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Nanomaterial-Based Sensing Technology for the Application in Breath Analyzer as for Early Disease Detection and Prevention

Michael Johnson[1]; Sampada Koirala[2]; Anna Rudie[3]; Qifeng Zhang[1,2,3]; Danling Wang[1,2,3]*

[1]Materials and Nanotechnology Program, North Dakota State University, Fargo, ND 58108, USA.

[2]Biomedical Engineering Program, North Dakota State University, Fargo, ND 58108, USA.

[3]Department of Electrical and Computer Engineering, North Dakota State University, Fargo, ND 58108, USA.

Corresponding Author: Danling Wang

Department of Electrical and Computer Engineering, North Dakota State University, Fargo, ND 58108, USA.

Tel: 701-231-8396; Email: danling.wang@ndsu.edu

Published Online: Jun 21, 2021

eBook: Recent Trends in Biotechnology

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Breath analysis nanocomposite; Chemiresistive response; Room temperature.

Abstract

A major challenge towards reducing the mortality of chronic diseases, such as diabetes and asthma, is the development of portable, affordable, and non-invasive techniques for early and fast disease diagnosis, real-time health monitoring, and in-time treatment. Breath is one type of biological fluid, like blood and urine, which can be used to detect biomarkers of diseases. The latter contains mainly non-volatile large molecules, such as proteins and other macromolecules, while breath contains a large number of Volatile Organic Compounds (VOCs). These VOCs directly link to metabolic activity in the body, and some of these VOCs can provide information on health conditions such as infections or metabolic diseases. For example, the exhaled breath in diabetes patients contain elevated acetone concentration, and Fraction of Exhaled Nitric Oxide (FENO) indicates asthma. Since breath is always readily available and can be repeatedly performed without creating infectious waste, embarrassment, or discomfort, measuring the levels of exogenous VOCs in breath could be an effective yet economical (breath supply is nearly infinite) and completely non-invasive method for disease diagnosis, therapy control, and assessment of health status. However, the VOC measurement based breath analyzer is very challenging. This is because exhaled human breath is very complex. It is a mixture of inorganic gases, over 1000 different VOCs, other typically nonvolatile substances, and high and extremely variable concentrations of humidity (relative humidity, RH 40-80%). In addition, VOCs in human breath are present in trace concentrations, typically Parts Per Billion volume (ppb_v) or lower. The current techniques used for breath analysis are mainly based on Gas Chromatography Coupled with Mass Spectrometry (GC-MS), Flame Ionization Detection (GC-FID), Selected Ion Flow Tube Mass Spectrometry (SIFT-MS), and laser spectroscopy. Although many of these are very accurate, they are very expensive and the equipment is bulky and needs expertise to operate. They cannot be used outside a laboratory or clinical setting and are therefore unable to provide affordable and convenient

Citation: Johnson M, Koirala S, Rudie A, Zhang Q, Wang D, (2021). Nanomaterial-Based Sensing Technology for the Application in Breath Analyzer as for Early Disease Detection and Prevention. Recent Trends in Biotechnology, MedDocs Publishers. Vol. 2, Chapter 1, pp. 1-8.

point-of-care testing, diagnosis, or monitoring. The development of chemiresistive-based electronic noses (e-noses) has opened the door for a new method of breath analysis that can be portable, inexpensive, easy to use, and ideal for point-of-care testing. However, because of the challenges of expanding diverse sensing materials to overcome the limitations of their sensing performance (e.g. elevated operating temperature, poor selectivity, and strong interference from water vapor), much effort is still required to develop new functional nanomaterials and new sensing mechanism which can meet the needs of increased accuracy, efficiency, and effectiveness of disease diagnosis and real-time healthcare services. In this chapter, we will describe a new generation of breath sensing technology based on newly synthesized nanomaterials: 1D/2D nanocomposites made by 1-Dimensional nanostructured metal oxide (such as TiO_2, KWO) and 2-Dimensional multilayered nanosheets (Ti_3C_2 MXene) with functionalized structures and surface properties. This new technique will take advantage of the merits of chemiresistive sensors (simple, small, low cost, and ease of fabrication) and novel nanocomposite unique properties (high surface to volume ratio, tunable structure, specific surface functional groups and extreme porosity) to achieve high performance of breath analysis at room temperature for early disease diagnosis and daily monitoring for chronic diseases, such as diabetes and asthma.

Introduction

Breath analysis

Human exhaled breath contains mostly nitrogen (78.04%), oxygen (16%), carbon dioxide (4-5%), hydrogen (5%) [1], inert gases (0.9%) [2], and water vapor. Other than that, it contains more than 1000 VOCs with concentration ranging from parts per trillion (ppt), parts per billion (ppb) to parts per million (ppm_v) [3], such as nitric oxide (10-50 ppb) [4], nitrous oxide (1-20 ppb) [4], ammonia (0.5-2 ppm) [5], carbon monoxide (0-6 ppm) [2], hydrogen sulfide (0-1.3 ppm) [6] acetone (0.3-1 ppm) [7], ethanol, isoprene (~105 ppb) [8], ethane (0-10 ppb), methane (2-10 ppm), and pentane (0-10 ppb) [4]. Most VOCs are not produced in the body (endogenous), but rather result from food consumption, exposure to environmental contaminants (exogenous), or drug metabolization [9]. However, some VOCs are closely correlated with the physiological state of humans, for instance, acetone and nitric oxide, can be used as biomarkers for detecting diabetes and asthma respectively. The precise detection of biomarker VOCs in the exhaled breath, can provide in-time information for early disease diagnosis and real-time health assessment. In this chapter, we focus on breath based sensor devices for applications in two chronic diseases: diabetes and asthma.

Breath markers

Currently, the most common devices used to monitor glucose levels by piercing the skin Include: Self-Monitoring Blood Glucose (SMBG), Continuous Glucose Monitoring (CGM) devices, and Flash Glucose Monitoring (FGM) devices. The requirement to penetrate the skin, that all three available glucose monitoring technologies use, has caused problems for people that rely on these devices and has contributed to people not checking as often as they should. Out of the three available technologies, SMBG devices are the most affordable yet the most painful and inconvenient and have caused a risk of skin reactions, allergies, and infections [10]. Acetone is one of the most prevalent components in the breath which has been studied in detail and linked to metabolic disorders. The concentration of acetone in the blood vessels supplying the upper airways by its respective blood: breath partition coefficient of ~340, are the key determinants of acetone concentration in breath [11,12]. The acetone level rises in patients with uncontrolled diabetes [9,13], as well as during regular overnight sleep in healthy people [14], and during prolonged fasting [15]. The acetone contained in the exhaled breath is a metabolic product of fat breakdown and therefore is anticipated to be a good index of fat-burning [16]. Glucose is the main source of energy in the human body. Insulin helps glucose molecules enter cells and be absorbed. In the case of inadequate insulin generation by the body (Type-I diabetes) or insulin-resistance of the cells (Type-II diabetes), the body is unable to derive energy from glucose and is forced to break down body fat to generate energy. Therefore, during ketogenesis, all ketone bodies, including acetone and carbon dioxide, are produced in the human body from fatty acids [17].

For acetone detection, there are many materials developed as the transducers in the gas sensors, such as Pt-InN [18], Polypyrrole (PPy)-WO_3 [19], Ni/InGaN/GaN [20], and Pd/TiO_2/Si [21]. In comparison to these materials, nanostructured $K_2W_7O_{22}$ (KWO), recently synthesized in our research group, shows very good sensing response to acetone even at a room temperature. This is because the new nanostructured material, KWO, exhibits excellent room-temperature ferroelectric properties and highly porous nanostructure. These are key factors to determine an effective chemiresistive reaction between polar acetone molecules and KWO [22] even at room temperature. Further studies confirm that KWO is a good candidate to detect breath acetone for the application of non-invasive diabetes diagnosis [22-27].

Exhaled Carbon Monoxide (CO) and Nitric Oxide (NO) are breath markers for respiratory disorders such as asthma, chronic obstructive pulmonary disease (COPD), and bronchiectasis [28,29]. In particular, Nitric Oxide (NO) plays an important role in cell signaling and its increased concentration in the breath can indicate the pathophysiology of asthma [30,31]. Asthma is confirmed linked to a high concentration of NO in exhaled air. This is because patients with asthma, produces a large amount of NO in the airway. Generally, a healthy human breath contains less than 25 ppb of NO, while in asthmatic patients it contains more than 50 ppb of NO [32-34]. The detection of exhaled nitric oxide fraction (FeNO), provides a non-invasive method for asthma diagnosis and tracking since increased NO exhalation as a result of Interleukin (IL)-13-induced induction of NO synthase in the airway epithelium has been well reported in asthamatic patients [34,35].

Techniques of detecting breath biomarkers in gas phase

The correlation between biomarker VOCs in human breath and health has been well studied. Hence, detection of VOCs can be a non-invasive and convenient method for early diagnosis of diseases and monitoring to control disease for complications at early stage. There are different techniques that have been developed to date to detect VOCs accurately such as Proton Transfer Reaction-Mass Spectrometry (PTR-MS), Selected Ion Flow Tube (SIFT-MS), laser spectroscopy, and Gas Chromatography (GC) [17,36,37]. Though these techniques are very accurate at detecting disease-related VOCs, they are very expensive and require high levels of experience to operate the instruments. Also, sampling and analysis take a long time, and preconcentration techniques are required [38]. All of these limit them to be well-

suited devices for daily utilization as the Point-Of-Care (POC) technology for disease monitoring and control.

Metal oxide chemiresistive gas sensors

Chemiresistive gas sensors based on Metal Oxide Semiconductors (MOS) have been widely used in biomedical applications. In contrast to the other methods (for example, GC-MS based techniques), such sensors have many advantages, including simplicity, high miniaturization potential [39], low strength and low cost output [40,41], which make them very attractive for routine clinical tests. The chemiresistive mechanism reveals that the sensing response of MOS based sensors is determined by the electrical and material properties of the MOS. Different material synthesizing techniques can change nanomaterial's structure and surface properties [42]. This can cause the change of its electrical property and then affect the sensing efficiency in terms of sensitivity, selectivity, productivity, and long term stability [41]. That means we can tailor sensing materials' properties, such as size, crystalline structure, and surface functional groups through material synthesis procedures to improve gas sensors' performance e.g., sensitivity, selectivity, stability, and detection limits. As for application in breath analysis, sensors should have these characteristics: 1) an extremely high sensitivity allows sensors to efficiently detect the low concentrations of VOC vapors (ranging from ppt to ppm) from human breath; 2) excellent selectivity as there are more than 1000 VOCs in human breath and only few of them are crucial for disease diagnosis; 3) excellent humidity tolerance human breath generally contains high and extremely variable concentrations of humidity (relative humidity, RH ~90%) [43]. If sensors can not show good resilience to humidity, the strong cross-interference of humidity can deteriorate devices long-term stability; lastly, 4) point-of-care measurement and Artificial Intelligent (AI) functionality Since diabetes and asthma are the most common chronic diseases, and patients with diabetes or asthma need to continuously monitor their health conditions and receive effective and in-time treatment. A device which can provide effective, reliable, miniaturized and affordable monitoring for individuals' healthcare management is urgently needed. New functionalized nanomaterials based gas sensors have great potential for application as a breath analyzer because the electrical and material properties that are easily adjusted through changing synthesis conditions in order to optimize sensor performance [44].

Discussion

Chemiresistive gas sensors

Chemiresistive gas sensors are a type of device which mechanism is mainly involved about surface absorption and electrical signal transduction. That means the change of material's electrical resistance can be caused by the interaction between sensing materials and the analytes. These are very simple devices including substrate, active transducer layer and electrodes. Figure 1 shows a basic schematic of a typical chemiresistive sensor as well as the signal it presents when interacting with an analyte gas. Also, chemiresistive sensors can be miniaturized as portable or wearable devices for daily use.

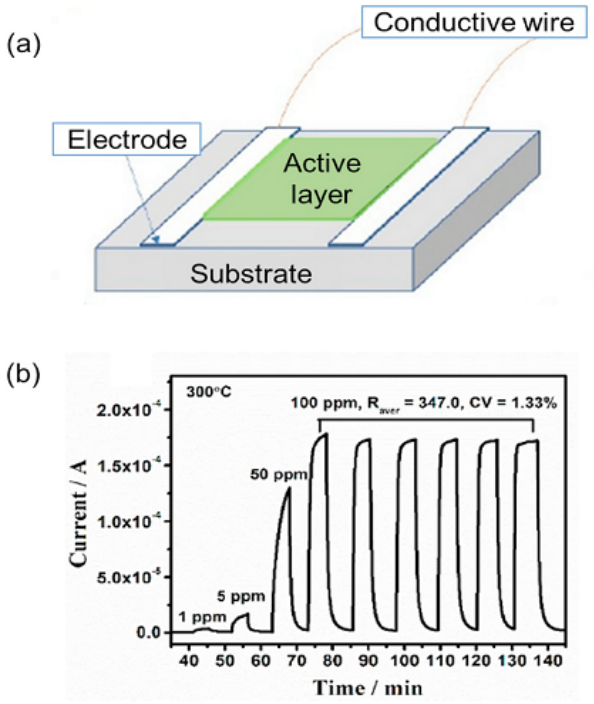

Figure 1: Illustration of chemiresistive gas sensor structure. (b) Typical response-recovery current curves toward acetone gas with different concentrations [47].

According to the sensing mechanism of chemiresistive gas sensors, the sensing material as the active layer plays the most important role in determining the sensing performance. To design a high-performance gas sensor, two components need to be considered. The first one is the thickness and porosity of the active sensing layer. In a compact metal oxide sensing layer, gases cannot penetrate into the layers and the gas sensing reaction is confined to the surface. In a more porous layer, gases can diffuse into the entire volume of the sensing layer and the gas sensing reaction can, therefore, take place at the surface of the individual grains, the grain boundaries, and the interface between grains and electrodes. Therefore, a porous layer is more suitable for breath VOC sensing [45]. The thickness of the sensing layer is also important [46,47]. To obtain optimal response, the thickness of the sensing layer should be as close to the thickness of the electron-depleted region. The second one is synthesizing functionalized sensing material for charge transfer. For example, for non-invasive diabetes diagnosis, it is important to synthesize optimal sensing material to detect breath acetone. Current chemiresistive sensors for breath acetone detection are using MOS nanomaterials which need to operate at elevated temperature with relative poor stability and selectivity. To further improve acetone sensor's performance, these MOS nanomaterials can also be used in conjunction with certain polymers or other 2-D nanomaterials, such as graphene, or multilayered Ti_3C_2 MXene to form nanocomposites. Pure as well as hybrid chemiresistive sensors will be discussed for designing a hand-held breathalyzer device for clinical and everyday use diagnosing and managing diabetes.

One of most important parameters to evaluate gas sensors is sensitivity. The standard equation for measuring sensitivity is presented here:

$$S\% = \left(\frac{R_g - R_a}{R_a} \right) \times 100$$

Where R_g is the resistance in the analyte gas, R_a is the resistance in air, and S is the calculated sensitivity expressed as a percent change from a controlled starting condition. The sensitivity can be best improved by either enhancing the transducer function or the receptor function. By improving the transducer function, the difference of the material's resistance between air and analyte gas is increased. The higher value of R_g - R_a in the above equation then presents an increase in sensitivity. The receptor function directly controls the R_a value, which, when lowered, increases overall sensitivity.

Starting with pure MOS nanomaterials, we can break it down into two distinct categories: *p*-type and *n*-type. This distinction is important as it dictates material's semiconducting property to exhibit an effective charge transfer, the sensor resistance to increase or decrease in response to increasing analyte concentration. The change in resistance will also depend on whether the analyte gas is a reducing gas or an oxidizing gas, which is summarized in Table 1. For a reducing gas, contact with the sensing material will donate electrons. A donation of electrons increases the charge carrier (electrons) in *n*-type semiconductors allowing for a drop in resistance, but this donation has the opposite effect on *p*-type semiconductors by decreasing the charge carrier concentration (holes) causing the resistance to increase. On the other hand, oxidizing gases will bind electrons causing an increase in resistance to *n*-type materials, while this action decreases the resistance of *p*-type MOS materials. This is a simplified explanation of the transducer function, which is the function that causes variable resistance in different concentrations of target gas and the main mechanism as shown in Figure 2. Further examination on the mechanism of this function will be discussed later.

Table 1: Characteristic sensing responses of p- and n-type sensors to reducing and oxidizing gases.

Sensing response behavior	*p*-type sensor	*n*-type sensor	Gases
Reducing gas	Increases resistance	Decreases resistance	H_2, H_2S, CO, NH_4, Ethanol, Acetone, CH_4
Oxidizing gas	Decreases resistance	Increases resistance	O_2, O_3, NO_x, CO_2, SO_2

Figure 2 demonstrates the sensing mechanism of chemiresistive sensors which include three major functions: **the receptor function, transducer function, and utility factor** [47,48]. The receptor function is related to the sensitivity and selectivity of the device and deals with how a sensing material responds to the target gas. The oxygen vacancy concentration generated in material can directly impact MOS based gas sensing performance. Also material's surface and unique properties such as ferroelectricity can make a major contribution to the receptor function. Therefore, the utilization of nanomaterials has been broadly applied to gas sensing not only due to their extremely high surface area to volume ratio but also other factors such as particle size, morphology, surface functional groups, and unique electric property, have a notable impact on the receptor function.

The transducer process (Figure 2) reveals how the response of each particle is transformed into the overall response of the sensing film and explains how efficiently free charge carriers transfer within the crystal. Theoretically, this process is mainly determined by the formation of the depletion region between junctions or grains. *n*-type nanostructured semiconductors will adsorb oxygen from the surrounding atmosphere, and the adsorbed oxygen attracts electrons forming O^-, O^{2-}, and O_2^- species during the synthesis. This causes an electron depleted layer, increasing the surface potential which then creates a potential barrier between adjacent grains, which hinders electron migration from one crystal to the next. The introduction of a reducing gas causes the oxygen species to be consumed, thus causing the potential barrier to decrease. This allows for easier transfer of electrons between crystal grains. Conversely, oxidizing gases will increase resistance by interacting with the material and binding more electrons, causing the depleted region to increase. This is the reason for the overall characteristic resistance responses of the *n*-type film as described earlier. *p*-type MOS sensor films still interact with atmospheric oxygen the same way *n*-type films do while they are fabricated; however, this interaction creates a hole accumulation layer. As a reducing gas interacts with the adsorbed oxygen species, the hole density decreases causing charge mobility to drop between grains. As a result, the resistance of the entire film rises while an oxidizing gas would create a larger hole accumulation area thus decreasing resistance. There are three factors playing an important role in the charge transfer and transportation in nanomaterials based gas sensors (here mainly referring to breath sensors): 1) *the grain size*, the size of nanomaterials is dramatically decreased which can introduce more density of defects like vacancies, dangling bonds, to prompt electron transportation. 2) *unique material property* such as the room-temperature ferroelectric property in nanostructured KWO. This unique property can sensitively detect chemicals such as acetone molecules with high dipole moment very easily and offers a favorable channel to transfer electrons. 3) *specific surface state*. Chemiresistive response is a process intensively relying on the surface state. The exposed crystal facet can selectively choose a certain component to introduce an effective response.

Finally, the utility factor is related to the material's morphology and defines the diffusion and reaction of the analyte gas through the sensing medium. This largely effects the sensing qualities such as response and recovery time and the film porosity as the most important parameter in achieving the highest utility factor. In a word, the highest performance of the sensor devices should be achieved by choosing proper receptor (sensing materials) and enhancing the interaction between target gas and sensing material (transducing and utility processes).

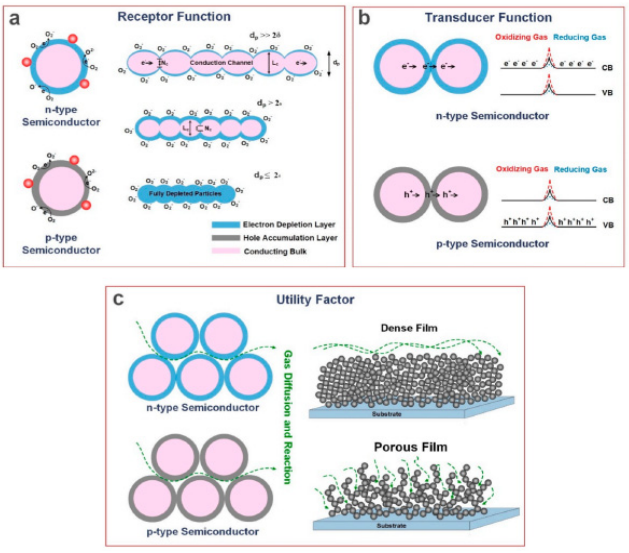

Figure 2: Three main factors controlling semiconductor gas sensors: **(a)** Receptor Function, **(b)** Transducer Function, and **(c)** Unility Factor [49].

Breath sensors for diabetes

As discussed earlier, breath acetone can be used as a biomarker for diabetes. [50,51] The range of acetone on the breath will vary from <0.7ppm (healthy) to >1.8ppm (diabetes), so any sensing technique needs to be able to operate within the range of 0.7 to 1.8 ppm, as well as be selective to acetone and no other components of the breath. Techniques to find the concentration of acetone on breath include GC-MS, solid-phase microextraction, and chemiresistive sensors [13]. Herein, a focus on chemiresistive sensors for detecting breath acetone will be expanded upon due to their promising features such as portable device design, reusability, and ease-of-use. Many MOS materials have been developed to date with the goal of acetone detection on exhaled breath, as shown in Table 2. As indicated, many of the sensors work at high temperatures exceeding 200°C. The high operating temperature is to help promoting the receptor function discussed earlier. However, newer materials such as $K_2W_7O_{22}$ (KWO) nanorods are shown to operate at room temperature thus require no heating element making the electronics design simpler and more power efficient [22,23].

Table 2: List of MOS materials used for acetone sensing for the diagnosis and monitoring of diabetes.

Material	Limit of detection (ppm)	Operating Temperature (°C)	*p*- or *n*-type semiconductor	Reference
In_2O_3 hollow porous nanofibers	0.25	300	*n*-type	[50]
WO_3 nanofibers functionalized by Rh_2O_3 nanoparticles	1	350	*n*-type	[51]
WO_3 porous nanofibers	0.1	270	*n*-type	[52]
WO_3 nanocrystals	0.05	300	*n*-type	[53]
Si doped WO_3 nanoparticles	0.02	350	*n*-type	[54]
SnO_2 porous fibers	1	300	*n*-type	[55]
SnO_2-MWCNT nanocomposites	0.5	200	*n*-type	[56]
ZnO nanorod arrays	1	300	*n*-type	[57]
ZnO hollow porous nanofibers	1	220	*n*-type	[58]
ZnO porous nanosheets	5	300	*n*-type	[59]
W doped NiO flower-like hollow spheres	0.1	250	*p*-type	[60]
Co_3O_4 nanosheets, fibers, and rods	5	160	*p*-type	[61]
$K_2W_7O_{22}$ nanorods	0.5	25	*p*-type	[22]
$K_2W_7O_{22}$ nanorods/Ti_3C_2 MXene nanosheets	0.1	25	*NA*	[23]

It is too extensive to cover all MOS materials designed for breath acetone sensing made to date, but some interesting examples will be discussed. For example, Si doped WO_3 (Si:WO_3) as the sensing material to detect acetone shows a very low limit of detection of 0.02 ppm [59]. Sensing tests of this material based sensor were promising: 1) such low detection limit can be reached even at a 90% RH; 2) the response and recovery times were all within a minute allowing for a fast use device; 3) good selectivity to acetone has been observed. More study using Si:WO_3 based device was set up to collect human breath over several minutes while being simultaneously compared to results also collected via proton transfer reaction-mass spectrometry (PTR-MS). These results are shown in Figure 3, which displays that the device has very similar readings of acetone concentration as the highly accurate PTR-MS. Furthermore, isoprene levels were recorded during physical activity to find if that would affect the sensor's accuracy since isoprene is a chemical known to increase concentration on the breath while exercising. It was found that even during physical activity the sensor remained in agreement with the PTR-MS. Overall, this is a promising device for acetone detection on human breath except it requires operation at 350°C, an elevated temperature.

Another promising material for acetone detection in the breath is a composite of one-dimensional $K_2W_7O_{22}$ nanorods and 2-dimensional Ti_3C_2 MXene nanosheets. This sensing material is specially unique because the nanocomposite based sensor can operate at room temperature with excellent sensing response, 250% sensitivity to 2.86ppm acetone (Figure 4), excellent water resistant capability (Figure 5), and low detection limit, 0.1ppm. This is appealing for the design of a simple portable breath acetone sensor as it lends itself to low-cost device fabrication as well as lower power consumption device.

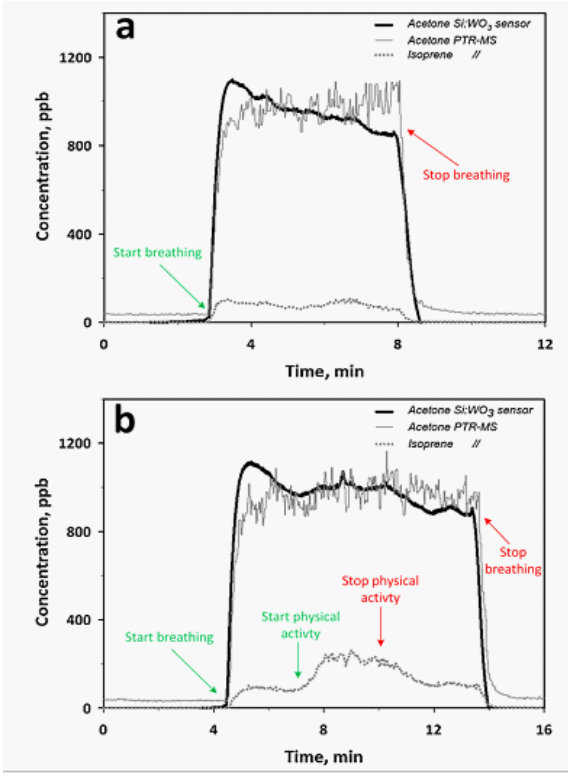

Figure 3: Measured acetone levels using Si: WO3 sensor as well PTR-MS **(a)** at rest and **(b)** during physical exercise [56].

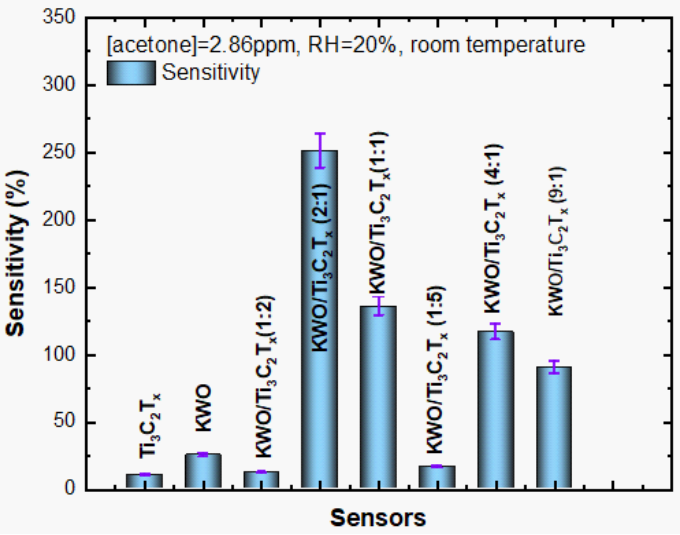

Figure 4: Sensing test on 2.86 ppm acetone at room temperature, RH = 20% using variable sensors based on $Ti_3C_2T_x$ nanosheets, KWO nanorods, KWO/Ti_3C_2Tx (1:2), KWO/$Ti_3C_2T_x$ (2:1),KWO/$Ti_3C_2T_x$ (1:1),KWO/$Ti_3C_2T_x$ (1:5), KWO/$Ti_3C_2T_x$ (4:1), and KWO/$Ti_3C_2T_x$ (9:1) [23].

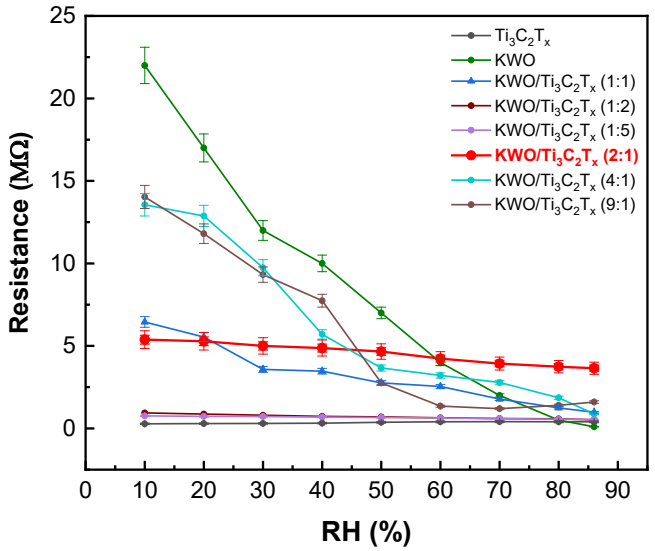

Figure 5: Resistance and RH relationship based on variable nanomaterials: $Ti_3C_2T_x$ nanosheets, KWO nanorods, KWO/$Ti_3C_2T_x$ (1:2), KWO/$Ti_3C_2T_x$ (2:1), KWO/$Ti_3C_2T_x$ (1:1), KWO/$Ti_3C_2T_x$ (1:5), KWO/$Ti_3C_2T_x$ (4:1), and KWO/$Ti_3C_2T_x$ (9:1) [23].

Breath sensor for asthma

Asthma symptoms often begin in early childhood and typically improve, or even disappear, after puberty. However, relapse is possible later in life and a method to assess inflammation and oxidative stress could provide a diagnostic tool to approach this condition. The most common breath analysis approach for diagnosing asthma is finding the concentration of Nitric Oxide (NO) in a patient's breath. An asthma patient can have a concentration upwards of 30 ppb NO in exhaled breath: nearly 4 times that of a healthy individual.

Like diabetes, MOS based breath sensors have been studied for their efficacy to diagnose and monitor asthma [64,65]. However, this area of study is not quite as extensively researched and could devote more efforts for the development of a well-designed sensor device. Additionally, like sensing breath acetone for diabetes, NO sensors have been primarily developed based on a chemiresistive mechanism. This means that the sensing materials developed should also satisfy the three main properties discussed earlier: Receptor function, transducer function, and utility factor.

The detection of NO for diagnosing Asthma is even more challenging as most NO_x species behave similarly, and thus it is difficult to design a breath sensor for asthma which shows great selectivity. Further, NO is also the biomarker for other diseases as well including hypertension, arthritis, lung disease, bronchiectasis in addition to inflammatory bowel disease of the colon and small intestine [66].

Until recently, WO_3 materials have been used to successfully sense NO gases [67]. The WO_3 MOS sensor showed peak sensitivity to NO at 200°C. However, the sensor was also responsive to NO_2 at a temperature of 300°C. So, a solution for high selectivity needs to be presented for a working NO sensor to diagnose asthma. One solution that has been researched is to design an electronic nose to differentiate between NO and NO_2 [68-70]. It has been shown that the grain boundary size of WO_3 nanomaterials has an effect on NO and NO_2 sensing [67]. So, to speculate, an electronic nose based around WO_3 nanomaterials with different grain boundary sizes could be used to accurately detect NO on the breath of asthma patients. Also, the nanocomposite made by 1D WO3 and 2D MXene can further improve the sensing selectivity to NO.

Conclusion

In this chapter, we have shown how versatile functionalized MOS materials can be used as chemiresistive sensors for biomedical purposes. The basic principles of MOS materials were explored in terms of a sensing film defining the three main properties of receptor function, transducer function, and utility factor which greatly impact sensing performance. Given this knowledge, specific examples in the areas of diabetes and asthma diagnosis and monitoring were explored as potential areas for non-invasive easy to use device design. Overall, MOS based chemiresistive sensors show a versatile array of uses that are robust and applicable to many areas of healthcare and health-monitoring.

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