

Chapter 2

Literature Review

Abstract This chapter discusses some of the key issues in breath analysis and reviews some previous research work in the areas which are particularly relevant to the present study. Following a brief introductory overview of the field, the chapter first presents the development of breath analysis. Traditional approaches like GC which have been used to analyze the compounds of breath and identify several diseases are then described. This is followed by a detailed introduction of current major approaches, e-noses, for breath analysis. The final section gives a short summary of the chapter.

Keywords Breath analysis • Electronic olfaction • Therapy monitoring • Chemical sensor • Disease identification

2.1 Introduction

Breath analysis is the examination of breath for the presence of certain compounds to determine the presence of some diseases and conditions in the human body. The breath is largely composed of oxygen, carbon dioxide, water vapor, nitric oxide, and numerous VOCs (Cao and Duan 2007). The type and quantity of the VOCs in the breath of any particular individual will vary but there is nonetheless a comparatively small common core of breath which is present in all humans (Phillips et al. 1999b). The molecules in an individual's breath may be exogenous or endogenous depending on their origin (Miekisch and Schubert 2006). Exogenous molecules are those that have been inhaled or ingested from the environment or other sources such as air or food and are hence of no diagnostic value (Risby and Solga 2006). Endogenous molecules are produced by metabolic processes. They pass from the blood through the alveolar pulmonary membrane and enter the alveolar air. As a result, the molecules in the breath have a direct relationship with their types, concentrations, volatilities, lipid solubility, and rates of diffusion when they circulate in the blood and cross the alveolar membrane (Sehnert et al. 2002). Table 2.1 summarizes the typical compositions from the breath of healthy persons and their concentrations (Phillips et al. 1999b, Risby and Solga 2006). Changes in the concentration of these molecules can suggest various diseases or at least changes in the metabolism.

Table 2.1 Typical compositions from the breath of healthy persons and their concentrations

Concentration (v/v)	Molecules
Percentage	Oxygen, water, carbon dioxide
Parts-per-million	Acetone, carbon monoxide, methane, hydrogen, isoprene, benzenemethanol
Parts-per-billion	Formaldehyde, acetaldehyde, 1-pentane, ethane, ethylene, other hydrocarbons, nitric oxide, carbon disulfide, methanol, carbonyl sulfide, methanethiol, ammonia, methylamine, dimethyl sulfide, benzene, naphthalene, benzothiazole, ethane, acetic acid

Table 2.2 Physiological origins of some endogenous breath molecules

Breath molecules	Physiological origins
Acetaldehyde	Ethanol metabolism
Acetone	Decarboxylation of acetoacetate
Ammonia	Protein metabolism
Carbon disulfide	Gut bacteria
Carbon monoxide	Production catalyzed by heme oxygenase
Carbonyl sulfide	Gut bacteria
Ethane	Lipid peroxidation
Ethanol	Gut bacteria
Ethylene	Lipid peroxidation
Hydrocarbons	Lipid peroxidation/metabolism
Hydrogen	Gut bacteria
Isoprene	Cholesterol biosynthesis
Methane	Gut bacteria
Methanethiol	Methionine metabolism
Methanol	Metabolism of fruit
Methylamine	Protein metabolism
Nitric oxide	Production catalyzed by nitric oxide synthase
Pentane	Lipid peroxidation

By studying the components of the breath, much can be learnt about the overall state of an individual's metabolism or physical condition. Table 2.2 presents some physiological origins of endogenous breath molecules (Risby and Solga 2006). These molecules are considered as biomarkers of the presence of diseases and clinical conditions. For instance, nitric oxide in breath can be measured as an indicator of asthma or other conditions characterized by airway inflammation (Deykin et al. 2002). Breath isoprene is significantly lower in cystic fibrosis patients with acute respiratory exacerbation (McGrath et al. 2000). Increased pentane and carbon disulfide have been observed in the breath of patients with schizophrenia (Phillips et al. 1993). Acetone has been found to be more abundant in the breath of diabetics (Deng et al.

2004; Fleischer et al. 2002), and breath ammonia is significantly elevated in patients with renal diseases (Davies et al. 1997). By detecting these molecules in breath, one can identify the diseases in an early stage and monitor their development.

Breath analysis has many advantages compared with other traditional methods such as blood and urine tests, including the following major ones. First, breath analysis is a noninvasive method, and it causes the least harm to both the subjects and the personnel who collect the samples. Second, its result can be obtained immediately, and third, the only requirement to collect a breath sample is that the subject must be breathing (Van Berkel et al. 2008). Therefore, increasing interest has been expressed about the applications of breath analysis in medicine and clinical pathology, both as a diagnostic tool and as a way to monitor the progress of therapies (Di Francesco et al. 2005; Dweik and Amann 2008).

2.2 Development of Breath Analysis

The breath analysis for the purpose of diagnosis has a long history. The ancient Greek physicians already knew that human breath could provide clues to diagnosis (Phillips 1992). For example, doctors in ancient Greece knew the existence of sweet breath was a dangerous sign and modern clinicians know that exhaled air from patients with diabetic ketoacidosis smells sweet like rotting apples. Ancient Greek physicians also recognized musty and fishy odors indicated a problem with liver, a urine-like smell indicated failing kidneys, and a putrid stench indicated a lung abscess. Olfaction diagnosis is also one of the basic diagnostic methods of Chinese Traditional Medicine, which has a history of 5000 years. The ancient Chinese doctors stated that the aroma of human breath could indicate the condition of the human body (Zhufan 2000). They found that foul breath is due to pathogenic heat in the stomach or indigestion and sour breath indicates food accumulation in the stomach.

Modern breath analysis started in the 1970s when Pauling et al. (1971) pioneered the analytical assessment of breath components by the GC analysis of exhaled air and identified more than 200 compounds in human breath exhaled after passing the blood/air interface within the lungs. Some of these compounds were associated with different pathological conditions.

With the technical progress of various analytical methods such as GC and the sensor system during the past few decades, breath measurement by GC and e-nose have become two common approaches. GC is a chemical analysis instrument for separating chemicals in a complex sample. By coupling with a detector, like Mass Spectrometry (MS) or Flame Ionization Detection (FID), it can positively identify the actual presence of a particular substance in a given sample. Despite its excellent sensitivity, GC usually requires the preprocessing of breath samples and separation for addressing target analytes, which renders this method less suitable for analyzing samples in real time. Besides, GC is expensive and hard to move. It requires skilled operators and qualified expert's interpretation. Therefore, it is difficult to implement GC as an online screening and quick diagnosis tool. For these reasons, e-nose might provide an alternative means of breath analysis.

E-nose utilizes chemical sensors to obtain ‘smell-prints’ of various gaseous sources and distinguish them with the help of pattern recognition algorithms, providing discrimination of gas mixtures irrespective of the individual molecular components. Compared with GC, e-nose measurement is regarded as a nonspecific test which principally follows an empirical approach. Although largely qualitative or semi-quantitative in nature, such approach is ideal for rapid screening for infectious diseases because the results can be obtained in minutes, rather than the days taken by traditional techniques (Turner and Magan 2004).

In the following sections, the current literatures about breath analysis by using both GC and e-nose are reviewed in detail. The reviewed contents are categorized according to the type of the diseases.

2.3 Breath Analysis by GC

In virtue of GC or GC linked with Mass Spectrometry (GC/MS), researchers can find out which biomarkers indicate some diseases and explain the pathological mechanisms associated with these diseases. The list of diseases reported below, is related to a series of works found in literature. Each of diseases is associated with certain biomarkers, which can be detected by GC or GC/MS.

2.3.1 Lung Cancer

In the past two decades, a noteworthy body of research about breath analysis has been oriented toward the identification of some particular VOCs as markers of lung cancer, one reason may be that the lung has a close connection with breath.

As early as 1985, by using a specially developed breath collection technique and computer-assisted GC/MS, Gordon et al. (1985) identified 22 VOCs, such as hexane, methylpentane, and benzene derivatives, in the exhaled air of patients with lung cancer. The GC/MS profiles of 12 diseased samples and 17 controlled samples were analyzed to distinguish patients from controlled group with the accuracy of over 80%.

Three years later, in 1988, O'Neill et al. (1988) also analyzed the compounds of exhaled breath from both lung cancer patients and healthy subjects, in virtue of GC/MS, and classified the compounds into 16 chemical classes, and then sorted all compounds into these chemical classes and classified the compounds at the >75% and >90% occurrence levels. Both the occurrence-rate components were then evaluated as diagnostic markers in a discriminant function model.

About a decade later, in 1999, Phillips et al. (1999a) collected breath samples from 108 patients with an abnormal chest radiograph and analyzed them by GC. The investigation found that a combination of 22 breath VOCs, predominantly alkane, alkane derivatives, and benzene derivatives, could discriminate between patients with and without lung cancer with 100% sensitivity and 81.3% specificity.

Table 2.3 The definition of sensitivity and specificity

		Test outcome		Sensitivity	Specificity
		Positive	Negative		
Actual condition	Positive	tp	fn	$\frac{tp}{tp + fn}$	$\frac{tn}{tn + fp}$
	Negative	fp	tn		

It is necessary to introduce the definition of sensitivity and specificity. In medicine, the reliability of a diagnosis is measured in terms of sensitivity and specificity, with the outcome being either positive (unhealthy) or negative (healthy). In the classification, the number of genuine sick subjects is denoted tp ; misidentified healthy subjects is fp ; genuine healthy subjects is tn ; the misdiagnosed sick subjects is denoted as fn (Blatt et al. 2007). Sensitivity and specificity are thus defined as in Table 2.3.

And then, in 2003, to evaluate VOCs in the breath as tumor markers in lung cancer, Phillips et al. investigated the breath compounds of 178 bronchoscopy patients and 41 healthy volunteers by using GC (Phillips et al. 2003a). In this study, the number of biomarkers of lung cancer was reduced to nine in comparison with the report issued in 1999 (Phillips et al. 1999a). The results showed that a predictive model employing the nine VOCs could identify the primary lung cancer with a sensitivity of 89.6% and a specificity of 82.9%.

In these studies, it turned out that some specific compounds occur in anomalous concentration in the breath of lung cancer patients.

2.3.2 Lipid Peroxidation

Alkanes (principally ethane and pentane) in the breath result from cellular injuries which cause an intracellular accumulation of oxygen-free radicals and accelerated peroxidation of polyunsaturated fatty acids (Van Gossum and Decuyper 1989). The peroxidation of lipids may result in membrane injury, with the dysfunction and death of the affected cells. From 1991, several research groups started to find the connection between the breath pentane and diseases related to lipid peroxidation.

Weitz et al. (1991) first measured pentane in the breath of 10 healthy control subjects and 20 consecutive patients with suspected acute myocardial infarction. The results showed the breath pentane concentration was higher in the acute myocardial infarction group than in the patient control and healthy control groups.

Then, by using a GC, Sobotka et al. (1993a) measured compounds in the breath of patients with chronic heart failure (CHF) and age matched controls in 1993, and found out that the patients with CHF excreted high concentrations of pentane.

In the same year, to determine the concentrations of pentane and other VOCs in the breath of patients with schizophrenia, Phillips et al. (1993) measured the exhaled breath in 25 patients with acute schizophrenic psychosis, 26 patients with psychiatric disorders other than schizophrenia, and 37 normal volunteers by GC/MS. The results demonstrated that the mean alveolar gradients of pentane and carbon disulfide were significantly higher in the patients with schizophrenia than in the control groups. As a result, schizophrenia could be detected by measuring the concentration of pentane and carbon disulfide in breath.

Next year, in 1994, Sobotka et al. (1993b) studied 37 consecutive outpatients with stable cardiac allograft function. Breath pentane levels were measured with GC. The investigation found out that breath pentane could be measured as a potential marker of acute cardiac allograft rejection.

In 1995, Phillips et al. (1995) first combined GC with a self-designed Breath Collecting Apparatus (BCA) to analyze the breath samples. The composition of the subject database was the same as Ref. Phillips et al. (1993). Pattern recognition models using 11 VOCs, such as 2-methylbatane, pentane, and dichloromethane, identified the patients with schizophrenia with a sensitivity of 80% and a specificity of 61.9%. The paper also indicated that the VOCs in breath were not significantly affected by drug therapy, age, sex, smoking, diet, or race.

In 1997, to determine if exhaled pentane levels were increased in acute asthma, Olopade et al. (1997) collected 12 acute asthma patients, 11 stable asthma patients, and 17 normal control subjects and analyzed them using a GC. The result showed exhaled pentane levels were similar in patients with stable asthma and in normal control subjects, while the levels were increased in patients with acute asthma.

In 2003, by using GC, Phillips et al. (2003c) analyzed breath VOCs in 30 patients with unstable angina confirmed by coronary angiography and in 38 age-matched healthy volunteers. They selected 8 VOCs, like pentane and hexane as biomarkers to construct a predictive model that correctly classified unstable angina patients with a sensitivity of 90% and a specificity of 73.7%.

2.3.3 Renal Diseases

This kind of disease is due to the inability of kidneys to filter blood substances, resulting in the accumulation of nitrogen-bearing waste products (urea), which are usually excreted in urine and blood. It then eventually causes ammoniacal breath of patients.

In 1997, Davies et al. (1997) used selected ion flow tube (SIFT) technique to quantify ammonia on the breath of 23 patients with end-stage renal failure. The study showed several compounds were present in patients' breath samples, including amine and alcohol, and in quantitative terms ammonia was by far the most significant abnormality. The study also monitored the reduction of breath ammonia during hemodialysis. Accordingly, ammonia can be regarded as a critical biomarker to detect renal failure and monitor the medical treatment of this disease.

2.3.4 Liver Diseases

Liver diseases were first investigated by Sehnert et al. (2002), based on abnormal concentrations of metabolic products in exhaled breath. Exhaled breath collected from 86 liver diseases patients and 109 healthy subjects were analyzed by GC. The experiments showed that subjects with chronic liver diseases could be differentiated from those with normal liver function by comparing the levels of breath carbonyl sulphide, carbon disulphide, and isoprene. These differences were confirmed and correlated by comparing the levels with standard clinical blood markers of liver diseases.

2.3.5 Breast Cancer

Breast cancer is accompanied by increased oxidative stress and induction of polymorphic cytochrome P-450 mixed oxidase enzymes (CYP) (Phillips et al. 2003b). Both processes affect the abundance of VOCs in the breath because oxidative stress causes lipid peroxidation of polyunsaturated fatty acids in membranes, producing alkanes and methylalkanes which are catabolized by CYP (Phillips et al. 2003b).

In 2003, Phillips, et al. (2003b) collected 201 breath samples from women with breast cancer and analyzed them by GC/MS in order to determine the volatile markers of breast cancer. Eight breath VOCs, like nonane and tridecane, 5-methylused were used to identify this disease. The breath test distinguished between women with breast cancer and healthy volunteers with a sensitivity of 94.1% and a specificity of 73.8% (Phillips et al. 2003b).

2.3.6 Diabetes

It has long been known that the blood of diabetics contains acetone. Diabetes occurs when the glucose produced by the body cannot enter the bloodstream to provide energy to cells. Glucose enters the cells of body with the help of insulin. If the body is not producing insulin (type 1 diabetes), or the body becomes less responsive to insulin (type 2 diabetes), glucose cannot get into the cells. As a result, the cells have to use fat as an energy source. In the process of metabolizing fat for energy, one of the by-products is ketones. When ketones are accumulated in the blood, it first causes ketosis, and then progresses to ketoacidosis, a form of metabolic acidosis (Laffel 1999). There are three ketone bodies—acetoacetate, acetone, and β -hydroxybutyrate in the blood. Among them, β -hydroxybutyrate is the predominant ketone present in severe diabetic ketoacidosis (Umpierrez et al. 1995).

As early as 1969, Tassopoulos et al. (1969) measured the breath acetone of 251 diabetics after overnight fasting, by using GC. At the same time, the authors also

measured the patients' venous β -hydroxybutyrate and blood glucose values, and showed that the concentration of breath acetone has quite a high correlation with both venous β -hydroxybutyrate and blood glucose values.

The relationship between breath acetone and plasma acetone was confirmed by Sulway et al. (1970) in 1970, who tested the plasma and breath acetone of 27 diabetics and discovered that the concentration of breath acetone and plasma acetone was linearly correlated with some scatter at the higher concentration.

Additionally, Crofford et al. (1977) proved that the concentration of acetone in the head space of the sealed container containing whole blood was approximately equal to the alveolar air acetone concentration. And then, in 1982, Owen et al. (1982) studied acetone metabolism in nine diabetic patients in moderate to severe ketoacidosis and observed that there was a positive linear relationship between the breath acetone production rate and the plasma acetone concentration. In 2004, Deng et al. (2004) analyzed the breath of healthy persons and patients with diabetes by using GC/MS. The results proved that the increased concentration of acetone in diabetics' breath could be used as a marker for diagnosis of diabetes.

2.3.7 *Pulmonary Tuberculosis*

Pulmonary tuberculosis may alter the VOCs in breath because both mycobacteria and oxidative stress resulting from mycobacterial infection generate distinctive VOCs in human body (Phillips et al. 2007).

Phillips et al. (2007) studied the breath of patients with pulmonary tuberculosis to determine if the breath contains biomarkers of this kind of disease in 2007. 130 different VOCs were consistently detected. The most abundant were naphthalene, 1-methyl-, 3-heptanone, etc. These VOCs were assayed by GC/MS in the breath of 42 patients hospitalized for suspicion of pulmonary tuberculosis and 59 healthy controls. Pattern recognition methods distinguished the healthy controls from the hospitalized patients with 100% sensitivity and 100% specificity.

2.3.8 *Summary*

Table 2.4 summarizes the key breath compounds associated with different disease types analyzed by both GC and pathological mechanism. Even though the clinical application of GC might be hampered by the need for expensive analytical equipment, the degree of expertise required to operate such instruments, and the length of time required to obtain results (Turner and Magan 2004), GC plays a critical role in confirming these compounds associated with certain diseases. These compounds not only help explain the pathological mechanism of these diseases, but also are of benefit to selecting proper sensors when designing the specific breath analysis system.

Table 2.4 Summary of key breath compounds associated with different disease types

Breath compounds	Associated conditions
Acetone	Diabetes (Deng et al. 2004)
Carbonyl sulphide, carbon disulphide, isoprene	Liver diseases (Sehnert et al. 2002)
Naphthalene, 1-methyl-, 3-heptanone, methylcyclododecane, etc.	Pulmonary tuberculosis (Phillips et al. 2007)
Nonane, tridecane, 5-methyl, undecane, 3-methyl, etc.	Breast cancer (Phillips et al. 2003b)
Benzene, 1,1-oxybis-, 1,1-biphenyl, 2,2-diethyl, furan, 2,5-dimethyl-, etc.	Lung cancer (Phillips et al. 2003a)
Ammonia	Renal disease (Davies et al. 1997)
Octane, 4-methyl, decane, 4-methyl, hexane, etc.	Unstable angina (Salazar 2003)
Propane, 2-methyl, octadecane, octane, 5-methyl, etc.	Heart transplant rejection (Phillips et al. 2004)
Pentane, carbon disulfide	Schizophrenia (Phillips et al. 1993)
Pentane	Acute myocardial infarction (Weitz et al. 1991)
Pentane	Acute asthma (Olopade et al. 1997)
Pentane	Rheumatoid arthritis (Humad et al. 1988)
Ethane	Active ulcerative colitis (Sedghi et al. 1994)
Nitric oxide	Asthmatic inflammation (Baraldi and Carraro 2006)
Nitric oxide, carbon monoxide	Bronchiectasis (Kharitonov et al. 1995), (Horvath et al. 1998)
Nitric oxide	COPD (Maziak et al. 1998)
Ethane, propane, pentane, etc.	Cystic fibrosis (Barker et al. 2006)

2.4 Breath Analysis by E-Nose

The idea of e-nose was inspired by the mechanisms of human olfaction. In general, basic elements of an e-nose system include an ‘odor’ sensor array, a data preprocessor, and a pattern recognition engine (Craven et al. 1996). Among them, the sensor array, like signal receptors, is the key part of e-nose. The application of sensor array on odor recognition was demonstrated firstly by Persaud and Dodd (1982). Currently, e-nose has undergone much development and been used to fulfill a large number of industrial needs, such as food, chemistry, fragrances, security, and environment (Rock et al. 2008). In addition to its contributions to analytical chemistry and biotechnology, artificial olfaction also has a significant impact on the field of medicine since the compounds listed in Table 2.4 may be detected by chemical sensors (Dickinson et al. 1998). Recently, the feasibility of using e-noses for monitoring the health of human and diagnosing diseases in an early stage has been demonstrated (Lin et al. 2001; Yu et al. 2005; Blatt et al. 2007; Dragonieri et al. 2007).

As early as 1997, Wang et al. (1997) designed an e-nose with one SnO₂ thin film sensor for diabetes diagnosis. The authors tested their device by using the breath samples collected from 18 patients and 14 healthy persons. The concentration of blood sugar of the subjects was used as reference. The results showed that the e-nose was able to diagnose diabetes with a sensitivity of 77.8% and a specificity of 35.7%.

In 2001, Lin et al. (2001) reported a study about the application of e-nose with six quartz crystal sensors to detect renal diseases. Discriminant Analysis (DA) was carried out to analyze the sensor signals. The clinical test result showed that the e-nose could discriminate the breath samples from 30 normal subjects, 83 uremia patients, and 61 chronic renal disease patients with a total correct classification of 86.78%.

In 2003, Yu et al. (2004) developed an e-nose with two SAW sensors for lung cancer detection. The breath samples of four patients with lung cancer and four normal subjects were collected by using Tedlar bags and then pre-concentrated by solid phase micro extraction (SPME) to increase the sensitivity. The e-nose was calibrated by 9 VOCs identified as the markers of lung cancer. An Artificial Neural Network (ANN) was used to recognize the lung cancer patients. The result showed that in four healthy samples, three of them were recognized correctly and one of them was recognized as suspected patient; in four patients, three of them were diagnosed correctly and one of them was diagnosed as suspected.

In 2003, Di Natale et al. (2003) used an e-nose composed by eight quartz microbalance (QMB) gas sensors to analyze the breath samples, which were collected from 60 individuals, 35 of them were affected by lung cancer, 18 individuals were measured as healthy, and 9 were measured after the surgical therapy. The application of a Partial Least Squares Discriminant Analysis (PLS-DA) found out that 100% lung cancer-affected patients were classified correctly, 94% healthy individuals were classified correctly, and 44% of post-surgery patients were classified correctly.

In 2005, Yu et al. (2005) developed a gas analyzing system using four conducting polymer sensors to analyze the breath samples from three diabetics and three normal people. The discrimination between patients and normal persons were interpreted by the PCA plus Euclidean distances with 100% sensitivity and 100% specificity.

In 2005, Machado et al. (2005) investigated exhaled breath of people by using a commercial e-nose, the Cyrano Sciences' Cyrano 320, comprising an array of 32 polymer carbon black composite sensors. PCA and Canonical Discriminant Analysis (CDA) sensor data were used to determine whether exhaled gases could discriminate between cancer and non-cancer. Support Vector Machine (SVM) analysis was used to create a cancer prediction model prospectively in a separate group of 76 individuals, 14 with cancer, and 62 without cancer. The results showed a sensitivity of 71.4% and a specificity of 91.9% of lung cancer detection.

In 2007, Dragonieri et al. also used Cyrano 320 to obtain the responses of exhaled air of patients with asthma and healthy controls. The responses were analyzed by LDA. Cross-validation values plus Mahalanobis distance were calculated for classification. The accuracy to classify the mild asthma and young controls is 100%, to classify severe asthma and old controls is 90%, to classify mild and severe asthma is 65%, and to classify two controlled groups is 50%.

In 2007, Blatt et al. (2007) reported their work about lung cancer detection by using an e-nose with 6 MOS sensors. They analyzed the breath of 101 persons, of which 58 as controls and 43 suffering from different types of lung cancer (primary and not) at different stages. Nonparametric LDA was used to extract the features of the sensors' responses. The features were classified by several supervised pattern classification techniques, based on different K-nearest neighbor (KNN) approaches, linear and quadratic discriminant classifiers, and on a feed forward ANN. The observed results showed an accuracy of 92.6%, a sensitivity of 95.3%, and a specificity of 90.5% for lung cancer diagnosis.

In 2009, Ogorodnik et al. (2008) analyzed VOCs from a breath sample of a patient with different lung diseases by using an e-nose with ten MOSFET sensors and four SnO_2 sensors. In total, 66 individuals—23 with asthma, 3 with chronic obstructive pulmonary disease (COPD), 12 with pneumonia, 13 with lung cancer, 4 in the past operation state (removed lung cancer), and 11 healthy volunteers were tested at two different times and ANN analysis was employed to classify the samples of cancer and other lung diseases. The results showed that the e-nose could identify lung cancer with 100% accuracy, identify healthy subjects with 100% accuracy, and identify asthma with 82.6% accuracy.

In 2009, using Cyranose 320, Dragonieri et al. (2009) analyzed the exhaled breath samples to discriminate patients with lung cancer from COPD patients and healthy controls. The breath samples were collected from 30 subjects, 10 patients with non-small cell lung cancer, 10 patients with COPD, and 10 healthy controls. The responses were analyzed by onboard statistical software. The method could distinguish non-small cell lung cancer from COPD and from normal people with 85% and 90% accuracy, respectively.

In 2010, Guo et al. (2010b) designed a breath analysis system, which includes 12 chemical sensors that are specially sensitive to the biomarkers and compositions in human breath. 108 healthy breath samples, 117 samples from diabetics, 110 samples from patients with renal diseases, and 110 samples from patients with airway inflammation were collected. PCA + KNN were used to evaluate the performance. The results showed that the system was not only able to diagnose these diseases with quite high accuracy, but in the case of renal failure was also helpful in evaluating the efficacy of hemodialysis (treatment for renal failure).

In 2010, by using the same system and the same diabetes breath samples, Guo et al. (2010c) proposed a method of monitoring the blood glucose levels of diabetics via measuring the concentration of breath acetone. A SVM classifier was used to evaluate the accuracy of classifying the samples into the groups with different blood glucose levels. The results indicated that the system was not only able to distinguish between breath samples from patients with diabetes and healthy subjects, but also to represent the fluctuation of blood glucose of diabetics. In the same year, Guo et al. (2010a) improved accuracy of diabetes condition monitoring by using a SRC method. Coupling with SRC, the system was able to classify these levels with a much better accuracy than the accuracy reported in Guo et al. 2010c.

In 2013, Saraolu et al. (2013) tried to develop an e-nose with 9 quartz crystal microbalance (QCM) sensors. The e-nose was used to measure the breath of 30

diabetes patients. Signals from 6 sensors were normalized then fed into a radial basis function neural network (RBFNN). The final average accuracy rate was 83.03 and 74.76% for HbA1c parameter predictions and glucose parameter predictions, respectively.

In 2014, an e-nose with 6 MOS sensors, 3 temperature modulated MOS sensors, a carbon dioxide sensor, and a temperature-humidity sensor was proposed by Yan et al. (2014). It was optimized for diabetes screening and blood glucose level prediction. Several optimization strategies, such as sensor selection, humidity and alveolar air ratio compensation, and inter-subject variance reduction, were implemented. The sensitivity and specificity of diabetes screening were 91.51% and 90.77%, respectively. The mean relative absolute error for BGL prediction was 21.7%. Experiments showed that the system was effective and that the strategies adopted in the system could improve its accuracy.

The same e-nose was further applied to collect breath samples from 5 kinds of patients, see Table 2.5. They have been proved to be related to certain breath biomarkers. The paper (Yan and Zhang 2016) proposed drift correction autoencoder (DCAE) to deal with instrumental variation and complex time-varying drift of e-noses. Experiments in the paper exhibited the potential of breath analysis systems as adjunct tools for disease screening.

To sum up, Table 2.5 concludes the current reports about the medical applications of e-noses.

From Table 2.5, we can see some limitations about the current researches: (1) Even though some works provided promising disease identification results, the sample number they used are not enough to provide a stronger statistical evidence to support the claim. (2) Most of the relevant systems have fewer sensors. We agree that it is not going to be very useful by simply adding more sensors. But it is necessary to provide a sufficiently redundant amount of sensors thus we can pick up the most sensitive ones in applications. Consequently, it therefore requires us to add more sensors in our system and collect enough typical samples for analysis.

2.5 Summary

This chapter reviewed some previous researches about breath analysis. General breath analysis approaches, like GC and e-nose, were introduced according to the type of the diseases analyzed. And some summaries were made about the disease biomarkers and current approaches. From these summaries, we can see that even though all of these methods work satisfactorily in breath analysis, the results could possibly be improved. The portable and low cost device is required to achieve a broad application in breath analysis.

Table 2.5 The application of e-noses in medicine

Diseases	Sensors	Database	Algorithm	Results
Diabetes (Wang et al. 1997)	1 SnO ₂ thin film sensor	18 patients	Fuzzy clustering	Sensitivity: 78%
		14 healthy persons		Specificity: 36%
Renal diseases (Lin et al. 2001)	6 quartz crystal sensors	30 healthy persons	DA	CRI/CRF: 90.16%
		83 uremia		Uremia: 79.52%
		61 chronic renal disease		Healthy: 100%
Lung cancer (Yu et al. 2004)	2 SAW sensors +GC	4 lung cancer	ANN	3 lung cancer
		4 healthy persons		2 suspected 3 healthy persons
Lung cancer (Di Natale et al. 2003)	8 QMB gas sensors	35 lung cancer	PLS-DA	Lung cancer: 94
		9 post-surgery		Post-surgery: 44
		17 healthy persons		healthy: 100%
Diabetes (Yu et al. 2005)	4 conducting polymer	3 diabetics	PCA + Euclidean distances	Sensitivity: 100%
		3 healthy persons		Specificity: 100%
Lung cancer (Machado et al. 2005)	32 carbon black and polymers sensors	14 lung cancer	SVM	Sensitivity: 71.4%
		62 healthy persons		Specificity: 91.9%
Asthma (Dragonieri et al. 2007)	32 carbon black and polymers sensors	10 mild asthma	PCA+Mahalanobis distances	Mild asthma and young controls: 100%
		10 severe asthma		Severe asthma and old controls: 90%
		10 younger controls		Mild and severe asthma: 65%
		10 older controls		Two controlled groups: 50%
Lung cancer (Blatt et al. 2007)	6 MOS sensors	43 lung cancer	Fuzzy-KNN	Sensitivity: 95.3%
		58 controlled patients		Specificity: 90.5%

(continued)

Table 2.5 (continued)

Diseases	Sensors	Database	Algorithm	Results
Lung cancer (Ogorodnik et al. 2008)	6 MOSFET sensors	23 asthma	ANN	Lung cancer: 100%
	4 MOS sensors	3 COPD		Healthy: 100%
		12 pneumonia		Others: 82.6%
		13 lung cancer		
		4 post surgery		
		11 healthy persons		
Lung cancer (Dragonieri et al. 2009)	32 carbon black and polymers sensors	10 lung cancer	PCA + Mahalanobis distances	Distinguish lung cancer from COPD: 85%
		10 COPD		From healthy: 90%
		10 healthy controls		
Diabetes renal diseases airway inflammation (Guo et al. 2010b)	12 MOS sensors	108 healthy	PCA+KNN	Diabetes: sensitivity: 87.67%
		117 diabetes		Specificity: 86.87%
		110 renal diseases		Renal diseases: sensitivity: 86.57%
		110 airway Inflammation		Specificity: 83.47%
				Airway inflammation: sensitivity: 70.20%
Diabetes (Guo et al. 2010a)	12 MOS sensors	90 diabetes:	PCA + SRC	Level 1: 50%
		4 level 1		Level 2: 83.67%
		49 level 2		Level 3: 60%
		20 level 3		Level 4: 76.47%
		17 level 4		
Diabetes (Saraoglu et al. 2013)	9 QCM sensors	30 patients	RBFNN	HbA1c: 83.03% BG: 74.76%

(continued)

Table 2.5 (continued)

Diseases	Sensors	Database	Algorithm	Results
Blood glucose (BG) and HbA1c level for diabetics (Yan et al. 2014)	6 MOS sensors	295 healthy 279 diabetes	PCA + SVM	Diabetes: 82.16%
	3 temperature modulated MOS sensors			CKD: 84.27%
	1 carbon dioxide sensor			Cardiopathy: 89.94%
	1 temperature-humidity sensor			Lung cancer: 81.34% Breast cancer: 82.92%
Diabetes chronical kidney disease (CKD) cardiopathy lung cancer breast cancer (Yan and Zhang 2016)	6 MOS sensors	125 healthy	DCAE + logistic regression	Diabetes: 82.16%
	3 temperature modulated MOS sensors	431 diabetes		CKD: 84.27%
	1 carbon dioxide sensor	340 CKD		Cardiopathy: 89.94%
	1 temperature-humidity sensor	97 cardiopathy		Lung cancer: 81.34%
		156 lung cancer		Breast cancer: 82.92%
		215 breast cancer		

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