Journal of Molecular Biomarkers & Diagnosis
ISSN: 2155-9929

Malagù and Landini, J Mol Biomark Diagn 2015, S:2
DOI: 10.4172/2155-9929.S2-012

Commentary Open Access

Simulation of Intestinal Gaseous Environment in Order to Verify the Capability of Nanostructured Chemoresistive Sensors to Detect Colorectal Tumor Markers (Benzene, 1-Iodo-Nonane, Decanal)

Cesare Malagù[1,2] and Nicolò Landini[1]

[1]Department of Physics and Earth Science, University of Ferrara, Via Saragat 1/c, 44122 Ferrara, Italy
[2]CNR-INO – Istituto Nazionale di Ottica, Largo Enrico Fermi 6, 50124 Firenze, Italy

Abstract

Studies have proven that neoplasia development and growth are linked to the production and spreading in the body of chemicals, originated from different sources. In the studied case of colorectal cancer (CRC), the main sources of these chemicals (together with the decay of these compounds into smaller products), are:

• Products from lipid bilayer peroxidation, generated for instance from contact with free radicals;

• Metabolites expelled as discard products from cancerous/benignant cells;

• Alteration of the microbiota in the intestine, leading to the variation in concentration of the metabolites produced from these microorganisms;

• Vascular endothelial growth factor (VEGF) produced from the tumor itself to stimulate angiogenesis and increase the vascularization in its direct surroundings.

Together with some published studies, from the same team, on the other three families of markers, in this work the goal is to study the first group, the peroxidation products, taking as markers the volatile organic compounds (VOCs), already known in literature, 1-iodo-nonane and decanal (highly reactive aldehydes maintaining the hydrophobic tails from the phospholipids), and benzene as sub-product (due to the fact that the main marker itself may turn into other chemicals due to various reactions, some of which are benzene itself and his bis-benzene compounds). These chemicals have been mixed with different concentrations of interferes, commonly produced in the digestive system from various sources (O_2, N_2, H_2, CH_4, H_2S, NO, NO_2, SO_2), thus to define which sensors (or sensor arrays) aremost sensitive, and selective, to the presence of the above indicated markers.

Nanostructured chemoresistive sensors, widely studied as environmental and industrial real-time monitoring devices, have been used in this work as an opening to a new field of application, the biomedical, with the final goal to provide a new technology to medics and biologists in order to screen the occurrence, and study the degenerative processes, of neoplasms.

Keywords: Sensors; Tumor; Colorectal cancer; Tumor marker

Materials and Methods

The proposed study has been realized with the aid of 8 different kind of nanostructured (composed of nanospheres) chemoresistive (changing their output voltage responses due to alterations in the chemical composition of the environment around them, with capability to detect variations down to 50 ppb) sensors, here listed:

- **TiTaV**, based on titanium, tantalum and vanadium oxides;
- **ST25 650**, based on tin oxides and titanium, with a firing temperature of 650°C;
- **STN**, based on tin, titanium and niobium oxides, with a firing temperature of 650°C;
- **ST20 650**, based on tin oxides and titanium, with a firing temperature of 650°C;
- **ST25 650+Au,** based on tin oxides, titanium and gold, with a firing temperature of 650°C;
- **ST30 650,** based on tin oxides and titanium, with a firing temperature of 650°C;
- **ZnO 650,** based on zinc oxide, with a firing temperature of 650°C;
- **ZnO 850**, based on zinc oxide, with a firing temperature of 850°C.

More information about these metal oxide (MOX) sensors can be found in the references [1-6].

The sensors have been thermo-activated by a heater printed on the back side of the sensors substrate, to allow each sensing film reach the proper working temperature (which varies between 200 and 650°C). Preliminary single gas tests (in which low quantities of the interferer or marker were sent together with synthetic air, 80% nitrogen and 20% oxygen, into the sensitive chamber) have been performed on each sensing film. After that, interferences in the following quantities

***Corresponding author:** Cesare Malagù, Department of Physics and Earth Science, University of Ferrara, Via Saragat 1/c, 44122 Ferrara, Italy, Tel: 39 0532 293111; E-mail: malagu@fe.infn.it

Received May 04, 2015; **Accepted** June 27, 2015; **Published** July 04, 2015

Citation: Malagù C, Landini N (2015) Simulation of Intestinal Gaseous Environment in Order to Verify the Capability of Nanostructured Chemoresistive Sensors to Detect Colorectal Tumor Markers (Benzene, 1-Iodo-Nonane, Decanal). J Mol Biomark Diagn S2:012. doi:10.4172/2155-9929.S2-012

(chosen to reproduce the relative concentrations of the gases in the intestine) have been done, both in dry and wet conditions:

- H_2S (100 sccm)+NO_2(100 sccm)+ C_6H_6(100 sccm)+ dry/wet synthetic air (200sccm), reported in Figure 1;
- SO_2 (10 sccm)+NO (10 sccm)+ C_6H_6(100 sccm)+ dry/wet synthetic air (380 sccm), (reported in Figure 2;
- CH_4(1 sccm)+H_2 (30 sccm – 1 sccm)+ C_6H_6 (100 sccm)+ dry/wet synthetic air (369 – 398 sccm), reported in Figure 3;
- CH_4 (1 sccm)+H_2 (30 sccm – 2 sccm)+ C_6H_6 (250 sccm)+ dry/wet synthetic air (219 – 247 sccm), reported in Figure 4;
- $C_{10}H_{20}O$ ($7.46 \cdot 10^{-4}$mol)+ $C_9H_{19}I$ ($2.57 \cdot 10^{-4}$mol)+wet synthetic air (300 sccm), reported in Figure 5.

The reasons to use these chemicals are various, and are reported in the following list:

- **Benzene:** tumor marker sub-product [7-9];
- **Methane:** produced from the fermentation of vegetables;
- **Hydrogen:** resulting from the digestion of meat;
- **Hydrogen sulfide:** resulting from the digestion of beef, broccoli and dry fruit;
- **Sulfur dioxide:** produced as result of surface reaction of hydrogen sulfide with sensors heated sensitive film [10];
- **Nitrogen oxide:** produced from bacterial activity, and is also a gastro-transmitter [11,12];
- **Nitrogen dioxide:** can be produced as result of helicobacter pylori presence in the stomach [13]
- **1-iodo-nonane:** is a tumor marker commonly analyzed in literature [7,8]
- **Decanal:** is a tumor marker commonly analyzed in literature [9].

Results and Discussion

The most notable results are summarized in the figures. As it is possible to see from Figures 1-5, the highest responses are given from

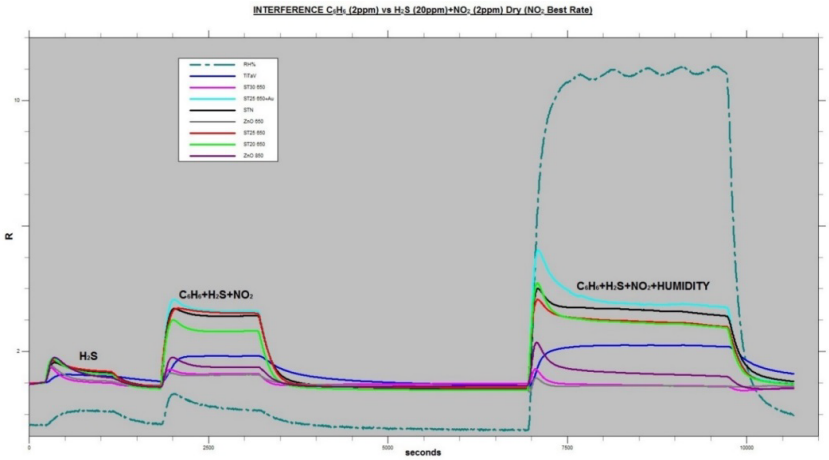

Figure 1: Sensors responses (normalized to 1), as a function of time, to H_2S (1st peak), C_6H_6 + H_2S + NO_2 (2nd peak), C_6H_6 + H_2S + NO_2 + humidity as interferer (RH%: 10.94), in dry conditions (3rd peak). Temperatures chosen are the ones at which the sensor responses to NO_2 are the lowest when compared to C_6H_6.

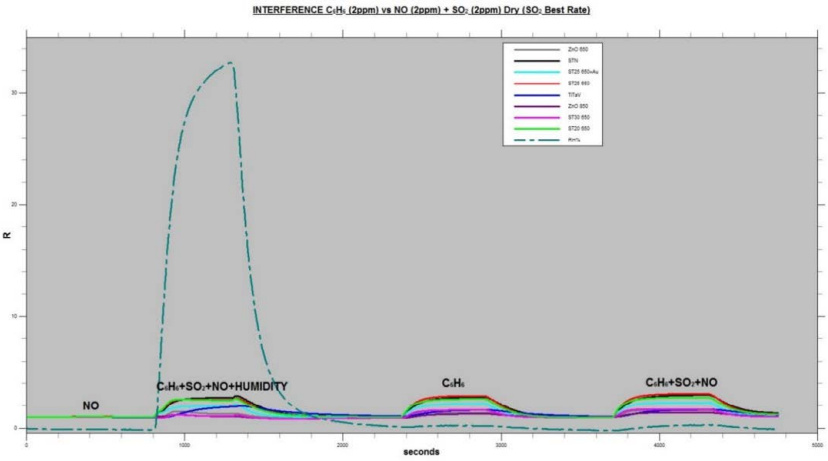

Figure 2: Sensors responses (normalized to 1), as a function of time, to NO (1st peak), C_6H_6 + SO_2 + NO + humidity (2nd peak), C_6H_6 (3rd peak), C_6H_6 + SO_2 + NO (4th peak). Temperatures chosen are the ones at which the sensor responses to SO_2 are the lowest when compared to C_6H_6.

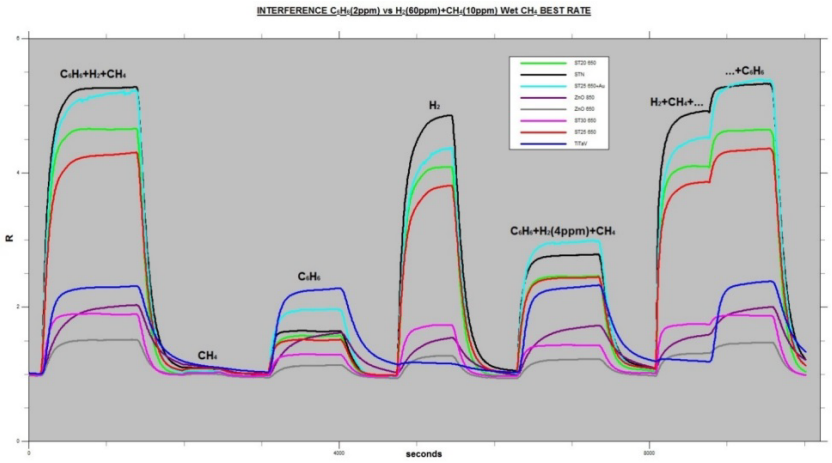

Figure 3: Sensors responses (normalized to 1), as a function of time, to CH_4 (1st peak), $C_6H_6 + H_2 + CH_4$ (2nd peak), C_6H_6 (3rd peak), H_2 (4th peak), $C_6H_6 + H_2 + CH_4$ with H_2 at nearly the same concentration of C_6H_6 (5th peak), $H_2 + CH_4$ and delayed addition of C_6H_6 (6th peak), $C_6H_6 + H_2 + CH_4$ + humidity as interferer (RH%: 23.92), in dry conditions (7th peak). Temperatures chosen are the ones at which the sensor responses to CH_4 are the lowest as compared to C_6H_6.

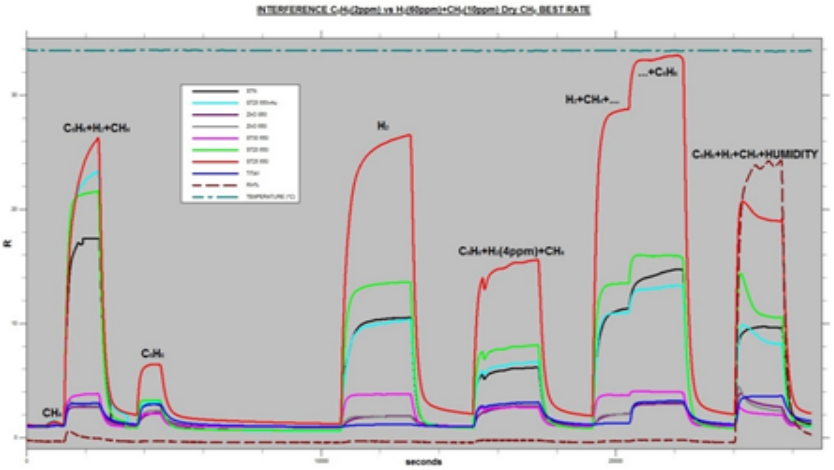

Figure 4: sensors responses (normalized to 1), as a function of time, to $C_6H_6 + H_2 + CH_4$ (1st peak), CH_4 (2nd peak), C_6H_6 (3rd peak), H_2 (4th peak), $C_6H_6 + H_2 + CH_4$ with H_2 at nearly the same concentration of C_6H_6 (5th peak), $H_2 + CH_4$ and delayed addition of C_6H_6 (6th peak). Temperatures chosen are those at which the sensor responses to CH_4 are the lowest as compared to C_6H_6.

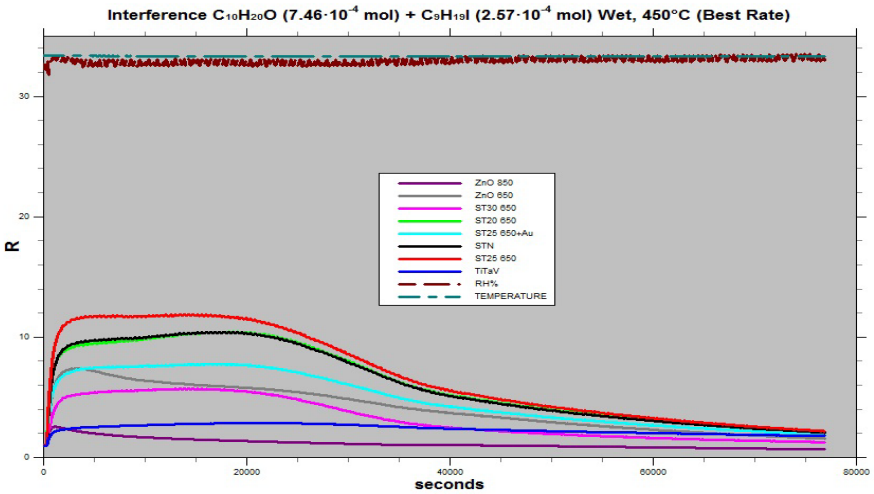

Figure 5: sensors responses (normalized to 1), as a function of time, to $C_9H_{19}I + C_{10}H_{20}O$ in wet conditions (RH%: 32.0) at 450°C.

ST-family sensors, especially while testing the tumor markers alone in wet condition, but the best selectivity is that of the TiTaV sensor which, as shown in the Figures 1-4, can discriminate completely the presence of benzene (the sub-product) from other interferences. This is crucial, because it is known that most of the membrane peroxidation products are instable and highly reactive (the two chosen aldehydes are photosensitive, and in the case of the decanal, air sensitive as well), especially in an hostile environment like the digestive system, and so, by using thermoactivated sensors to be sure that all the markers reaching degrades into simpler molecules, allows to think about a threshold system to distinguish the presence of these sub-markers in abundance, compared to a healthy patient.

Contribution from humidity, as shown in graphics, varies considerably depending on the mixture of the chosen gases, as well as from the modality of injection (using it as an environmental factor, keeping it stable for the whole test, lowers the responses from all sensors, while using it as an interferer, may not affect responses or even raise it for some particular synthesis).

From the tests another result has been obtained: adding a tumor marker after the sensors have reached stability in a mixture made with interferers, not only shows the response to the VOC itself, but also a global response higher than the one obtained by injecting all the chemicals together. This shows the high sensitivity of sensors even in environments with highly reactive compounds.

Conclusions

Nanostructured chemoresistive sensors have been used to analyze different mixtures of gases, tested to simulate, on their relative concentrations, the intestine environment. Tumor markers have been added to the mixtures, with concentrations close to the ones indicated in literature as indicative of tumor presence.

As seen from the tests performed, sensors not only give high responses to mixtures of markers (as shown in Figure 5), but some of them (like TiTaV) also completely discriminate the effects of interferers, like hydrogen and methane, from the marker behavior.

Arrays of sensors, like the one studied in this work, can be used together with dedicated software to identify different behaviors to different mixtures, allowing one to refine the detection of tumor markers.

Therefore, chemoresistive sensors have proven to be a promising technology to develop new diagnostic devices for tumor pre-screening.

References

1. Malagù C, Fabbri B, Gherardi S, Giberti A, Guidi V, et al. (2014) Chemoresistive gas sensors for detection of colorectal cancer biomarkers. Sensors (Basel) 14: 18982-18992.
2. Carotta MC, Benetti M, Guidi V, Gherardi S, Malagù C, et al. (2006) Nanostructured (Sn, Ti, Nb) O2 solid solutions for hydrogen sensing. MRS Proceedings 915: 68210.
3. Carotta MC, Cervia A, Natale Vdi, Gherardi S, Giberti A, et al. (2009) ZnO gas sensors: A comparison between nanoparticles and nanotetrapods-based thick films. Sensors and Actuators B: Chemical 137: 164-169.
4. Carotta MC, Ferroni M, Gnani D, Guidi V, Merli M, et al. (1999) Nanostructured pure and Nb-doped TiO2 as thick film gas sensors for environmental monitoring. Sensors and Actuators B 58: 310-317.
5. Carotta MC, Guidi V, Malagù C, Vendemiati B, Zanni A, et al. (2005) Vanadium and tantalum-doped titanium oxide (TiTaV): A novel material for gas sensing. Sensors and Actuators B 108: 89-96.
6. Guidi V, Malagù C, Carotta MC, Vendemiati B (2012) Printed semiconducting gas sensors. Printed films: Materials science and applications in sensors, electronics and photonics, Woodhead publishing series in electronic and optical materials: 278-334.
7. Peng G, Hakim M, Broza YY, Billan S, Abdah-Bortnyak R, et al. (2010) Detection of lung, breast, colorectal, and prostate cancers from exhaled breath using a single array of nanosensors. Br J Cancer 103: 542-551.
8. Probert CSJ, Ahmed I, Khalid T, Johnson E, Smith S, et al. (2009) Volatile Organic Compounds as Diagnostic Biomarkers in Gastrointestinal and Liver Diseases. Journal of Gastrointestinal and Liver Disease 18: 337-343.
9. Altomare DF, Lena M Di, Porcelli F, Trizio L, Travaglio E, et al. (2013) Exhaled volatile organic compounds identify patients with colorectal cancer. British Journal of Surgery 100: 144-150.
10. Rodriguez JA, Chaturvedi S, Kuhn M, Hrbek J (1998) Reaction of H2S and S2 with Metal/Oxide Surfaces: Band-Gap Size and Chemical Reactivity. The Journal of Physical Chemistry B 102: 5511-5519.
11. Vermeiren J, Van de Wiele T, Verstraete W, Boeckx P, Boon N (2009) Nitric Oxide Production by the Human Intestinal Microbiota by Dissimilatory Nitrate Reduction to Ammonium. J Biomed Biotechnol.
12. Tari A, Kodama K, Kurihara K, Fujihara M, Sumii K, et al. (2002) Does serum nitrite concentration reflect gastric carcinogenesis in Japanese Helicobacter pylori-infected patients? Digestive Diseases and Sciences 47: 100-106.
13. Kondo T, Mitsui T, Kitagawa M, Nakae Y (2000) Association of fasting breath nitrous oxide concentration with gastric juice nitrate and nitrite concentrations and Helicobacter pylori infection. Digestive Diseases and Sciences 45: 2054.

This article was originally published in a special issue, **Cancer Biomarkers** handled by Editor(s). Dr. Sudhir Srivastava, Cancer Biomarkers Research Group, National Institute of Health, USA; Dr. Shou-Jiang Gao, The University of Texas Health Science Centre at San Antonio, USA; Dr. Kenneth Maiese, University of Medicine & Dentistry of New Jersey, New Jersey Medical School, USA