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RESEARCH ARTICLE

INNOVATIVE METHOD FOR THE DIAGNOSIS of DISEASES: E NOSE

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ABSTRACT

E-nose systems can be used in different applications which are varying from explosive and chemical hazardous detection to health applications using breath analysis such as lung cancer, and Covid -19 diagnosis. One of the best practices of the E-nose application is breath analysis for disease diagnosis. Exhaled breath is a mixture of water and Volatile Organic Compounds (VOCs) in very low concentration which was shown via Gas Chromatography(GC) or other possible technologies. Electronic Nose (E-Nose) seems to be the best solution to the development of analyzing system for diagnosis using breath. Conventional E-nose incorporates non-selective gas sensors that are called sensor array and data recognition part which having artificial intelligence algorithm. Due to the performance of gas sensors is negativily effected by the humidity in the environment, the most important problem encountered in practice is the negative effects of uncontrollable external effects such as humidity on the E-nose system.

In this study, a $CaCl_2$ tube was equipped to the gas inlet of the E Nose system to reduce the effect of variable humidity in environments. The tube enabled that only the gas of interest passes onto the sensors and trap the ambient humidity. Positive results on sensor responses are shown by using PCA method. It is assumed that this approach will make significant contributions to the development of methods based on breath analysis.

Keywords: *Gas Sensor, Disease Diagnosis, VOC Detection, SAW Sensor, E-Nose*

1. INTRODUCTION

Humans release to the environment complex molecules which of them volatile and nonvolatile by the effect of an individual's genetics, health, diet, and stress during their life. Many body odors include being olfactory messengers, which convey information about health and physiological status between individuals. Measuring the changes in the breath profile is a recommended method for the easy diagnosis of diseases. However, technological impossibilities in terms of the changes in the breath profile. In modern life, the scents have been taken into account for disease detection again because it is a non-invasive technique. Gas sensors could provide ideal platforms to solve this problem for realizing portable, hand-held breath. Exhaled breath is a mixture of water and Volatile Organic Compounds (VOCs) in very low concentration which was shown via Gas Chromatography(GC) or other possible technologies. [1-3].

Since the 1970s, most researchers were focused to explain the composition of the human breath. It has been shown that exhaled breath includes some chemicals such as ethanol, phenol, benzene, propanol, acetone, and their derivatives. In the following years, research activities were carried out to reveal the relationship between the disease and these chemicals [4-6]. The main reason for the evolution of the studies is VOCs that originate from organs that are transported by the bloodstream, to the alveoli, where diffusion into the exhaled breath takes place[7].

VOCs present in exhaled breath as result of part of the metabolic process such as fractioning of larger molecules. The major fractions of saturated hydrocarbons in exhaled breath are from oxidative stress and resulting in extensive cellular damage. On the other hand, saturated hydrocarbons such as Isoprene and derivatives could be from the chemical reaction for cholesterol biosynthesis or bacterial origin in the human body. The decreases in isoprene levels have reported as the effect of acute respiratory distress syndrome, cystic fibrosis, and asthma [8-10]. Also, isoprene levels can change in physiological and pathophysiological conditions (including hemodialysis, general anesthesia, liver disease and cancer). Breaths which include sulphur-containing were reported for incomplete metabolism of methionine via the transamination pathway[11] and ammonia level is also influenced by cigarette smoking [12] in the range of 245–2935 ppb in breath for normal healthy humans[13]. This level may be related to bacterial production in the oral cavity [7].

Using the breath analysis for the diagnosis of disease, several factors and parameters should be taken into consideration. Because, the biological mechanism of the human body is a complex and non-linear process thus, exhaled breath includes a complex composition. Therefore, the correct relationship must be established between the markers which are indicating the disease. This process must be completed with the cooperation of clinical study and instrumental chemistry unit using GC-MS and other functional devices. In practice, Chromatography (GC) and Mass Spectrometry (MS) are commonly used as devices with solid-phase extraction (SPE) and solid-phase microextraction (SPME) for the analysis of breath. Via help of the unique spectrum and retention time of each molecule can be separated from another's and/or derivatives. Although GC-MS produces high accuracy results, it is quite expensive and requires expert staff to use. For this reason, research and development activities are carried out on alternative, inexpensive, and easy-to-use devices. Electronic Nose (E-Nose) seems to be the best candidate as an alternative technology to obtain highly accurate data for the diagnosis. Conventional E-nose incorporates non-selective gas sensors[14] that are called sensor array and data recognition part which having artificial intelligence algorithm. The working methods of E-nose were mimicked from the mammalian olfactory system for the discrimination of odors. In the E-Nose system; odor receptor cells and neural processing are represented by the gas sensors and microprocessor as a respectively[15]. Utilizing sensor arrays, an E-nose detects patterns in complex mixtures which may have include water vapor of exhaled breath VOCs [7].

One of the challenges of the practical application of electronic noses is that the interested gases are a small part of the whole ambient atmosphere and shadowing of water vapor to all signals. Technically, sensors may also be sensitive to water vapor which can be call background gases thus, the sensor signals cannot represent the analyzed atmosphere[16]. Therefore, the E-nose must be highly selective against only interested gases. This is why sensor development studies will increasingly continue to

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obtain the perfect solution to the interesting problem. Many researchers all over the world have been working development of sensors using different sensing materials and methods.

The gas sensing mechanism of a Surface Acoustic Wave (SAW) sensor is based on the absorption of gas molecules by the sensing film, then changing of velocity and attenuation of the wave. These changes can be measured by the oscillator circuit with high accuracy and sensor responses occur via frequency shift. Film conductivity is one of the parameters of wave attenuations. The frequency shift of the SAW sensor's in terms of wave propagation $(\frac{\Delta v}{v_0})$ and attenuation $(\frac{\Delta \alpha}{k})$ can be given in equation 1 and 2.

$$\frac{\Delta \alpha}{k} = \frac{K^2}{2} \frac{v_0 C_s \sigma_s^2}{\sigma_s^2 + (v_0 C_s)^2} + 4C_e \frac{f_0}{v_0^2} (\Delta h G'') \quad (1)$$

$$\frac{\Delta v}{v_0} = -C_m f_0 \rho_s + 4C_e \frac{f_0}{v_0^2} (\Delta h G') - \frac{K^2}{2} \frac{\sigma_s^2}{\sigma_s^2 + (v_0 C_s)^2} \quad (2)$$

Where, K^2 is the electromechanical coefficient, $\sigma_s = \sigma h$ is surface conductivity, G' and G'' is a constant number which is realted to elasticity properties of sensing film, σ is bulk conductivity, C_s is the total dielectric permittivity of the substrate and sensitive film. The electrical charge of the sensitive film is one of the reasons for the frequency shift of SAW. When the analyte is absorbed by the sensing film, the surface electric charge changes and causes a change in wave velocity[17, 18]. This process is one of the important mechanisms of SAW in frequency shift and K^2 is an important factor determining the perturbation of the SAW.

This study is focused on establishing the right relationship between the exhaled breath and gas sensor systems. In general, a gas sensor is consisting of two components; a transducer and sensing materials. The role of these components is transferring chemical signals to the electronic signals without knowledge loss in the sensor system. The size of the sensor system should decrease according to modern device requirements such as the More Law postulate. Therefore, the fabrication of transduction systems benefits from the help of microfabrication techniques and it has become possible to produce functional structures with small dimensions. The other component, sensing material determines the features of the sensor such as stability, accuracy. Metal oxides [19], macrocyclic organic molecules, and metal-organic-frames are often used materials in gas sensors. In this article, we are not considering the interaction between the sensing materials and measured because our sensors had been prepared before analyzed and published in a different journal. We are considering to avid dominant background gases shadow effect on sensor response during the designing of the device for health or any other application.

2. MATERIALS AND METHOD

2.1. Sensors

In this study, the dual-port resonator SAW transducers having 433 MHz frequency (SAW Components Dresden GmbH, Germany) located on a TO-39 socket were used. Metal oxide nanoparticles that are mixed with polymers and macrocyclic organic molecules were used as sensitive materials. Our sensors were prepared before for the determination of lung cancer diagnosis inbreathe

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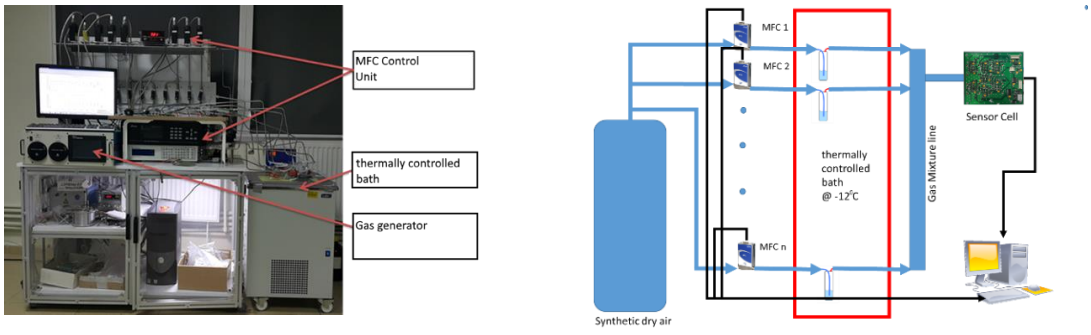
and published in different journals. Therefore, in this study, we are not mentioning sensor preparation, sensing materials, sensitivity, selectivity, and sensing mechanism of our used sensor.

Table 1. Sensor list and sensitive materials.

Sensor Number	Coating Materials
Sensor 1	Compound Number 11 at [20]
Sensor 2	Compound Number 12 at [20]
Sensor 3	S1 at [2]
Sensor 4	S2 at [2]
Sensor 5	S3 at [2]
Sensor 6	S4 at [2]

2.2. Sensor Measurements in Controlled Atmosphere

Sensors were tested against VOCs using two different test systems. First of all (Fig. 1a,1b), it is a conventional test system having a thermally controlled bath that can generate gas using bubblers with synthetic air as the carrier gas and generated gas concentration is changing range of 500-5000 ppm. The desired gas concentration was adjusted by mixing pure dry air and gas stream saturated with the analyte in a different ratio. Total gas flow was kept at 300 sccm (ml/min) and all flows were adjusted by using Mass Flow Controller (MFC, MKS Instruments Inc., USA) with computer-driven. Sensors were exposed to the desired concentration and/or binary mixed gases and also were kept at 22°C during the measurement to avoid the negative effect of temperature and environmental conditions. All measurements were carried out sequentially in dry air and gas (figure 6 in section 3.1).



(a) **(b)**

Figure 1. a) Photo, and b) Schematic representation of conventional sensor test system.

The second test system has two temperature-controlled chambers with mass flow controller which were used for dilution and carrier. Each chamber can be adjusted from 30°C to 110°C, regulated to ±0.01°C to provide accurate, precise results. The carrier stream mixes with the calibration gas in the chamber and is then fed forward to the mixing tee (Fig. 2a). This system contains a permeation tube to the regeneration of low concentration gas. The generated gas concentration depends on the chamber temperature.

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The sensors were kept in temperature-controlled chambers of 4 ml volume and frequencies of each SAW sensor were read out respectively using a multiplexing technique. To avoid high frequencies of the operation frequency difference between reference and sensor SAWs were processed and the seventh uncoated device was used as a reference.

Prepared sensors were performed using the first system against VOCs such as toluene, hexane, ethanol, isoprene, and a binary mixture of water vapor. The concentrations of each gas were varied in the range of 100–5,000 ppm and water vapor was varied in the range of 20-80 %. The performance of the sensors against VOCs in low concentration was determined via the used gas generation device with permeation tubes (Fig. 2b). Gas generation device generated the gases which concentration was varied between 0.14 ppb and 4.2 ppb at 100 sccm synthetic dry air gas flow (Table 2).

The reason for generation low concentration wherein the real application trace gas concentration is very low such as varying 1-5 ppb in lung cancer patient breathing.

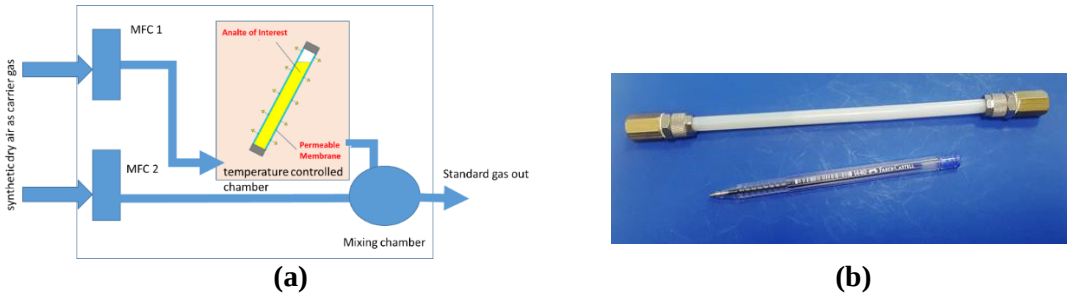

Figure 2. a) Schematic representation of gas generation system, and b) homemade permeation tube.

Table 2. Considered VOCs and concentration of in 100 sccm gas flow for the homemade permeation tube.(1 mg/ml = 1000 ppb).

VOCs	The amount of Total Mass before(mg)	The amount of Total Mass After(mg)	Duration (min)	Evaporated Mass(mg)	The amount of mass evaporating per minute in 100 sccm gas flow(mg)	Concentration (ppb)
Toluene	75.5804	75.2987	8580	0.2817	0.00032	0.32
Hexane	87.0454	86.8156	6720	0.22970	0.00034	0.34
Ethanol	87.707	87.6070	6720	0.100	0.000149	0.14
Isoprene	76.626	76.1722	1080	0.4538	0.00420	4.20

2.3. Sensor Measurements in Uncontrolled Atmosphere

One of the challenges for medical application which based on the gas sensor (E-Nose) is the interference effect and resulting in decreasing sensitivity and selectivity. The best way to reduce this negative situation is to include effective solutions to eliminate these effects in the system. The water vapor has a negative effect on gas sensors because of having high polarity and gets adhere to the

surface of the sensor. It is necessary to carry out some pre-processing steps in order to remove analytes from the sample that may have negative effects on the measurement setup or sensors to obtain high accuracy data with minimum error. The best known of these processes is the addition of kind of solid-phase extraction (SPE) solutions. SPE works as a separator to remove interferences constituents in the sample from collected health and the environment[21].

It is necessary to carry out some pre-processing steps in order to remove analytes from the sample that may have negative effects on the measurement setup or sensors to obtain high accuracy data with minimum error. The best known of these processes is the addition of kind of solid-phase extraction (SPE) solutions. SPE plays a crucial role in sample pretreatment, removal of interferences, and elimination of sample constituents in health and environmental analyzes [21]. Kind of solid-phase extraction (SPE) solutions. SPE plays a crucial role in sample pretreatment, removal of interferences, and elimination of sample constituents.

In this study, SPE columns (Agilent catalog number: GT-C-AT010C) were used to enrich total analytes up to detectable levels and elimination of undesired molecules in breath samples. Water vapor was trapped by the using $CaCl_2$ column located before SPE columns. Thus, water molecules were removed from the samples without changing the quantity of interested gas.

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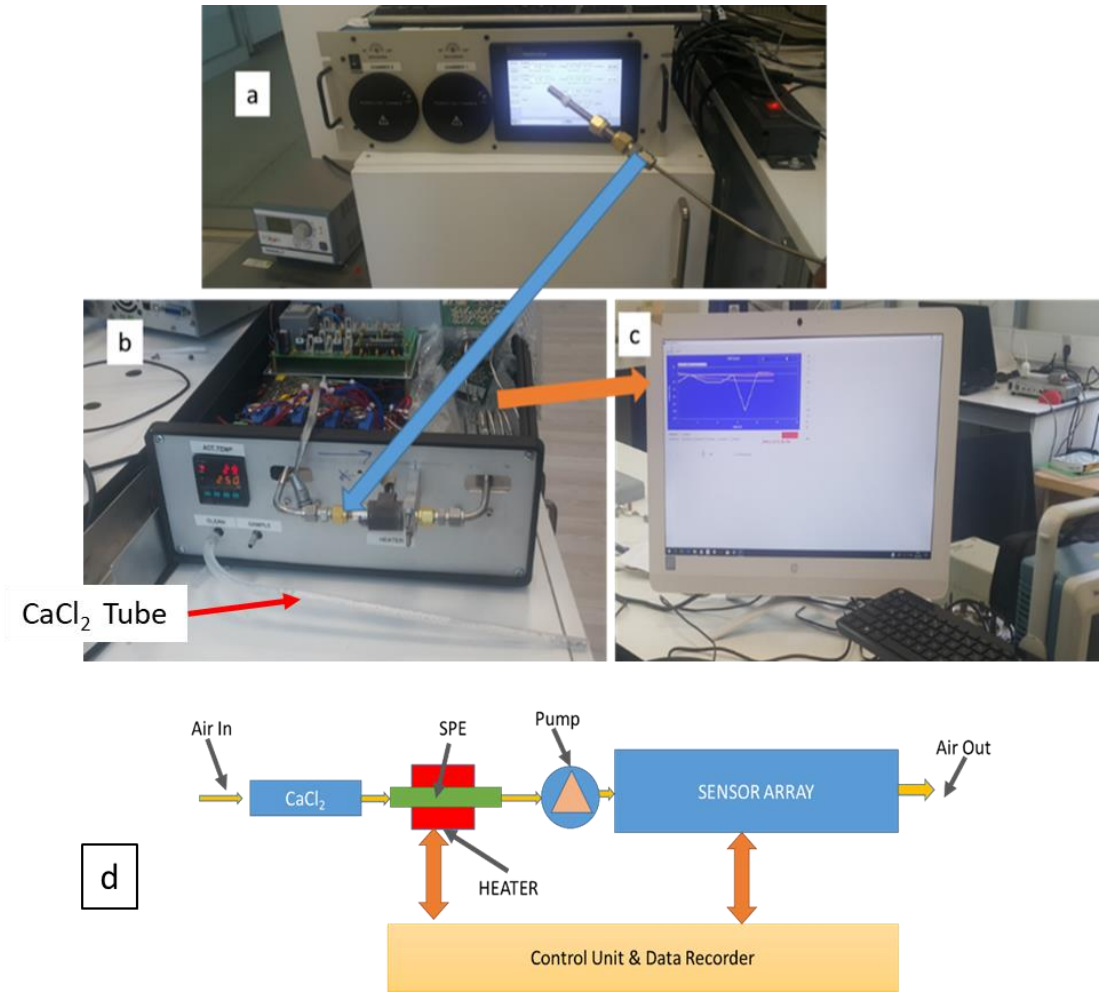

Figure 3. a) Gas generator (at the gas collecting stage) b) E-Nose mesurement system and $CaCl_2$ tube c) Data collection software interface d) Schematic representation of E-nose system. SPE columns were marked between Fig. 3a to 3b with blue arrow. The raw sensor data was transferred to the PC via RS 232 interface in each 2 s. Data transfer line was marked with orange arrow.

In the real application, humidity levels in the test ambient cannot be under control, and analytes concentrations varying as well as 1-5 ppb. To obtain performance data in real ambient of E-nose, SPE tubes were exposed to analytes using the gas generator at 100 sccm flow for the accumulation at three different times (30, 60, and 120 min). After the collection procedure than, the SPE column was placed into the E-nose system and flash heated for the fast desorption in a few seconds, and the sensor was exposed to desorbed gases to obtain responses (Fig. 3). Arranging the application in this way is the copy from the standard GC-MS procedure with the thermal desorption system. Measurement environment temperature was at room temperature and humidity was varying 45-60 % RH. Despite this change in humidity resulting from the measurement ambient, the humidity sensor (SHT 75) that

was placed in the sensor array did not read more change and the readings were around 15%. This value is at the border of the region where humidity sensors are linear and for this reason, it may not be able to measure with high accuracy at a very low humidity value. So, it is possible that the actual moisture value was lower than the measured. The temperature of the air was also not increased during the gas flowing into the sensor chamber and temperature changes were lower than 2-3°C at RT.

3. RESULTS and DISCUSSION

Using conventional test systems that are shown in Fig. 1, toluene, hexane, ethanol, and isoprene were exposed to sensors with single gas and mixture background humidity at 80 %. The reason for measurement configuration is to observe the effect of moisture on sensor responses. The second evaluation was performed using gas generation to getting sensor performance at the low-level concentration ambient.

3.1. Sensor Performance at in Controlled Atmosphere

The obtained response of sensors to VOC's vapor in dry air and with the %80 humidity background are depicted in Fig. 4,5, respectively. The sensor responses are linearly increasing or decreasing with concentration. A linear fit to the response data (frequency shifts during analyte exposure from baseline) vs. concentration was made and the slope is the sensitivity (Hz/ppm). The response of each sensor is different from the others for each gas, theses case is a desired event for the E-Nose application. Even if simple Artificial Intelligence (AI) algorithms can be sufficient to distinguish these different situations and identification of gas ambient.

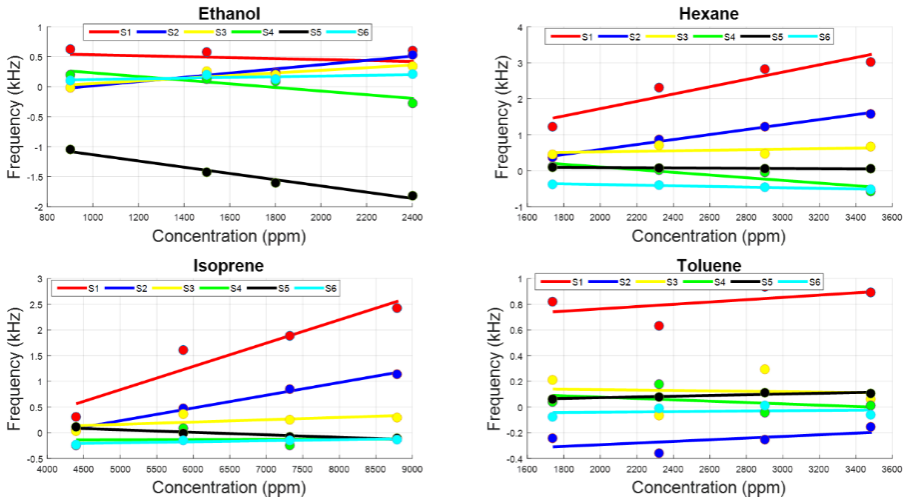

Figure 4. Sensor responses against the considered VOCs at 0 % Rh condition.

The characteristics of the sensors varied depending on the acoustoelectric effect formulated in Equation 2. Sensor 4 and 5 have an opposite response for ethanol and isoprene at 0 % Rh while they sensed the toluene sharply. In 0 % Rh gas ambient (Fig. 4, Toluene) the sensors have lower responses in positive direction on the contrary to the other sensors. Furthermore, in the 80 % Rh gas ambient the sensors have higher responses in negative direction, and also sensor 4 has a low response in positive

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direction (Fig. 4 and Fig. 5). The results reveal that the adsorbed gas by the sensitive materials is changed surface mass, conductivity, and elasticity.

The generated acoustic wave propagates onto the surface of the transducer and inside of the sensing film. In any change of characteristics due to the absorption or adsorption step is affected from the amplitude and velocity of the wave. This acoustoelectric effect has been discussed before and how the sensor response changes with under these effects [17].

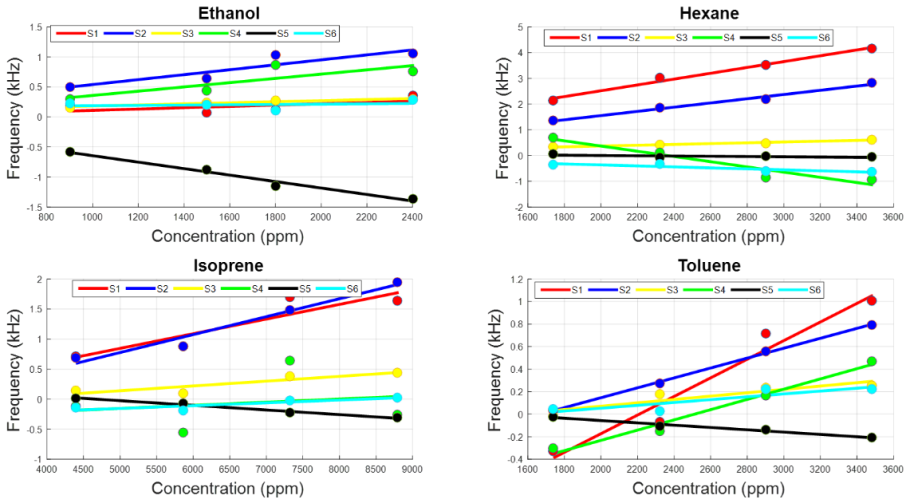
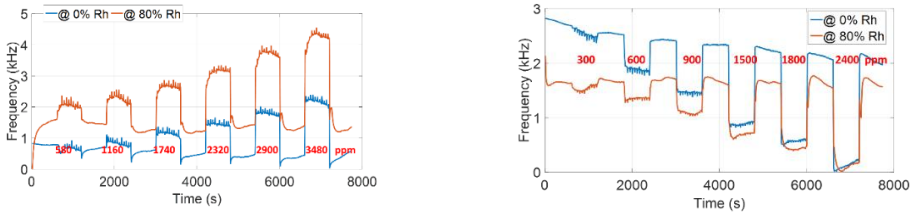


Figure 5. Sensor responses against the considered VOCs at 80 % Rh condition.

Besides this, background humidity is having a negative or positive effect on the sensor responses thus response characteristics are change depends on humidity level (Fig. 6). In this case, it will not be easy to discriminate each gas medium from each other with high accuracy using AI that is the main part of E-Nose.



(a) **(b)**

Figure 6. a) Responses of Sensor2 against hexane and b) Responses of Sensor5 against ethanol at 0 % and 80 % Rh ambient.

The gas media becomes complex with the including of humidity to the gas environment. This situation has a negative or positive effect on the sensor response decrease and increase (Fig. 6a , 6b). Since this interaction will occur at every humidity level, it will necessitate the addition of a new

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dimension to the data during the processing. For this reason, all negative parameters on the system must be removed such as humidity. The best solution to prevent humid from reaching the sensors but not retaining other gases is to add $CaCl_2$ in front of the sensors.

3.2. Sensor Performance at in Uncontrolled Atmosphere

Up to now, the effect of humidity change on the sensor response is discussed. The algorithms for the analysis of data will never be sufficient to understand and determine the real environment. The complexity of the real atmosphere is seen in Fig. 7-10. During the measurement, periodicity could not be performed because uncontrolled atmosphere tests were carried out manually. Therefore, the gas on and off times for each measurement have minor differences, and to make a clear, duration of "gas on" is marked on the graphs as shown in Fig. 7-10. Sensors were tested against ethanol, isoprene, hexane and toluene with three different concentrations. Gas concentrations were adjusted via gas collecting by using SPE in 30, 60, 120 min. Typical experiments were performed in approximately 300 s gas exposure and purging with environmental air which is passing through $CaCl_2$, respectively. "Gas On" in Fig. 7-10 in all graphs depicts the gas exposure time which marked with red, blue, and black for 30, 60, and 120 min gas collecting duration respectively.

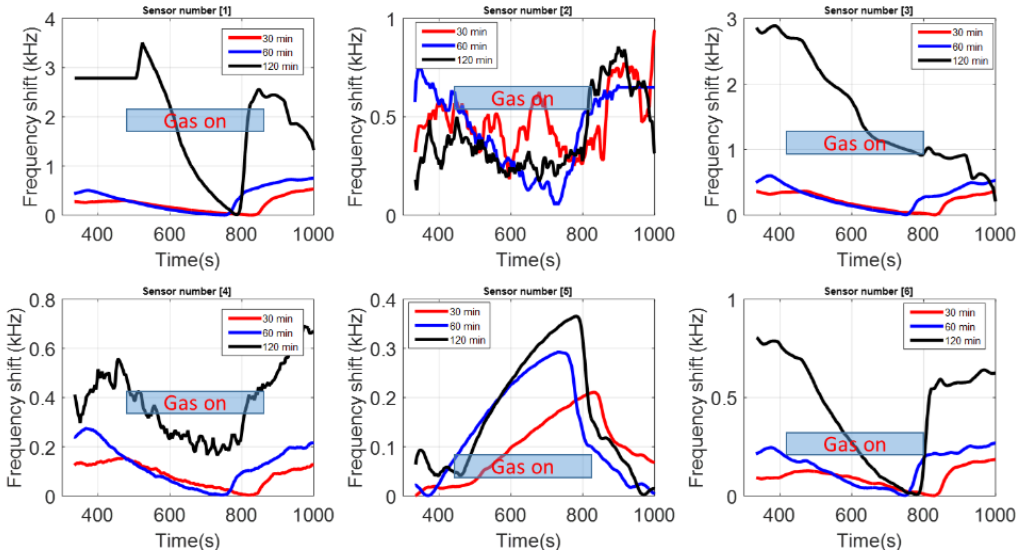

Figure 7. Responses of the sensors against ethanol with three different concentrations.

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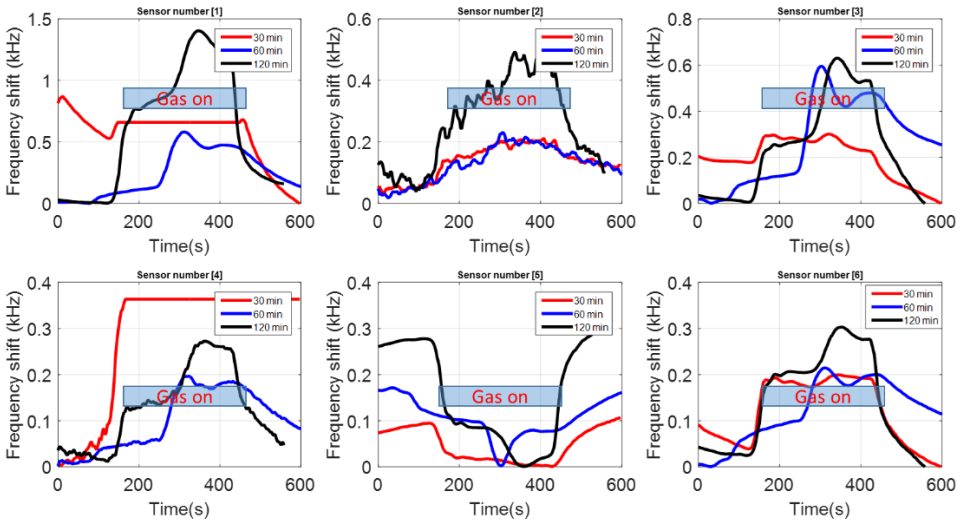

Figure 8. Responses of the sensors against isoprene with three different concentrations.

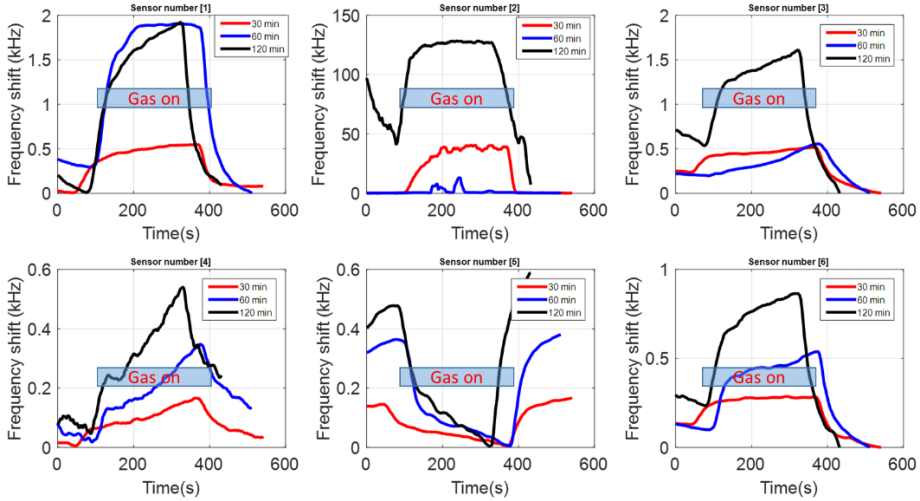

Figure 9. Responses of the sensors against hexane with three different concentrations.

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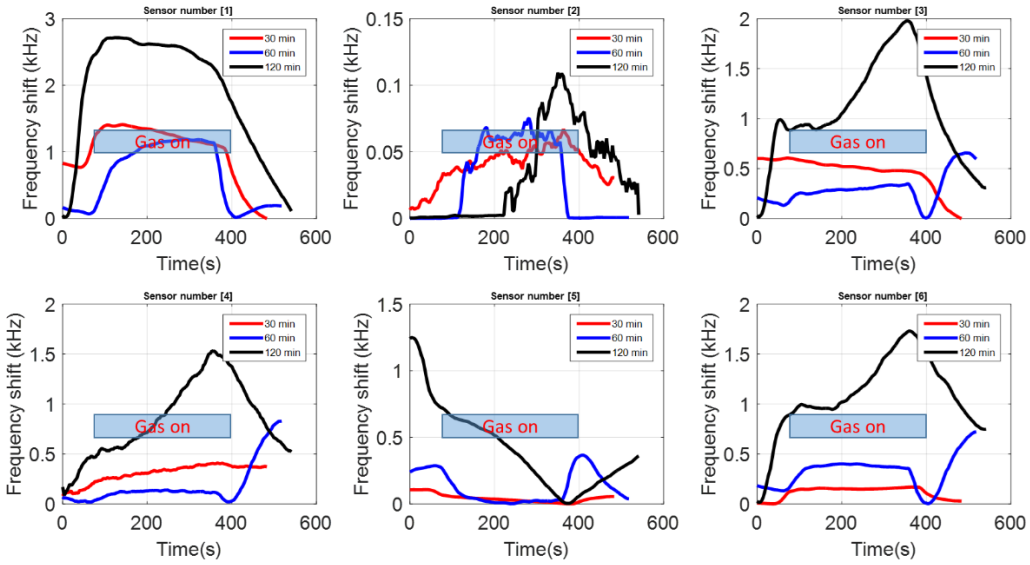

Figure 10. Responses of the sensors against toluene with three different concentrations.

Sensor responses increased as parallel as accumulation time of SPE and measurement ambient has not affected the response. $CaCl_2$ was absorbed water vapor in the air and prevented reaching the sensors. This situation has been observed via changing 1-2% on the humidity level on the humidity sensor. The interaction between gas and sensors has specified the selectivity and sensitivity. The sensitivity of the SAW-based sensor depends not only on the interaction relationship between gas and sensors but also on the acoustoelectric effect. According to equation 1, if the $4C_e \frac{f_0}{v_0^2}(\Delta hG')$ term increases by the effect of absorption and/or decreases the conductivity of the sensor film response direction will be changed. This effect can be seen by comparing sensor responses of sensor5 and sensor6 against ethanol and other gases. Consequently, the elasticity part is another important parameter of SAW-based sensors and whether it will be dominant or not depends on the type of interaction between the gas and the sensor.

The difference in sensor behavior in the uncontrolled and controlled atmosphere can be seen in the response pattern on Sensor2. The uncontrolled atmosphere is one of the best examples in the real application. Because of, although it is desired to remove moisture from the uncontrolled gas samples during the application it is not possible to say that this is achieved completely. For this reason, partial changes in the sensor characteristics will be expected in this situation. The sensor2 has a good response in Fig. 4,5 on the contrary in the uncontrolled atmosphere has a lower response except for hexane. Similar situations are partially present on other sensors.

3.3. Principal Component Analysis

Principal Component Analysis (PCA) is a mathematical method for mapping data to how does distributed and dependent on each other. This method decreases the dimensionality of data while keeping the relation of variations. Therefore, the data which has more than two variables can be shown clearly using two-dimension. The largest eigenvalue of the normalized data set and its

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corresponding eigenvector are defined as the first PCA, and then the second and third PCA vectors are defined by relative numbers. The relative numbers can be plotted to understate the relation between the data sets of similarity or dissimilarity and whether samples can be grouped[22, 23]. The main purpose of PCA applications on sensor data is to reveal the possible variations in the sensor characteristics caused by the detected gases and varying humidity. To obtain the best PCA classification each sensor must have a different sensing profile compared to others. PCA was performed after normalization of the sensor response and centering thanks to GNU Octave which is free license mathematical software[24]. PCA analysis in a mapping of loadings and scores is shown in Fig. 11.

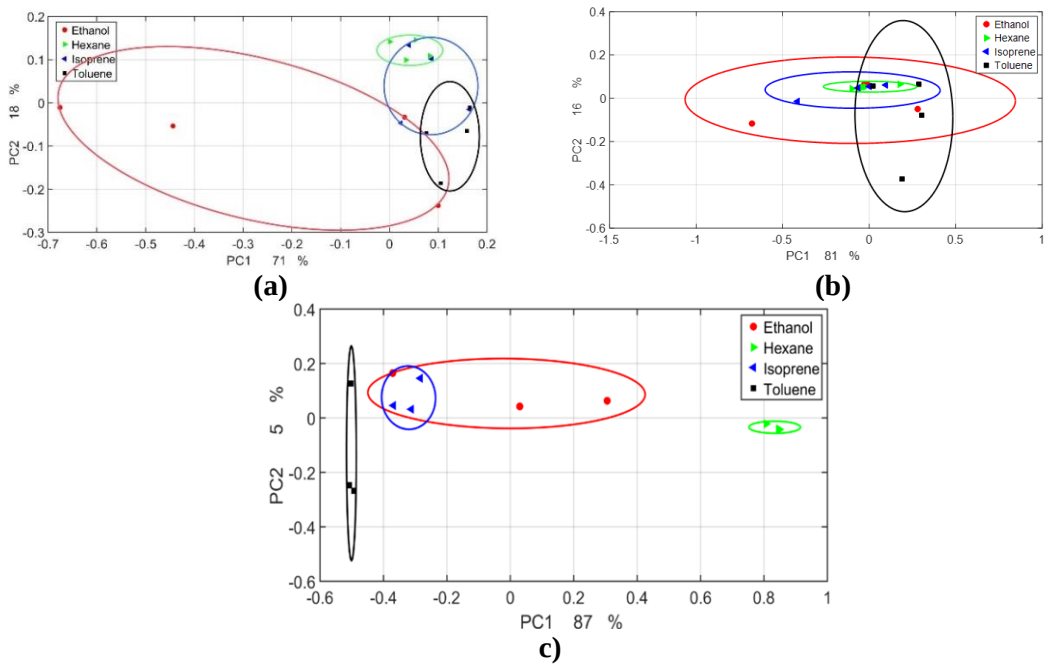

Figure 11. PCA mapping of recorded sensor data at a) 0 % Rh, b) 80 %Rh, and c) laboratory atmosphere with added $CaCl_2$ tube in front of E-Nose system.

The first two principal components contain about 100 % of the total variance. The analyte locations were found to be separated on the PCA map for the controlled atmosphere that can be shown in Fig. 11a. The varying humidity was caused by the change of PCA pattern and also the location of analytes in the PCA map was intertwined (Fig. 11b). Using $CaCl_2$ was being positive effect removing the intertwine problem and the distance of the analyte location was being increased as can be seen in Fig. 11c. In fact, that, this positive distribution in the PCA map shows us the advanced data processing methods such as Artificial Neural Network or Deep Learning can identify the gas components easily.

4. CONCLUSION

Many studies in the literature were conducted in dry air and special condition. Therefore, the high sensitivity and selectivity of the sensors or high-rate discrimination performance of the data analysis

methods can be seen. On the contrary, in the real case, these methods or performance cannot obtain the case of the complex atmosphere as well as the varying humidity level. E-nose systems can be used in different applications which are varying from explosive and chemical hazardous detection to health applications using breath analysis such as lung cancer, and Covid-19 diagnosis. The most critical important problem encountered in practice is the negative effects of the uncontrollable changing of ambient humidity.

In this study, it was proposed to equipped the $CaCl_2$ tube to prevent the humidity effect on the sensor. However, it should not be overlooked that $CaCl_2$ may also have partial absorption properties for some gases. $CaCl_2$ may be preferred in applications depending on where the E-nose will be used. It is predicted that there will be significant improvement especially in studies on breath analysis such as diagnosis of lung cancer or COVID 19. Up to now, various methods have been used to prevent the effect of the humidity on the sensor signals [25, 26]. These methods are based on mathematical models and specific algorithms. It is impossible to claim that these methods have high performance at high humidity and low analyte concentrations. In this study, it has been shown that the success of the proposed method was obtained at very low concentrations regardless of humidity level.

Another important obtained result is that the SAW sensor responses against VOC's are more pronounced with this method and they are dissociated from the effect of the humidity. This effect can be more easily seen by comparing the PCA results.

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