Selective Nanosensor Array Microsystem For Exhaled Breath Analysis

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Abstract

This work describes a novel concept of a three-nanosensor array microsystem that may serve as a handheld breath analyzer for disease diagnosis. The specification and performance of a simple metal oxide nanosensor operating between three distinct temperatures are discussed, focusing on the need for a non-invasive blood cholesterol monitor. Interfacing the sensor array to an integrated circuit for electrical readout and temperature control provides for a complete microsystem capable to capturing a single exhaled breath and analyzing it with respect to its relative content of isoprene, carbon dioxide, and ammonia gas. This inexpensive sensor technology may be used as a personalized medical diagnostics in the near future.

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Keywords: Nanosensor array; microsystem; breathanalyzer

1. Introduction

Exhaled human breath is a mixture of N₂, O₂, CO₂, H₂O, inert gases and hundreds of other trace gases [1-3]. The latter include inorganic molecules such as NO, NH₃ or CO and volatile organic compounds (VOCs) such as acetone, ethane and isoprene, with concentrations ranging from ppb to ppm. The composition of breath varies a lot from person to person, both qualitatively and quantitatively, particularly as far as trace gases are concerned. VOCs are products of core metabolic processes while inorganic molecules are related to health conditions and can reflect a potential disease of the individual or a recent exposure to a drug or an environmental pollutant. To this date, breath analysis has hardly met the

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promise of an easy, affordable, non-invasive, medical diagnostics technology [4-5]. There is a lack of inexpensive sensor technologies that would detect and monitor the concentration of a single gaseous compound in the complex odor mixture with high specificity and at low (trace) concentrations of interest, in the presence of numerous interfering compounds. (Optical detectors could do that in some cases, e.g. selective ethane detection [6], but they are too costly to be considered personalized medicine tools that would be available over the counter). Therefore, there is a need of a few selective gas sensors to detect and monitor several of these biomarkers in exhaled breath for disease diagnosis purposes. Gouma has developed and demonstrated single sensor handheld breath-analysis targeting devices utilizing resistive chemosensing technology [7-9]. The advantages of these tools have been the low cost of fabrication of the sensor and the device, the use of nanotechnology that obviates any need of cooling the sensor chamber or impacting the device portability, the simplicity of acquiring the sample (single exhale into a mouthpiece), the ease of collecting and analyzing the sensing data obtained, and the promising stability and reliability of the prototypes obtained. Gouma’s earlier research [7-11] has demonstrated that it is possible to control the microstructure of nanocrystalline metal oxide films and the operating temperature of the sensor so as to employ oxide polymorph phases that are sensitive to only a specific class of gaseous analytes or even be specific to a single species. The concept has been extended in this paper to the detection of multiple biomarkers by sensor arrays through temperature control of a simple metal oxide thin film-based gas-sensing element. An inexpensive and portable breath analyzer concept based on a novel microsystem is described in this paper.

2. Experimental Methods

Precursors of molybdenum isopropoxide were used. These alkoxides were mixed with n-butanol to obtain 0.1M solutions [12]. Since the materials were reactive to atmosphere, the mixing was done inside a glove box under nitrogen atmosphere. After mixing, the sols were mechanically agitated for 5 minutes inside the glove box and then sealed airtight. Ultrasonic agitation was then performed for 2 hours and the sols were allowed to age and settle. A black opaque liquid was obtained after 24 hours of aging that was the sol of molybdenum trioxide. Thin films of this material were deposited on sensor substrates by spin coating. These films were deposited on 3mmx3mm alumina substrates with platinum interdigitated electrodes on one side and platinum heaters on the reverse side. Thin films of 150nm thickness (MO-2) or 250nm (MO-1) were deposited on the substrates and were allowed to dry before heat-treating them in air at 500°C for 10hrs. Several gases were used for sensing, which were either flown in individually or in mixtures, and the flow rates were computer-controlled. The change in current upon exposure to gas was measured over a constant applied voltage of 1V. Sensing tests were carried out at three different temperatures: 420°C, 450°C, and 500°C. The sensors are discussed with respect to their relative response to isoprene, carbon dioxide, and ammonia, as a function of operating (testing) temperature. The reported sensitivities were calculated using the formula $S = \frac{\Delta R}{R_o}$, where $R_o$ is the sensor baseline resistance, $R_g$ is the sensor resistance in the presence of the gas and $\Delta R = R_g - R_o$.

3. Results and Discussion

3.1 Temperature control for selective chemosensing

Our group has been using a crystallo-chemical approach to achieve selective gas oxide interactions for different classes of gases and oxide crystallographic arrangements [7-8, 13]. Furthermore, studies carried out on the SnO$_2$ system by Semancik’s group at NIST [14] have identified a correlation between the gas selectivity and the operating temperature of this sensing system. Considering that metal oxides are polymorphic systems and each phase has a temperature range of stability, it is possible by changing the operating temperature of a polymorphic metal oxide sensor to change the relative fraction of it’s various
phases, thus achieving variable gas selectivity. Therefore, one single binary oxide may be sufficient to build multisensor arrays for the selective detection of several gaseous biomarkers at once, by simply individually controlling the temperature at which the stabilization heat treatment and the sensing process will take place through the use of resistive heaters incorporated to each sensor substrate. For this work, our studies focus on the MoO$_3$ system that has two known phases up to 500°C. By employing temperature control the relative phase content of the material changes (see Table 1 below) (as determined by DSC, XRD, and TEM measurements [13]; its relative gas selectivity also varies, as it will be demonstrated below:

Table 1. Relative phase distribution in the sensing films as a function of temperature

<table>
<thead>
<tr>
<th>Phases of MoO$_3$ sensor</th>
<th>420°C</th>
<th>450°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclinic (β-MoO$_3$)</td>
<td>72.1% ±5%</td>
<td>23.2%±5%</td>
</tr>
<tr>
<td>Orthorhombic (α-MoO$_3$)</td>
<td>77.85%±5%</td>
<td>76.8%±5%</td>
</tr>
</tbody>
</table>

3.2 Testing gas determination

Isoprene (2-methyl-1,3-butadiene) is a reactive aliphatic hydrocarbon [15]. The amount of isoprene in expired breath is an indirect measure of cholesterol synthesized and its concentration corresponds to the activity of the enzyme producing cholesterol in the human body [16]. Hence measuring isoprene concentration should aid in monitoring the blood cholesterol levels non-invasively. This need focused our interest in an isoprene detector that can be used to monitor breath isoprene concentrations. The work reported here presents the sensing conditions suitable for selective isoprene detection in the presence of other interfering gases, which are somewhat related to the exhaled breath environment. Measuring the concentration of carbon dioxide (CO$_2$) in the exhaled breath is important to evaluate the quality of the breath sample [17]. Therefore, a CO$_2$ selective sensor in a sensor array needs to be used for quantitative breath-analysis, for calibration purposes. Ammonia is a common breath metabolite and our earlier studies showed that α-MoO$_3$ acts as a specific ammonia sensor at 500°C [18-19]. It is also known that the β-phase of MoO$_3$ that is favored at lower temperatures in nanostructured materials is not selective to this gas [13]. Therefore, the sensor array in this study involves a sensor operating at 420°C, another operating at 450°C, and a third one operating at 500°C. Sensing data for the latter sensor have been reported elsewhere [13, 18-19] and will not be discussed in detail here. It is stated however that the sensing film at 500°C is specific to ammonia gas.

4. Design of circuits for electrical readout and temperature control

The sensor behaves electrically as a resistance and therefore a specialized multi-channel instrumentation is required to obtain readouts. The electrical resistance of each of the sensors in array is being composed of a combination of two series resistances. First, a baseline resistance is present, $R_b$, that varies across sensor design and even across sensor with the same design. Due to the fabrication and anticipated aging of the device, this baseline resistance does record a variation, $\Delta R_b$. Second, another series resistance is added which reacts to the amount of the targeted gas it is designed to sense, $\Delta R_{gas}$. Thus, the total resistance of a gas sensor in the array is given by $R_{sens} = R_b + \Delta R_b + \Delta R_{gas}$. The readout circuit is designed for the range of sensor baseline resistances from 1kΩ to 100MΩ, with the detectable resistance change
ratio from 0.05% to 10%. Since the system has to react to a change in resistance caused by the gas \( (\Delta R_{\text{gas}}) \), in order to keep the measurement as precise as possible in the given range, the system must be insensitive to the baseline resistance \( (R_b) \).

![Graphs showing sensor selectivity at different temperatures](image)

**Fig. 1.** (a) Relative sensor selectivity at 420°C operating temperature. Note the high sensor selectivity to isoprene gas.; (b) Relative sensor selectivity at 450°C operating temperature.

**Summary:** By altering the operating temperature of a sensor based on a single metal oxide film, that is a MoO\(_3\) resistive-type gas sensor, the phase composition and relative distribution is tailored to obtain variable gas selectivity. A three-sensor array is described which allows for monitoring isoprene, CO\(_2\) and ammonia concentration in a complex environment similar to exhaled breath. A microsystem is designed that integrates temperature control on the same mixed-signal VLSI chip.

**References**