Memristive Aptasensors for Theranostics

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***Abstract*—A new application in the nano-biosensing field gives proof that the coupling of nanofabricated wires exhibiting memristive electrical characteristics and DNA-aptamers, may provide definitely innovative nano-bio-sensors for ultrasensitive label-free detection of cancer biomarkers, as well as, for effective screening of therapeutic compounds. This scheme, paves the way to a holistic approach where both the diagnosis and therapeutics can be taken into consideration.**

***Index Terms*—Memristive properties DNA-aptamers Cancer diagnostics Drug detection Silicon nanowires**

I. Introduction

There has been a growing interest in recent years involving the implementation of memristive structures and devices. Theoretically introduced for the first time by L. Chua [1,2], nanoscale devices exhibiting memristive behavior can be nowadays fabricated by various materials and show immense potential in plethora of applications [3-5]. A new application gives proof that the coupling of DNA-aptamers and silicon nanowire-arrays with memristive electrical response, leads to a high-performance biosensors for the detection of disease biomarkers as well as monitoring of therapeutic compounds. Charged residues uptaken on the surface of these special nanodevices, play a pivotal role on the resulting electrical response. This finding is theoretically illustrated through modelling and simulations [6], as well as, experimentally confirmed by the electrical characterization of a layer-by-layer formed multilayer of charged polyelectrolytes (PE), created by repeated electrostatic adsorption of oppositely or similarly charged PE layers [7]. In this framework, these devices are implemented as novel biosensors leverages the modification of the hysteretic properties before and after the bio-modification for achieving an efficient detection of biological processes [6-8].

II. Materials and Methods

A. Memristive Aptasensors nanofabrication.

The nano-biosensor suggested combines top-down nanofabrication approach for the realization of the memristive wires, as well as, bottom-up strategies for the acquisition of the final memristive Nano-Bio-Sensor.

First, silicon nanowire arrays exhibiting memristive electrical response are acquired through a top-down nanofabrication process using e-beam lithography, and Deep Reactive Ion etching process (DRIE) as described in [8]. This process finally results in suspended silicon nanowire-arrays anchored between two NiSi pads, that serve as the electrodes for the I-V

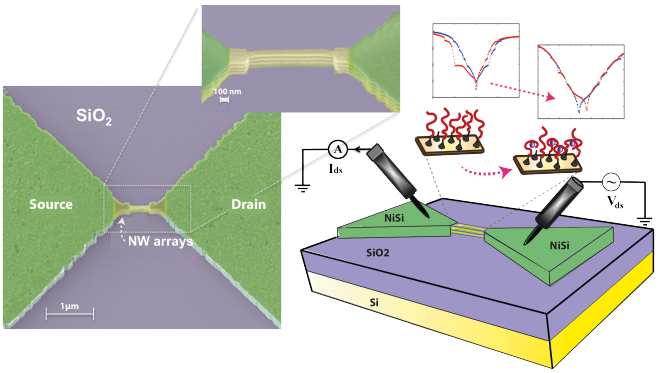

Fig. 1. Schematic representation and SEM micrograph depicting the nanowire arrays anchored between the NiSi pads

monitoring. Surface treatments implementing suitably selected biological materials and bio-functionalization strategies, give rise to memristive aptasensors.

More specifically, for the diagnostics application, the nanodevices are first subjected to surface treatment implementing affinity approach and biotin-streptavidin pair, and then, to incubation in 2 μM DNA-aptamer with affinity to Prostate Specific Antigen (PSA) [biotinylated anti-PSA DNA-aptamer (5'-[biotin tag] TTT TTA ATT AAA GCT CGC CAT CAA ATA GCT TT-3'] in Phosphate-buffered saline (PBS).

Meanwhile, in the therapeutics field, DNA-aptamers developed for specific interaction with Tenofovir (TFV) are used as probe molecules. First, the nanodevices are subjected to a gas phase silanization in order to form a homogenous layer of (3-Glycidyloxypropyl) trimethoxysilane molecules. What follows is the incubation of the nanowire substrates in a solution of 2 μM TFV-aptamer (5'-Aptamer-C6 Amino-3'). In both cases, prior to use, the DNA-aptamers were activated at 95 °C and then gradually cooled to room temperature.

B. Memristive Aptasensors analytical performance.

The electrical characteristics of the nanofabricated memristive structures are acquired using a probe station and a Keithley 6430 semiconductor characterization system in a two-terminal configuration by double sweeping the source to drain voltage between -2.4 V and +2.4 V. Electrical characterization performed on wires after the nanofabrication process indicates a hysteretic loop at zero voltage for the forward and the backward regimes of the current. In these devices, the memory effect depends on the charge carrier rearrangement at the

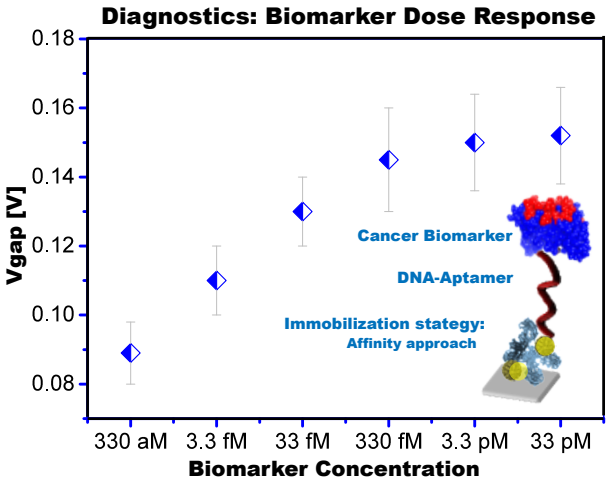

Fig. 2. Calibration curve related to the average voltage gap versus the dose-response of the biomarker concentration.

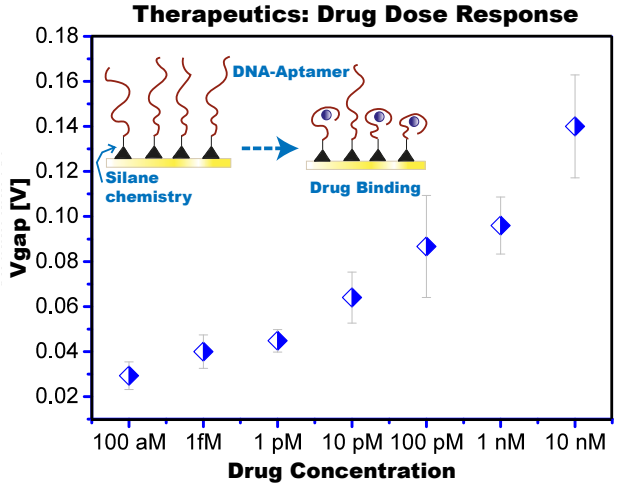

Fig. 3. Calibration curve related to the average voltage gap versus the dose-response of the therapeutic compound concentration.

nano-scale due to external perturbations, such as an applied voltage bias. However, when biological substances are present on the surface of the device a voltage gap between the two current minima is introduced in the semi-logarithmic electrical characteristics (fig.1) that is affected by the type and concentration of biomarkers introduced, thus leading to a label-free bio-detection method [6-8].

III. Results and Discussion

A. Memristive Aptasensors for diagnostics.

In the diagnosis field, the implementation of nanofabricated memristive aptasensors successfully addresses the issue of the early detection of cancer biomarkers, obtaining a high performance, ultrasensitive electrochemical biosensor for the label-free detection of PSA, thanks to the capability of detecting extremely small traces of cancer markers [7]. PSA is the main biomarkers of prostate cancer, one of the most common cancer types worldwide, and is hereby used as a model biomarker for the bio-detection. The fabricated memristive aptasensors are implemented for PSA sensing via consecutive incubations in increasing biomarker concentrations in the range of [aM-pM]. The obtained dose-response for the specific target, namely, the average voltage gap with increasing antigen concentration, is presented in fig.2, where an increasing trend is acquired with respect to the antigen uptake reaching an average value of 152 mV for a concentration of 33 pM.

B. Memristive Aptasensors for therapeutics.

Furthermore, a new class of memristive aptasensors is suggested for continuous monitoring of therapeutic compounds with TFV, an anti-HIV drug, implemented as model drug. Solutions of TFV are applied in the concentration range of [aM-nM] and the average voltage difference with increasing TFV concentration is presented in fig.3. An increasing trend of this parameter of the hysteresis is depicted following the dose increase. The detection is performed for drug concentrations belonging within and slightly below the clinical range, opening to the possibility for future applications with also highly diluted clinical samples. This is a quite important result that clearly demonstrates the efficiency of the proposed method.

IV. Conclusion

In the present work, novel nano-biosensors based on the combination of the memristive properties of nanofabricated wires and the DNA-aptamers character provide a complete approach considering both diagnostic and therapeutic applications. In the diagnostics field the nanofabricated memristive aptasensors successfully achieve sensing of cancer biomarkers at low concentrations obtaining a ultrasensitive, label-free biosensor. In addition, in the therapeutics domain, the suggested memristive aptasensors efficiently address the issue of drug detection showing great promise in medical practice especially in the field of personalised medicine, which still lacks of analytical methods for the continuous monitoring of therapeutic compounds.

Acknowledgment

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References

(1) L. Chua, IEEE Trans. Circuit Theory, 18, 5, 1971.
(2) L. Chua, Appl. Phys. A, 102(4), 765-783, 2011.
(3) G. Rose, J. Rajendran, H. Manem, R. Karri, and R. Pino, Proc. IEEE, 100(6), 2033-2049, 2012.
(4) R. Waser and M. Aono, Nat. Mater. 6833-840, 2007.
(5) Y. Pershin and M. D. Ventra, Neural Netw. 23 (7),881-886, 2010.
(6) I. Tzouvadaki, F. Puppo, M.A. Doucey, G. De Micheli, S Carrara, IEEE Sensors Journal, 15(11), 6208-6217, 2015.
(7) I. Tzouvadaki and P. Jolly, X. Lu, S. Ingebrandt, G. de Micheli, P. Estrela and S. Carrara, Nano Lett. 16, 4472-4476, 2016.
(8) I. Tzouvadaki, C. Parrozzani, A. Gallotta, G. De Micheli, S. Carrara, BioNanoSci. 5(4),189-195, 2015.