Electronic Nose System Based on Quartz Crystal Microbalance Sensor for Blood Glucose and HbA1c Levels From Exhaled Breath Odor

Hamdi Melih Saraoğlu, Ali Osman Selvi, M. Ali Ebeoğlu, and Cihat Taşaltın

***Abstract*— It is known that the rate of acetone in human breath changes in diabetics. The organs in the human body produce different gases. During cleaning of the blood, which is transmitted to the lungs and into the blood gases, the breath passes through the alveoli. Human breath acetone concentration is very low (0.1–10 ppm). This paper aims to determine human blood glucose and HbA1c levels from exhaled breath as a non-invasive method with the help of an electronic nose system based on quartz crystal microbalance (QCM) sensors. The amount of acetone vapor, which is the marker of blood glucose, is 0.1–10 ppm in human expiration. Data of the QCM sensor used in the electronic nose are compared against glucose and HbA1c parameters in blood by using a radial basis function neural network (RBFNN). When breath data are implemented to the RBFNN, the average accuracy rate is 83.03% and 74.76% for HbA1c parameter predictions and glucose parameter predictions, respectively.**

***Index Terms*— Breath, concentrator, electronic nose, diabetes, glucose, HbA1c, neural network, radial function, QCM sensor.**

I. Introduction

GLUCOSE is an energy source necessary for human organism and the suggested amount for human body is between 75mg/dl-115mg/dl (4.9mmol/lt – 6.9mmol/lt) [1]. Diabetes illness structurally occurs when glucose molecules in human blood are not burned by necessary metabolism and so when the blood level rises. The diabetic people must keep their blood glucose level under control.

Two different blood test parameters have been used during the diagnosing and controlling of the illness. Glucose parameter indicates the glucose blood just after blood sample is taken and HbA1c parameter indicates the average level of blood glucose in the last 3 months.

Bedside clinical devices (1% error rate) and the patient's self-used measuring devices (6-7% error rate) are examples of invasive systems [2]. Invasive systems are based on the blood extraction technique with single-use apparatuses by damaging the skin. Invasive techniques are commonly used during diagnosis and treatment process of the illness and they give pain to human body during application process. Therefore, non-invasive measurement methods in which other body parameters are used instead of blood are preferred [3].

Every organ in human body produces a different structured gas. Gases passing through the organs during the cleaning of the blood in lungs are transferred to the breath by means of alveoli. Diseases occurred in organs make up differences in the concentrations produced by gas components. Illness is diagnosed by finding these differences in healthy and sick humans [4]–[6]. It is known that in diabetes acetone rate in human breath change [5], [7]–[14].

Acetone concentration in human breathe is very low as 0.1 ppm to 10 ppm. The detection of the low-level concentration by sensors and the analysis is difficult. For this reason intensification of volatile organic compounds is required [16]. For this purpose, the zeolite material is used in the system as condenser.

In order to differentiate odors in human breath, an electronic nose containing QCM sensors is used. Electronic noses are the devices which contain chemical sensors such as electrochemical semiconductor -based (MOS, MOSFET, etc.) oscillating mass detector sensors (QCM, SAW, etc.), and ionization-based sensors and which can do precise measurements of the odors that cannot be detected by human nose. Electronic nose sensitivity is proportional to the perceived sensitivity in accordance with the selected input sequences [17], [18]. Sensor series used in electronic nose is a group consisting of n numbered sensors. These sensors can identify many different physical, chemical compounds, odors, by changing them into quantities, such as frequency and amplitude [19].

This paper conducted before "*Determination of Blood Glucose Level Based Breath Analysis by a Quartz Crystal Microbalance Sensor Array*" given reference number 24, blood glucose value is predicted by LMNN (Levenberg – Marquardt Neural Networks) by the help of the electronic nose obtained by QCM sensor array. Result of the study has an accuracy 79,87% for glucose parameter predictions. In this study, the existing experimental setup is revised and glucose and HbA1c values are predicted according to the sensor values obtained from electronic nose. Three-fold cross-validation test is used as well as RBFNN (Radyal Basis Function Neural Networks)

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when Glucose and HbA1c parameters are measured. In order to get the best prediction value, optimum network method is used with the help of a program.

This paper was supported by the Scientific and Technological Research Council of Turkey (TUBITAK) under Project 104E053: "Diagnosing System Design for Medical Applications Using by QCM-SSC Gas Sensor Array", the necessary experimental apparatus are set up in order to analyze the response of QCM (Quartz Crystal Microbalance) based Electronic Nose to the breath of diabetis [20]. Numerical data obtained from the test device are used to determine blood glucose and HbA1c parameters in the patients' breath by evaluating the numerical data with the Radial Basis Neural Networks. In the paper, Radial Basis Function Neural Networks is preferred since it provides a better educational result on the clustered data sets and it has a better performance on function convergence problems [20], [21]. In the experiments done by Radial Basis Function Neural Networks, 30 patients' breath samples were used for the glucose parameter with the range of 90.29 mg/dl and 443.2 mg/dl, for HbA1c parameter with the range of 5.6% and 10%.

II. Electronic Nose

In this paper, QCM sensors are used in an electronic nose system. An electronic nose mimics the mammalian nose's ability to identify and quantify a wide range of volatile chemicals. Electronic noses commonly consist of a small number of sensors, each with a distinct but broad and overlapping sensitivity to a range of chemicals. When an odor is presented to the electronic nose, most if not all sensors will respond to some extent. However, some will respond far more strongly than others. This pattern of varied responses from the sensor array is characteristic of the particular applied chemical. The output of the odor sensors is typically amplified, filtered, and converted into digital form by interface electronics. When an unknown odor is presented to the electronic nose, a pattern recognition process is performed to compare the pattern of sensor responses with stored templates. The best match is used to classify the unknown odor in terms of the stored templates [19], [22].

An electronic nose is a device that identifies the specific components of an odor and analyzes its chemical makeup in order to identify it. An electronic nose consists of a mechanism for chemical detection, such as an array of electronic sensors, and a mechanism for pattern recognition, such as a neural network. Electronic noses were originally used for quality control applications in the food, beverage, and cosmetics industries, and have also been used in aerospace research as well as in military and health applications [11], [22]–[25].

III. QCM (Quartz Crystal Microbalance) Sensors

Electrical signals coming from the sensors are obtained by the sensor perception of physical or chemical changes in the environment. Electrical quantities of the sensors change when volatile compounds in odors contact with sensor array. Sensor arrays are preferred instead of a single sensor in order to have a better perception [19].

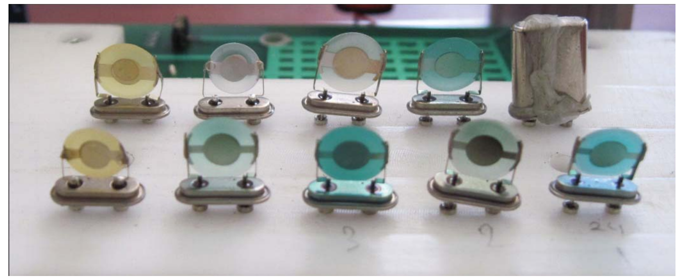

Fig. 1. QCM sensors used for electronic nose.

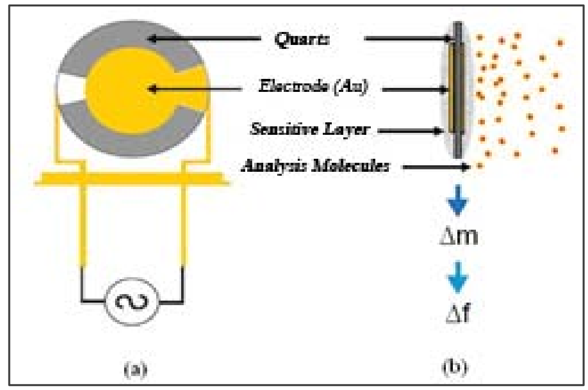

Fig. 2. (a) Front-view. (b) Side view of QCM sensor.

QCM sensors produced by TUBITAK Marmara Research Center Materials Institute Sensor Group are used in the electronic nose system used in this system [19].

The quartz crystal microbalance (QCM) is an ultrasensitive weighing device that utilizes the mechanical resonance of piezoelectric single crystalline quartz. Piezoelectric crystalline quartz, originally discovered by Pierre and Jacques Curie in 1880, is characterized by the ability of an external electric field to induce a mechanical strain in a material, where the direction of the induced strain can be controlled via the orientation of the cut in the crystal with respect to the crystal lattice [26]. The QCM sensor structure is shown in Fig. 2.

The QCM is a useful acoustic sensor device. The principle of the QCM sensor is based on changes Δf (Hz) in the fundamental oscillation frequency in relation to adsorption/absorption of molecules from the gas phase. As an initial approximation, the frequency change Δf (Hz) results from an increase in the oscillating mass Δm(g) [22], [26].

$$\Delta f = -\frac{C_f \cdot f_0^2}{A} . \Delta m \tag{1}$$

where:

Δf : frequency change (Hz)
C_f : mass sensitivity constant of the quartz crystals
A : area of the sensitive layers (cm^2)
Δm : mass changes (g)
f_0 : fundamental resonance frequency of the quartz crystal.

The piezoelectric crystals which are used in this study are AT-Cut, 10 000-MHz quartz crystals (ICM International Crystal Manufacturers Co., OK) with gold plated electrodes

TABLE I
THE REFERENCE NUMBERS OF QCM SENSORS USED FOR ELECTRONIC NOSE

Sensor Number	Referance Number
QCM 1	133
QCM 2	172
QCM 3	129
QCM 4	154
QCM 5	257
QCM 6	91
QCM 7	98
QCM 8	92
QCM 9	24

(diameter ∅ = 3 mm) on both sides mounted in a HC6/U crystal holder which has a 1.5–225 MHz frequency interval. The sensor performance such as sensitivity, selectivity and time response is largely influenced by the properties of the sensing films. QCM is highly sensitive to mass changes in the presence of a coating that interacts with the target gas [27], [29]. The characteristics of QCM gas sensors depend on the kinds of sensing films coated on their electrodes. A number of materials has been successfully employed in the coating of QCM sensors such as zeolites, fullerene C60, chiral materials, polyprrole, carbon graphites, ITO films, and oligonucleotides [22], [30].

In this paper, both sides of each piezoelectric crystal are coated with different phthalocyanine solutions by means of jet spray technique. The solvent molecules with saturated C–C bonds such as ethanol, methanol, tetrachloromethane, dichloromethane interact with phthalocyanine films predominantly by formation of hydrogen bonds and the sensor response to π-bond containing compounds such as acetone, tetrachloroethylene, benzene, etc., is the result of their $\pi - \pi$ interaction with the conjugated phthalocyanine ring. The sensors are developed at TUBITAK [22], [30].

In the electronic nose used in an intensifier measurement setup, 9 QCM sensors with different perception characteristics and 1 reference sensor are used. Resonance frequencies of the sensors are 10 MHz. The QCM sensor consists of AT-cut piezoelectric quartz crystal which has the same diameter (4 mm) on both surfaces, symmetrical, circular, metal (Au) electrode. AT-cut QCM sensors are preferred since they behave more stable against temperature and humidity and they are more sensitive to changes in surface mass [19]. The reference numbers given by manufacturer of QCM sensors found in electronic nose and used in the system are given in Table 1.

QCM s in Electronic Nose are transferred to the computer by using data set RS-232 serial communication protocol consisting of a frequency value of every 7 seconds.

IV. MEASUREMENT SETUP

For the purposes of this study, a measurement mechanism was developed for determination of the blood glucose level from human breath odor. The mechanism, which is designed to detect VOCs in breath, includes; a concentrator (VOCs have a lowconcentration in human breath, so the function of the concentrator is to absorb material from the breath and provide higher concentrations of VOCs to the QCM sensors), a pump for pulling the breath from the Tedlar (polyvinyl fluoride) sampling bag (used to keep breath samples for experiments without damaging its chemical properties), dry airbag containing a carrier gas and used for cleaning the QCM sensors, five valves, a PC for data processing and registration and an electronic nose system with a QCM sensor array (Fig. 3) [22].

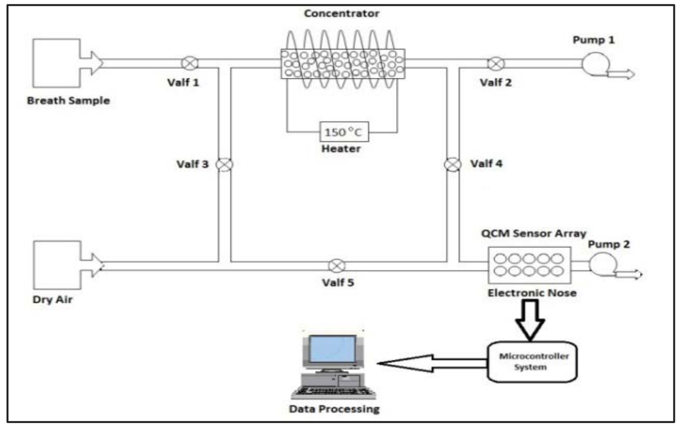

Fig. 3. The scheme of measuring mechanism.

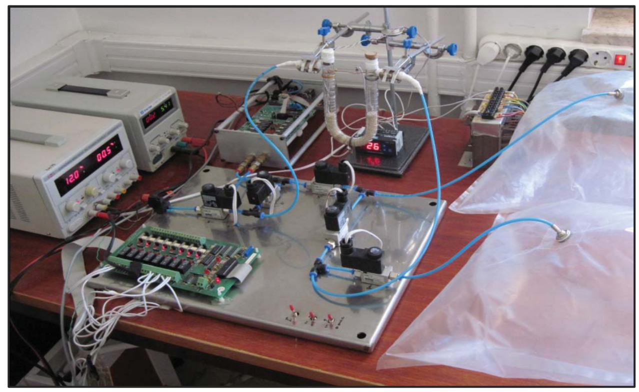

Fig. 4. The image of measuring mechanism.

There are five valves in the measurement mechanism as shown in Fig. 4. Valves 1 and 2 as well as valves 3 and 4 are designed in order to function together (ON/OFF). Valves 1 and 2 provide breath samples which pass through the concentrator via a pump. Valves 3 and 4 provide adsorbed gas by supplying dry air as a carrier gas to the sensors. Valve 5 provides the sensors with dry air to clean them [22].

The concentrator used in this mechanism consists of a chemical adsorbent/absorbent material. There are different holding materials for sensing each VOC in breath. Using the appropriate adsorbent, desired VOCs can be detected among the hundreds of gases present in breath by QCM sensors. VOCs exist in amounts of low concentration in breath. However, the QCM sensors could not respond to such low concentration odors. In order to increase the frequency responses of the QCM sensors, absorbed VOCs are desorbed by a heated concentrator and given to the QCM sensors over short time duration with

TABLE II
EXPERIMENTAL PROTOCOL

Protocol Step	Period	Process
Step 1	30 min	**Breath sample pass through the concentrator:** Room temperature, 1 and 2 numbered valves on, Number 1 numbered pump works.
Step 2	10 min	**Heating:** All of the valves off, heater works for 150 ^{o}C.
Step 3	5 min	**Cleaning Sensors:** 5 numbered valve on, heater works, cleaning the sensors with dry air.
Step 4	8 min	**Breath sample apply QCM sensors:** 3 and 4 numbered valves on heater works for 150 ^{o}C, 2 numbered pump works.
Step 5	5 min	**Cleaning Sensors:** 5 numbered valve on, cleaning the sensors with dry air.

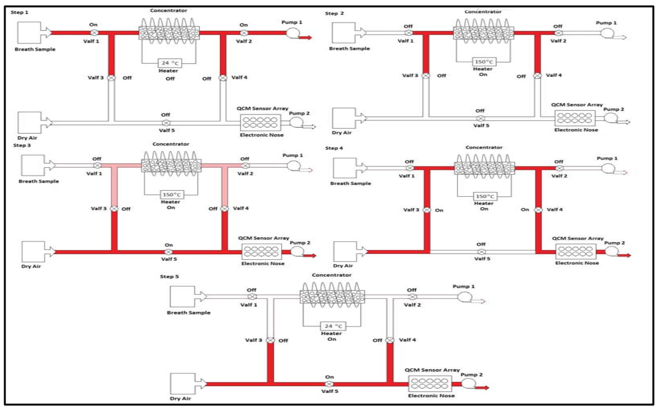

Fig. 5. Measurement steps.

the help of carrier gas (dry air) at a high concentration. In this paper, to determine glucose level from breath, zeolite (Aldrich zeolite molecular views 3A, 1.6-mm Pellets, catalog no: 33, 428-6) was used in the concentrator unit as a chemical adsorbent/absorbent material, because it is known that zeolite can be used to capture acetone in breath [16], [22].

A. Experimental Protocol

The prepared experimental protocol includes five steps. Duration of each step and order is determined by the experiments in the form that it will not disrupt the breath sample by the working of electronic nose. After obtaining the breath sample, the bronchial breathing bag is connected to the test assembly. The protocol prepared with a computer control is initiated after this point. In Table 2 the steps of experiment protocol is shown [31].

In fig 5 the working order of experiment protocol is given.

V. THE PREPARATION OF THE OBTAINED DATA FOR PROCESSING

In this paper, breath samples of 30 patients in total are taken in Dumlupınar University School of Medicine Blood Collection Center. Glucose values of breath samples represent the patients between 90,29 mg/dl and 443,2 mg/dl patients and HbA1c values represent the patients between %5,6 and %10 patients .

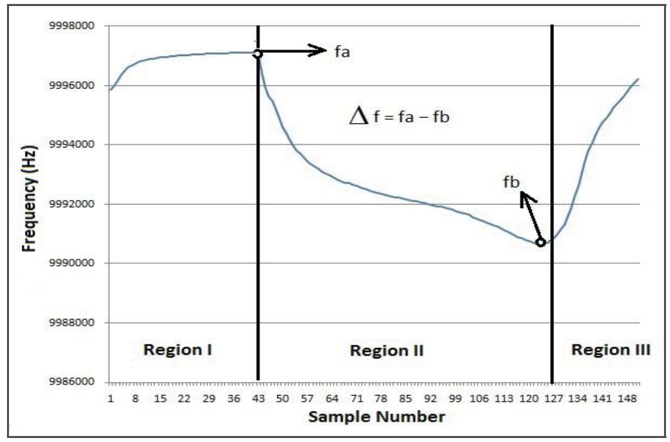

Fig. 6. Frequency change regions.

When the sensor responses are analyzed, it is seen that a curve is formed depending on the frequency change. When the experimental process is proceeded as a whole an instantaneous change in each sensor enables the formation of these curves. Sensors are active in three separate stages during the experimental process. Frequency differences of each sensor are taken due to the frequency variation in these regions. When Fig 6 is examined it is seen that sensors are active in three distinct regions [31].

In the first region, dry air (N2 + O2) is applied to the QCM sensor. In this way the gas molecules on sensors are kept clean and the sensor frequency value is held on the sensor base-line value. This value is the value while sensor has no substance on it. In the second region, sensor frequency decreases over time. In this region, the gas molecules in the breath of patients exposed to the sensor concentrator material are applied. Sensor captures specific molecules due to its chemical structure and so QCM mass increases and frequency value decreases. In the third region, the sensor is cleaned by dry air again and it moves towards the base-line value (Fig. 6) [31].

In the operations done after this point, sensors are normalized by taking their frequency differences (fa-fb) in order to be able to use them in artificial neural networks. The normalization formulas are provided below.

$$X = \frac{\mathrm{Max}_{\mathrm{valueofdata}} - \mathrm{Max}_{\mathrm{valueofdata}}}{0.7 - 0.3}$$
$$Y = \frac{0.7 - 0.3}{0.7 - \mathrm{Max}_{\mathrm{valueofdata}/x}}$$
$$\mathrm{Normalizasyon} = \frac{\mathrm{datavalue}}{x} + y \quad (2)$$

Frequency responses of different sensors to the different patient breath are shown in Table 3 as frequency values.

VI. DATA PROCESSING BY RADIAL-BASED ARTIFICIAL NEURAL NETWORKS

A. Radial-Based Artificial Neural Networks

In multi-layer networks, activation functions of processing elements are the types of which derivatives can be taken and which rise according to the entered values. These are the

TABLE III
SENSOR VALUES OF SOME PATIENTS

Patient Number	**Sensor 3**			**Sensor 6**		
	Fa(Hz)	**Fb(Hz)**	**Δf**	**Fa(Hz)**	**Fb(Hz)**	**Δf**
Dpu_015	9996732	9990344	6388	10001424	10000836	588
Dpu_029	9996812	9989844	6968	10001452	10000780	672
Dpu_038	9996964	9989924	7040	10001472	10000740	732
Dpu_037	9997148	9989848	7300	10001472	10000704	768
Dpu_024	9996600	9989744	6856	10001424	10000796	628
Dpu_018	9996876	9990012	6864	10001452	10000756	696
Dpu_007	9996692	9990080	6612	10001436	10000740	696
Dpu_021	9996844	9989928	6916	10001436	10000768	668
Dpu_002	9996476	9990992	5484	10001416	10000844	572
Dpu_027	9997036	9990064	6972	10001452	10000764	688
Dpu_025	9997532	9990536	6996	10001472	10000820	652
Dpu_090	9996012	9990284	5728	10001460	10000768	692

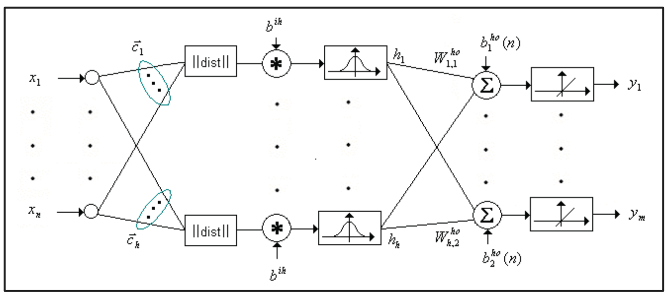

Fig. 7. Radial-based artificial neural networks used for application [22].

mathematical functions which give high value to the high values and which gives low value to the lows. These type processors are used in the absence of such a clustering or classification. However, some of the clusters in the case of data processing elements in the hidden layer is expected to have such a structure. This type of clustering procedures is common in practice. Therefore, the radial base artificial neural networks (RBFNN) which can work with pre-clustered data have been developed [20].

An RBFNN has a multilayer structure consisting of a single hidden layer of locally tuned units which are fully interconnected to an output layer of h units, as shown in Fig. 7 [21].

In this paper, 6 QCM sensor values as well as humidity sensor used as an input to RBFNN are applied. Frequency difference values as well as the first value of sensors are applied as input when the sensor values are applied. Glucose or the estimated HbA1c values are obtained at the output of RBFNN.

All hidden units simultaneously receive the twelve-dimensional real valued input vector. The input vector to the network is passed to the hidden layer nodes via unit connection weights. The hidden layer consists of a set of radial basis functions. Associated with i th hidden unit is a parameter vector, called j a center. The hidden layer node calculates the Euclidean distance between the center and the network input vector and then passes the result to the radial basis function. All the radial basis functions are the same type (Gaussian) [21].

B. Implementation of Data to ANN and Evaluation of Data

The sensor values obtained from Electronic Nose forms a curve due to the structure of QCM (see Fig 6). The frequency differences between the peak and radix point of each QCM sensors give the intensity of gas molecules. All sensor responses for each patient were examined and the sensors that give the most appropriate response were used for training artificial neural network. In some sensors the range may be bigger since frequency values are at Megahertz level in order to apply to ANN. Therefore, data were normalized in itself between 0,3 – 0,7 . In this paper, radial based network system and the artificial neural network application were conducted.

Due to radial basis function, in practice, the most appropriate constants are found by changing the network weights and spreading coefficient factor continuously, so the optimal network for the data group are formed. On the program written in Matlab, data was used by the desired clustering method with K-fold cross-validation test [32]. Training and simulations were conducted on radial basis neural network with loops. Meanwhile, the radial function diffusion interval has been changed randomly and continuously. Number of neurons in the hidden layers is limited to 50 due to the small number of data. When the desired error rate was reached for each cross-validation ANN training was ended and data was recorded. Blood glucose and HbA1c predicted values were found by denormalizing of the obtained ANN results (Fig. 8).

Values obtained from artificial neural networks are compared with actual values and it is valued with % accuracy value. Equation 3 is used in finding the accuracy rate % [21].

$$\%|\text{Accuracy}| = 100 - \sum \left(\left| \frac{\text{SimulationResult} - \text{TestTargetResult}}{\text{TestTargetResult}} \right| \right) \quad (3)$$

In order to determine whether ANN training results have a better prediction on glucose or on HbA1c parameter, ANN tendency on 30 patients was conducted by Three-fold cross-validation test. In the trainings conducted on the patient group representing Glucose and HbA1c values together, five sensors giving meaningful responses (QCM sensors numbered

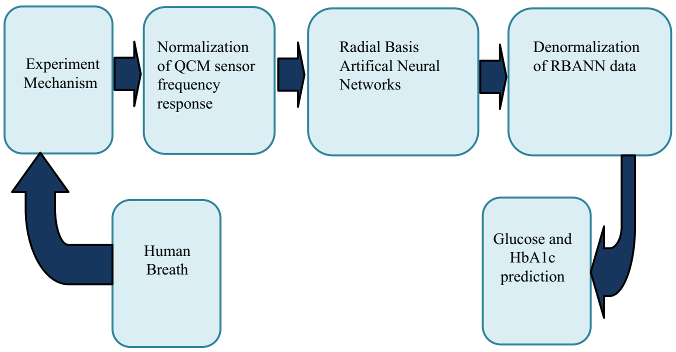

Fig. 8. Data proceeding procedure.

TABLE IV
THREE-FOLD CROSS-VALIDATION TEST RESULTS FOR GLUCOSE (30 PATIENTS) AND HBA1C (30 PATIENTS)

Parameters	Sensors used for RBFANN		
	3, 6, 7, 8, 9 numbered QCM + Humidity Sensors		
	Maximum	Minimum	Average
Glucose Accuracy (%)	99,91	50,45	**74,76**
HbA1c Accuracy (%)	99,53	53,7	**83,03**

TABLE V
THE RELATIONSHIP BETWEEN GLUCOSE AND HBA1C VALUES AND ANN ESTIMATION RESULTS

Patient Number	Real Blood Glucose Value (mg/dl)	Predicted Blood Glucose Value from Breath (mg/dl)	Real Blood HbA1c Value (%)	Predicted Blood HbA1c Value from Breath (%)
Dpu_018	103,92	110,26	6,5	6,58
Dpu_021	106,95	84,64	6,4	5,58
Dpu_027	116,30	125,88	6,3	6,58
Dpu_090	120,00	131,44	6,39	6,30
Dpu_083	123,00	121,47	5,99	6,26
Dpu_019	131,32	131,44	6,3	7,06
Dpu_039	131,56	152,47	6,6	7,26
Dpu_042	136,48	141,37	8,1	7,22
Dpu_092	137,00	136,58	6,58	8,67
Dpu_040	160,00	152,91	9,6	6,58
Dpu_001	185,92	170,03	9,8	7,27

3,6,7,8,9) and humidity sensor frequencies were applied to RBFNN.

The training results are shown in Table 4 accordingly, it is found that accuracy rate for glucose parameter was 74.76% while it was 83.03% for HbA1c. As a result, HbA1c parameter was predicted more accurately compared to glucose parameter.

Table 5 shows the relationship between the RBNN estimation results and Glucose and HbA1c values of the patients

VII. RESULTS AND SUGGESTIONS

QCM sensor data of Electronic Nose was compared with the blood glucose and HbA1c parameters by using Radial Based Function Artificial Neural Networks. For the trials done by Radial Basis Neural Networks, the breath samples of 30 patients were used for the glucose parameter with the range of 90.29 mg/dl and 443.2 mg/dl, for HbA1c parameter with the range of 5.6% and 10%.

Accuracy rate for glucose parameter was found to be 74.76% while it was 83.03% for HbA1c parameter when breath data was applied to RBFANN. When the two values were compared, it was found that error rate of HbA1c parameter was lower than glucose parameter. According to the investigation carried out with experiments, moisture changes in breath caused by environmental conditions had negative effect on experiment process. Therefore, the reactions of sensors were also added to artificial neural network as input since the moisture in human breath had negative effect on the experiment result.

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