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Label-Free Ultrasensitive Memristive Aptasensor

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KEYWORDS: DNA aptamers; Biosensors; Cancer diagnosis; Memristive behavior; Silicon Nanowires.

ABSTRACT

We present the very first worldwide ever-reported electrochemical biosensor based on Memristive Effect and DNA aptamers. This novel device is developed to propose a completely new approach in cancer diagnostics. In this study, an affinity-based technique is presented for the detection of the Prostate Specific Antigen (PSA) using DNA aptamers. The hysteretic properties of memristive silicon nanowires functionalized with these DNA aptamers provide a label-free

and ultrasensitive bio-detection technique. The ultra-sensitive detection is hereby demonstrated for PSA with a limit of detection down to 23 aM, best ever published value for electrochemical biosensors in PSA detection. The effect of polyelectrolytes on our memristive devices is also reported to further show how positive or negative charges affect the memristive hysteresis. With such an approach, combining memristive nanowires and aptamers, memristive aptamer-based biosensors can be proposed to detect a wide range of cancer markers with un-precedent ultrasensitivities to also address the issue of an early detection of cancer.

INTRODUCTION

Structures like semiconductor nanowires (NWs) show great potential for biosensing applications due to their high surface-to-volume ratio and the possibility of a direct electrical readout. NWs are frequently reported, especially as the channels of field effect transistors in label-free and miniaturized bioassays to detect different biomolecules. On the other hand, several memory effects have been widely reported as appearing in nature¹ as well as in electronic-based devices². A theory for a broad range of systems showing memory effect behavior was developed more than 30 years ago by Chua *et al.*³ and very recently reported again by Strukov *et al.*⁴ In these bipolar systems, the memory effect depends upon the charge carriers' rearrangement at the nanoscale level due to external voltage perturbations. Moreover, memory-effect devices have been fabricated using various materials^{5,6} and implemented in different applications^{7,8}. The present study demonstrates a new application of silicon NW devices that manifest this kind of memory effect: label-free bio-detection based on the hysteretic properties of memristive silicon-NW devices functionalized with anti-PSA DNA aptamers, which provide affinity for PSA as a target. PSA is here used as a case study of a prostate cancer biomarker target to demonstrate the

applicability of such a new approach for important diagnostics applications, such as early diagnostic of prostate cancer. PSA is a 30 kDa kallikrein protein used as a marker for prostate cancer (PCa); altered levels of PSA in blood above 4 ng/mL (ca. 133 pM) indicate the possibility of prostate cancer and patients are referred to further tests⁹. Such a probe (DNA aptamer)/analyte (PSA) couple was used in order to fabricate ultrasensitive sensors for detection of very low concentration of biomarkers, thus, for the efficient sensing of cancer disease in early stages. DNA aptamers are single stranded DNA sequences that are designed to bind a specific target. More specifically, DNA aptamers are synthetic DNA receptors developed via an *in vitro* selection technique to bind with high specificity and selectivity to a specific target analyte, like for example a protein, by undergoing a conformational change. DNA aptamers possess many advantages over antibodies such as the possibility for continuous monitoring, enhanced stability, specificity and reproducibility. All these characteristics make them as potential candidates to design novel and more specific biosensors¹⁰.

RESULTS AND DISCUSSION

Surface characterization

The surface morphology of the fabricated memristive devices was studied using scanning electron microscopy (SEM) (Figure 1). The SEM micrograph depicts the Si-NW arrays anchored between the NiSi pads, which serve as electrical contacts of the free-standing NW. Schottky-barrier junctions are formed between the Si and NiSi terminals. Due to the top-down nanofabrication process used (see materials and methods section), the width along the structures is not perfectly homogenous. However, this can increase the freely available area for DNA

aptamer binding, which increases DNA aptamer loading and hence better performance of the biosensor.

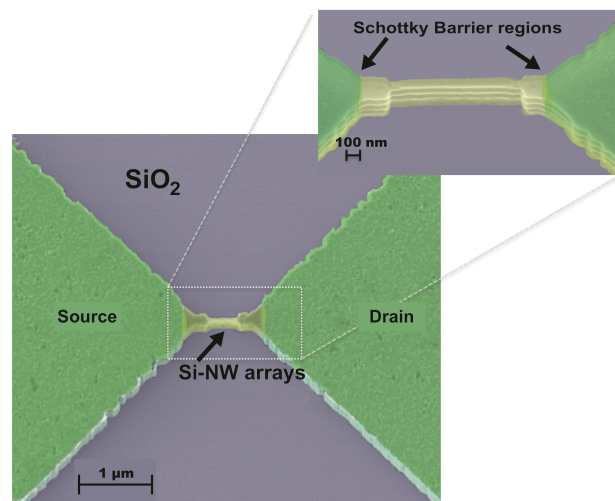


Figure 1. Morphological SEM analysis of Si-NW arrays anchored between NiSi pads.

The effect of charged residues

Before developing the memristive aptasensor, the nanodevices were characterized for the effects of charged macromolecules by using a polyelectrolyte (PE) multilayer. PEs are linear macromolecular chains bearing a large number of charged groups when dissolved in a suitable polar solvent. Among them, PSS (Poly (sodium 4-styrene sulfonate)) is a strong polyelectrolyte negatively charged in a wide pH range while PAH (Poly (allylamine hydrochloride)) is a weak polyelectrolyte positively charged in neutral or acidic solution or it can be neutral at a pH value above 10¹¹. In the case of multilayers of PAH/PSS, each adsorption step leads to a charge inversion on the surface due to the charge overcompensation effect. Subsequent depositions finally result in a PE multilayer stabilized by strong electrostatic forces established among PSS and PAH¹². The electrical characterization performed on bare nanofabricated wires indicates a

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hysteretic loop at zero voltage for the forward and the backward curves of the current⁸. In these devices, the memory effect depends on the charge carrier rearrangement at the nanoscale due to external perturbations, such as an applied voltage bias. When charged substances are present on the device surface, the hysteresis is modified and the current minima for the forward and the backward regimes occur at different voltage values. In this case, a voltage gap is created in the semi-logarithmic current-voltage characteristics as a further memory effect on the voltage scan across the nanostructure. The presence of charged substances around the freestanding nanowire creates an electrical field surrounding the channel of the memristive device that controls the channel current⁸. The average voltage gap value after deposition of each layer of PE is shown in Figure 2. Two PE concentrations are implemented 200 nM and 50 μ M. The first electrical measurements are performed after treatment with Piranha solution leading to the appearance of the voltage gap. Afterwards, the first PAH adsorption results in narrowing of the voltage gap of 0.09 V difference for 200 nM concentration and 0.16 V difference for the case of 50 μ M of PE respectively. This change is a result of the change in the charge density at the surface of the device due to the positively charged PAH, an effect that is even more pronounced when using an higher concentration of PAH: as more positive charges are present on the surface, a larger voltage gap change is registered. The adsorption of the negatively charged PSS shifts again the average voltage gap to a higher value of 0.17 V and further treatment with PAH results in a new decrease of the average voltage gap value of 0.15 V for 200 nM concentration of PE. Thus, it is demonstrated that further alternating exchange of the PE solution causes an alternating output signal, which slowly reduces in amplitude. This effect is very similar to the voltage gap trend exhibited in the case of the previously reported antibody-antigen binding⁸. In addition, the consecutive adsorption of the same type of PE (successive adsorption of PSS is presented in

Figure 2) tested by implementing the highest concentration of PE results in the acquisition of one direction trend for the voltage gap that increases from the value of 0.05 V to 0.21 V. This one direction trend can be correlated to the increasing voltage gap with the antigen concentration uptake discussed later in this paper.

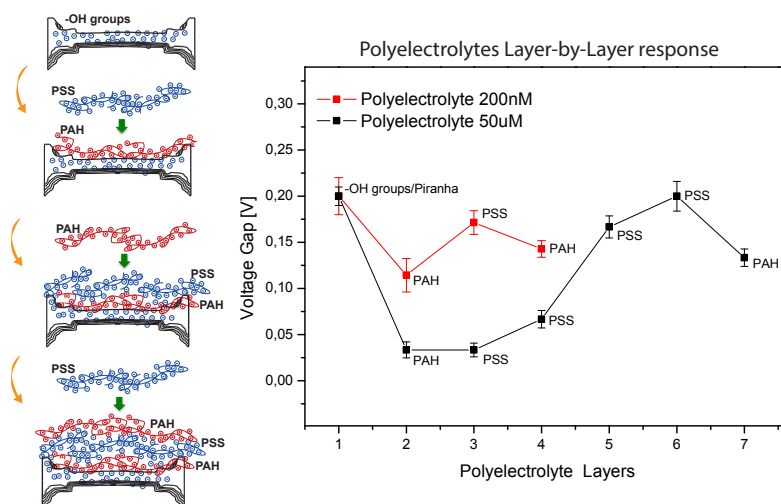


Figure 2. Formation of a multilayer of PEs by repeated electrostatic adsorption of oppositely charged PE layers; Average voltage gap value obtained from electrical characterization of devices treated with Layer-by-Layer deposition of PEs for 200 nM (red points) and 50 μ M (black points). The error bars stand for the standard deviation of the voltage gap measured for 14 devices.

Analytical performance

Similarly to what we have observed with PEs, the incorporation of charged biomolecules on the nanostructure produces a change in the voltage gap. The presence of biological substances typically contributes to extra charges surrounding the device creating an all-around bio-gate effect due to the charged groups present in the biomolecules⁸. As a consequence, and in correspondence to the behavior observed in the case of non-biological molecules, the position of

the current minima for the forward and the backward regimes changes introducing a voltage gap in the semi-logarithmic current-voltage characteristics as depicted in Figure 3(a), which, demonstrates an indicative voltage gap opening upon the uptake of 3.3 fM of PSA. The average voltage gap after the bio-modification of the device with DNA aptamers and increasing antigen concentration is presented in Figure 3(b). A voltage gap of average value of 0.027 V is first obtained for DNA aptamer bio-modified NWs and an increasing trend is acquired with the antigen uptake reaching an average value of 0.152 V for a concentration of 33 pM. On the hand, using a random DNA sequence as control (see supplementary information), no significant voltage gap difference is observed (<5% difference) even at a high PSA concentration of 33nM. This demonstrates the specificity and the efficiency of the proposed method. The obtained dose-response for the specific target presented in Figure 3 follows indeed a typical polynomial fit of second order (quadrant equation) with a root mean square value (R-Square) of 0.99 and intercept of -0.12 ± 0.04 V. A very low limit of detection (LOD) of 23 aM is calculated from 10 independent samples following the method reported by Armbruster *et al.*¹³ The demonstrated LOD is the best ever published so far among electrochemical biosensors for PSA reported in literature (Table 1).

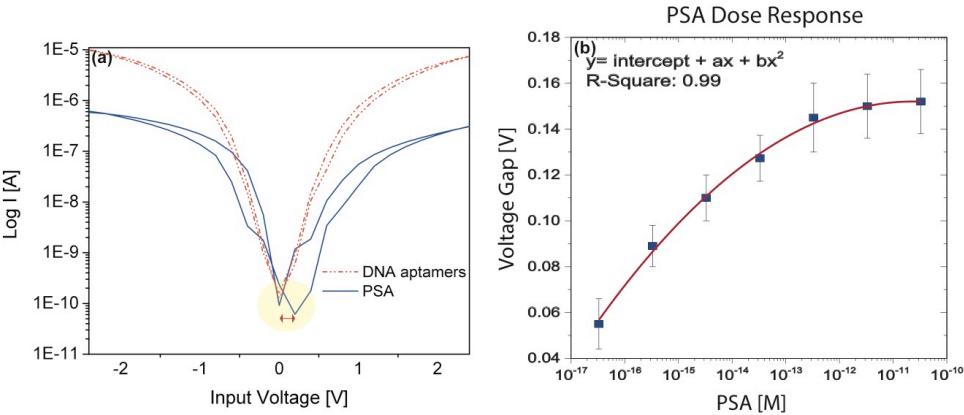


Figure 3. (a) Indicative electrical characteristics demonstrating the introduction of the voltage gap occurring upon bio-modification of the surface of the nanodevice. (b) Calibration curve related to the average voltage gap versus dose-response of 10 nanodevices. The reported error bars are the standard deviation of measurements related to these 10 nanodevices.

Table 1. State of the art list of reported PSA electrochemical aptasensors to date

Method	Electrode surface	LOD	Reference
Quartz Crystal Microbalance with Dissipation mode/ Electrochemical Impedance Spectroscopy (EIS)	Gold electrodes	37 nM	Formisano <i>et al.</i> ¹⁴ (2015)
Square Wave Voltammetry	GCE	pM range	Souada <i>et al.</i> ¹⁵ (2015)
EIS	Gold electrodes	30 pM	Jolly <i>et al.</i> ¹⁶ (2015)
Differential Pulse Voltammetry (DPV)	Glassy carbon electrode (GCE)	7.6 pM	Liu <i>et al.</i> ¹⁷ (2012)
EIS	GCE	0.15 pM	Kavosi <i>et al.</i> ¹⁸ (2015)
EIS	Gold electrodes	fM range	Yang <i>et al.</i> ¹⁹ (2015)
EIS (capacitance measurement)	Gold electrodes	30 fM	Jolly <i>et al.</i> ²⁰

			(2016)
DPV	GCE	300 aM	Kavosi <i>et al.</i> ¹⁸ (2015)
Memristive aptasensor	Si-nanowires	23 aM	Present work

The voltage gap is typically acquired in DC⁸. An AC analysis was also performed in this study for different concentrations of antigen as a complementary characterization. The impedance curves obtained from the electrical characterization of the nanofabricated devices with respect to different antigen concentrations are shown in Figure 4. The device was electrically characterized after the bio-functionalization with DNA aptamers and for four antigen concentrations in the range 33 aM – 330 fM. The corresponding charge transfer resistance values increase from 32% for 33 aM of PSA to 65% for 330 fM. The fact that the charge transfer resistance is increasing with the PSA uptake is coherent with the increased voltage gap registered with increasing PSA uptake. In fact, the large voltage gap may be associated to the larger energy required to move back charge carriers in the NW channel and this could be attributed to a larger charge transfer resistance. From this standpoint, it can be concluded that the results acquired by AC analysis confirm the outcomes obtained by DC analysis.

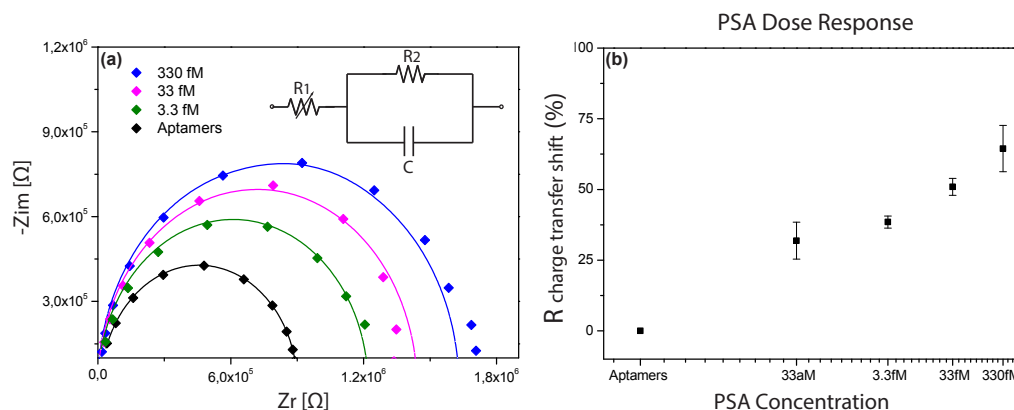


Figure 4. (a) Nyquist plots after DNA aptamer immobilization and after interaction with different concentrations of PSA; the inset shows the Randles circuit used for data fitting. (b) Average dose response charge transfer resistance shift from 9 nanofabricated devices. The reported error bars are the standard deviation of measurements related to these 9 nanodevices.

CONCLUSIONS

In the present work, a novel and definitely innovative aptasensor based on the memristive effect is presented. Memristive properties of silicon nanowires are used to develop an ultrasensitive PSA biosensor based on DNA aptamers. The modification of the related electrical-conductivity hysteresis due to the presence of charged macromolecules was investigated and fully characterized by through the deposition of layer-by-layer polymeric films. The nanofabricated memristive devices were then used to obtain the best ever-fabricated ultrasensitive electrochemical biosensor for the label-free detection of PSA. The demonstrated Limit of Detection (LOD) of the obtained devices is measured about 23 aM, well below the clinically relevant range of detection for PSA in patient samples. The demonstrated LOD actually is 13 times less with respect the best ever published in the literature so far among many electrochemical biosensors proposed for PSA. Such devices can be easily integrated in LoC (lab-on-a-chip) and PoC (point-of-care) devices for cancer diagnostics, it is fully compatible with

standard Silicon technology, and can easily address the issue of an early detection of cancer thank to the possibility to detect extremely small traces of cancer markers.

MATERIALS AND METHODS

Materials

Biotin ($\geq 99\%$ (TLC), lyophilized powder (B4501)), streptavidin (*Streptomyces avidini* (S4762)), biotinylated DNA aptamer (5'-[biotin tag] TTT TTA ATT AAA GCT CGC CAT CAA ATA GCT TT-3'), PSS and PAH were received in powder form ($M_w = 70,000$ Da) are all purchased from Sigma-Aldrich. PSA (Millipore Angebot R-1939458.1; 539834) was purchased from Merck. The piranha solution was prepared as a mixture of $H_2O_2:H_2SO_4$ in a 1:2 ratio. 10 mM Phosphate Buffered Saline (PBS) pH 7.4 was filtered through a syringe filter with 0.22 microns pore size and Phosphate Buffer (PB) was prepared as 10 mM solution of pH 5.5.

Surface modification

Memristive Si-NW devices were obtained through a top-down nanofabrication process as described by Tzouvadaki *et al.*²¹ The device surface was treated with piranha solution for 15 min at 70 °C as a cleaning and –OH activation step. The formation of PE multilayers was based on the consecutive adsorption of polyions with alternating charge using the Layer-by-Layer (LBL) technique as described by Chen & McCarthy²². The PE multilayer was formed by consecutive alternate adsorption of positively charged PAH and negatively charged PSS prepared PE solutions (concentrations of 50 μ M and 200 nM prepared in PB) and realized by alternately incubation of Si-NW structures for 20 min at room temperature (RT). For the biological sensing the nanodevices were first subjected to 200 μ g/mL biotin dissolved in PBS for 2 h at RT and then to 100 μ g/mL streptavidin in PBS for another 2 h at RT in dark. Finally, the substrate was

incubated overnight in 2 μM of biotinylated anti-PSA DNA aptamer solution in PBS at 4 $^{\circ}\text{C}$ in a humidity chamber. Prior to use, biotinylated DNA aptamers were activated at 95 $^{\circ}\text{C}$ for 10 min before being gradually cooled to room temperature for 30 min²³. The fabricated memristive aptasensors were investigated for their analytical performance by using PSA at different concentrations in the range of [aM-pM] via consecutive 1 h incubations. Figure 5 illustrates the bio-functionalization steps of the surface, as well as the antigen uptake. After all incubation steps the substrates were washed twice with the corresponding buffer solution and dried in a N_2 flow.

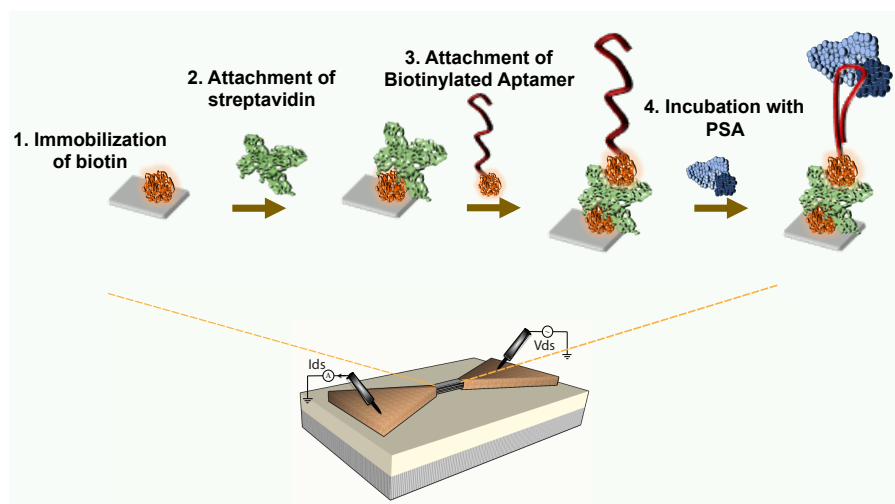


Figure 5. Schematic illustrating the affinity based fabrication process of the memristive aptasensor.

Electrical Characterization methodology

The electrical characteristics of the nanofabricated memristive structures of mean width of 90 nm and length of 980 nm were acquired using a probe station and contact probes configuration in the semi-logarithmic scale using a Keithley 4200SCS Semiconductor Characterization System from Tektronix GmbH in a two terminal configuration with Source Measurement Unit (SMU), by double sweeping the source to drain voltage between -2.4 V and +2.4 V at a fixed 0 V back-gate

potential. These measurements allow the observation of the changing hysteresis properties of the memristive sensors as a function of the surface treatment that leads to a charge variation. The hysteresis was studied in terms of voltage gap calculated between the forward and backward current minima of the $I_{ds}-V_{ds}$ curves. All the measurements were carried out at RT under a stable humidity environment. Impedance data was acquired using Ivium technologies CompactStat in the frequency range of [1-1000 Hz], amplitude of 1 V in a bias potential of 2.4 V.

SEM Analysis

SEM analysis of the nanofabricated structures was carried out using a Scanning Electron Microscope Merlin from Zeiss. Si-NW arrays configurations were defined using e-beam lithography masks. Imaging performed for 2 kV and stage at 19.5° (main image Figure 1), 15 kV and stage at 34.9° (inset image Figure 1)

ASSOCIATED CONTENT

Supporting Information Results obtained with the control sample. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Authors Contributions

I.T. and P.J. performed sensor fabrication, experiments and preparation of manuscript. X.L. helped with impedance measurements and analysis and PEs solutions preparation. The work was supervised by S.I., P.E., G.D.M. and S.C. The paper was written by I.T. and P.J. and revised by S.I., P.E., G.d.M. and S.C.

‡These authors contributed equally.

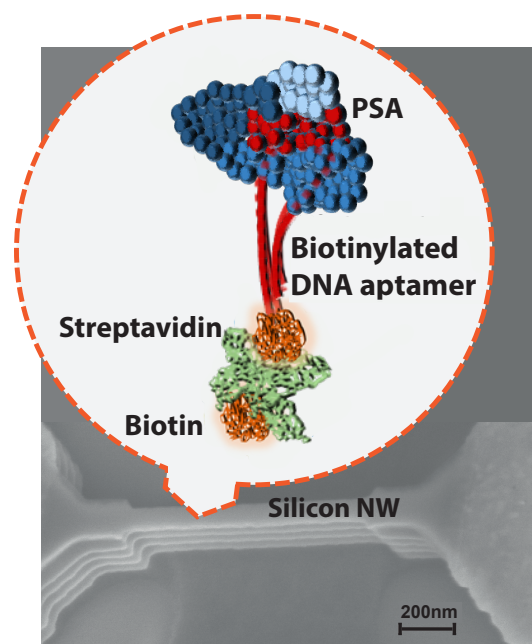
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REFERENCES

1. Lehn, J.-M. *Chem. Soc. Rev.* **2007**, 36 (2), 151-160.
2. Wu, J.; McCreery, R. L. *J. Electrochem. Soc.* **2009**, 156 (1), P29-P37.
3. Chua, L. O.; Kang, S. M. *Proc. IEEE.* **1977**, 65 (6), 915-929.
4. Strukov, D. B.; Snider, G. S.; Stewart, D. R.; Williams, R. S. *Nature (London, U.K.)*. **2008**, 453 (7191), 80-83.
5. Berzina, T.; Smerieri, A.; Bernabò, M.; Pucci, A.; Ruggeri, G.; Erokhin, V.; Fontana, M. *J. Appl. Phys.* **2009**, 105 (12), 124515.
6. Son, D. I.; Kim, T. W.; Shim, J. H.; Jung, J. H.; Lee, D. U.; Lee, J. M.; Park, W. I.; Choi, W. K. *Nano Lett.* **2010**, 10 (7), 2441-2447.
7. Sacchetto, D.; Gaillardon, P.-E.; Zervas, M. N.; Carrara, S.; De Micheli, G.; Leblebici, Y. *IEEE Circuits Syst. Mag.* **2013**, 13 (2), 23-41.
8. Carrara, S.; Sacchetto, D.; Doucey, M.-A.; Baj-Rossi, C.; De Micheli, G.; Leblebici, Y. *Sens. Actuators, B.* **2012**, 171, 449-457.
9. Catalona, W. J.; Smith, D. S.; Ratliff, T. L.; Dodds, K. M.; Coplen, D. E.; Yuan, J. J.; Petros, J. A.; Andriole, G. L. *N. Engl. J. Med. New England.* **1991**, 324 (17), 1156-1161.
10. Jolly, P.; Formisano, N.; Estrela, P. *Chem. Pap. - Chem. Zvesti.* **2015**, 69 (1), 77-89.
11. Mauser, T.; Déjugnat, C.; Sukhorukov, G. B. *Macromol. Rapid Commun.* **2004**, 25 (20), 1781-1785.
12. Riegler, H.; Essler, F. *Langmuir.* **2002**, 18 (17), 6694-6698.
13. Armbruster, D. A.; Tillman, M. D.; Hubbs, L. M. *Clin. Chem.* **1994**, 40 (7), 1233-1238.

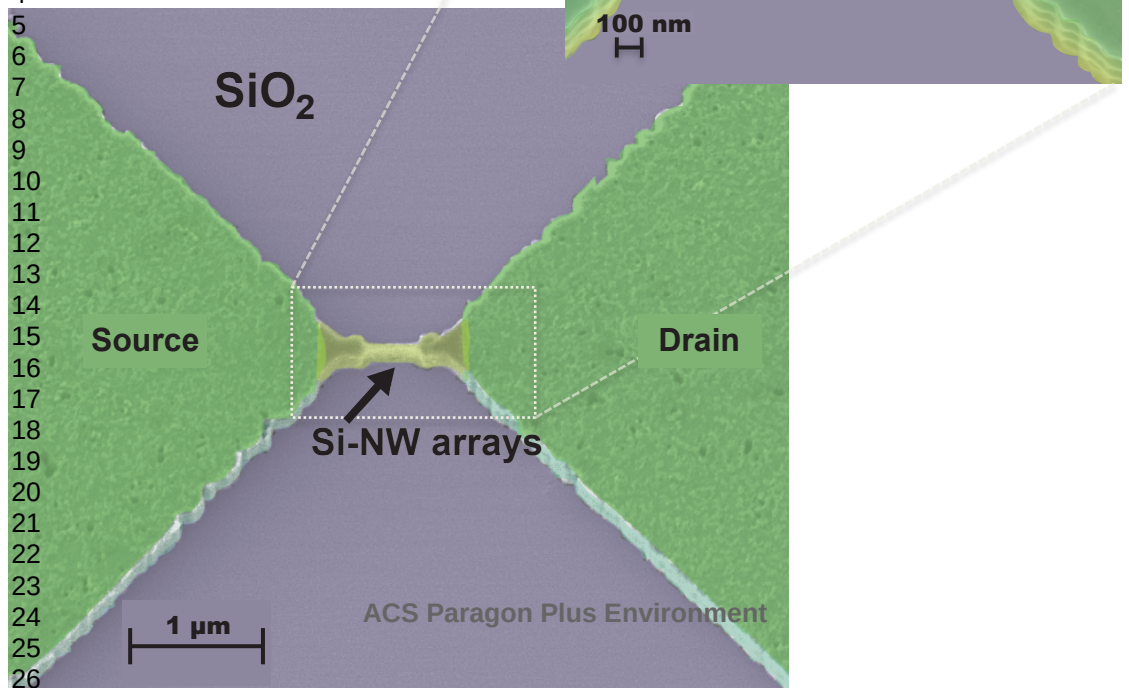
14. Formisano, N.; Jolly, P.; Bhalla, N.; Cromhout, M.; Flanagan, S.P.; Fogel, R.; Limson, J.L.; Estrela, P. *Sens. Actuators B*. **2015**, *220*, 369-375
15. Souada, M.; Piro, B.; Reisberg, S.; Anquetin, G.; Noël, V.; Pham, M.C. *Biosens. Bioelectron.* **2015**, *68*, 49-54.
16. Jolly, P.; Formisano, N.; Tkáč, J.; Kasák, P.; Frost, C.G.; Estrela, P. *Sens. Actuators, B*. **2015**, *209*, 306-312.
17. Liu, B.; Lu, L.; Hua, E.; Jiang, S.; Xie, G. *Microchim. Acta*. **2012**, *178*, 163-170.
18. Kavosi, B.; Salimi, A.; Hallaj, R.; Moradi, F. *Biosens. Bioelectron.* **2015**, *74*, 915-923.
19. Yang, Z.; d'Auriac, M.A.; Goggins, S.; Kasprzyk-Hordern, B.; Thomas, K.V.; Frost, C.G.; Estrela, P. *Analyst (Cambridge, U.K.)*. **2015**, *140*, 2628-2633.
20. Jolly, P.; Tamboli, V.; Harniman, R.L.; Estrela, P.; Allender, C.J.; Bowen, J.L. *Biosens. Bioelectron.* **2016**, *75*, 188-195.
21. Tzouvadaki, I.; Parrozzani, C.; Gallotta, A.; De Micheli, G.; Carrara, S. *J. Bionanosci.* **2015**, *5* (4), 189-195.
22. Chen, W.; McCarthy, T. J. *Macromolecules*. **1997**, *30* (1), 78-86.
23. Savory, N.; Abe, K.; Sode, K.; Ikebukuro, K. *Biosens. Bioelectron.* **2010**, *26* (4), 1386-1391.



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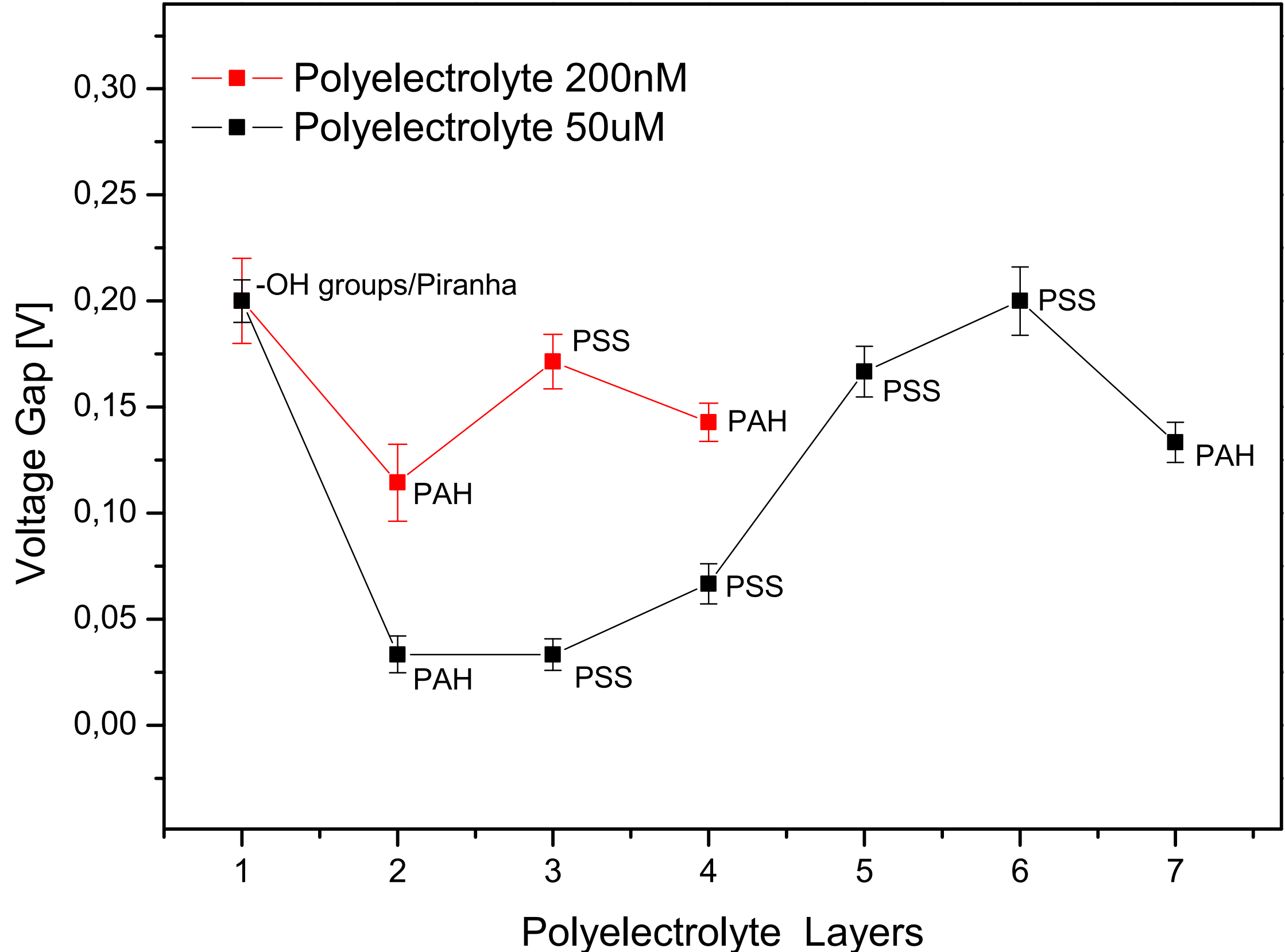
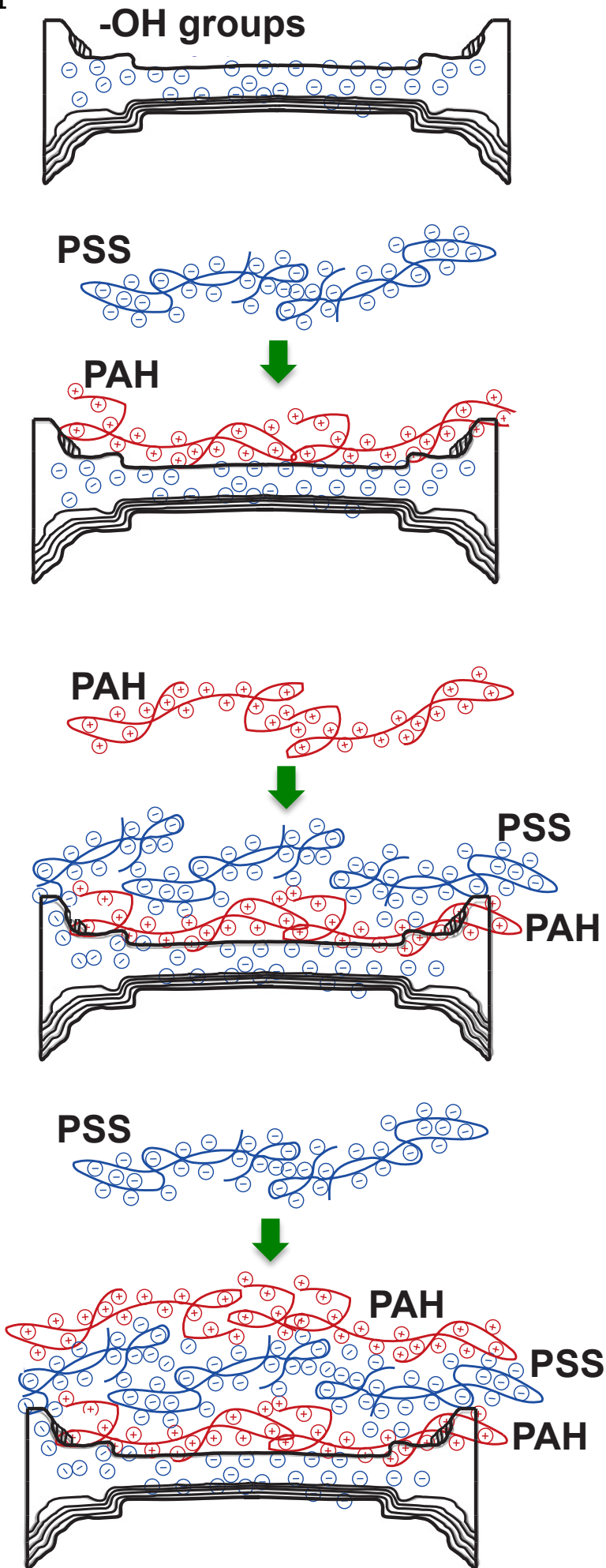
Nano Letters

Schottky Barrier regions

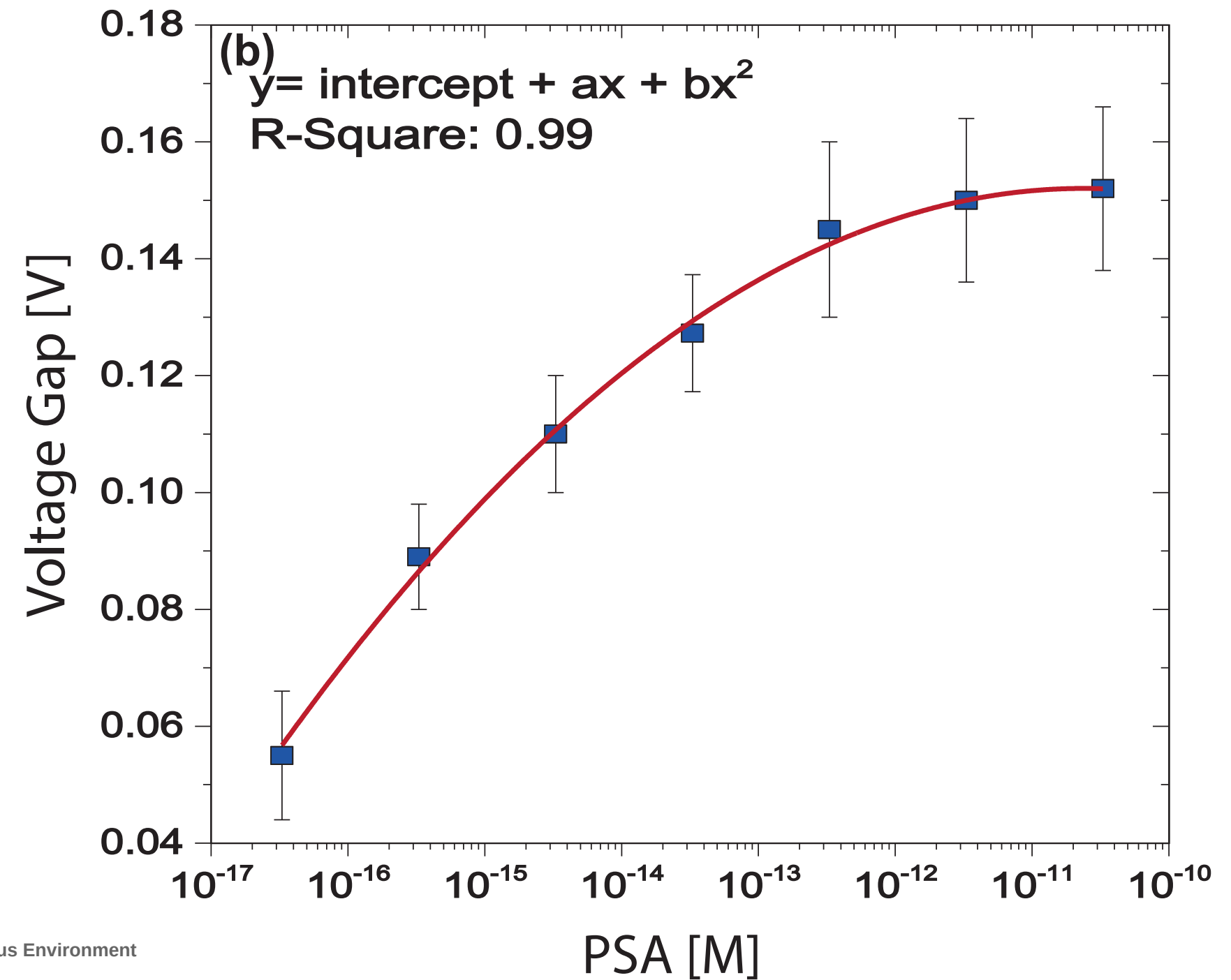
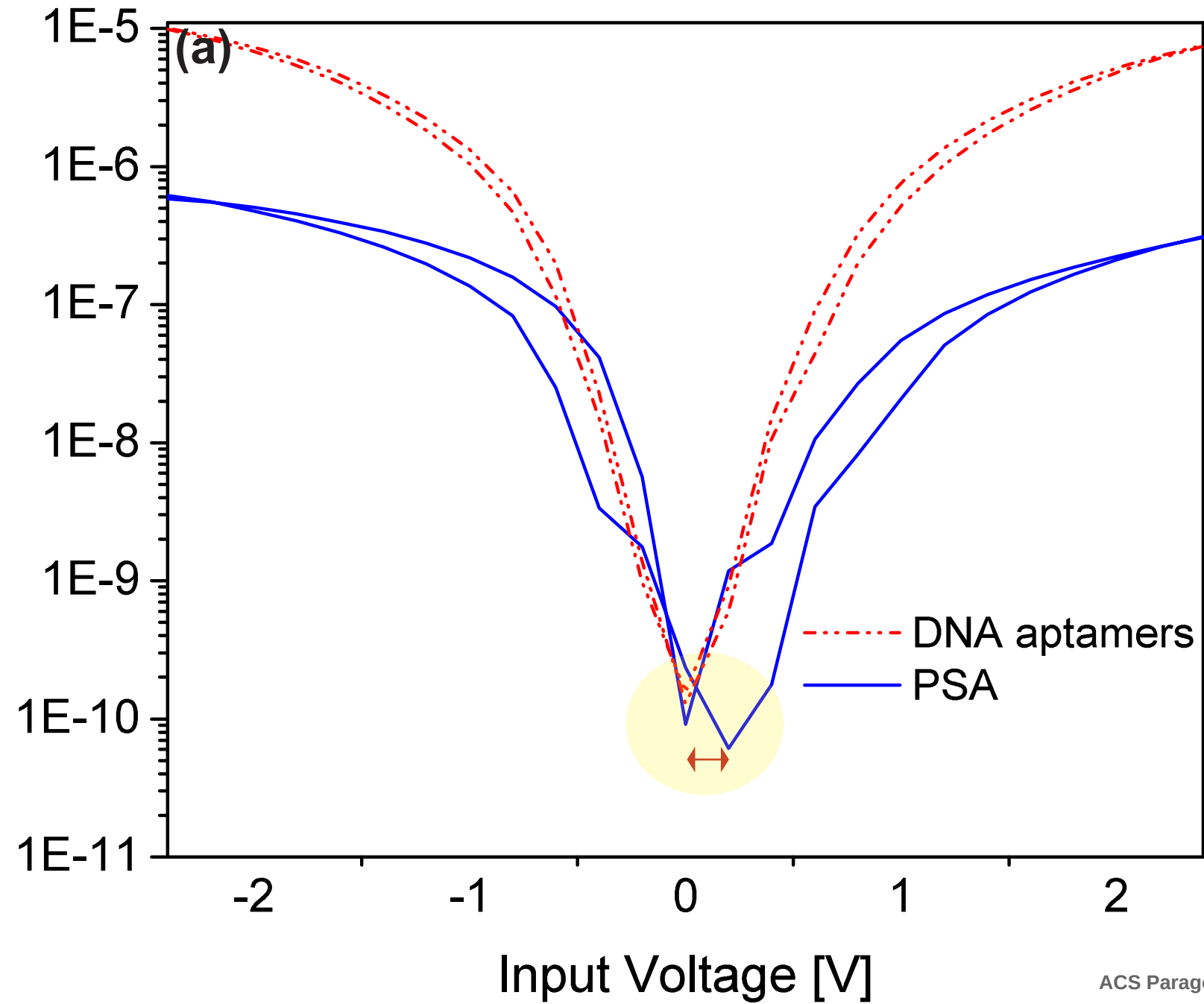


Polyelectrolytes Layer-by-Layer response

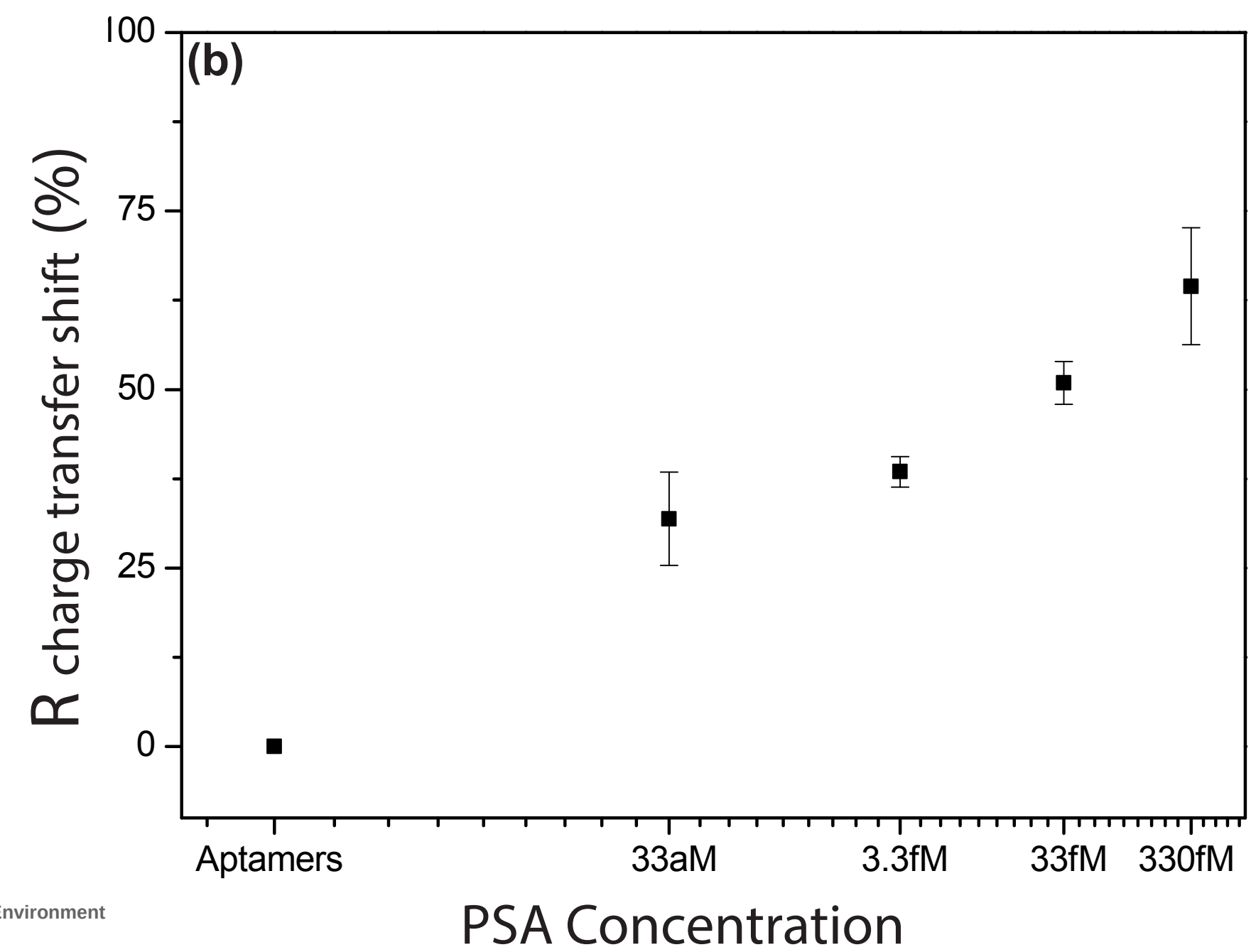
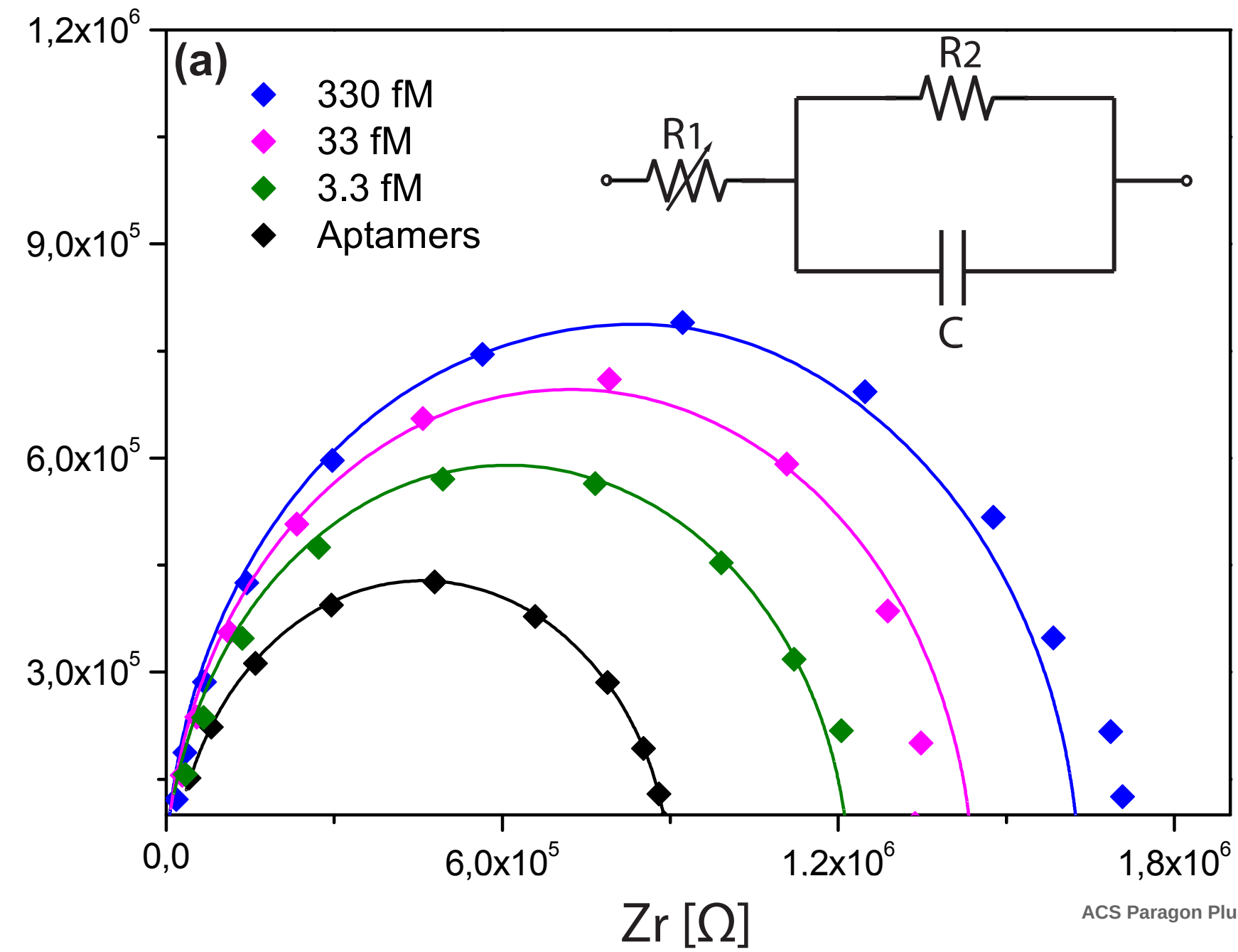
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PSA Dose Response

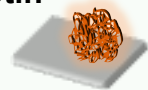


PSA Dose Response



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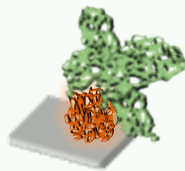
1. Immobilization of biotin



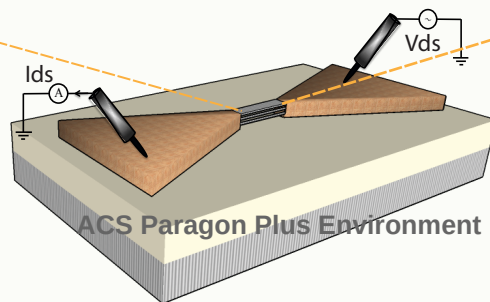
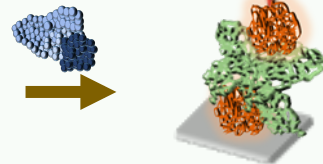
2. Attachment of streptavidin

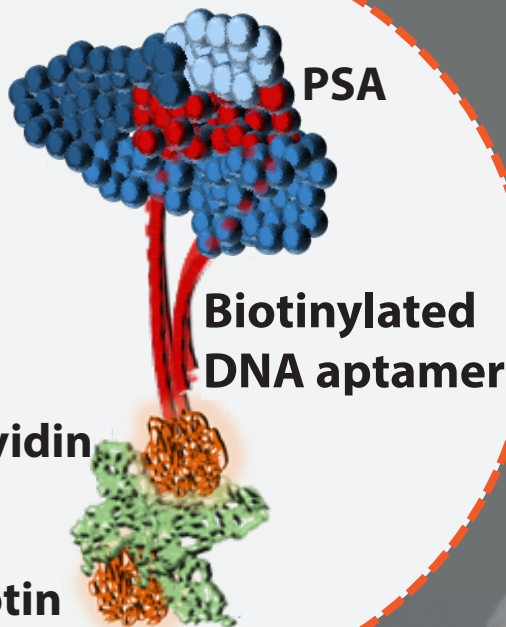


3. Attachment of Biotinylated Aptamer



4. Incubation with PSA



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Silicon NW

ACS Paragon Plus Environment

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