Front. Phys. 11(2), 116801 (2016)
DOI 10.1007/s11467-015-0519-4

RESEARCH ARTICLE

Sniffing lung cancer related biomarkers using an oxidized graphene SAW sensor

Xin-Fang Zhang (张鑫方), **Zheng-Wei Zhang** (张正伟), **Yan-Lan He** (何焰兰), **Yi-Xing Liu** (刘一星), **Shuang Li** (黎双), **Jing-Yue Fang** (方靖越), **Xue-Ao Zhang** (张学骜), **Gang Peng** (彭刚)†

College of Science, National University of Defense Technology, Changsha 410073, China

Corresponding author. E-mail: †penggang@nudt.edu.cn

Received July 31, 2015; accepted October 13, 2015

Decane is one of the volatile organic compounds (VOCs) in human breath. Successful detection of decane in human breath has vast prospects for early lung cancer diagnosis. In this paper, a novel detecting device based on a filter surface acoustic wave (SAW) gas sensor is presented. SAW sensors coated with a thin oxidized graphene film were used to detect decane in parts per million (ppm) concentrations. Control and signal detection circuits were designed using a vector network analyzer with a detection resolution of insertion loss down to 0.0001 dB. The results showed that the SAW sensor could respond quickly with great sensitivity when exposed to 0.2 ppm decane. This device shows tremendous potential in medical diagnosis and environmental assessment.

Keywords decane, graphene oxide, lung-cancer biomarker, SAW gas sensor

PACS numbers 68.43.-h, 81.05.U-

1 Introduction

Up to 48% of lung cancer patients could survive if they are diagnosed successfully in the early cancer stages and are promptly treated [1]. However, the existing diagnostic methods, such as X-ray and CT, are of limited use in the early stages of lung cancer. To address this issue, researchers recently began developing rapid methods for detecting VOCs associated with lung cancer [2, 3] in human breath during the early stages of cancer. Decane is an important VOC biomarker of lung cancer [4, 5]. A total of 42 volatile organic compounds related to lung cancer have been identified using gas chromatography/mass spectrometry [6]. Decane, one of the VOCs with high molecular weight, was selected as a biomarker for detection in a lung-cancer electronic nose system [7]. In fact, the chemical and physical properties of non-polar decane molecules are similar to hydrocarbon biomarkers such as n-undecane, tridecane, 4-methyl-tetradecane, hexadecane. Since decane [8] is a non-polar molecule and because little charge transfer occurs between decane and selective adsorbates, it is difficult to use traditional gas sensors for detecting low decane concentrations [9]. Many gas-sensitive materials have been reported, including graphene, carbon nanotubes, metal nanoparticles, metal oxides, carbon black, and organic conductive polymers [10–13]. Among these, recently graphene has attracted much interest and many meaningful results have been reported [14–16]. Graphene and graphene oxide (GO) should have the most potential as adsorbates materials because of their large specific surface area (about 2600 $m^2 \cdot g^{-1}$) [17]. This feature [18, 19] gives graphene oxide (GO) a greater contact surface area for absorbing target gas molecules. In addition, graphene and GO can still maintain good stability, even at the nanometer scale or as a single benzene ring. In this paper, a SAW sensor with GO, instead of graphene, is used for cancer-related VOC detection because GO is non-conducting. This may help avoid the use of an insulator film on top of the SAW sensor, thus reducing the electromechanical coupling effects resulting from graphene conductive films. The SAW sensor based on the mass effect in the process of transportation shows good sensitivity for macro and non-polar molecules [20].

2 Materials and methods

2.1 Materials

Graphene oxide was synthesized from mature graphite

power (300 mesh, Aladdin Co. Ltd, Shanghai, China) using a modified Hummer's method [21, 22]. The SEM image in Fig. 3(c) shows a wrinkled surface of graphene oxide, it is result from uneven heating during the GO film deposition process.

A SAW device with an appropriate frequency is necessary to ensure sensor performance with high sensitivity and lower detection limits. The following factors should be considered: a high center frequency of the SAW device, high sensitivity for gas detection [23], SAW device high operating frequency, and the high noise level [24]. The commercial RF3404 with a 433.92 MHz dual port surface SAW (RF Monolithics, Inc.) was used as a sensing element. The center frequency of the commercial device is 433.922 MHz and the corresponding insertion loss is 3.183 dB (Fig. 1).

2.2 Sample preparation

First, a sensitive film with proper thickness should be coated onto the SAW sensor propagation path. There are many thin film coating methods, including spin coating, sputtering, and LB film preparation among others. A suitable coating method is needed since the length of propagation path in the RF3404 double end SAW element is narrow. In this paper, the GO-sensitive film was coated onto the propagation path of the SAW device by brushing a GO solution with the help of a microscope and a single hair of a brush. AFM measurements showed that the thickness of the films in this case were about 150–200 nm as shown in Fig. 2. In N_2 gas, the insertion loss spectrum of the sensor with GO-sensitive film is shown in Fig. 1. The center frequency of the SAW sensor device was 433.920 MHz and the corresponding insertion loss was 4.265 dB. The difference of the center frequency is about 2 KHz between the sensitive film with and without the coating.

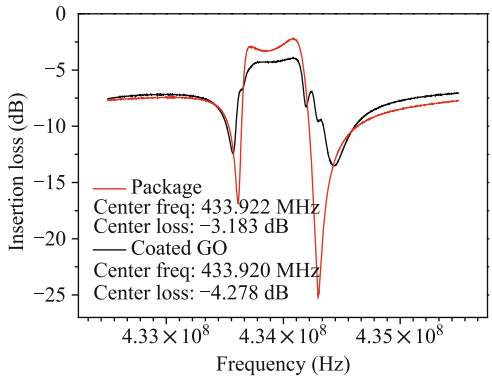

Fig. 1 The frequency characteristic of 433.92 MHz double-end SAW filter, and the coating GO film sensitive SAW filter.

2.3 Test

The SAW devices were mounted into a 250 mL test chamber. The chamber was evacuated for 1 hour to remove any molecules adsorbed during the sample preparation process. The N_2 gas supply was split into two gas branches, one flowing through a bubbler with decane to generate an almost saturated vapor, and the second branchbeing the carrier gas stream with concentration adjustment, which can dilute the concentration of detected gas. These two branches are later mixed to achieve the desired decane concentration or to simply measure the response in a saturated decane environment. Two mass flow controllers were used to control the gas flow of these branches. The carrier gas stream could be set from 0 to 10000 ± 10 sccm, and the decane vapor flows could be adjusted from 0 to 1000 ± 1 sccm. Decane vapors with different concentration were flowed into the test chambers. As the GO-SAW sensor contacts the mixed gas stream, the insertion loss changes accordingly. The network analyzer AV3656A (The 41st Institute, Electronics Technology Group Corporation, China) was used to record the time excursions of the signal during the decane exposures of the SAW sensor, indicating the changes in insertion loss for the

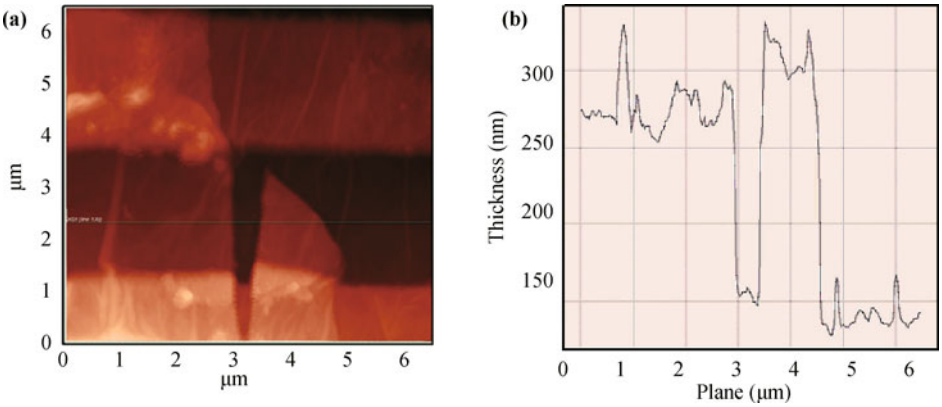

Fig. 2 **(a)** AFM image; **(b)** Thickness measurements.

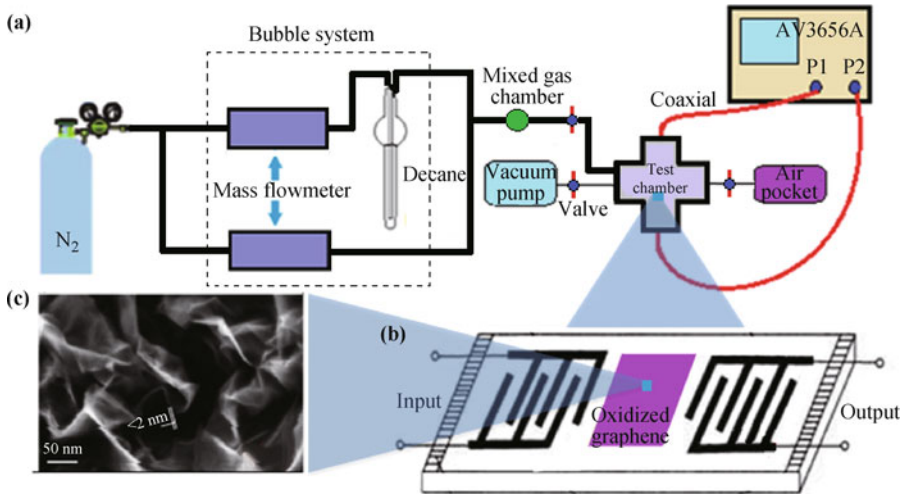

Fig. 3 Diagram of the test system. **(a)** The overall profile of the test system. **(b)** The SAW filter with graphene oxide on the propagation path. **(c)** SEM image of graphene oxide-sensitive film on the gas sensor sample.

SAW device. During the experiment, the flow rate (4000 sccm) and the room temperature were maintained to eliminate the influence of gas velocity.

3 Results and discussion

The sensor performance was tested with 19.5 ppm decane where the SAW sensor had a stable signal in N_2. The GO-sensor was maintained in pure N_2 for 5 min, subsequently exposed to 19.5 ppm decane for 5 min, and finally flushed with pure N_2 for another 5 min. This process was repeated four times. The insertion loss at the fixed frequency of 433.92 MHz is shown in Fig. 4(a), with the insertion loss increasing when the sensor was exposed to decane. The graphene oxide SAW sensor had very good reproducibility, with the average variation of insertion loss only about 0.02 dB. The response and recovery time of the GO SAW sensor is 28 and 37 s, respectively.

Figure 5(a) showed the response of the SAW filter coated with GO to decane at a decane concentration ranging from 2 to 50 ppm. Based on the experimental insertion loss data in Fig. 5(a), the response varied as a function of decane concentration with the corresponding dependence on decane concentration as shown in Fig. 5(b). The magnitude of the response varied from 0.0013 to 0.007 dB. The sensor responded nonlinearly to decane concentration in the range of 2–50 ppm concentration as vapor concentration increased. This occurred as a result of saturation of the GO-SAW sensor when decane concentration reached 35 ppm. With this device, we were capable of measuring relative responses of insertion loss values as small as 0.03% with a signal-noise ratio of 3:1. The lower detection limit is about 0.2 ppm decane.

4 Conclusions

A SAW sensor based on an oxidized graphene film was fabricated for the detection of the lung cancer-related biomarker decane at varying concentrations. The results showed that the sensor has high sensitivity (down to 0.2

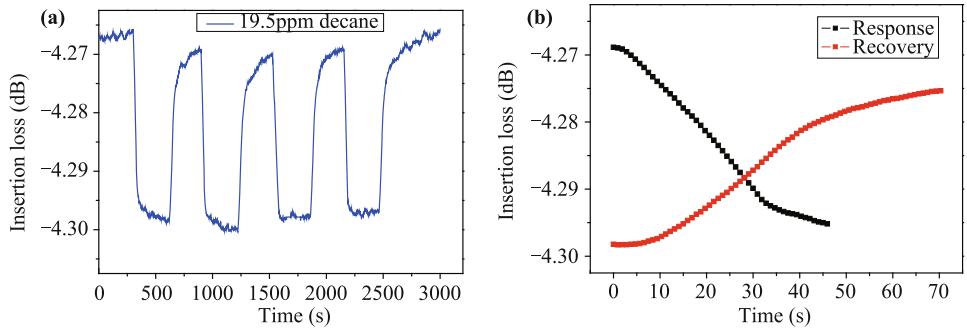

Fig. 4 Time response of the sensor at 19.5 ppm decane. **(a)** Repetition experiment of the sensor and **(b)** response time and recovery time at 19.5 ppm decane.

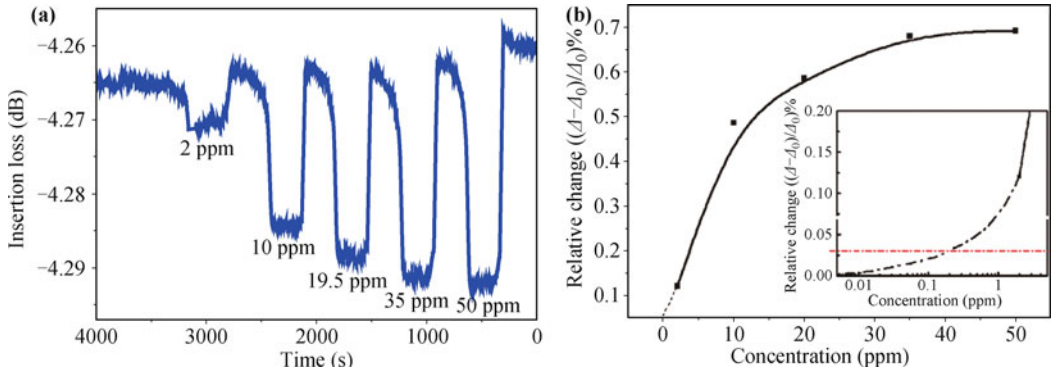

Fig. 5 **(a)** Insertion loss of GO-SAW sensor at different concentrations of decane of 2 ppm, 10 ppm, 20 ppm, 35 ppm, and 50 ppm. **(b)** Relative change $(\Delta - \Delta_0)/\Delta_0$ as the function of decane concentration, (where Δ_0 is the insertion loss of the detector in the absence of analyte, and the Δ is the steady-state loss change upon exposure of the detector to decane). The insert is the relative response at low concentration of decane.

ppm decane), good reproducibility, and quick response and recovery properties. The oxidized graphene film is an ideal candidate for SAW devices for detecting the cancer-related biomarker decane. Consequently, SAW devices using this gas-sensor technology have great potential application for the diagnosis of VOCs related to certain diseases.

Acknowledgements This work was supported by the National Natural Science Foundation of China (Grant No. 11104348), the Advanced Research Foundation of the National University of Defense Technology (Grant No. JC15-02-01), the Open Foundation of State Key Laboratory of High Performance Computing (Grant No. 201301-02), and the Open Foundation-Based on the Innovation Platform of Hunan Key Laboratories (Grant No. 13 k022).

References

1. Y. Adiguzel and H. Kulah, Breath sensors for lung cancer diagnosis, *Biosens Bioelectron* 65C, 121 (2014)
2. M. Phillips, J. Herrera, S. Krishnan, M. Zain, J. Greenberg, and R. N. Cataneo, Variation in volatile organic compounds in the breath of normal humans, *J. Chromatogr. B Biomed. Sci. Appl.* 729(1–2), 75 (1999)
3. M. Phillips, K. Gleeson, J. M. B. Hughes, J. Greenberg, R. N. Cataneo, L. Baker, and W. P. McVay, Volatile organic compounds in breath as markers of lung cancer: A cross-sectional study, *Lancet* 353(9168), 1930 (1999)
4. A. Jemal, R. Siegel, E. Ward, Y. Hao, J. Xu, T. Murray, and M. J. Thun, Cancer statistics, *CA Cancer J. Clin.* 58(2), 71 (2008)
5. H. J. O'Neill, S. M. Gordon, M. H. O'Neill, R. D. Gibbons, and J. P. Szidon, A computerized classification technique for screening for the presence of breath biomarkers in lung cancer, *Clin. Chem.* 34(8), 1613 (1988)
6. G. Peng, M. Hakim, Y. Y. Broza, S. Billan, R. Abdah-Bortnyak, A. Kuten, U. Tisch, and H. Haick, Detection of lung, breast, colorectal, and prostate cancers from exhaled breath using a single array of nanosensors, *Br. J. Cancer* 103(4), 542 (2010)
7. G. Peng, U. Tisch, O. Adams, M. Hakim, N. Shehada, Y. Y. Broza, S. Billan, R. Abdah-Bortnyak, A. Kuten, and H. Haick, Diagnosing lung cancer in exhaled breath using gold nanoparticles, *Nat. Nanotechnol.* 4(10), 669 (2009)
8. X. Chen, M. Cao, Y. Li, W. Hu, P. Wang, K. Ying, and H. Pan, A study of an electronic nose for detection of lung cancer based on a virtual SAW gas sensors array and imaging recognition method, *Meas. Sci. Technol.* 16(8), 1535 (2005)
9. R. F. Machado, D. Laskowski, O. Deffenderfer, T. Burch, S. Zheng, P. J. Mazzone, T. Mekhail, C. Jennings, J. K. Stoller, J. Pyle, J. Duncan, R. A. Dweik, and S. C. Erzurum, Detection of lung cancer by sensor array analyses of exhaled breath, *Am. J. Respir. Crit. Care Med.* 171(11), 1286 (2005)
10. J. Zhang, J. Liu, Q. Peng, X. Wang, and Y. Li, Nearly monodisperse Cu_2O and CuO nanospheres:?Preparation and applications for sensitive gas sensors, *ChemInform* , 37 (2006)
11. M. E. Franke, T. J. Koplin, and U. Simon, Metal and metal oxide nanoparticles in chemiresistors: Does the nanoscale matter? *Small* 2(1), 36 (2006)
12. J. Chen and N. Tsubokawa, Novel gas sensor from polymer-grafted carbon black: Vapor response of electric resistance of conducting composites prepared from poly(ethylene-block-ethylene oxide)-grafted carbon black, *J. Appl. Polym. Sci.* 77(11), 2437 (2000)
13. J. J. Miasik, A. Hooper, and B. C. Tofield, Conducting polymer gas sensors, *J. Chem. Soc., Faraday Trans.* 82(4), 1117 (1986)
14. J. W. Jiang, Graphene versus MoS_2: A short review, *Front. Phys.* 10(3), 106801 (2015)
15. Y. Li, H. Zhang, D. W. Yan, H. F. Yin, and X. L. Cheng, Secondary plasmon resonance in graphene nanostructures, *Front. Phys.* 10(1), 102 (2015)

16. C. Stampfer, S. Fringes, J. Güttinger, F. Molitor, C. Volk, B. Terrés, J. Dauber, S. Engels, S. Schnez, A. Jacobsen, S. Dröscher, T. Ihn, and K. Ensslin, Transport in graphene nanostructures, *Front. Phys.* 6(3), 271 (2011)

17. Y. Zhu, S. Murali, W. Cai, X. Li, J. W. Suk, J. R. Potts, and R. S. Ruoff, Graphene and graphene oxide: Synthesis, properties, and applications, *Adv. Mater.* 22(35), 3906 (2010)

18. D. A. Dikin, S. Stankovich, E. J. Zimney, R. D. Piner, G. H. Dommett, G. Evmenenko, S. T. Nguyen, and R. S. Ruoff, Preparation and characterization of graphene oxide paper, *Nature* 448(7152), 457 (2007)

19. Z. Zhang, X. Zhang, W. Luo, H. Yang, Y. He, Y. Liu, X. Zhang, and G. Peng, Study on adsorption and desorption of ammonia on graphene, *Nanoscale Res. Lett.* 10(1), 359 (2015)

20. M. Penza, C. Martucci, and G. Cassano, NO_x gas sensing characteristics of WO_3 thin films activated by noble metals (Pd, Pt, Au) layers, *Sens. Actuators B Chem.* 50(1), 52 (1998)

21. W. S. Hummers Jr and R. E. Offeman, Preparation of graphitic oxide, *J. Am. Chem. Soc.* 80, 1339 (1958)

22. V. V. Krylov, Effect of surface phenomena in solids on surface acoustic waves, *Prog. Surf. Sci.* 32(1), 39 (1989)

23. A. A. Oliner, Acoustic Surface Waves (Topics in Applied Physics Volume 24), Berlin and New York: Springer-Verlag, 1978, p. 342 (For individual items see A79-16052 to A79-16055)

24. A. M. Committee, Recommendations for the definition, estimation and use of the detection limit, *Analyst* 112(2), 199 (1987)