Intelligent Electronic Nose System for Detection of VOCs in Exhaled Breath

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Abstract

Significant progress has been made recently in detection of highly sensitive volatile organic compounds (VOCs) using chemical sensors. Combined with the progress in design of micro sensors array and electronic nose systems, these advances enable new applications for detection of extremely low concentrations of breath-related VOCs. State of the art detection technology in turn enables commercial sensor systems for health care applications, with high detection sensitivity and small size, weight and power consumption characteristics. We have been developing an intelligent electronic nose system for detection of VOCs for healthcare breath analysis applications. This paper reviews our contribution to monitoring of respiratory diseases and to diabetic monitoring using an intelligent electronic nose system for detection of low concentration VOCs using breath analysis techniques.

Keywords: Intelligent Electronic Nose System, Breath Analysis, Lung Cancer, COPD, Diabetes

1. INTRODUCTION

Humans exhale more than a thousands of different compounds during breathing, including many volatile organic compounds (VOCs). Exhale product reflects different biochemical processes, including those that are associate with metabolism of disease related cells. Several lines of evidence suggest that metabolic pathways in disease associated cells produce volatile compounds that differ from those produced by healthy tissues. This implies that breath analysis can be used for diagnosis because alterations in the concentration of spome compounds are associated with various diseases or altered metabolism. Breath compounds are present in parts-per-billion with respect to volume (ppb) or in even lower quantities.

More than 3000 VOCs have been catalogued recently [1, 2]. VOCs that were detected in human respiration were associated indoor air, airway surfaces, blood, and peripheral tissues of the body [3]. The exhale of humans mostly consists of nitrogen, oxygen, carbon dioxide and water vapor, which collectively account for 99% of exhale. The remaining 1% contain trace gases from several ppm carbon monoxide to several ppb. It may be very difficult to detect breath VOCs using chemical sensor arrays. We have been developing an intelligent sensor system for non-invasive health care monitoring, which combines a laboratory based sensor module, a pattern recognition subsystem and non-invasive sampling of VOCs that are exhaled by patients into a highly intelligent sensor system that allows for the rapid processing of these samples. The system assists in early and rapid monitoring of changes in the patient's state, and facilitates decision making by medical personnel for treatment of such patients.

In this paper, we introduce the analysis of exhaled breath for potential primary lung disease screening using an array based gas sensing system that incorporate an automated solid phase micro extraction (SPME) desorption system to enable the use of the system in clinical validation studies. Aiming to increase the sensitivity of detection, SPME pre-concentration was implemented for sampling of headspace air and the response of the sensor module to different concentrations of volatiles emitted from the SPME fiber was evaluated. One potential application, to the diabetic screening for discriminating between patients and controls, is discussed in this paper. Blood samples from diabetic patients were analyzed in terms of the blood glucose and glycated hemoglobin content, to validate the sensors array system’s performance.
2. INTELLIGENT ELECTRONIC NOSE SYSTEM APPLICABLE TO RESPIRATORY DISEASE MONITORING

2.1 Approach

There are many respiratory diseases including lung cancer, chronic obstructive pulmonary disease (COPD), and asthma. Among these, lung cancer and COPD are leading causes of death worldwide. However, diagnosis of these diseases often lacks timeliness, because available diagnosis methods are not sufficiently sensitive and specific. Evidence suggests that some diseases can be detected by odor analysis of exhaled breath; olfaction has been a common diagnostic tool in medicine and physicians were trained to use their sense of smell from the time of Hippocrates. For example, it is known the exhale of patients with uncontrolled diabetes smells like rotten apples, owing to the presence of acetone in the exhale of these patients [4].

We have been developing a fast reliable method for screening of lung disease, using the electronic nose technology. The system for screening lung disease, such as lung cancer, was designed using a metal oxide type array of chemical sensors with an SPME fiber, for detection of low concentrations of compounds in exhaled breath [5]. We collected real samples from patients to determine whether the samples can be differentiated on the basis of the volatile compounds present in them. Our approach is to use SPME for sampling and pre-concentration of volatiles from the headspace. SPME is a technique for sampling and pre-concentrating from the headspace, using a fiber with a hydrophilic and/or hydrophobic coating [6]. The fiber adsorbs and/or absorbs the analytes in the headspace, and is easy to handle. The system was tested on the exhaled breath of lung cancer patients as well as healthy subjects. Among the different lung diseases, lung cancer accounts for 28% of cancer-related deaths and for yearly worldwide death of nearly 1.3 million people [7]. In addition, it is very difficult to screen very early stages of lung cancer. The key marker volatiles were detected as the volatile compounds in the exhaled breath. The SPME technique combined with gas chromatography-mass spectrometry (GC-MS), enables early diagnosis of lung cancer. The results obtained in this GC-MS study allow us to build a portable system for exhaled breath analysis using an array of gas sensors. The proposed system can be used, for point of care monitoring of prospective lung cancer patients.

2.2 System Design

Commercially available metal oxides sensors have been used, modified, and refined for detection of the most probable key markers of lung cancer in the exhaled breath; the biomarkers were founded available in the literatures [7]. A sensor array chamber has been developed, and is shown in Figure 1. For exhaled breath sampling from patients and controls, the SPME approach was used, to pre-concentrate the low concentrations of emitted volatile compounds. An instrument was constructed that incorporated an automated SPME desorption system, sensor arrays combined with electronic circuit, and a data processing system, to enable to use of this system in clinical validation. Samples that are collected from patients and controls were analyzed in a preliminary study, using an instrument based on the electronic nose technology, as shown in Figure 2.
2.3 Experimental Results

Human breath contains more than a thousands of different compounds including large number of VOCs (Volatile Organic Compounds).

Many approaches have been proposed for profiling of VOCs in patients with COPD and/or lung cancers. There approaches can be classified into two categories. Methods in first category uses GC-MS for identification and quantification of a wide variety of separate breath VOCs. Methods in the second category uses an array of chemical sensors in combination with signal processing methods, such as pattern recognition algorithms.

Methods that use sensor arrays have been applied to discriminate asthma, diabetes, COPD, and lung cancers, based on the exhaled breath analysis. Here, we demonstrate a system for screening of lung cancer and/or COPD.

The system shown in Figure 2 was developed using an array of metal oxide type chemical sensors with SPME fiber, for detection of low concentration compounds in the exhaled breath.

The collected date were processed using multi-dimensional analysis. To validate the system’s functioning, we used ethanol, toluene, and decane, which may be target VOCs in lung disease (Fig. 3).

The system was tested by measuring and characterizing the exhale breath of lung cancer and COPD patients as well as healthy subjects, for classification as shown in Figure 4. Figure 4 illustrates the discrimination between patients and healthy controls, according to the measurement results. The use of the SPME fiber is also expected to alleviate the effect of humidity in the exhaled breath.

3. INTELLIGENT ELECTRONIC NOSE SYSTEM APPLICABLE TO DIABETES

3.1 Approach

Frequent screening and accurate blood glucose measurements are essential for the diagnosis, effective management and treatment of diabetes. Therefore, many efforts have been made to develop efficient and sensitive techniques for measuring blood glucose levels.

A number of invasive enzymatic and non-enzymatic methods and systems have been reported for the detection of glucose.

In general, glucose levels are determined from a small sample of blood collected by stabbing the patient’s finger. This test is performed every 2 to 3 months or every day, while it does not pose a risk to healthy adults receiving diabetes screenings, it is not comfortable for people with diabetes.

Thus, it is desirable to develop non-invasive methods for diabetes monitoring, which do not require blood sampling.

Acetone is one of the volatile organic compounds present in respiration, and acetone that is present in the exhale of diabetic patients was found to be a combustion metabolite of body fat. Acetone in the blood is excreted as urine or breath. It has been determined that the concentration of acetone released during exhalation is 0.3 to 0.9ppm for healthy people, while it can be 1.8ppm or higher for diabetic patients [8-10].

A method for measuring the amount of acetone in the exhalation using a GC-MS, an electrochemical sensor, and a gas sensor such as a metal oxide was studied. Since acetone in the exhalation is present in a low concentration and contains a variety of VOCs, the sensor should be selective for acetone and should be...
able to detect low concentrations of this gas.

### 3.2 System Design

An intelligent electronic nose system, consisting of a sensor array, a data acquisition board, and a data analysis unit for clustering, was developed for use in diabetes screening application.

The sensor array used for gas measurement was manufactured by depositing indium and tungsten using an electron beam, and applying the glancing angle deposition (GLAD) method at the Korea Institute Science Technology (KIST).

The fabricated sensor array is shown in Figure 5.

The data acquisition by the sensor was performed using the ADC of the ATmega 128 processor, and the measured data were transmitted to a personal computer for analysis. In this study, principal component analysis (PCA) was used to compare patients with the normal controls.

Exhaust gas was supplied to the electronic nose by a Tedlar bag, using the SPME fiber. The SPME fiber allows to exclude moisture from the collected exhaled gas, and ensure that only the gas of interest is transmitted to the sensor.

SPME fibers are generally used for GC-MS analysis, and polar or non-polar gases are adsorbed depending on the material coated on the fiber.

Figure 6 shows the combination of the SPME delivery system and the chamber with the array of sensors.

An intelligent electronic system has been developed to measure the exhale breath samples, as shown in Figure 7.

### 3.3 Experimental Results

Subjects with diabetes were analyzed after the approval was obtained from the Dongsan Hospital's institutional review board (IRB).

The selected subjects were diabetic patients and normal controls, as determined by doctor's examination.

Normal subjects and 20 patients were selected for study. Participants' personal information was protected by assigning a specific code to each breath sample before it was used in the study. The subjects were organized as shown in Table 1.

The body mass index (BMI) of the subjects were similar, and the effect of obesity on the patients and normal subjects could be ruled out. Blood sugar test (BST) is often used for diagnosis and management of diabetes.

The normal level of blood sugar is below 100mg/dl, and values above 126mg/dl are considered to be associated with diabetes. Glucose corresponds to fasting blood sugar, which is similar to BST. Glucose is commonly used for blood glucose levels measurements. HbA1C is an indicator of the degree of glycosylation of hemoglobin in the blood, and it reflects changes in the blood sugar levels that occur on the scales of 2 to 3 months.

| Table 1. Clinical data pertaining to the study participants |
|-----------------|----------------|----------------|----------------|
|                | Age (years) | BMI (kg/m²) | BST (mg/dl) | Glucose (mg/dl) | HbA1C (%) |
| Control        | 56±8        | 24±2         | 102±9.5      | 101±14          | 5.59±0.32 |
| Diabetes       | 61±11       | 25±3         | 132±54.9     | 138±52.72       | 7.3±1.81  |
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depending on the average lifetime of red blood cells. In the present study, HbA1C was 5.59% for the normal group and 7.3% for the diabetic group.

Sensitivity to gases for in the eight sensors of the array, which was controlled by a standard gas to mass flow controller, suggest that the device is promising for practical applications. The target gas level was 2.5ppm of ethanol, 2ppm of acetone, 1ppm of toluene and 1ppm of NO, and the response of the array of sensors is shown in Fig 8.

The sensitivity of the sensor was expressed as Rg / Ra or Ra / Rg.

The results were analyzed in terms of the PCA to determine the feasibility of distinguishing between affected patients and normal controls.

The samples used in the PCA were 16 normal subjects and, 15 diabetic subjects. Nine samples were excluded from the analysis owing to the errors in the measurement process. The results of the PCA analysis are shown in Fig 9.

The two groups were distinguished by the line that was perpendicular to the line that connected the centers of clusters. In the PCA results, the group of patients was separated from the group of normal controls, but some samples appeared in different regions.

For the group of normal controls, subjects’ blood tests, BST values, glucose levels, and HbA1C levels were within the error range, and the result of the blood glucose control for the diabetic patients was also included in the normal group.

The level of BST and glucose in the diabetic patients included in the normal group was 126 mg/dl, which is similar to that measured for normal subjects. The HbA1C levels in these diabetic patients were close to normal values of 6%, and these were evaluated as the cases in which the glycemic control was progressed by the drug prescription after the diagnosis of diabetes.

4. CONCLUSIONS

The research effort for detection of VOCs using an array of chemical gas sensors with proper sampling technology has been extend to monitoring or diagnosing diseases using breath analysis.

Recently, GC-MS has been used analysis of more than 100 VOCs. Some of these VOC gases are generated by the body metabolism and the underlying metabolic processes are being studied.

A variety of medical applications that use electronic nose systems are available. Among other applications, these systems can apply to detection of many respiratory tract diseases including lung cancer, chronic obstructive pulmonary disease (COPD), and asthma.

Among these, lung cancer and COPD are the leading causes of death worldwide.

A representative example is acetone, which is present in the excretion of diabetic patients, and its metabolism has also been studied. This provides an opportunity to use this compound as a marker in diabetes monitoring applications.

In this study, we presented an electronic nose system with an array of chemical sensors, for measuring and analyzing the expiratory flow in the patients with respiratory tract diseases and diabetes.

However, the proposed system still has some limitations related
with the collection of breath samples, including conditioning on the type of meals. To overcome these problems, it is necessary to understand the chemical components of these disease marker.

Although for diabetic patients it is known that acetone is released following the breakdown of fatty acids, the detailed metabolic processes remain to be elucidated.

Expiration-based disease diagnostics using an electronic nose system is important, but the overall pattern of gas released into patients' breath is considered to be important. In addition, it is necessary to implement electronic nose system that will exclude extraneous gases discharged after accumulation of inhale by the subjects' living environment.

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REFERENCES