



EDMI Microsystems and Microelectronics

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

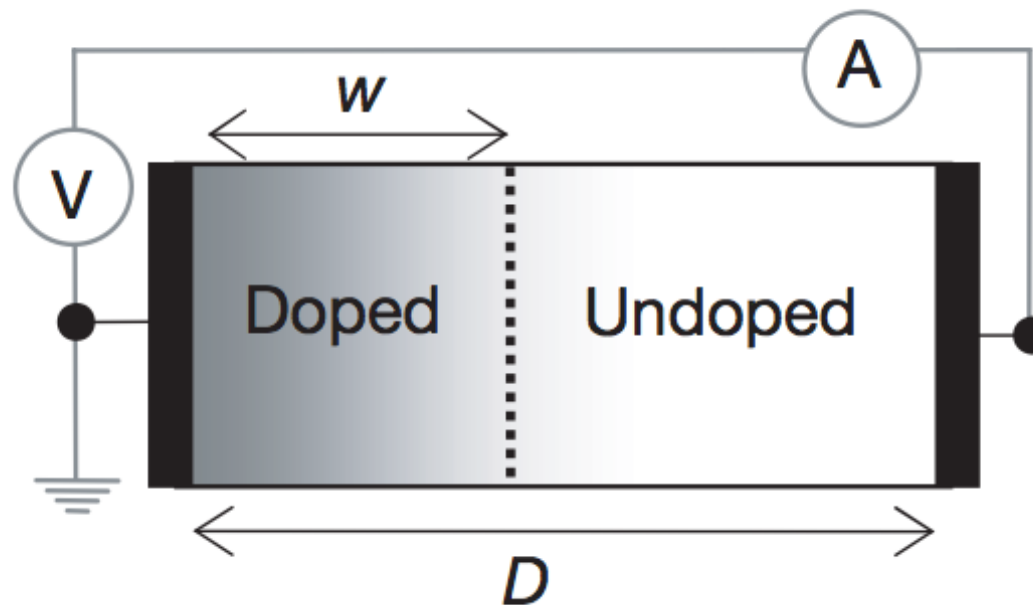
Lecture #14

CMOS for Sensing (and computing!) with Memristors

Memristive Sensors Milestones



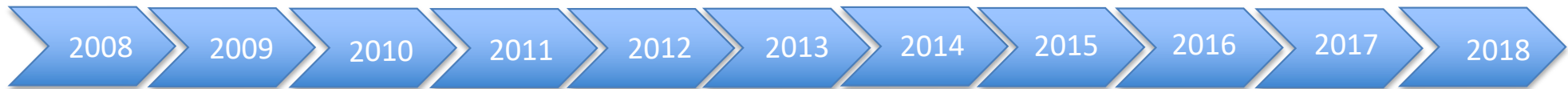
Strukov &
Williams



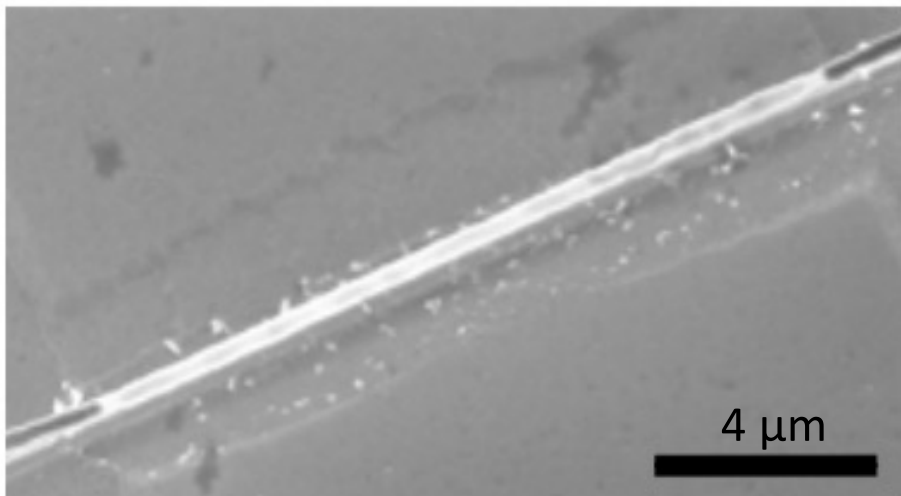
w-state model

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

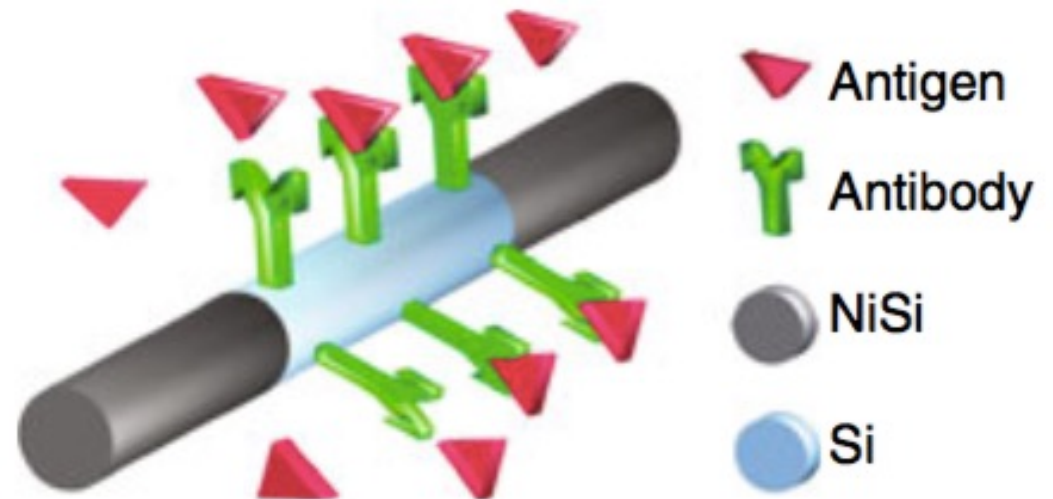
Memristive Sensors Milestones



AntiRabbit

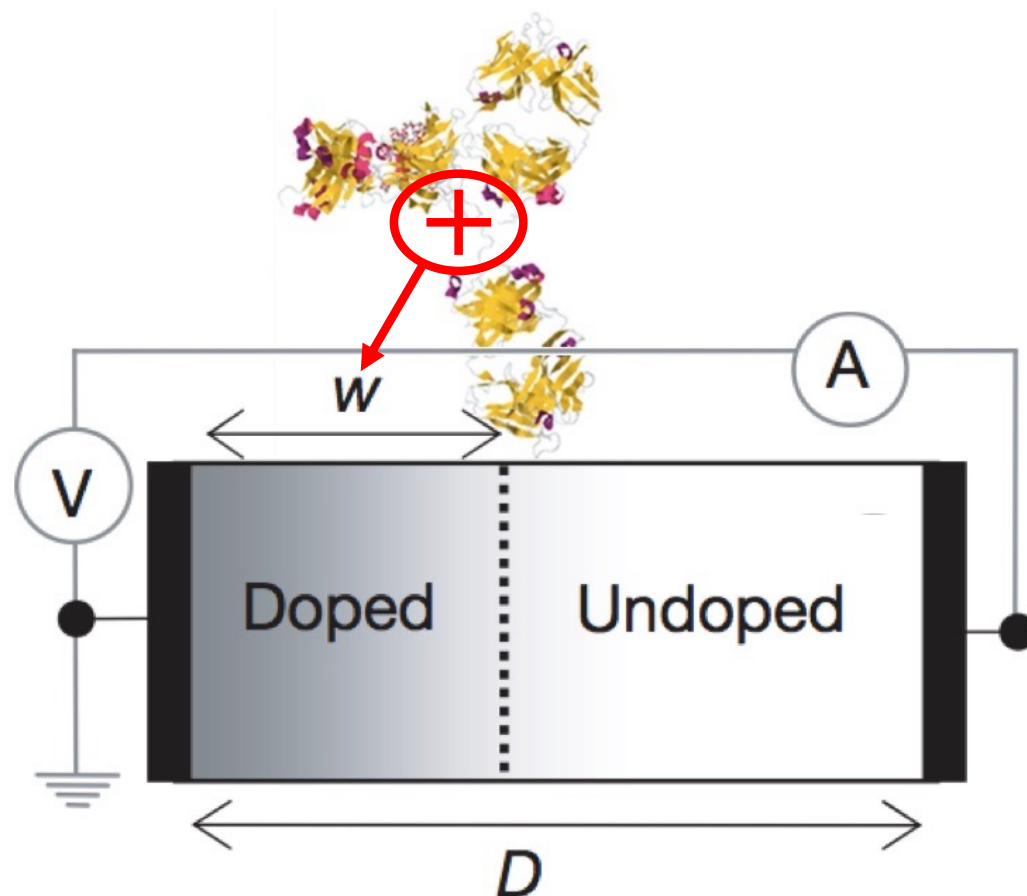


D. Sacchetto et al. / BioNanoSci. 1 (2011) 1–3



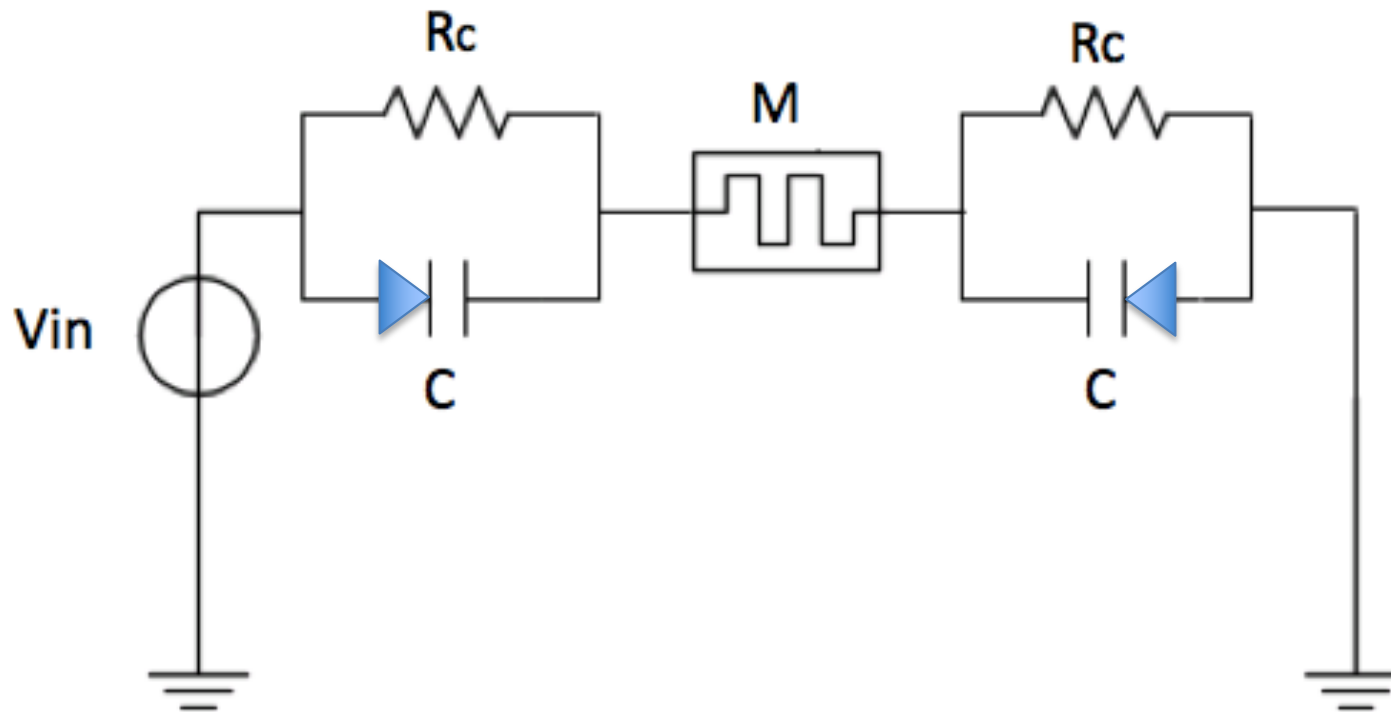
Suspended functionalized silicon nanowire with NiSi regions
Bio-functionalized with Antibodies

Why the Voltage Gap appears in Memristive Biosensors?



Biomolecules affect the w -state of the device

Memristive Model



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

Memristive Model

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

Antigen concentration [fM]	Voltage gap [Volts] <i>Experimental values</i> [9]	Capacitance (C) [nF]	Voltage gap [Volts] <i>Simulation values</i>
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

Memristive Sensors Milestones

2008

2009

2010

2011

2012

2013

2014

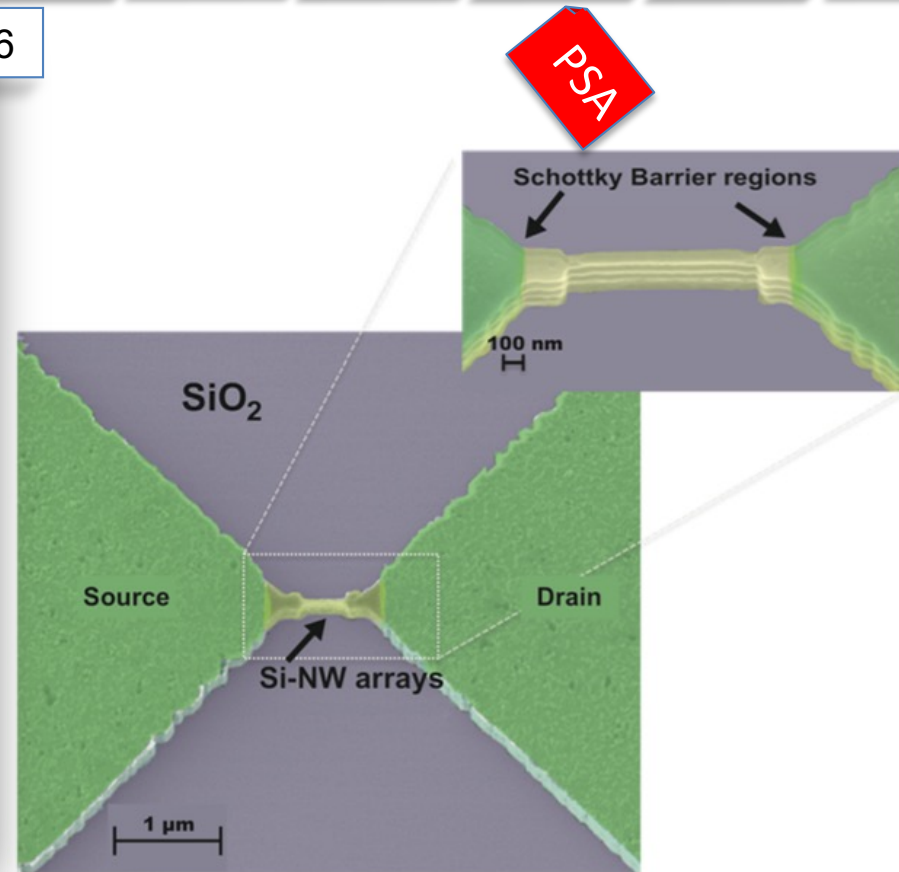
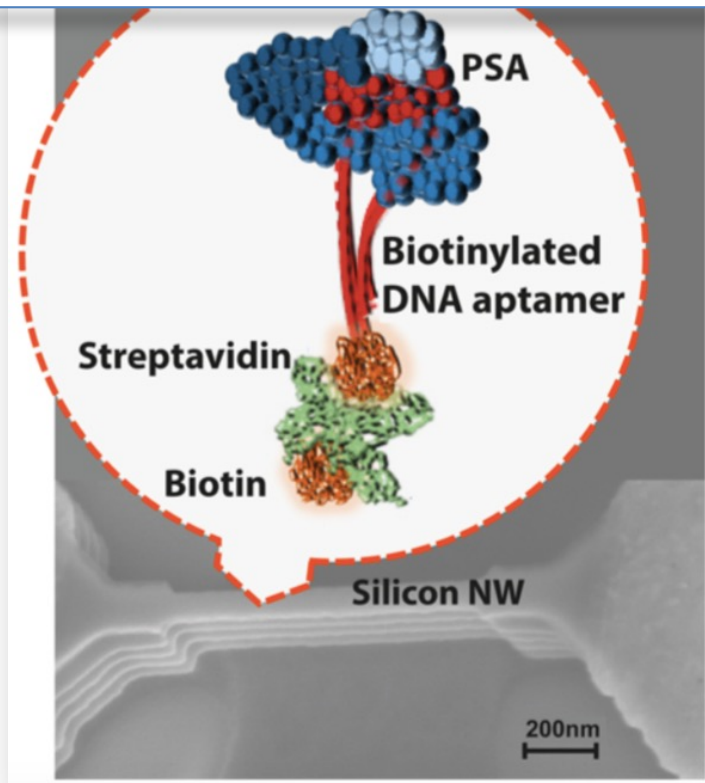
2015

2016

2017

2018

I. Tzouvadaki et al. / Nano Lett. 16(2016) 4472–4476

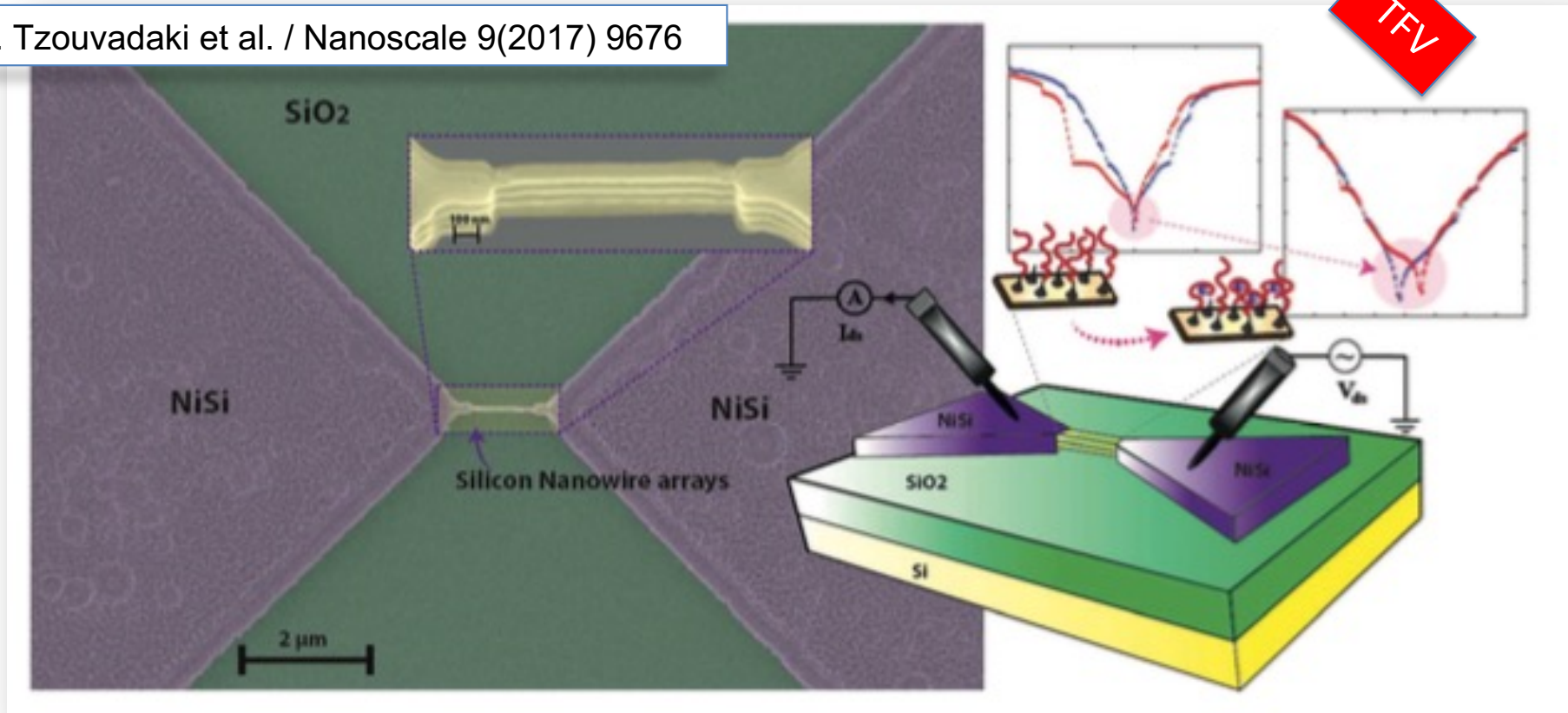


Very first worldwide ever-reported electrochemical biosensor based on a memristive effect and DNA aptamers

Memristive Sensors Milestones

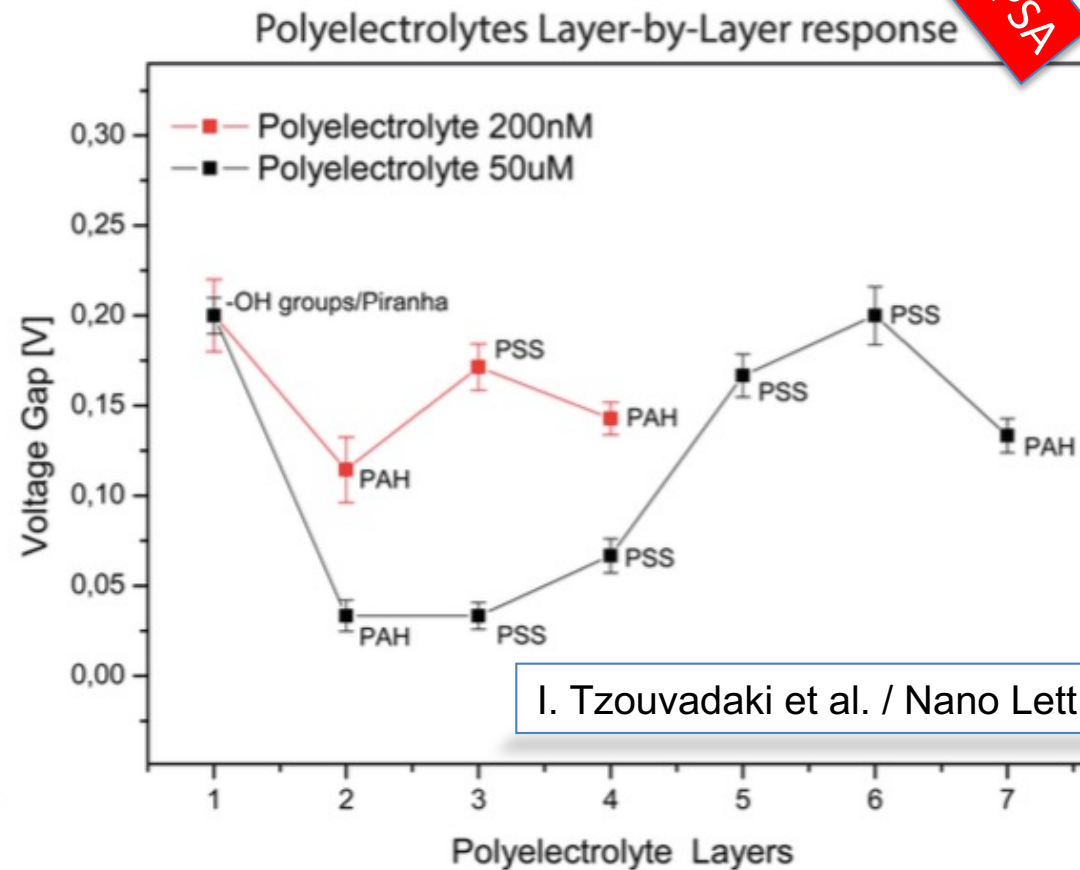
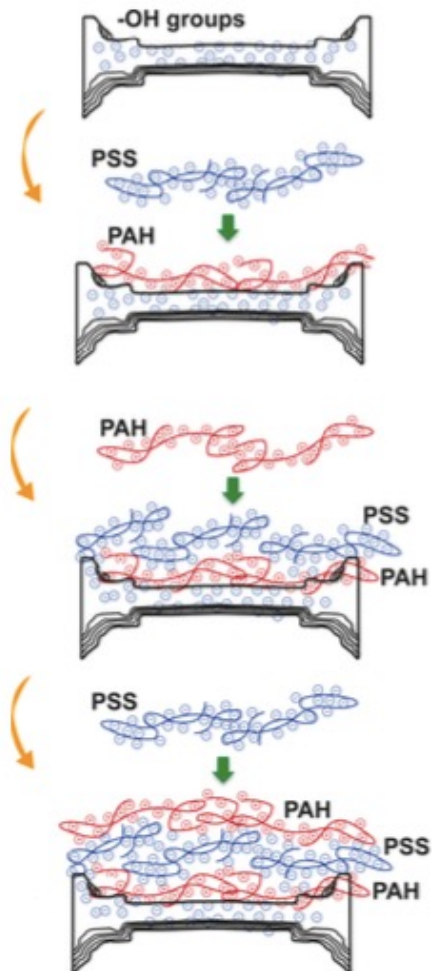


I. Tzouvadaki et al. / Nanoscale 9(2017) 9676



Ultrasensitive label-free Aptamer-based memristor to monitor therapeutic compounds

Memristive Sensors Milestones



I. Tzouvadaki et al. / Nano Lett. 16(2016) 4472–4476

Memristive Sensors Milestones

2008

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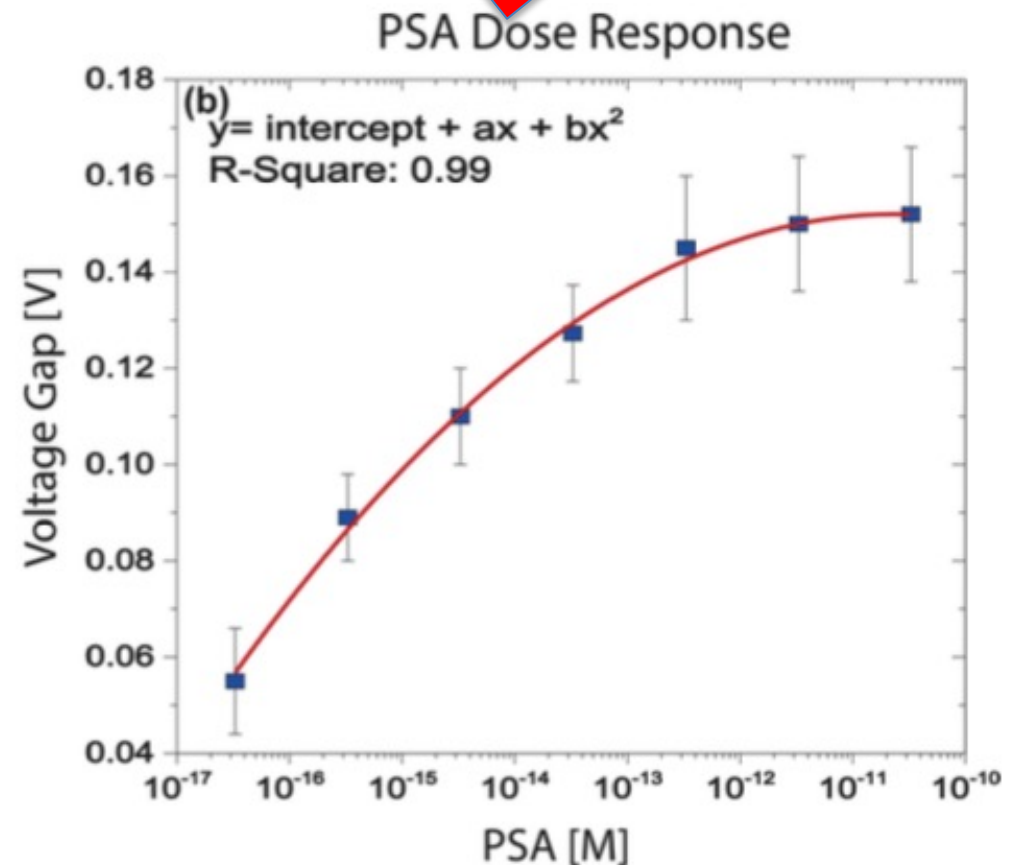
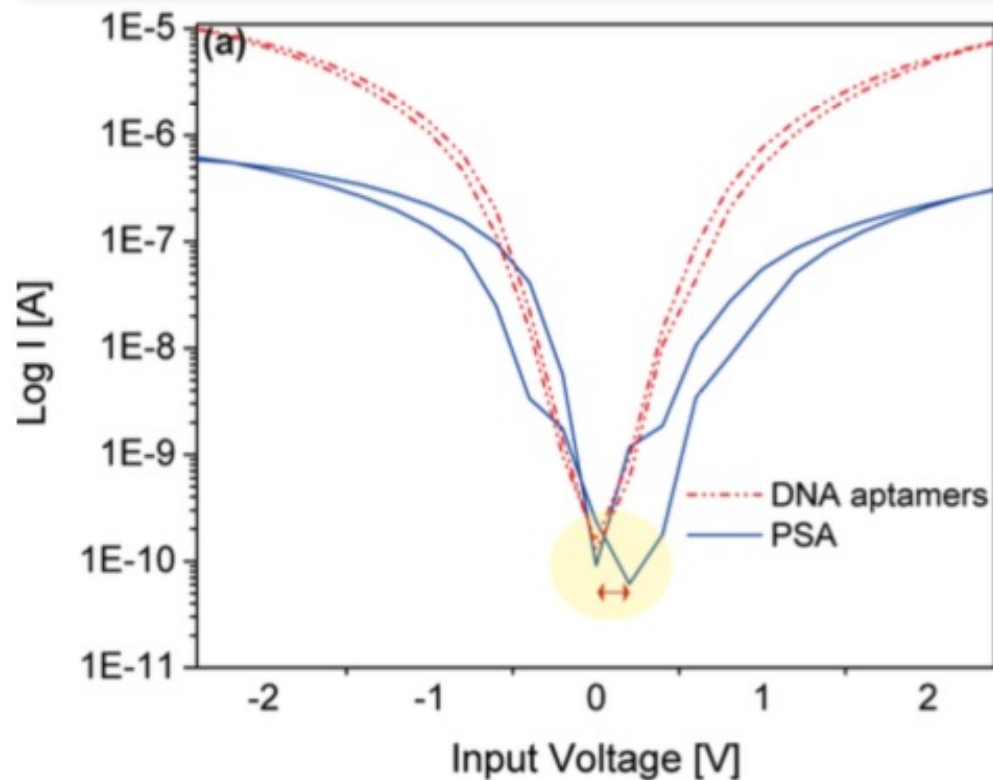
2015

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2017

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I. Tzouvadaki et al. / Nano Lett. 16(2016) 4472–4476

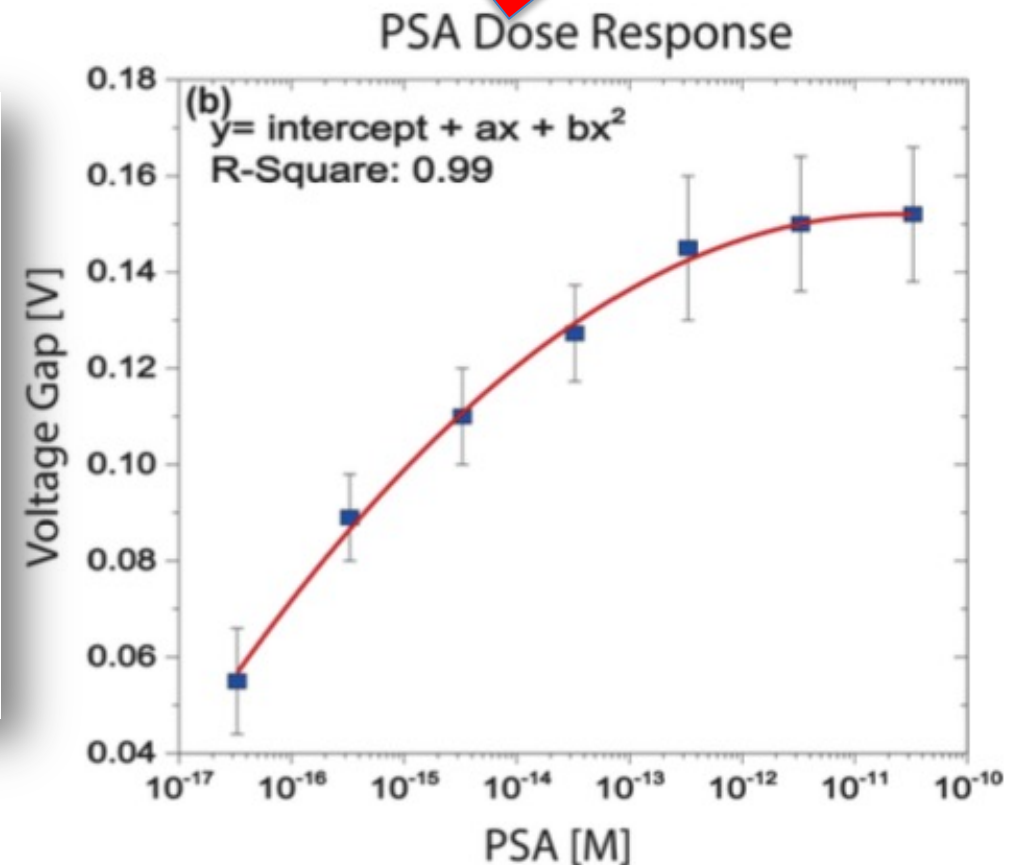


Memristive Sensors Milestones



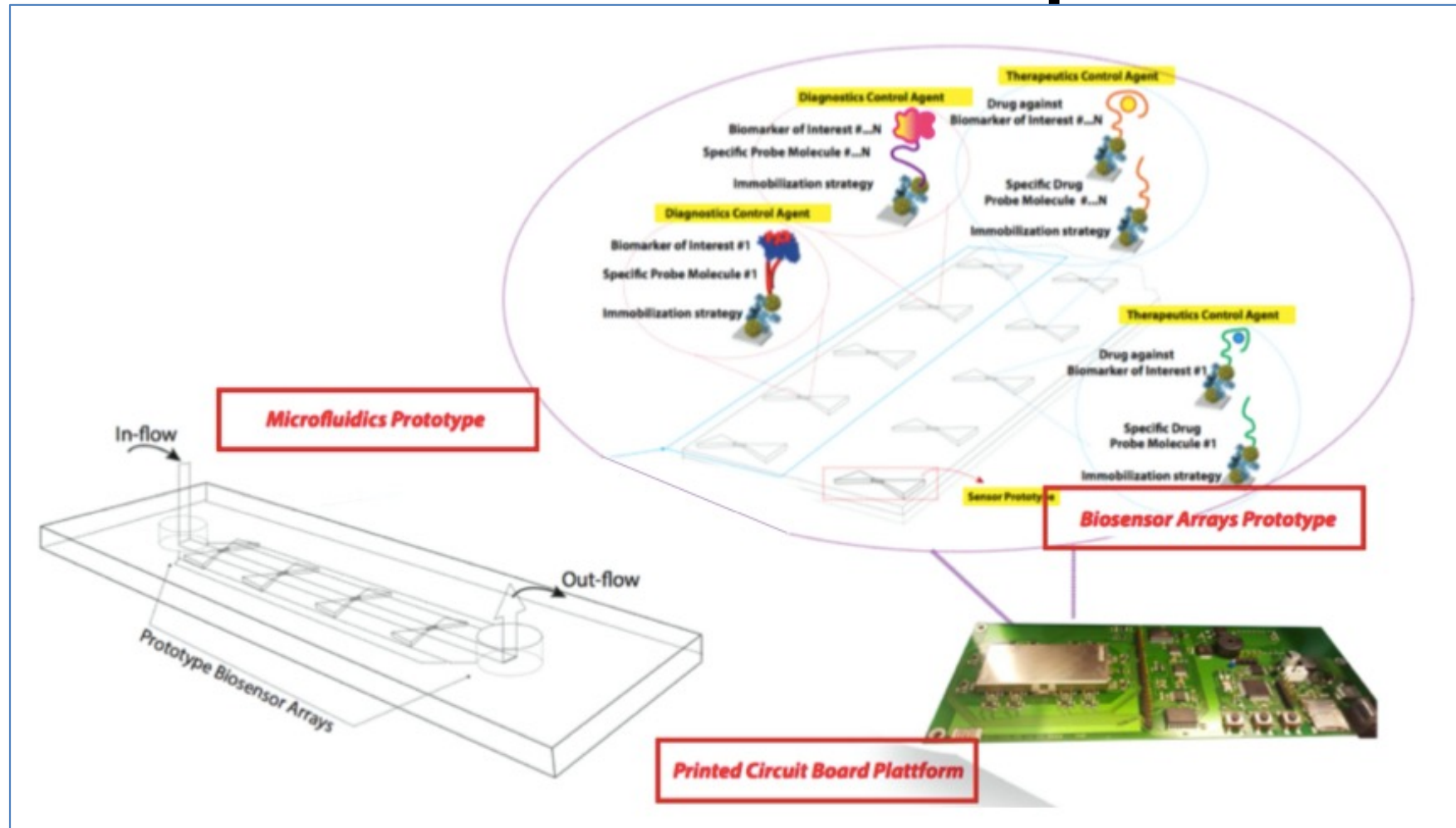
I. Tzouvadaki et al. / Nano Lett. 16(2016) 4472–4476

electrode surface	LOD	reference
gold electrodes	37 nM	Formisano et al. ¹⁴ (2015)
GCE	pM range	Souada et al. ¹⁵ (2015)
gold electrodes	30 pM	Jolly et al. ¹⁶ (2015)
glassy carbon electrode (GCE)	7.6 pM	Liu et al. ¹⁷ (2012)
GCE	0.15 pM	Kavosi et al. ¹⁸ (2015)
gold electrodes	fM range	Yang et al. ¹⁹ (2015)
gold electrodes	30 fM	Jolly et al. ²⁰ (2016)
GCE	300 aM	Kavosi et al. ¹⁸ (2015)
Si-nanowires	23 aM	present work



Best Ever Biosensors for Cancer Markers by Aptamers

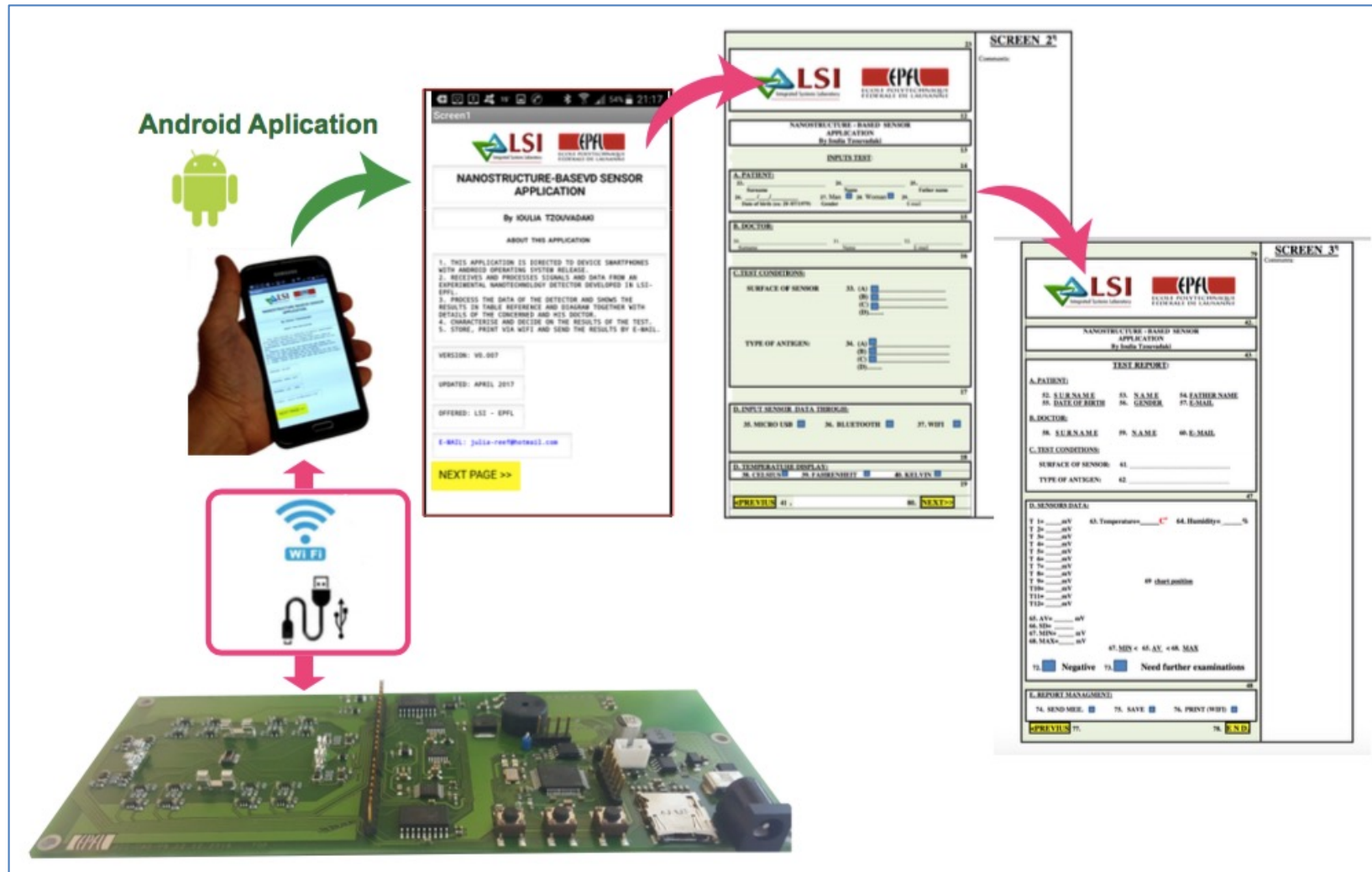
Multi-Panel on Chip



I. Tzouvadaki et al. / IEEE Sensors Journal 14(2019) 5769–5774

Memristive Multipanel Platform for Theragnostics with Microfluidics

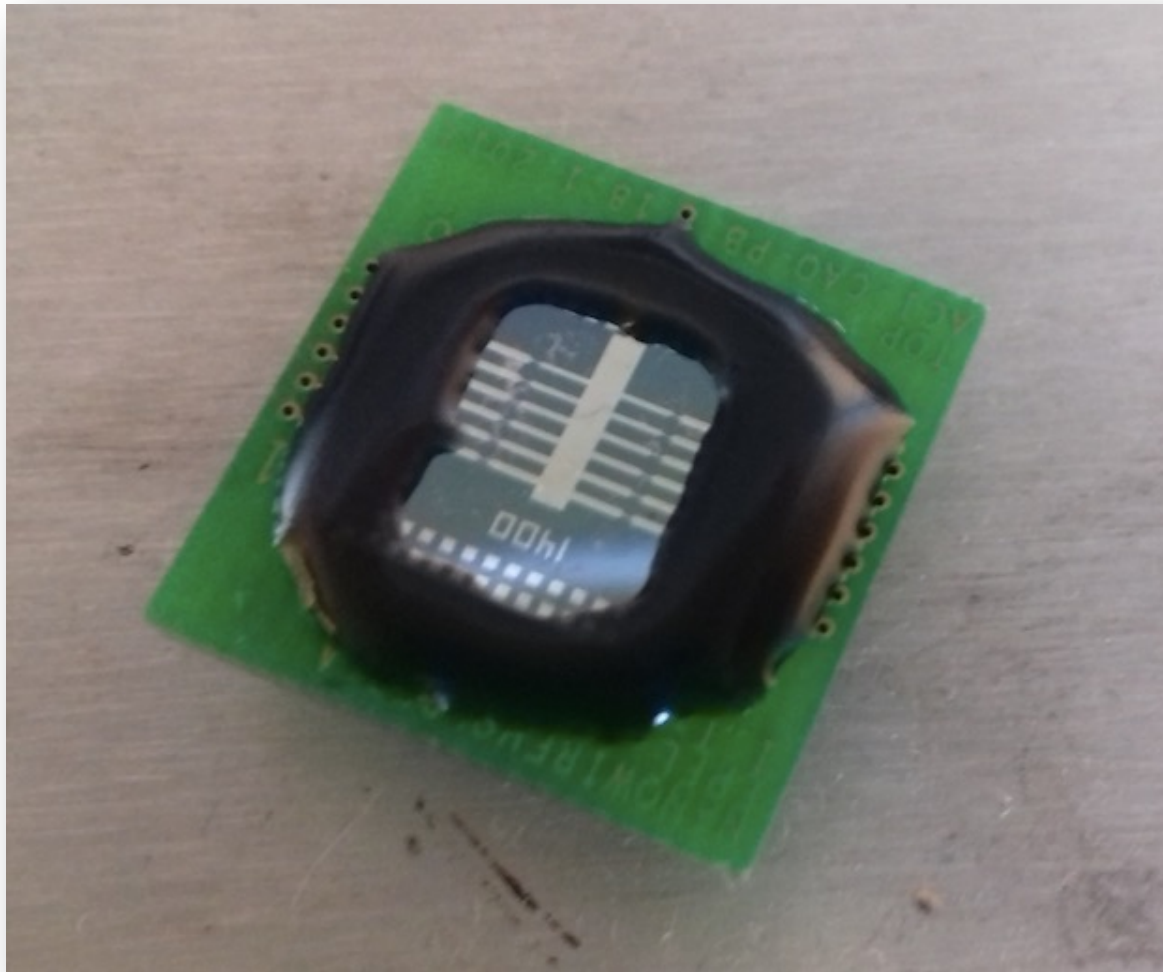
Android Application



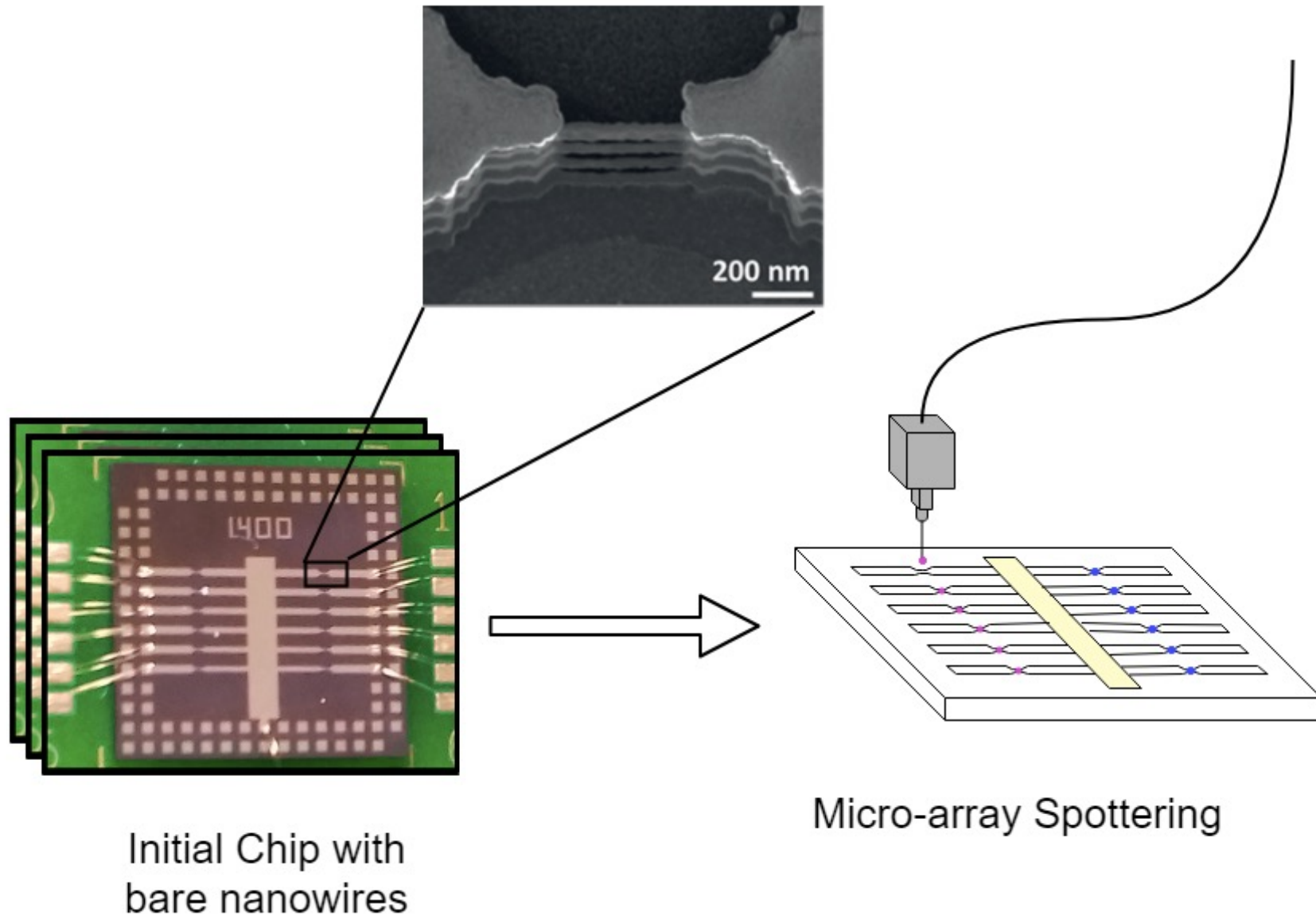
Memristive Sensors Milestones



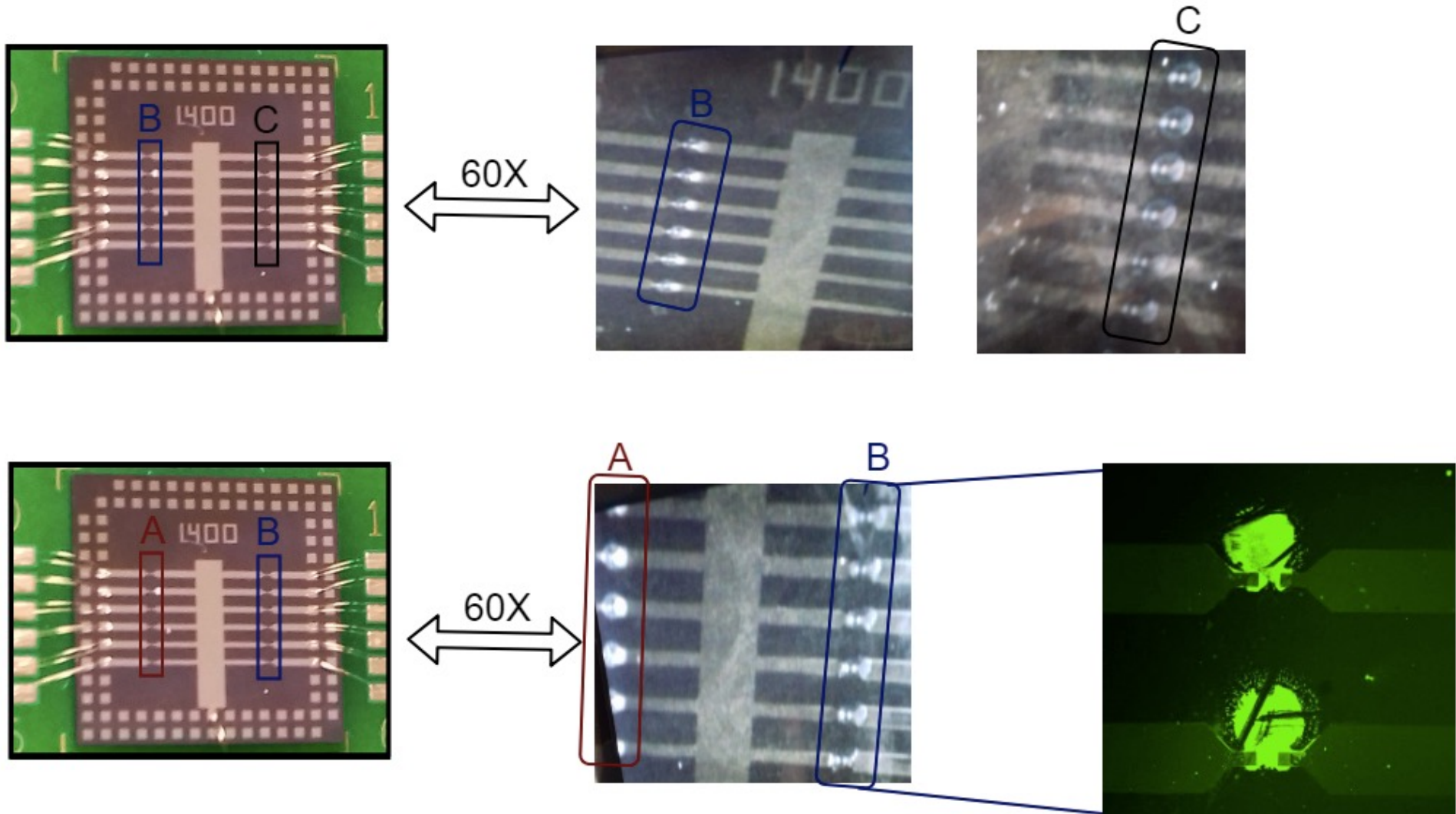
Gramzyme
Interferron- γ



Automated Spotting for Multiplexing



Multiplexing for Specific Cancer Markers

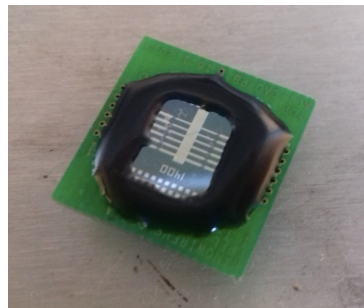
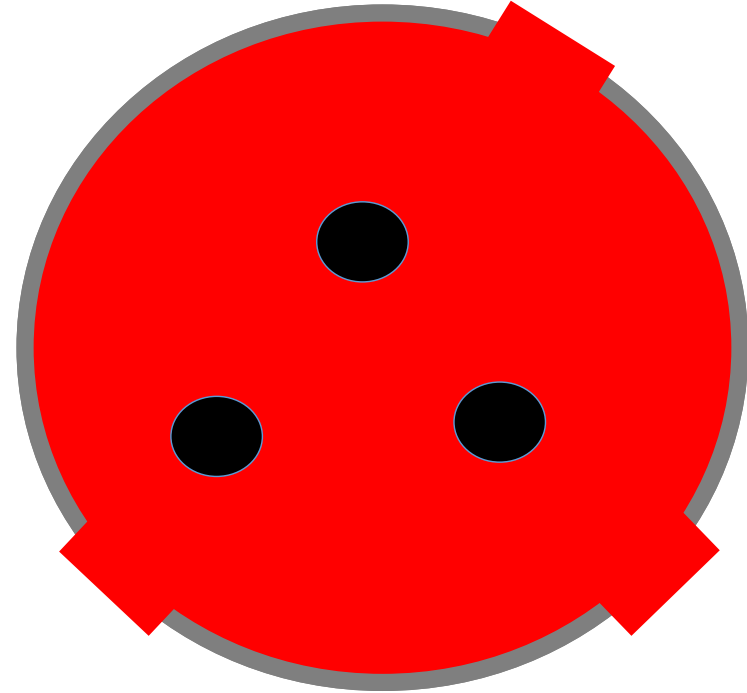
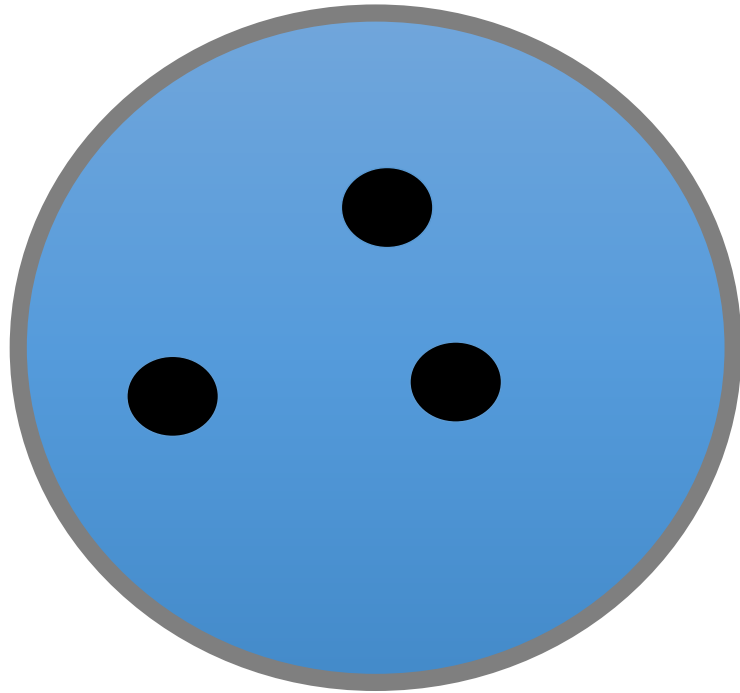


A: Granzyme

B: Ifn- γ

C: Gelatine

Non-Activated versus Activated CD8 T Cells



→ Detection!

Non-Activated versus Activated CD8 T Cells

2010

2011

2012

2013

2014

2015

2016

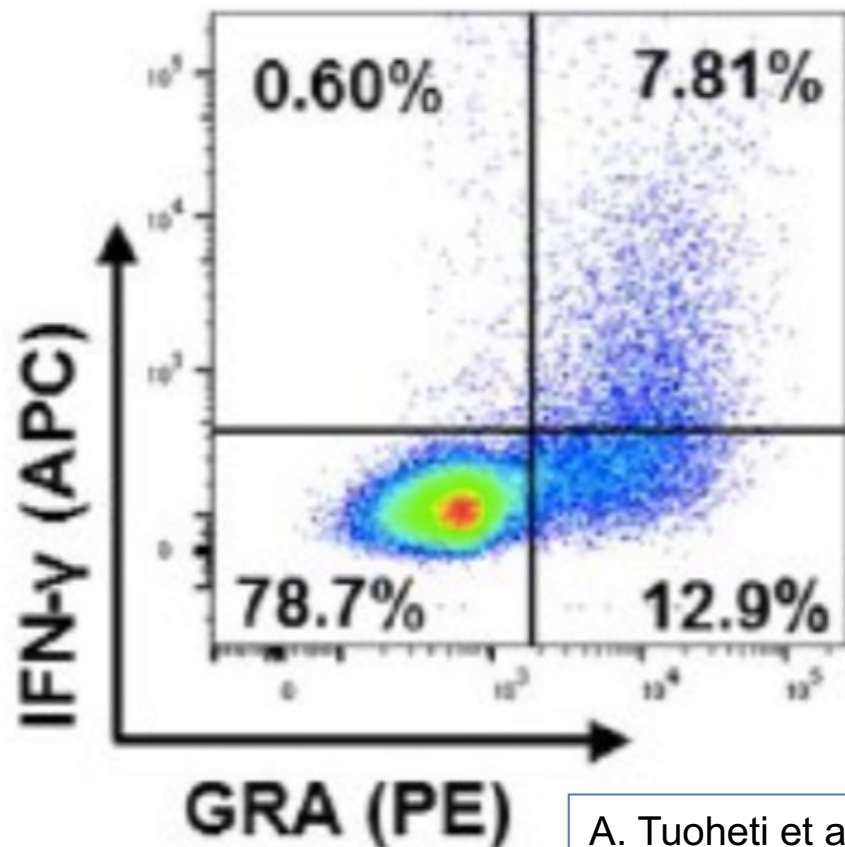
2017

2018

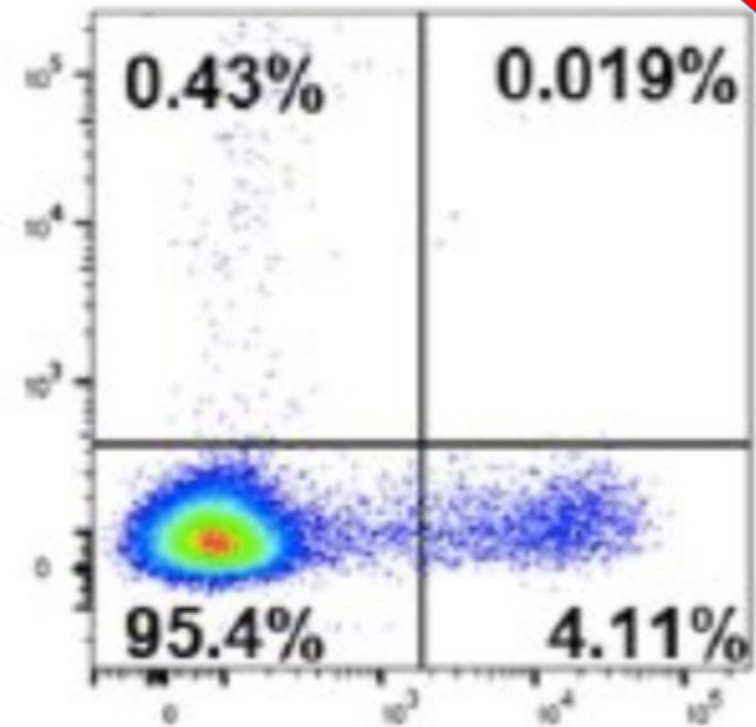
2019

2020

Gramzyme
Interferon- γ



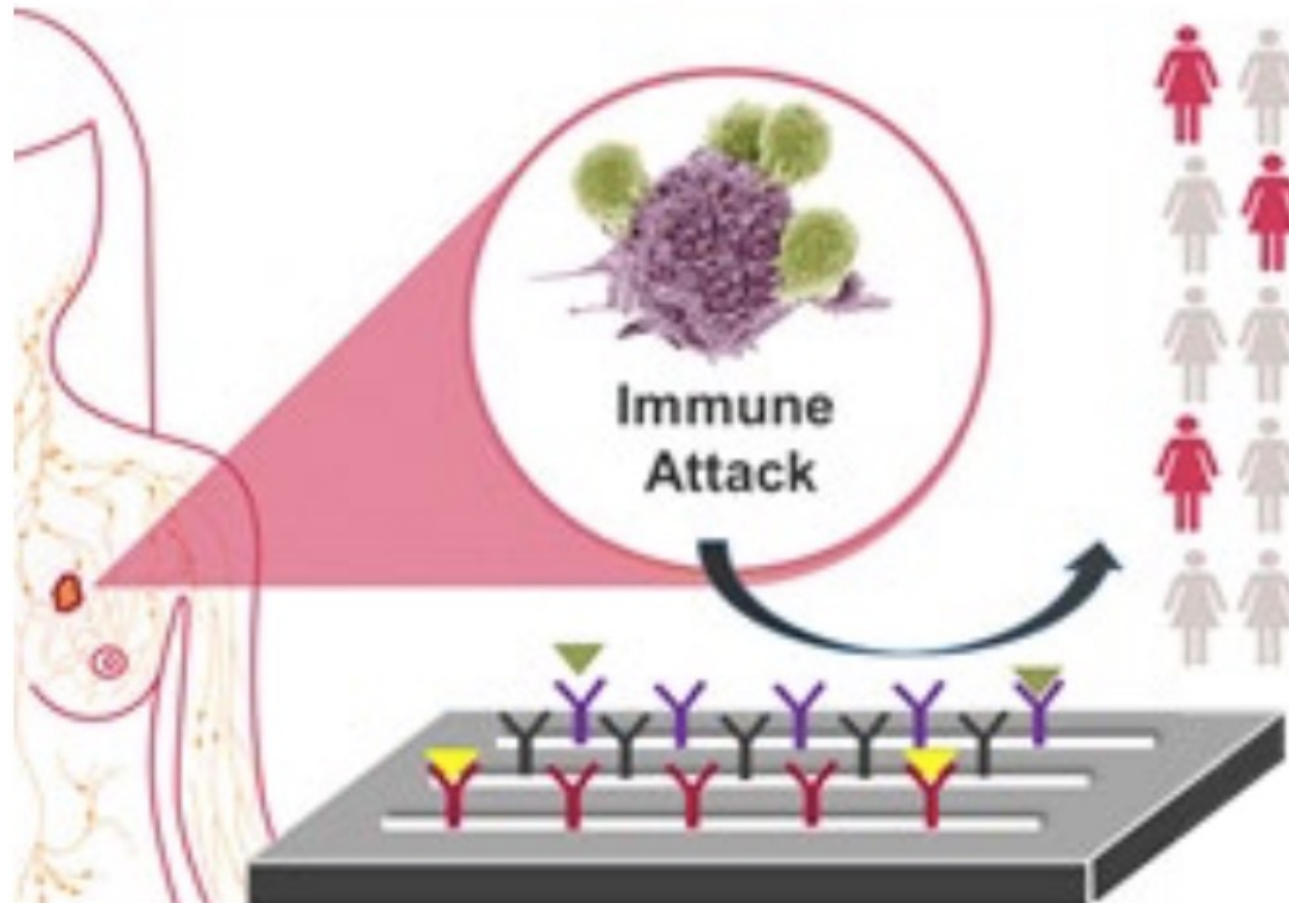
Activated



Non-activated

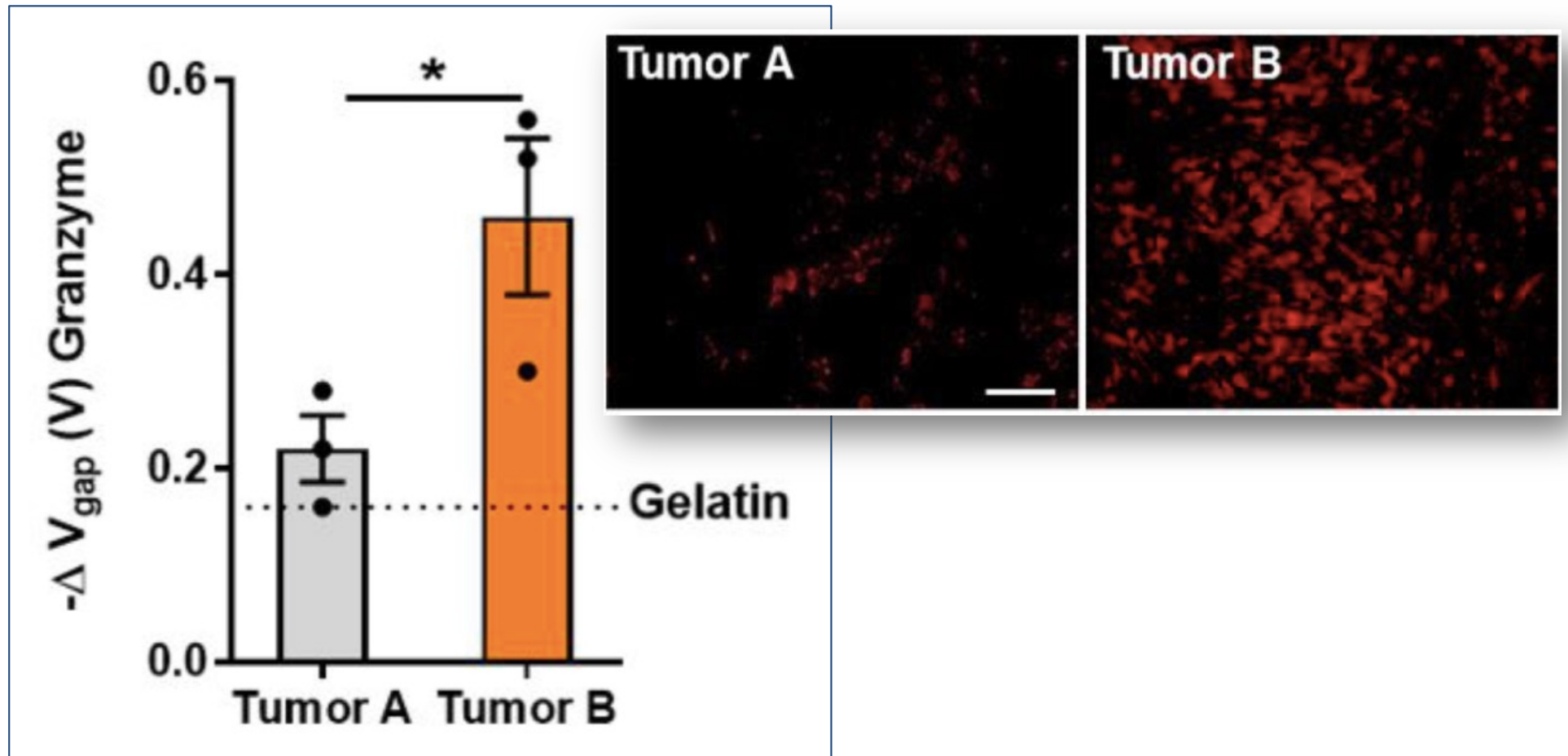
A. Tuoheti et al. / British Journal of Cancer Research 3(2020) 341 – 348

Brest Cancer Patients Stratification with Memristive Biosensors



A. Tuoheti et al. / British Journal of Cancer Research 3(2020) 341 – 348

Differentiating kind of Tumour with Memristive Biosensors

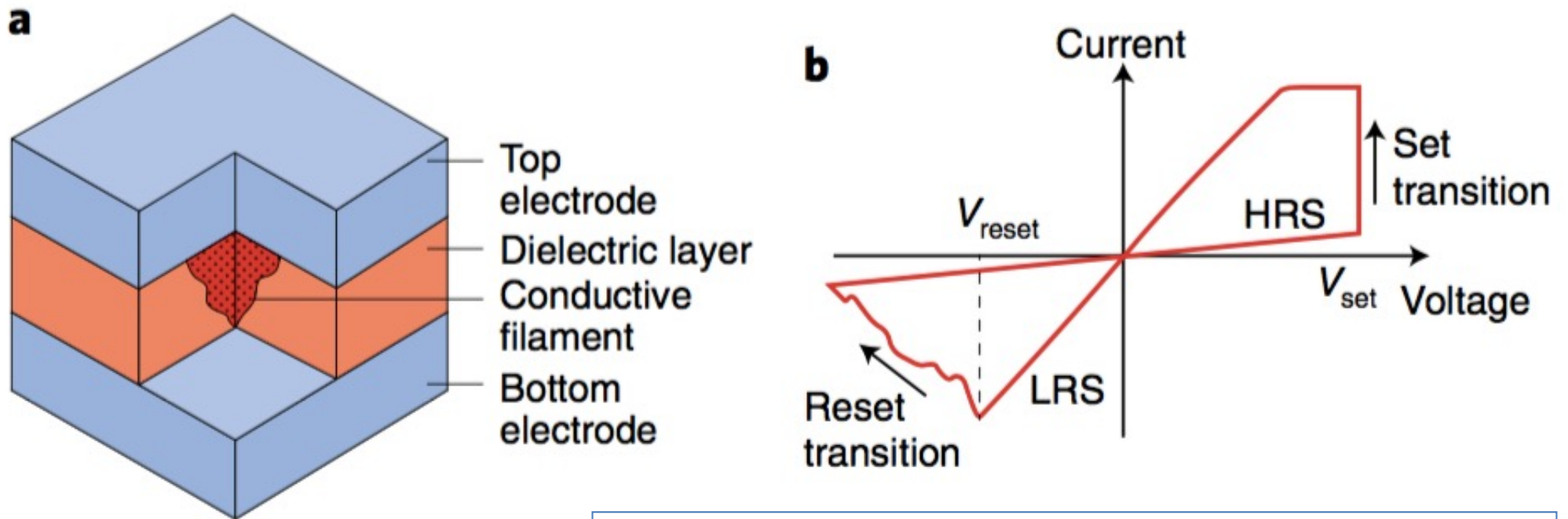


A. Tuoheti et al. / British Journal of Cancer Research 3(2020) 341 – 348

Key Messages:

- Measurements with **Memristive Biosensors** are much away more powerful than with conventional devices.
- To diagnose correctly Cancer, we definitely need measure **multiple cancer markers**.
- To correctly stratify Cancer Patients, we definitely need to **compute probability indexes** on a set of multiple cancer biomarkers.

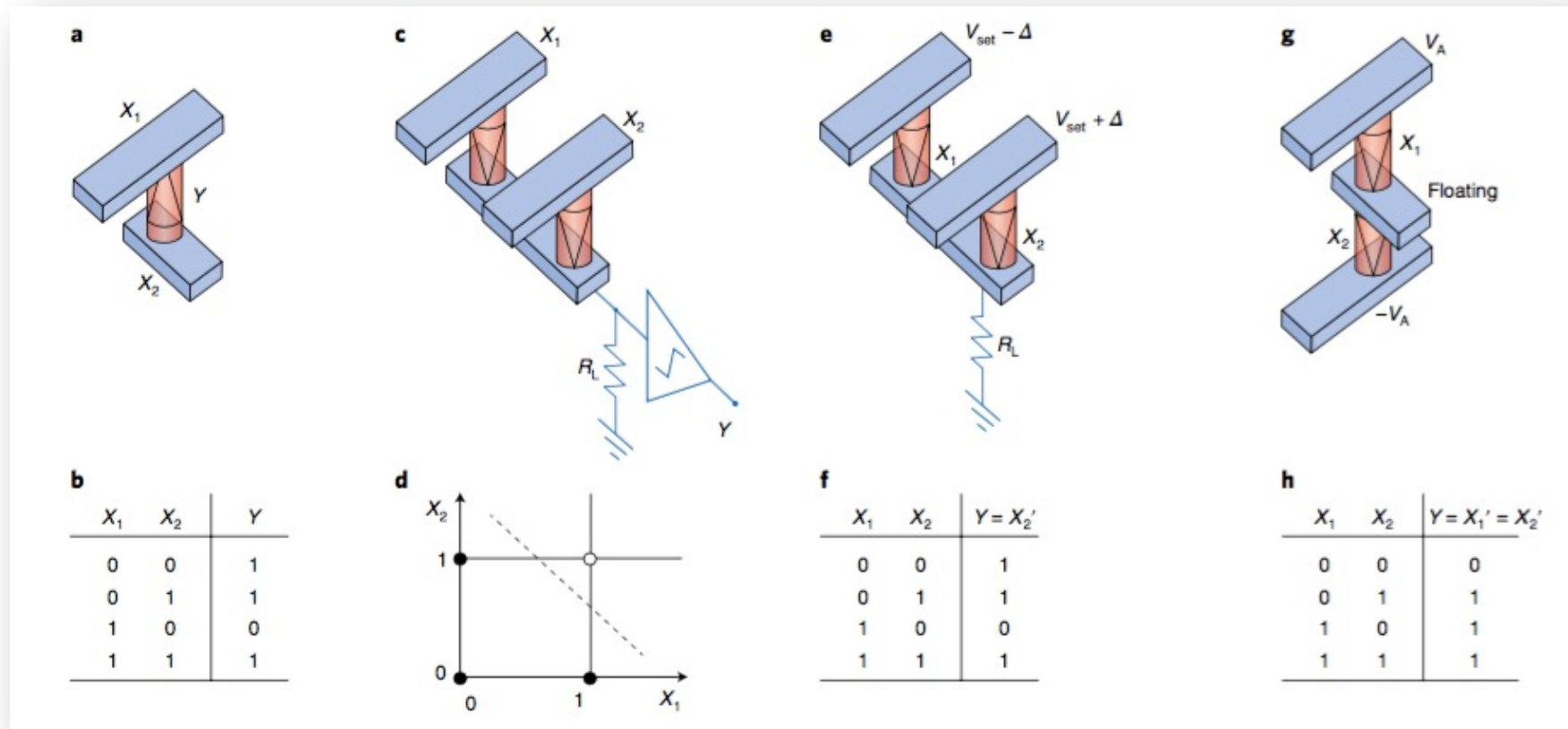
In-Memory Computing Device



D. Ielmini and H.-S.P. Wong, Nature Electronics 1(2018) 333-343

Computational RRAM memory devices

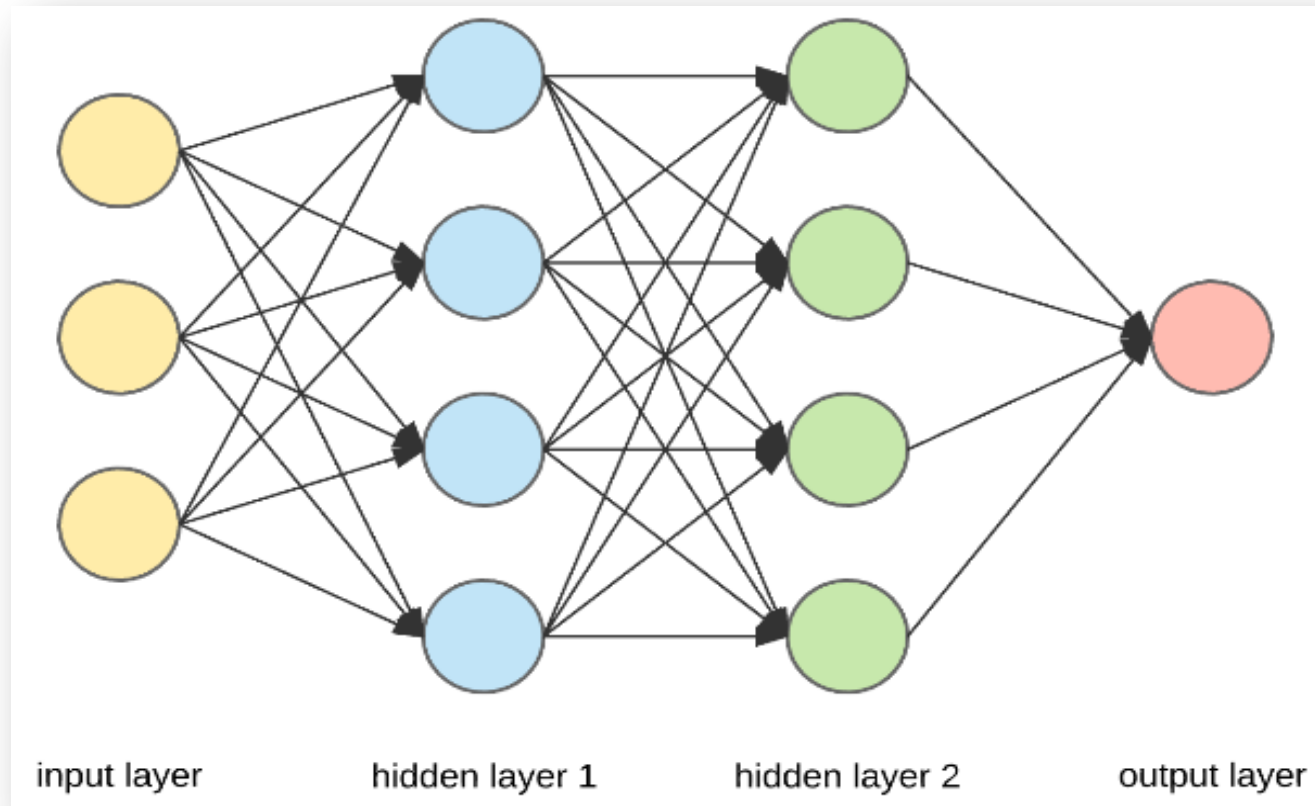
In-Memory Computing



D. Ielmini and H.-S.P. Wong, Nature Electronics 1(2018) 333-343

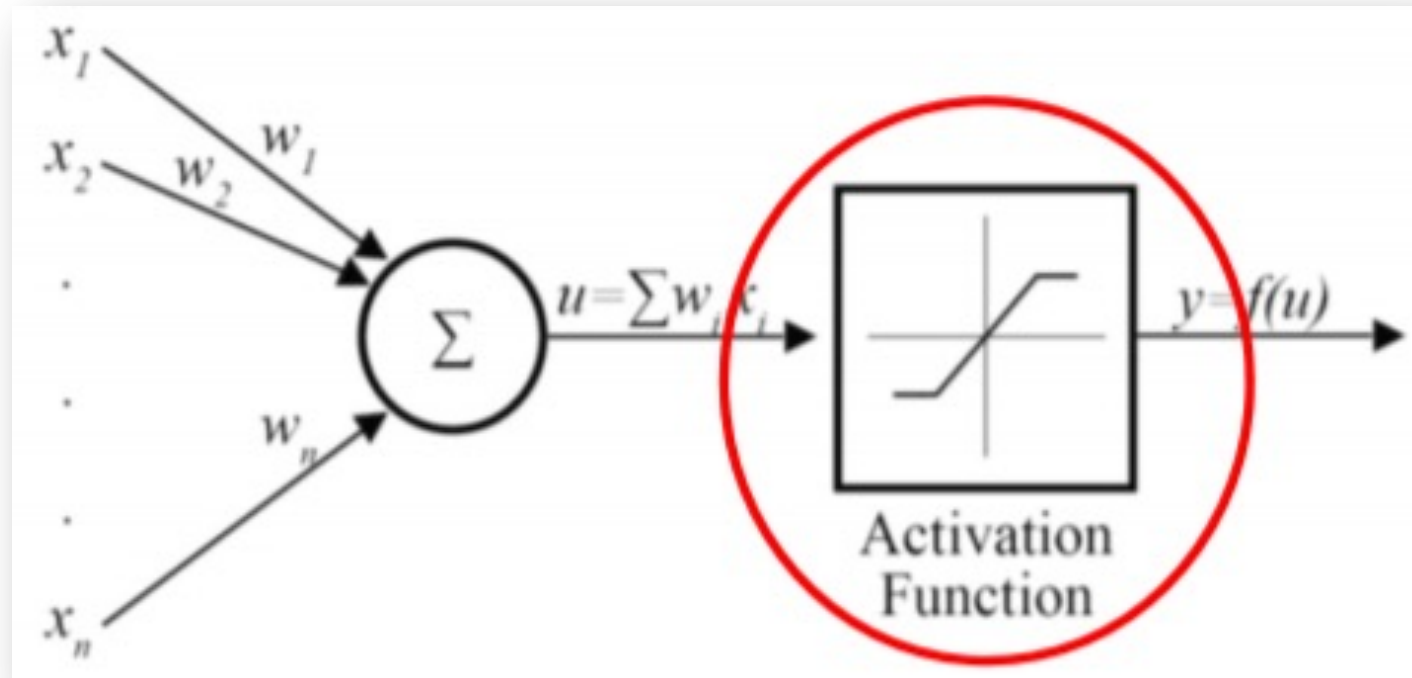
In-Memory Computing with RRAM-based
digital logic gates

Artificial Intelligence by Deep Learning



Neural networks are multi-layer networks of neurons that
Compute by classify things, make predictions, etc.

Key device for Deep Learning



Deep learning is based on « neurons » (artificial), which typically “learn” on inputs by an Activation Function that changes their “transmitting state”

Artificial Intelligence in Hardware



Image credit

J. Fingas / www.engadget.com on Sept, 26th, 2021

VICTOR HABBICK VISIONS/SCIENCE PHOTO LIBRARY via Getty Images

Neuromorphic chips need for roughly 100 billion neurons

Costs of Computing Chips

COMPUTING

A \$2 Billion Chip to Accelerate Artificial Intelligence

A new chip design from Nvidia will allow machine-learning researchers to marshal larger collections of simulated neurons.

By Tom Simonite

April 5, 2016

Billion neurons may cost Billion \$

Supersize AI on Whole Wafer!

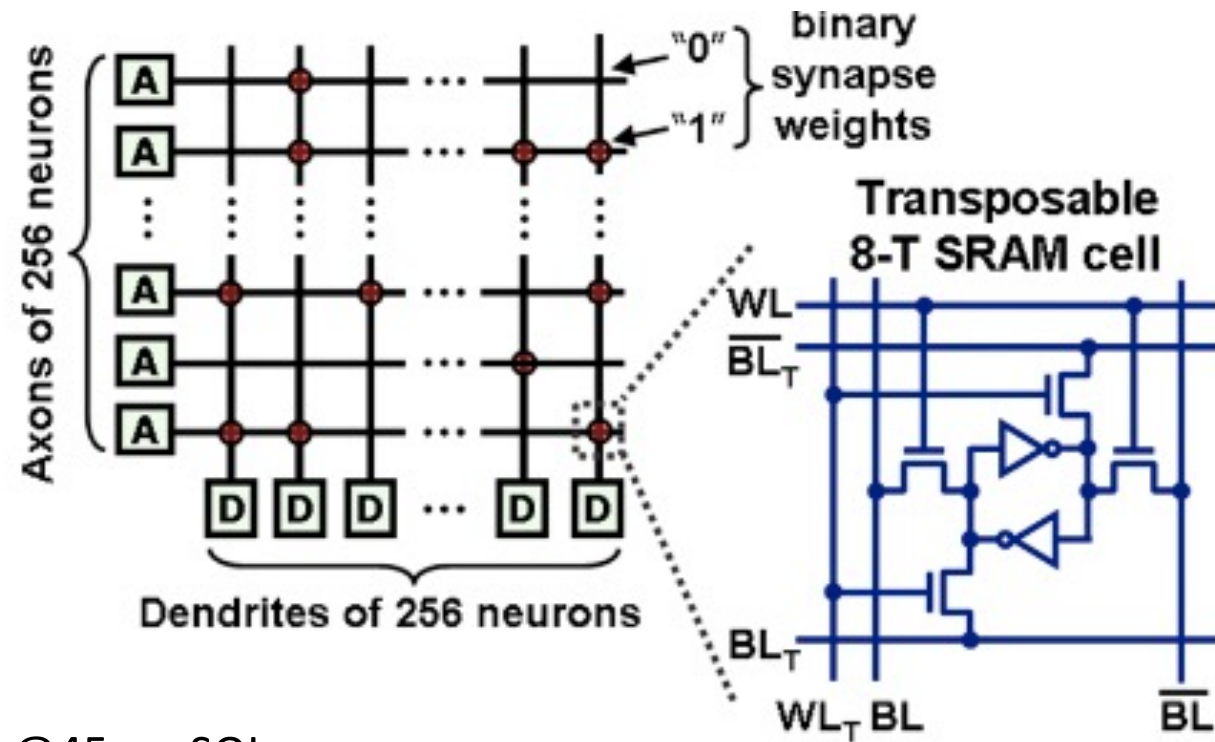


	WSE 2	WSE	Nvidia A100
Size	46,225 mm ²	46,225 mm ²	826 mm ²
Transistors	2.6 trillion	1.2 trillion	54.2 billion
Cores	850,000	400,000	7,344
On-chip memory	40 gigabytes	18 GB	40 megabytes
Memory bandwidth	20 petabytes/s	9 PB/s	155 GB/s
Fabric bandwidth	220 petabits/s	100 Pb/s	600 gigabytes/s
Fabrication process	7 nm	16 nm	7 nm

IEEE Spectrum, issue on July, 2021

Cerebras's wafer-size chip boasts 2.6 trillion transistors

Complexity of Computing Chips



@45nm SOI

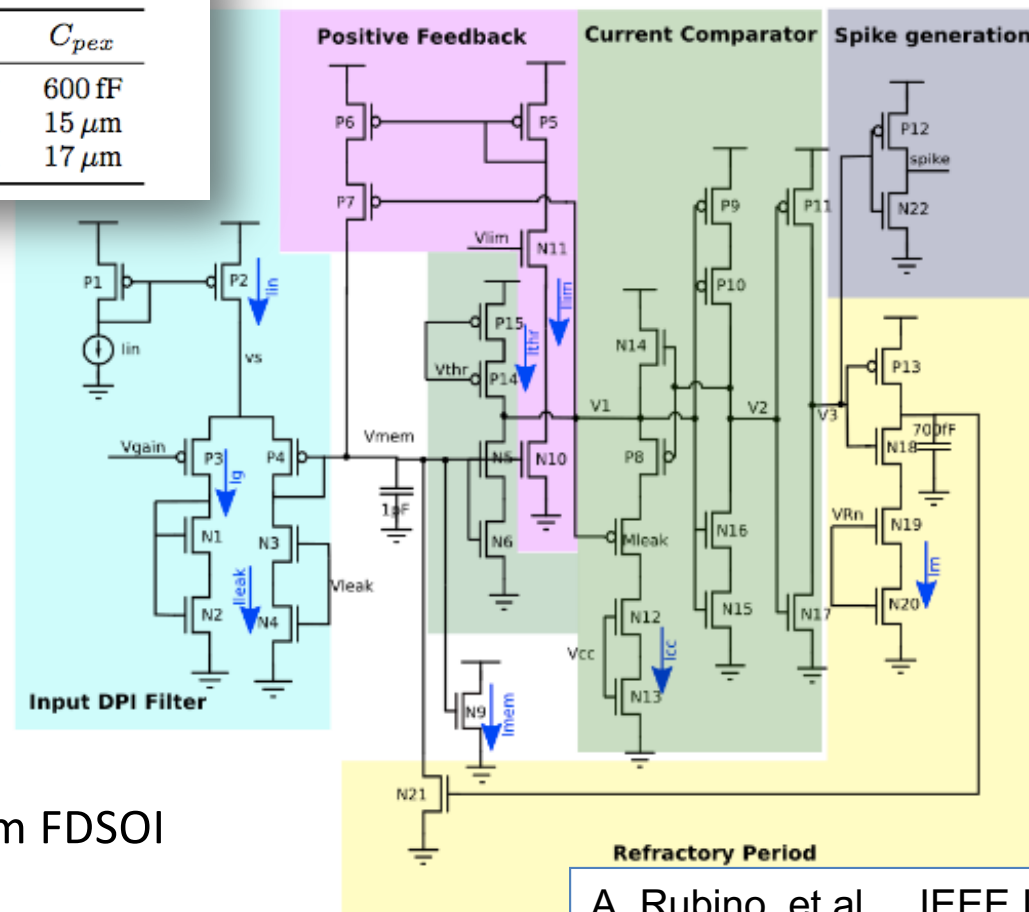
Jae-sun Seo, et al., , IEEE CICC 2011

How many transistors do we need for realizing a single CMOS neuron?

Complexity of Computing Chips

CAPACITANCE VALUES AND SIZES USED IN THE DESIGN

	C_{mem}	C_{ahp}	C_{ref}	C_{pes}
Value	1 pF	2 pF	700 fF	600 fF
Width	20 μm	28 μm	16 μm	15 μm
Length	20 μm	30 μm	19 μm	17 μm

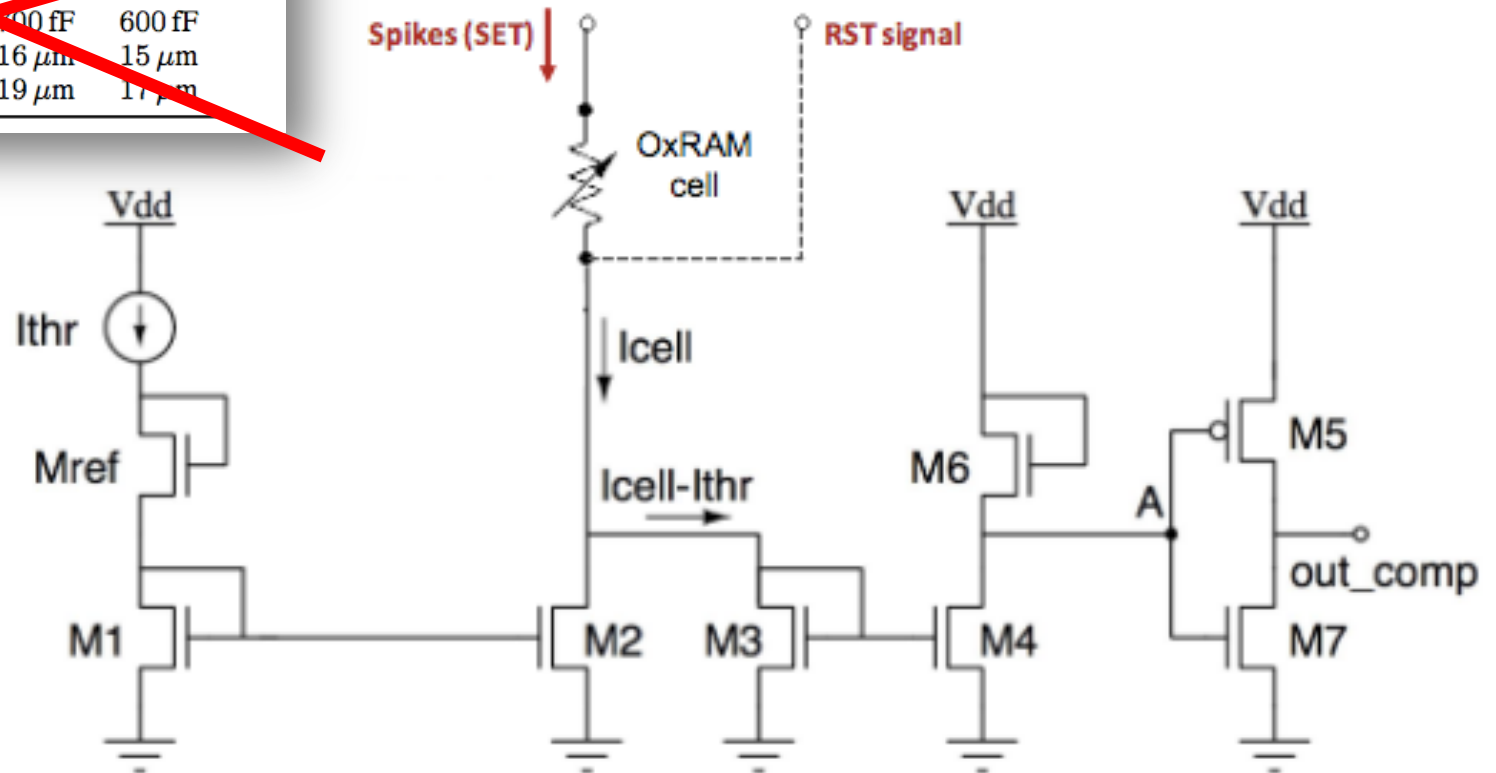


How many transistors do we need for realizing a single CMOS neuron?

Complexity of Computing Chips

CAPACITANCE VALUES AND SIZES USED IN THE DESIGN

	C_{mem}	C_{hp}	C_{ref}	C_{pex}
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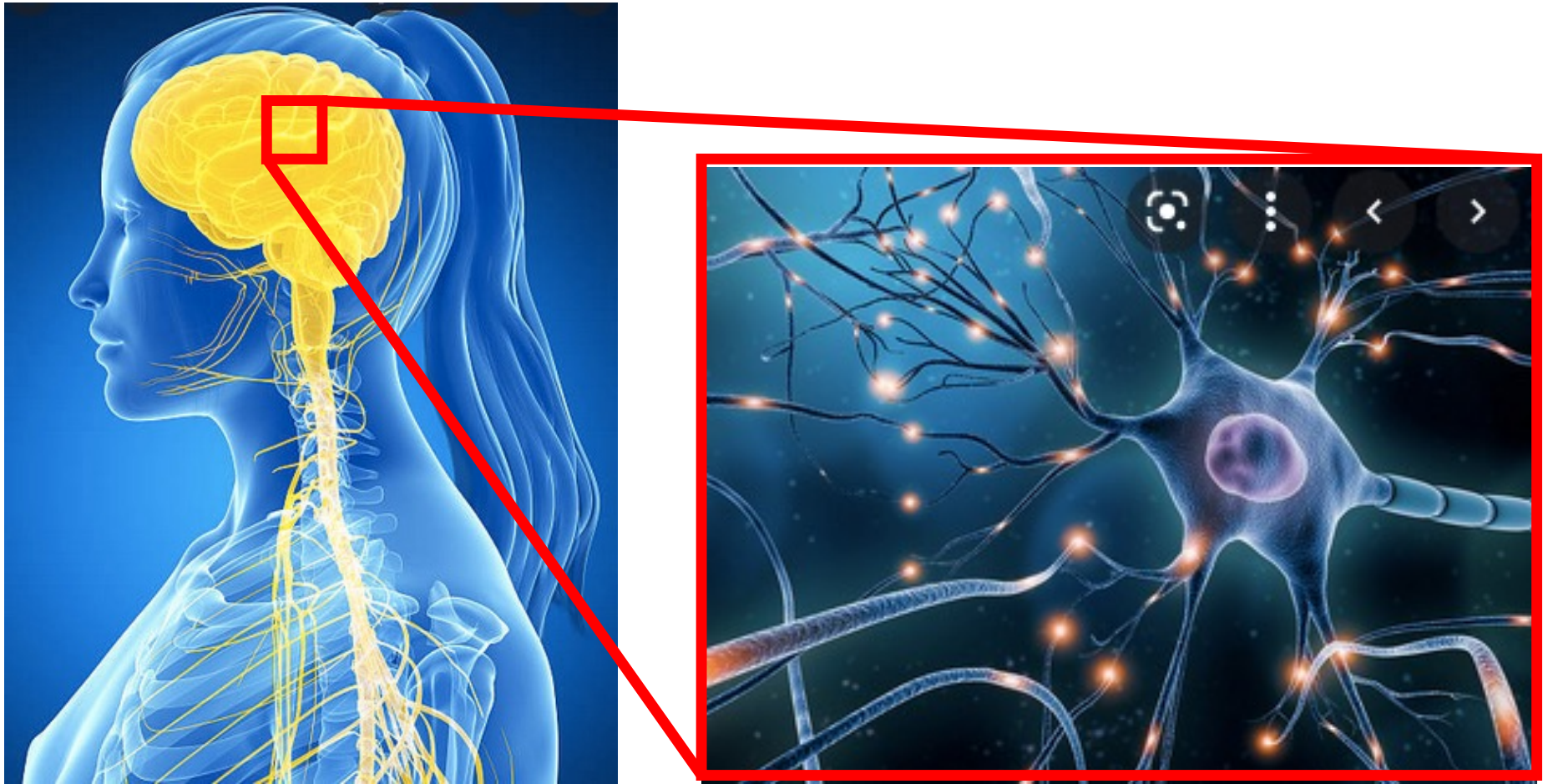


@130nm CMOS-OxRAM

H. Aziza, et al., , IEEE NEWCAS, 2019

How many transistors do we need for realizing a single CMOS neuron?

Biological Computation



Biological neuron (natural) are « single devices » which change Activation Function « by leaning », so from their past, which means coding the past in a different state!

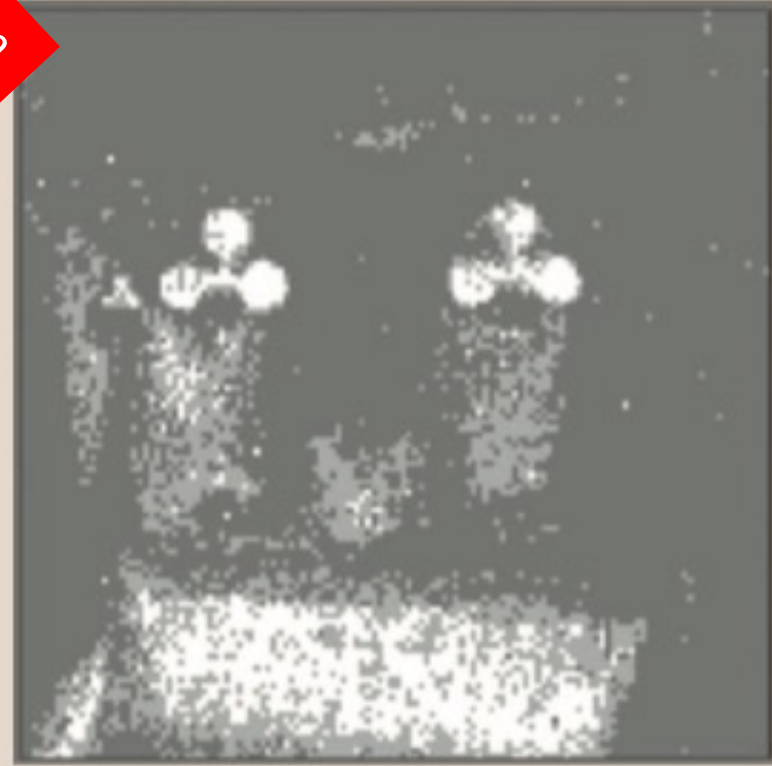
In-Memory Computing

So, If we succeed in getting a device that works like natural neurons we may develop machines computing like human brain !

Memristive Sensors Milestones

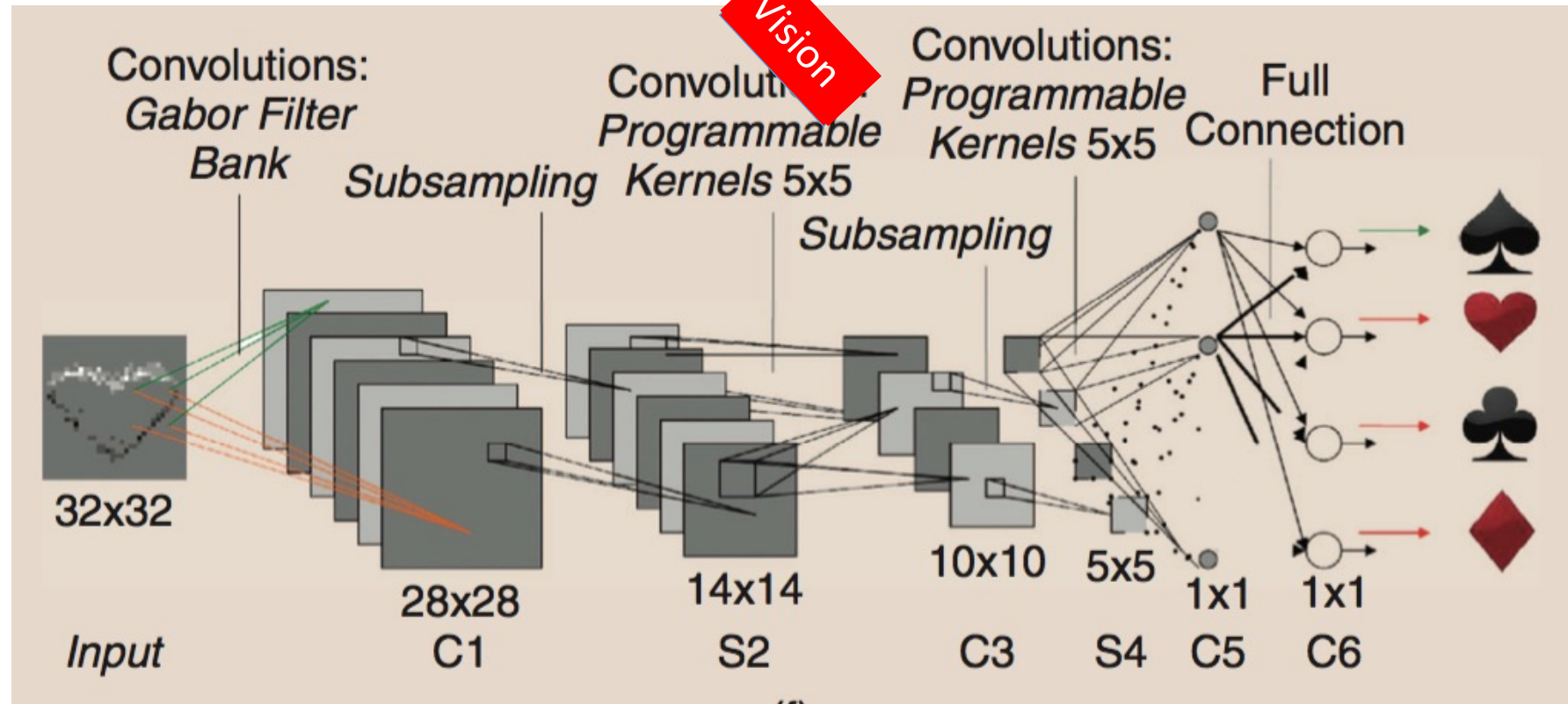


Vision



T. Serrano-Gotarredona, et al. / IEEE CAS Mag. 13 (2013) 74-88

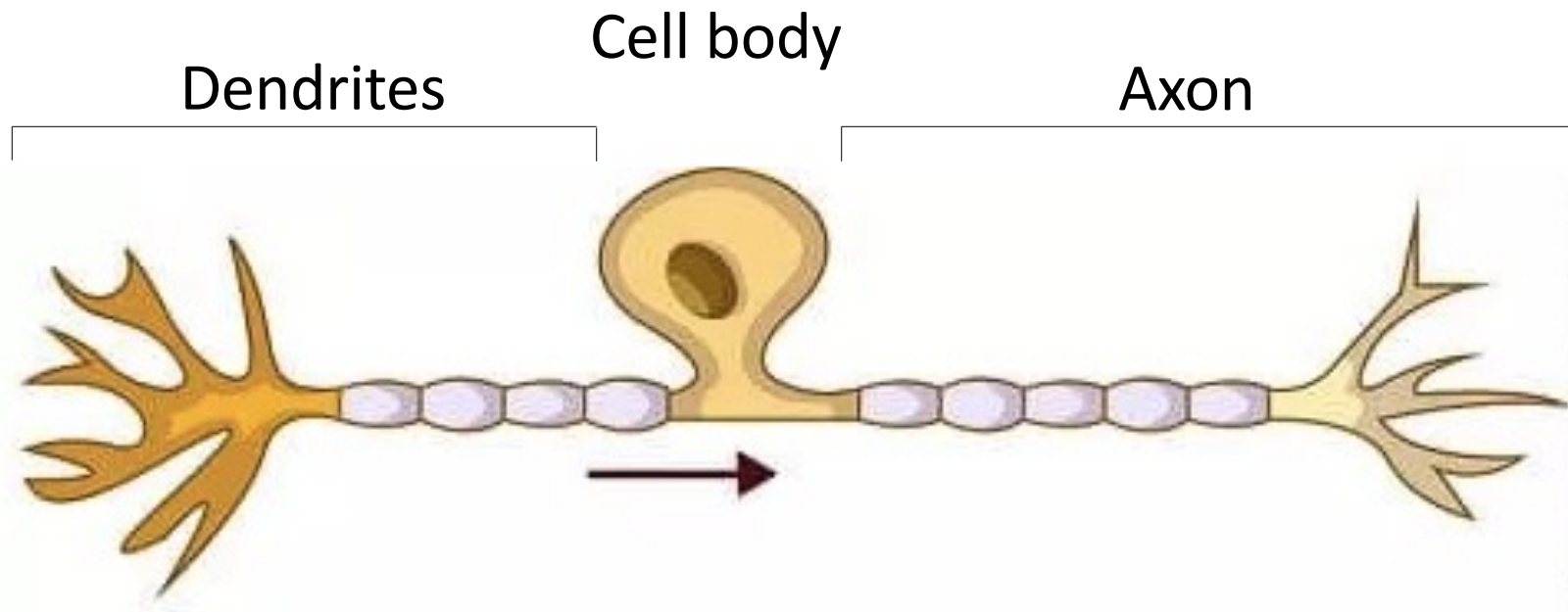
Memristive Sensors Milestones



Event-driven sensing and classification by
CMOS/memristors integrated in an artificial retina

T. Serrano-Gotarredona, et al. / IEEE CAS Mag. 13 (2013) 74-88

Biological Sensing

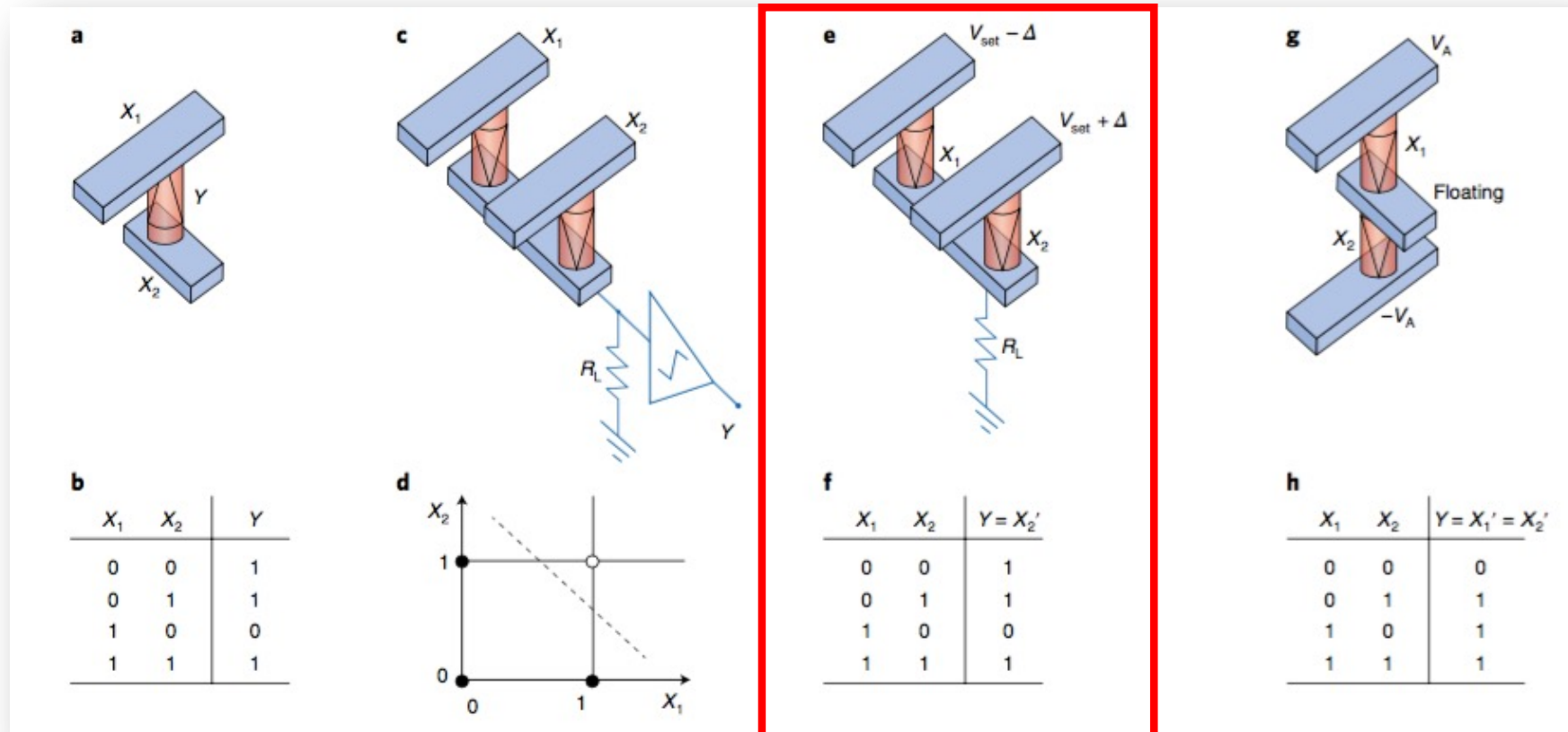


Human nervous system contains several kind of neurons, including sensory neurons

In-Memory Sensing

So, If we succeed in getting a device
that works like natural neurons we may
develop machines computing like
human brain and...
...like human peripheral nervous
sensing system,
we may also develop machines to
SENSE & COMPUTING !!!

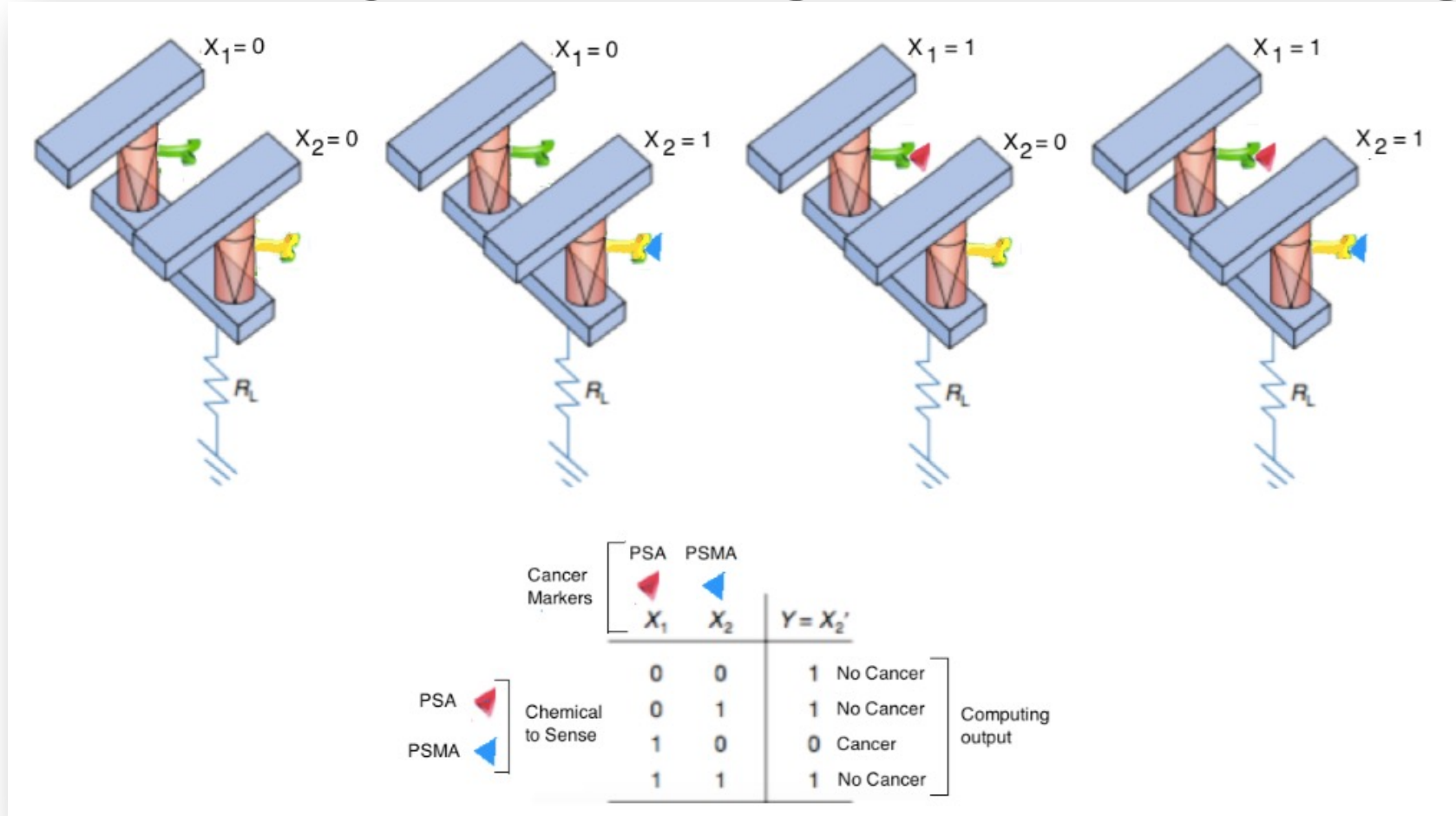
In-Memory Computing



D. Ielmini and H.-S.P. Wong, Nature Electronics 1(2018) 333-343

In-Memory Computing with RRAM-based
digital logic gates

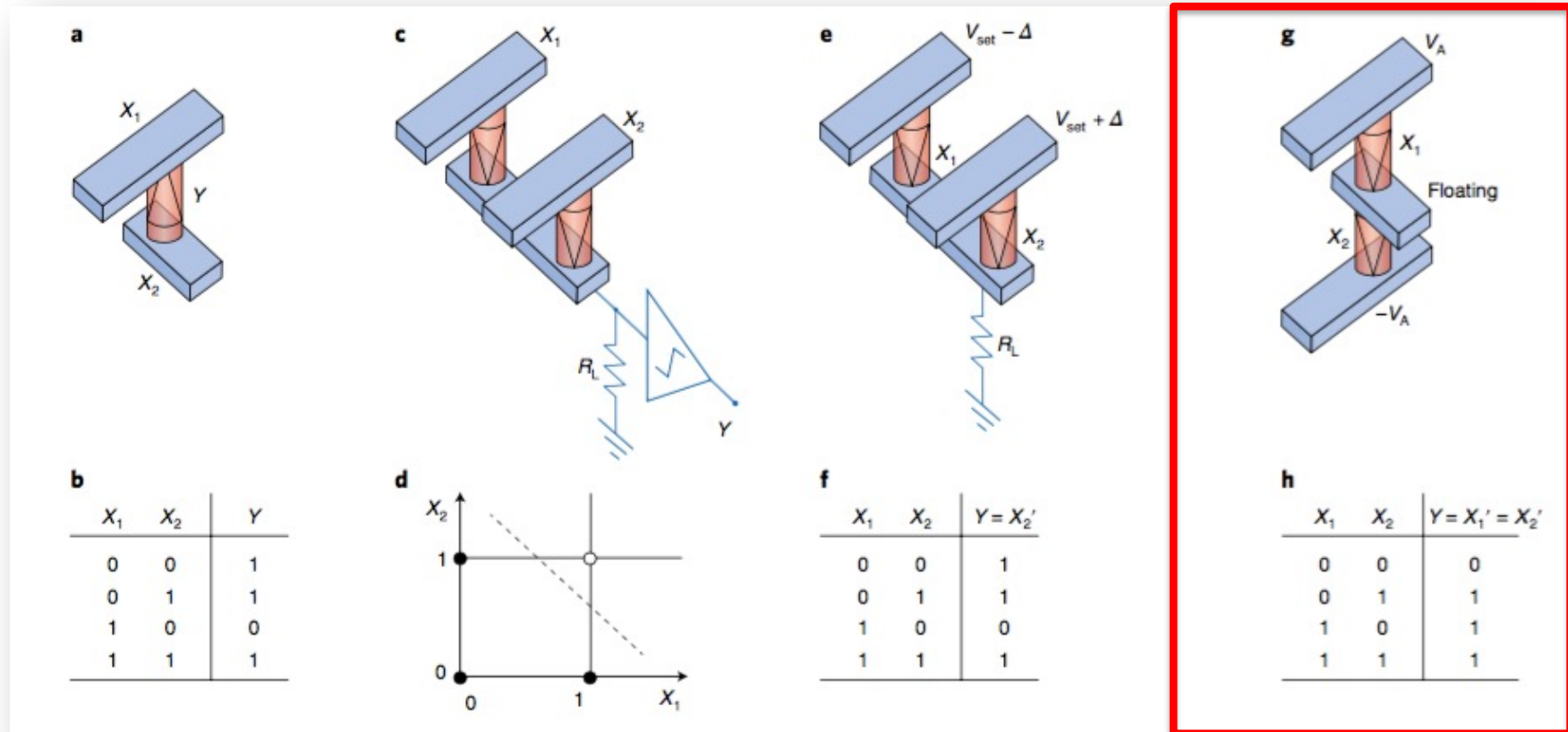
In-Memory Sensing & Computing



S.Carrara, et al., SNF Grant, 2021

In-Memory Sensing with RRAM-based
sensing digital logic gates

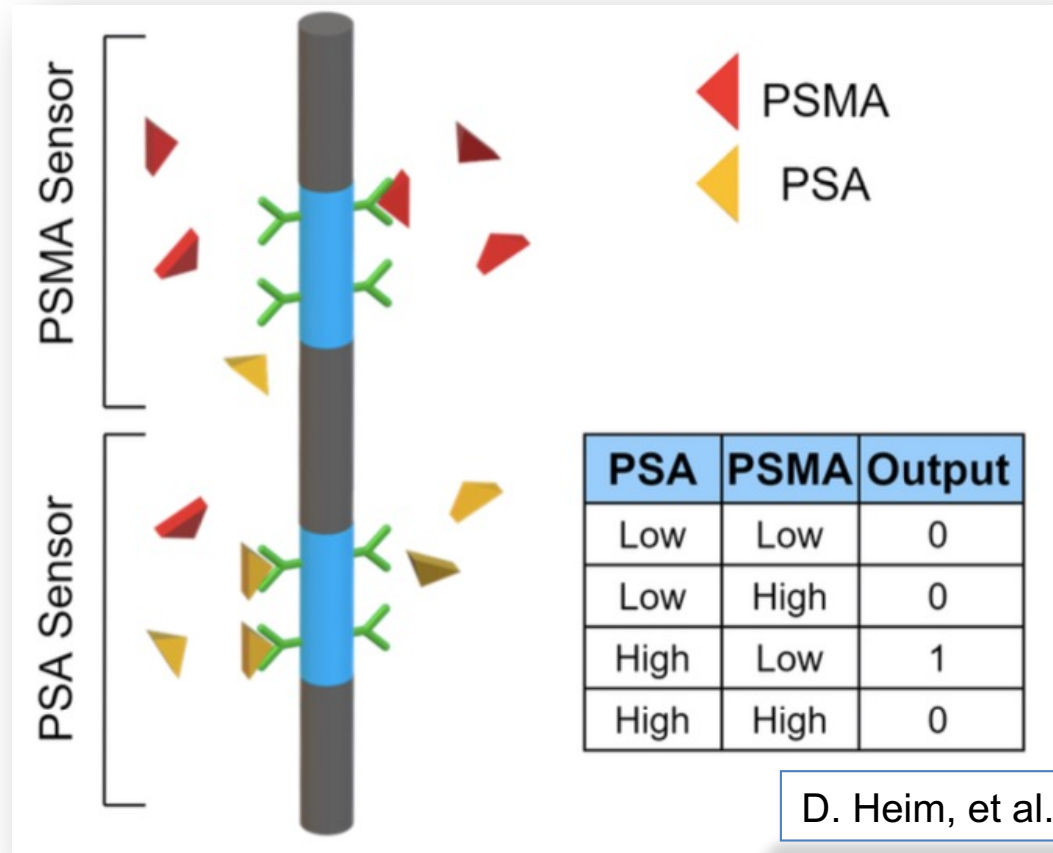
Back to Several Architectures



D. Ielmini and H.-S.P. Wong, Nature Electronics 1(2018) 333-343

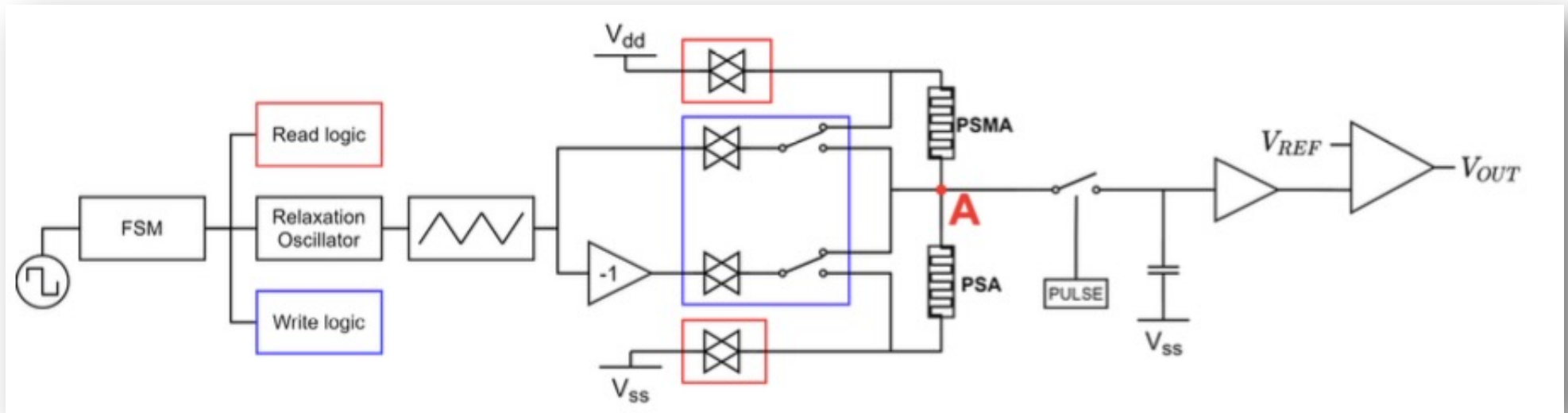
In-Memory Computing with RRAM-based
digital logic gates

Novel Approach in Edge Computing In-Memory Sensing of Cancer Markers



Two sensors interact with each other to perform a logical operation already at the sensor node

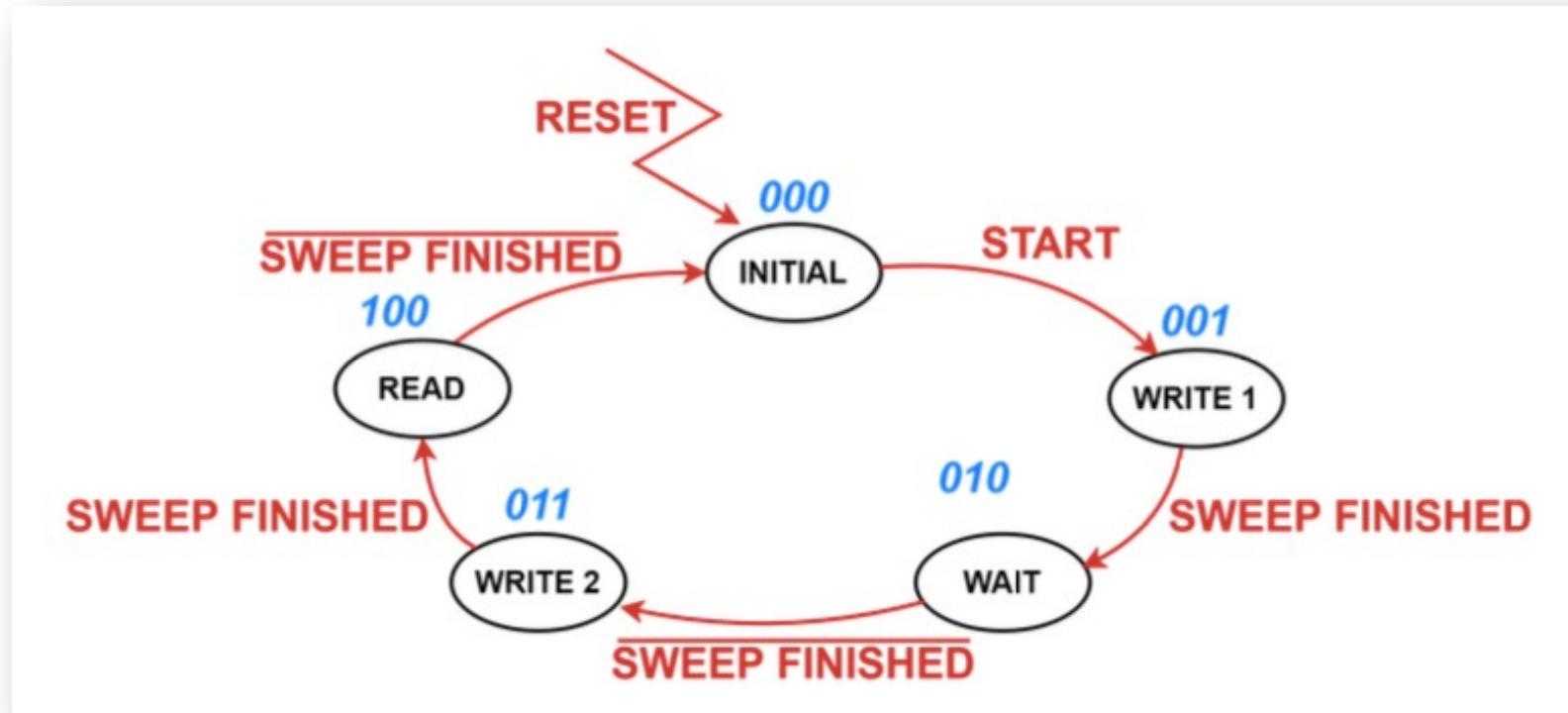
Novel Approach in Edge Computing In-Memory Sensing of Cancer Markers



D. Heim, et al., IEEE ISCAS 2022

Block diagram of the entire circuit. A Finite State Machine (FSM) is used to control switches for writing and reading the biosensors states

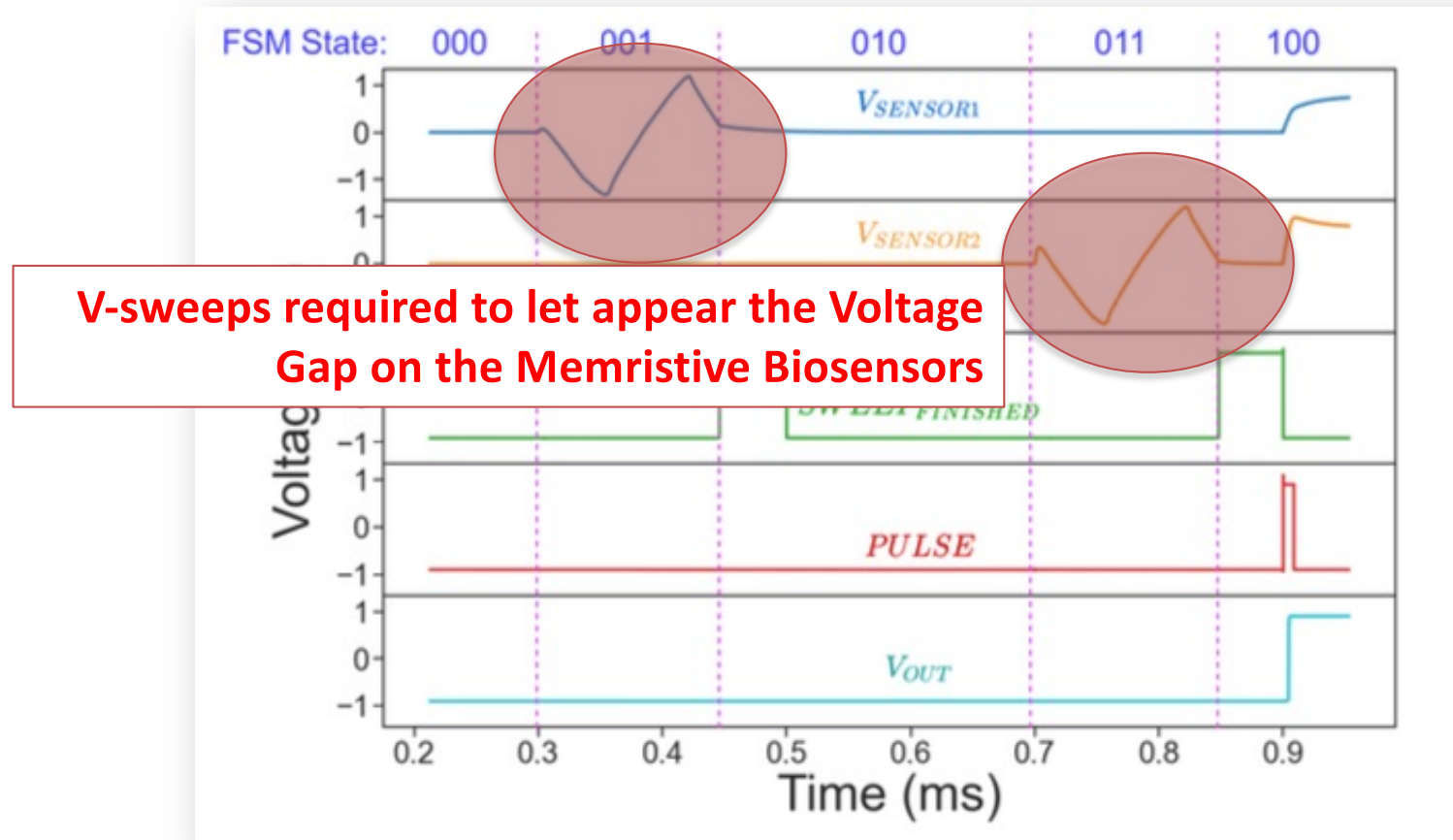
Novel Approach in Edge Computing In-Memory Sensing of Cancer Markers



D. Heim, et al., IEEE ISCAS 2022

Finite state machine diagram for writing and reading the biosensors states

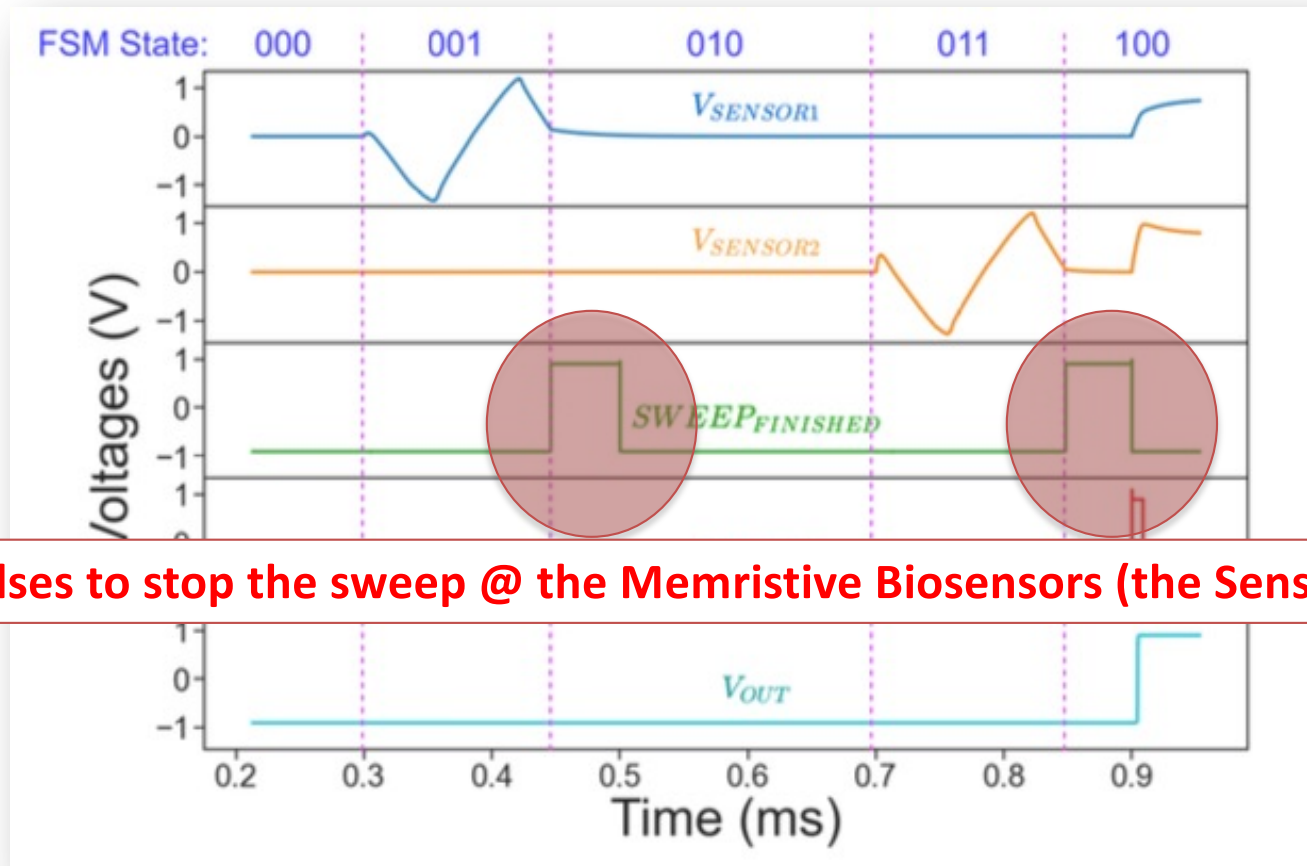
Novel Approach in Edge Computing In-Memory Sensing of Cancer Markers



D. Heim, et al., IEEE ISCAS 2022

Finite state machine states and main system signals

Novel Approach in Edge Computing In-Memory Sensing of Cancer Markers

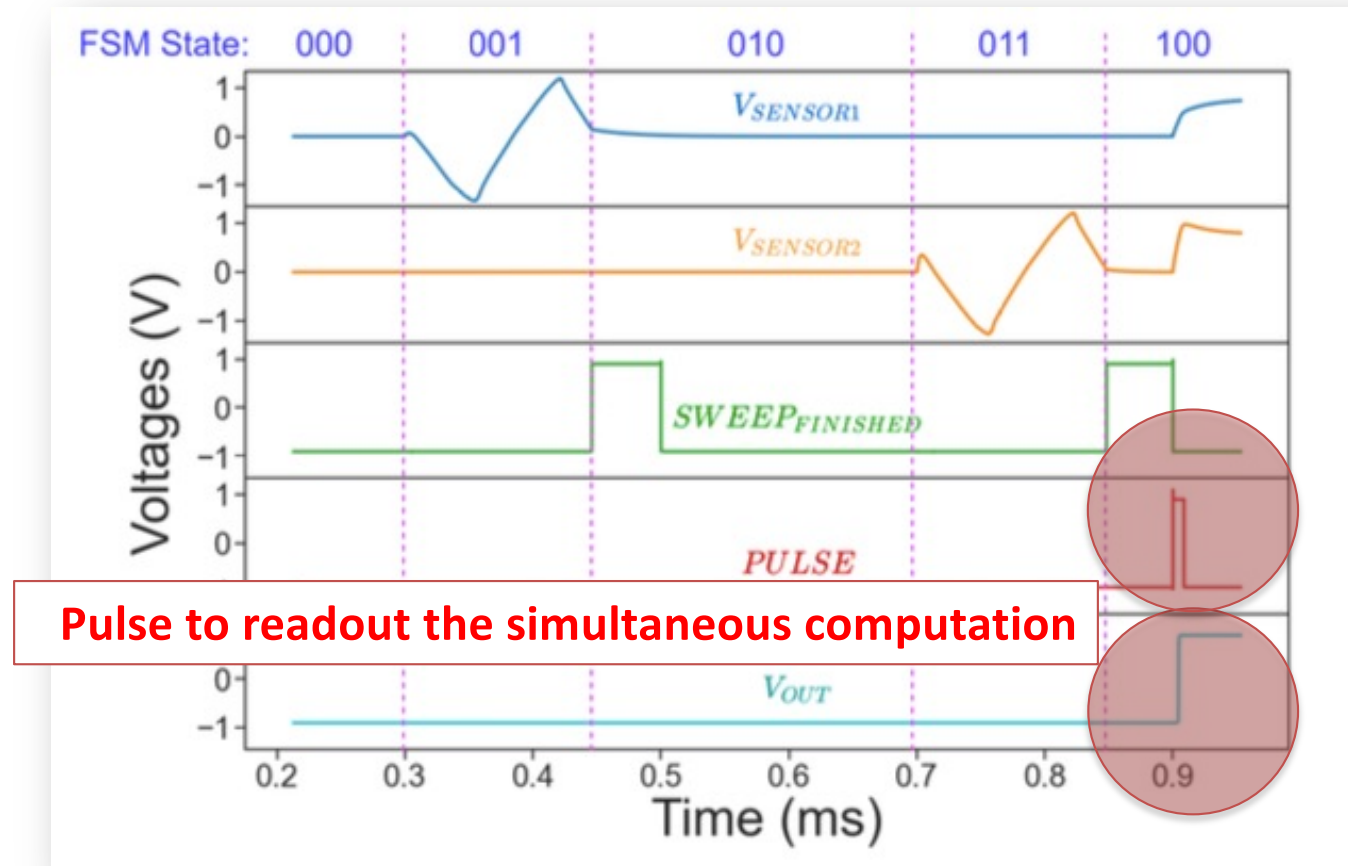


Pulses to stop the sweep @ the Memristive Biosensors (the Sensing!)

D. Heim, et al., IEEE ISCAS 2022

Finite state machine states and main system signals

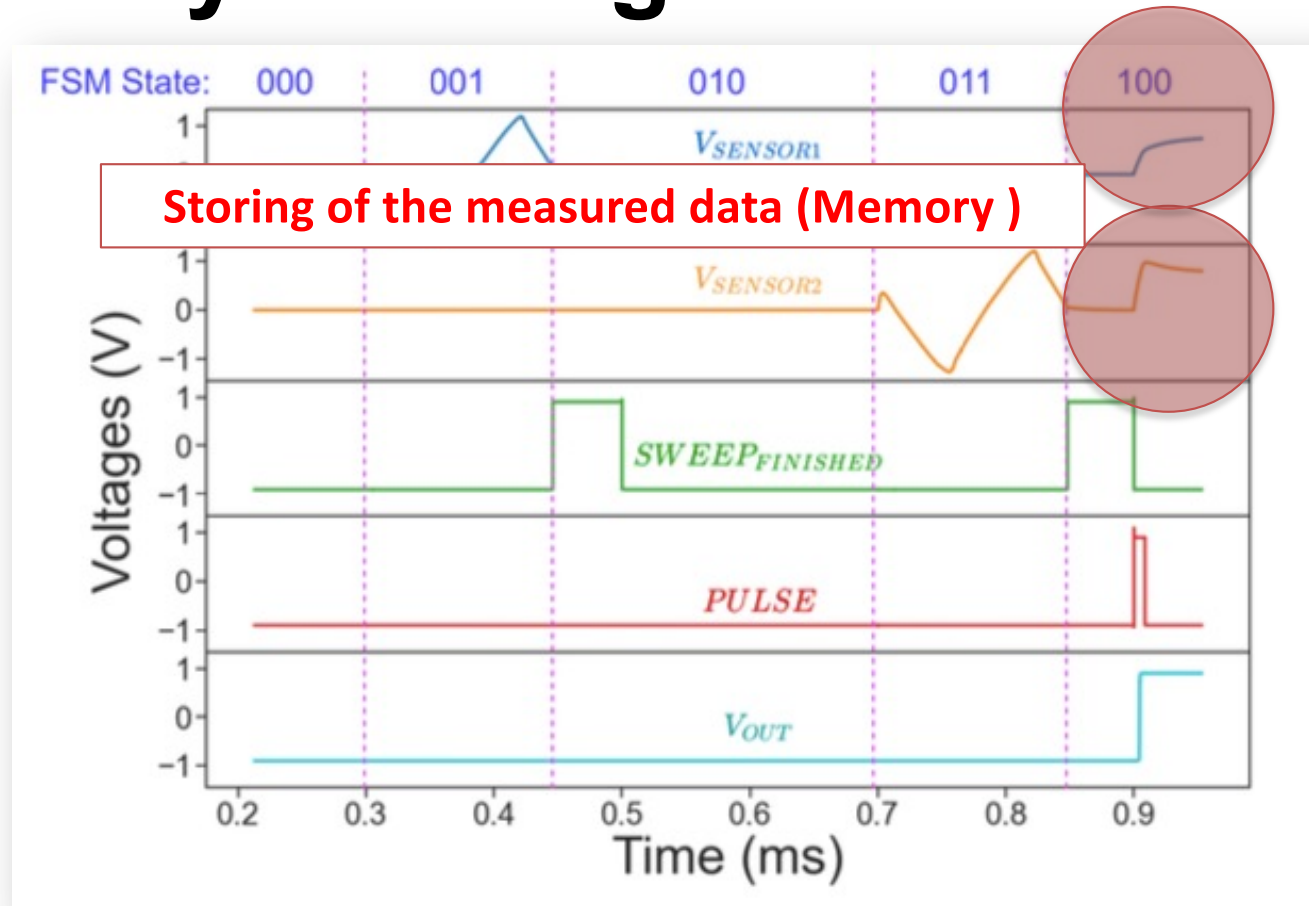
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D. Heim, et al., IEEE ISCAS 2022

Finite state machine states and main system signals

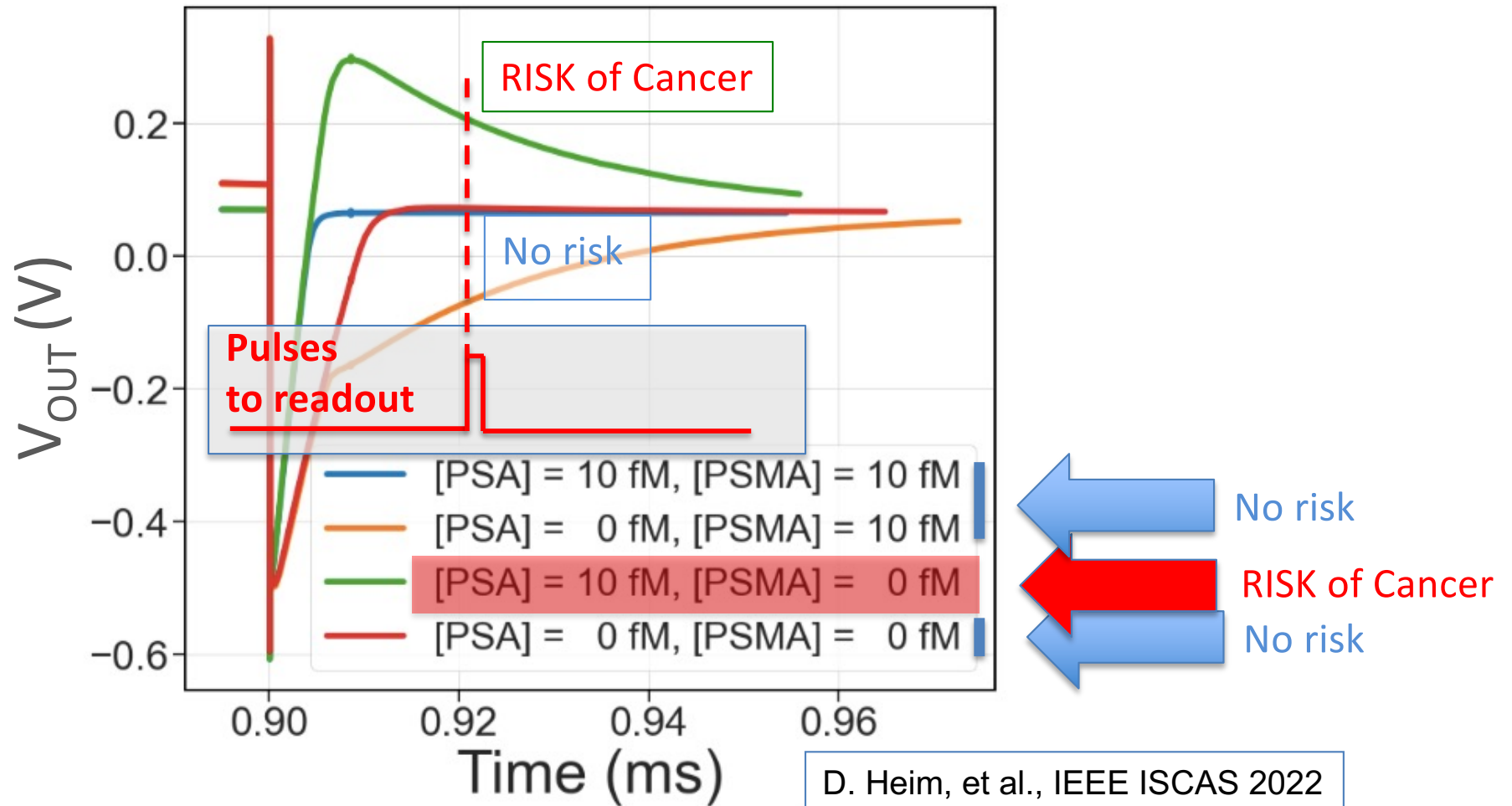
Novel Approach in Edge Computing In-Memory Sensing of Cancer Markers



D. Heim, et al., IEEE ISCAS 2022

Finite state machine states and main system signals

Novel Approach in Edge Computing In-Memory Sensing of Cancer Markers



Novel Approach in Edge Computing In-Memory Sensing of Cancer Markers

		PSMA				
		0 fM	3 fM	7 fM	10 fM	12 fM
PSA	0 fM	0.86	0.79	0.70	0.58	0.43
	3 fM	0.95	0.88	0.78	0.66	0.49
	7 fM	1.07	0.99	0.90	0.76	0.58
	10 fM	1.20	1.13	1.03	0.89	0.70
	12 fM	1.36	1.30	1.22	1.07	0.90

D. Heim, et al., IEEE ISCAS 2022

Output Voltages directly as “Risk Probability for Cancer” for different concentrations of PSA/PSMA

Summary

- That's possible to realize artificial neurons with single devices: the **Memristors**!
- The development of Memristive devices for Sensing aims gave rise to the new field of **Memristive Sensors**.
- The coupling of Memristive Sensors with biomolecules gave rise to the new field of **Memristive Biosensors**.
- Coupling the capability of computational architecture based on memristors and memristive sensors we can realize new **“in-Memory Sensing & Computing”** machines.
- Case study: simultaneous computation of multi-biomarkers is really key to succeed in **Cancer Diagnostics**!