EPFL

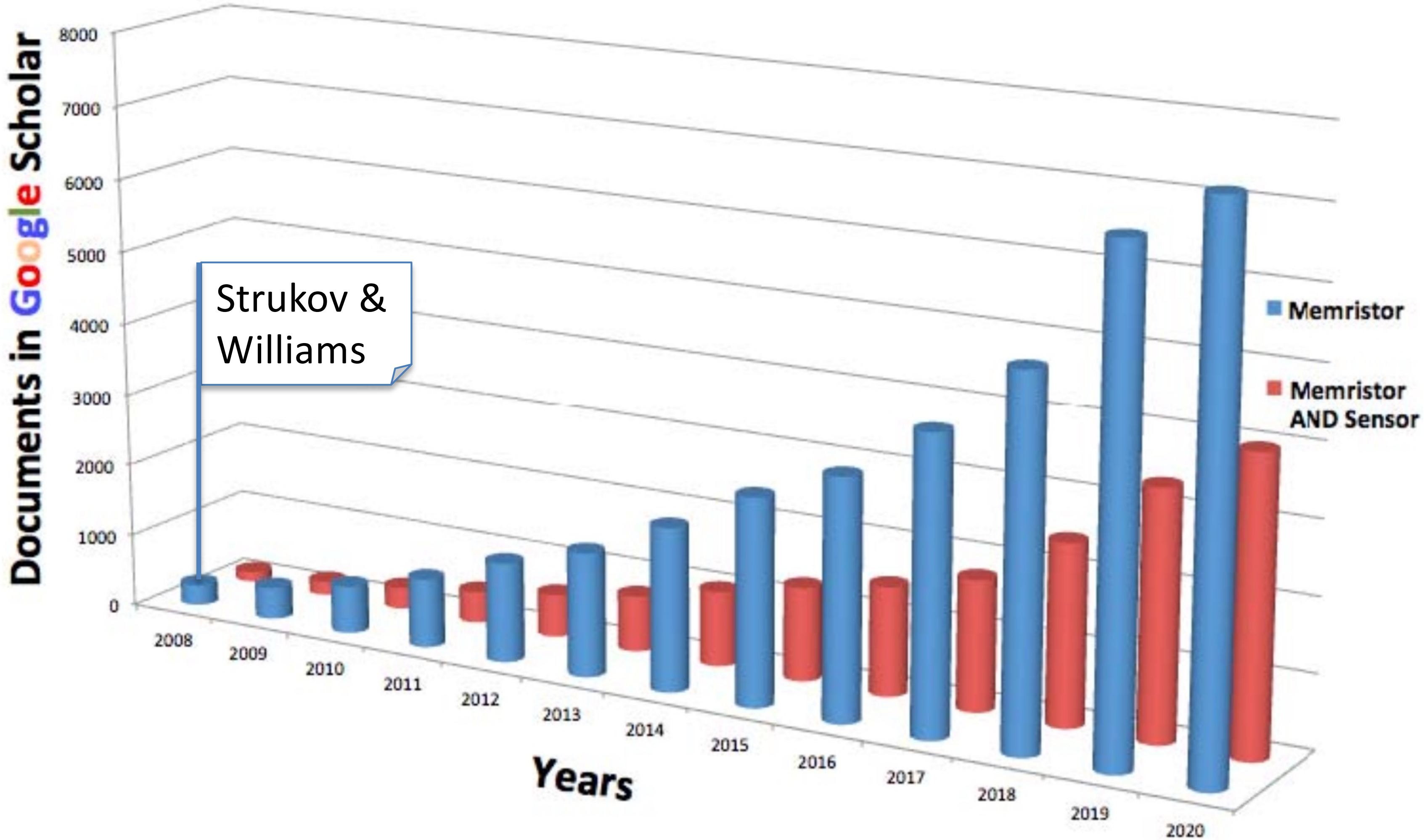
EDMI Microsystems and Microelectronics

MICRO-614: Electrochemical Nano-Bio-Sensing and Bio/CMOS interfaces

Lecture #10

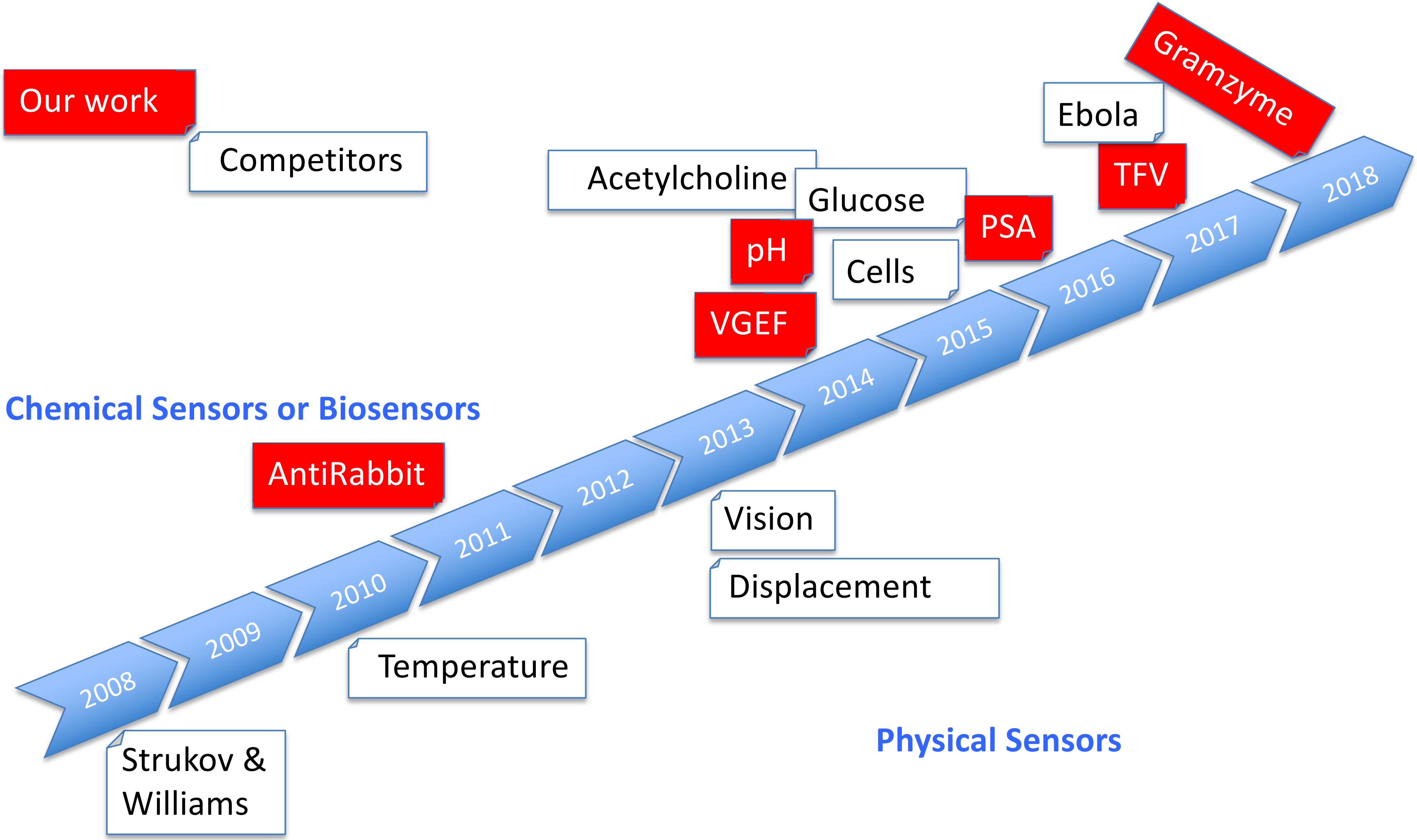
Nanotechnology to enhance ISFET sensing: *Ultrasensitive Memristive Biosensors*

Published Works on Memristors



16.700 papers published so far from 2008 with keyword «Memristor»
10.100 papers published so far from 2008 with also keyword «Sensor»

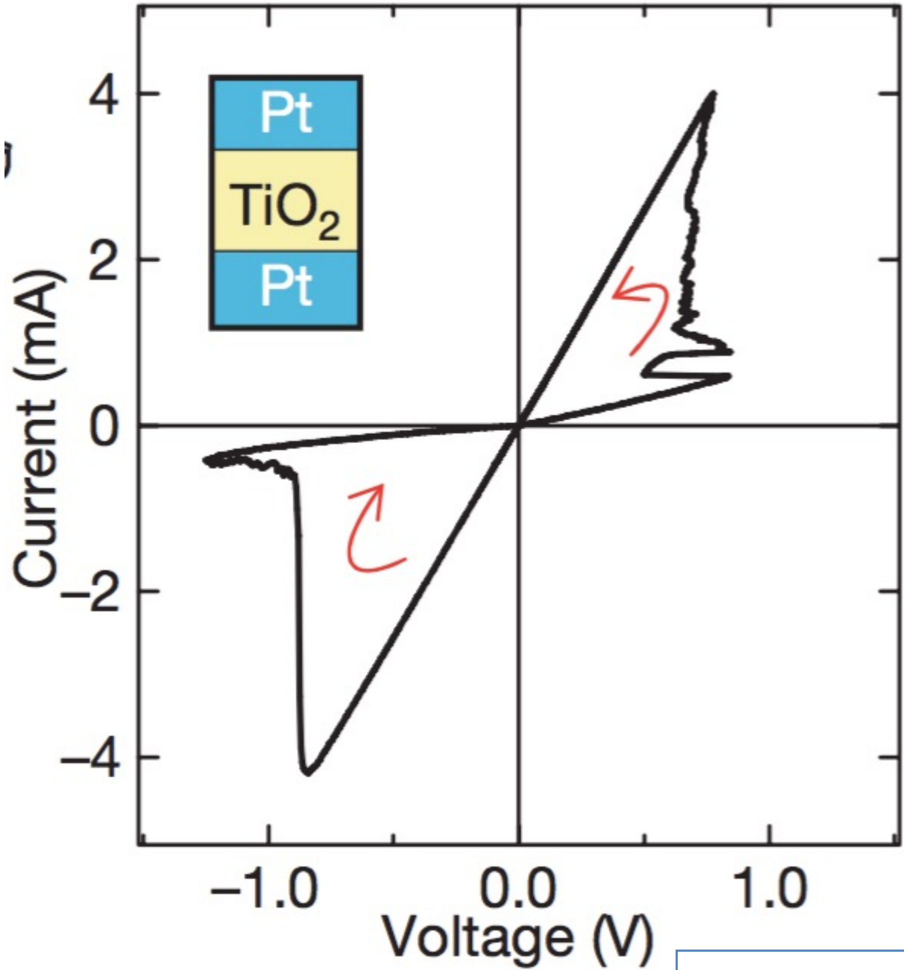
Memristive Sensors Milestones



Memristive Sensors Milestones

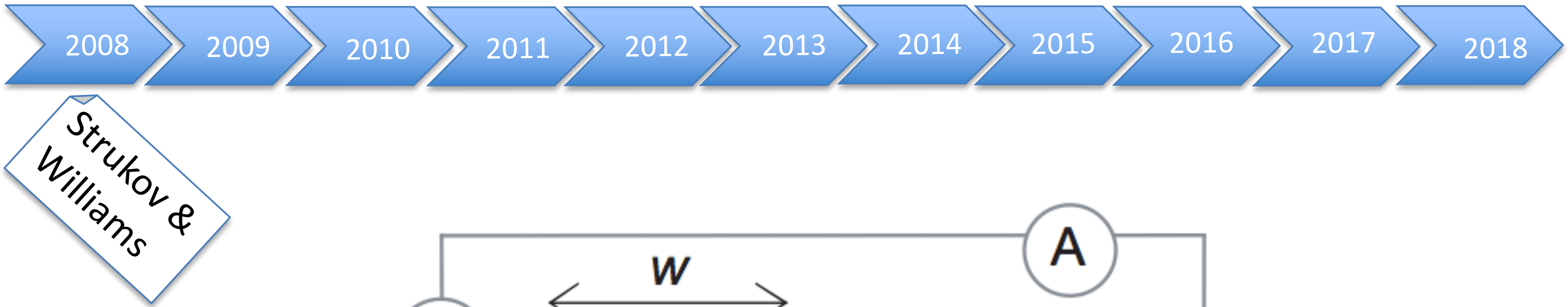
2008 → 2009 → 2010 → 2011 → 2012 → 2013 → 2014 → 2015 → 2016 → 2017 → 2018

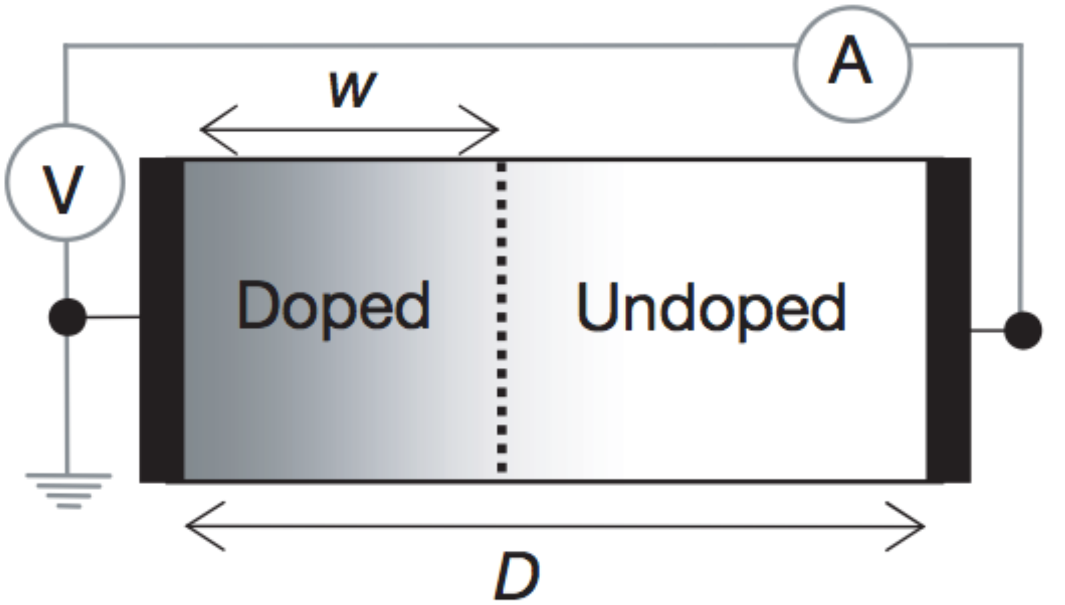
Strukov & Williams



D.B. Strukov, al et S. Williams, Nature 2008

Memristive Sensors Milestones

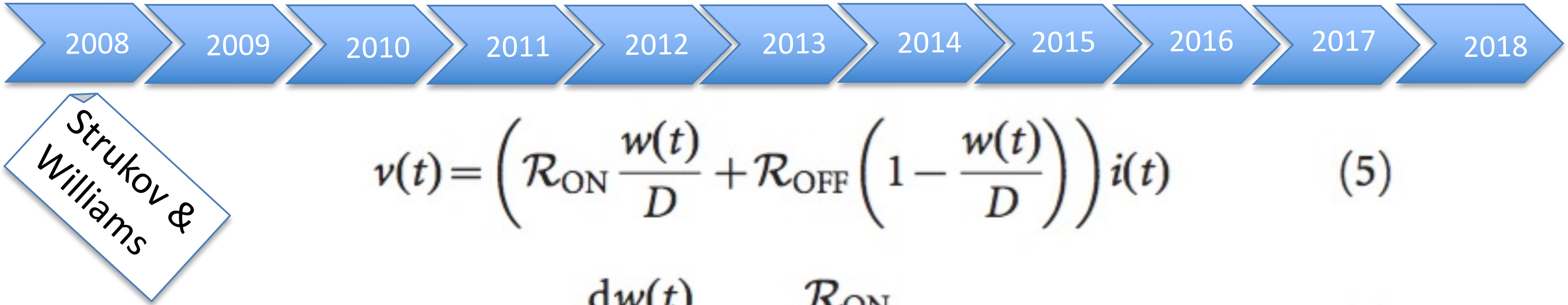




w-state model

D.B. Strukov, al et S. Williams, Nature 2008

Memristive Sensors Milestones



$$v(t) = \left(\mathcal{R}_{\mathrm{ON}} \frac{w(t)}{D} + \mathcal{R}_{\mathrm{OFF}} \left(1 - \frac{w(t)}{D} \right) \right) i(t) \qquad (5)$$

$$\frac{\mathrm{d}w(t)}{\mathrm{d}t} = \mu_{\mathrm{V}} \frac{\mathcal{R}_{\mathrm{ON}}}{D} i(t) \qquad (6)$$

which yields the following formula for $w(t)$:

$$w(t) = \mu_{\mathrm{V}} \frac{\mathcal{R}_{\mathrm{ON}}}{D} q(t) \qquad (7)$$

By inserting equation (7) into equation (5) we obtain the memristance of this system, which for $\mathcal{R}_{\mathrm{ON}} \ll \mathcal{R}_{\mathrm{OFF}}$ simplifies to:

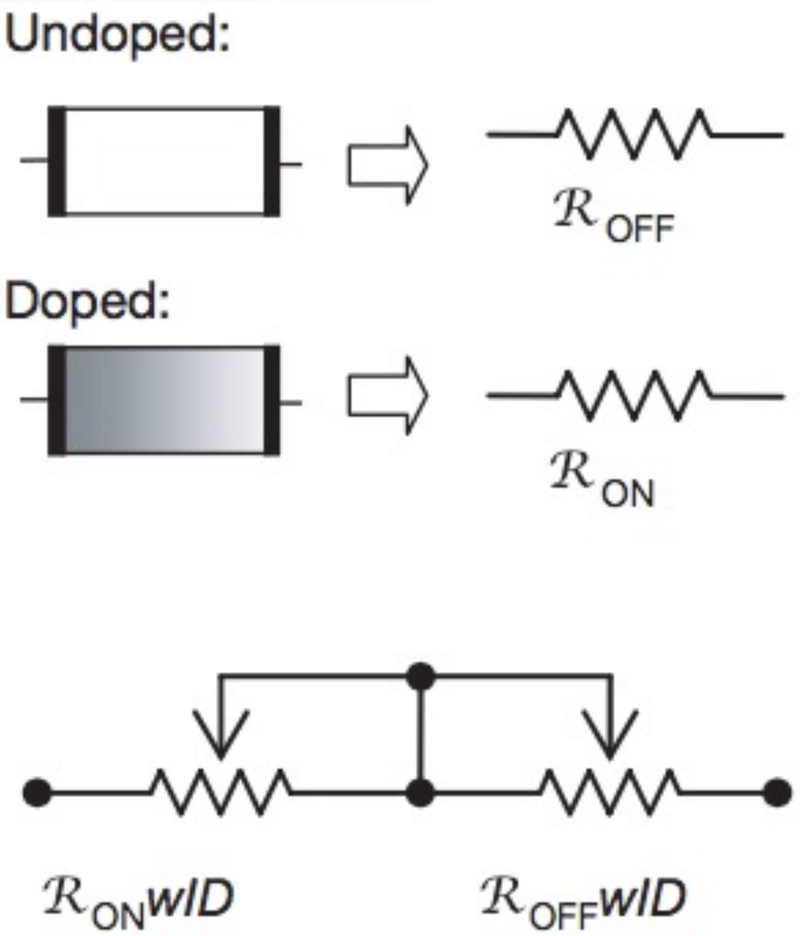
$$M(q) = \mathcal{R}_{\mathrm{OFF}} \left(1 - \frac{\mu_{\mathrm{V}} \mathcal{R}_{\mathrm{ON}}}{D^2} q(t) \right)$$

D.B. Strukov, al et S. Williams, Nature 2008

Memristive Sensors Milestones

2008 · 2009 · 2010 · 2011 · 2012 · 2013 · 2014 · 2015 · 2016 · 2017 · 2018

Strukov & Williams

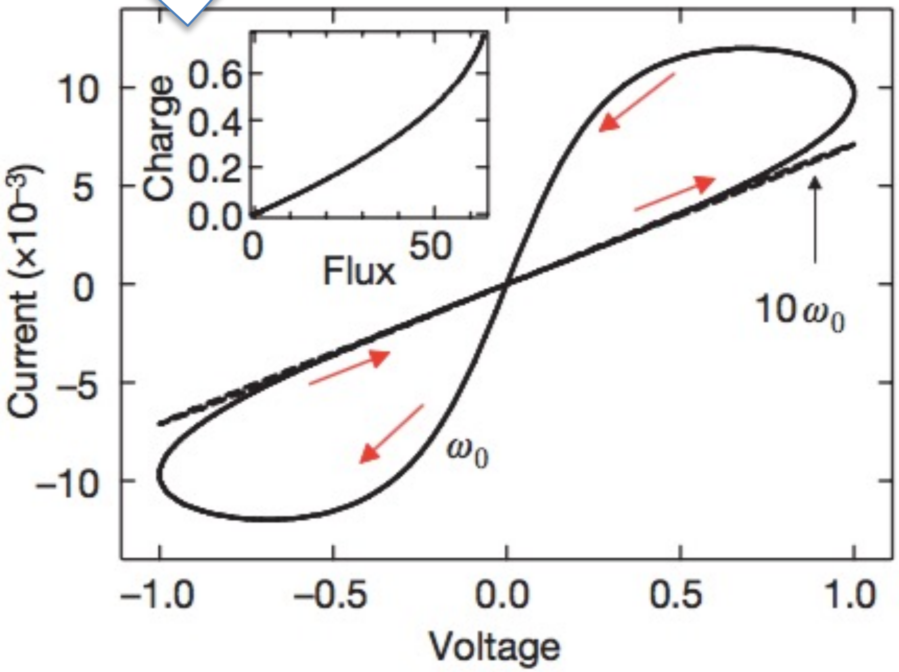


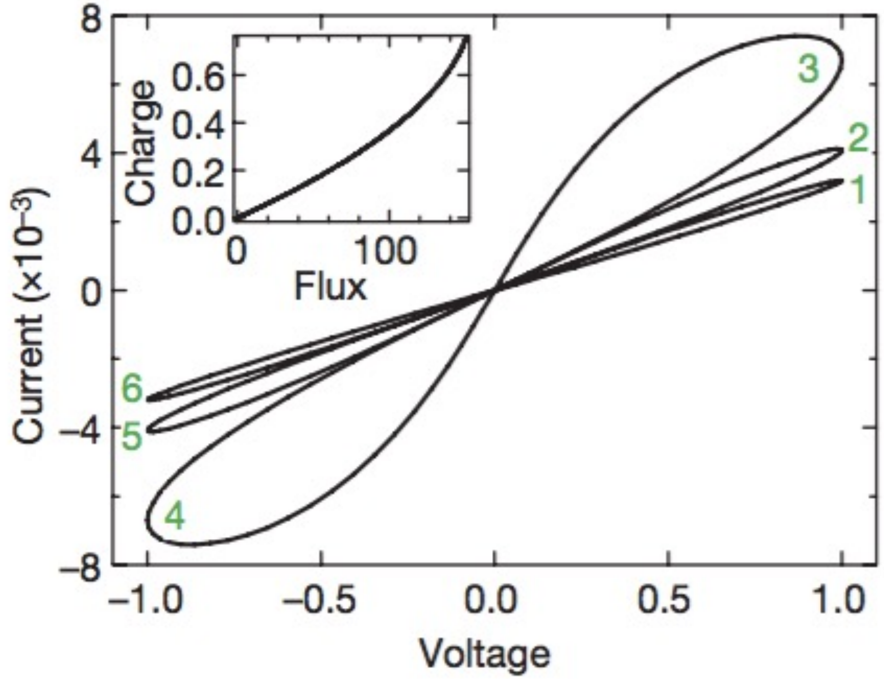
D.B. Strukov, al et S. Williams, Nature 2008

Memristive Sensors Milestones

2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018

Strukov & Williams





D.B. Strukov, al et S. Williams, Nature 2008

Limits of Detection with Antibody based Cancer Biosensors

TECHNOLOGY	Det. Limit	in Chip	Marker	Reference
QCM	0,61 nM	Yes	PSA	Y.Ukudag / Biosens. and Bioel. (submitted)
Micro-Cantiliver	10,0 pM	Yes	gene 1-8U	J.Zhang / Nature Nanotech. 1(2006) 214-220
AFM	Single Cells	No	-	Cross / Nature Nanotech 2(2007) 280-283
SPR	7,69 nM	Yes	AFP	Y. Teramura / Anal. Biochem. 365 (2007) 201–207
IS-FET	27,3 fM	Yes	PSA	G.Zheng / NATURE Biotech 10 (2005) 1294-1301
C-Measurements	62,7 nM	Yes	IgM-SCCA	S.Carrara / Sens. Actuators B136(2009) 163-172

The Limit Of Detection (LOD) is in the range 27 fM ÷ 63 nM

Limits of Detection with Aptamer based Cancer Biosensors

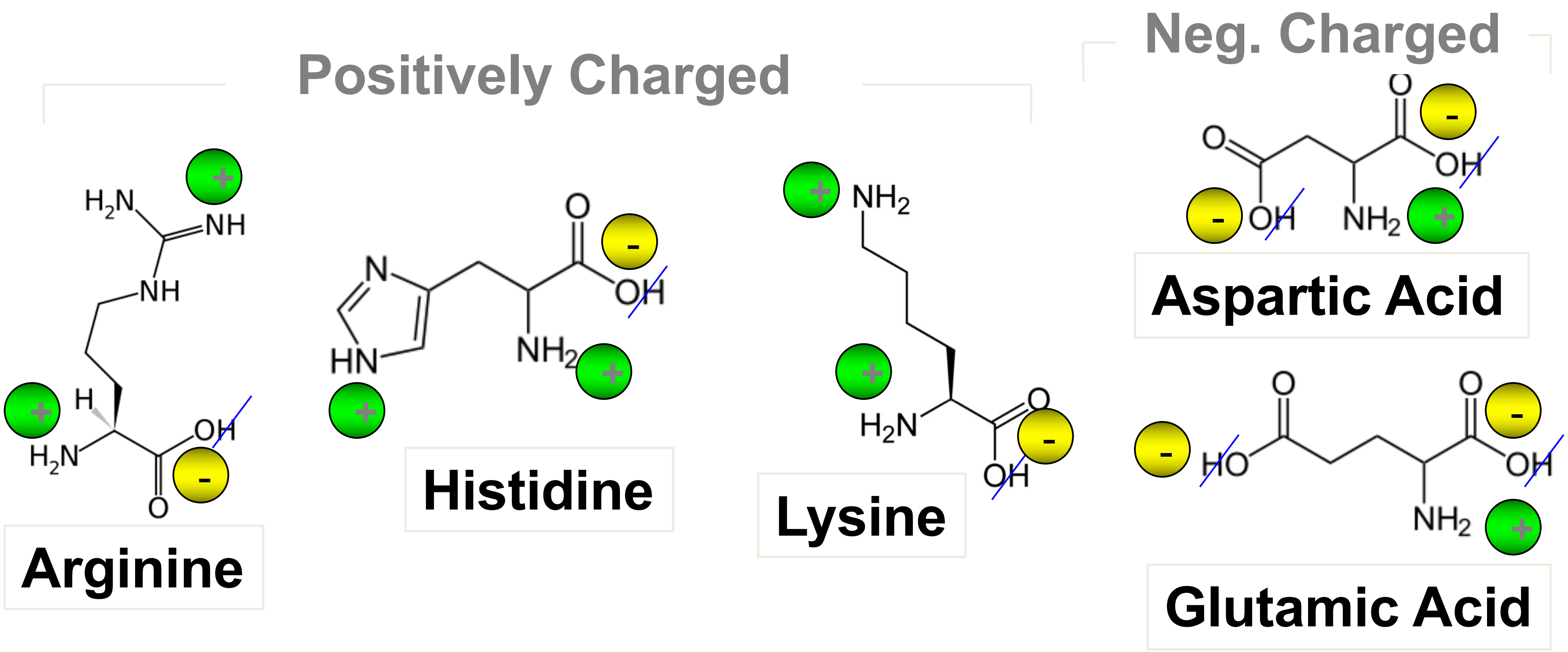
Table 1. State of the Art List of Reported PSA Electrochemical Aptasensors to Date

method	electrode surface	LOD	reference
quartz crystal microbalance with dissipation mode/electrochemical impedance spectroscopy (EIS)	gold electrodes	37 nM	Formisano et al.[14] (2015)
square wave voltammetry	GCE	pM range	Souada et al.[15] (2015)
EIS	gold electrodes	30 pM	Jolly et al.[16] (2015)
differential pulse voltammetry (DPV)	glassy carbon electrode (GCE)	7.6 pM	Liu et al.[17] (2012)
EIS	GCE	0.15 pM	Kavosi et al.[18] (2015)
EIS	gold electrodes	fM range	Yang et al.[19] (2015)
EIS (capacitance measurement)	gold electrodes	30 fM	Jolly et al.[20] (2016)
DPV	GCE	300 aM	Kavosi et al.[18] (2015)

I. Tzouvadaki et al., Nano Letters, 16(2016) 4472-4476

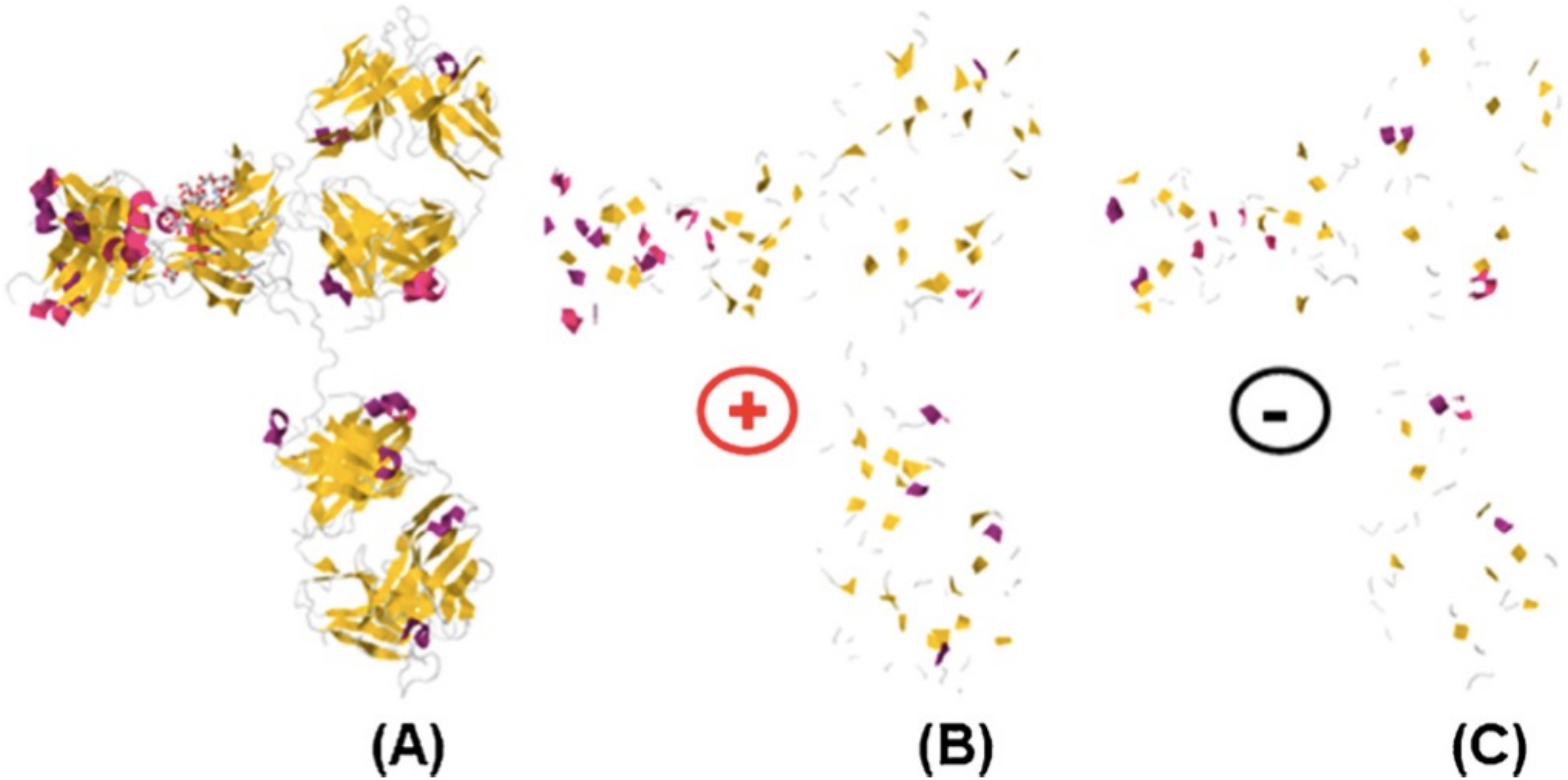
The Limit Of Detection (LOD) is in the range 300 aM ÷ 37nM

Protein Charges



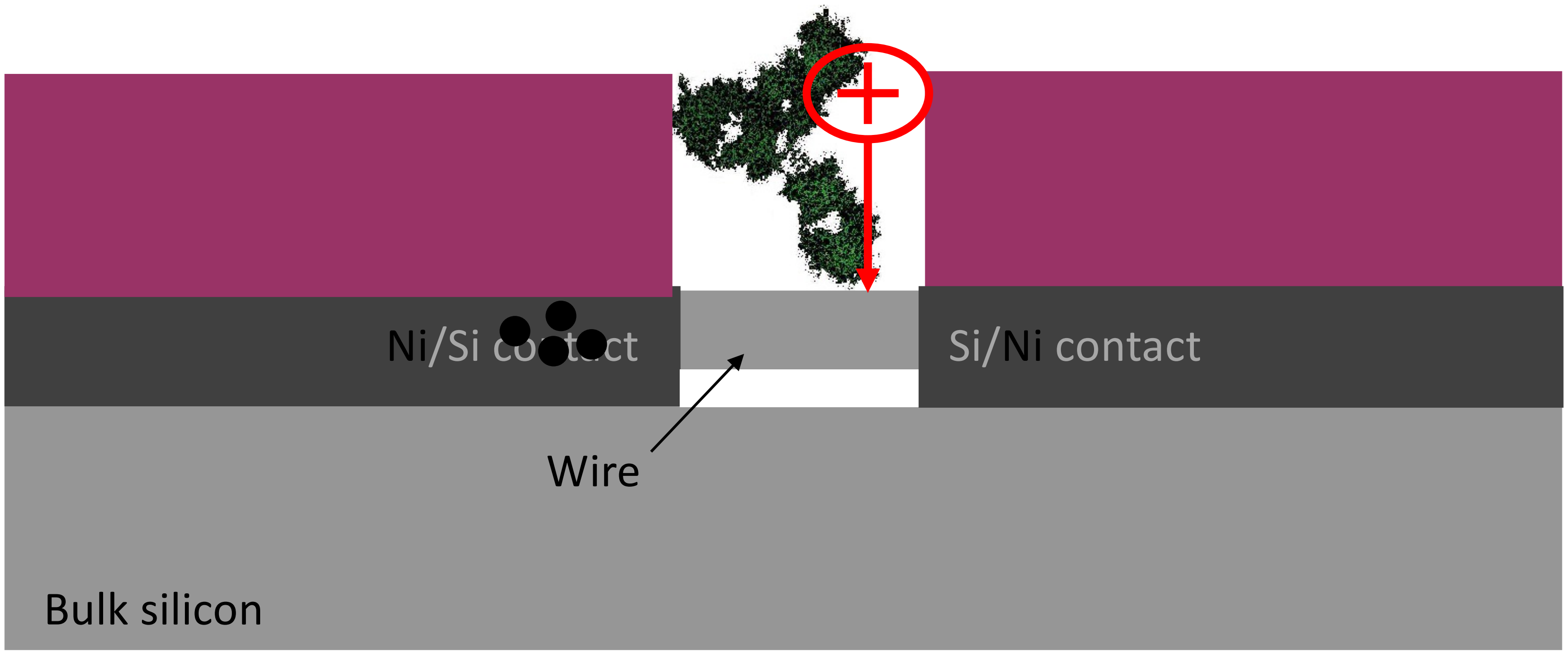
Charged Amino Acids

Protein Charges



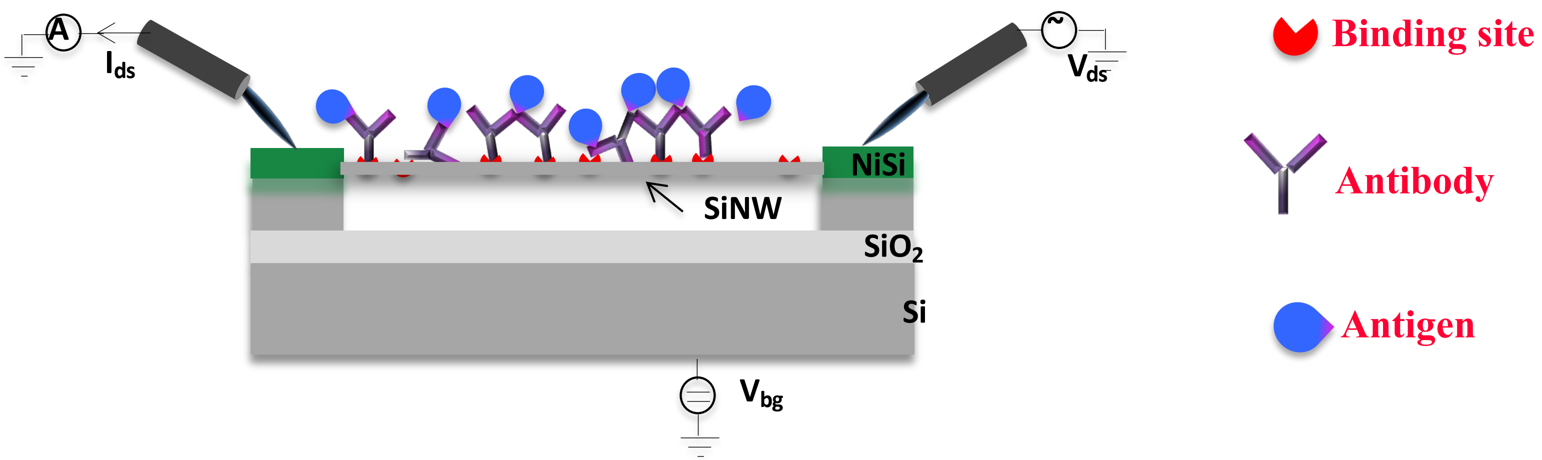
Charged Residues in an Antibody by protein DB

Charge-based-Sensing



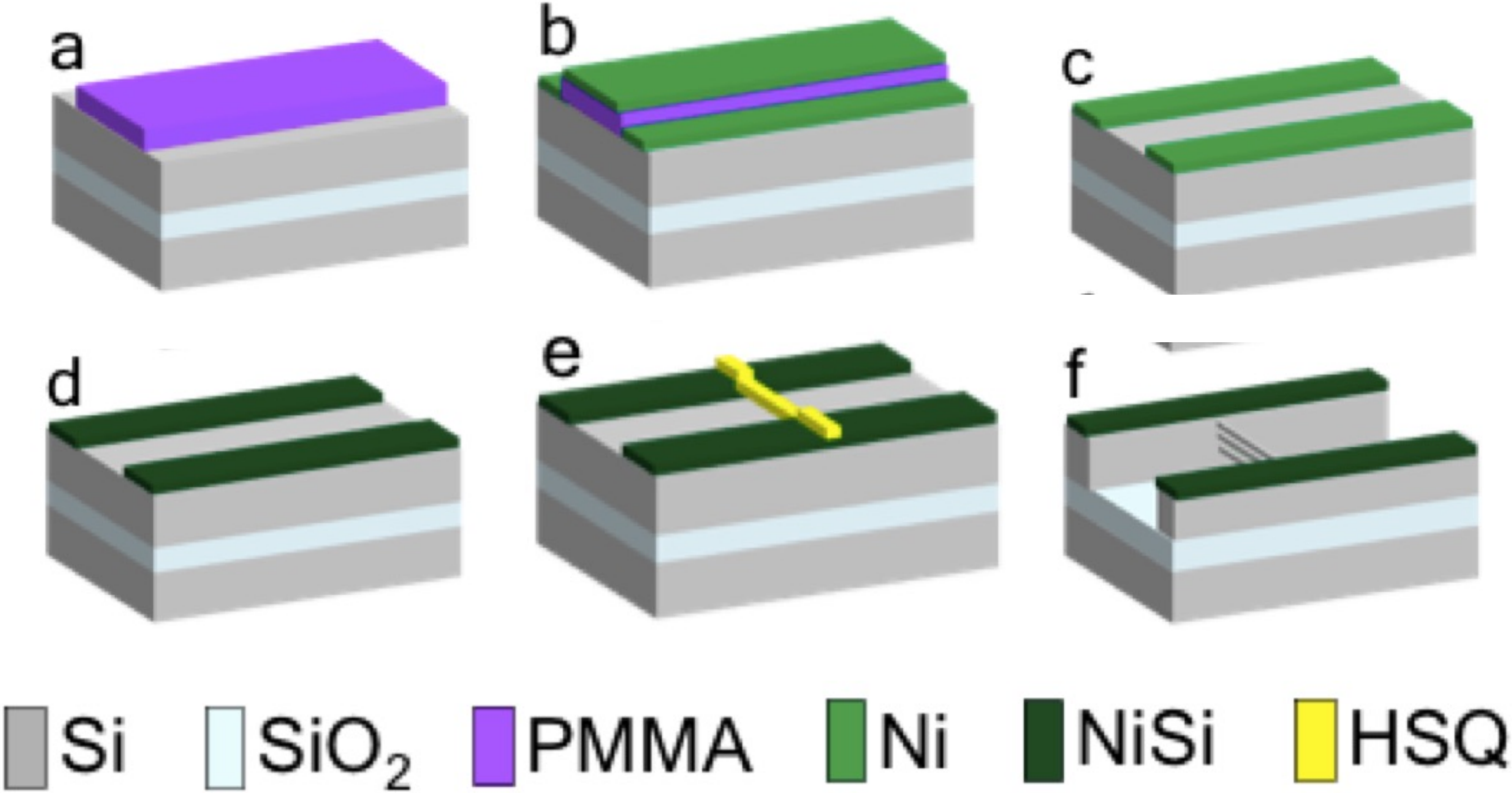
The charging from molecules affects the conductivity in the silicon channel

Bio-Functionalization



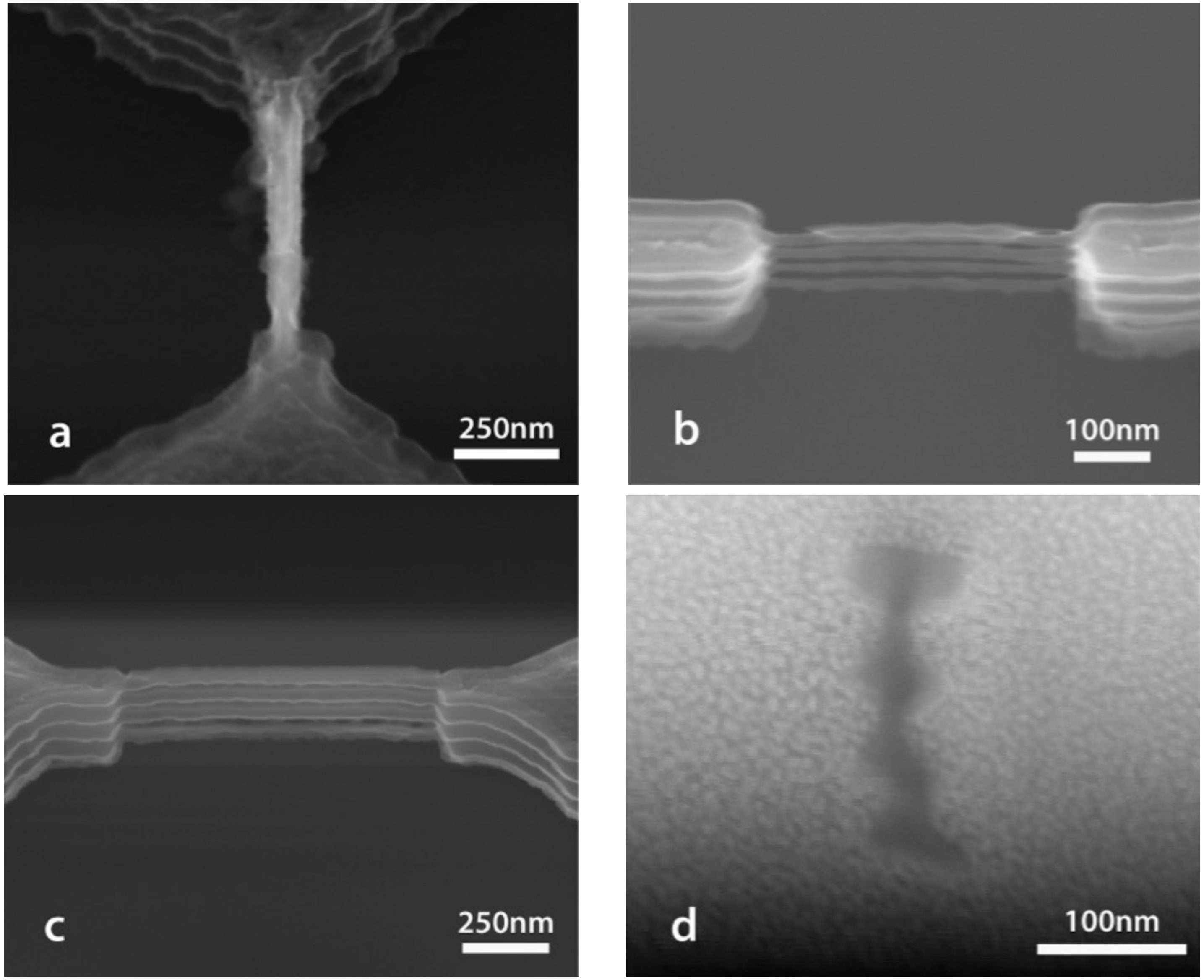
Biosensing Measures are acquired on air after the Antibodies immobilization and the Antigens uptake

Fabrication Process for Memristive Biosensors



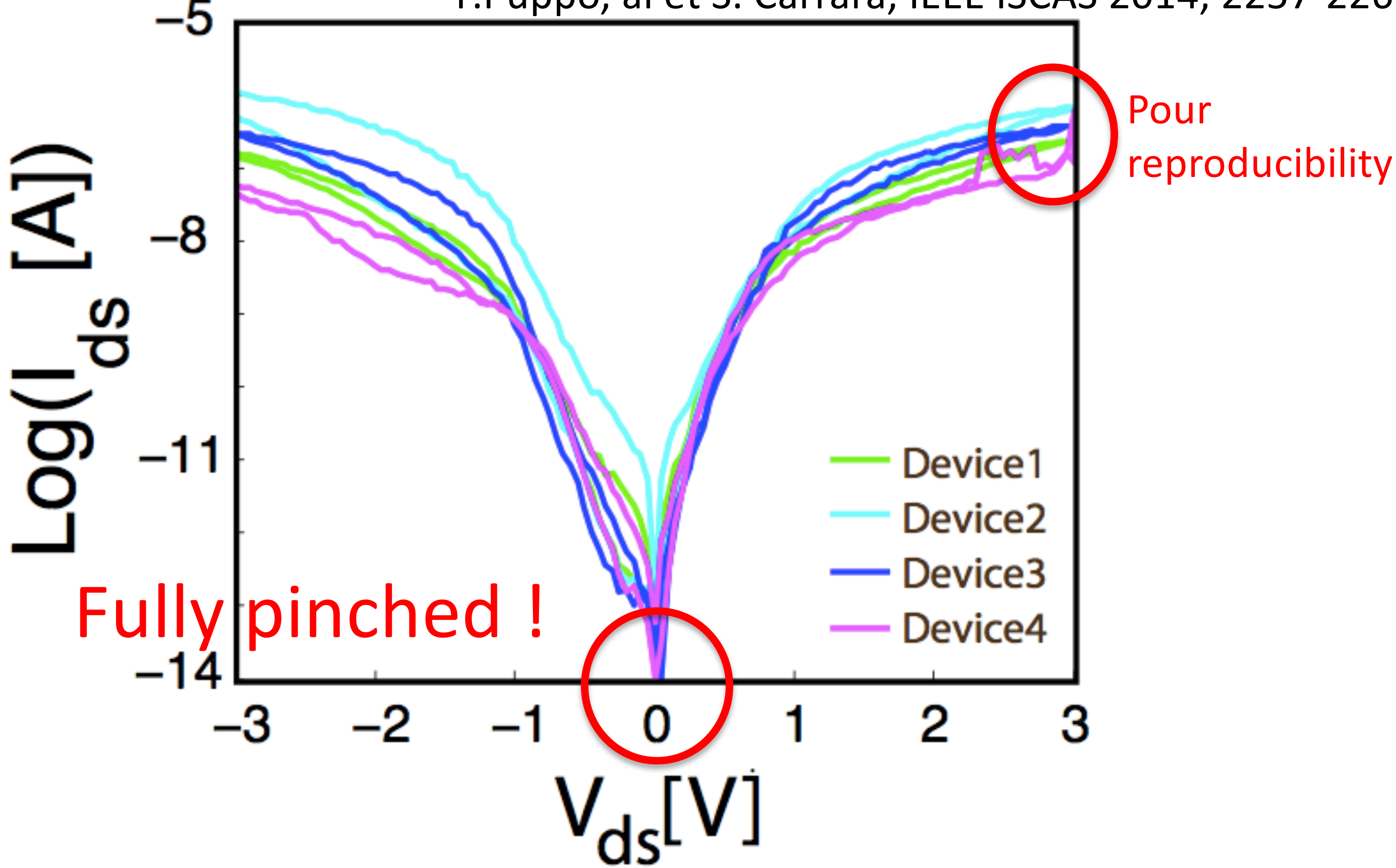
Fabrication Results

F.Puppo, al et S. Carrara, IEEE ISCAS 2014, 2257-2260



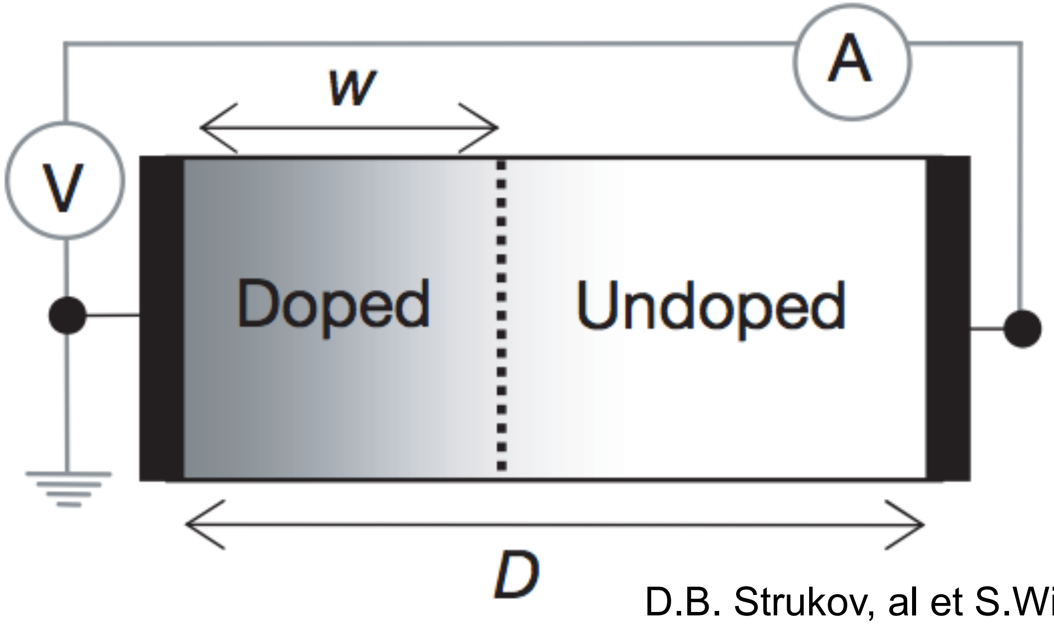
Memristive hysteresis

F.Puppo, al et S. Carrara, IEEE ISCAS 2014, 2257-2260



Fully punched Memristive Hysteresis is registered on bare nanowires

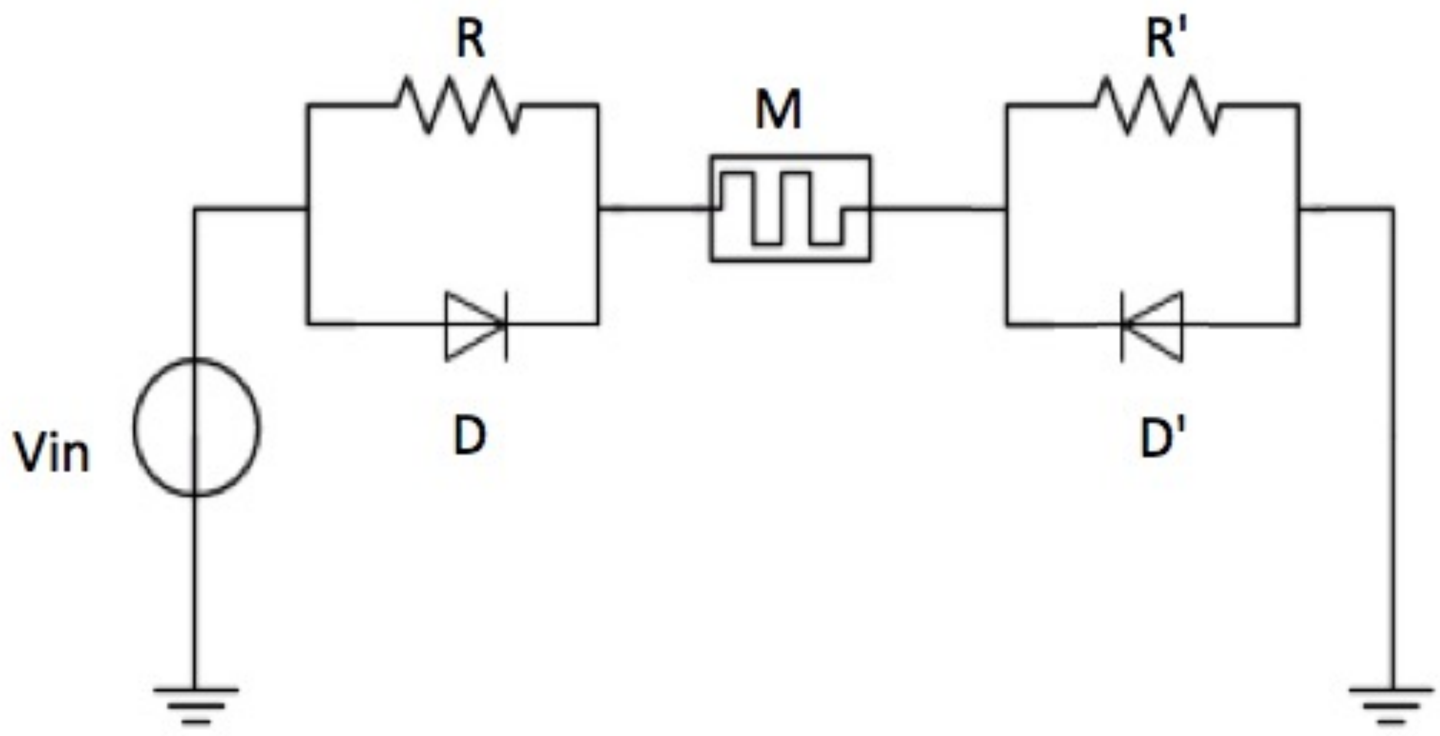
Strukov/Williams Theory



D.B. Strukov, al et S.Williams, Nature 2008

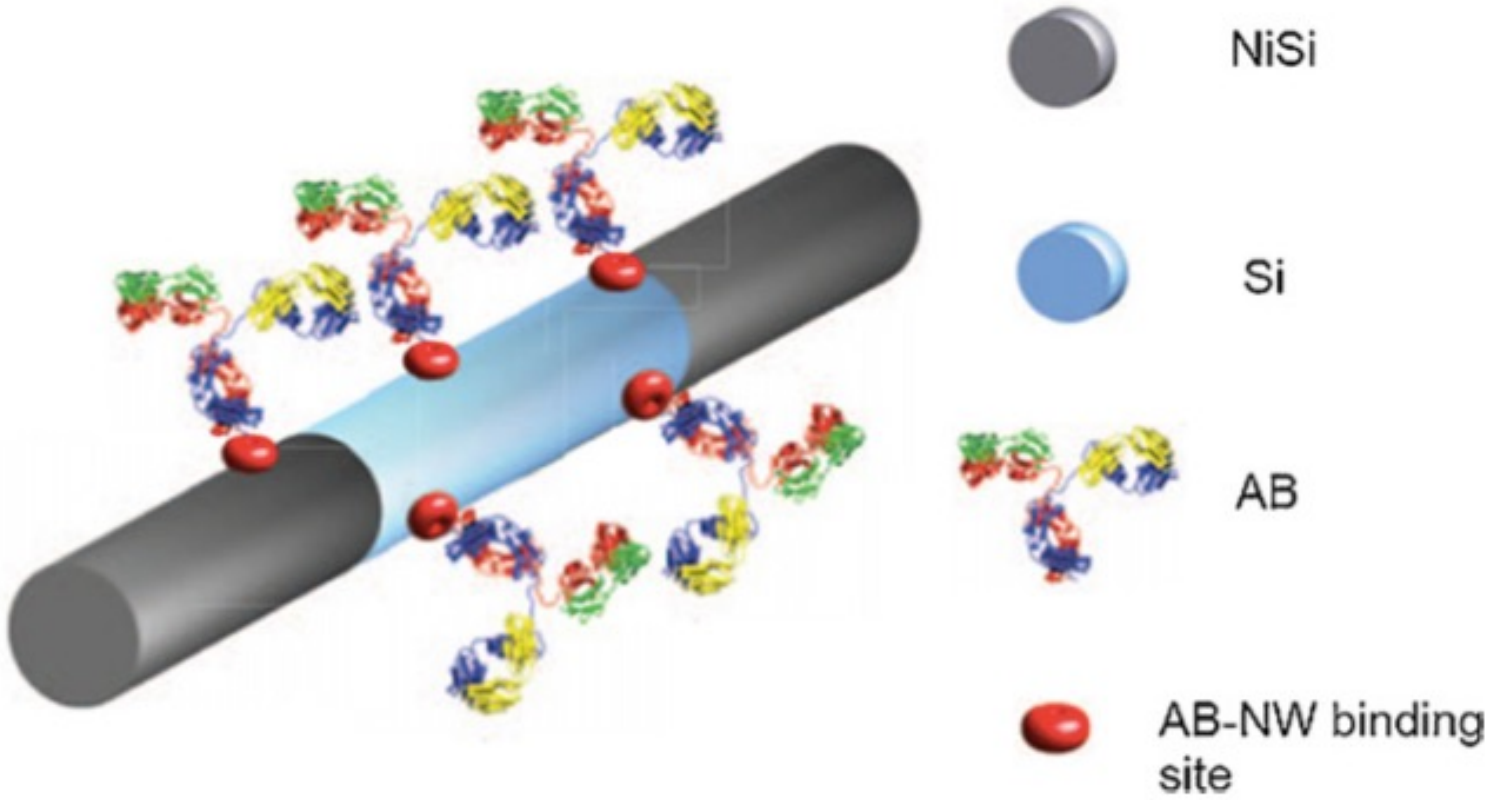
w-state model

Memristive Model



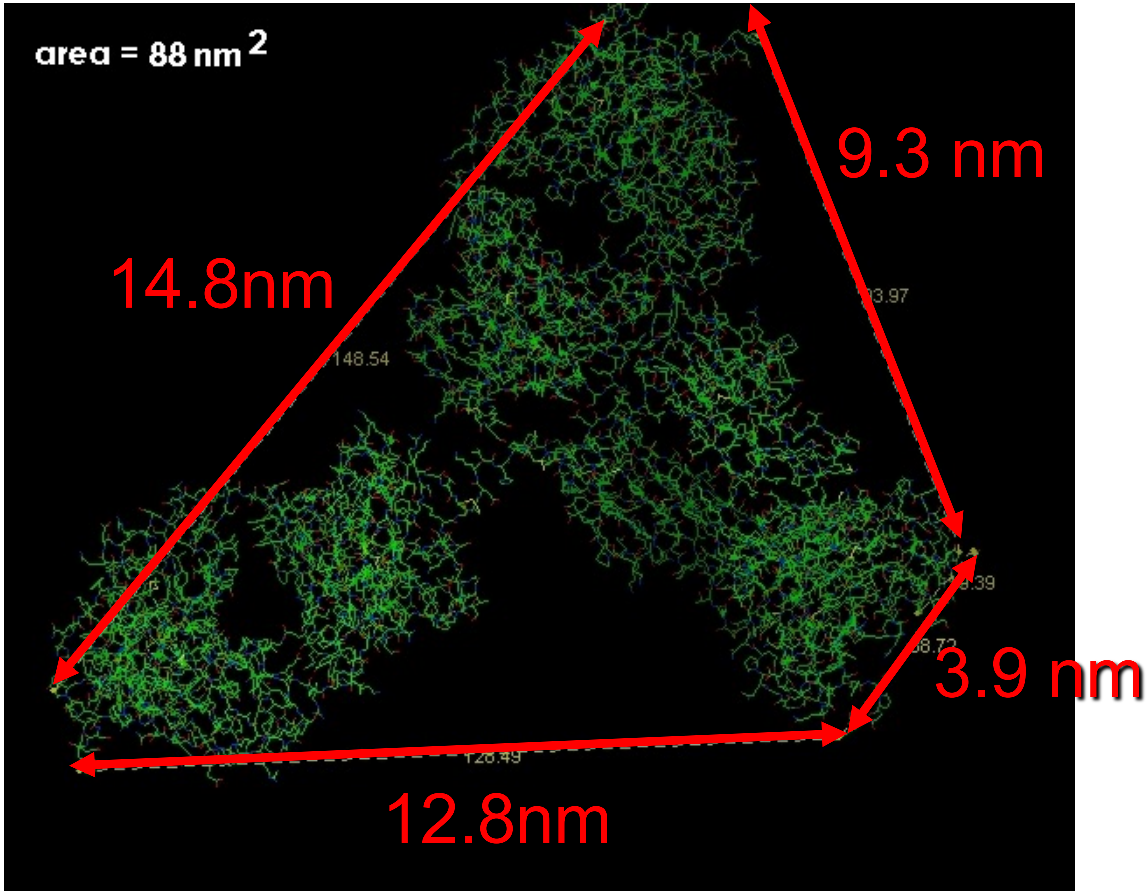
Model of our Nanowires based on a pure Memristor and two Schottky Barriers

Bio-Functionalization



Antibodies against VEGF are deposited by covalent binding on the surface of sensing **NANO**-wires

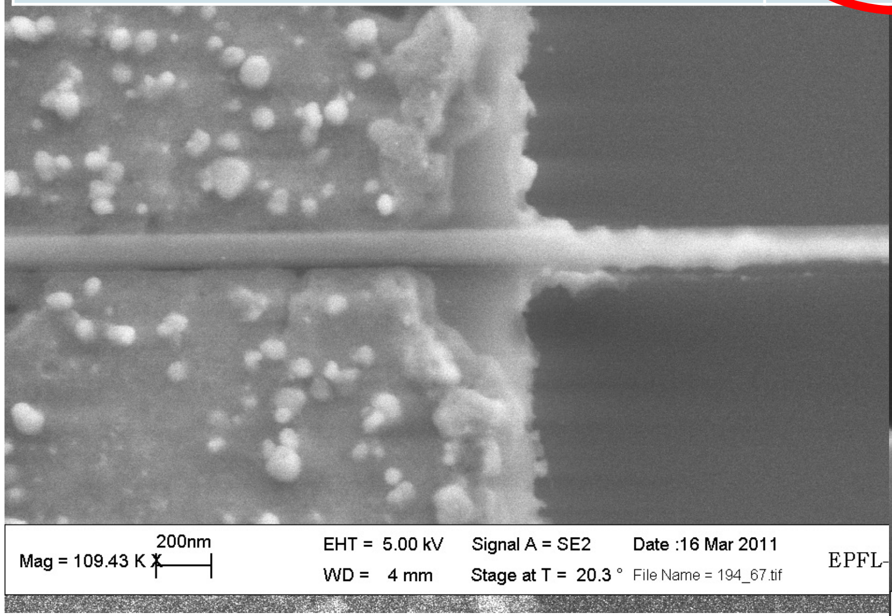
The size of an Antibody

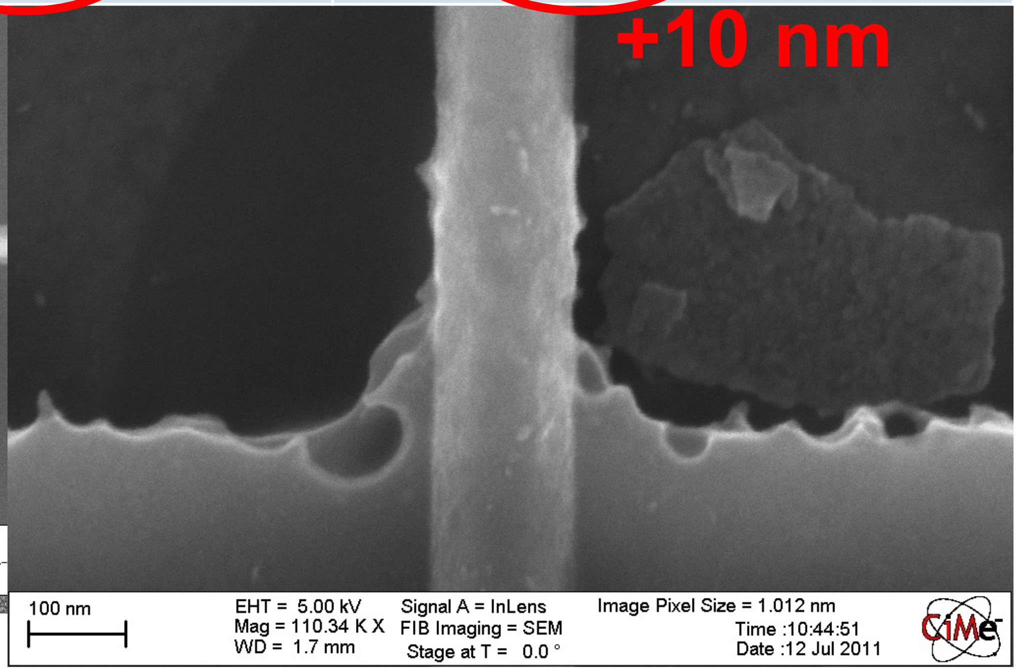


Bio-Functionalization by SEM

Diameter measurements:

	Nanowire	Nanowire + Antibody
Mean Diameter (nm)	128.21±8.57	138.93±3.93

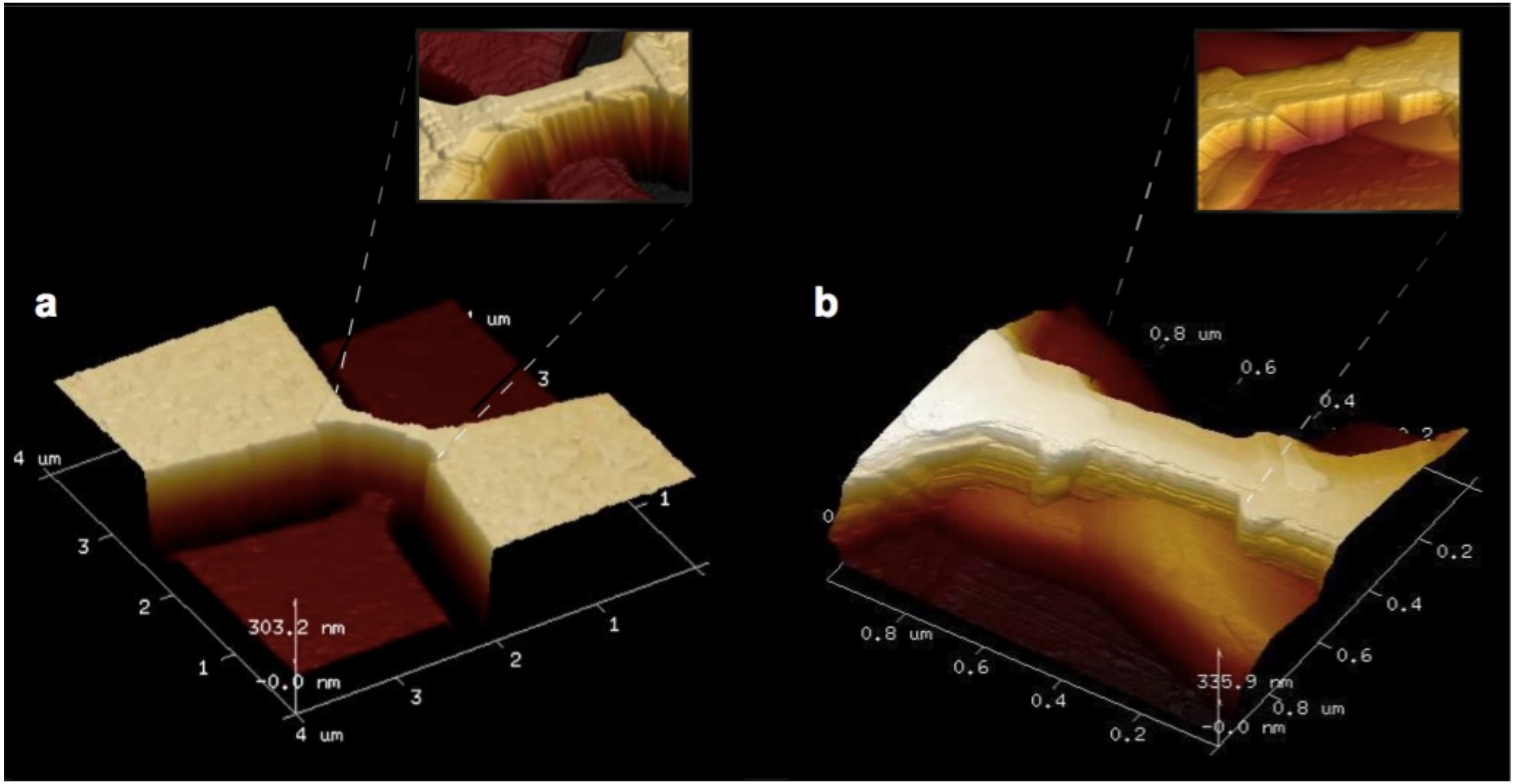




Before (left) and after (right) modification with anti-VEGF antibodies

Bio-Functionalization by AFM

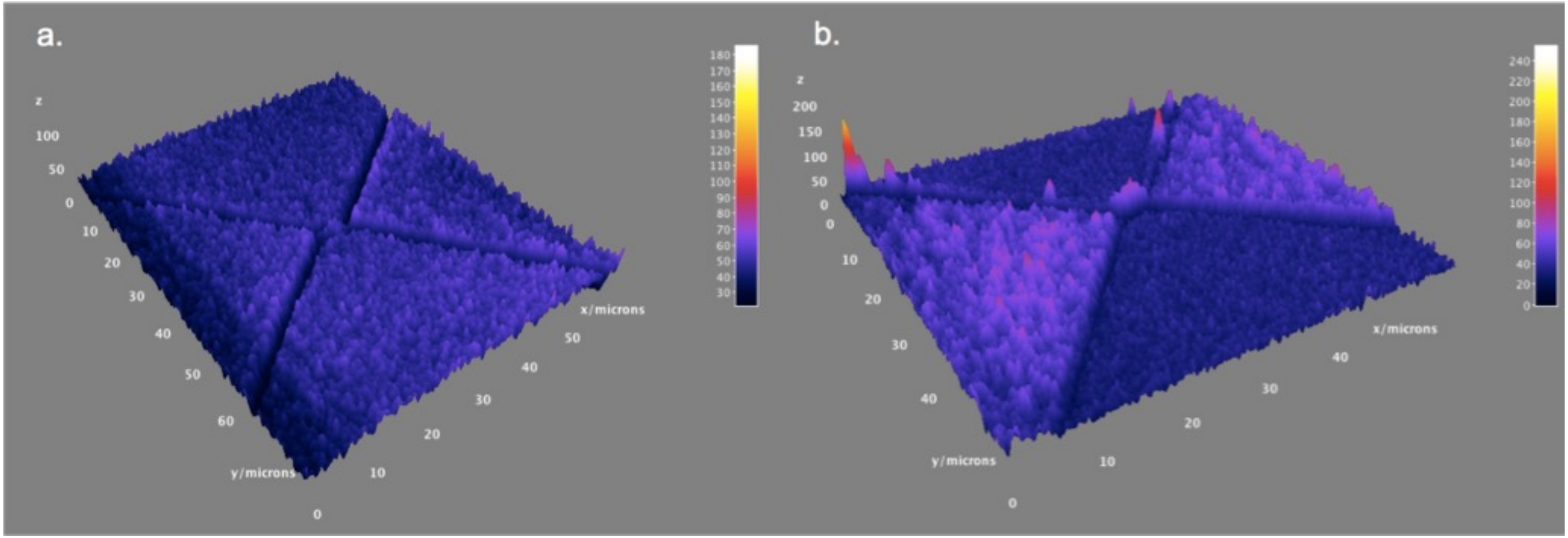
I. Tzouvadaki et al., Journal of Materials Chemistry B., 2016, in press



Before (left) and after (right) the modification with PSA antibodies

Bio-Functionalization by Fluorescence

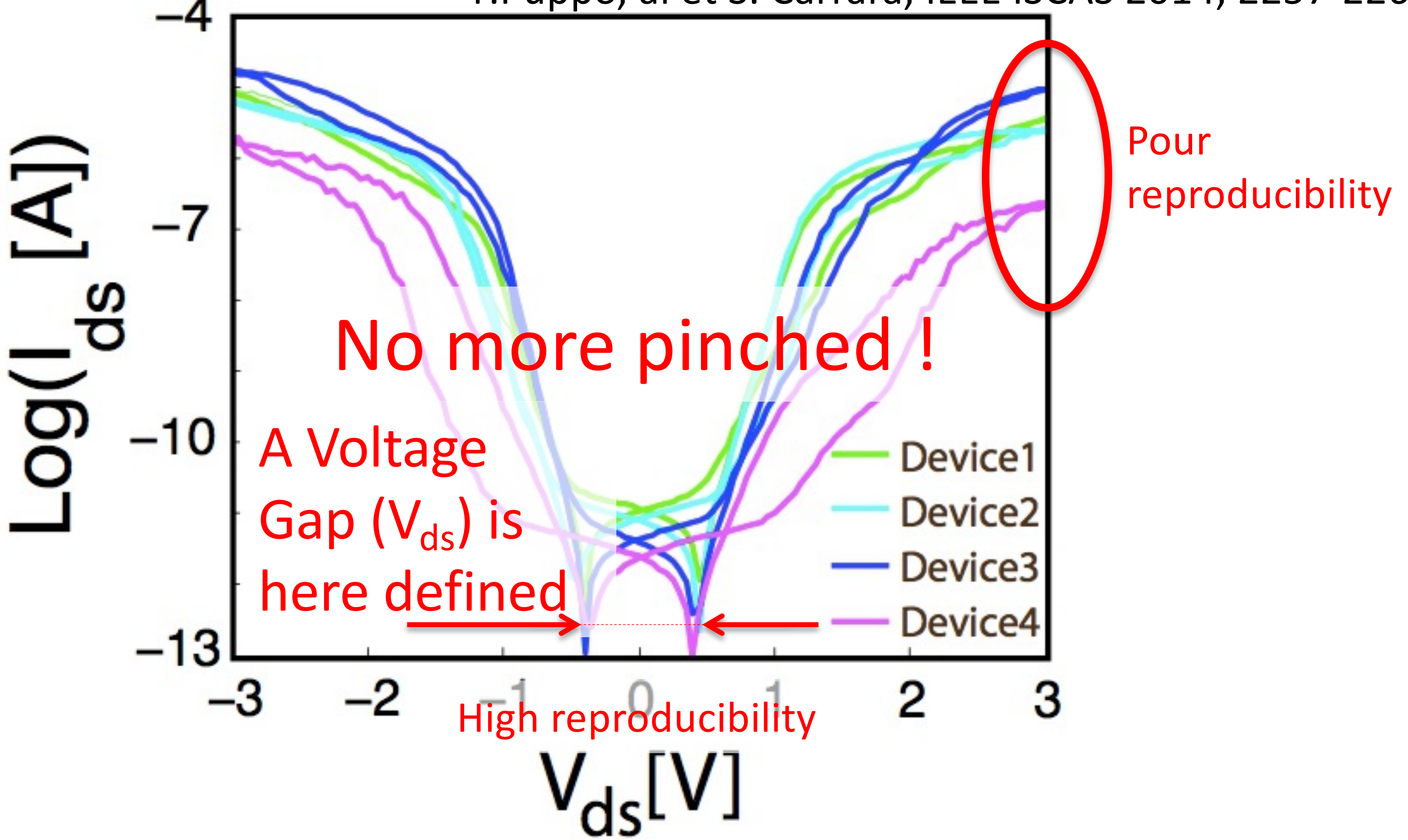
I. Tzouvadaki et al., Journal of Materials Chemistry B., 2016, in press



Before (left) and after (right) the modification with PSA antibodies

Functionalization with Antibodies

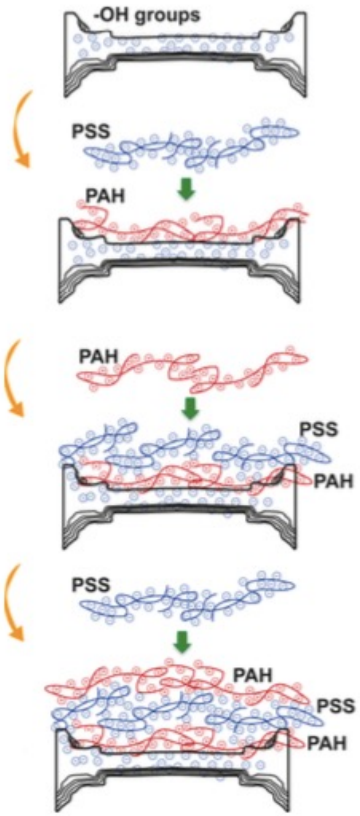
F.Puppo, al et S. Carrara, IEEE ISCAS 2014, 2257-2260

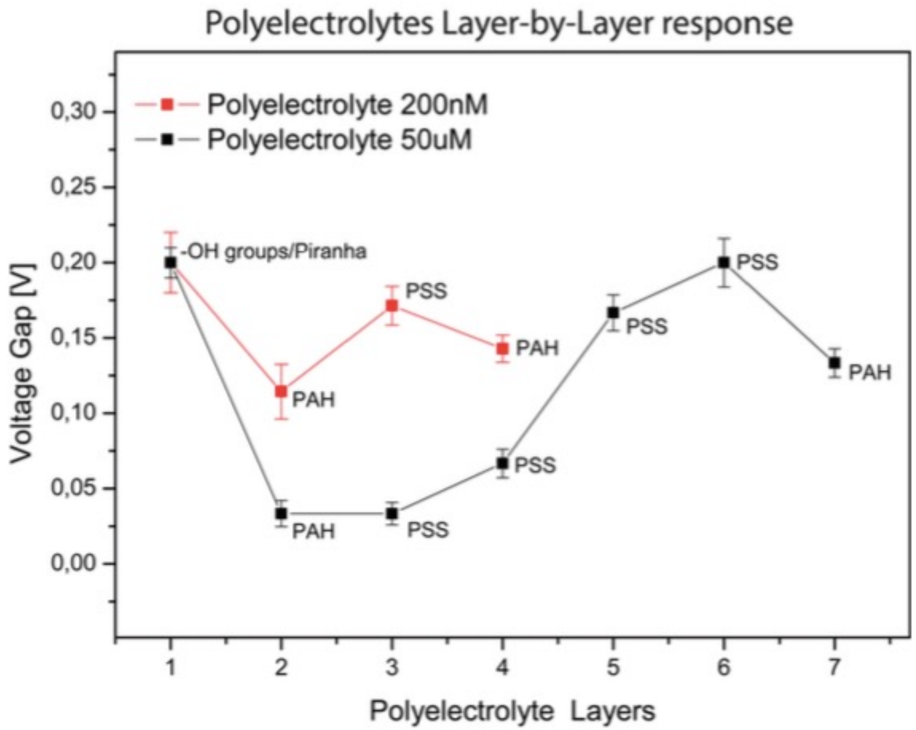


Fully punched Memristive Hysteresis is lost on bio-functionalized nanowires

Layer-by-Layer Charges Transfer

I. Tzouvadaki et al., Nano Letters, 16(2016) 4472-4476

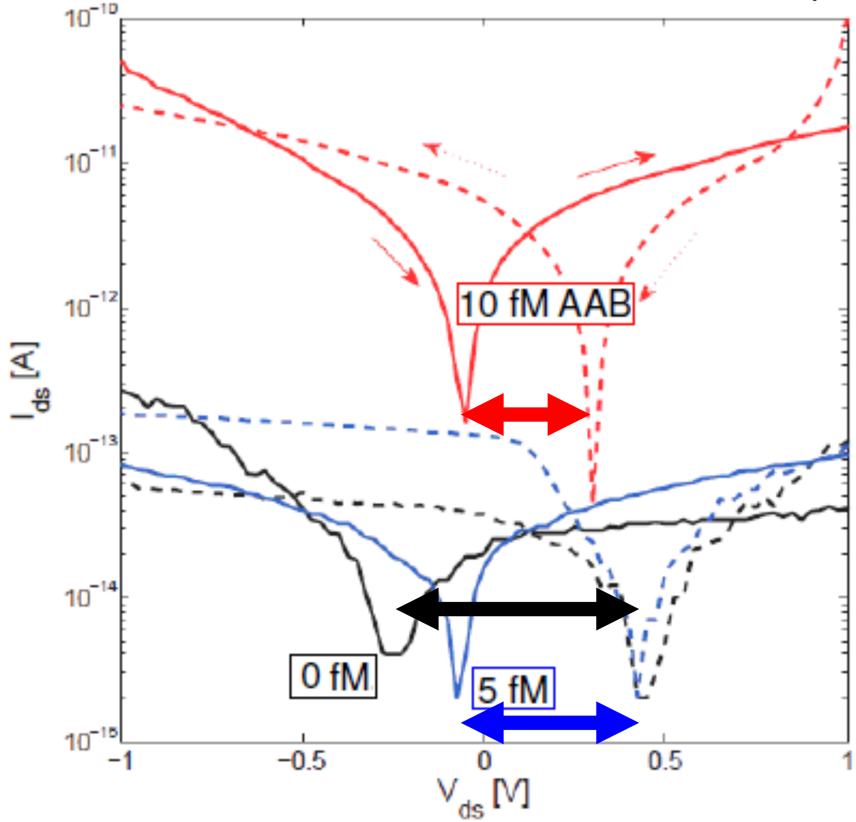




Negatively (PSS) or Positively (PAH) charged polymers change the V_{gap} in opposite directions

Bio-Detection affects Memristive lost

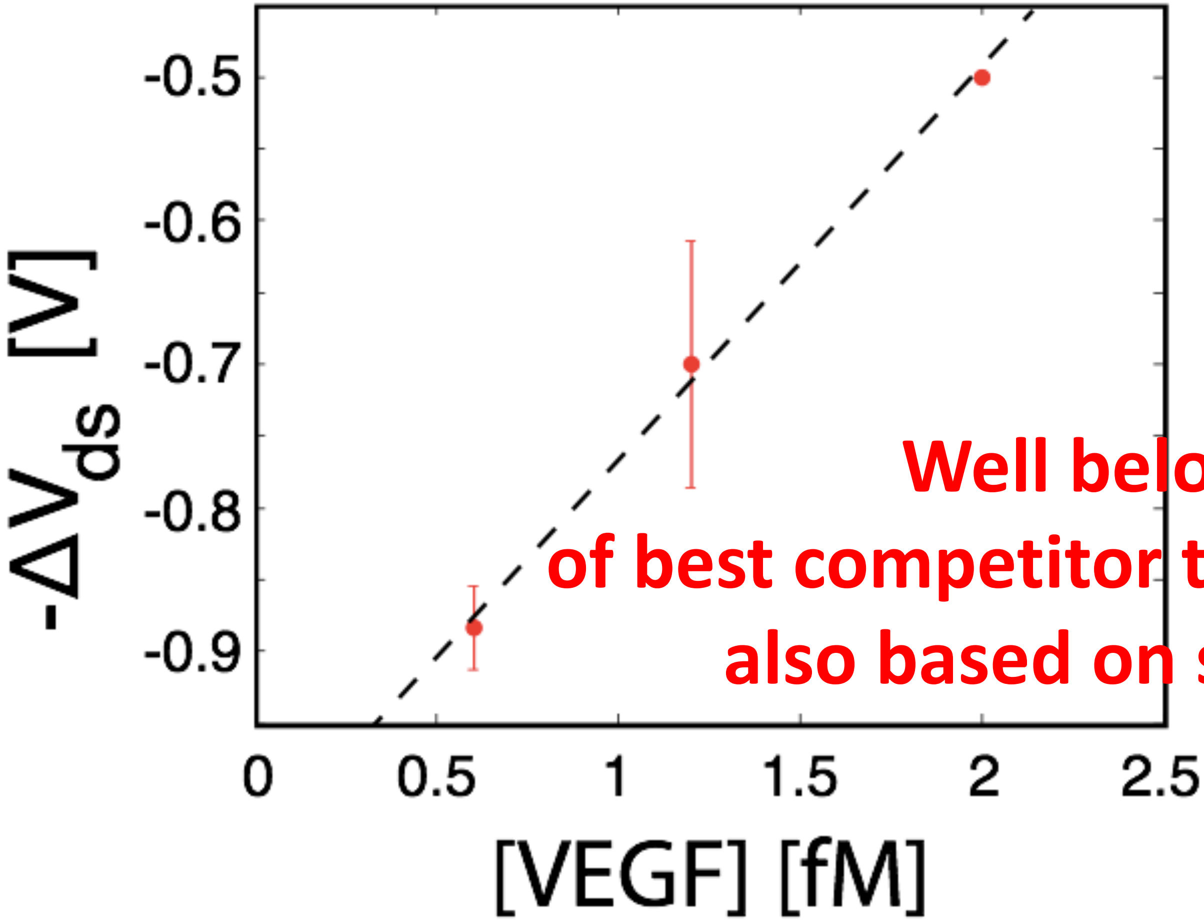
S. Carrara, D. Sacchetto et al. / *Sensors and Actuators* B 171–172 (2012) 449–457



Current minima gaps clearly showing the trend of memristive-biosensors behavior with increasing antigen concentration

Tumour Marker Detection

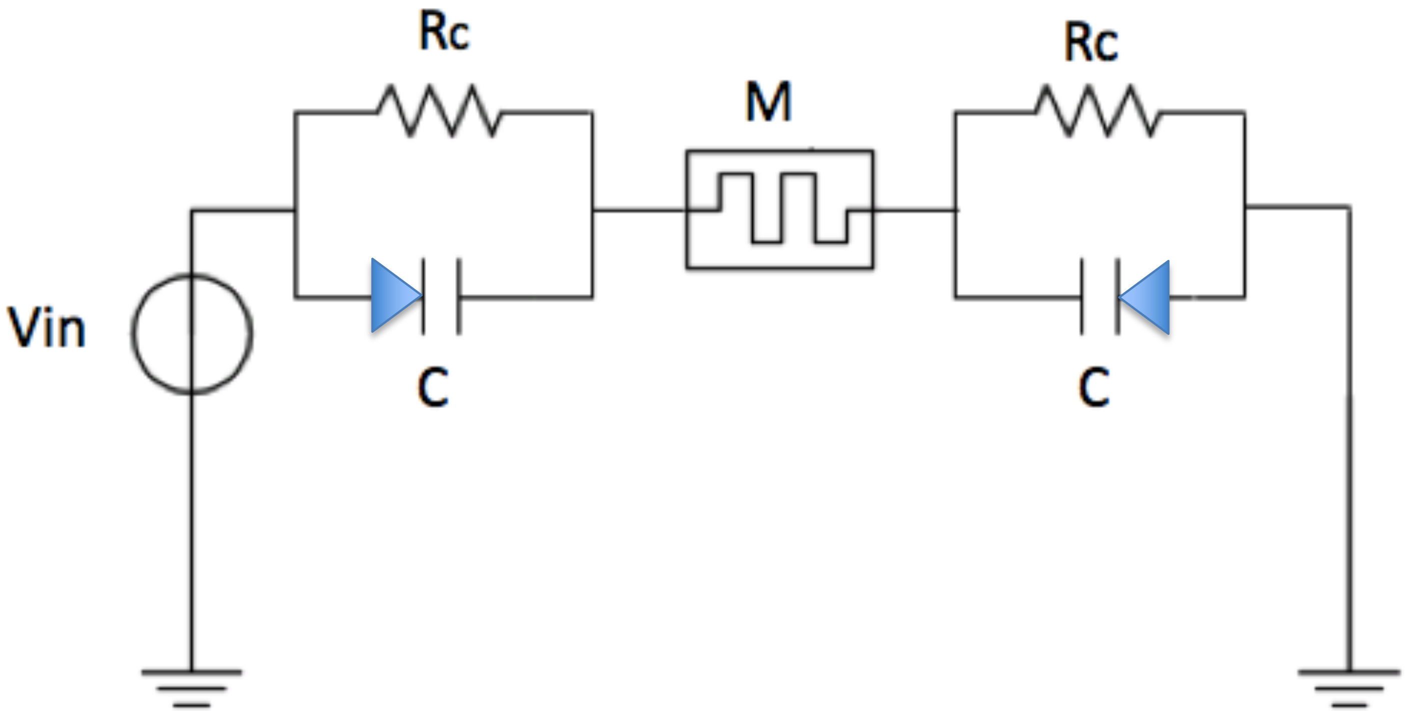
F.Puppo, al et S. Carrara, IEEE ISCAS 2014, 2257-2260



Well below 27,3 fM of best competitor technology also based on silicon NW

The Voltage Gap (V_{ds}) is used to detect the Vascular Endothelial Growth Factor (VEGF)

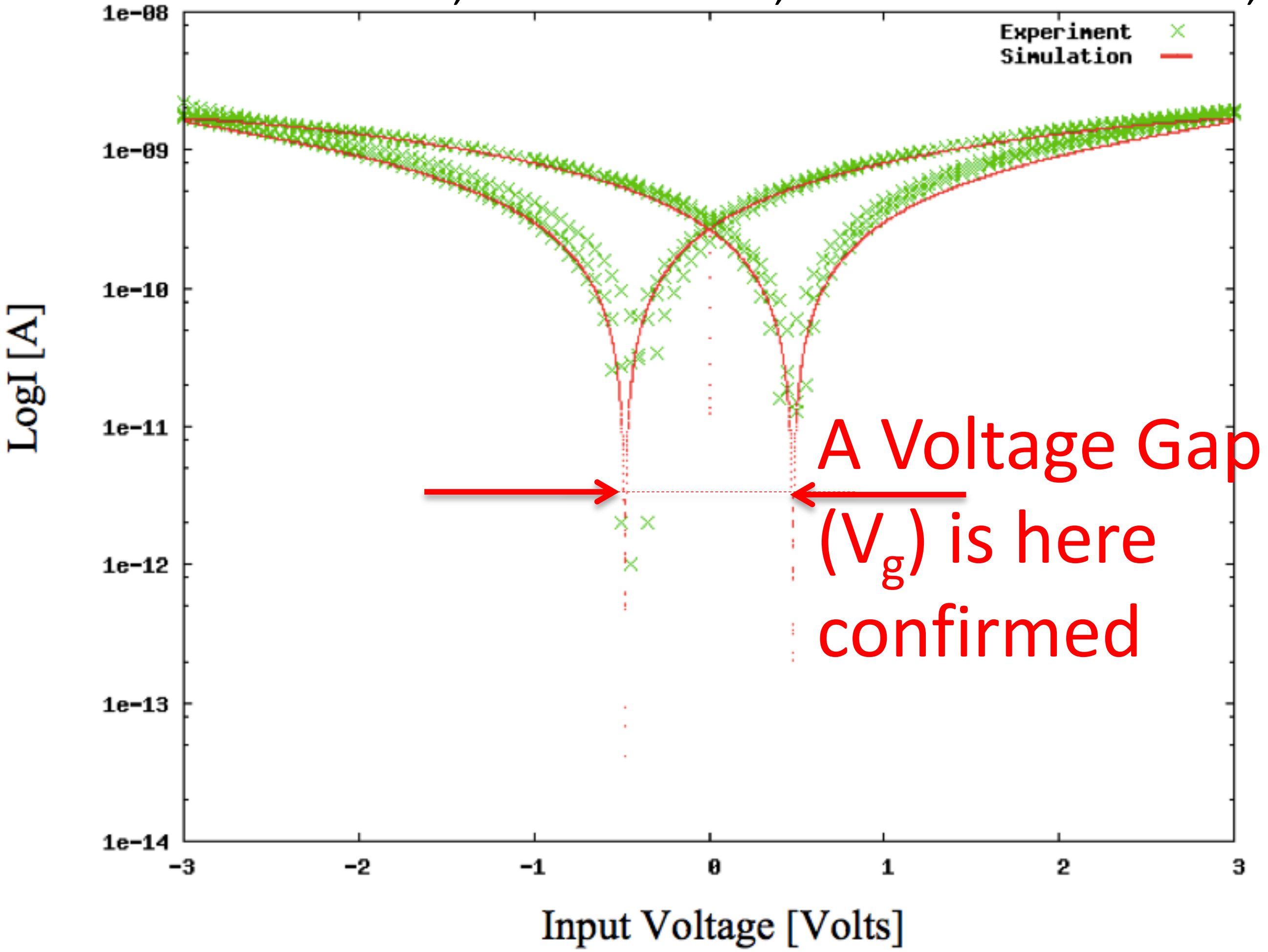
Memristive Model



The Non-pinched Hysteresis is initially modelled by the capacitance of the two Schottky Barriers

Memristive Model Results

I. Tzouvadaki, al et S. Carrara, *Sensors & Actuators B*, 2014, submitted



The Model fit very well the non-pinched Hysteresis acquired on bio-functionalized nanowires

Memristive Model

I. Tzouvadaki, al et S. Carrara, *IEEE Sensors Journal 15*(2014) 6208-6217

Antigen concentration [fM]	Voltage gap [Volts] *Experimental values* [9]	Capacitance (C) [nF]	Voltage gap [Volts] *Simulation values*
0	0.84	36	0.844
5	0.56	24	0.563
10	0.37	15	0.362

Typical values of the excess capacitance reported in literature are **around 43nF**. It is the combination of the space charge capacitance characterizing the diode and of the diffusion capacitances due to the carriers injection

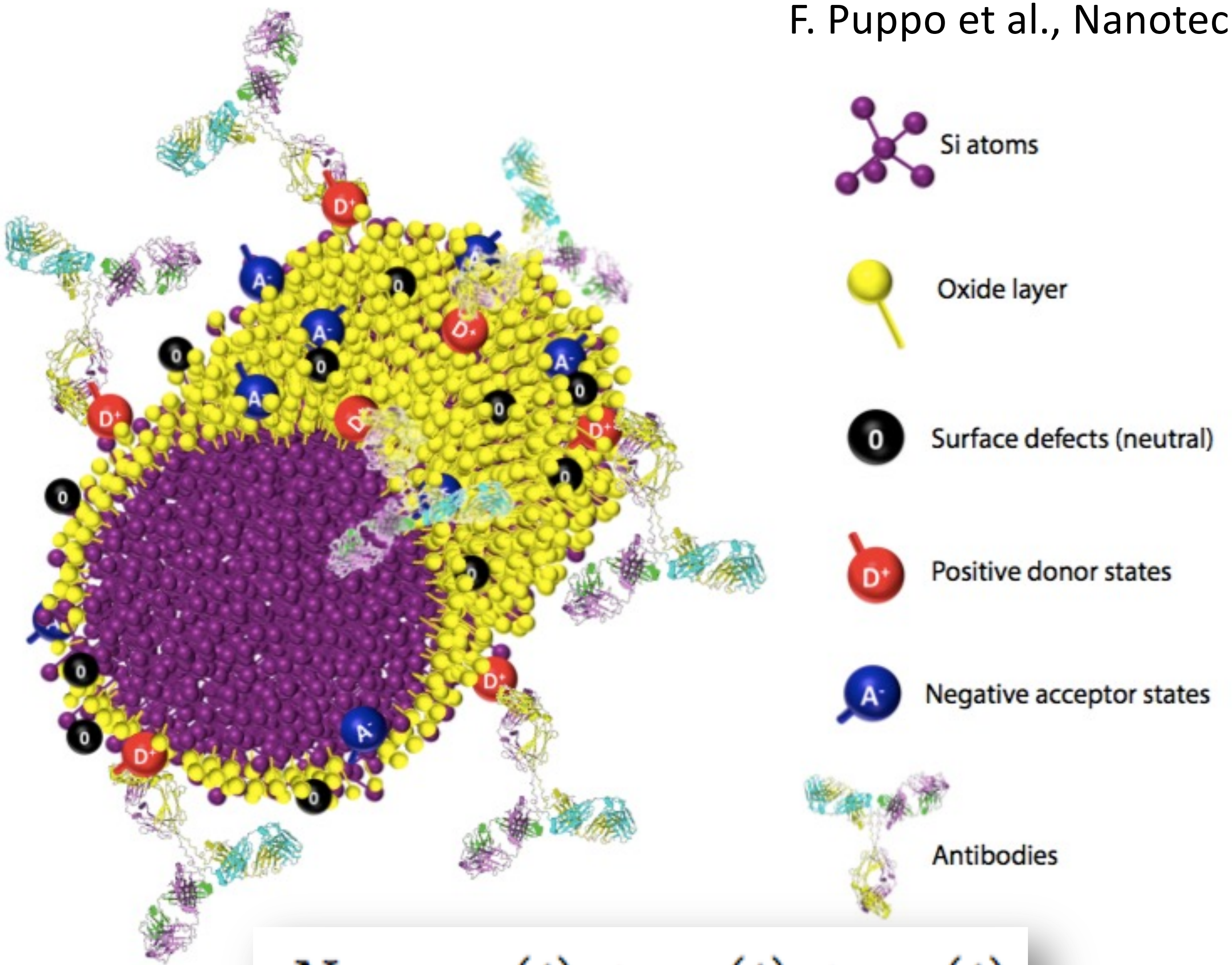
J. Werner, et al., *Phys. Rev. Lett.*, 1988, **60**, 53-56

While typical capacitance values concerning only contributions by the depletion area are in the range of pF

M. Bleicher & E. Lange, *Solid State Electron.*, 1973, 16, 375-380

Surface Trap Mediated Electronic Transport

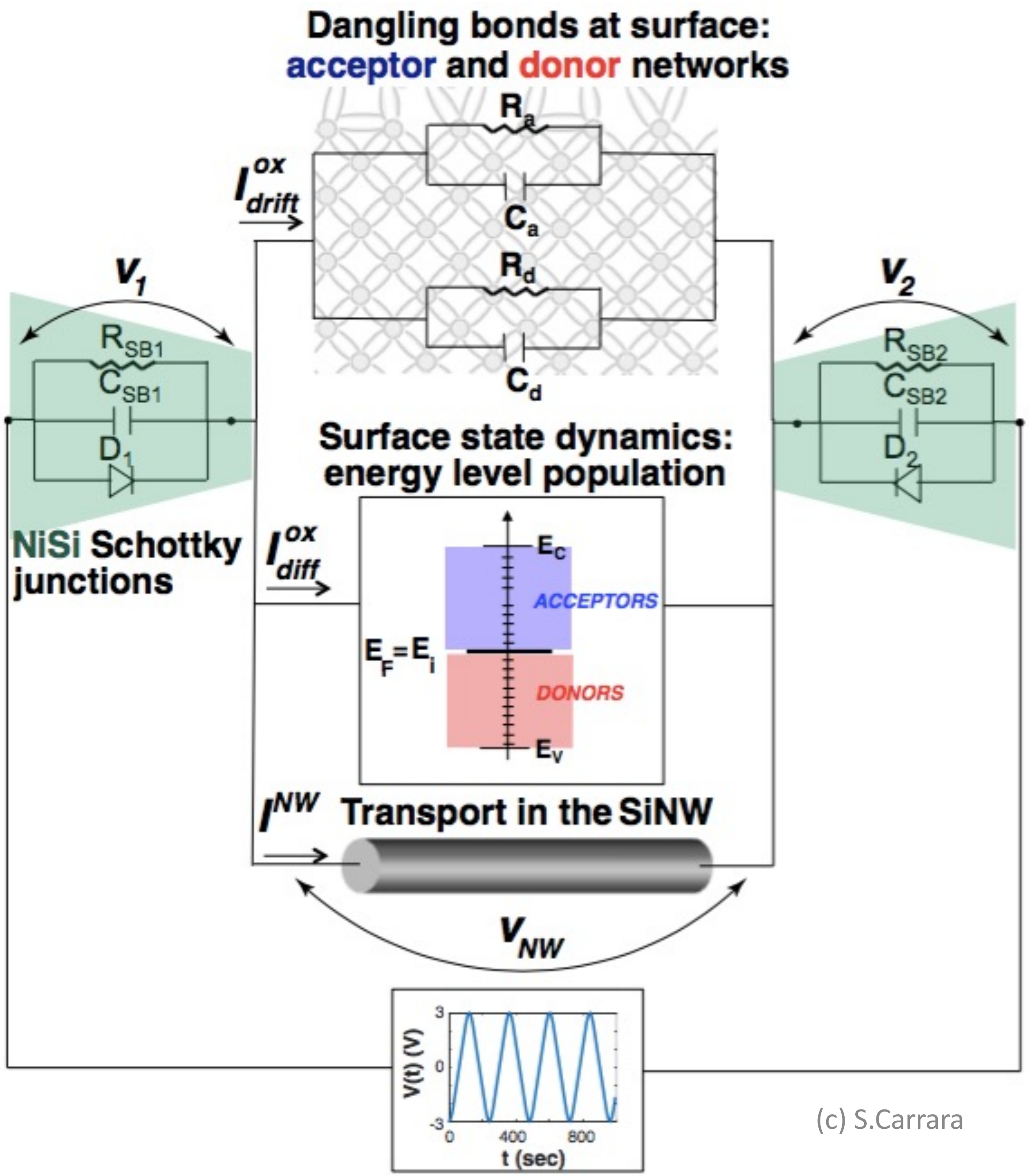
F. Puppo et al., Nanotechnology, 2016



$$N_0 = n_a(t) + n_d(t) + n_n(t)$$

Surface Trap Mediated Electronic Transport

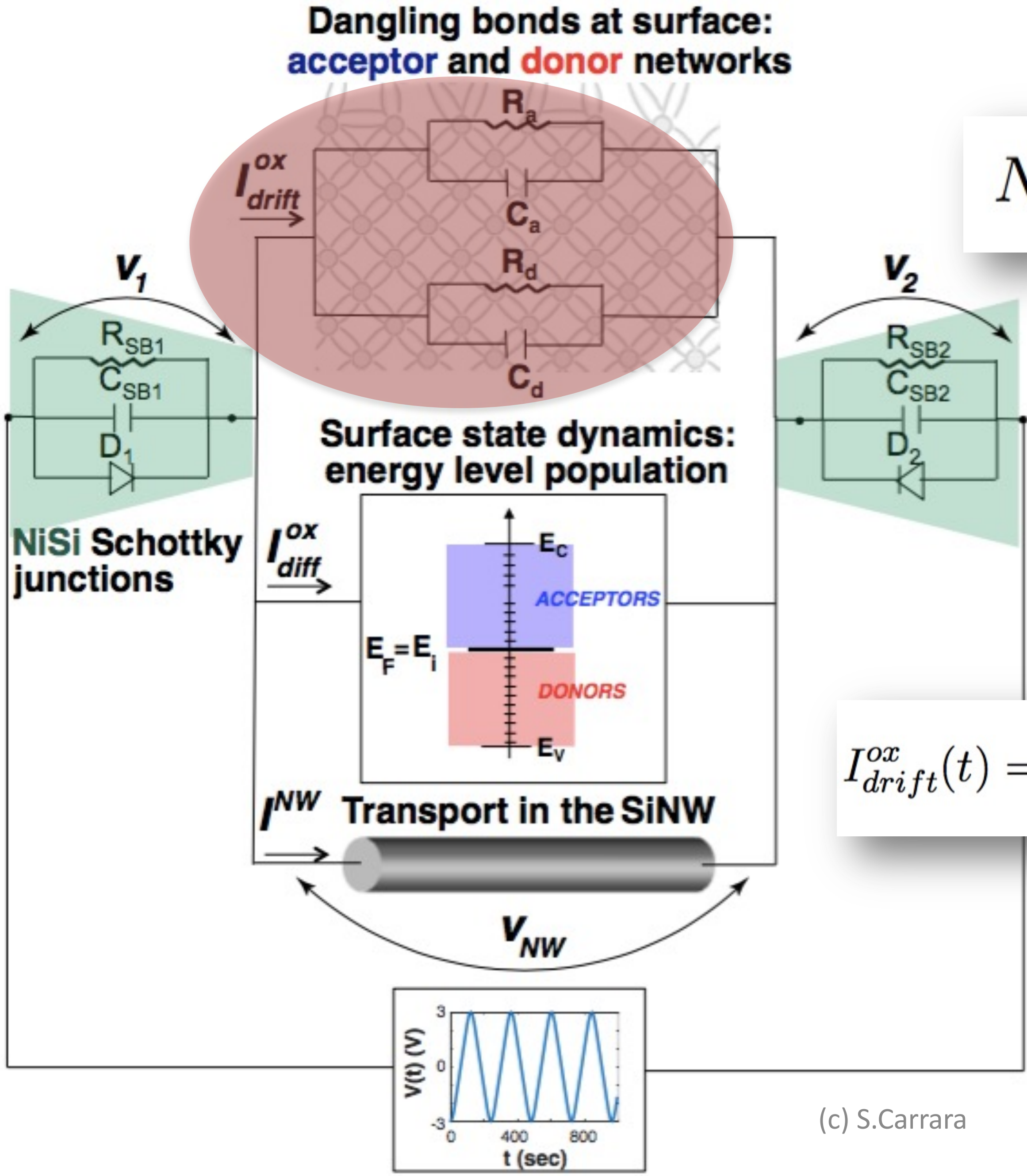
F. Puppo et al., Nanotechnology, 2016,



Equivalent circuit
Modeling the
different mechanisms
of transport in the
memristive nanowire

Surface Trap Mediated Electronic Transport

F. Puppo et al., Nanotechnology, 2016



$$N_0 = n_a(t) + n_d(t) + n_n(t)$$

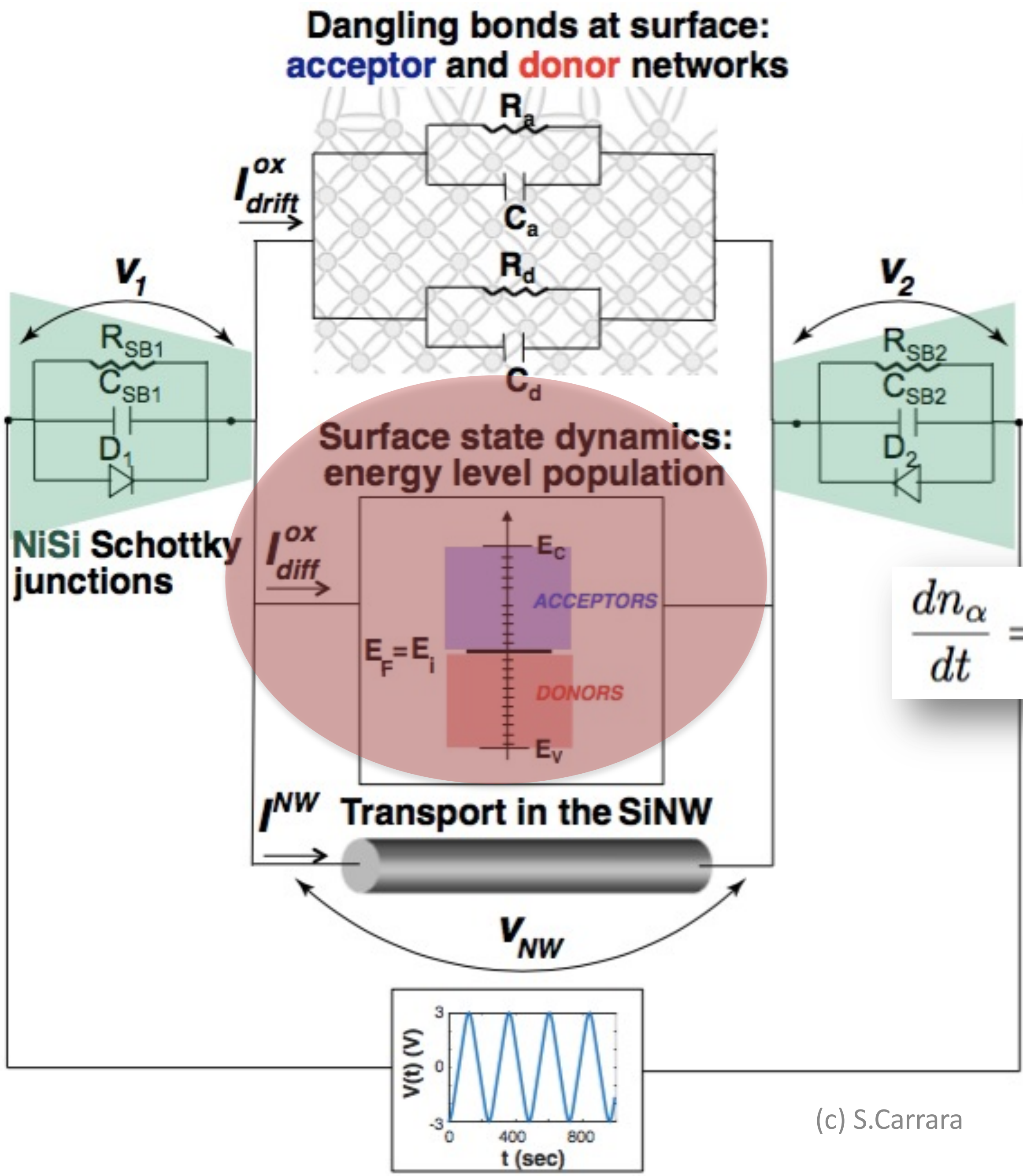
$$R_\alpha = \left[\frac{q n_\alpha \mu_\alpha}{L} A e^{\frac{\Delta E}{k_B T}}\right]^{-1}$$

$$C_\alpha = \tilde{C}_\alpha \frac{n_\alpha(t)}{N_0}$$

$$I^{ox}_{drift}(t) = \frac{R_a + R_d}{R_a R_d} V_{NW}(t) + \frac{d}{dt}[(C_a + C_d) V_{NW}]$$

Surface Trap Mediated Electronic Transport

F. Puppo et al., Nanotechnology, 2016



$$N_0 = n_a(t) + n_d(t) + n_n(t)$$

$$I^{ox}_{diff} = e\left(-f_a \frac{dn_a(t)}{dt} + f_d \frac{dn_d(t)}{dt}\right)$$

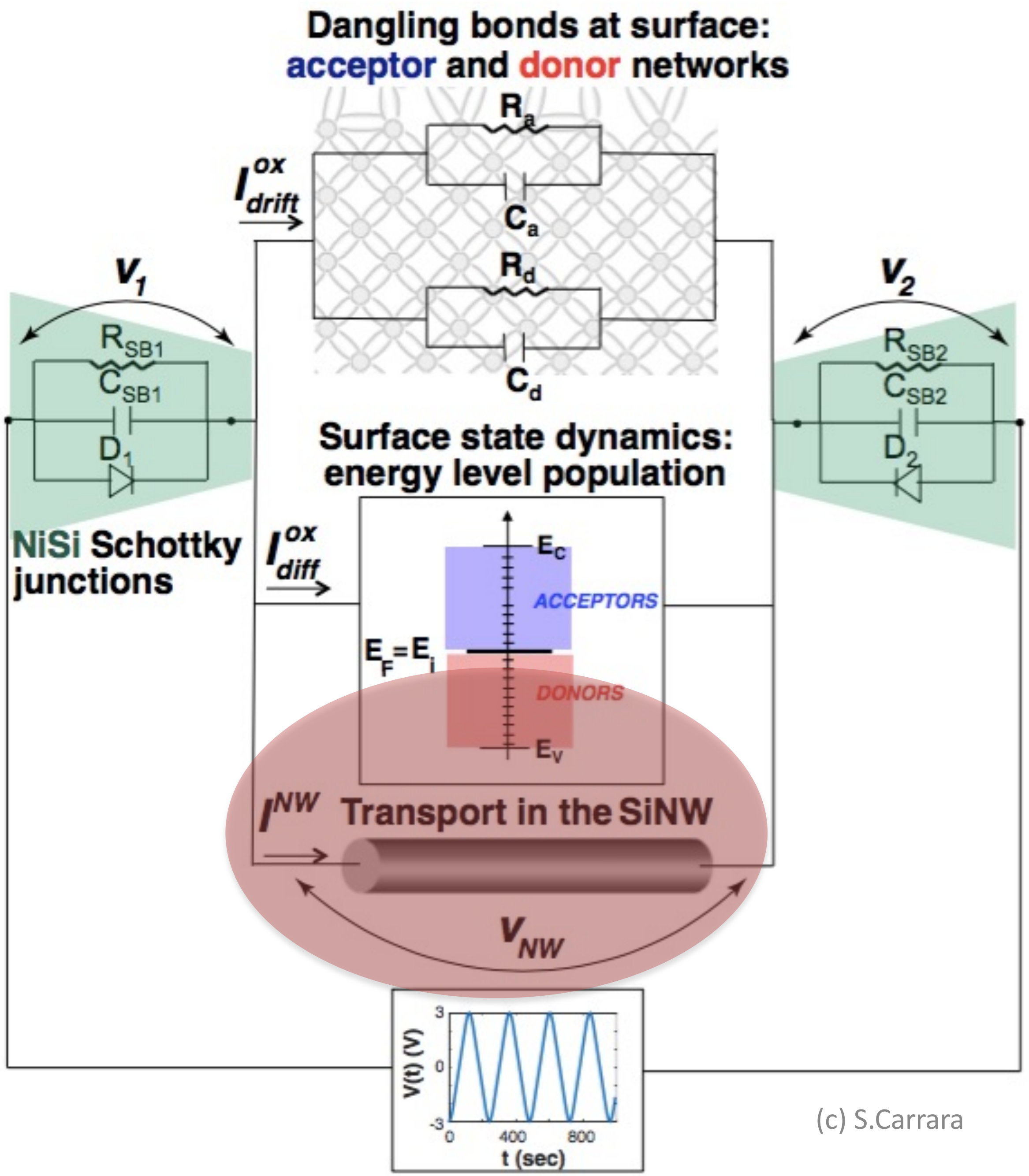
$$\frac{dn_\alpha}{dt} = -k^\alpha_\alpha(V_{NW})n_a + k^\alpha_n(V_{NW})n_n$$

$$k^\alpha_\alpha(V_{NW}) = k^\alpha_{\alpha 0} e^{\frac{-\beta_\alpha(E^\alpha_\alpha - eV_{NW})}{\sigma T}}$$

$$k^\alpha_n(V_{NW}) = k^\alpha_{n0} e^{\frac{(1-\beta_\alpha)(E^\alpha_n - eV_{NW})}{\sigma T}}$$

Surface Trap Mediated Electronic Transport

F. Puppo et al., Nanotechnology, 2016

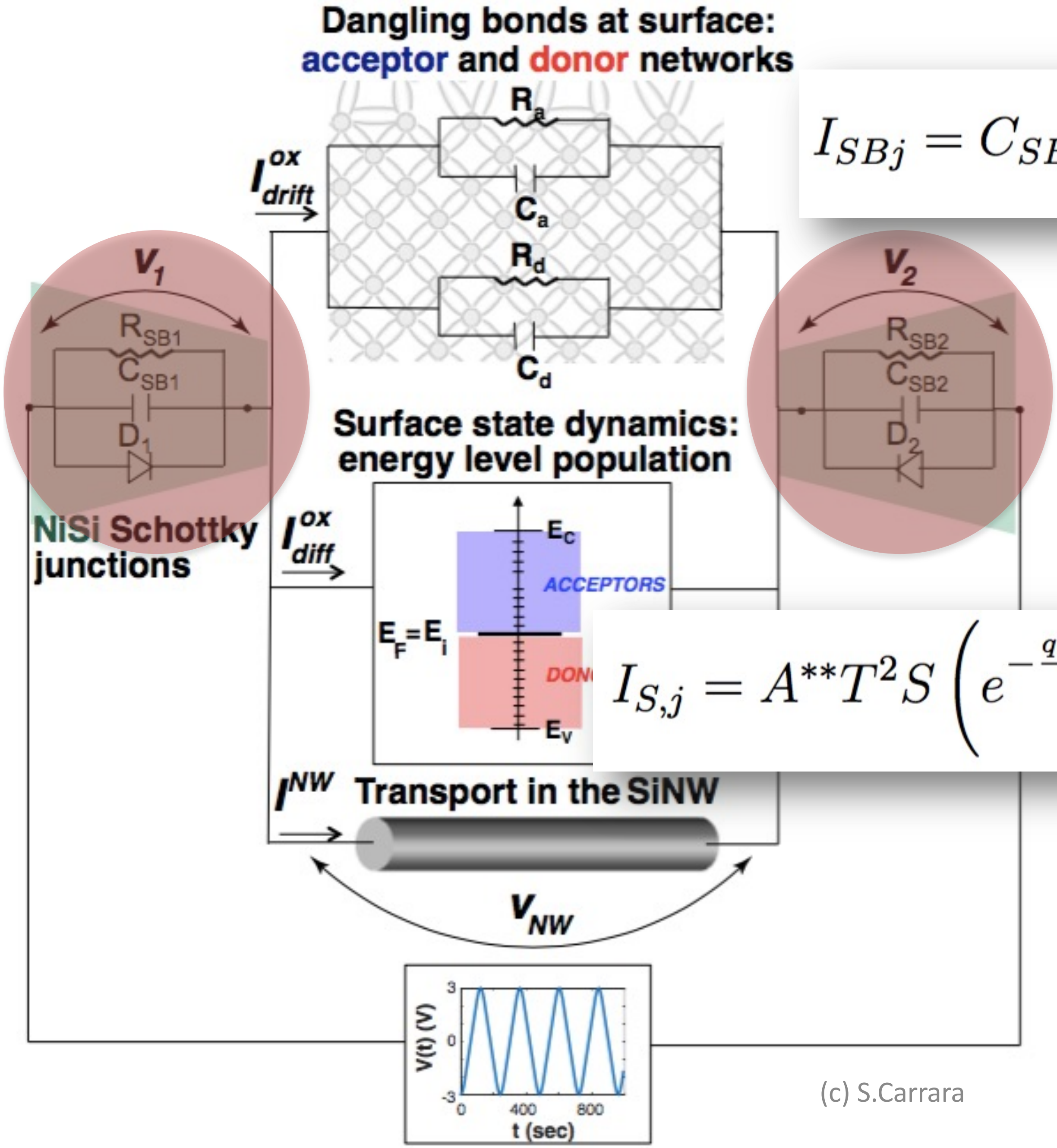


$$I^{NW}_{drift} = \frac{V_{NW}}{R_{Si}}$$

$$I^{NW}_{diff} = -f_s \frac{d(Q_1 + Q_2)}{dt}$$

Surface Trap Mediated Electronic Transport

F. Puppo et al., Nanotechnology, 2016



$$I_{SBj} = C_{SBj}\frac{dV_j}{dt} + \frac{V_j}{R_{SBj}} + I_{Sj}(e^{\frac{qV_j}{k_BT}} - 1)$$

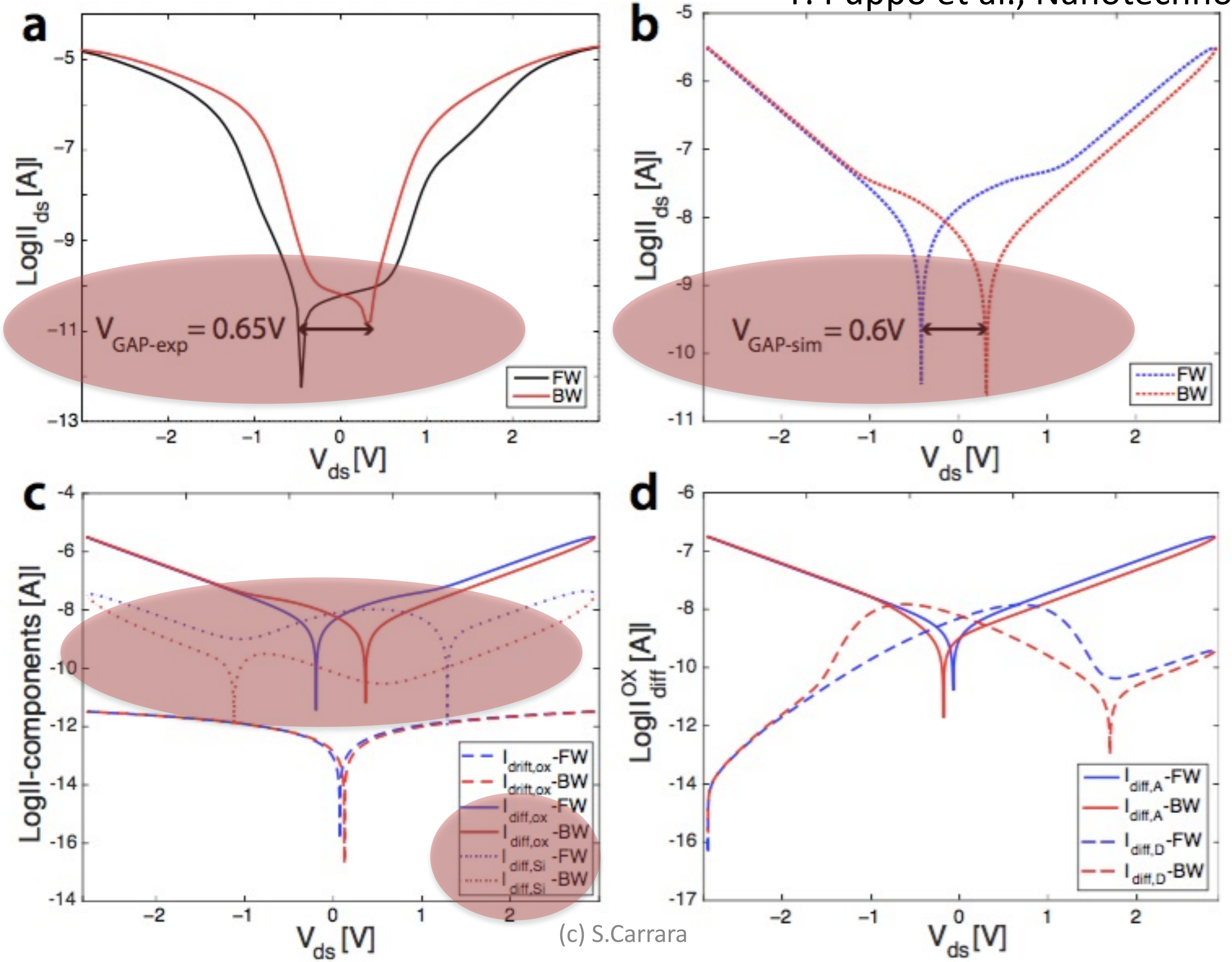
$$C_j = C_{j0}(1 - V_j/\phi_{bi})^{-\gamma}$$

$$R_c = \frac{k_B}{A^{**}Tq}e^{[q\phi_{bi}/k_BT]}$$

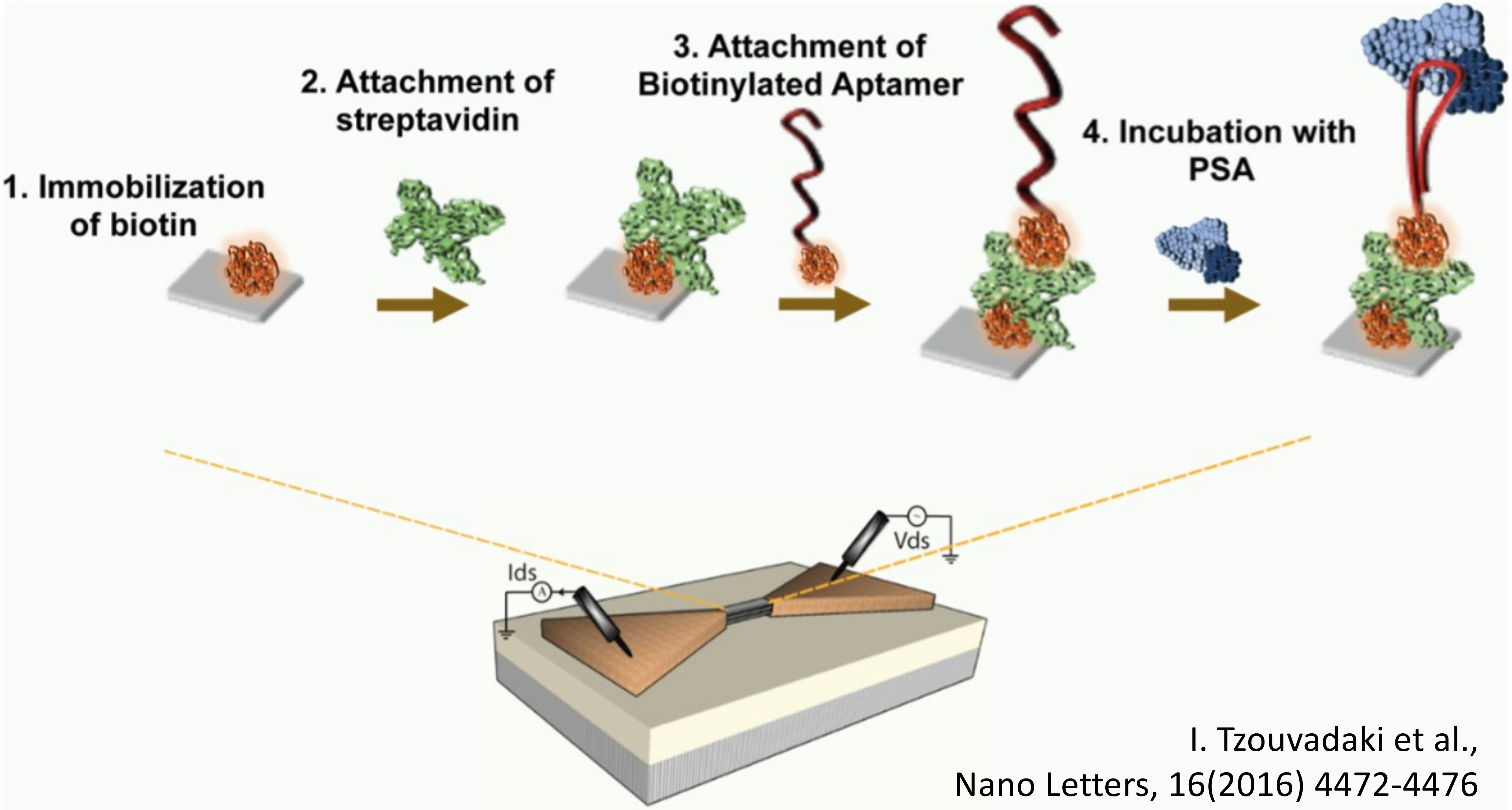
$$I_{S,j} = A^{**}T^2S\left(e^{-\frac{q(\phi_{bi}-\Delta\phi_{bi})}{k_BT}} + e^{-\frac{q(E_{Si,gap}-\phi_{bi}+\Delta\phi_{bi})}{k_BT}}\right)$$

Surface Trap Mediated Electronic Transport

F. Puppo et al., Nanotechnology, 2016



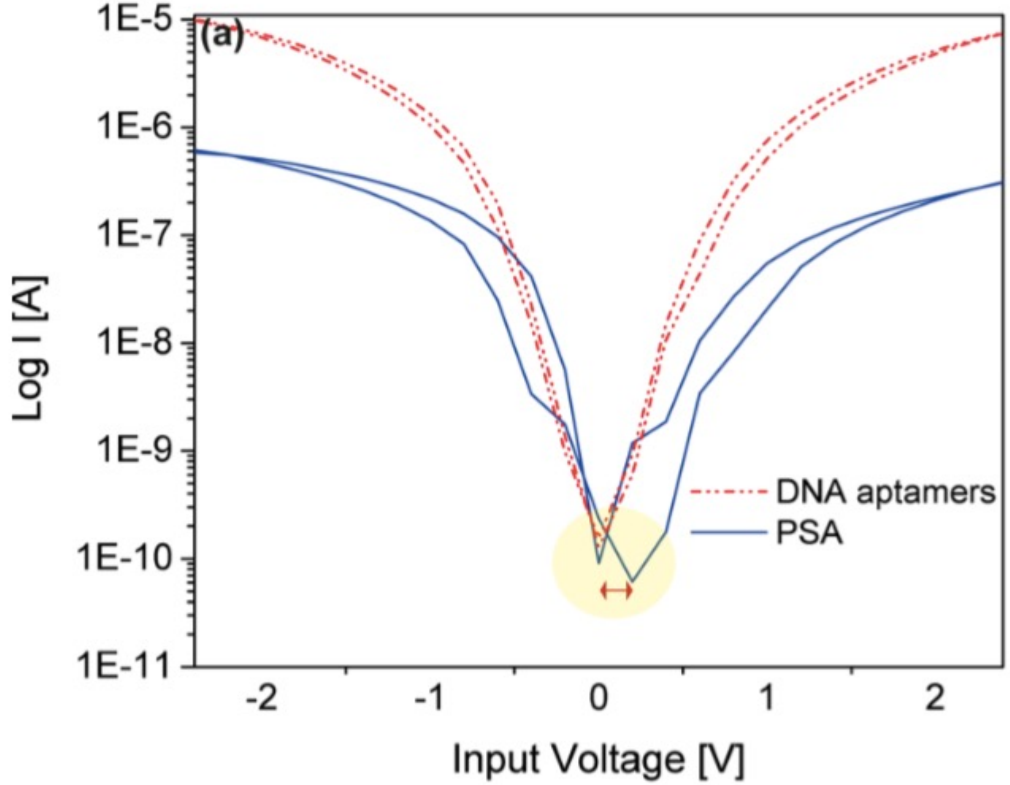
Aptamers Based Memristive Biosensors

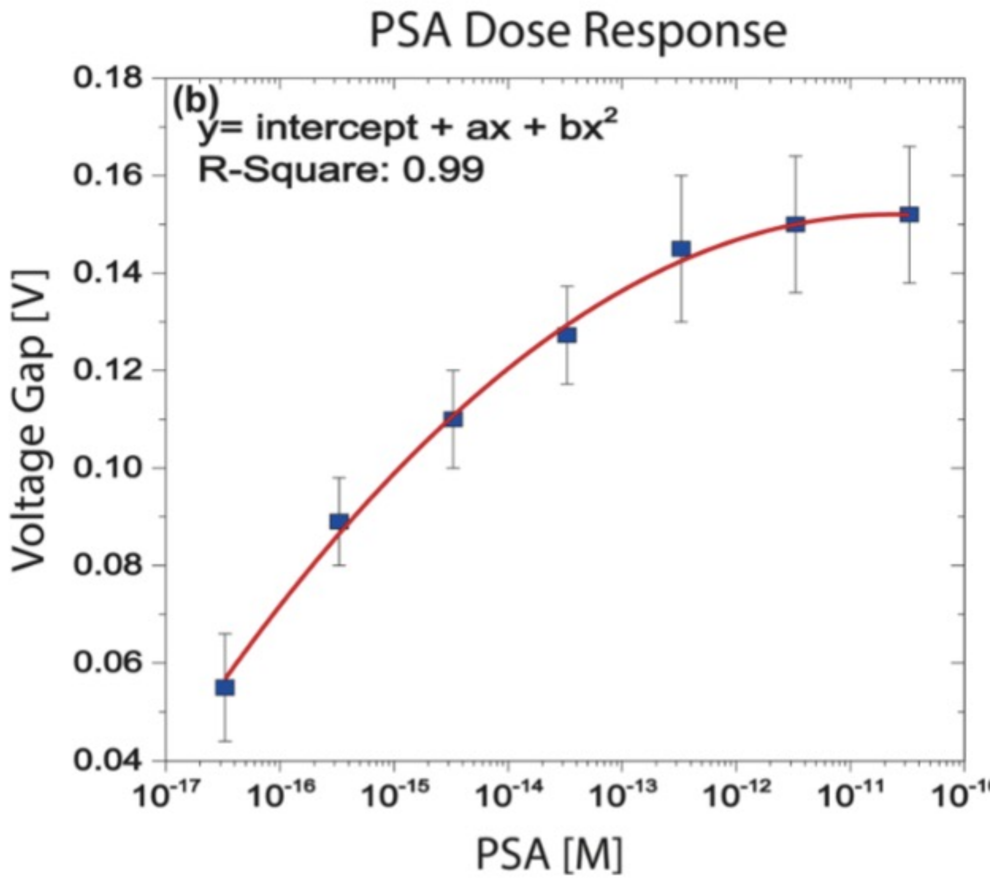


I. Tzouvadaki et al.,
Nano Letters, 16(2016) 4472-4476

Memristive Aptamer Sensor for PSA

I. Tzouvadaki et al., Nano Letters, 16(2016) 4472-4476





(a) V_{gap} upon bio-modification and (b) calibration versus dose(response of 10 sensors)

The Best Aptamer Sensors for PSA

I. Tzouvadaki et al., Nano Letters, 16(2016) 4472-4476

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EIS	gold electrodes	30 pM	Jolly et al.[16] (2015)
differential pulse voltammetry (DPV)	glassy carbon electrode (GCE)	7.6 pM	Liu et al.[17] (2012)
EIS	GCE	0.15 pM	Kavosi et al.[18] (2015)
EIS	gold electrodes	fM range	Yang et al.[19] (2015)
EIS (capacitance measurement)	gold electrodes	30 fM	Jolly et al.[20] (2016)
DPV	GCE	300 aM	Kavosi et al.[18] (2015)
memristive aptasensor	Si-nanowires	23 aM	present work

Our Limit Of Detection (LOD) is now down to 23 aM

Drug Detection: Therapeutics

I. Tzouvadaki et al., Nanoscale, accepted 2017

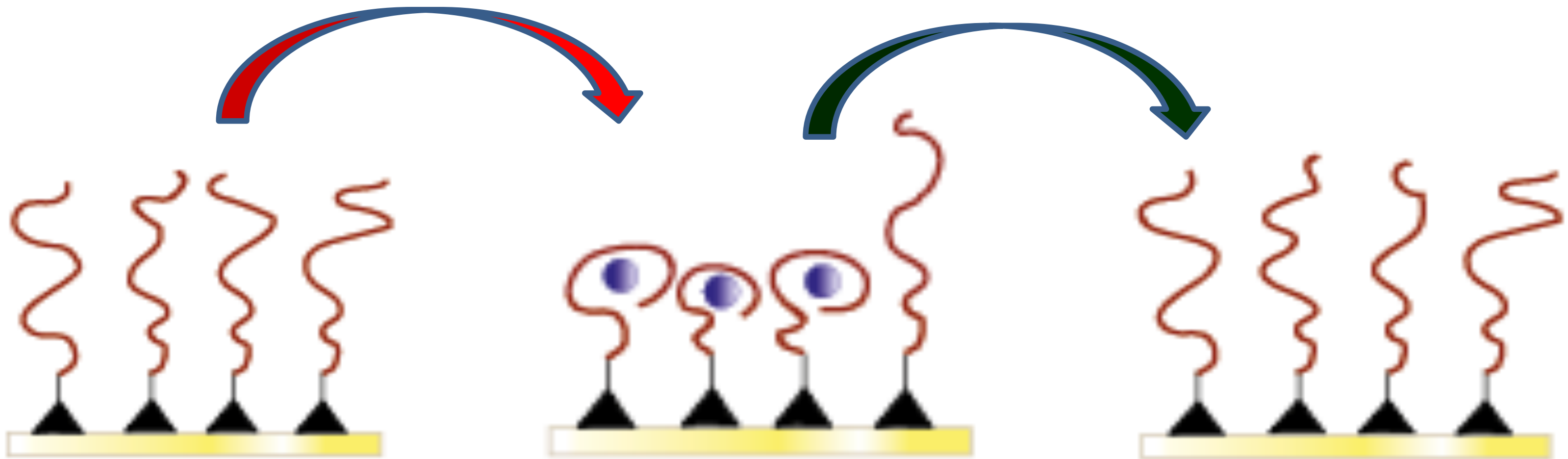
Target drug	Method*	Surface	LOD (nM) Buffer	LOD (nM) Bio-matrix	Linear Range (nM)	Ref.	Comments
6-mercaptopurine	Voltam	Graph-ite/Polypyrrole/MWCNT	-	80	200 - 100000	Karimi-Maleh H. (2015)	Diluted human urine
Paracetamol	Voltam	MWCNT*	2.9	-	5 – 1000	Goyal RN. (2010)	-
Penicillin	Voltam	Boron-dopped diamond	-	320	400 - 100000	Švorc Ľ. (2012)	Human urine
Tamoxifen	Voltam	Enzyme/Polyaniline/Pt	0.2	-	27 - 297	Radhapyari K. (2013)	-
Clenbuteral	Voltam	Benzedithiol-GNPs*	-	43.96	100 - 800	Bo B. (2013)	Diluted rat urine
Chloramphenicol	Ampero	Cds NPs/GNPs	0.14	-	0.15 – 2.94	Kim D-M. (2010)	-
Artesunate	Ampero	Gr-Polyaniline Nano-composite	0.031	0.035	0.13 - 1	Radhapyari K. (2013)	Highly diluted human serum
TFV	BSI	Glass chip	2.5	-	Up to 20	Kammer MN (2014)	-
TFV	LC-MS	-	-	680	1360 to 350000	Simiele M. (2015)	Human urine
TFV	Voltam	HMDE*	450	870	Up to 17000	Jain R. (2013)	Diluted and precipitat-ed human plasma
TFV	LC-UV	-	-	10.4	35 to 3480	Barkil ME. (2007)	-
TFV	LC-MS	-	-	7	35 to 3480	Barkil ME. (2007)	-
TFV	**Field Effect**	**MOSFET**	**1.2 nM**	**-**	**1 to 100**		**-**
TFV	**Memristive**	**Si-nanowire arrays**	**0.0033**	**3.4**	**0.001 to 1000**	**Present work**	**Undiluted Human serum**

Voltam: voltammetry; Conduc: conductance; Ampero: amperometry; BSI: back scattering interferometry; LC: liquid chromatography; MS: mass spectroscopy; UV: ultra violet; MWCNT: multiwalled carbon nanotubes; GNP: gold nanoparticle; HMDE: hanging mercury drop electrode

Aptamer regeneration

- ❑ **Drug Continuous monitoring**

- ❑ **Drug Binding – Aptamer unfolding & Drug release**



(c) S.Carrara

Aptamer regeneration

I. Tzouvadaki et al., Nanoscale 2017