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A HYBRID ELECTRONIC NOSES' SYSTEM BASED ON MOS-SAW DETECTION UNITS INTENDED FOR LUNG CANCER DIAGNOSIS

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In this paper, a hybrid electronic noses' system (HENS) based on MOS-SAW detection units intended for lung cancer diagnosis is proposed. The MOS gas sensors are used to detect the VOC molecules with low molecular weight (LMW), and the SAW sensors are adopted for the detection of VOC with high molecular weight (HMW). Thus, the novel combination of these two kinds of gas sensors provides higher sensitivities to more of VOC species in breath than that of using only a single kind of sensor. The signals from MOS-SAW detection units are then recognized by a multi-model diagnosis method. Applying four algorithms, six models were established for diagnosis and tested by leave-one-out cross-validation method. The model by artificial neural network (ANN) was selected as the best model to analyze breath samples. 89 clinical samples were tested with MOS-SAW ANN diagnostic model, which takes the features derived from both the MOS and SAW sensors. It shows the highest sensitivity of 93.62%, and the highest selectivity of 83.37%. The study shows that, promisingly, our HENS is effective during screening of lung cancer patients, especially among the people of high risk.

Keywords: Hybrid electronic noses' system; MOS-SAW; VOCs; breath diagnostic model; lung cancer.

1. Introduction

Malignant tumor has become the life threatening disease of human, people are devoting themselves to find an effective way for monitoring cancer and its treatment.[1–3] Currently, a number of biomarkers for lung cancer have been identified in breath.[4–6]

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Since the breath analysis is a noninvasive, fast and low-cost approach, it is ideally suited for population-based studies both in developed and underdeveloped world. The electronic nose technology, with the advantages of fast response and portable size, has been widely studied in the application of lung cancer diagnosis through breath test.[7,8]

Although there is still no last word in the research of breath biomarkers relating to lung cancer, the results from different research team are all a combination of different kinds of VOCs.[4–6] Therefore, the electronic nose must be sensitive enough to many kinds of VOCs to work as an efficient breath diagnostic tool. However, the common electronic nose based on single kind of sensors, such as metal oxide semiconductor (MOS) sensors and conductive polymer (CP), cannot detect all of the biomarkers, and furthermore, it cannot supply all of the useful information and give a reliable detection result.

In this paper, we propose a hybrid electronic noses' system (HENS) based on MOS-SAW detecting units. The MOS gas sensors are applied to detect the VOCs whose molecular weights are lower than 150, e.g., benzene, styrene, n-hexane, while the SAW sensors are adopted for the detection of VOCs with molecular weights higher than 150, e.g., tridecane and tridecanone. As a result, HENS takes both of the two kinds of sensors' advantages and provides a better diagnostic precision for lung cancer than the system adopting single detecting method we have developed before.

2. Methods

The HENS is composed of four units, such as enrichment unit, MOS detection unit, SAW detection unit and diagnosis unit, shown in Fig. 1. The patients' breath within Tedlar bag is pre-concentrated by a Tenax-TA® tube, which is equipped in the enrichment unit. After the thermal desorption at 260°C for 3 min with the carrier gas flow of 100 standard cubic centimeter per minute (sccm), the enriched VOCs are carried into the MOS detection unit and SAW detection unit, respectively, as shown in Fig. 2.

In the MOS detection unit, nine MOS sensors (Figaro TGS813, TGS822, TGS2600, TGS2602, TGS2620 and Winsen MQ2, MQ3, MQ6, MQ138), as shown in Fig. 3(a), are chosen on the basis of Turner's research papers about the components in breath, like ammonia, acetone, ethanol, methanol and

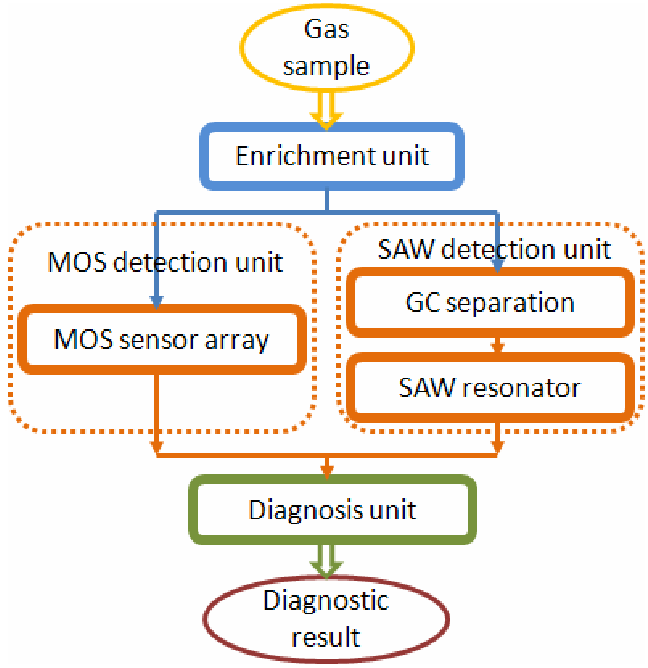


Fig. 1. Diagram of the MOS-SAW-based electronic nose system.

isoprene.[9,10] The outputs from this sensor array can be influenced by the variation of the ambient factors such as temperature, humidity and air velocity. In order to diminish these influences, the array is packaged in a small chamber of Teflon®.[11] These sensors have high sensitivity to the VOCs with low molecular weights like benzene, styrene, n-hexane, which are considered as the biomarkers of lung cancer.[12]

Uncoated SAW resonators and GC seperation are adopted in the SAW detection unit. Moreover, the uncoated SAW resonators are much more suitable for analyzing breath than the SAW sensors with delay line or with sensitive film coated.[13] We have developed a SAW resonator using ST-cut quartz, which has a low temperature coefficient. The sensor's central frequency is 250 MHz; the insert loss is −5.96 dB. The differential structure is to diminish the environmental influences, as shown in Fig. 3(b). When the VOCs come out from the capillary column, they will be condensed on the surface of the temperature controlled SAW resonator, generating a series of frequency changes. The VOCs are captured by the sensor for condensation, so the SAW resonator has a high sensitivity to the high molecular weight VOCs with high boiling point.

Two response signals of one sample obtained from the MOS and SAW detecting units are filtered by appropriate filters. In the following step, features

(a) (b)

Fig. 2. Detection units of the HENS. (a) The MOS detection unit. (b) The SAW detection unit.

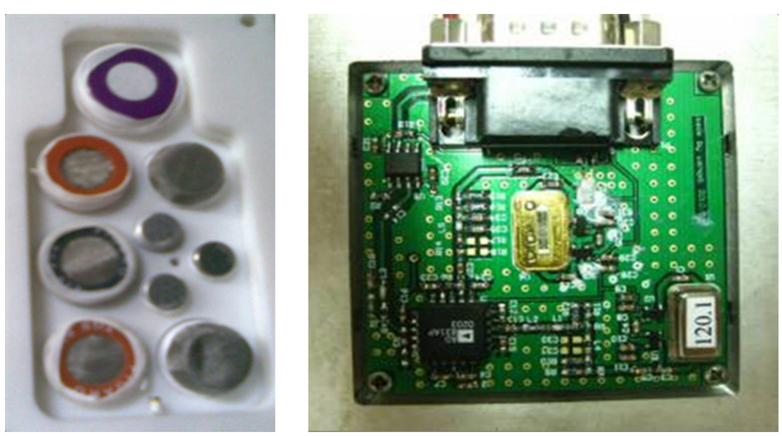
extracted from these two sets of signals are normalized to make compensation for the scale difference between the features of all the samples. We employ principle components analysis (PCA), linear discriminant analysis (LDA), artificial neural network (ANN) and partial least squares (PLS) to establish diagnostic models. The method of leave-one-out cross-validation is adopted to test these models. The model with the highest sensitivity and selectivity will be selected to validate the ability of this electronic noses' system to diagnose lung cancer.

3. Results and Discussion

Benzene, styrene and n-hexane are selected to calibrate the MOS detection unit as the low molecular weight VOCs, and tridecane and tridecanone are selected as the high molecular weight VOCs for the SAW detection unit. All of the five VOCs given above are considered as part of the lung cancer biomarkers.

The MOS detection unit is calibrated by benzene, styrene and hexane with five concentrations, i.e., 0.01 ppm, 0.1 ppm, 0.2 ppm, 0.3 ppm and 0.4 ppm. Similarly, the SAW detection unit is calibrated by tridecane and tridecanone with five concentrations, i.e., 1 ppb, 3 ppb, 5 ppb, 7 ppb and 10 ppb.

The calibration results are shown in Fig. 4. It can be seen that both the detection units have a low detecting limit to the low and high molecular weight VOCs, respectively, and the combination of these two kinds of sensors can adapt to the complexity of lung cancer diagnosis through breath analysis.



(a) (b)

Fig. 3. The gas sensors in the detection units. (a) The MOS sensors array. (b) The SAW sensors.

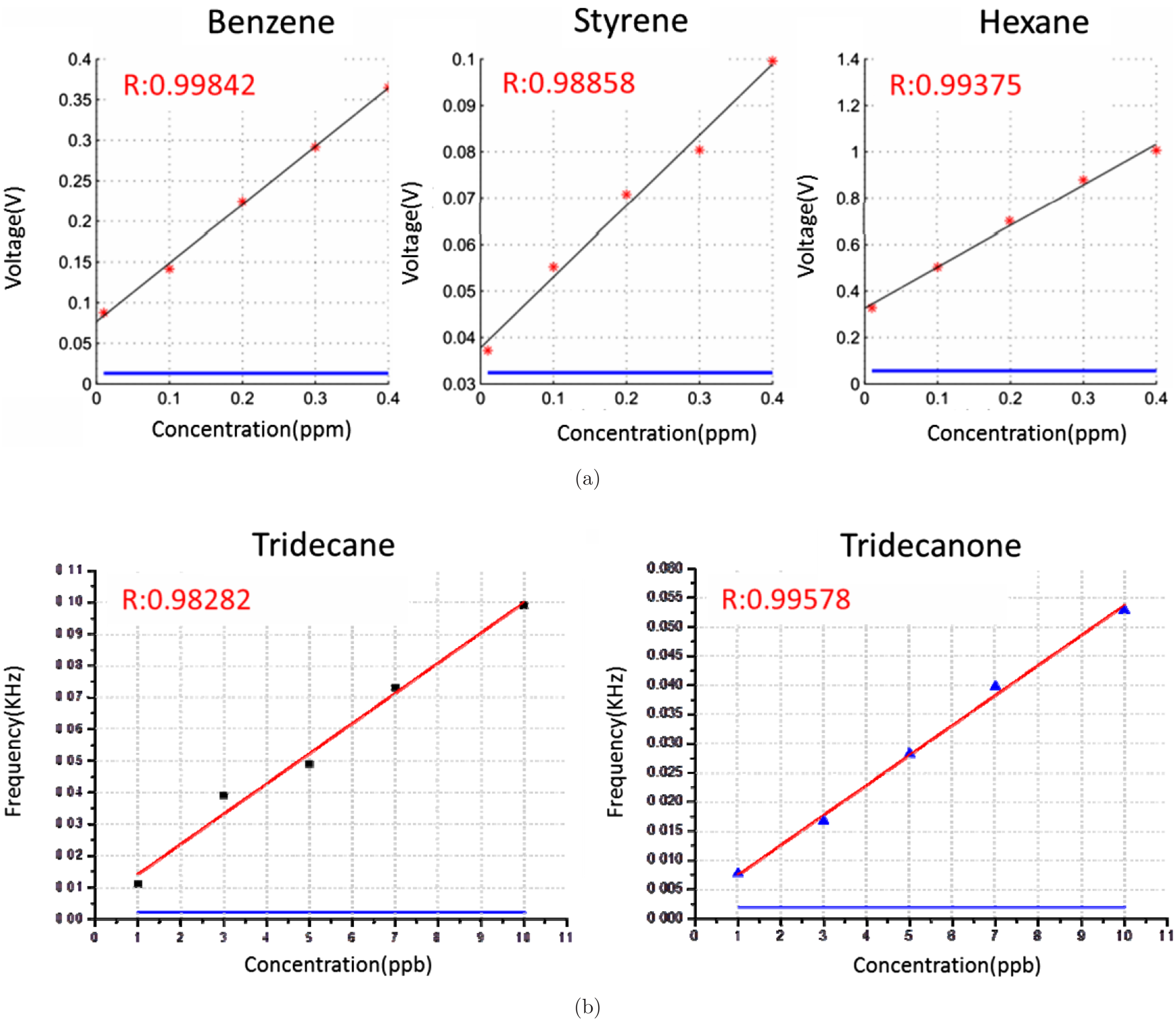


Fig. 4. Sensitivity and selectivity of the detection units to the VOCs. (a) Calibration results of the MOS detection unit to benzene, styrene and n-hexane. (b) Calibration results of the SAW detection unit to tridecane and tridecanone.

The 89 breath samples came from 42 healthy persons and 47 lung cancer patients. There are strict criteria when selecting the subjects: The healthy controls were selected from the synchronous physical examination of healthy people and the healthy family members of the lung cancer patients. In the physical examination, both the spirometry and chest X-rays were performed. If any abnormality was detected, the subject would be excluded. The family members of the lung cancer patients were also asked for chest X-rays examination to avoid the possibility of chronic bronchitis. Besides, the healthy controls must have no respiratory symptoms (e.g., cough, dyspnea and hemoptysis), and no acute illnesses such as peptic ulcer, oxyhepatitis and coronary heart disease. The patients with comorbidities such as AECOPD, peptic ulcer, oxyhepatitis, coronary heart disease and diabetes were excluded. Besides, the patients who had surgery, radiotherapy, and chemotherapy were also excluded.

The information of the subjects is listed in Table 1. The samples range from male to female, smoker to nonsmoker and alcohol drinker to nondrinker with ages from 30 to 80. The histology and lung cancer stage of the patients are listed in

Table 1. Statistical information of the samples.

Healthy	42	Male	14	Smoker	6	Drinker	5	Age	30−75
		Female	28	Nonsmoker	36	Nondrinker	37		
Patient	47	Male	35	Smoker	24	Drinker	18	Age	32−80
		Female	12	Nonsmoker	23	Nondrinker	29		

Table 2. The histology and lung cancer stage of the patients.

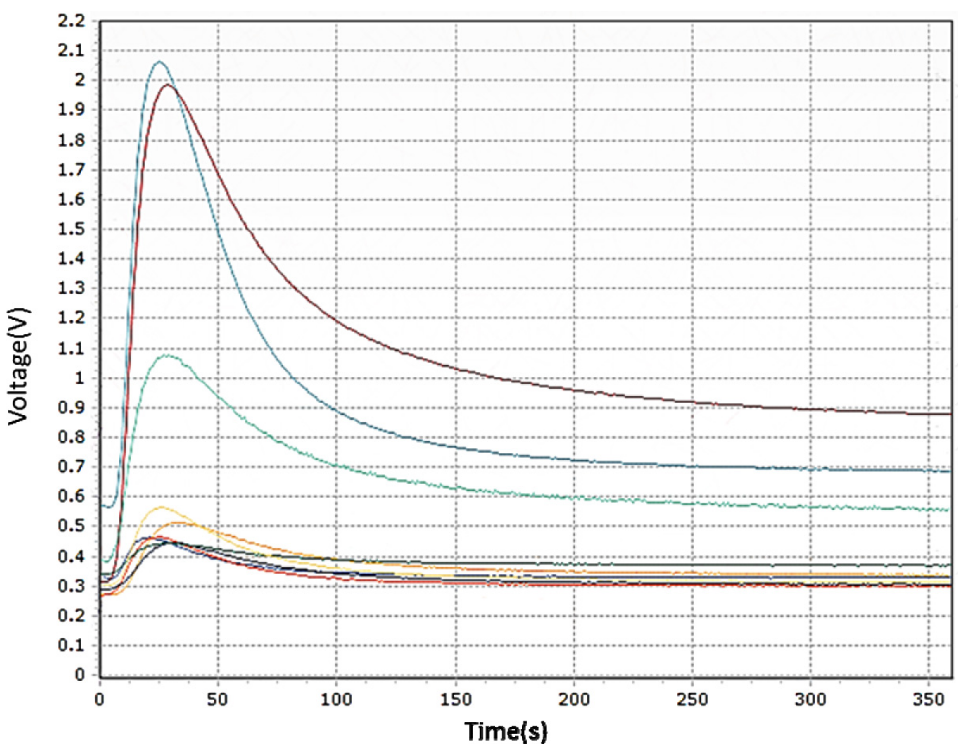
Histology		Stage	
Small cell lung cancer	5 patients	I	3 patients
Adenocarcinoma	22 patients	II	7 patients
Squamous cell carcinoma	14 patients	IIIA	4 patients
Bronchioloalveolar carcinoma	1 patients	IIIB	14 patients
Indefinite of histology	5 patients	IV	19 patients

the Table 2. The sampling was done in the Sir Run Run Shaw Hospital.

All the patients and controls are asked to eat nothing and ban smoking for 12 h (test in the morning), and avoid high-fat dinner the day before the measurement. The subjects use clean water to gargle half an hour before the test.

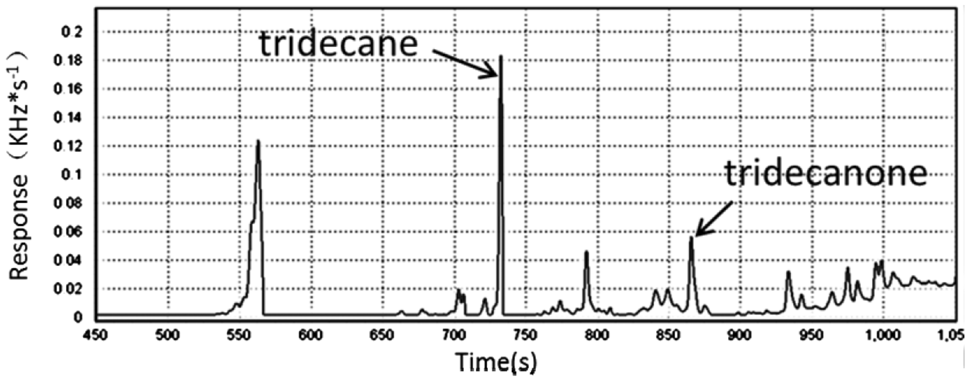
Detection results of the two detection units for one lung cancer patient are shown in Fig. 5. Then, 110 features were extracted from these two responses for each sample, and six diagnostic models are established: LDA, ANN, PLS, PCA-LDA, PCA-ANN and PCA-PLS. Because of the nonlinear relationship between the diagnostic result and the signal features, both the sensitivity and selectivity (lower than 70%) of the models based on PCA, LDA and PLS cannot satisfy the requirements very well. Finally, ANN is selected to build the diagnostic model in application.

Three kinds of ANN diagnostic models are established separately: Model based on features of MOS detection unit, the one based on features of



(a)

Fig. 5. Detecting results to the lung cancer patient. (a) Response signals of MOS detection unit. (b) Response signals of SAW detection unit.



(b)

Fig. 5. (*Continued*)

Table 3. Comparison of diagnostic models established from response features of different detection units.

Model I: Based on features of MOS detection unit		Model II: Based on features of SAW detection unit		Model III: Based on features of MOS and SAW detection units	
Sensitivity	Selectivity	Sensitivity	Selectivity	Sensitivity	Selectivity
74.47%	69.05%	91.49%	57.14%	93.62%	83.37%

SAW detection unit and another one based on features of both MOS and SAW detection units. The accuracies of each model obtained through the leave-one-out cross-validation method are compared in Table 3 shown above.

The sensitivity and selectivity to model I are both not good enough for diagnosis. Although the sensitivity to model II is 91.49% which is much higher than that of the former, the selectivity is only 57.14% even much lower than 69.05%. The model III, which is established on the features of both MOS and SAW detection units, has the highest sensitivity of 93.62%. Besides, the selectivity substantially is improved to 83.37% satisfying the requirements of breath testing.

A separate analysis of smokers and nonsmokers had been done by the GCMS before the HENS was established. The result shows that some specific VOCs are higher due to the tobacco smoking, such as 6, 10-dimethyl-2-hendecanone, but smoking does not adversely affect the accuracy of the breath test. So this separate analysis was not performed by the HENS.

4. Conclusion

In this paper, we have proposed a hybrid electronic noses' system based on MOS-SAW sensors for the breath diagnosis of lung cancer. The MOS gas sensors are used to detect the VOCs with low molecular weight, while the SAW sensors are adopted for the detection of VOCs with high molecular weights. The ANN diagnostic model based on the features of MOS and SAW detection units has reached the sensitivity of 93.62% and the selectivity of 83.37%. Otherwise, the results also indicate that the HENS based on MOS-SAW sensors has significant advantage over electronic nose consisting of single kind of gas sensors in breath testing for lung cancer.

For the sake of application into large-scale screening, the further work will be on reduction of testing time and the size of the instrument. Therefore, the technology of fast gas chromatography could be introduced into HENS, and different kinds of sensors would be integrated to form an entire structure and conduct more efficient analysis.

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