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Acetone Discriminator and Concentration Estimator for Diabetes Monitoring in Human Breath

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Abstract

This study investigates the core of the development of an electronic nose envisioned for non-invasive blood glucose monitoring. Tungsten Trioxide (WO_3), tin dioxide (SnO_2) and zinc oxide (ZnO) homemade gas sensors have been exposed to various concentrations of acetone and ethanol in the presence of water vapor in order to create a dataset containing the changes in the resistance of the sensitive layer of sensors during the experiment. For the pattern recognition part of the system, this work reports the extraction of six features: two conventional steady-state features, two transient features and two features extracted from transform domain. The ReliefF algorithm is then used for the selection of the most efficient features. A classification method based on support vector machine using a linear Kernel function is employed and to estimate the gas concentration of acetone and ethanol, the same training data in the classification step are used to create a prediction model based on LS-SVM. A classification accuracy of 100% is achieved and the concentration of acetone and ethanol is estimated with a root mean square error of 0.2236 and 0.6639 respectively.

Keywords: Acetone, electronic nose, feature extraction, gas sensor, support vector machine.

1. Introduction

Diabetes mellitus is a chronic disease that affects 1 in 11 adults according to the International Diabetes Federation [1], it is caused either by a lack of secretion of insulin, a use default by the body or in some cases both [2]. This serious illness affects the lifestyle of the patients because of the complications related to the abnormal glucose level that circulates in the blood, for example, it damages the eyes, the

kidneys, the nervous system, the heart and the blood vessels over time and it can even cause death [2], [3].

In fact, nowadays diabetes is considered as being the ninth major cause of death around the world [1] which makes the prevention and the monitoring of the disease progression a primordial step in the diagnosis, control and the monitoring of the patient's health condition by himself or clinicians [4], [5].

Blood glucose monitoring devices that are on the market offer only a limited number of measurements per day while a diabetic needs continuous real time blood glucose monitoring CGM to be informed in the case of severe hyperglycemia or hypoglycemia especially for patients who are dependent on insulin [6], [7]. In addition to this, conventional glucometers require that patients prick their finger each time to get the amount of blood needed for the sensor operation, and it is so painful that there are some people who reduce the number of measurements just to avoid the pain [8]. So, the CGM ideal device must be non-invasive, portable, accurate, low-cost, easy to use and does not require much calibration [7], [9], [10], [11].

In recent years, studies have shown that urine, tears, saliva, sweat and exhaled breath can be used to measure changes in glucose concentration indirectly instead of blood [12]. In this work, we are interested in the use of exhaled breath analysis for non-invasive blood glucose monitoring, a method that offers the advantage of being a mixture that is not as complex as urine and blood and that the collection of samples is not a complicated process [13]. In fact, a single human breath contains about 500 volatile organic compounds (VOC), many of them are considered as biomarkers that can indicate the state of many diseases non-invasively [12], [14]. The body of a diabetic use fat for energy, this conversion causes the production of acetone that is extracted in the breath and urine. It has been proven that the concentration of exhaled acetone is well correlated with the blood glucose concentration [12], [15], [16] this is the reason why we are focusing on the development of a system that makes it possible to measure very low acetone concentrations.

One of the most powerful techniques for VOC detection is the use of an electronic nose (e-nose) which is able to detect, quantify and even identify in some cases the desired gas molecules in a gas mixture sample [9], [17]. E-nose is an intelligent artificial system that mimics the human olfactory system, it consists of a gas sensor matrix coupled to a data acquisition system. The obtained data will be processed through a classification program in order to identify and quantify the examined gas [17], [18], [19], [20].

One of the most challenging parts of the development of an e-nose is the design of the sensor array which must be both selective and sensitive especially because the acetone is in the breath with a small concentration which varies between 0.2 ppm and 0.8 ppm for a normal person and exceeds 1.8 ppm for a diabetic person [13], considering that those people are not fasting, or under ketogenic dieting or in a workout [21].

Among the best types of sensors that can be chosen are the semiconductor oxide metal-based sensors, these sensors are widely used because of their low cost, miniaturization and

their high sensitivity compared to other types [15] [22]. For this purpose several materials have been used as a sensitive layer, in this paper we are interested in three of the most used materials in this subject: tungsten trioxide (WO_3), tin dioxide (SnO_2) and zinc oxide (ZnO).

The first one is based on WO_3 , the second on SnO_2 and the third on ZnO . The sensors were tested in the presence of acetone, ethanol and water vapor. On the other hand, we developed a pattern recognition algorithm that was tested with the database consisting of sensors responses.

In fact, pattern recognition in the field of gas analysis can be defined as the process that allows the identification of the odors present in a gas mixture [23], [24].

The feature extraction is of paramount importance in pattern recognition, its aim is to extract the useful and non-redundant information in the original signal [25], [26]. It is already proven that the right selection of features increases the performance of the e-nose system [27].

In gas analysis for e-nose applications, features are either extracted from the steady state of sensor response or from the transient response or some signal transforms such as fast Fourier transform (FFT) and discrete wavelet transform (DWT) [27].

The proposed method in this study is based on the extraction of six features: two steady-state (fractional difference and difference), two transient (integral and first derivative) and from transform domain (FFT and DWT) with the selection of the best relevant features among them.

In the present paper, authors use support vector machine (SVM) based method for data classification. SVM is among the classifiers that have proven their efficiency in recent years since its appearance in 2000 by Vapnik [28].

Since SVM is also a supervised learning method that allows to predict the target values after creating a model based on the training data [29], [30], here we discuss the use of Least Squares Support Vector Machine (LS-SVM) for estimating acetone and ethanol concentration.

The paper is organized as follows. In Section 2 we describe our experimental setup; the next section presents the proposed method. Section 4 is focused on the results and discussion. At the end, the conclusions are illustrated in Section 5.

2. Experimental Setup

For the sensors realization the first step was the deposition of the metal oxide sensitive layers (WO_3 , SnO_2 or ZnO) by magnetron cathode sputtering RF on silicon substrates containing platinum contact electrodes.

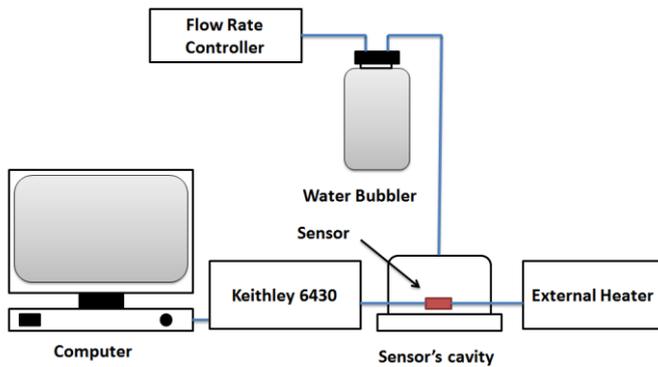


Fig. 1. Experimental set-up

After nano-particle film deposition, the sensors go through thermal annealing in dry air for 2 hours at 500°C in order to stabilize the oxide layer. Actually, each resulting active film has a thickness of 50 nm.

The block diagram of the experimental set up used for sensor's measurements is shown in Fig. 1.

The responses of WO_3 , ZnO and SnO_2 transducers to different concentrations of acetone and ethanol in the presence of water vapor were recorded separately. In our study, both water vapor and ethanol are considered as interfering elements.

As shown in the Fig. 1 during the experiments, the sensor is placed in a homemade test chamber made of stainless steel, the stainless steel avoid VOC adsorption.

The operating temperature of the detectors is fixed at 250°C for the three types; it is reached using an external heater. For the production of the concentrations of the chosen gases we used a water-containing bubbler where we insert the ethanol or acetone in liquid form using a micro needle, the liquids are diluted with distilled water and the amount of liquid introduced is calculated using the Dubowsky formula [31] in order to have the chosen concentrations. In facts, all sensors were exposed to 0, 1, 2, 5 and 10 ppm of each gas, a flow rate controller (0254, Brooks Instrument thermal mass flow) was used to control the flow of gas.

Keithley 6430 (Tektronix company) measures the voltage across via resistance and a computer controls the data acquisition via an HP-VEE Program.

2.1 Resistance response

Fig. 2, illustrates the typical resistance response curves of SnO_2 , ZnO and WO_3 gas sensors in the presence of different gases with 1 ppm at the operating temperature of 250°C that we considered as the optimal temperature for our transducers. At the beginning of the experiment, the sensors

are powered for 30 minutes before starting the measurement. This step is very important for the stabilization of the sensitive film of each sensor for the reproducibility enhancement.

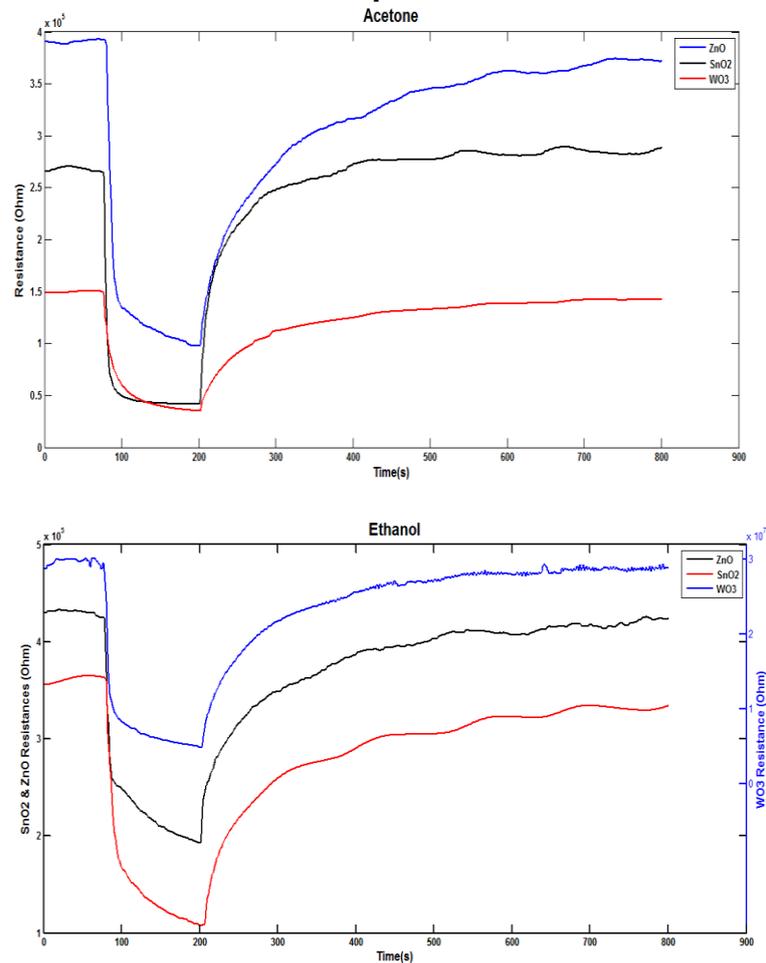


Fig. 2. Response curve of ZnO, SnO_2 and WO_3 gas sensors in presence of: (a) Acetone, (b) Ethanol.

The resistance of gas sensors decreased quickly when exposed to acetone or ethanol due to the gases reducing nature. We notice that the response and the recovery speeds of the SnO_2 sensor in the presence of acetone were faster than those of the ZnO and WO_3 sensors. Furthermore, the response and the recovery speeds of all the sensors were quite comparable to each other in the presence of ethanol. We also observe that 1 minute response time is adequate for the sensors to achieve a steady state, especially for the SnO_2 sensor. For the recovery time, 15 minute was applied for all sensors to completely return to their original baseline. The same concentrations were selected for the both gases: 0, 1, 2, 5 and 10 parts per million (ppm). We repeat the operation of gas injection twice for each gas and for each concentration, which gives us 20 measurements for each sensor.

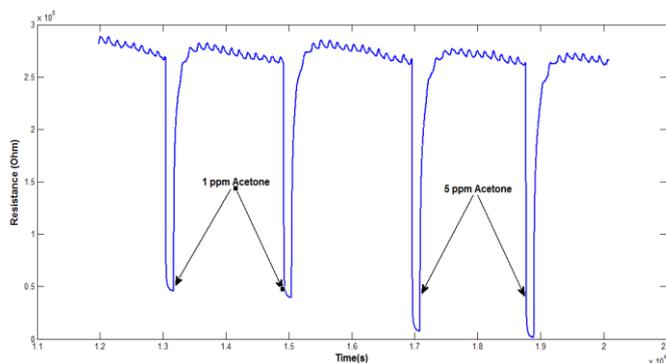


Fig. 3. Response of SnO₂ sensor exposed to 1ppm and 5 ppm acetone at 250°C.

2.2 Gas sensing behavior

The response of SnO₂ sensor for 1 ppm and 5 ppm acetone exposure were shown in Fig. 3 for two exposure cycles of each concentration at the operating temperature of 250°C. For practical use in different applications, a good gas sensor must have the ability to produce the same pattern for the same conditions. Perfect repeatability is a very important feature to make a commercial sensor. As we observe, the SnO₂ sensor has very short response and recovery time that are almost stable for variant exposures and an agreeable repeatability was seen.

3. Signal Processing

The most important signal processing elements of an E-nose are its feature extraction and classification techniques, which use the sensor's response to extract and select the most relevant features and implement the pattern recognition methods in order to classify the different odors.

3.2 Feature Extraction

The goal of feature extraction is to extract relevant information from the e-nose response with less redundancy, to obtain an optimal recognition result. However, it is still a great challenge to select features to improve the pattern recognition accuracy [30].

According to the studies of feature extraction in the past twenty years, there are many feature extraction techniques which have been applied in e-nose applications. In general, the features employed in the area of e-nose can be categorized into two main sections: Features extracted from the steady-state part, and features extracted from the transient part of the sensor response. Another approach to extract features for e-noses is based on some transforms and then the coefficients of these transforms will be used as new features to separate classes. For this study, we have selected six features as characteristic parameters.

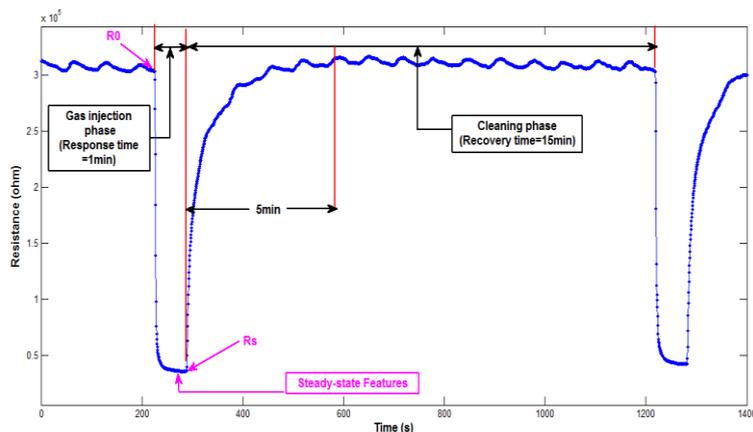


Fig. 4. Example of response Curve of SnO₂ in presence of Acetone with 10 ppm

We have first used two main conventional features as steady-state descriptors [32], fractional difference and difference (see Fig. 4), whose expressions are shown by the following equations (1) and (2):

$$\text{Fractional difference} = \frac{|R_s - R_0|}{R_0} \quad (1)$$

$$\text{Difference} = |R_s - R_0| \quad (2)$$

• R_0 : the initial resistance of a sensor calculated as the final value of its resistance before the injection gas phase.

• R_s : the steady-state resistance calculated by averaging the last five seconds of the injection gas phase.

Fractional difference effectively serves to reduce the effect of the temperature on the sensors, in addition the fractional difference is helpful to linearize the process that generates a concentration dependence in metal oxide chemiresistor sensors.

On the other side, the difference feature is generally used to eliminate the additive errors, which are added both to the steady-state and baseline response.

It has been proven that features extracted from the transient response are more informative than the steady-state features [25]. For this reason, we have used two characteristics as transient features, integral and derivative.

Integral may reflect the accumulative total of the reaction degree change and derivatives may reflect the sensor reaction rate to the odor.

The integral and derivative expressions are shown by the following equations (3) and (4) [33] :

$$\text{Integral: } I = \int_a^b f(t) dt \quad (3)$$

with $f(t)$ is the sensor response value, a represents the start response time of the gas injection phase, b is the end of the recovery time of the cleaning phase, and t represents a time point between a and b .

$$\text{Derivative: } f'(t_i) = \frac{f(t_{i+1}) - f(t_i)}{t_{i+1} - t_i} \quad (4)$$

with t_i is the time point from a to the start time of the cleaning phase, and $f(t_i)$ and $f(t_{i+1})$ represent the sensor response value at t_i and t_{i+1} time points, respectively.

The integral and derivative features have been investigated for the response and recovery time [25]. The derivative feature presents better performance considering only the gas injection phase. On the other hand, the integral feature presents better performance considering the whole curve analysis (gas injection phase + cleaning phase). In this study, instead of using the whole cleaning phase with 15 minutes, only 5 minutes will be used as a recovery period, since after 5 minutes the response curve is almost stable, see Fig. 4.

As features extracted from transform domain, we have used the most frequently transforms in signal processing step of an e-nose, which are Fast Fourier transform (FFT) [34] and the discrete wavelet transform (DWT) [35]. The Fourier transform, which used the sine and cosine as the basis functions, decomposes the response signal of the gas sensor into the superposition of the DC component and different harmonic components, and the amplitude of each component can be selected as a feature. In this study for the FFT feature we have used the amplitudes of the DC component.

Wavelet transformation [35] is an extension of Fourier transform. It maps the sensor response signals into a new space with basis functions precisely localizable in time and frequency space. The DWT divides the signal into the approximation (low frequency) and details (high frequency) at each scale or level. The coefficients are extracted by convolving the mother wavelet and the signal, which means that they represent the correlation degree. In this study, to guarantee the orthogonal requirement of feature extraction,

we have used the Daubechies family (DB1) as the mother wavelet.

Like the integral and derivative features, the DWT has been also investigated in three time intervals, response time, recovery time and the complete curve (i.e. from the response time to the next when a new odor is present). The DWT feature presents better performance considering the whole curve analysis (gas injection phase + cleaning phase) [25]. In this study, for both FFT and DWT we have used the whole curve to calculate the FFT and the DWT coefficients and only 5min will be used as a recovery period, since after 5 min the response curve is almost stable as we said earlier.

3.2 Feature selection

To choose, precisely, the most relevant features in order to make a separation of the two classes of gas, we used the ReliefF algorithm [36], which is one of the most effective strategies in the feature selection. This algorithm is known for his robustness, and can work perfectly with datasets of highly interdependent features, even for incomplete and noisy data. Another suitable characteristic for this algorithm, it can be used in multi-class problems [37].

For the majority applications of e-nose, it is a challenge to choose the best classification method for gas identification. Depending on different odors and employed sensors, we can select different classifier for each combination. The recent methods are turning to statistical learning techniques; the most widespread of them is the SVM (support vector machine). SVM is a supervised learning technique widely used for both classification and regression problems [38], with the possibility to work with large data. This technique deals well with nonlinear discrimination problems by plunging the data into a larger space in which the classification problem is linearized. The goal of this technique is to find a separating hyper-plane, with the largest margin possible between classes. For this reason we chose to work with Lib-SVM (A Matlab Library for SVM) [39]. This library helps users to easily use SVM as a tool.

3.3 Quantitative Analysis

After the classification step and the identification of the target gas, the following process will be the concentration estimation for quantitative analysis of the analyte. In this study, we chose the least squares version of the SVM (LS-SVM) in the regression mode to estimate the gas concentration. This version can perform calculations faster than the original version.

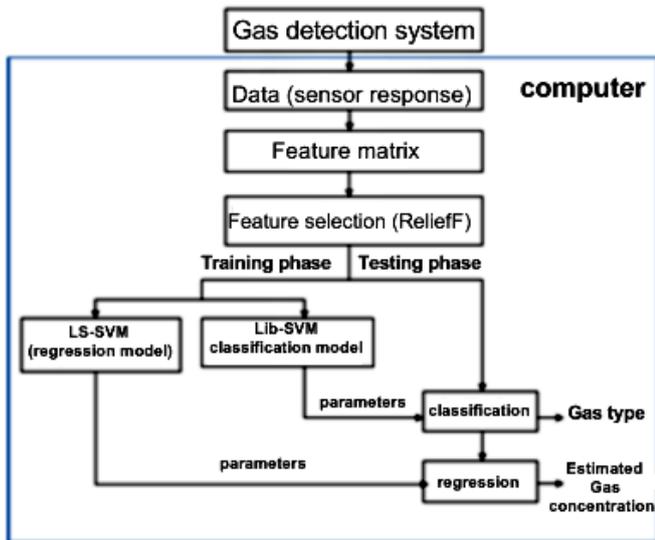


Fig. 5. Flowchart of the proposed e-nose.

The LS-SVM method provides a high degree of accuracy for concentration prediction, particularly for data sets for which a considerable nonlinearity can be expected.

In our study we use the regression mode of the LS-SVMLab toolbox v1.8 in Matlab [40]. Using this toolbox, in the experimental step we can create a mathematical model in order to predict the gas concentrations. Concerning the kernel function of the model, LS-SVM works with four types, which are linear, polynomial, radial basis function (RBF) and multi-layer perceptron (MLP). After choosing the kernel function, the most important next step is the selection of the model parameters to get a good estimation of gas concentration [41, 42]. In our empirical study, these parameters were found by using some optimization algorithms. First, suitable starting points are determined by coupled simulated annealing method (CSA). Next, from the starting points, the final parameters are calculated by multidimensional unconstrained non-linear optimization. The obtained parameters are the regularization parameter γ and the squared kernel parameter (σ^2).

4. Results and Discussion

4.1 Feature matrix

Let “I” be the feature matrix, which will constitute the database. In this work, the rows, which represent the measurement; are the various combinations of different classes of gas and concentrations at the operating temperature of 250 °C. Whereas the columns, which represent the variables; are the selected six features extracted from the response of every sensor.

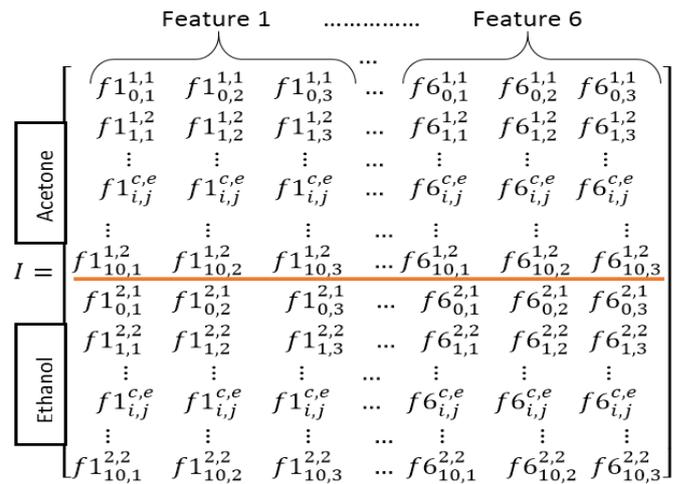


Fig. 6. The feature matrix

In our case, every line or measurement is represented by eighteen features (three sensors and six features). The organization of all features is represented in the following matrix (fig. 6):

whereas $f1_{i,j}^{c,e}$, $f2_{i,j}^{c,e}$, $f3_{i,j}^{c,e}$, $f4_{i,j}^{c,e}$, $f5_{i,j}^{c,e}$, $f6_{i,j}^{c,e}$ represent the fractional difference, difference, derivative, integral, FFT and wavelet features, respectively, for each class “c”, exposure cycle “e”, concentration “i” and sensor “j”.

$c = 1, 2$; is the class number, they correspond to acetone and ethanol, respectively.

$e = 1, 2$; is the exposure cycle, they correspond to the first and the second sample of the repeatability, respectively.

$i = 0, 1, 2, 5, 10$; gas concentration (ppm).

$j = 1, 2, 3$; the sensor number, they correspond to the SnO₂, WO₃ and ZnO, respectively.

All features of the matrix are then normalized, which means that each column is normalized between 0 and 1.

4.2 ReliefF algorithm for feature selection

The resulting six feature vectors were used with target values for the selection of the best relevant features that have the ability to separate the two types of gas (Acetone and Ethanol). We calculated the weights of six features. To better observe the values, we have multiplied all the values by 100, so we will get $(-100 \leq W[i] \leq 100)$, while $W[i] \leq 0$ means that this feature i has no relevance. All results are presented in the next table I.

Table I - ReliefF algorithm results

FEATURES	WEIGHTS	RANKING
FRACTIONAL DIFFERENCE	4.6338	5
DIFFERENCE	3.9008	6
DERIVATIVE	6.5427	1
INTEGRAL	5.3418	4
FFT	6.3716	3
WAVELET	6.5426	2

Regarding the results of this table, we observe that some features are more relevant than the others, and we can easily see the difference. The Derivative has the most pertinent feature for gas identification, followed by the Wavelet coefficients, which confirms the good results of gas identification based on transient response and transform domain.

4.3 Classification with LIB-SVM

After the feature extraction step with the ReliefF algorithm, the best two features (Derivative and Wavelet coefficients) are selected to learn the classifier in order to identify the tested gases. The performance of the classifier was evaluated by the accuracy. In his study, we used the LIB-SVM-3.23 package for the multi-class classification phase, with the optimal regularization parameter $C=1$. The training and testing data were acquired by dividing the raw data in two groups, 50% of the data were used for training and the rest 50% were used for testing.

A set of SVM methods, based on different kernel types, were evaluated in order to select the best kernel type. Efficient results were obtained with linear kernel function, LIB-SVM achieve the classification accuracy of 100%. The other methods based on polynomial, radial basis function and sigmoid give only 50% for the accuracy.

4.4 Estimating Gas Concentration Using LS-SVM

As in the classification stage; the same 50% of the training data are employed to create a mathematical model for the LS-SVM, and the rest 50% are used to test the accuracy of the model. After comparing the results of different kernel function, we choose the RBF kernel, which work very well with such type of data, as considered also in other studies [43, 44].

For the evaluation of the proposed method, we use the root mean square error (RMSE) to compare between the actual concentrations and the predicted values. RMSE expression is shown by the following equation (5):

$$RMSE = \sqrt{\frac{\sum_{i=1}^n (y_i - f_i)^2}{n}} \quad (5)$$

Where y_i , f_i , n are actual concentration, predicted concentration, and the number of data, respectively.

For the input data of the LS-SVM, instead of working with the standard method which uses the sensor resistance ratio between R_0 and R_s as input to determine the gas concentration, we propose a new method which uses, for each sensor, a single feature that gives the best result for the concentration estimation. So, the input data of the LS-SVM will be the combination of the best three features plus a vector of the target gas concentration. As result, for the acetone the best three features of SnO_2 , WO_3 and ZnO are difference, derivative and integral, respectively. For the ethanol the best three features of SnO_2 , WO_3 and ZnO are fractional difference, Fourier and derivative, respectively.

Fig. 7 shows the regression plot to estimate the concentration of the acetone and ethanol, where the vertical axis is the estimated concentration using LS-SVM and the horizontal axis is the real concentration. Perfect estimation leads to find points in the diagonal, which means that the estimated values of the gas concentration match the real values. (i.e., $x=y$).

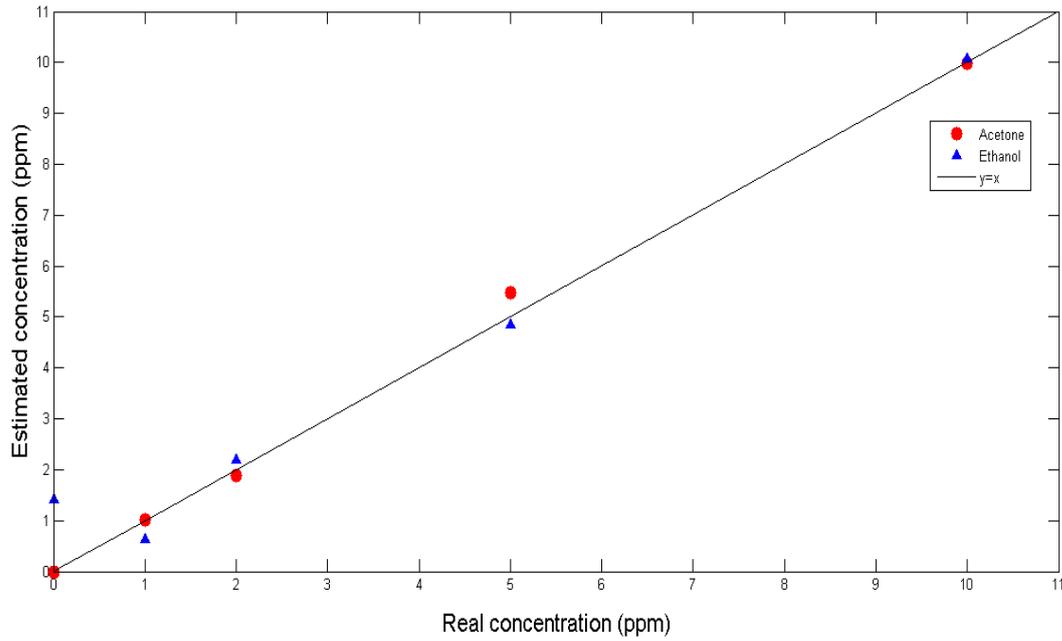


Fig. 7. Quantitative estimation, real concentrations (X-axis) and predicted concentrations (Y-axis)

As can be seen in Fig. 7, with the exception of the first point for ethanol, all the estimated concentrations are predicted very well, since all the values are very close to the diagonal. For the quantitative analysis, the general performance is evaluated by the RMSE.

Table II show the RMSE results between the real and the estimated concentrations of the standard method using the sensor resistance ratio $\frac{R_0}{R_s}$ for each sensor, the combination of the three ratios and the proposed method.

As can be seen from the RMSE values, our method presents the best result to estimate the concentration for both acetone and ethanol with an error of 0.2236 and 0.6639 respectively. By comparing this with the conventional method used to estimate the concentration even in gas sensors sold on the market we can clearly see that our method is much better.

The presented procedure and the use of the LS-SVM algorithm helped to define which of the working conditions, applied to the investigated gas sensing layer, was most informative for gas detection.

So, based on the combination of the best three features of diverse sensors using LS-SVM, we can determine with high precision the estimated gas concentration especially for the acetone which will be used for acetone detection in the breath of diabetes mellitus patients.

Table II Root Mean Squared Error (RMSE) results for different method.

INPUT OF LS- SVM	GAS	
	ACETONE	ETHANOL
$\frac{R_0}{R_s}$ (SnO ₂)	266.0717	0.9459
$\frac{R_0}{R_s}$ (WO ₃)	236.3854	1.6644
$\frac{R_0}{R_s}$ (ZnO)	2.2222	1.211
$\frac{R_0}{R_s}$ (SnO ₂ , WO ₃ , ZnO)	1.1985	0.7533
OUR METHOD	0.2236	0.6639

5. CONCLUSION

In this study, a sensor array made of three different semiconductor gas sensors is applied to classify and predict

acetone and ethanol concentrations using an SVM classification algorithm.

In this approach, six different features were selected from the sensors response, the selection of the most effective features based on the ReliefF algorithm shows that the use of transient features and features extracted from transform domain is the best method for gas recognition. Classification accuracy of 100% was achieved using the LIB-SVM classifier based on a linear kernel function.

Also, a new method based on the implementation of only the best feature for each sensor in the LS-SVM algorithm is proposed for the estimation of the gas concentration. The quantitative prediction of acetone and ethanol concentration is obtained successfully with a root mean square error of 0.2236 and 0.6639 respectively.

The results of this work confirm that the good selection of the extracted features and classifier leads to a better performance of the electronic nose in both the fields of gas identification and gas concentration prediction.

Further studies aim to use the proposed technique to design and develop an effective portable electronic nose device for continuous non-invasive blood glucose monitoring by using our three homemade sensors accompanied by a humidity sensor and a temperature sensor plus the algorithm described in this manuscript and test the system on human breath samples then do some clinical in vivo studies to validate the obtained results.

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