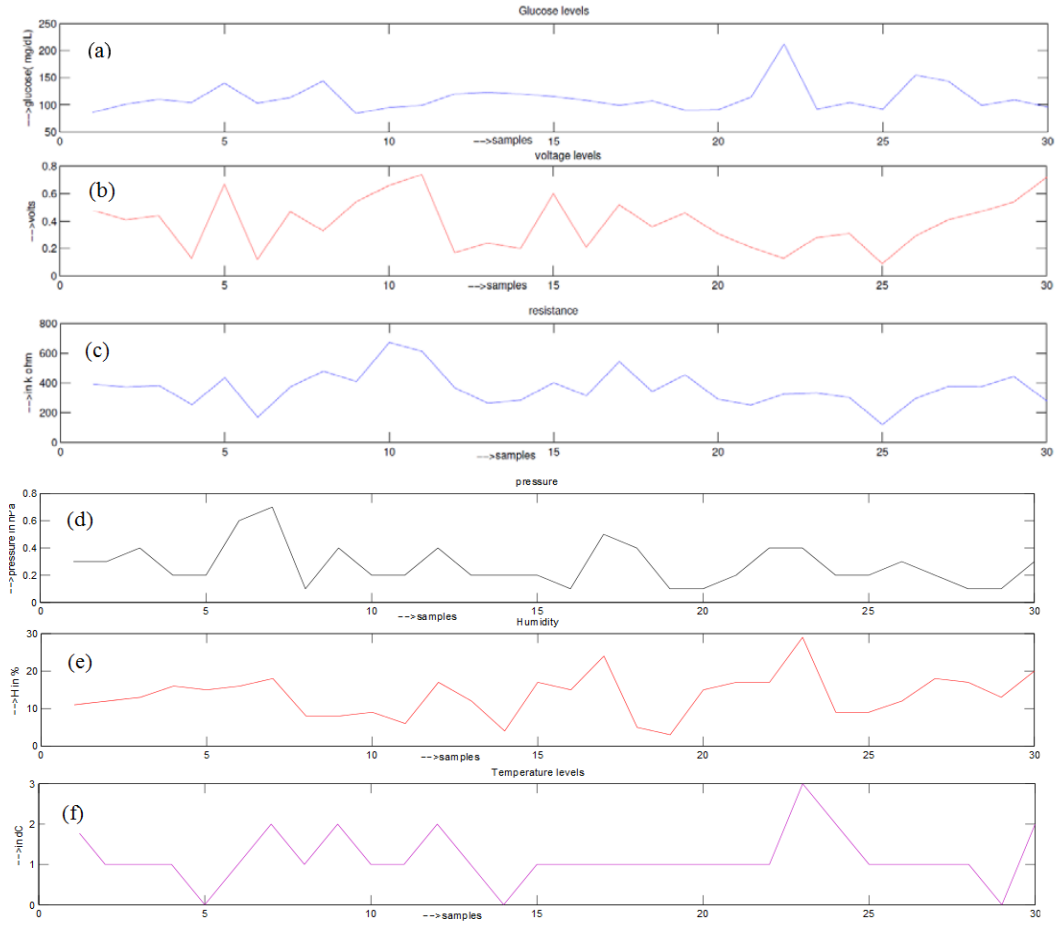

Figure 8: (a) Blood Measurements of Glucose, (b) to (f) Hardware System Sensor Readings for (b) voltage, (c) resistance, (d) pressure, (e) humidity and (f) temperature

Conclusion

A novel hardware system has been developed for non-invasive measurement and mapping of acetone levels from human breath, for practical use in prevention of hypoglycemia in diabetics. The research focuses on hardware and supporting software development comprising an alternative method for monitoring blood glucose levels without direct extraction of a blood sample; through the processing of acetone composition in the breath. Final classification is based on the measurement and intended degree of physical activity, and customized to the user, for recommendations in lifestyle management.

With approximately 1000 chemicals in the human breath and 35 identified as biomarkers, an electro-chemical sensor was utilized and calibrated, for use with a novel algorithm that extracts acetone through real-time calculation of a change of resistance of the sensor to the acetone gas. A relationship between acetone concentration (in ppm) and voltage was established for reading validation, using a voltage divider electronic circuit. Since the Arduino analog pin has a range of 0 to 5 volts, the voltage is split into 1023 segments and the value obtained from the sensor becomes a voltage with a step change of 0.0048V. The relationship between acetone concentration (in ppm) and voltage was established and an accuracy of 92.3% was achieved.

Breath sample results containing acetone concentrations and voltage output mappings were compared against ketone test results from urinalysis and direct blood sampling; showing a positive correlation for acetone in the human breath and acetone from both urinalysis and the blood samples. The experimentation was performed on four diabetic type 1 subjects. Extension of the work would involve measurement of a greater number of patient participants, also for type 2 subjects. Details of the intelligent classification process for decision support in lifestyle management are to be published in a separate paper.

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