Memristor-Based Devices for Sensing

Francesca Puppo[†], Marie-Agnès Doucey[‡], Massimiliano Di Ventra[§], Giovanni De Micheli[†] and Sandro Carrara[†*]
[*]Integrated System Laboratory (LSI), École Polytechnique Fédérale de Lausanne, 1015 Lausanne, CH
[†]Ludwig Center for Cancer Research, Université de Lausanne, 1015 Lausanne, CH
[§]Department of Physics, University of California, San Diego, La Jolla, CA 92093-0319, USA
[*]Corresponding author: sandro.carrara@epfl.ch

***Abstract*—In this paper we propose CMOS-compatible Memristive-Biosensors as label-free, highly sensitive sensors for in-air detection of Vascular Endothelial Growth Factor (VEGF) molecules. The memristive behavior of the fabricated devices is strongly affected by molecules in proximity of the wire surface. In this paper, we demonstrate the reproducibility of the measurement based on the memristive voltage gap. We also show the successful sensing of femto-molar amounts of VEGF. Specifically, we demonstrate a correlation between the decreasing behavior of the voltage gap and the increasing concentrations of VEGF. The voltage gap dependence on the pH of the initial solution is also shown as a further proof of the ionic interactions occurring at the SiNW surface. All measurements are performed in air, under controlled humidity; this makes our approach more sensitive thanks to the lowered Debye screening effect of counterions.**

I. Introduction

The interest for memristive devices has been rapidly increasing in recent years, thanks to the very different applications they can be used for [1], [2]. The majority of current research on memristive systems is dedicated to the study and implementation of memories. Thanks to their potential for both high connectivity and high density, memristors have been used to design cellular neural networks and brain synapses in neuromorphic circuits [3]–[5]. Given their higher density storage and low cost, all the non-volatile two-terminal memristive technologies are also suitable candidates to replace flash memory [1]. Recently, new investigations on the memristive effect in Silicon Nanowires (SiNWs) have pointed out the great opportunity of using the memristive effect in nano-scale structures for biosensing [6]–[8]. Many works already exist in literature on the use of SiNWs for molecular detection [9], [10] However, the sensing with nanowires is only exploited by the Ion-Sensitive Field-Effect Transistor (ISFET) paradigm. According to this approach, the detection occurs upon direct measurement, in liquid environment, of the change in the DC conductance of the nanowire due to attachment of target molecules on the functionalized surface [11].
In this paper, we instead report new insights for a completely novel molecular sensing in dry conditions based on nanofabricated memristors functionalized with bio-molecular thin films. The pinched hysteresis loop [3] is affected by biomolecules in the fabricated NWs. Biological species induce a variation in the so called voltage gap [6]–[8]. Here, we demonstrate that this voltage difference can be used to sense femto-molar concentrations of biomarkers, such as the Vascular Endothelial Growth Factor (VEGF). We also report recent findings on the role of the ionic mobility in forming liquid thin films [12] on the memristive voltage gap in our sensors.

II. The Memristive-Biosensor in air

The memristive SiNW is modified with antibodies and then incubated in solutions of target molecules. The antigen proteins approaching the SiNW surface bind to the complementary antibodies. The sensor is then dried and the electrical measurements are performed in controlled dry conditions [8]. The proposed approach is novel with respect to the well known sensing method in solution used in standard ISFET-based biosensors. First, improved sensitivity in dry conditions is ensured by an increased Debye length deriving from the absence of counterions from the electrolytic solution [13]. Second, the detection measurement is based on the so called voltage gap, that is the difference in potential between the forward and backward current minima of the memristive IV characteristics [7], [8], [14]. The voltage gap is used as reliable parameter for high sensitive detection.

III. Experimental procedures

A. Fabrication of Memristive SiNWs

The memristive SiNWs were fabricated using Silicon-On-Insulator (SOI) substrates. The process flow is summarized in Fig. 1. First, Electron-Beam Lithography (EBL) and Lift-Off were used to define two Ni areas from a 30nm-thick layer of Nickel evaporated on the silicon device (a-c). Then, silicidation of Nickel was obtained by annealing performed by successive exposition of 20 minutes in forming gas at 200°C, 300°C and 400°C, respectively. Thus, two NiSi pads were formed (d) and lately used as metallic contacts for electrical characterization [8]. Hence, SiNWs were defined using a second EBL mask (Fig. e) and a specially tuned Deep Reactive Ion Etching (DRIE) (also called Bosch process) [14]. This technique is used to produce a scalloped trench in a monocrystalline silicon substrate. Repeated DRIE cycles lead to vertically-stacked, free-standing SiNWs anchored between two NiSi pillars (f).

B. Set-up for electrical characterization

Source to drain I_{ds}-V_{ds} characteristics were acquired by double sweeping V_{ds} between -5 and +5 Volts, at a fixed back-gate potential V_{bg} of 0 Volts. These measurements enabled us to observe the changing memristive voltage gap as function of the gating effect of VEGF molecules [6], [7]. All measurements were performed on dried samples, in Room Temperature (RT) and under controlled humidity [8].

C. Chemicals

Chemicals unless stated otherwise were purchased from Sigma-Aldrich (St-Louis, MO).

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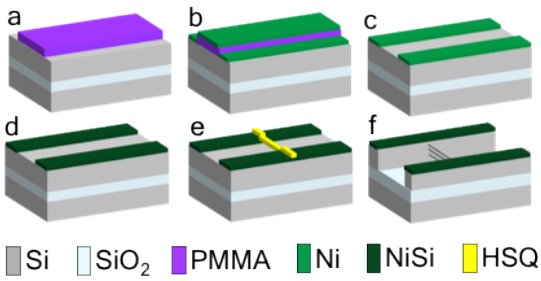

Fig. 1. Schematic process flow summarizing the fabrication of memristive free-standing SiNWs.

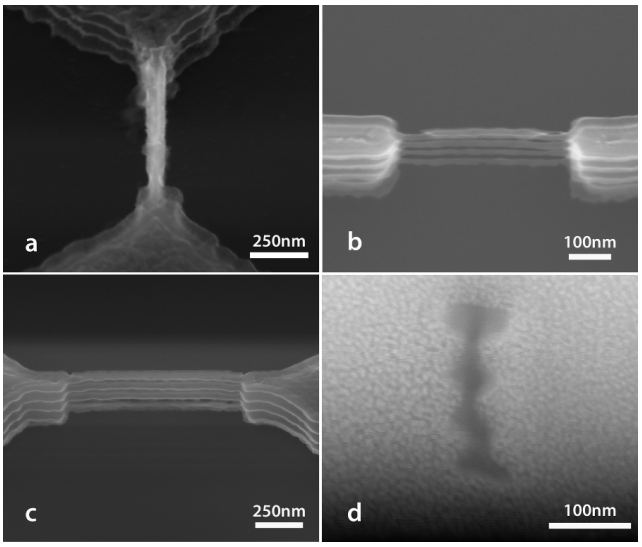

Fig. 2. Fabricated SiNW based memristive-biosensors. (a) Zoom in top view on free-standing SiNWs bridging NiSi pillars. (b,c) Tilted SEM images on vertically-stacked NWs with different sizes. (d) Cross-section showing the scalloped trench.

1) Surface functionalization for immuno-detection: Memristive SiNWs were modified by covalent attachment of anti-VEGF monoclonal antibody (R&D Systems, clone 26503) with GPTS (glycidoxypropyltrimethoxysilane) [15]. The detailed procedure has been already described in [7], [8]. After cleaning in Piranha solution, the silicon substrate was incubated in ethanol containing 10 mM acetic acid and 1% GPTS. The surface was dried under a N_2 stream and then for 15 min at 110°C in a dried oven. The surface was incubated over night in a humid chamber at RT with PBS (Phosphate Buffer Saline) containing 0.5 mg/ml of anti-VEGF solution. The remaining active GPTS-derived groups were blocked by ethanolamine 10 mM. Once removed the excess of ethanolamine, the surface was blocked by an additional incubation with PBS containing 3% gelatin from cold water fish skin. The modified surface was washed and stored in PBS at 4°C until use.

2) Immuno-sensing protocol: The prepared memristive-biosensors were exposed to different concentrations of the target molecules by incubation for 1 hour at RT in PBS solution containing VEGF proteins. For each concentration of VEGF solution, the sample was incubated, washed in PBS to remove the unreacted antigen molecules, and gently dried under N_2 flow. The memristive device was then used for electrical characterization (Section III-B). Once the measurement was finished, the whole process was repeated with an increased concentrations of VEGF.

3) pH measurements: Measures on pH were performed in order to test the effect of ionic species on the memristive-biosensor. Saline solutions with different pH were prepared and used for the experiments. The pH of a starting 150 mM NaCl solution was moved towards either bigger or smaller values by adding small volumes of NaOH or HCl, respectively. The pH was tested by mean of a pH-meter (pHenomenal pH Lab Set pH1000L by VWR).

IV. Results and Discussion

A. The Memristive-Biosensor at the nano-scale

Fig. 2 presents some images of the fabricated memristive SiNWs. A top view SEM image of the device (a) shows the reached limit sizes of the wire diameter. The SEM image clearly show NiSi pads connecting the SiNWs, as demonstrated by the different brightness of Silicon and Nickel-Silicide surfaces. The tilted SEM images (b, c) show vertically-stacked, free-standing SiNWs obtained via top-down silicon processing (Section III-A). Memristive-biosensors with different sizes were fabricated in order to test the repeatability of the process and the performances of the bio-sensing too. Fig. 2(b) and 2(c) reports NWs 35 $\pm$ 10 nm wide and 411 $\pm$ 14 nm long, and NWs 90 $\pm$ 9 nm wide and 1000 $\pm$ 14 nm long, respectively. The images show the scalloped trench produced in the Silicon layer by the performed Bosch process. The cross-section of one device is illustrated in Fig. 2(d). It clearly shows the grooves produced in the monocrystalline Si layer that are defining the vertically-stacked NWs.

B. The effect of biomolecule: the lost ideal pinched hysteresis

Fig. 3 and Fig. 4 shows the logarithmic source to drain current versus bias potential in the case of 4 SiNWs 35 $\pm$ 10 nm wide and 411 $\pm$ 14 nm long tested before and after the surface functionalization with anti-VEGF. The electrical measurements were performed under controlled relative humidity of 60% and at RT [8]. Fig. 3 clearly demonstrates that the memristive effect of the fabricated NWs matches well with the memristor theory [3], as confirmed by the pinched hysteresis loop in bare NWs. The same is lost upon bio-functionalization of the device (Fig. 4). Antibodies show a net charge contribution and act as a gate by creating an electric field surrounding the source-drain channel of the biosensor. This electric field induces a voltage gap effect appearing as the voltage difference between the current minima for backward and forward regimes [6]–[8].

C. The voltage gap as repeatable sensing parameter

I_{ds}-V_{ds} characteristics were acquired at RT and under controlled humidity of 60% on a sample of 18 NWs with length 411 $\pm$ 14 nm and a width of 35 $\pm$ 10 nm. In Fig. 3 and 4 only 4 curves are reported for clarity in the diagram. The characteristics clearly show the non-repeatability of the current parameter, as highlighted by the different values in the y-coordinate. Unlike the current data, not reaching the level of reproducibility needed for bio-detection based on conductance changes, voltage gap measurements demonstrated a well repeatable behavior. Specifically, the devices were clearly

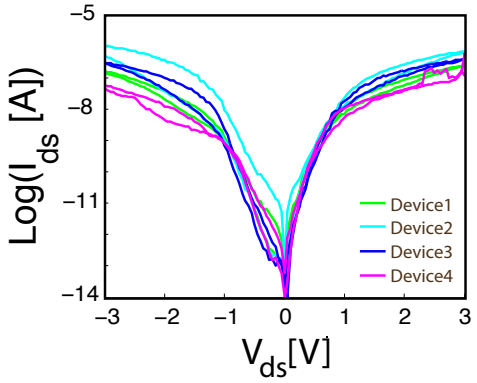

Fig. 3. Pinched hysteresis loop in bare SiNWs.

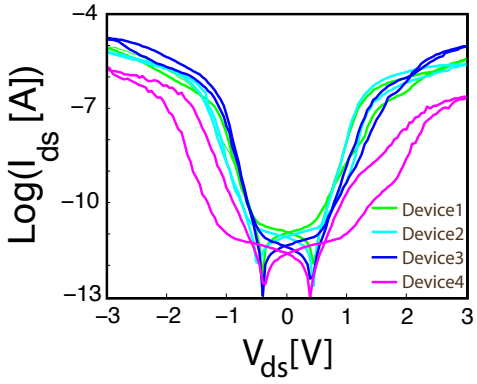

Fig. 4. Voltage gap appearance in NWs modified with anti-VEGF.

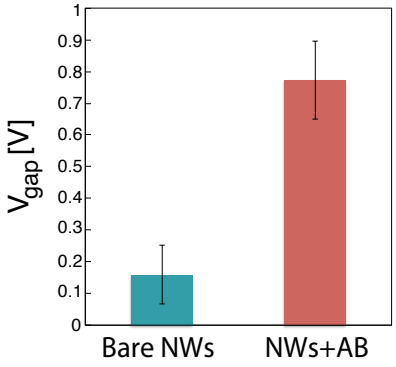

Fig. 5. Statistical distribution (N=18) of the voltage gap before and after the bio-modification.

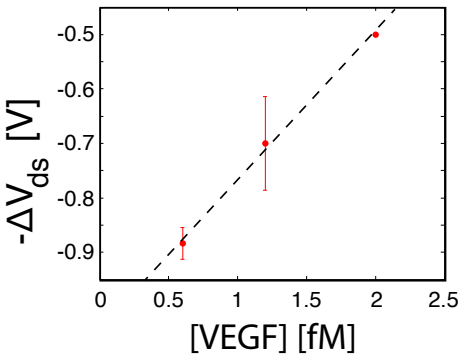

Fig. 6. In air detection of VEGF 0.6 fM, 1.2 fM, and 2.1 fM with the memristive-biosensor. Statistic on a set of 4 devices.

behaving as pure memristors before any modification was performed; as consequence of the biomolecule proximity to the channel, the same wires, tested after the surface modification with anti-VEGF, evidently showed the appearance of a voltage gap. As further proof of the reproducibility of the parameter trend, Fig. 5 shows the distribution of the memristive voltage gap over the complete set of 18 memristive devices. The error bars stand for the standard deviation of the measurement. This error is largely dependent on the top-down fabrication process which cannot results in perfectly equivalent structures. In addition, the measurement set-up, is not trivial. The environment conditions affect the acquisition [8]. The voltage value at which forward and backward curves cross the zero-point current is not null, and defines a non-ideal pinched hysteresis. The pure ideal memristor is not easy to find in literature, neither to fabricate. In our case the memristive effect is probably due to the nano-scale dimensions of the device [6], [7], [14], and it is strongly affected by charged molecules found in proximity of the surface. Specifically, water molecule adsorption onto bare SiNWs contributes to this effect [8], slightly increasing the voltage gap in bare NWs too.

D. Femto molar in-air detection of VEGF with the memristive voltage gap

Fig. 6 shows the calibration curve for VEGF molecules. Four similar memristive-biosensors were tested on air with three different antigen concentrations (0.6 fM, 1.2 fM, and 2.1 fM) accordingly to the procedure explained in Section III-B. The error bars stand for the standard deviation calculated on a set of 4 devices. The experiment clearly demonstrates the high sensitive capability of the proposed sensor that takes advantage of the lowered screening effect of counterions in the dry environment [13]. The voltage gap decreases in the considered femto-molar range as function of the antigen concentration, thus enabling the detection of VEGF molecules. The results confirm data in literature [7], and evidently show the effect of bio-molecules on the memristive effect. As a consequence of the different interactions of free antibodies and antibody-antigen complexes, the rising behavior of the voltage gap in anti-VEGF NWs is now decreasing upon uptake of increasing concentration of VEGF. This drop brings the device back to the ideal memristor case [3]. The voltage-gap sensing approach is based on charge redistribution and charging effect in memristive NWs deriving from the different charge residues of biomolecules in proximity of the sensing interface. To prove that, further measures on pH were conducted. They are summarized in the following Section IV-E.

E. Ionic interactions

The role of charges in the voltage gap approach was studied by testing the memristor sensor in air after subsequent expositions to solutions with different pH (Section III-C3). The results demonstrated that ions, such as [H^+] and [OH^-] ions, has a strong effect on the memristive phenomena, too. Fig. 7 refers to the mean behavior of the voltage gap as function of increasing pH, that were set to 3.2, 6.2, and 14. Each

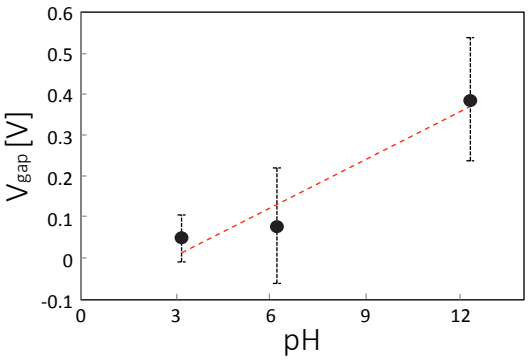

Fig. 7. Effect of pH on the memristive voltage gap.

value points was calculated as mean value on a sample of 5 NWs. The error bars stand for the standard deviation. The voltage gap behavior clearly showed an increase as function of the increasing pH; i.e., an excess of negative ions, such as $[OH^-]$ in the solution, leads to the increased voltage memory in the NW. The rising behavior here illustrated demonstrates the role of charges in the propose memristive-biosensor in air. In addition, it also suggests that the dry environment in which we are supposed to work is not completely dried. Indeed, the sensitivity of the hysteretic $I_{\rm ds}$-$V_{\rm ds}$ to the pH proves that a water thin-film is formed at the NW surface. Water adsorption can easily occur on silicon dioxide surfaces when exposed to the humid environment [8]. It also happens when the surfaces are coated with a monolayer of highly concentrated salts, due to the adsoprtion of H_2O molecules on the formed salt cluster [16]. Even more evident, it occurs with antibodies and antigens too, due to the water shell of proteins [17]. Memory effects also confirm the existing liquid-like thin film onto the sensor [12]. In this film, the dissolved ions from the starting solution are free to move toward the hydroxyl groups of the native oxide onto the nanowires, and consequently polarize the sensor surface.

V. Conclusion

In this paper, new insights on the use of silicon nanowires for label-free, highly sensitive memristive-biosensors are reported. The fabricated NWs show a pinched hysteresis characteristic, and thus match well with the memristor theory. The memristive devices are functionalized with anti-VEGF antibodies and used for the detection of VEGF, biomarker highly active in tumor tissues and vascular diseases. The modification of the NW surface with biomolecule affects the memristive hysteresis of the device, and a voltage difference between the current minima appears. Contrarily to the current values, the voltage gap phenomenum is highly repeatable under controlled dry conditions, and can thus be feasibly used for biodetection. The calibration of the memristive-biosensor for VEGF analytes, in air, is also shown; it confirms that high-sensitive measurements in the femto-molar range can be performed. The role of charges in the memristive sensing approach is also justified by the voltage gap dependence on inorganic ions, such as $[H^+]$. The latter, together with the memory effect, also demonstrates the formation of a liquid-like thin film at the sensor surface.

Acknowledgment

The authors would like to acknowledge Michele De Marchi for device processing and imaging assistance and very stimulating discussion. This work was supported by the multidisciplinary FNS grant (CR32I3 135073) and by an ERC grant (ERC-2009-Adg-246810).

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