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Portable Immunosensor Based on Extended Gate—Field Effect Transistor for Rapid, Sensitive Detection of Cancer Markers †

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Abstract: We present an immunosensor for the rapid and sensitive detection of the p53 oncosuppressor protein and of its mutated form $p53_{R175H}$, which are both valuable cancer biomarkers. The sensor is based on the accurate measurement of the source-drain current variation of a metal oxide semiconductor field-effect transistor, as due to the gate potential changing arising from charge release upon the selective capture of a biomarker by the partner immobilized on a sensing surface connected to the gate electrode. A suitable microelectronic system is implemented to combine high current resolution, which is needed to be competitive with standard immunoassays, with compact dimensions of the final sensor device.

Keywords: biosensor; immunosensor; cancer markers; EG-FET

1. Introduction

A biosensor is a device able to detect biomolecules due to their interaction with a metal or a semiconductor surface suitably modified with organic or biological nanostructures, whose properties are sensitive to the presence of the selected analyte [1]. The specific interaction between the target biomolecule and the sensing surface results in a recognition event, which is then transduced by electronic components (such as FET, MOSFET, OFET, CCD, CMOS,…) into a signal that can be processed. The obtained signal is analyzed by an embedded software and the response is transmitted to the final users by a read-out system.

Among biosensors, immunosensors are particularly efficient, due to the high specificity of the antigen-antibody interaction behind the biorecognition event, and they play an important role in a wide range of applications in biomedical clinical diagnosis, food safety, and environmental control [2]. Field-effect transistors (FET) immunosensors have been developed as promising alternatives to conventional immunoassays, since they present real-time and rapid response, require small sample volume, and exhibit high sensitivity and selectivity [3]. In such devices, the source-drain current (I_{ds}) is measured while applying constant voltages, both between drain and source electrodes (V_{ds}) and at the gate electrode (V_{gs}). The antigen-antibody conjugation occurs at the gate dielectric surface, suitably biomodified, and affects the I_{ds} due to charge release to the gate and then its potential.

Therefore, an unknown biomarker concentration in solution can be correlated to the corresponding I_{ds} variation.

Nevertheless, FET-based biosensors present two main limitations for future commercial uses: (1) a single target species can be detected; (2) the FET sensor is single-use, unless regeneration techniques are implemented. These limitations can be overcome by connecting the FET gate electrode with an external, disposable, sensing area (the extended gate, EG; Figure 1a). The gate potential is then tuned by the charge release occurring upon selective capture of the biomarker (antigen) by the complementary partner (antibody) immobilized on the EG surface [4,5]. This configuration is particularly appealing for commercial purposes, since the implementation of single-use EGs can open the perspective towards multipurpose sensor devices.

In this context, we have developed an EG-FET based immunosensor for the rapid and sensitive detection of the p53 oncosuppressor protein and of its mutated form $p53_{R175H}$, which are both valuable cancer biomarkers [6]. The sensor is based on the accurate measurement of the source-drain current variation of a commercial n-type metal oxide semiconductor field-effect transistor (MOSFET), suitably connected with a microfabricated EG (Figure 1b). A microelectronic system is also implemented, to combine high current resolution (i.e., high biomarker sensitivity) with compact dimensions of the final sensor device.

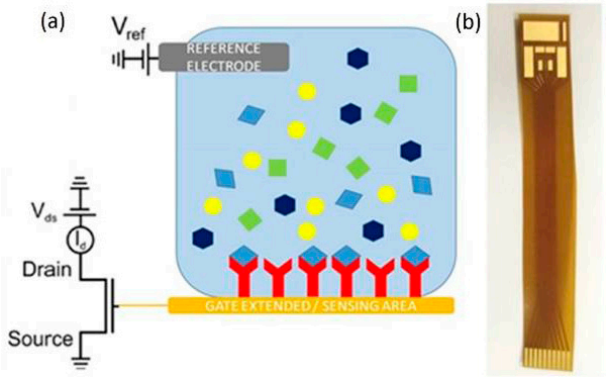

Figure 1. (**a**) Scheme of the EG-MOSFET sensing set-up, showing the MOSFET gate connected to the EG sensing area, suitably functionalized with the antibody (red Y) upon which the analyte solution is flowing. The reference electrode is also shown. (**b**) The microfabricated Kapton substrate hosting the gold coated areas and the Ag/AgCl reference electrode.

2. The Sensing Surface

The gate electrode of a commercial n-type MOSFET (ALD110900, Advanced Linear Devices Inc., Sunnyvale, CA, USA) has been connected with a 70 × 11 mm flexible Kapton substrate platform, 50 μm thick, with microfabricated gold coated areas, which are used as EG electrodes. An Ag/AgCl reference electrode has been integrated in the platform. The EGs have been functionalized with the antibodies of the biomarker to be captured, as previously reported [7]. During the sensing experiments, the EG is immersed in the analyte solution, whose potential is set by the Ag/AgCl reference electrode (V_{ref}) on the same Kapton substrate. The EG potential is then obtained by the combination of V_{ref} and charge accumulation due to the antigen-antibody interaction. As a consequence, the I_{ds} measured upon constant applied voltage between drain and source electrodes (V_{ds} = 0.1 V) becomes a valuable parameter to estimate the antigen concentration in the solution. In particular, upon functionalization of the EG with anti-p53, the I_{ds} measured as a function of V_{ref} decreases with the p53 concentration in solution (Figure 2). Concentration as low as 200 pM can be detected, by using an high sensitive current reading system.

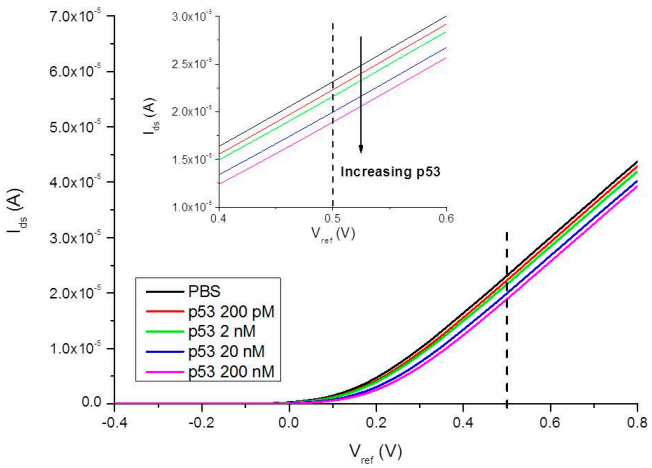

Figure 2. I_{ds} of an n-type MOSFET measured as a function of V_{ref}, by using a microfabricated extended gate functionalized with anti-p53 immersed in solutions at different p53 concentration (0, 200 pM, 2 nM, 20 nM, 200nM).

3. The Microelectronic System

To combine high current resolution with compact dimensions of the final sensor device the sensing surface (EG) and the transduction element (MOSFET) have been coupled with a microelectronic system composed of a precision voltage source (100 mV) connected to a Rshunt. This latter is, in turn, connected to the MOSFET drain electrode (Figure 3). When the MOSFET is in its linear region, the current flowing within the Rshunt is detected by an operational amplifier (zero drift, low bias). The analog output of the operational amplifier is then digitalized by using a 24bit sigma delta Analog to Digital Converter (ADC), while a microcontroller will process the value of ADC by using a specific algorithm (firmware, embedded software). Current variation in the I_{ds} signal as low as 10 nA can be detected by such an interface.

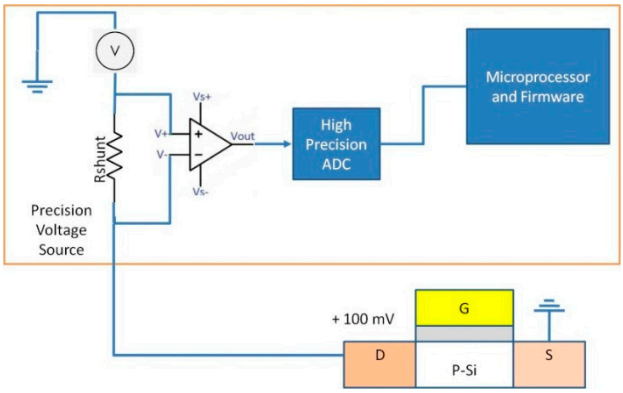

Figure 3. Scheme of the microelectronic sub-system for the sensor device.

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Conflicts of Interest: The authors declare no conflict of interest.

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