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Biosensors & Bioelectronics Vol. 12. No. 9–10, pp. 1031–1036, 1997

0956–5663/97/$17.00

PII: S0956–5663(97)00059-6

A novel method for diabetes diagnosis based on electronic nose§

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(Revised version received 24 March 1997; accepted 6 May 1997)

Abstract: A novel non-invasive method for diabetes diagnosis based on an electronic nose is proposed in this paper. The principles of the method and results of clinical experiments are presented. These results show the convenience, painlessness and non-invasiveness of the method. ©1997 Elsevier Science Limited

Keywords: non-invasive diagnosis, diagnosis of diabetes, electronic nose, biosensor

INTRODUCTION

Diabetes, one of the most common endocrinopathies, is a chronic life-long disease caused by a carbohydrate metabolic block. The International Diabetes Associate (IDA), located in Brussels, published a report that there are more than 100 million diabetics in the world, affecting 6% of all adults. In industrial countries, diabetes is the third greatest cause of death, second only to heart diseases and cancer. In China, according to statistics, about 700 000 diabetes cases occur every year among those over the age of 25, making up 0·13% of the population. With the improvement of life conditions, the incidence of diabetes has increased steadily. The conditions of diabetics are very complicated and vary frequently, so it is difficult to cure. If the diabetes cannot be well controlled, the functions and metabolism of some tissues and organs will be disordered, which results in weakness, poor immunity and complications. These complications can bring great pain to patients and even endanger their lives. Diabetes can be well controlled by such convenient means as adjusting diet, if it is diagnosed in time. Otherwise, once it reaches an advanced stage, it can result in serious diseases, such as heart diseases, renal diseases, blindness and paraplegia, etc. The President of the IDA believes that early diagnosis is the only hope for a diabetes cure. A possibly advantageous diagnosis *via* odors, which is called 'xiuzhen' in Chinese medicine, has been applied in clinics since ancient times in China. Accordingly, we proposed applying the electronic nose, which mimics artificial olfactory recognition, to diabetes diagnosis. This novel method has proved convenient, efficient and simple to operate. It causes no pain or invasion to patients, so it has a bright prospect and great practical value.

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§Paper presented at Biosensors '96, Bangkok, May 1996.

ETIOLOGY OF DIABETICS AND FEATURES OF THEIR EXPIRED AIR

As mentioned above, diabetes is caused by the disturbance of carbohydrate metabolism. The main symptom of diabetes is high blood sugar concentration. Diabetics cannot make full use of glucose iterally. Simultaneously, fat resolution is accelerated to produce more fatty acid which can be converted into ketone bodies. The latter, if only a few are produced, can be completely utilized by tissues, especially muscles. But when the production is high enough to exceed the capacity of utilization, they will be excreted and form ketonuria. Acetone is a volatile compound and can be expired while breathing, forming acetone expired gases. So the expired breath of diabetics often smells like decaying apples, which give off acetone.

ODOR RECOGNITION BASED ON ELECTRONIC NOSES

Structure and principle of an electronic nose

During diagnosis, the patient is required to expire a certain volume of gases from the nose to a container. Diagnosis is realized by an electronic nose, which determines whether there exists acetone in the examinee's expiration. Fig. 1 shows the schematic representation of an electronic nose system, which simulates the human olfactory system (Shumer, 1990; Wang *et al.*, 1996). Human osmesthesia is a procedure of gas molecule recognition. Gas molecules first enter the primary neuron (formed by a receptor and olfactory neuron). Receptor signals pass to the olfactory bulb through the axon. The olfactory bulb is formed by about 10 000 secondary neurons, assembling together to adjust and refrain signals from the primary neuron. The final signals will be sent to the cerebrum to make the corresponding decision and recognition.

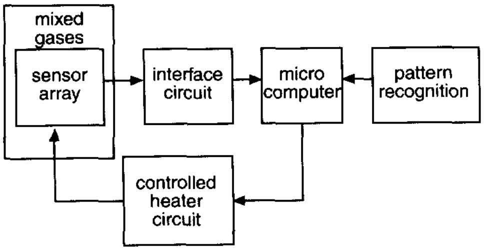


Fig. 1. The structure of electronic nose.

The odor sensors, an important part of the electronic nose, are formed by a gas sensor array. Because a single odor sensor lacks selectivity and sensitivity, we apply sensing elements with different selectivities and sensitivities to form a sensor array and make every element work at different temperatures through a controlled heater circuit. Thus, a flexible olfactory sensor array and optimum recognition are obtained. The response signals to expired gases, produced by the sensor array, are fed into the computer *via* the preprocessing circuit and interface circuit. Different kinds of odors can be classified and recognized by algorithms such as ANN pattern recognition and fuzzy cluster pattern recognition.

Preparation of sensitive material

At present, odor sensors are mostly made from metal-oxide-semiconductor sensing material, biological and polymer organic sensing material, etc. Among them, metal-oxide-semiconductor sensing material is the most widely used because of its broad ranges of gases, high sensitivity, rapid response and ease of manufacture. With the development of microelectronic and microprocessing technology, sensors made of the material have the potential for good uniformity, miniaturization and integration. General defects of odor sensors are poor selectivity, stability and sensitivity. We introduced nanometric techniques to the making of odor sensors and realized nanometric construction of odor sensing material based on the sol–gel technique. The sol–gel preparation technique makes it possible to produce semiconductor sensing material at the molecular level. In the processing of sol–gel, components are mixed with each other in the liquid phase at the molecular level to prepare homogeneous highly pure material or homogeneous mixed material of the required components, which finally form nanometric crystalline grains. The technique evidently improves uniformity and stability of the sensors and offers the basis for an optimum odor sensor array and its stable function.

We prepared a SnO_2 thin film sensor with high selectivity for acetone. While processing the sol–gel some catalysts, including Sb, Ce and Pd, are mixed into the SnO_2 solution. Then the solution is dip-coated on Si substrate and sintered. Fig. 2

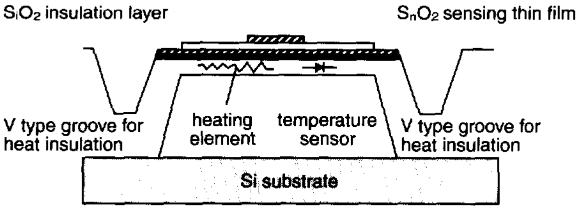


Fig. 2. The structure of integrated odor sensors.

shows the structure of the integrated odor sensors (Wang *et al.*, 1997).

Recognition algorithm

Several odor analysis methods have been introduced to electronic noses (Wang *et al.*, 1995; Wang & Xie, 1996). Here, a non-supervised fuzzy clustering algorithm, which is discussed in detail elsewhere (Wang & Xie, 1996), is applied to the analysis of the sensor responses. If in feature space, samples of diabetics are clustered as a class and those of normal persons are clustered as another, then diabetics can be distinguished from normal persons.

SYSTEM OPTIMIZATION

A flexible design for artificial olfactory sensors is proposed as follows. Generally, olfactory sensors work at a constant temperature and humidity.

Here we make gas sensing elements work at different temperatures according to the design of optimum feature space in pattern recognition, so that gases to be recognized take up different pattern areas in feature space. It is known from theory analysis and experiments that semiconductor gas sensors have different sensitivity and selectivity at different temperatures as shown in Fig. 3. That is, sensor response y is a function of gas concentration, temperature and humidity:

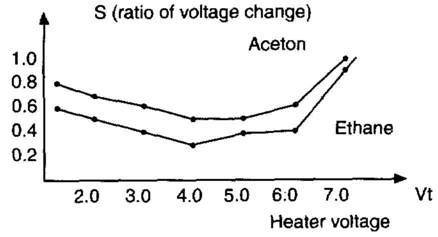


Fig. 3. Relation between sensor responses and temperature t or heating voltage V_t.

$$y = F(c,t,h) \tag{1}$$

An optimum temperature can be selected to improve the clustering proper recognition rate. We propose the following method to obtain an approximate optimum temperature (Wang *et al.*, 1995a).

We are given m kinds of gases G_1, G_2,…G_m which correspond to one pattern S_1, S_2,…S_m. Clustering is thus defined: finding areas for patterns S_1, S_2,…S_m in feature space according to their dissimilarity with each other, so that every feature point belongs to one and only one area, that is

$$S_1 \cup S_2 \cup \ldots S_k = S, S_i \cap S_j = 0 \; \forall i \neq j \tag{2}$$

Several measurements of disimilarity have been proposed. Here we use Euclidean distance as the measurement of dissimilarity.

Suppose the sensor array consists of p sensing elements. We take n_i samples for pattern S_i and each sample is a vector composed of sensor responses, marked as $(y_1,y_2 \cdots y_p)$. Before recognition, we normalize the sample vector to be $(y_1',y_2' \cdots y_p')$, where

$$y_i' = \frac{y_i}{\sum_{j=1}^{p} y_j} \tag{3}$$

and take the normalized vector as the feature vector. The feature vector corresponding to the kth sample in class S_i is marked as x_{ik}.

Let x_i be the geometrical center vector of pattern S_i in feature space

$$\mathbf{x}_i = \frac{1}{n_i} \sum_{k=1}^{n_i} \mathbf{x}_{ik} \tag{4}$$

The dissimilarity between patterns S_i and S_j is

$$D^2(\mathbf{x}_i,\mathbf{x}_j) = \|\mathbf{x}_i - \mathbf{x}_j\|^2 \tag{5}$$

where $D^2(\mathbf{x}_i,\mathbf{x}_j)$ is the square of Euclidian distance. Since $\mathbf{x}_i$ is a function of working temperature t of the sensor, the dissimilarity is also a function of temperature t. Thus, total dissimilarity among m pattern areas is defined:

$$D^2(t_1,t_2 \cdots,t_p) = \frac{1}{2m^2} [\sum_{i=1}^{m} \sum_{j=1}^{m} D^2(\mathbf{x}_i,\mathbf{x}_j)] \tag{6}$$

where t_1, t_2,…t_p are working temperatures of each sensing element. The temperatures corresponding to the greatest total disimilarity are taken as optimum temperatures.

As an example, we discuss the responses of a sensor array, formed by two gas sensing elements, to three gases A, B and C (respectively, acetone, alcohol and ethane).

Fig. 4 illustrates the distribution of pattern areas in feature space. Obviously, at this temperature some pattern areas are overlapped and difficult to discern from each other. According to Eq. (5), the dissimilarities between the three odor response modes are, respectively,

$$D^2_{ab}(\mathbf{x}_a,\mathbf{x}_b) = \left(\frac{1}{n_a}\sum_{k=1}^{m}\mathbf{x}_{ak} - \frac{1}{n_b}\sum_{k=1}^{m}\mathbf{x}_{bk}\right)^2 \quad (7)$$

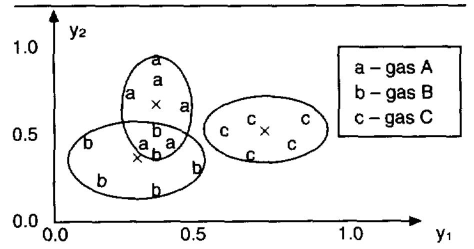
$$D^2_{bc}(\mathbf{x}_b,\mathbf{x}_c) = \left(\frac{1}{n_b}\sum_{k=1}^{n}\mathbf{x}_{bk} - \frac{1}{n_c}\sum_{k=1}^{n}\mathbf{x}_{ck}\right)^2 \quad (8)$$

$$D^2_{ca}(\mathbf{x}_c,\mathbf{x}_a) = \left(\frac{1}{n_c}\sum_{k=1}^{n}\mathbf{x}_{ck} - \frac{1}{n_a}\sum_{k=1}^{n}\mathbf{x}_{ak}\right)^2 \quad (9)$$

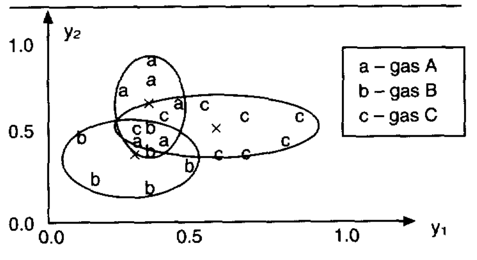
where $\mathbf{x}_{ak}$, $\mathbf{x}_{bk}$, $\mathbf{x}_{ck}$ are the normalized response vectors of the *k*th test in three gases A, B and C, respectively. n_a, n_b, n_c are the sample numbers for gases A, B and C.

Total dissimilarity can be written as

$$D^2(t_1,t_2) = \frac{1}{2*3^2}[D^2_{ab}(t_1,t_2) + D^2_{bc}(t_1,t_2) + D^2_{ca}(t_1,t_2)] \quad (10)$$



(a) Gas A is mixed with gas B



(a) Three kinds gas are mixed together

Fig. 4. Responses of two element to three gases. y_1',y_2' are features, normalized according to Eq. (3). (a) Gas A is mixed with gas B. (b) Three kinds of gas are mixed together.

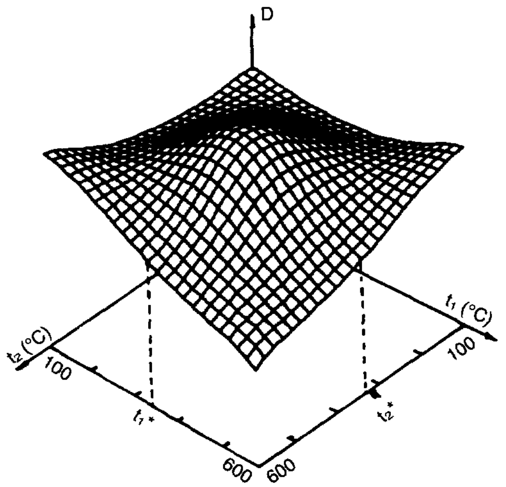


Fig. 5. Curved surface of dissimilarity at different temperatures.

A typical three-dimensional diagram is plotted in Eq. (10) and shown as Fig. 5.

The temperatures t_1^*, t_2^*, which correspond to the greatest dissimilarity, can be found in Fig. 5 and are adopted as the optimum working temperatures. Experiments show that recognition of the three gases can be improved substantially at these temperatures, as shown in Fig. 6.

EXPERIMENTS AND DISCUSSIONS

A preliminary experiment to verify the above method has been made by examination of diabetics and normal persons at Zhejiang Hospital. Thirty-two volunteers, 18 diabetics and 14 normal persons attended our experiments. All the diabetics had been diagnosed as having idiopathy diabetes. We tested their expired gases with the odor sensor array consisting of five sensing elements before a meal, 0·5 after a meal, 1 h after a meal and 2 h after a meal, respectively,

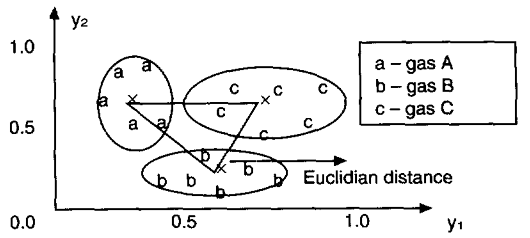


Fig. 6. The response pattern at optimum temperatures t_1^*, t_2^*.

TABLE 1 Blood sugar level and gas analysis results for detection before a meal

	Test time	*Number with higher blood sugar*	*Number of class I among column 1*	*Number with normal blood sugar*	*Number of class I among column 2*	*Percent of higher blood sugar(%)*	*Percentof class I(%)*
Diabetics	Before meal	12	11	6	3	66·7	77·8
	0·5 h after meal	14	13	4	2	77·8	83·3
	1 h after meal	18	18	0	0	100	100
	2 h after meal	16	16	2	1	88·9	88·9
Normal people	Before meal	2	1	12	4	14·3	35·7
	0·5 h after meal	1	0	13	2	7·14	14·3
	1 h after meal	2	0	12	0	14·3	0
	2 h after meal	2	1	12	0	12	7·14

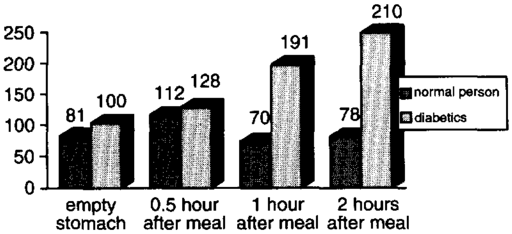


Fig. 7. The test results of blood sugar concentration of diabetics and normal people.

and then recognized the responses for each detection. Simultaneously, blood sugar was detected as a comparison, as shown in Fig. 7. During analysis, sensor responses were normalized according to Eq. (3).

We designated all samples to cluster into 2 classes, namely classes I and II. Recognition results are shown in Table 1. From the results we can find that class I has a high correlation with diabetics and class II corrsponds with normal persons.

Noticeably, before a meal, most diabetics are diagnosed correctly, while some normal persons are mistaken for diabetics. We assume the main reason for that is hunger, which can also lead to a rise of acetone concentration. This is testified by the fact that their acetone concentration was restored to normal 1 h after a meal. On the other hand, the acetone concentration of diabetics stays high after a meal. This means detection of expiration after a meal may give valuable diagnosis information. We hope further experiments will prove the gas analysis of expiration to be a valuable diagnosis term.

CONCLUSION

A novel method for diabetes diagnosis has been proposed based on olfactory recognition. The experiment shows that diabetics may be successfully discerned from normal people. In comparison with common methods for prevention and cure or diagnosis, this method has such advantages as convenience, efficiency, painlessness and non-invasiveness.

ACKNOWLEDGEMENTS

This work is supported by the National Natural Science Fund of China (No. 39400034) and the Zhejiang Province Natural Science Fund of China (No. 396082).

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