EXHALED BREATH ANALYSIS BY RESISTIVE GAS SENSORS

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Abstract

Breath analysis has attracted human beings for centuries. It was one of the simplest methods to detect various diseases by using human smell sense only. Advances in technology enable to use more reliable and standardized methods, based on different gas sensing systems. Breath analysis requires the detection of *volatile organic compounds* (VOCs) of the concentrations below individual ppm (parts per million). Therefore, advanced detection methods have been proposed. Some of these methods use expensive and bulky equipment (*e.g.* optical sensors, *mass spectrometry* – MS), and require time-consuming analysis. Less accurate, but much cheaper, are resistive gas sensors. These sensors use porous materials and adsorption-desorption processes, determining their physical parameters. We consider the problems of applying resistive gas sensors to breath analysis. Recent advances were underlined, showing that these economical gas sensors can be efficiently employed to analyse breath samples. General problems of applying resistive gas sensors are considered and illustrated with examples, predominantly related to commercial sensors and their long-term performance. A setup for collection of breath samples is considered and presented to point out the crucial parts and problematic issues.

Keywords: resistive gas sensors, data processing, exhaled breath analysis.

1. Introduction

Resistive gas sensors were introduced more than 30 years ago and are commonly applied in industry, safety, and food analysis systems because of numerous reasons. The sensors are relatively fast, low-cost, and reliable elements. They require low power consumption and DC resistance measurement as an output signal. The sensors may operate for a few years without any specific maintenance. Periodical cleansing by pulse overheating is usually sufficient for their continuous operation. Other gas sensing techniques can be more accurate and selective but are often much more expensive and require bulky apparatus. An overview of various gas sensing methods can be found elsewhere [1].

The sensors are made of porous metal-oxide material (*e.g.* SnO_2, WO_3, TiO_2, ZnO, In_2O_3), activated for gas sensing at elevated temperature, up to about 450°C. The mechanism of gas

sensing is based on the process of adsorption-desorption. Ambient gas replaces oxygen molecules on the surface of porous material and changes its DC resistance between the terminals [2]. This process depends on operating temperature and gas molecules present in ambient atmosphere. It depends on the size of grains used in the porous sensing materials and can accelerate for nanoparticle mono-sized grains [3]. Sensitivity and selectivity of the gas sensing layers depend on the applied material, operating temperature and possible additives of noble metals to the metal-oxide material [4]. Therefore, a change of the operating temperature is the simplest way to modify the rate of the adsorption-desorption process for a detected ambient gas and, as a result, to change sensitivity to the gas. Sensitivity can also be improved by applying a heat pulse increasing temperature for a short time interval. A pace of dynamic changes of DC resistance is characteristic for different gases. Another popular method applies additives of noble metals to catalyse the adsorption-desorption process. The mentioned methods improve selectivity and sensitivity of resistive gas sensors, but these parameters still require improvement.

Further enhancement may be done by considering low-frequency resistance fluctuations as an additional source of information about the ambient atmosphere [5, 6]. Mechanisms of noise generation are independent of the mechanisms determining DC resistance. Low-frequency noise intensity depends on potential barrier fluctuations and requires less energy to be modified than DC resistance [7]. Low-frequency noise intensity can be even a few hundred times more sensitive to selected gases than DC resistance [3]. Moreover, the noise power spectrum is a vector and can be more informative than a single value of DC resistance only. It detects even components of a mixture of gases by an enhanced detection algorithm [8]. We can apply statistical functions other than the power spectrum (*e.g.* bi-spectrum) to improve detection by low-frequency resistance fluctuations [9]. There is the experimental evidence that two-dimensional materials (*e.g.* graphene flakes) can use low-frequency noise to improve gas sensitivity [10]. Voltage noise measurements require a low-noise sensitive measurement setup. Commercial gas sensors, having DC resistance up to hundreds of kΩ, can be applied in cheap and simplified electronic systems using this method [11]. Higher DC resistances require a more complicated measurement setup, but can be still used in practical applications. Similar units were used in a prototype breath analysis system [12]. This system was applied to analysing samples collected by using an adsorbent, preserving the VOCs for 2–3 months in a refrigerator, and further releasing them to a glass vial by heating in an oven. The setup was also used to analyse the breath samples exhaled by patients during a medical check-up.

Some gas sensing layers exhibit the photocatalytic effect (*e.g.* WO_3, TiO_2) which can also be used to modulate their physical properties, as the above-mentioned changes of operating temperature. Additional energy of light irradiation can decrease operating temperature and induce better gas selectivity when the energy level is adequately selected. The high-energy UV light was often used for cleansing selected gas sensing layers [13]. The influence of UV light depends on the morphology of gas sensing layer (its porosity determining a depth where UV light induces serious changes of adsorption rate and spectral parameters, such as absorption or reflection). Therefore, its application to enhanced gas sensing looks very promising. There are various UV LEDs of different UV wavelengths which can improve selectivity of resistive gas sensing layers similarly as dopants of noble metals. All mentioned problems limit possible applications of resistive gas sensors to breath analysis. On the other hand, a significant decrease of production costs of such commercial gas sensors and their sensitivity to some VOCs being markers of different diseases (*e.g.* Ethanol, Ammonia, Acetone, CO, NO_x, SO_x, H_2S, *etc.* [14, 15]) has improved the situation.

More than two thousands of different VOCs in exhaled breath have been identified by *mass spectrometry* (MS) for various diseases [16, 17]. Composition of the identified VOCs for some illnesses is a unique one and can be used to diagnose several diseases by less time-consuming

methods than the MS method. Only tens of the emitted VOCs are indicative of selected illnesses. A few papers published detailed research results based on data sets of up to a few hundreds of patients [17, 18]. A new generation of resistive gas sensors is much cheaper, uses less gas sensing material, and requires lower energy consumption. A few companies offer such sensors (*e.g.* SGX Sensortech, Figaro, Micralyne, Bosch Sensortec, Sintef) [19]. Their cost of production is often below 1$. The size of an array of gas sensors based on MEMS (*micro-electro-mechanical systems*) technology is similar to a surface-mounted resistor and is usually offered with a necessary digital interface to be connected to a computer system without any additional elements. A few tens of mW is required for their continuous operation. Their gas sensing layer is only a few microns thick. It means that the MEMS technology reduced even a thousand times the energy consumption of commercial gas sensors and enabled their application in smartphones to air pollution monitoring. These advantages should begin their massive applications, also if their measurement accuracy in smartphone applications stays limited.

2. Methods and materials enhancing gas sensing

The layers of golden nanoparticles, functionalized with organic ligands [20, 21], are more selective to different VOCs than the commercial gas sensors, made of metallic oxides. These new resistive sensors can operate at room temperature. The golden nanoparticles provide conductivity. The organic ligand provides sites for the sorption of the VOCs of interest and works as iden- tification elements. It means that such sensors can selectively attract the VOCs, also with their concentration below ppb level. This feature is desirable. Unfortunately, high selectivity immobi- lizes the organic receptors occupied by the attracted VOCs. This effect often means permanent capturing the detected VOCs and might poison the sensor or prolong its recovery time.

Numerous studies on other resistive nanomaterials are reported. Nanoparticles, silicon nano- wires or carbon nanotubes are successfully used for gas sensing. These materials are expanded and can be used to detect deficient concentrations of VOCs (*e.g.* by graphene flakes using flicker noise [10]). Unfortunately, these materials are not available as commercial sensors.

The main drawbacks of resistive gas sensors are related to their specific behaviour. The sensors exhibit drift of their DC resistance during their operation. This effect can be reduced by heat- pulse cleansing (*e.g.* by applying higher voltage to the heater for at least a few seconds) or considering only relative changes of DC resistance for gas detection. We have to calibrate the sensors systematically if cleansing is not applied. Otherwise, by assuming a trend component in the observed DC resistances, we can apply a method reducing this component as proposed for slowly changing measurement results [22].

Another drawback of resistive gas sensors is their non-linear response to crossing gases (the gases present in ambient atmosphere of a gas sensor but beyond the need for detection). The recorded DC resistance is a single value and can be modified by different gases of various concentrations. A breath sample is a mixture of different compounds. Therefore, their response depends on the presence of different gases. Resistive gas sensors are susceptible to humidity, and their response can be modified by its changes in a similar way as by exhaled VOCs of gases. The influence of moisture may be reduced by including its recorded values by an additional sensor into the detection algorithm to be convinced about its limited effect. We can also remove humidity before analysis of exhaled breath. It requires additional preparation of the breath sample (*e.g.* by using an adsorbent that does not preserve moisture). The enumerated drawbacks limit the accuracy of breath sample analysis, but the resistive gas sensors can be successfully applied for this aim [23].

The presented methods of enhancing gas sensing by resistive layers are quite constrained. Therefore, we apply an array of resistive gas sensors of different, but again limited, selectivity for given gases. The array requires parallel measurements of DC resistances, but they can be performed with the use of the same measurement setup. The array of gas sensors can be prepared using the MEMS technology with reduced energy consumption, as a tiny electronic chip (*e.g.* MiCS-6814 produced by SGX Sensortech). A block diagram of the gas sensing system detecting VOCs is presented in Fig. 1. A set of N independent gas sensors is used to identify the VOCs of interest. Their sensitivity values to different VOCs overlap, but the applied data processing reduces this effect. All sensors require a voltage bias and electronic units to modulate their physical properties. The DC resistances can be preliminarily processed. It should minimize the influence of other factors, like drift or humidity, on the sensor response. The most straightforward processing requires evaluation of DC resistance difference, its relative value or normalization (module or absolute value). The relation between gas concentration and DC resistance can be approximated by an exponential function. Therefore, employing a logarithm of the measured DC resistance is the simplest way to linearize the dependence of gas concentration on the measured parameters.
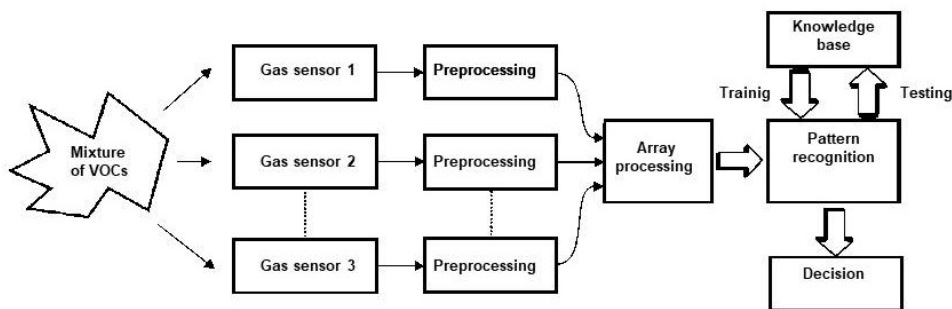

Fig. 1. A block diagram of the gas sensing system using resistive gas sensors.

These new quantities, obtained from DC resistances after necessary preliminary processing, form a data vector and are used for further processing as the input data vector (Fig. 2). Various
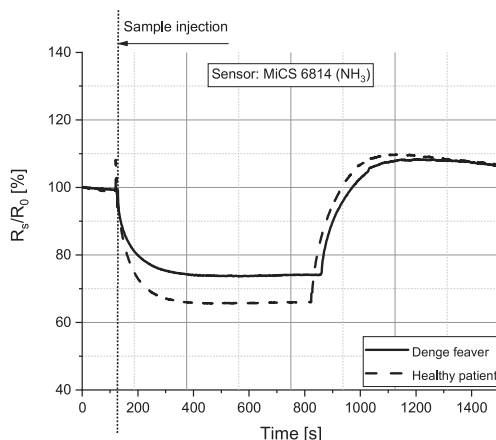

Fig. 2. Data processing applied to the array of resistive gas sensors.

detection algorithms can be used to determine a medical diagnosis. It is necessary to build a model by using the test data and a known medical diagnosis determined by a reference method (*e.g.* by a red blood test). A decision about medical diagnosis is undertaken by comparing the results with the results from the knowledge base.

A rate of correct medical diagnoses depends on the entire breath sampling process and a selected detection algorithm. Our paper presents details of the breath sample collection, necessary data processing, and detection algorithm. We conclude that the presented setup applying a commercial MEMS resistive gas sensor can be used for an early medical check-up. Its further improvement can be reached by introducing more selective gas sensors, based on nanomaterials.

3. Breath analysis setup

Breath samples have to be correctly collected to ensure as high as possible concentration of VOCs, characteristic for the examined disease [12]. The simplest method of assuring high concentration of VOCs is to use the tidal volume of exhaled breath when the squeezed bronchial vesicles emit the VOCs. They can be collected automatically by measuring the pressure of the blown air. The electronically controlled valve opens the gas chamber when the pressure drops, and the micropump shifts the tidal volume to the gas chamber with an array of gas sensors (Fig. 3). Such a system was proposed and built as a part of a smartphone (*www.sniffphone.eu*) to detect gastric cancer, which has a specific set of VOCs of relatively high intensity. The presented solution can be easily applied during a medical check-up by blowing, without any additional breath sample preparation. Another method uses an adsorbent to preserve the exhaled VOCs. The analysis is made after heating the adsorbent to 200°C for 10–15 min. and then releasing the adsorbed VOCs. A selected heating temperature does not affect the VOCs present in the breath sample.
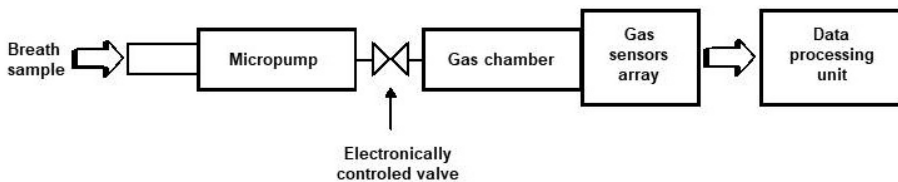

Fig. 3. A block diagram of the breath sample analysis system.

The applied gas chamber was of 20 ml volume, and the gas sensor required about 400 s to saturate its resistance. It means that performing a medical diagnosis should be possible after a few minutes. The gas chamber started to be ventilated by room air after about 850 s from the beginning of the measurement. The sensor recovered to its original conditions after about additional 1000 s. The example presents the data (Fig. 4) collected in a hospital in Cucuta, Colombia, at room temperature of 30°C and relative humidity of 60%. A noticeable difference between two patients (the healthy one and the infected one with dengue fever) was observed. The exhaled breaths induced different responses and recovery times, and relative changes of DC resistance. Similar differences were observed for the examined series of patients. Only some of the applied commercial resistive gas sensors responded to the VOCs induced by the examined illness. This result is significant because it is very promising for developing a fast medical diagnosis done at limited costs.

All differences can be utilized by detection algorithm to give correct diagnoses. The presented time series can be considered as common examples for the resistive gas sensors. We can allege

that the differences between the experimental data relate only to the shapes of the recorded time series (on and off slopes, area, peak height, *etc*.).

DC resistance of each gas sensor is measured and saved for further processing. We can propose different detection algorithms of various computational complexity. The simplest methods can employ a tiny processor controlling the measurement setup, but of a limited computing power. The up-to-date technology can use cloud computing of the recorded data after necessary pre-processing, reducing the number of data samples transmitted to the cloud.

4. Data processing methods

Data processing is carried out by analysing the recorded time series of DC resistances. An example of time series of relative values of the recorded DC resistances of an MiCS 6814 sensor (NH_3 sensor, SGX Sensortech Limited, UK) is shown in Fig. 4. The moment of recording the tidal volume is marked as "Sample injection".
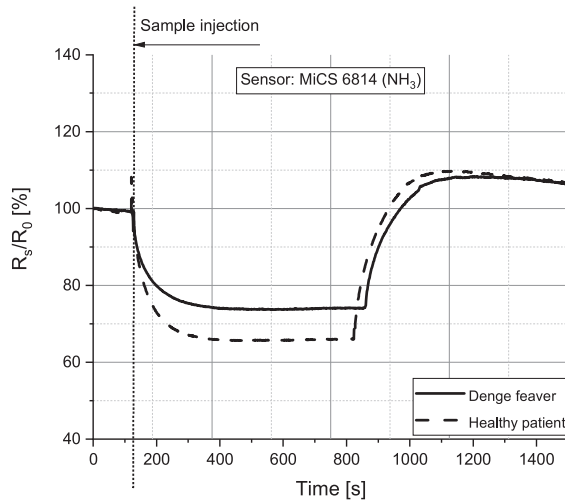

Fig. 4. An example of responses of a resistive gas sensor exposed to exhaled breath samples.

Various methods of the recorded data processing for medical diagnosis can be used. A review of the most popular methods can be found elsewhere [24]. Some ways are available in MATLAB software, statistics and machine learning toolbox. The toolbox helps select the most promising method by analysing the introduced data and determining the way that gives the best results. Unfortunately, we generally cannot determine which algorithm is the optimal one. We have some overall suggestions about pre-processing to ensure acceptable detection results. Some of the suggested methods are presented in Fig. 2, but we have to consider others as well. In general, the recorded time series of DC resistances can include additive noise or interference (periodic or random pulses) which should be filtered out before further processing. Different filtering methods can be applied, like low-pass filtering, moving average filtering, Kalman filtering, or Savitzky-Golay filtering.

Except for DC resistances, we should extract other features characterizing the recorded time series (Fig. 2). These features can non-linearly depend on gas concentration . Therefore, the

linearization of the extracted data is very efficient for the applied detection algorithms. A non-linear function (*e.g.* logarithmic, square root) linearize the input data. The pre-processed data are collected from different gas sensors, and therefore should be distributed differently. Thus, the operation of scaling is applied to standardize the distribution and mean value of the recorded parameters. Next, the dimension of the formed data vector should be reduced to expose the most informative parameters or their linear combination.

Two techniques are used to extract the most informative parameters:

– *Principal Components Analysis* (PCA), based on obtaining the most varying parameters or their linear combination by applying the linear transformation of the analyzed data into a new coordinate system of lower dimensionality;

– *Fisher's Linear Discriminant* (LDA), based on classification and finding the maximum separation between the means of the projected classes.

Both methods assume the unimodal Gaussian density distribution of the sets of parameters.

Finally, the parameters have to be classified to detect (or not) a disease. There are numerous classification algorithms. Neural networks or algorithms considering the distance between the distributed samples are often used for classification. An overview of popular classification algorithms for chemical sensing can be found elsewhere [25]. The algorithms require parameter adjustment and should be carefully selected when a limited dataset is used to build a model. There is a risk of model overfitting in a similar way as approximation of a dataset by a too high polynomial.

5. Conclusions

The research problems related to medical diagnosis by exhaled breath analysis are still challenging. One of the main reasons is a lack of resistive gas sensors with long-term stability, as well as low concentrations of the detected VOCs. Therefore, the exhaled breath has to be collected appropriately. Next, the pre-processing and detection methods should be attentively selected to reduce the stability problems of sensors and an impact of unavoidable environmental changes during the data collection. These issues were presented in the paper.

Acknowledgements

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