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Devices for screening and monitoring of tumors based on chemoresistive sensors

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Abstract

In this work two devices are presented, named SCENT A1 (A1) and SCENT B1 (B1), composed of chemoresistive sensors. Such devices are capable of discriminating the different compositions of gas mixtures emitted by stools, for colorectal cancer screening (A1), and by blood, for tumors monitoring (B1), according to defined sampling protocols. Results have been acquired by a LabView® software and statistically treated (e.g. quadratic discriminant analysis, QDA) and show to be encouraging with an error of 5% for SCENT A1. Preliminary results of SCENT B1 proved to be promising. Further studies will be carried out for clinically validating the two devices.

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Keywords: tumor; colorectal cancer; blood; feces; screening; monitoring.

1. Introduction

One of the great challenges of medicine is to prevent the degeneration of benign tumors into malignant and/or metastatic stages and the monitoring of patients in the years after surgery, in order to avoid tumor recurrence. In particular, colorectal cancer (CRC) is one of the widely diffused tumors but, if early diagnosed, it has also a high curable rate. Each tumor has a specific pattern of gaseous biomarkers, produced by the peroxidation of the cell membrane or by the alteration of cellular metabolic activity with cancer. These biomarkers influence the composition of the human body fluids (e.g., blood, breath, intestinal gases) and, in the specific case of CRC, of feces. We have developed two devices, named SCENT A1 (A1) and SCENT B1 (B1) [1, 2], capable of discriminating the different compositions of the gaseous fumes emitted by stools, for CRC screening (A1), and by

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blood, for tumor monitoring (B1), according to defined sampling protocols. More than 160 tests with fecal samples and 47 with blood samples have been performed, with both tumor affected (TA) and control subjects (CS) samples, in order to identify the most discriminating combinations of sensors. TA samples have been provided after surgery, thanks to the Hospital S. Anna of Ferrara. CS feces come have been collected after normal defecation.

Nomenclature

CS	control subjects samples
TA	tumor affected samples
CRC	colorectal cancer

2. Experimental section

Studies on the physics of nanostructures, both from the experimental and theoretical point of view, show the capability of nano-powders to detect gases in lower concentration with respect to their coarser counterparts. This is due to surface effects, which can be explained with a treatment that is borderline between classic and quantum solid state physics [3].The core of the two medical devices is composed of chemoresistive sensors arrays, capable of modifying their resistance once in contact with gas. These sensors are based on semiconductor nanostructured materials, they have a high sensitivity (tenths of part per billion) and they are little selective if taken singularly, conversely they show high selectivity if organized in specific arrays. The choice of the best discriminating sensor arrays is the basis of the functioning the devices presented here. A1 and B1, shown in Fig.1, 2, have a similar setup with little differences, e.g., in the casing of the sensing core, which has five sensor allocations for A1 and four for B1 [1, 2]. In the following subsection is presented a description of the activities carried out in this work.

Fig. 1: the device A1 for CRC preventive screening through fecal exhalation analysis.

Fig. 2: the device B1 for tumor monitoring through blood exhalation analysis.

2.1. A1: preventive screening of CRC

The device A1 (Fig. 1) allows the casing of sensors combined in a 5-units array, whose negative interaction with external environment are reduced thanks to carbon filters and anti-bacterial filters 0.2μm. Filtered air, inflated by a dedicated pump, flows through the circuit and pollutes the sensors chambers with the exhalations of the sample contained in the box. Stool samples have been provided by the University Hospital S. Anna of Ferrara inside standard containers (ARTSANA SpA Feces Container STER 18140) which have been frozen immediately in order to maintain the composition of their content. The latter can instead be altered at ambient temperature, because of the bacterial activity inside feces. A wide range of sensing materials has been tested and the most discriminating sensor array has been selected, composed by sensors listed in the second column of Table 1. Quadratic discriminant analysis (QDA) technique has been employed to increase the discriminating power of the chosen array. It is a

statistical method aimed to find a combination of features that characterizes or separates two or more classes of data [4]. In Fig. 3 the result of QDA for A1 (10 CS and 6 TA) is shown. The error is of 5% with only one false positive. A1 test should be carried out in parallel to fecal occult blood test (FOBT) which has a sensitivity of 59.7÷65.9 percentage [5].

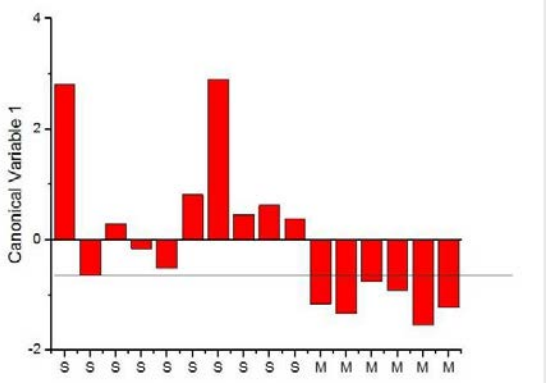

Fig. 3: QDA results with 10 CS and 6 TA samples. CS are indicated with the letter S and TA are indicated with the letter M. Tests have been performed with A1. The horizontal line represents the estimated limit, which divides true negatives from true positives tests. Only a false positive has been found with an error of 5%

Table 1: list of sensor types chosen for the sensors array of A1 and B1, respectively.

SENSORS	A1 (fecal tests)	B1 (blood tests)
1	$SmFeO_3$ (a)	Tin and titanium oxide with addition of gold
2	Tin and titanium oxide	ZnO
3	$SmFeO_3$ (b)	$SmFeO_3$
4	W and Mn oxide	CdS
5	Tin and titanium oxide with addition of gold	/

2.2. B1: tumor monitoring and metastasis identification

Tests with B1 (Fig. 2) have a dual purpose: first, they show how the eventual presence of blood in feces could affect the sensor responses, second they allow to obtain a fast and precise method to identify tumors through the analysis of blood exhalations. This should represent an efficient method for the health status monitoring of people who have undergone the removal of a tumor mass. The sensors composing the array of B1 are listed in the third column of Table 1. Tests have been performed by examining different populations of test subjects, both females and males, aged between 20 and 83 years old. They have been classified in four different groups:

- anesthetized individuals;
- tumor affected individuals (in particular colorectal cancer);
- metastasis affected individuals, who already underwent surgeries or chemo- and radio-therapy;
- healthy individuals (control group).

All blood samples have been put inside long test tube (2cc) with purple caps containing anticoagulant agent K3 EDTA, in order to prevent the coagulation of the specimens, keeping the same chemical bottom.

In Fig. 4 it appears that responses to TA are clearly higher than to CS. The effect of anesthesia is negligible. In Fig. 5, the Gaussian curves obtained from the mean and standard deviation calculated by combining the responses of B1, show a net distinction between CS and TA blood samples, in particular in the presence of metastasis.

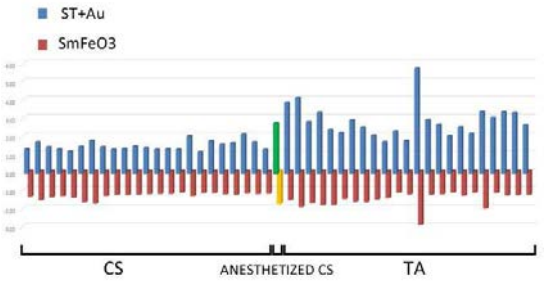

Fig. 4: responses of two sensors of the B1 array to 23 CS, 1 anesthetized CS and 23 TA samples. Responses to TA are clearly higher than to CS. The effect of anaesthesia is negligible.

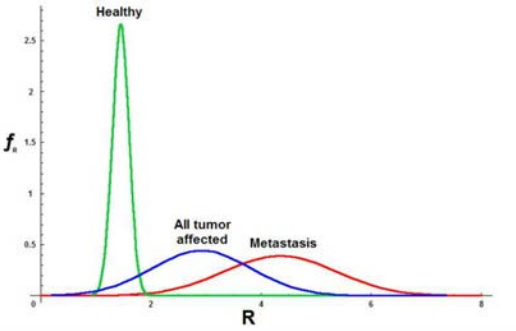

Fig. 5: Distributions obtained from the mean and standard deviation calculated by combining the responses of B1 array. The distinction between CS and TA blood samples is evident, in particular in the presence of metastasis.

3. Conclusions and future perspectives

Results are highly encouraging for both devices. In particular, with A1, the discrimination between feces of patients with colorectal cancer and feces of healthy controls with the chosen array is evident, with an error of 5% with QDA technique. In May 2016 has started the clinical validation of A1, in comparison to colonoscopy at the Hospital S. Anna (Ferrara) as a gold standard, having obtained permission from the ethics committee. People who resulted positive to FOBT have the opportunity of undergoing our non-invasive test. This protocol will serve to obtain the sufficient statistic for the certification of the device, the results of which will be published in a future work. Other tests with B1 will be carried out to increase the statistics before clinical validation.

Acknowledgements

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