Memristive Biosensors Integration With Microfluidic Platform

Alessandro Vallero, Ioulia Tzouvadaki, Francesca Puppo, Marie-Agnès Doucey, Jean-François Delaloye, Giovanni De Micheli, and Sandro Carrara

***Abstract*— The integration of nanoscale sensors with microfluidic platforms is a powerful tool for the design of robust biosensing devices that present high reliability and the advantage of a quick data acquisition. In addition, microfluidic based lab-on-a-chip sensors require minute amounts of clinical samples and cancer biosensing products. However, the integration of nanostructures in such more complex configurations may significantly complicate the electrical readout process. The aim of the present work is to develop improved devices for cancer prognosis based on nanofabricated Memristive Biosensors integrated for the first time with a microfluidic structure. The effective readout of the Memristive Biosensors electrical response is enabled through a series of specially designed metal line extensions realized accordingly in order to fully retain the sensing output signal.**

***Index Terms*— Aluminium connections, memristive biosensor, microfluidics, silicon nanowire.**

I. Introduction

NOWADAYS, plethora of nanotechnology applications is reported in healthcare field, especially related to the development of more precise nanofabricated devices for prognosis and treatment of various diseases [1]. Furthermore, a lot of research effort has been made for the integration of microfluidics to different types of nanofabricated biosensors dealing with fluid samples, since this strategy allows us to reduce waste of material and detection time by guiding the sample directly to the core of the sensor [2] [3] [4] [5] [6] [7] [8]. Recently developed sensors targeting at the detection of biological aerosols transfer air particles into liquids in order to take advantage of microfluidic configurations [9]. Moreover, microfluidics can be implemented for automatic functionalization and detection step for multiple chips [10].

Nanofabricated Memristive Biosensors have been reported for cancer biomarkers detection application [11] [12] [13] [14] [15] [16]. The core of the Memristive Device consists of two-terminal, vertically-stacked, Schottky barrier, silicon nanowire devices obtained by electron beam lithography and Bosch etching process. The nanowires are anchored between two Nickel Silicide (NiSi) pads to which a potential difference is applied. The devices show a memory behavior equivalent to a memristor [17] [18] electrically contacted by two asymmetric Schottky barriers [19]. The first use of the term memristor is attributed to Leon Chua in 1971 [17], who first postulated the existence of a fourth basic circuit element in addition to resistor, inductor and capacitor, which provides a functional relation between charge and flux. In 2011, new efforts on applications of memristive systems started, following the statement that all two-terminal non-volatile memory devices based on resistance switching are memristors [20].

The biodetection through the implementation of Memristive Biosensors is performed by measuring the variation of a voltage gap introduced between the two hysteretic current minima in the semi-logarithmic current to voltage characteristics that rises after functionalization of the device with biological molecules. This gap is affected by the concentration of receptor molecules, like cancer biomarkers, that bind to the sensor, leading to a label free detection of biomarkers in the fM range [11] [12] [16].

The Integration of such Memristive nanowire based Biosensors in platforms combining microfluidics and develop lab-on-a-chip devices requiring minute amounts of clinical reagent may increase likelihood of effective cancer biosensing while reducing detection time and waste of material. Until now, the biofunctionalization procedure was based on exposure of the sensor to target molecules by standard drop casting method, in which a drop of solution is introduced in the area of the sensor. However, the drop expands also at areas beyond the area of interest and consequently chemicals and organic molecules are wasted during the process and larger amount of solution is required in order to compensate. With the implementation of a microfluidic, instead, chemicals and organic molecules are concentrated in the area of interest allowing the use of smaller amounts of both solutions for functionalization and sample to analyze. Moreover, the introduction of microfluidics in the integration concept enable an easier transport of the system, since it is sufficient to block the inlet and outlet of the channel to keep all biological reagents in humid environment, a crucial condition for organic molecules safe storage. A further advantage of such integration is that it may facilitate an automatic biofunctionalization and detection steps paving the way for real time monitoring and biodetection process.

However, the incorporation of nanostructure configurations to a microfluidic platform is not straightforward since it complicates the electrical readout process of the nanosensor. The electrical readout acquisition is based so far on the NiSi pads that serve as the electrical contacts of the nanofabricated device, thus, the detachment of the microfluidic is necessary in order to perform the electrical characterization.

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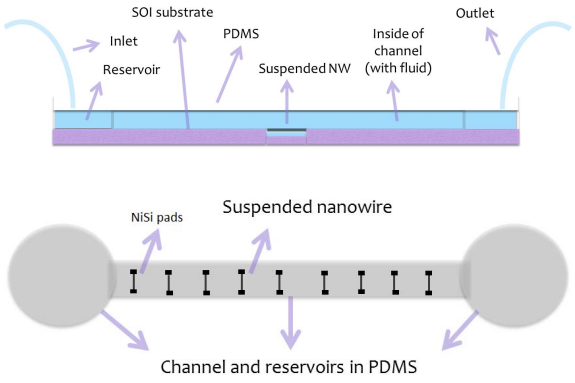


Fig. 1. PDMS microfluidic (side view in the top image, top view in the bottom one).

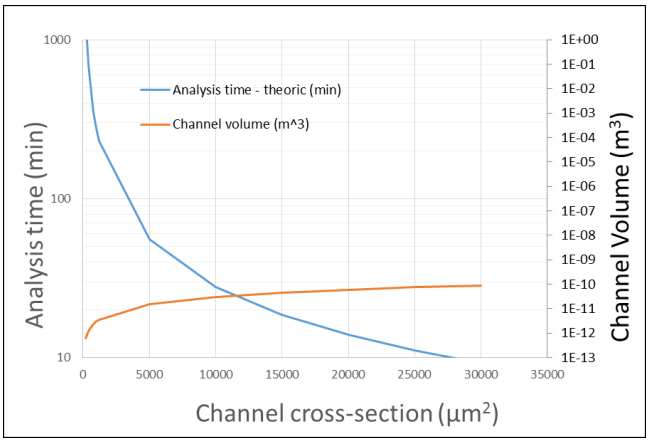


Fig. 2. Analysis time and channel volume as functions of channel cross-section.

This detachment of the microfluidic causes serious damages to the experimental platform affecting the functionality of the sensor. Typically the integration with fluidic systems requires long connections to bring signals to the electronics frontend. A different type of device, in which Aluminum (Al) lines extensions to NiSi pads are designed and realized. The Al connections allow more flexible electrical characterization of the system instead of directly on the NiSi pads, enabling integrated measurement procedure. Nevertheless, the electrical response of the Memristive Device is importantly affected by the further introduction of resistive elements in the circuit. Specifically, the introduction of additional resistance might diminish or even completely mask the memristive effect of the device and consequently there is possible risk to affect the functionality of the biosensor. To this end a computational study [13] has been carried out to investigate the additional resistance tolerance of the system and finally to define the possibilities and the restrictions of the integration of Memristive Biosensors with additional elements that would enable an effective readout in more complex platforms.

In this work, the Memristive Biosensor platform is accordingly integrated with additional metal elements for enabling the effective electrical readout following the restrictions raised by the computational study outcomes. Most importantly, the design and realization of a microfluidic is carried out as well as the integration for the first time of the microfluidic configuration with the Memristive Biosensor platform targeting at the detection of breast cancer markers.

II. Microfluidic Design

The microfluidic consists of PDMS (polydimethilsiloxane) [21] [22], which is an economic and flexible material, compatible with plethora of solvents used in organic reactions [23]. The fluidic is designed in order to have a central channel with a reservoir at both edges to achieve better flux lines as well as to make the introduction of inlet and outlet easier. Reservoirs and channel have the same thickness of $20\mu m$. The sensor part is composed by a set of nine arrays of suspended nanowires in the middle of the channel which are perpendicular to the flux (see Fig. 1).

Since the main advantage of the microfluidic is to keep the solution in a small area around the nanowires, the channel should be the smallest possible. Different widths and thicknesses of microfluidic have been tested, while the length has been kept constant and equal to $3mm$, which is required in order to obtain nanowires separated by $300\mu m$. This ensures a more homogeneous flux and enough space between metal lines to avoid discharges. Experiments performed showed that, with thickness and width below $20\mu m$, the channel resistance to the flux is too high to allow the solution to pass through. Moreover, it is also necessary that the total analysis time is restricted to the minimum possible, to provide a fast medical analysis. As shown in Fig. 2, these two conditions lead to the choice of designing a channel with a height of $20\mu m$ and width of $500\mu m$, resulting in a cross section of $10\,000\mu m^2$ (where time has been calculated by considering also the time needed for the fluid to pass through the pump tubes).

III. Materials and Methods

A. Nanodevice Fabrication

The Memristive Devices are fabricated through a topdown fabrication process, using commercially available (100) oriented Silicon-On-Insulator (SOI) wafer. The nanostructures are defined using electron beam lithography, etched trough a Deep Reactive Ion etching process (DRIE) of crystalline silicon and anchored between two NiSi junctions. When biological substances are present on the surface of the device the hysteresis, originally pinched at zero voltage, appears shifted to different voltage values: a voltage gap between the two minima is introduced in the semi-logarithmic electrical characteristics. The gap is affected by the concentration of biomarkers (see Fig. 3), leading to a label-free biodetection method [11] [12].

For the realization of the Al metal lines for the electrical connections, first a photolithography mask for the Al lines configuration is designed and fabricated. The design of the mask is prepared using Cadence Virtuoso software and the layout of the lines is imported onto a commercially available (100) oriented SOI wafer that already includes the silicon nanowire devices anchored between two NiSi junctions.

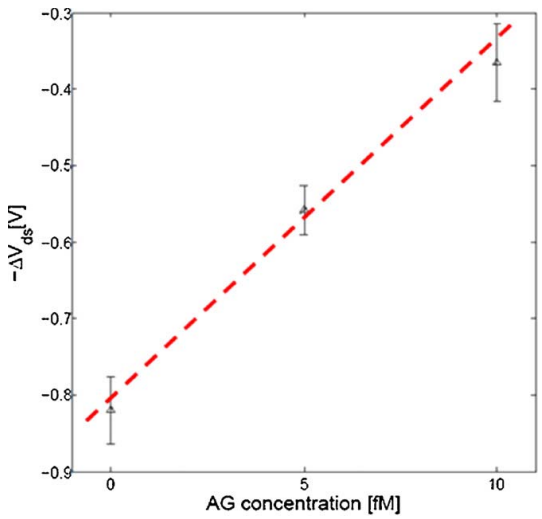


Fig. 3. Voltage gap values with respect to antigen concentration [16].

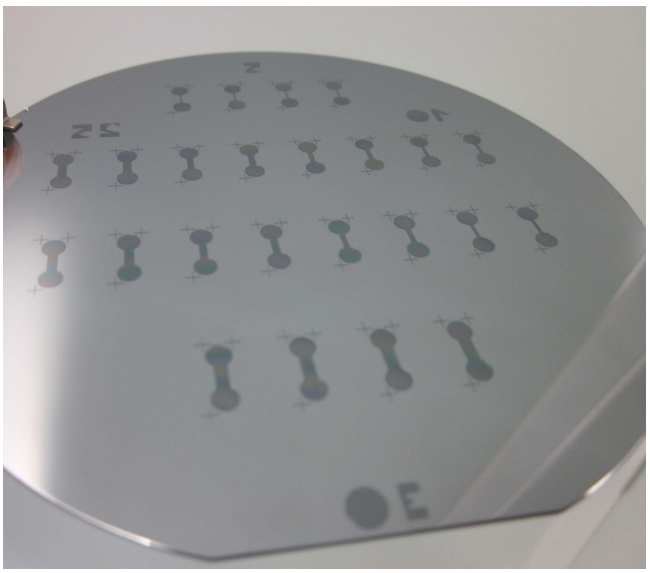


Fig. 4. SU-8 mold. The numbers identify the channels with different widths.

The wafer is first coated with a bilayer photoresist consisting of AZ1512 positive photoresist and LOR (Lift-Of-Resist), used for exposure and liftoff process respectively. The metal lines are created through Physical Vapor Deposition (PVD) of 100nm Aluminium on the wafer surface followed by a liftoff in SVC-14 solution. Finally the wafer is diced in single chips in order to allow the integration with the microfluidic platform and used for biodetection purposes.

B. Microfluidic Fabrication

The microfluidic circuit allows us to optimize both washing and detection steps by establishing a constant flux of fluid on the nanowires. The channels consist of PDMS (polydimethylsiloxane) [21] [22], a silicon-based organic polymer.

In order to achieve a good attachment of PDMS to SOI, a SU-8 [24] mold is implemented. The SU-8 is a negative resist. A 20μm thick SU-8 layer (GM 1060) is poured onto a simple test wafer of Silicon of 100mm of diameter, then steps of spin coating, softbake, exposure (which utilizes a mask related to the fluidic structure designed by the software Virtuoso), post-exposure bake and development in PGMEA and isopropanol solution follow. The mold appearance is shown in Fig. 4.

Sylgard 184 has been used for the PDMS Silicone base and curing agent. The base and the curing agent are poured into a plastic container on a scale in a 10:1 ratio, in order to obtain a PDMS piece with the right elasticity, then mixed and degassed. The mold surface is treated with TMCS (chlorotrimethylsilane) in order to ease the de-molding step before pouring the fluid, degassed PDMS over it and baking in an oven at 80°C for one hour. The PDMS piece can then be detached and punctured to create inlet and outlet holes.

The surface of the nanowires has to be activated before functionalization and microfluidic attaching in order to have hydroxyl groups (OH) that can bind silanes. Silanes are used as crosslinks to bind antibodies to the nanowires. The usual way to activate the surface of the nanowires is by piranha etching. However, piranha is an etchant for Aluminium. So, in this case, a localized plasma oxygen, which does not harm the Al lines, is used. The localization of the plasma flux and the high power allow for the formation of long lasting hydroxyl groups on the surface of the nanowires.

After surface activation of nanowires by localized plasma oxygen, the PDMS is introduced in a normal plasma oxygen to activate its surface and bind it to the SOI. The exposure time of PDMS to plasma and the power applied have to be tuned accordingly, since a too low power or time can result in a not complete generation of hydroxyl groups (OH), while too much can result in overoxidation (i.e., formation of rough brittle layers of silica that prevent the establishment of a complete surface contact). The microfluidic channel is then aligned with the nanowires on the chip by a PDMS aligner, a tool that was designed and fabricated appropriately for this application in order to enable the alignment process between the nanowire and microfluidic configuration, and the attachment is performed.

C. Nanodevice Functionalization

A Gilson Minipuls 3 peristaltic pump is used to perform the functionalization procedures. The velocity that nanowires can withstand without breaking is not high (about $3mm/s$), so the pump rotational speed is kept low (0.50 rpm) when the PDMS channel is connected to the tubing. An overview of tubing, channel and pump connections used are shown in Fig. 5(a), while details of pump tubes connected to outlet, inlet and to the chip with the microfluidic is showed in Fig. 5(b), 5(c), and 5(d) respectively.

To reduce bubbles in the circuit, different connection setups have been tested and the best one resulted with tubing of 0.25mm of inner diameter, inlet and outlet holes of 1.2mm diameter and metal connectors of 0.8mm diameter. This con-

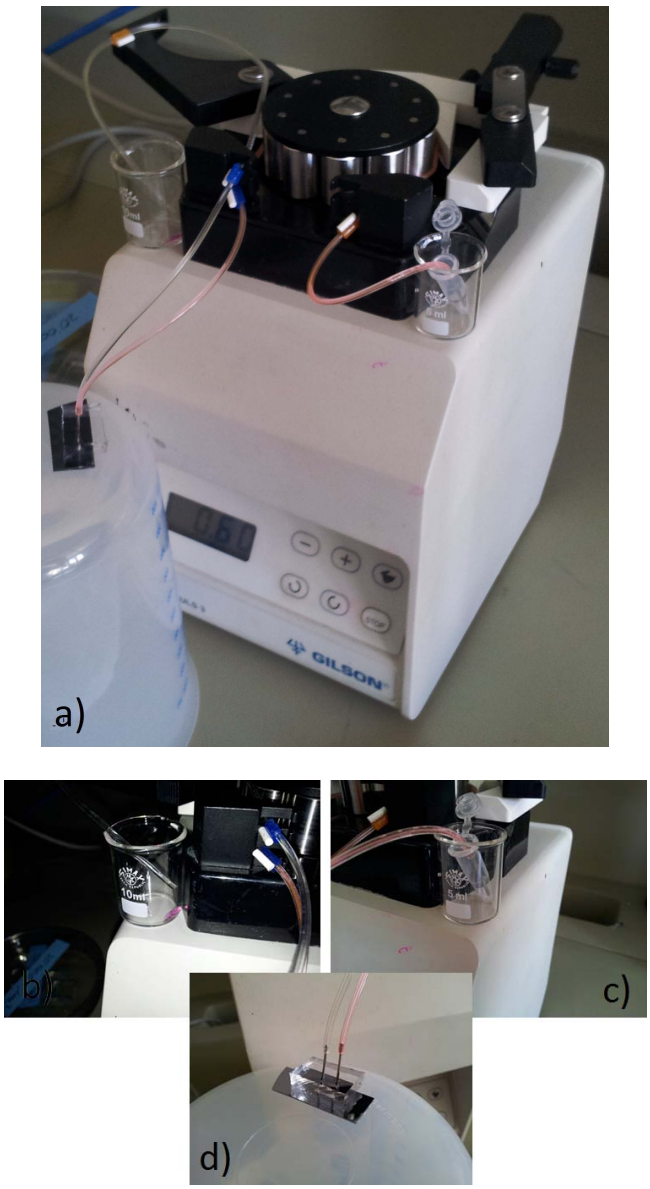


Fig. 5. Experimental configuration and connections setup.

figuration allows us to exploit the high elasticity of PDMS walls that, even if wider than connectors, perfectly close around them. Moreover, the big holes do not exert a resistance high enough to break the PDMS during the insertion of connectors.

Different steps of solution pumping and washing are performed for different chemicals in order to functionalize the nanowires. At the end of the process, specific antibodies are attached to each wire, while on the surface a passivation layer that prevents non-specific binding is present. Without the microfluidic, each washing step is usually repeated three times in a shaker, with a lot of wasting of solution. Thanks to the microfluidic and the relatively high speed of flow in the channel, only one washing step of 10 minutes for a total of $20\mu L$ of solution used is necessary, allowing a high decrease of wasted material. The device is stored in fridge at a temperature of 4°C with the channel filled by 10 % PBS (phosphate buffered saline) solution until use.

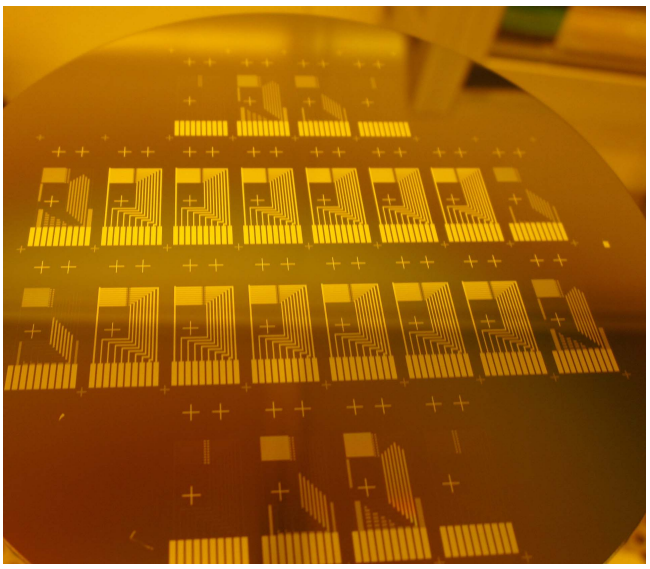


Fig. 6. SOI wafer which 24 chips which have pads made of annealed NiSi.

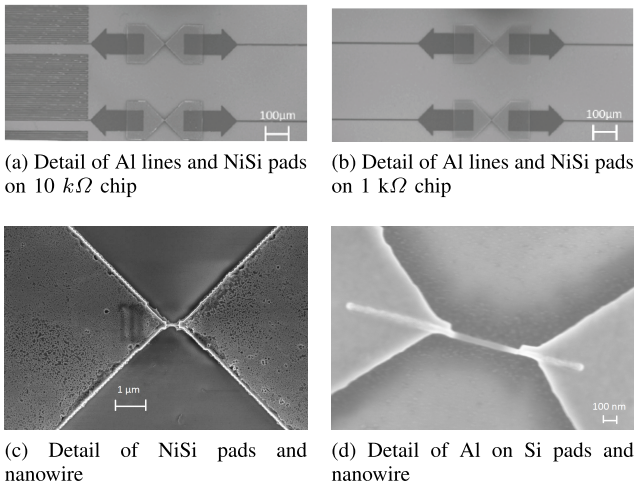
D. Testing Procedure

Measurements consisted of: incubation of the devices with anti-rabbit antibodies (AAB) in tumor extracts solution for one hour, followed by washing steps with PBS (phosphate buffered-saline) solution to remove excess of antigen and extracts and drying by air gun. Three different five minutes long washing steps, one with 100% PBS solution and two with a 10% one, were performed in order to achieve a good quality removal of excess antigens and tumor extracts and to prevent deposition of salts present in PBS, which could have altered the measure. The results obtained were expressed as current between the two terminals of the device versus the potential applied to these terminals, which were labeled following the terminology used for nanowire-based FETs (field-effect transistors): I_{DS} and V_{DS}.

IV. Results

Two SOI wafer, with 24 chips each, are produced using the method described in Section III. In the first one, pads are made of annealed NiSi (see Fig. 6), while in the second one pads are made of Al on Si without an annealing step and no lines are present. The produced devices are inspected by both optical and scanning electron microscope to check the correctness of the process. Fig. 7(a) and 7(b) shows the NiSi pads of the first SOI and the Al lines extensions. The lines represented come from two different chip configurations and are thin and in a serpentine shape in order to add a different value of in series resistance to the sensors. Fig. 7(c) and 7(d) depicts the nanowires and the pads of the SOI with NiSi pads and with Al pads respectively.

Measurements are performed on different chips obtained from the SOI wafer (see Fig. 8) by applying a voltage sweep to the Al contacts of the chips obtained from the first wafer



(a) Detail of Al lines and NiSi pads on 10 $k\Omega$ chip

(b) Detail of Al lines and NiSi pads on 1 kΩ chip

(c) Detail of NiSi pads and nanowire

(d) Detail of Al on Si pads and nanowire

Fig. 7. Images depicting different details of the SOIs.

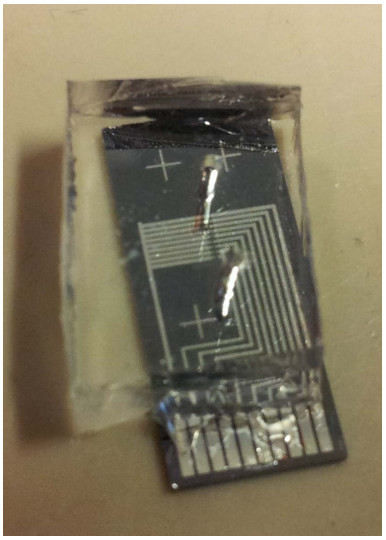
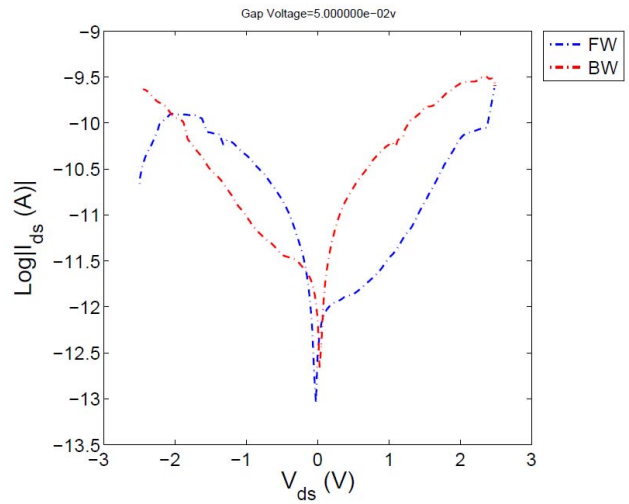
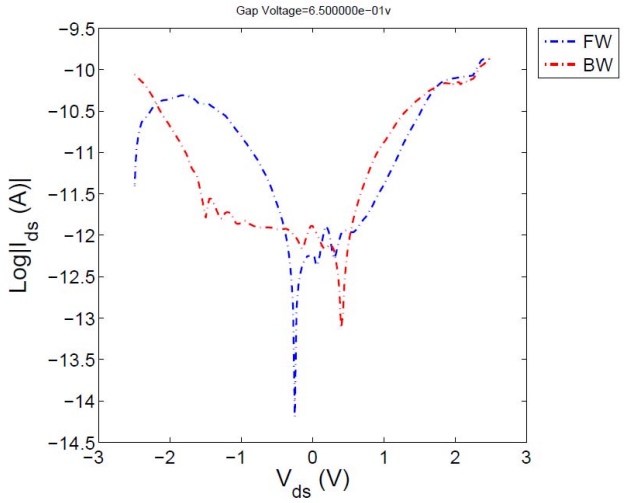


Fig. 8. Chip with attached microfluidic in PDMS.



(a) Before functionalization



(b) After functionalization

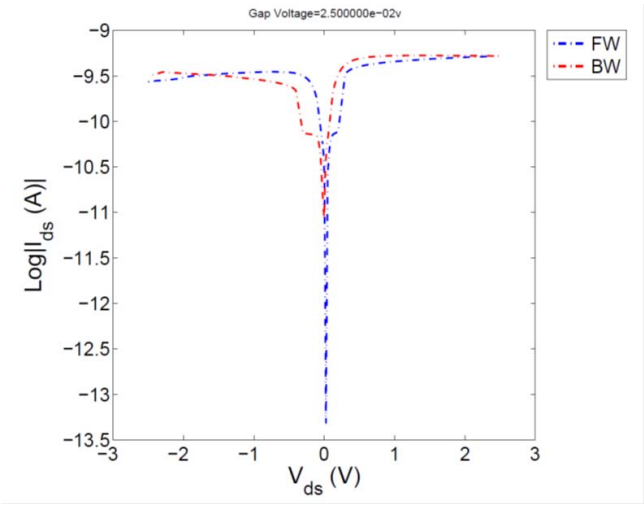
Fig. 9. I-V characteristic of a functionalized nanowire with NiSi pads.

or to the Al pads of the chips obtained from the second one. On the second wafer, in particular, tests are performed also to investigate the relation between the material of the pads and the voltage gap. The chips undergo steps of functionalization (see Section III-C for more details about the functionalization procedure), exposure to antigen solution with tumor extracts, drying and measurement.

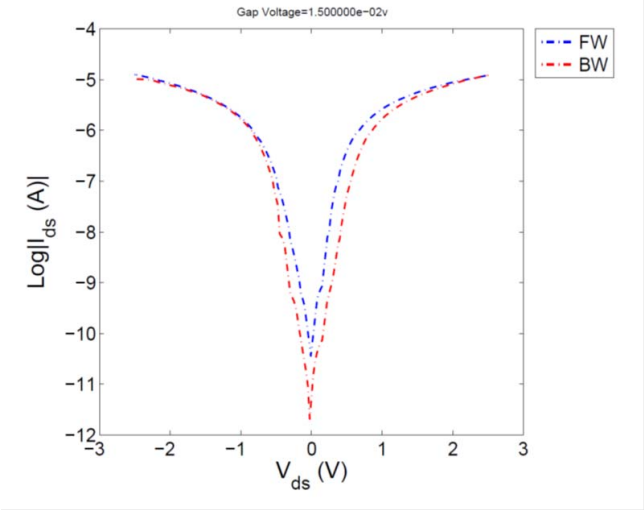
Results show that the gap is present on chips derived from the first wafer (annealed NiSi pads), as expected (see Fig. 9). Instead, no gap is detected on the ones from the second wafer both after functionalization and exposure to cancer biomarkers, as shown in Fig. 10. This finding is in agreement with the hypothesis that the voltage gap is strongly related to the NiSi electrodes implemented, fabricated through an appropriate annealing procedure.

In order to check the actual binding of antibodies to the nanowire surface and the effectiveness of the microfluidics, another functionalization, exposure to antigen and measurement procedure on chips is performed without the microfluidic circuit and a fluorescent detection of the antibody molecules is carried out on chips both with and without the microfluidic circuit after the measurement step. Results are the same for what concerns I-V characteristic, while fluorescent detection shows that microfluidics works in confining fluids on the nanowires area. As expected, some antibodies attach outside the sensor area (on the SiO_2). A comparison between the drop casting method and the microfluidic one is shown in Fig. 11.

The presence of antibodies on nanowires surface of chips with Al on Si pads is a further evidence that the voltage gap is due to the Nickel or the annealing step. Instead, the memristive effect appears not related to these factors, as demonstrated by the presence of the hysteresis loop in both cases (Figs. 9 and 10). This demonstrates that pads made by a simple deposition of Al on Si do not allow for the creation of a working biosensor, since its working principle, i.e., the voltage gap, is not achieved with this configuration. Further studies will be carried out to better understand this



(a) Before functionalization



(b) After functionalization

Fig. 10. I-V characteristic of nanowire with Al pads.

(a) With microfluidic (b) Without microfluidic (drop casting)

Fig. 11. Fluorescent detection of bonded antibodies on chips with Al on Si pads.

important phenomenon, which could open a new era for this type of devices.

V. Conclusion

Memristive Biosensors enable precise measurements of low concentrations of biological molecules. They are versatile for what concerns the detection target that is depending on the molecules attached to the nanowires during the functionalization process. Moreover, the detection mechanism is label-free.

The sensor exploits memristive effect and a voltage gap, which rises upon functionalization of the nanowires, to detect molecules of various types, depending on the type of functionalization performed, with a precision of the order of fM.

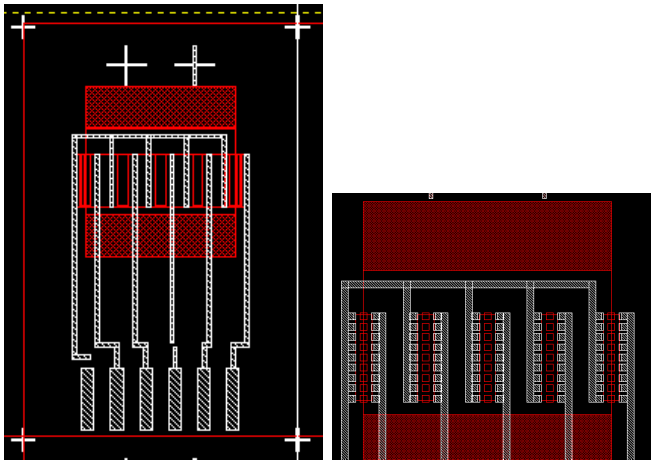


Fig. 12. Multiplex layout.

The fabrication procedure presented in Section III lead to the creation of two wafers with 24 chips each. The first wafer have pads made of annealed NiSi, while the second one presents pads made of Al on Si. A microfluidic in PDMS has been designed, fabricated, attached to the chips and tested. Chips obtained from each wafer have been tested both prior and after the functionalization step. The most interesting result was the absence of voltage gap in I-V characteristic of functionalized nanowires with Al on Si pads. This demonstrates a relation between gap and composition of the pads.

Further improvements could be implemented by the use of syringe or capillary pumps for a better control of the flux and the creation of a multiplex system to allow simultaneous detection of different molecules (a possible layout of the new chip, designed using Cadence Virtuoso, is shown in Fig. 12) or the use of a different material for the microfluidics. PDMS, even if useful because of its low cost and elasticity, presents problems like its drawback of contaminating other materials, making it not the best one for applications at industrial level. Materials like PMMA (polymethylmethacrylate) and PUMA (polyurethanemethacrylate) could solve this and other issues [25].

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Switzerland) according to the declaration of Helsinki and upon written informed consent.

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