



EDMI Microsystems and Microelectronics

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

Lecture #15

Portable, Implantable, and Wearable Devices,...& Beyond!!!

Glucometer on iPhone



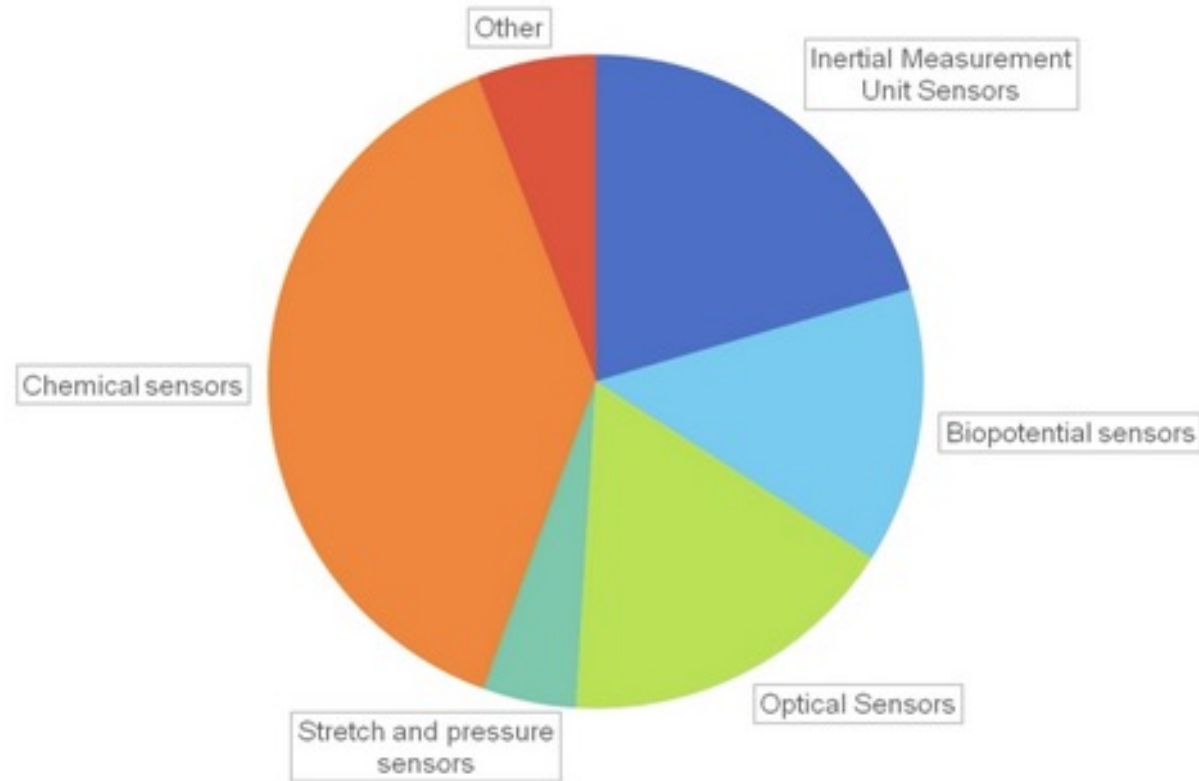
Wearable Glucometer by Abbot



Wearable Devices by 2025

Relative Market Size by Wearable Sensor Type in 2020

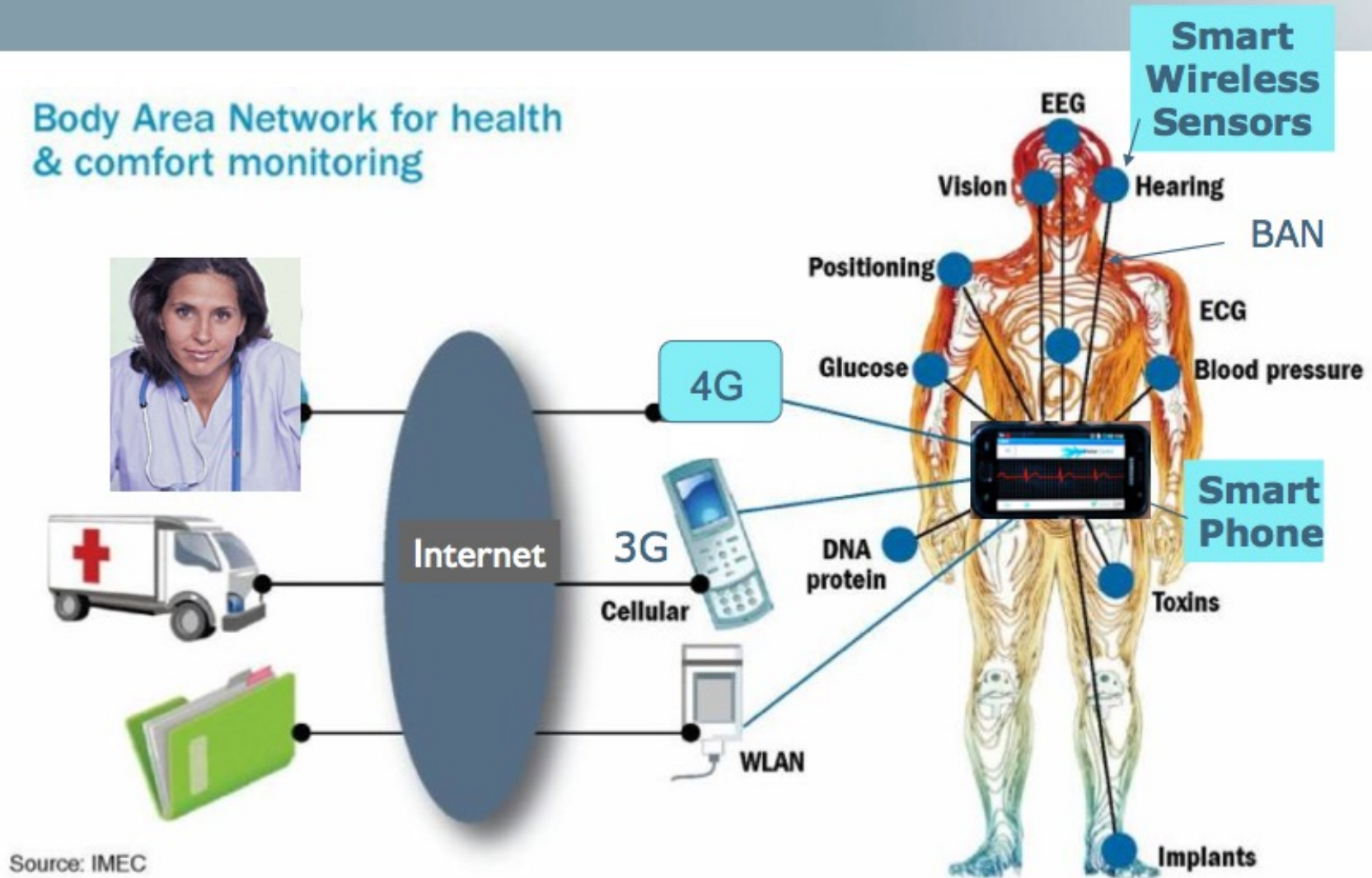
IDTechEx



Market analysis report that there will be 3 billion wearable sensors by 2025, with an overall market size of about US\$70 billion

Fully-Connected Human++

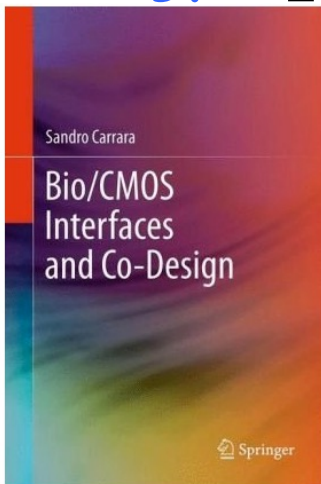
Body Area Network for health
& comfort monitoring



Courtesy, Hugo De Man (IMEC)

Toward innovative systems we need:

1. Fully integration of **Bio**molecules to assure specificity
2. Fully integration of **Nano**-structures to assure sensitivity
3. Proper **CMOS** frontends to assure
 - (i) Precise Current measurements,
 - (ii) Multiplexing for multi-metabolites,
 - (iii) Reliability in Temperature and pH



Bio/Nano/CMOS Co-design !

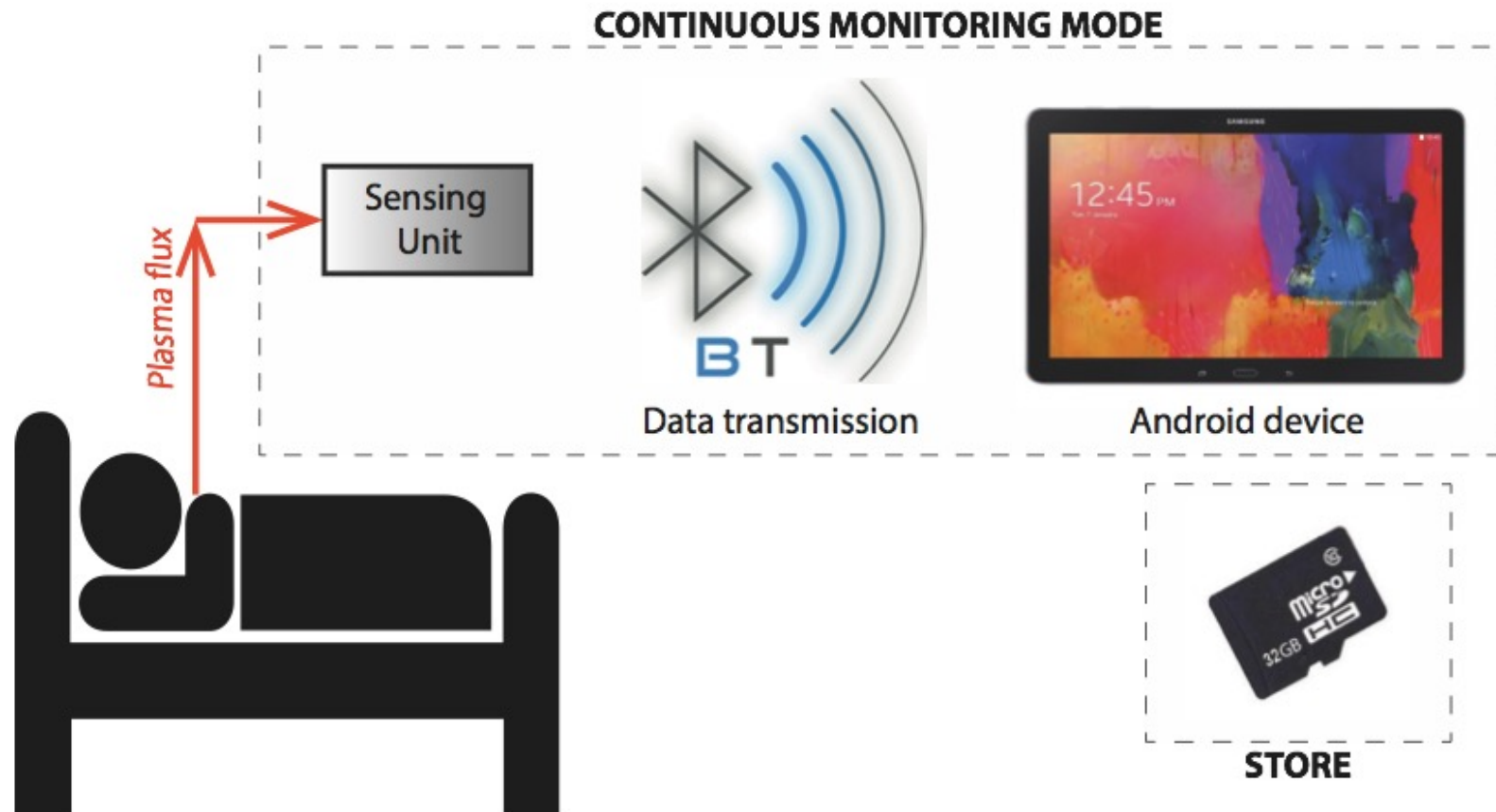
Portable, Implantable, 'n' Wearable



Monitoring scenarios

(c) S.Carrara

Portable: e.g., Intensive Care Units



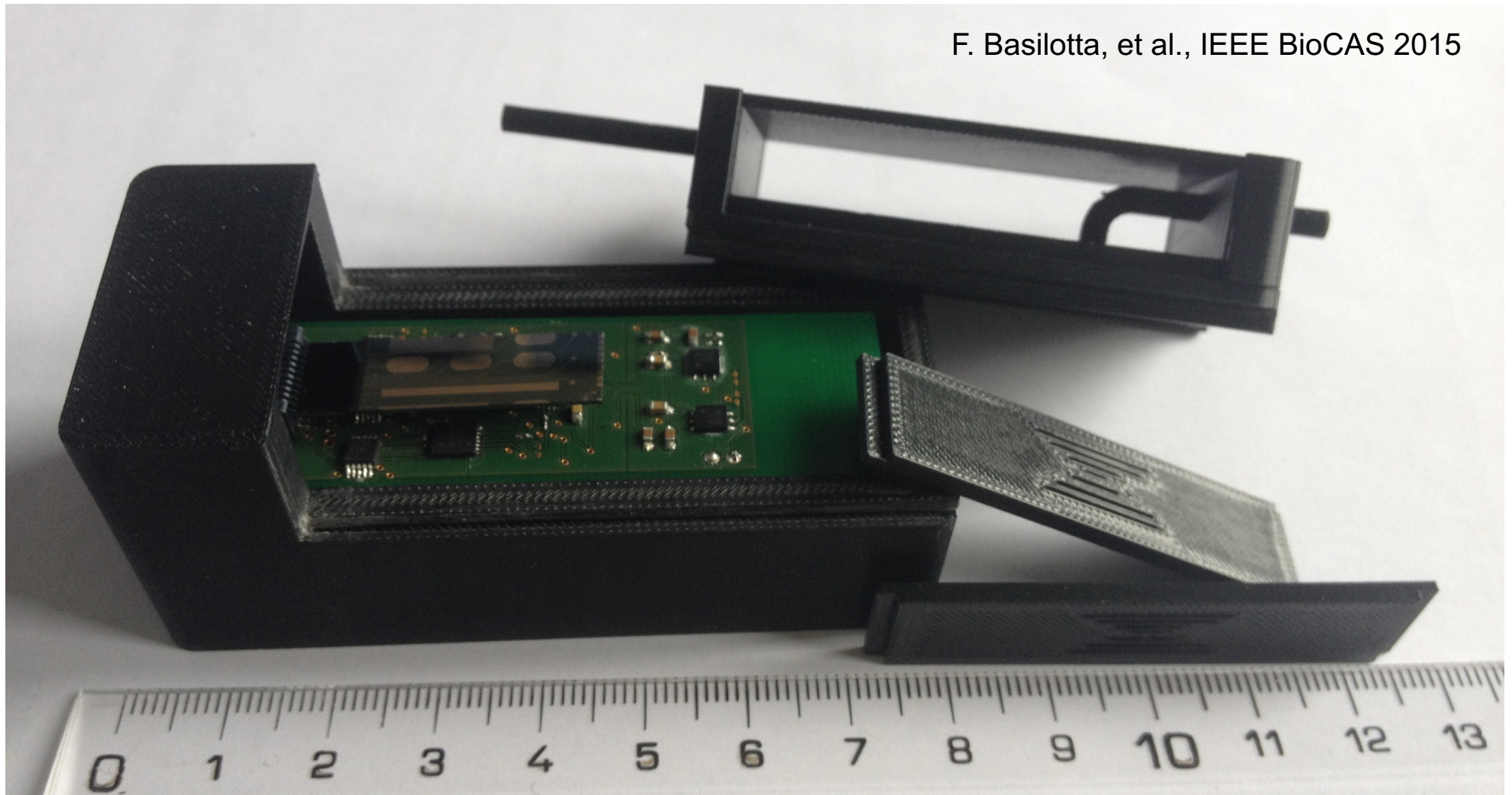
F. Stradolini, et al., IEEE Sensors Journal 16(2016) 3163 - 3170

Monitoring scenario where the main parameters of the patient are continuously displayed on an Android mobile device

(c) S.Carrara

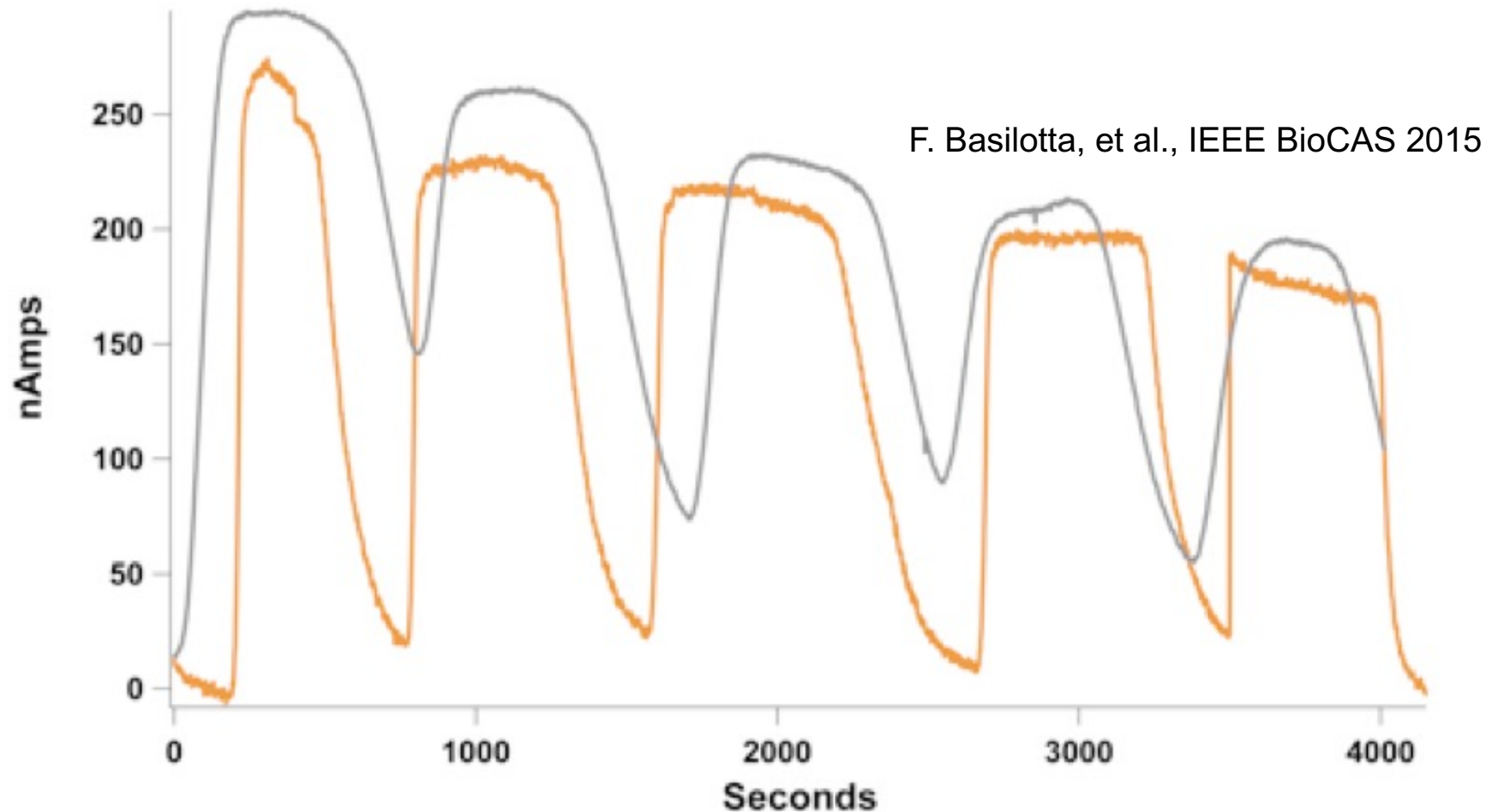
Monitoring in Intensive Care Units

F. Basilotta, et al., IEEE BioCAS 2015



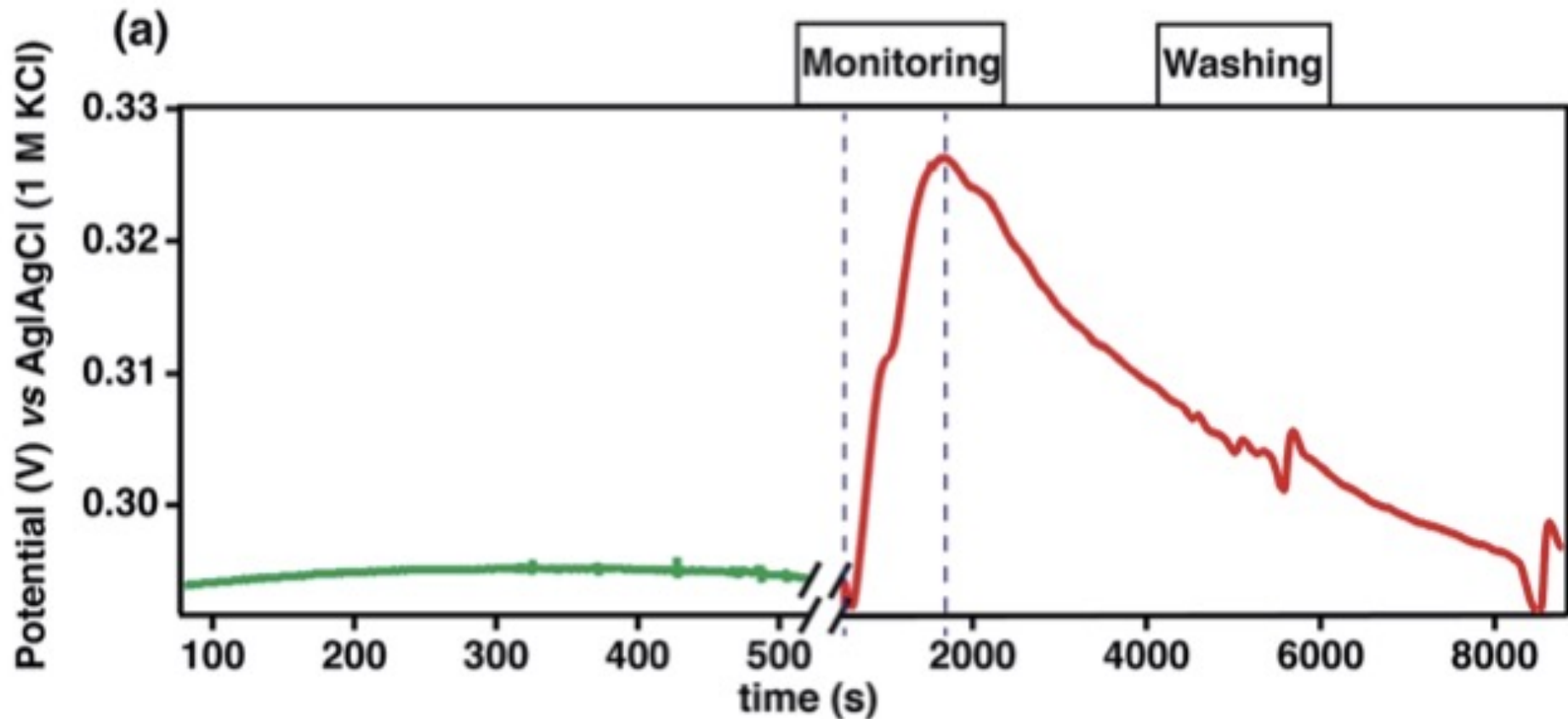
The whole system with the Android™ interface that allows connectivity too

Glucose and Lactate in flux



Chronoamperometry for glucose (grey) and lactate (orange)
acquired with the fluidic system

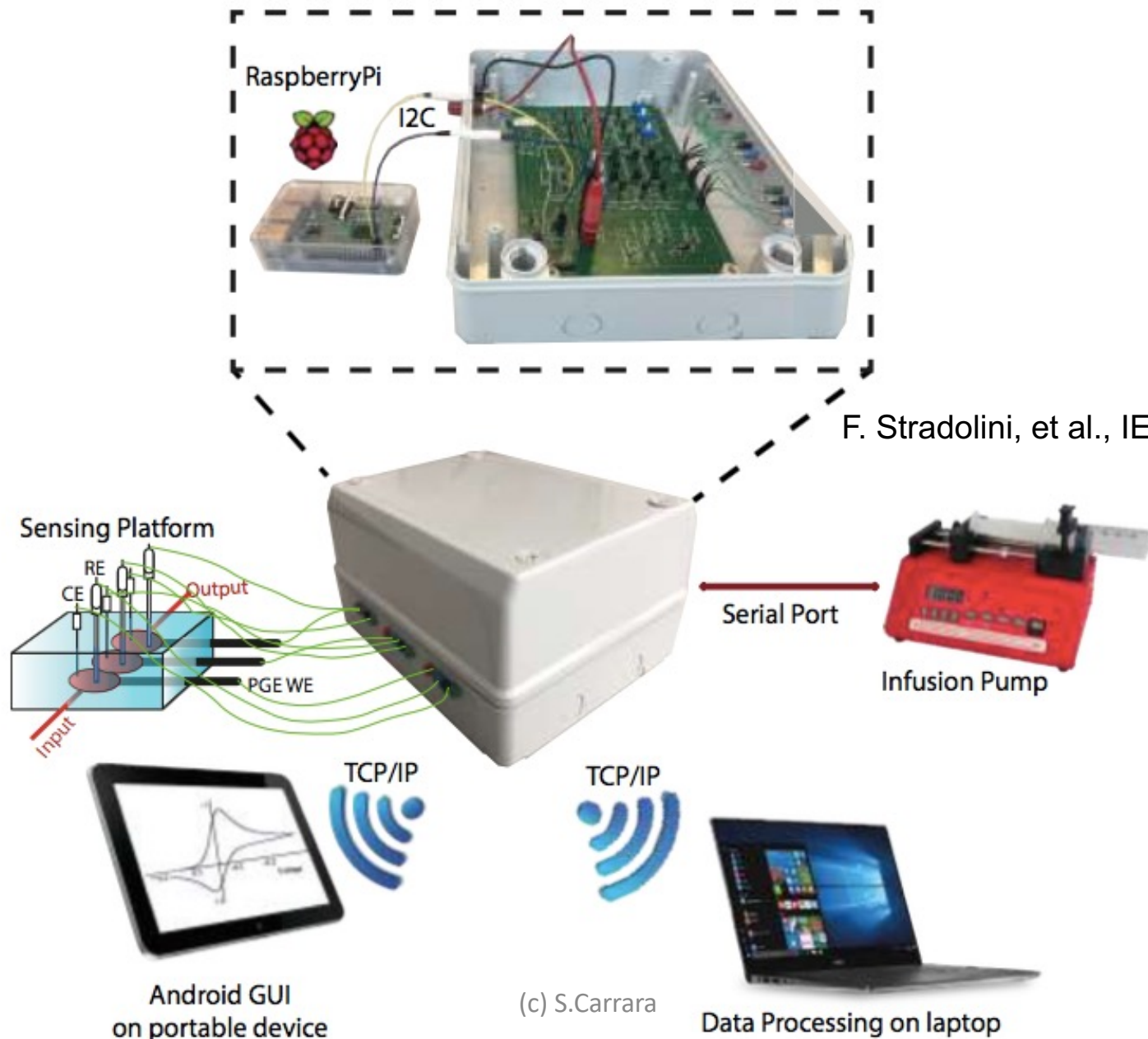
Emulation of Organs Failure



I. Taurino, et al., RSC Advances 6(2016) 40517-40526

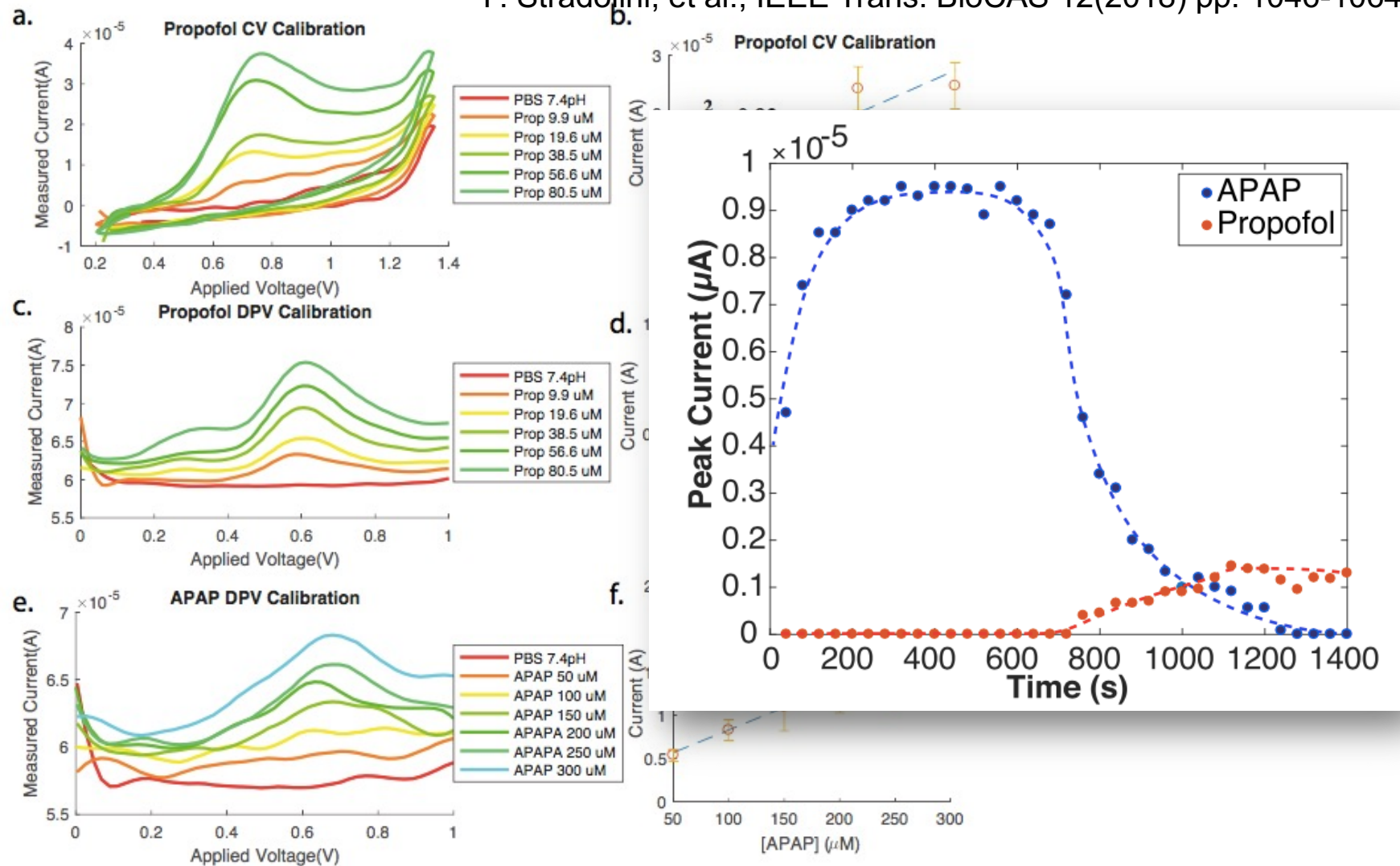
K^+ acquisitions during cell' osmotic chock

Monitoring and Injection in Surgery



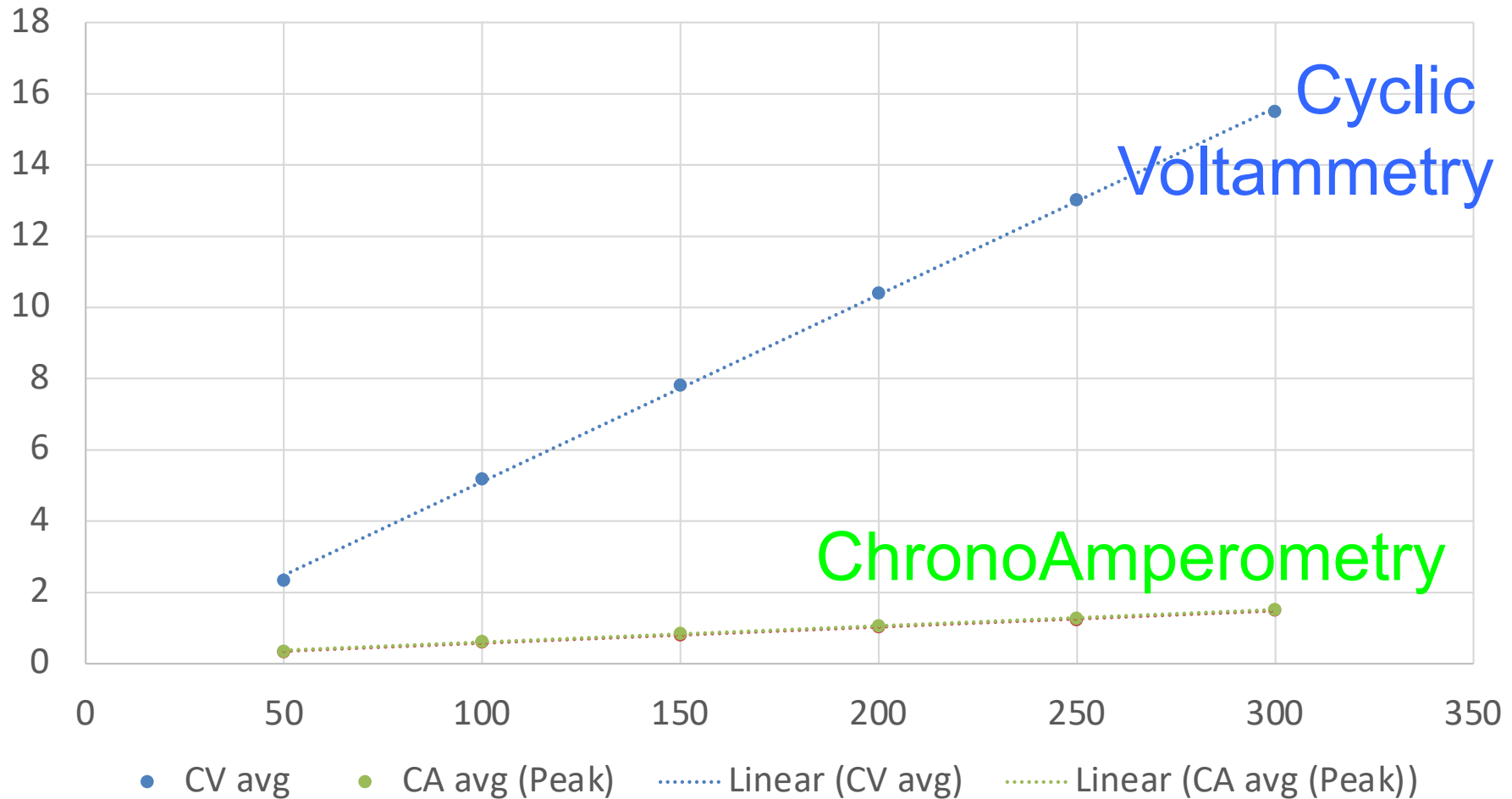
Detection of Anaesthetics

F. Stradolini, et al., IEEE Trans. BioCAS 12(2018) pp. 1046-1064



Sensors for Propofol, Paracetamol, and Midazolam have been successfully developed and tested

Chrono vs Cyclic: which best?



Paracetamol detection in
Chronoamperometry or in Cyclic Voltammetry

(c) S.Carrara

Lab vs Field: what change?

Stirring vs Non-Stirring

Usually, all the papers about electrochemistry we find in literature are showing data acquired with a Stirrer that assure best conditions with respect diffusion phenomena.

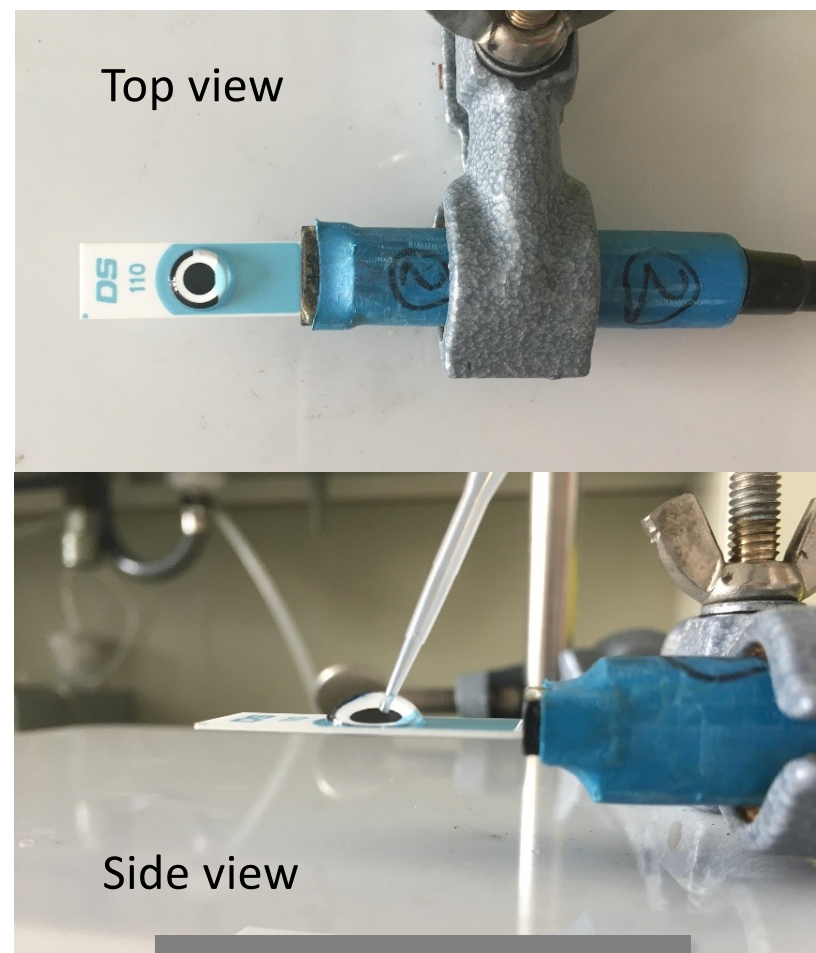
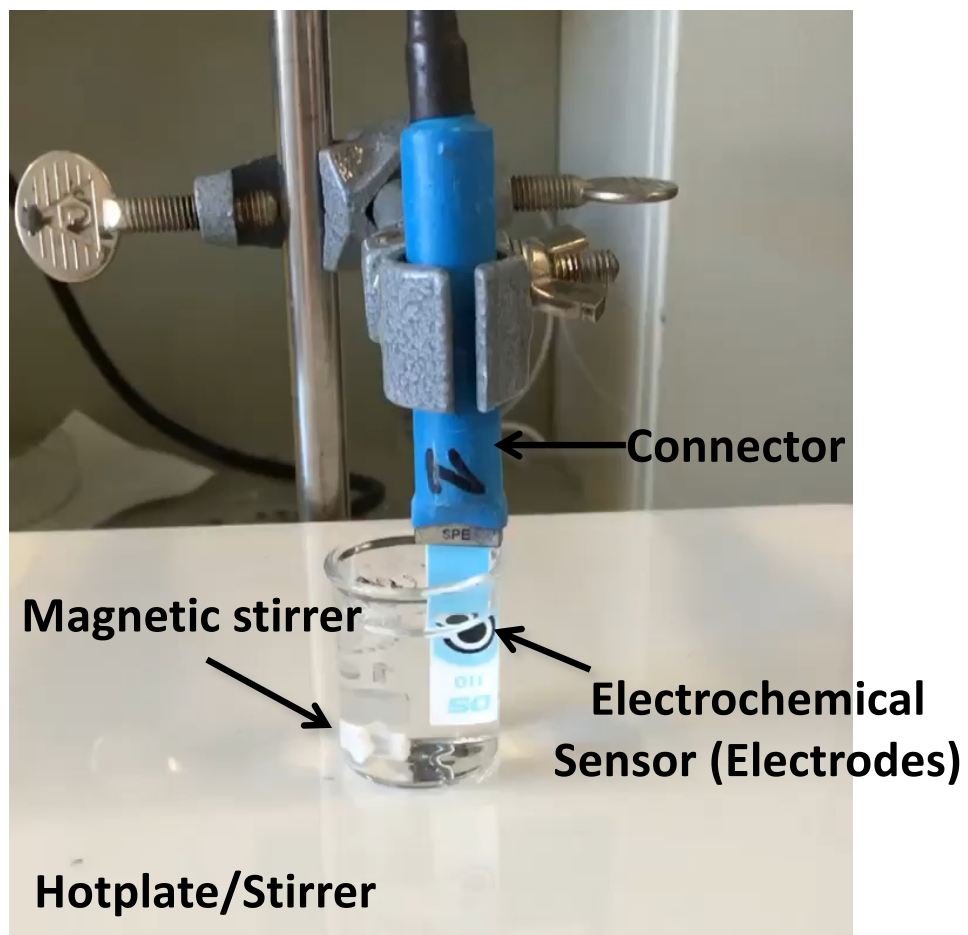
Does any conclusion we read on those papers be applied, for example, to measure on-the-skin?

The Stirrer



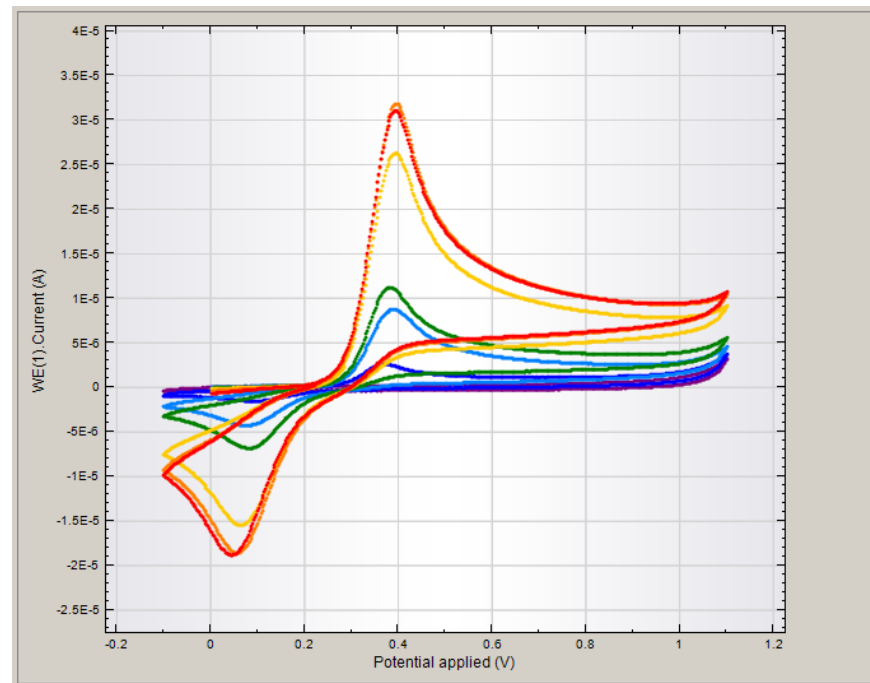
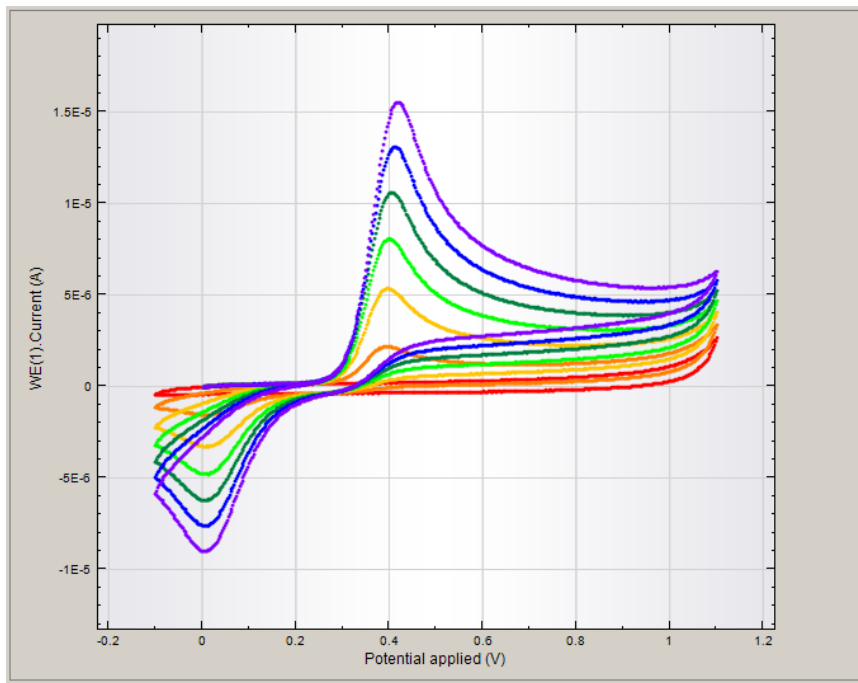
Reality vs Ideality

Stirring vs non-Stirring



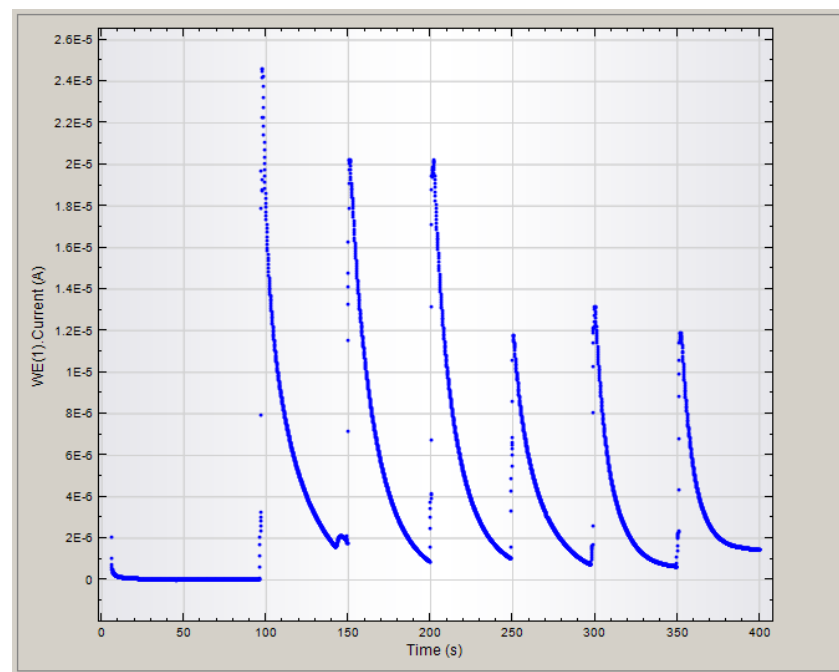
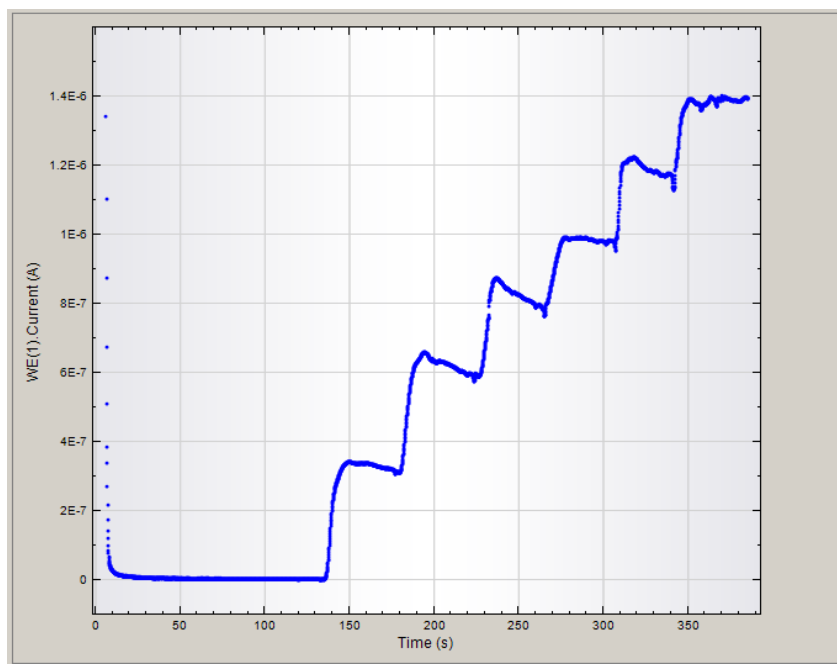
Cyclic Voltammetry

Stirring vs non-Stirring



Chronoamperometry

Stirring vs non-Stirring



APAP 0-300 μ M at 0.4V, acquisition each 50 sec. in both the cases

CV vs CA

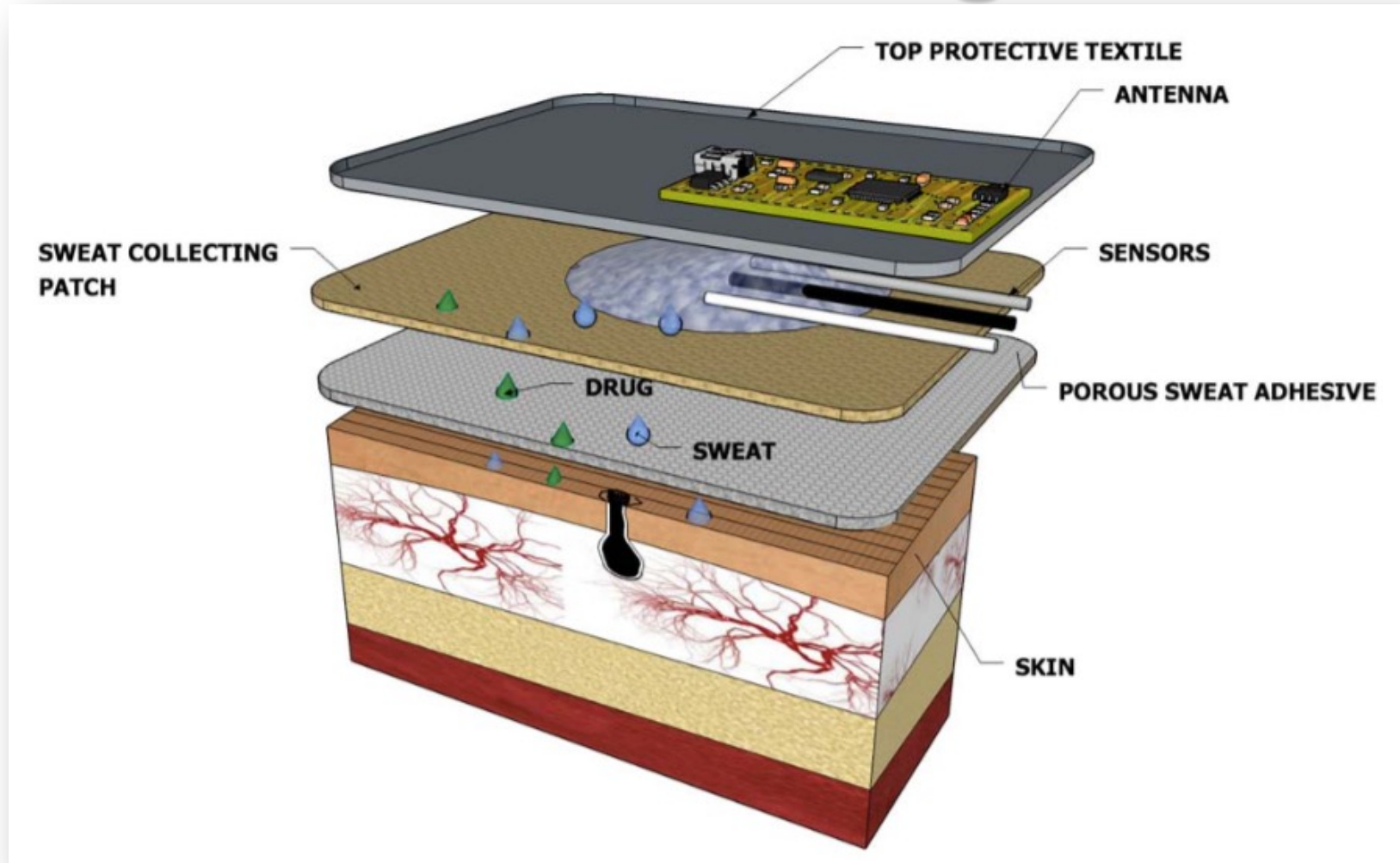
Stirring vs non-Stirring

	Stirring	Water drop
Sensitivity in CV	2.62	0.13
Sensitivity in CA	0.0045	0.012
Overall SD	low	high

In CV, both sensitivity and standard division in normal experiment are better than water drop. Therefore, the *limitation of detection of water drop experiment is worst* (higher) *than normal experiment*.

In CA, result is almost the same as CV but sensitivity is higher in water drop experiment. Maybe because of the injection position.

Wearable Monitoring Devices



T.Kilic, al. et S.Carrara / ICECS 2016

Metabolites Monitoring on the skin

(c) S.Carrara

Metabolites on the skin

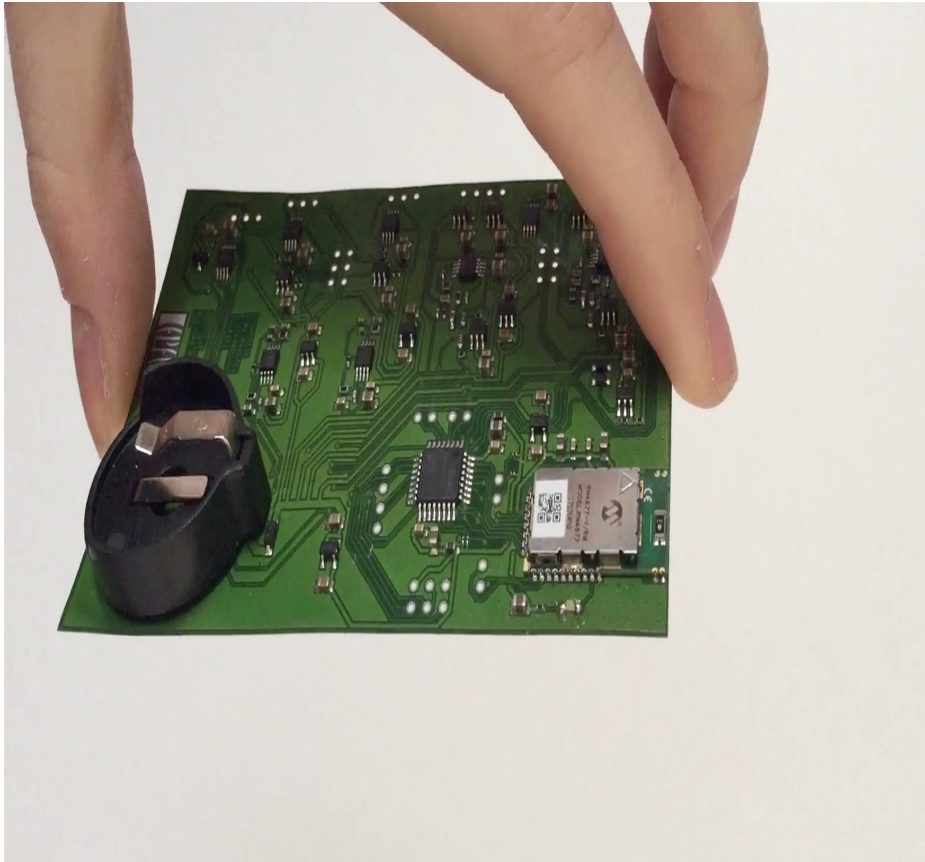
I.Ny Hanitra, et al., IEEE MeMeA 2018

Wearable Sensors

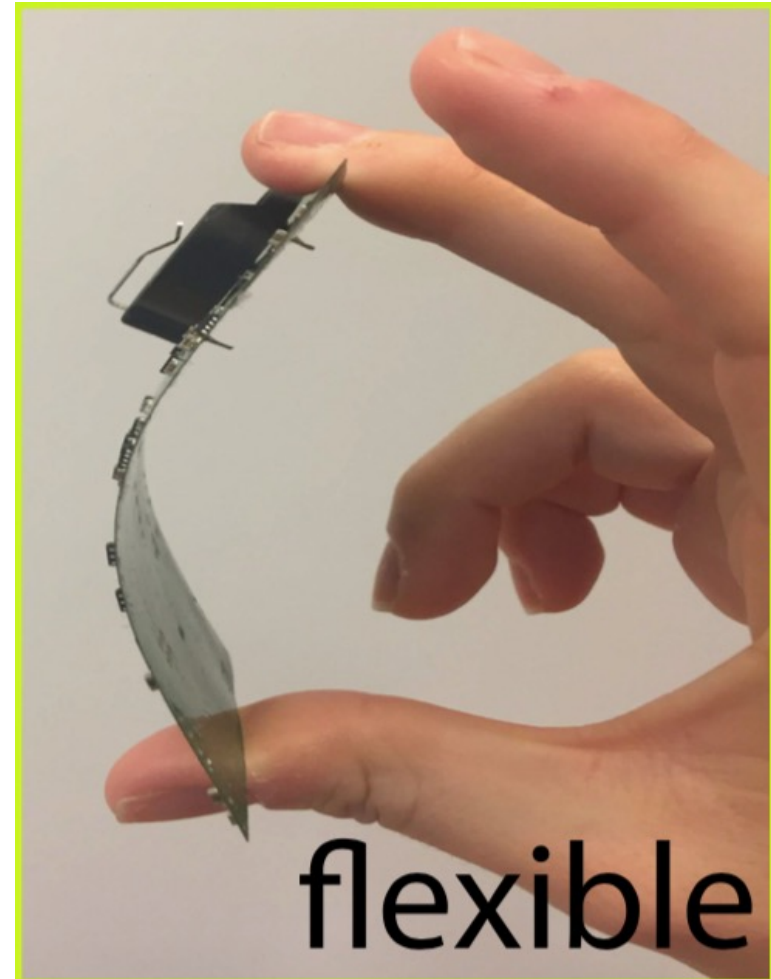


Wearable Electronics

Flexible Electronics



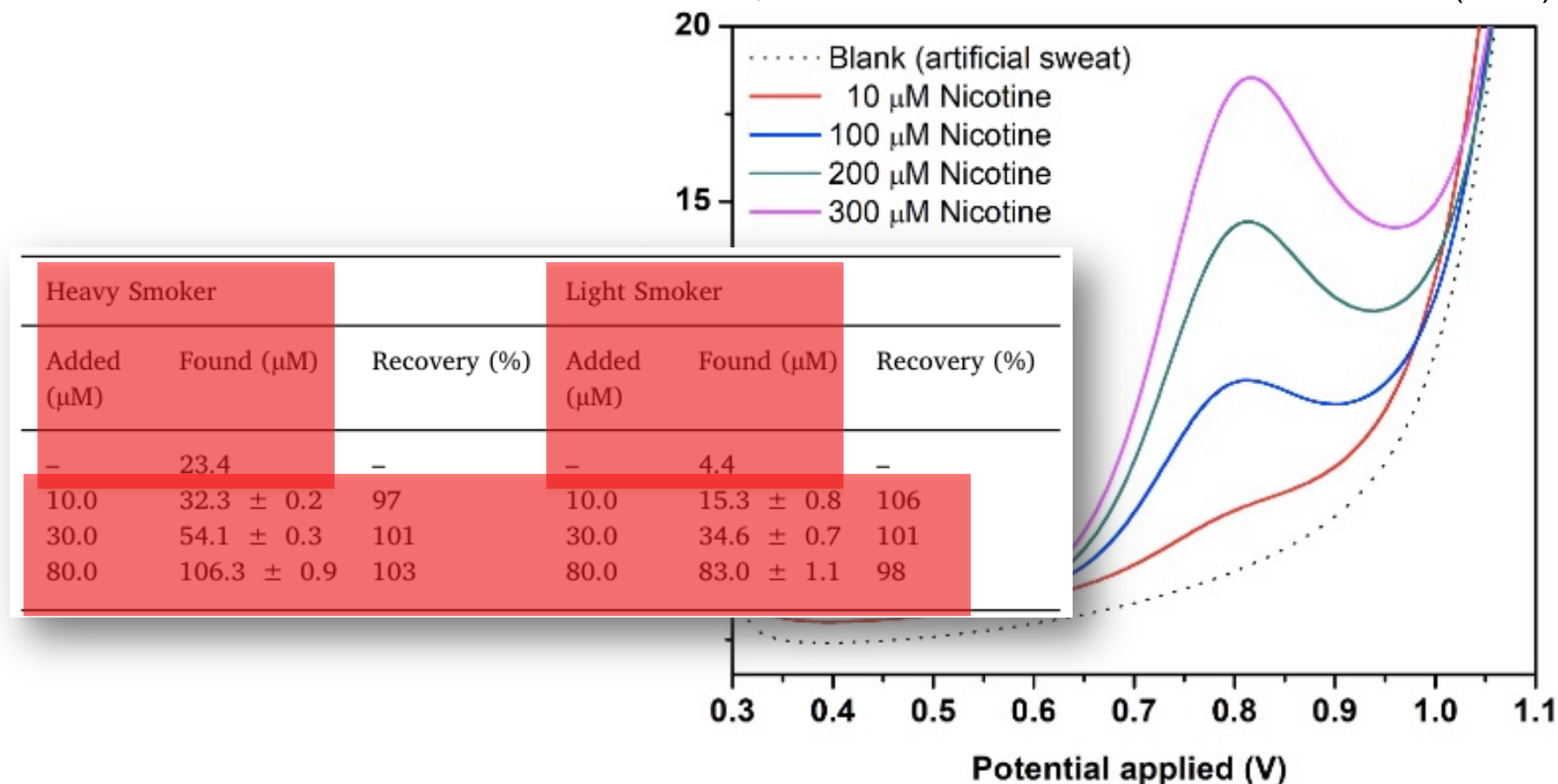
I.Ny Hanitra, et al., IEEE MeMeA 2018



The Detection system has been realized
on flexible PCB

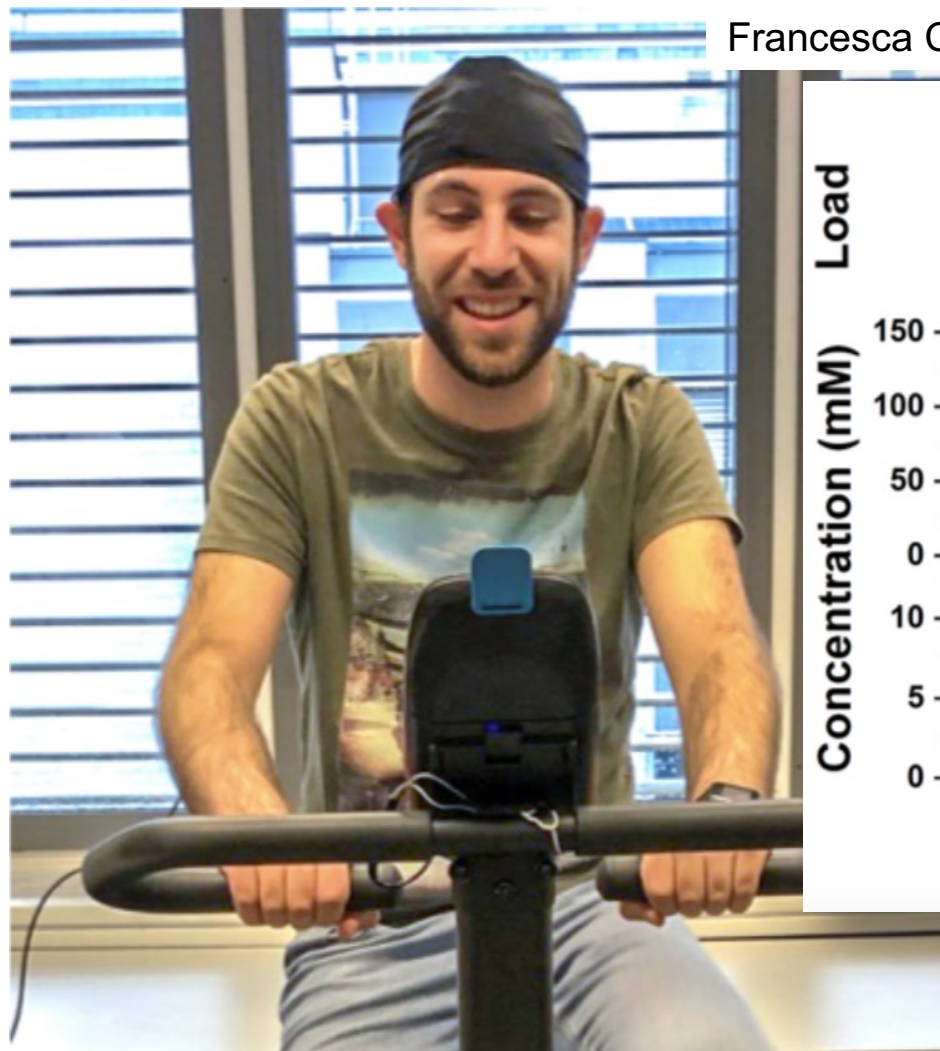
Nicotine @ Wearable

E. Mehmeti, al. et S.Carrara / Microchemical Journal 158(2020) 105155

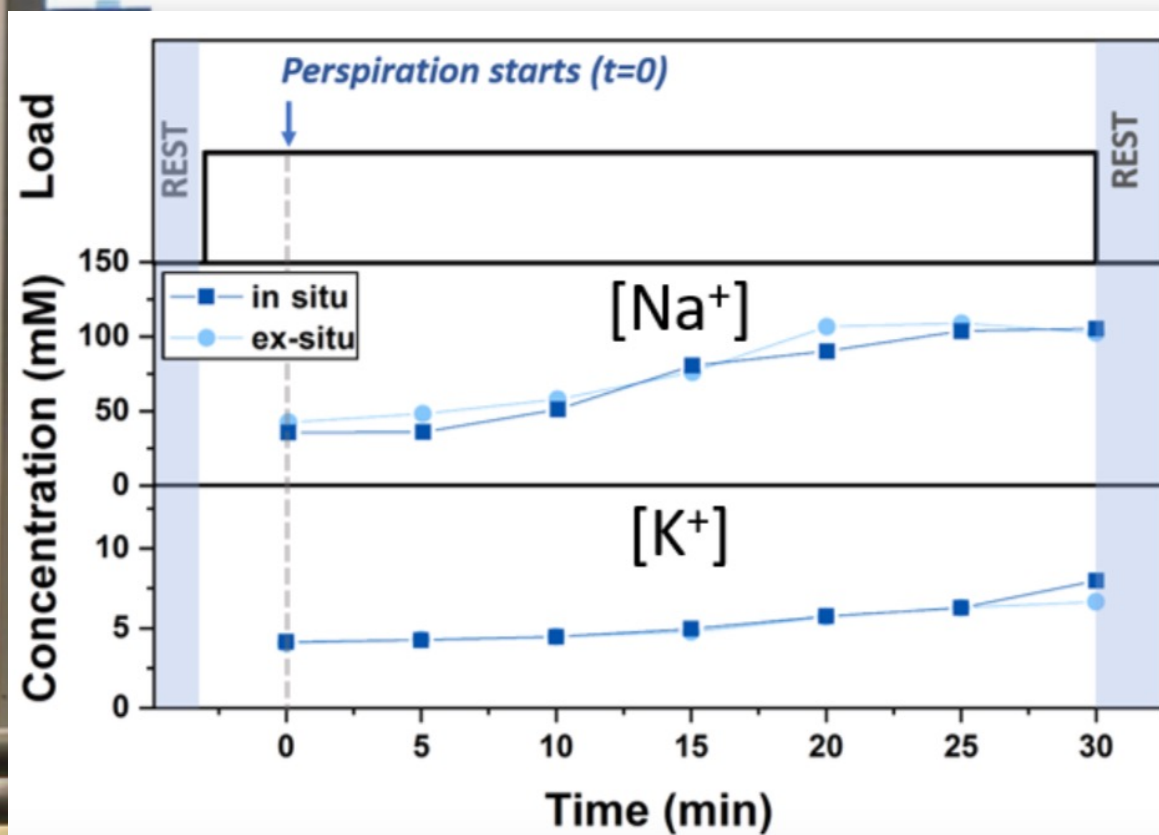


The Detection of Nicotine on the skin of heavy and light smokers

Na⁺ & K⁺ @ Wearable



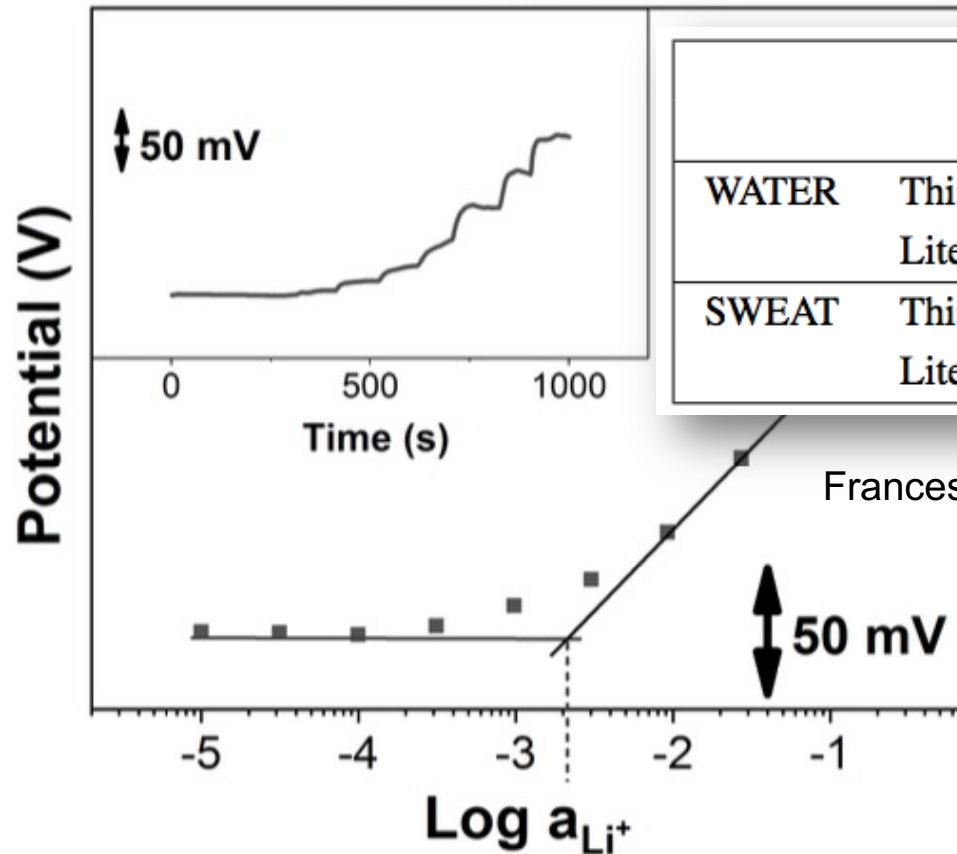
Francesca Criscuolo, al. et / Sensors And Actuator B, 2020 submitted



The Detection of ions in sportsmen

Li⁺ @ Wearable

Artificial sweat

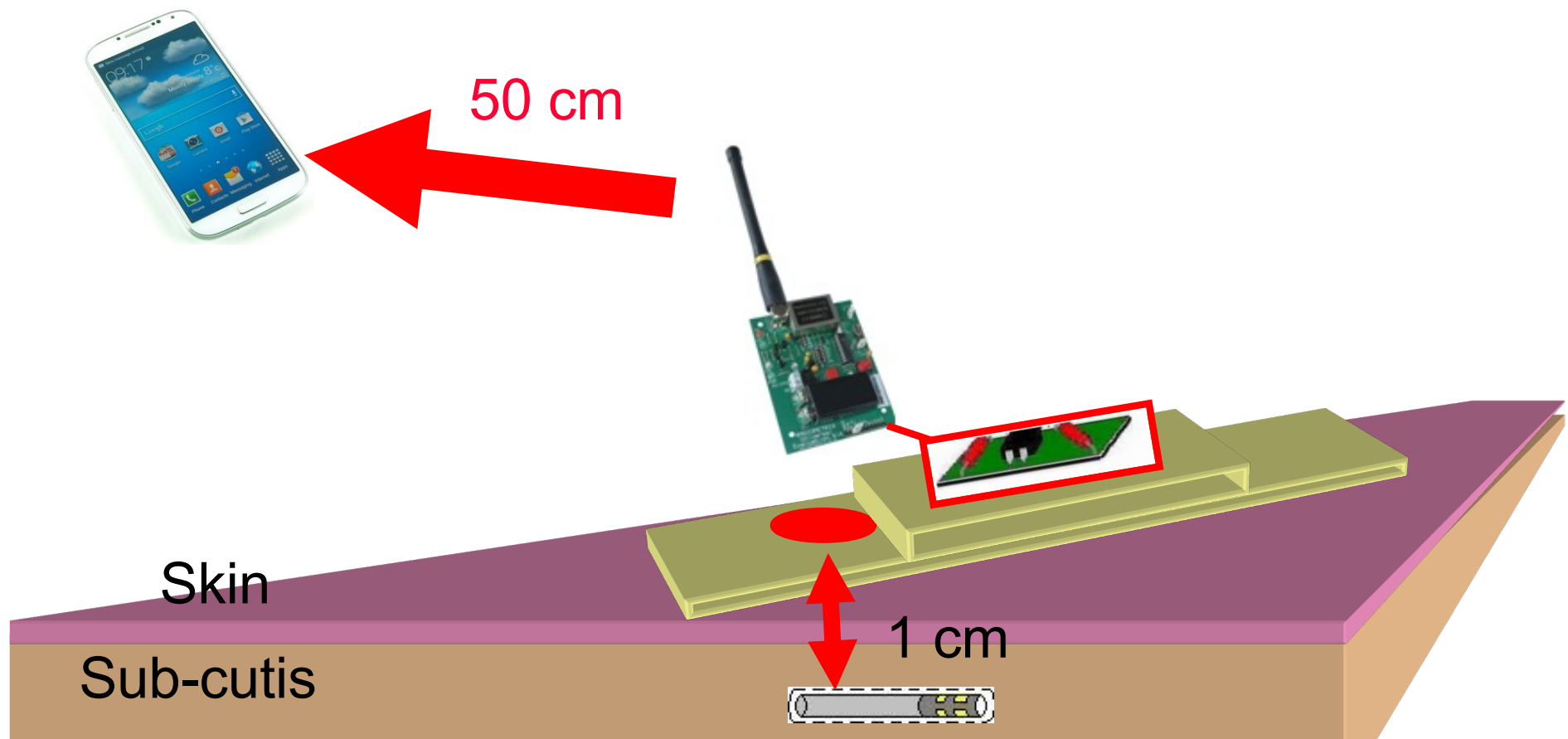


		sensitivity [mV/decade]	LOD (M)
WATER	This work (flexible)	59.6 ± 1.5	$(5.9 \pm 2.6) \times 10^{-5}$
	Literature (rigid) [27]	58.7 ± 0.8	$(1.3 \pm 0.4) \times 10^{-5}$
SWEAT	This work (flexible)	56.8 ± 3.9	$(1.7 \pm 0.6) \times 10^{-3}$
	Literature (rigid) [31]	57.6 ± 2.1	$(1.4 \pm 0.2) \times 10^{-3}$

Francesca Criscuolo, al. et / IEEE Sensors Journal, 2020 in press

Non-invasive monitoring of Lithium
as Drug in Bipolar Disorder

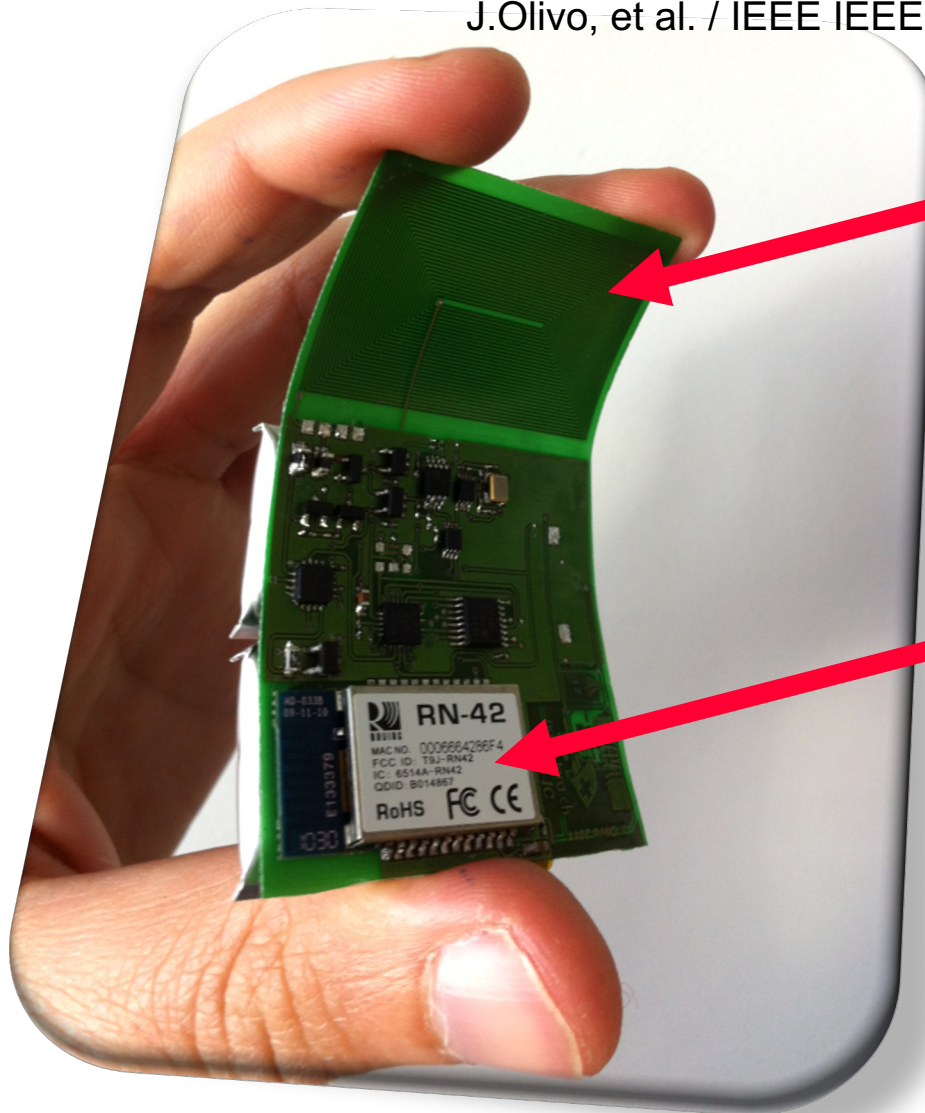
Under-the-Skin Devices & Wearable



An antenna very close to the chip is required for the remote powering

The Realized Remote Powering Patch

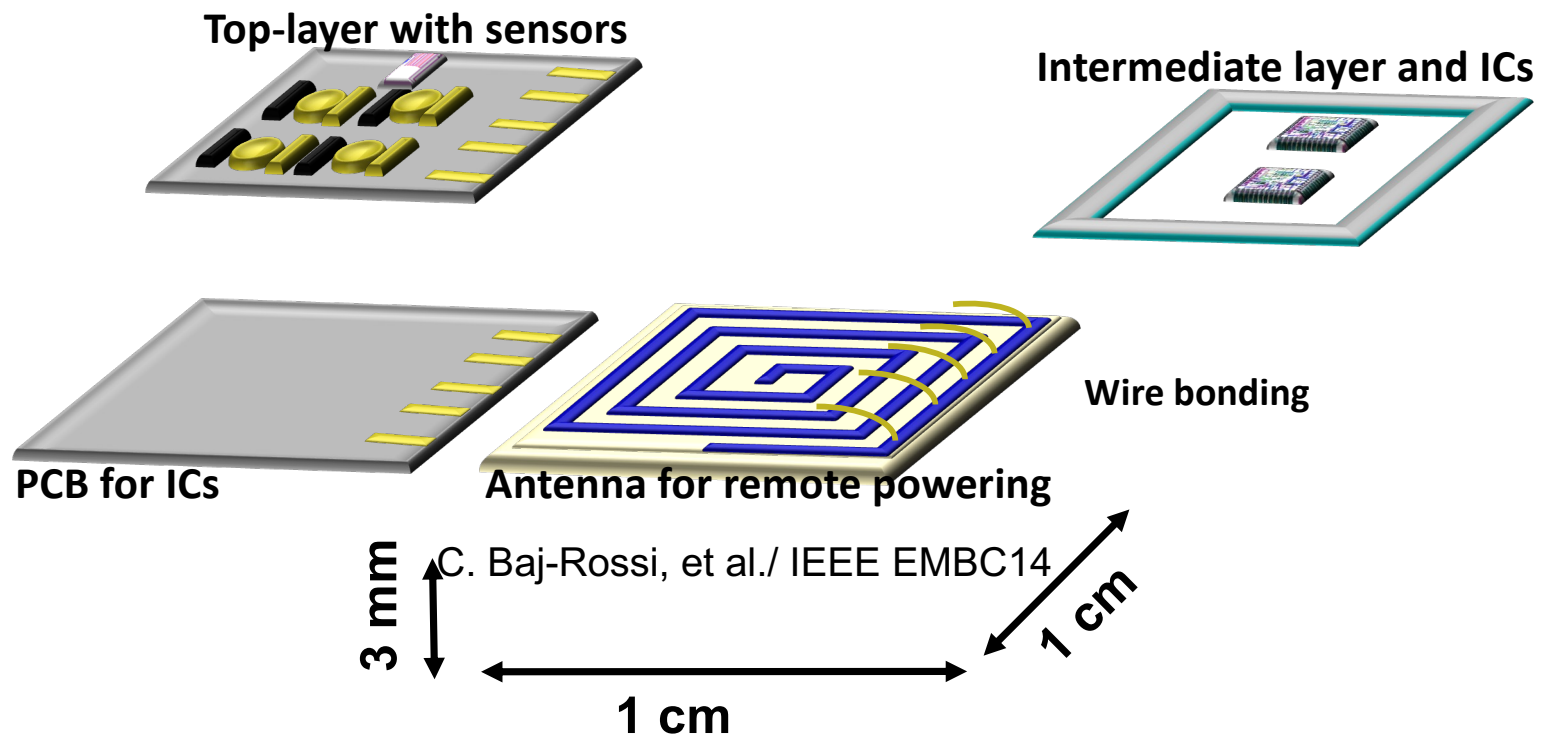
J.Olivo, et al. / IEEE IEEE Trans. BioCAS 7(2013) pp. 536-547



The patch has been realized with off-the-shelf components

(c) S.Carrara

Under-the-Skin Device: button' size



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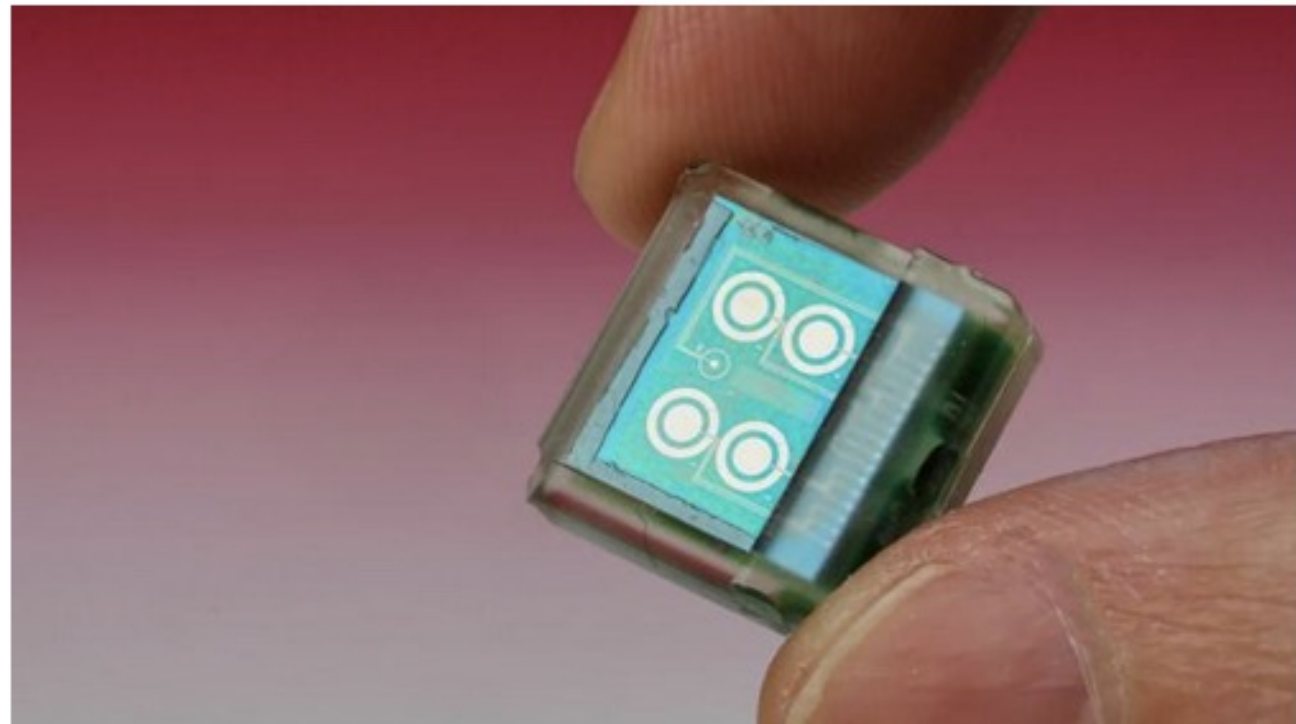
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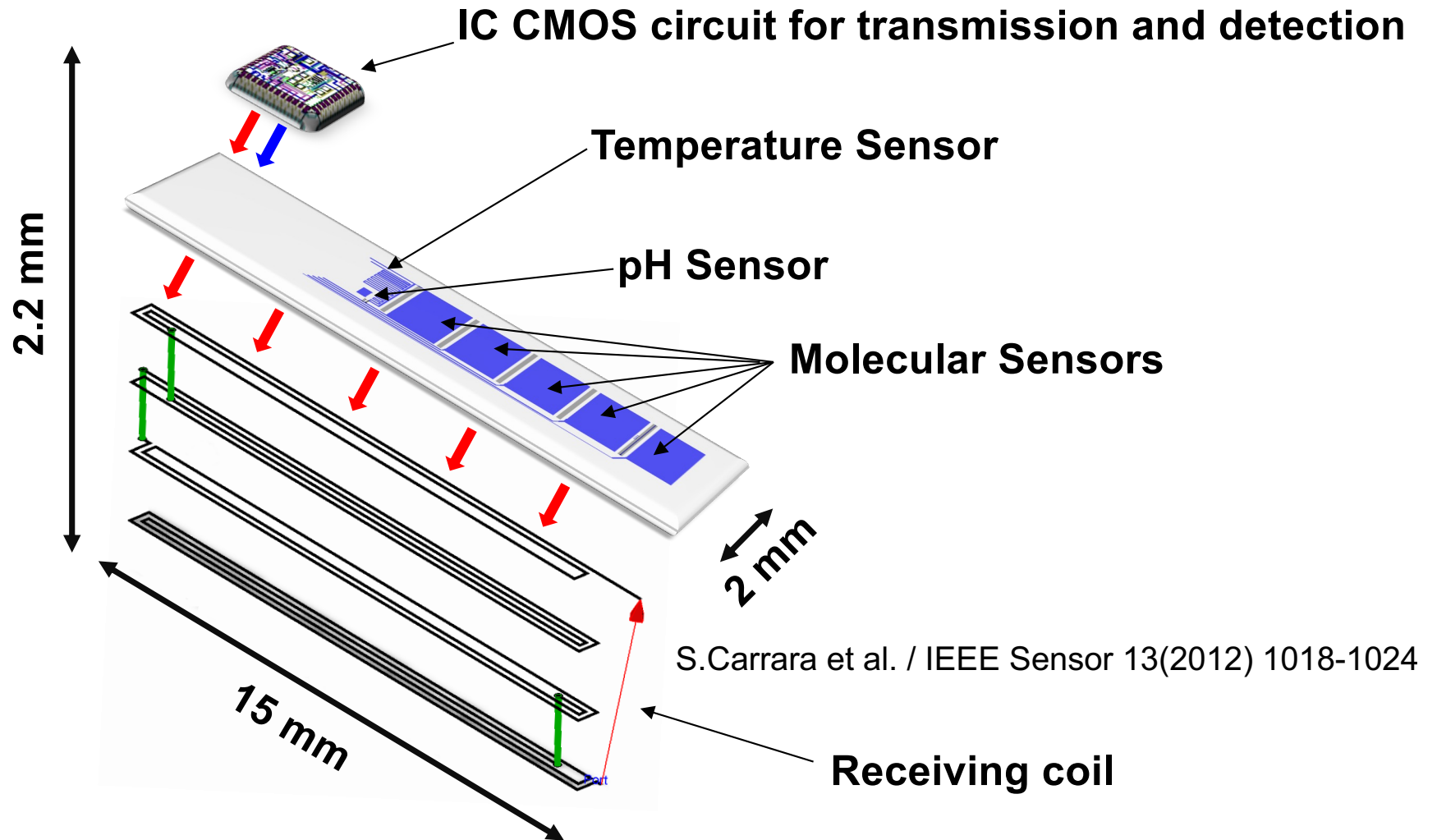
A subcutaneous biosensor chip to revolutionize tomorrow's medicine

May 29, 2015 9:26 AM

[Relaxnews](#)



Under-the-Skin Device: needle' size



Minimally invasive with size within that of a surgery needle

Injectable with biocompatible packaging

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20 March 2013 Last updated at 01:49 GMT

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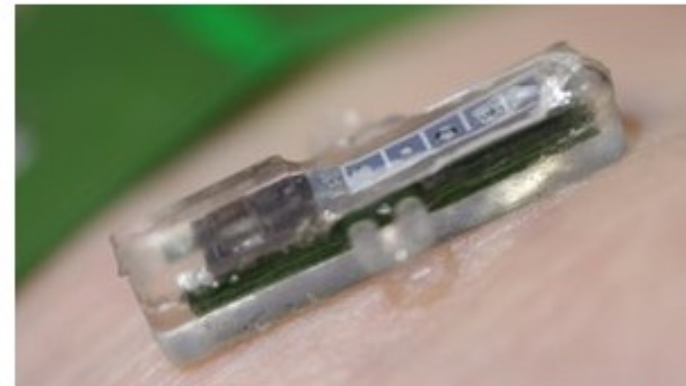
'Under the skin' blood-testing device developed

By Michelle Roberts
Health editor, BBC News online

Scientists say they have developed a tiny blood-testing device that sits under the skin and gives instant results via a mobile phone.

The Swiss team say the wireless prototype - half an inch (14mm) long - can simultaneously check for up to five different substances in the blood.

The data is sent to the doctor using radiowaves and Bluetooth technology.



The device sits under the skin and takes multiple readings

(c) S.Carrara

Syringe-injectable electronics: Reveal LINQ™



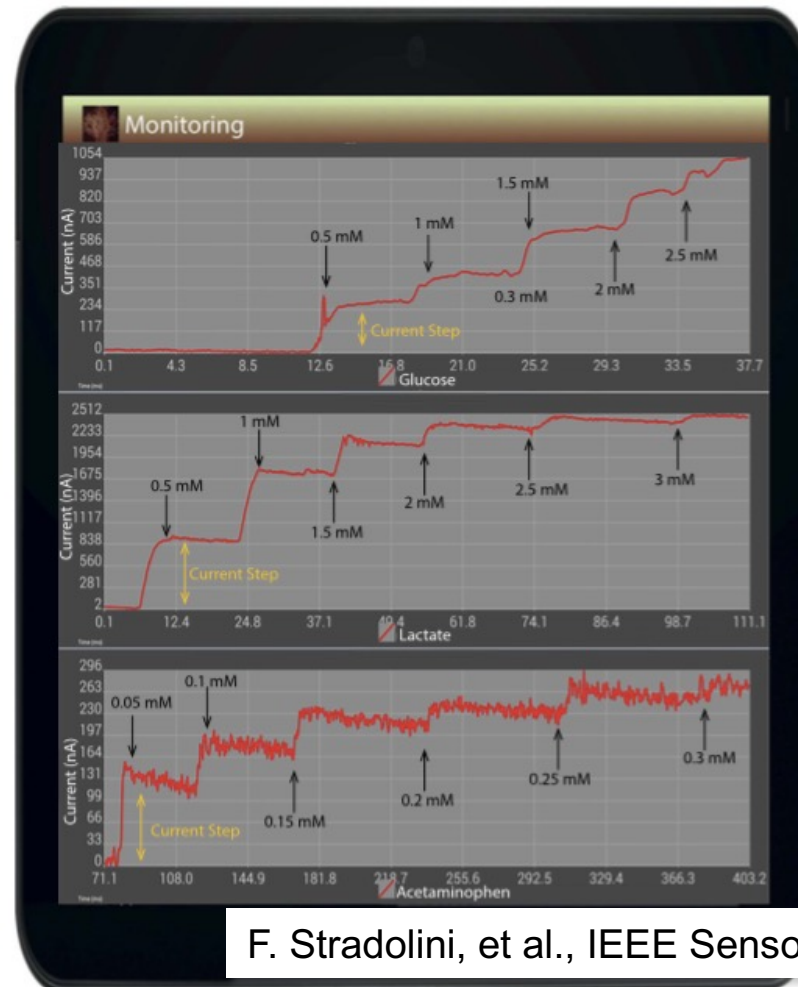
Mark Phelps by Medtronic, and the Reveal LINQ™ system

Android Users Interface

Glucose →

Lactate →

Paracetamol →



The whole system with the Android™ interface that allows connectivity too

Connectivity with Smart-Watch

Smartwatches deliver alerts to intensive care doctors

Patients in intensive care must be constantly monitored. Their vital signs are recorded in real time by a series of biosensors. If an anomaly is detected, an alert is sent to the doctor on duty.



Live Demo @ BioCAS17



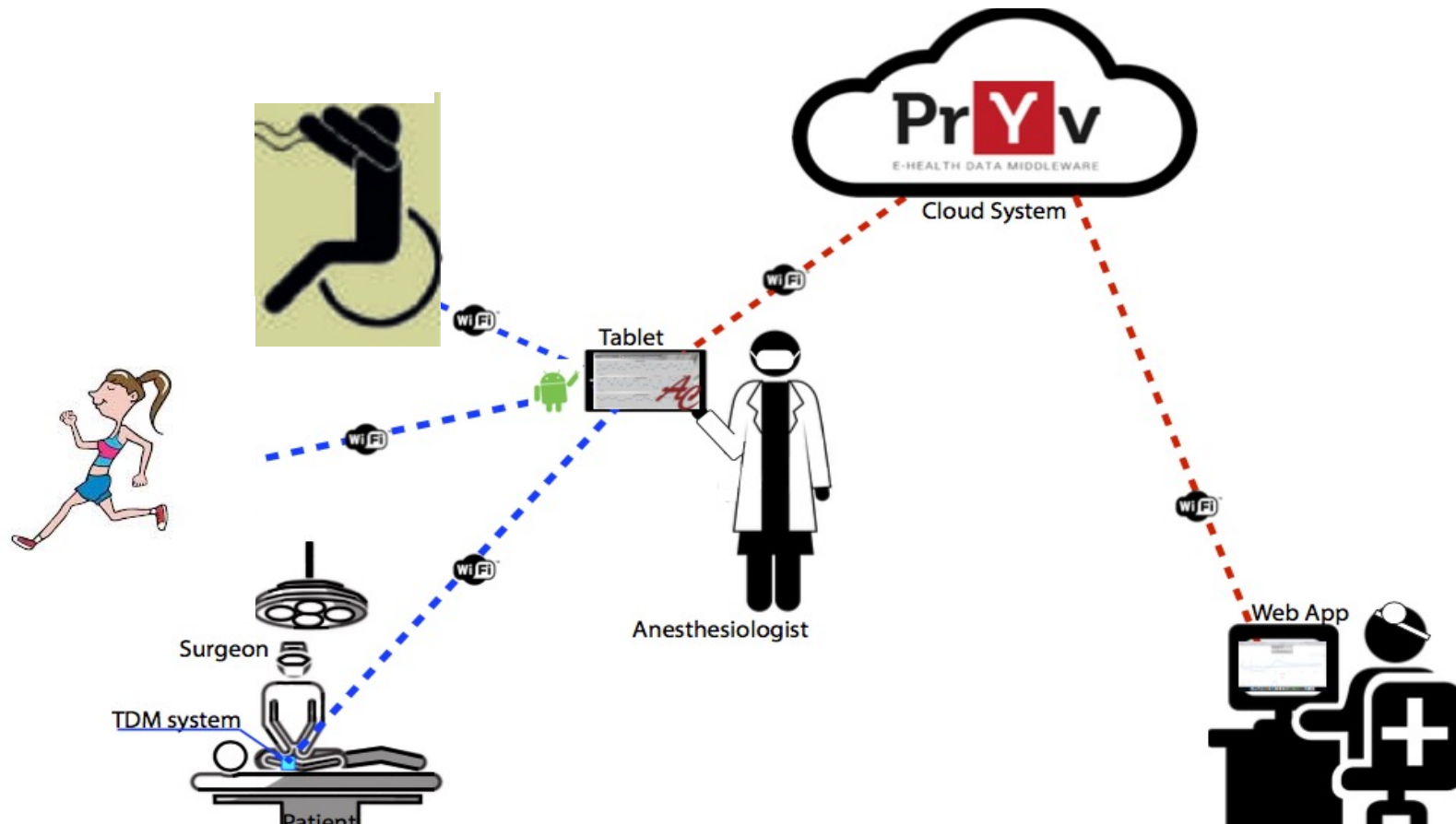
F. Stradolini, et al., MOBILHEALTH 2016



Connectivity till the smart-watch by the WiFi network has been successfully investigated as well

(c) S.Carrara

Connectivity by through the Cloud



N.Tamburrano, et al., IEEE ISCAS 2018, invited paper

Connectivity by through the cloud has been successfully investigated too

(c) S.Carrara

Portable, Implantable, 'n' Wearable!



Monitoring scenarios

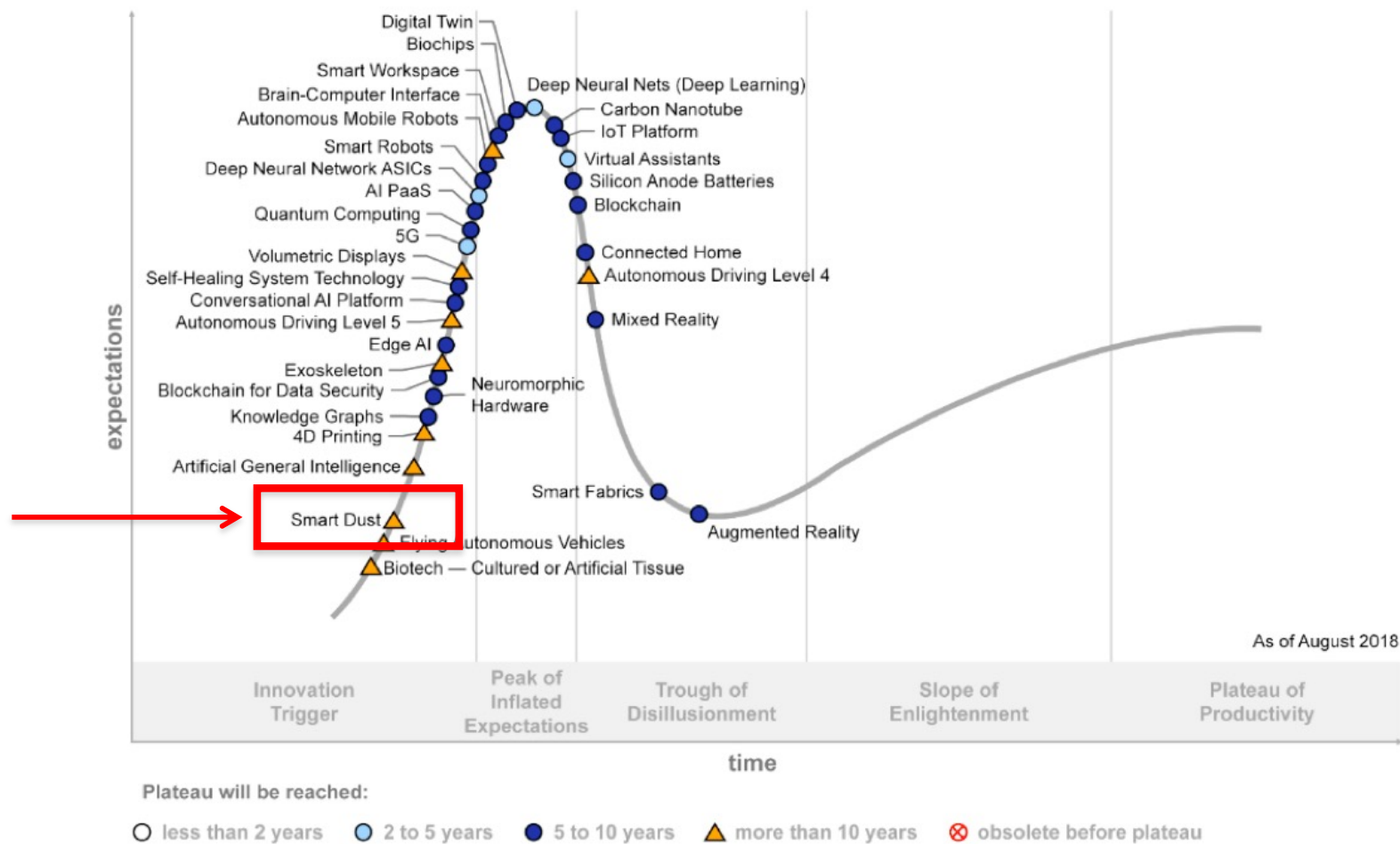
Beyond Implantable and Wearable Devices: Body Dust !

Body Dust: Drinkable Electronics



Monitoring scenarios

Hyper Curve with Smart Dust



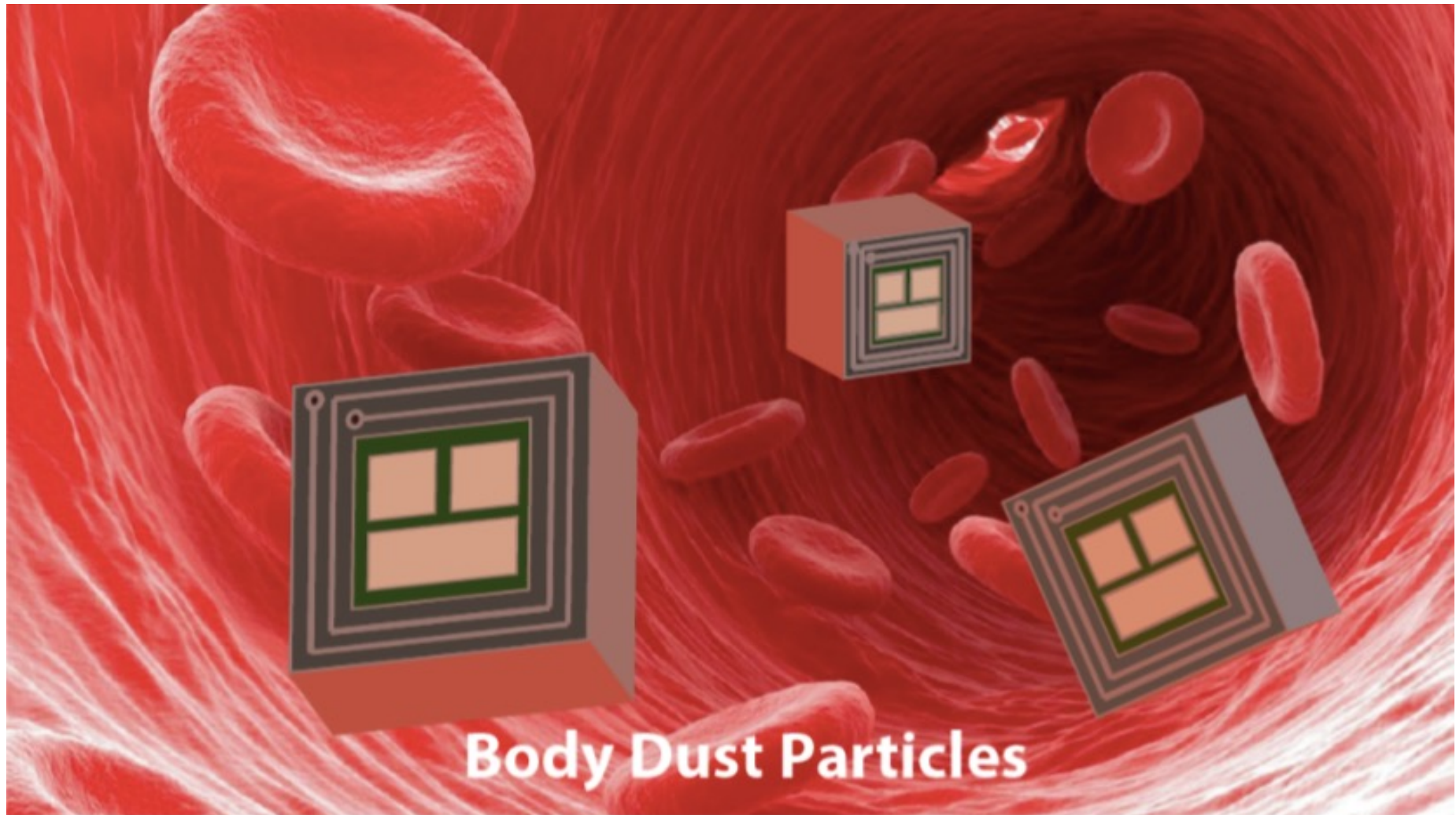
According to Gartner, “Smart dust” is set to take the technology industry by storm in the next decade [<https://www.gartner.com>]

The innovative concept of **BODY DUST**



Imagine to drink a water that contain an electronic Dust that spread in your body and then provide diagnostics

Body Dust

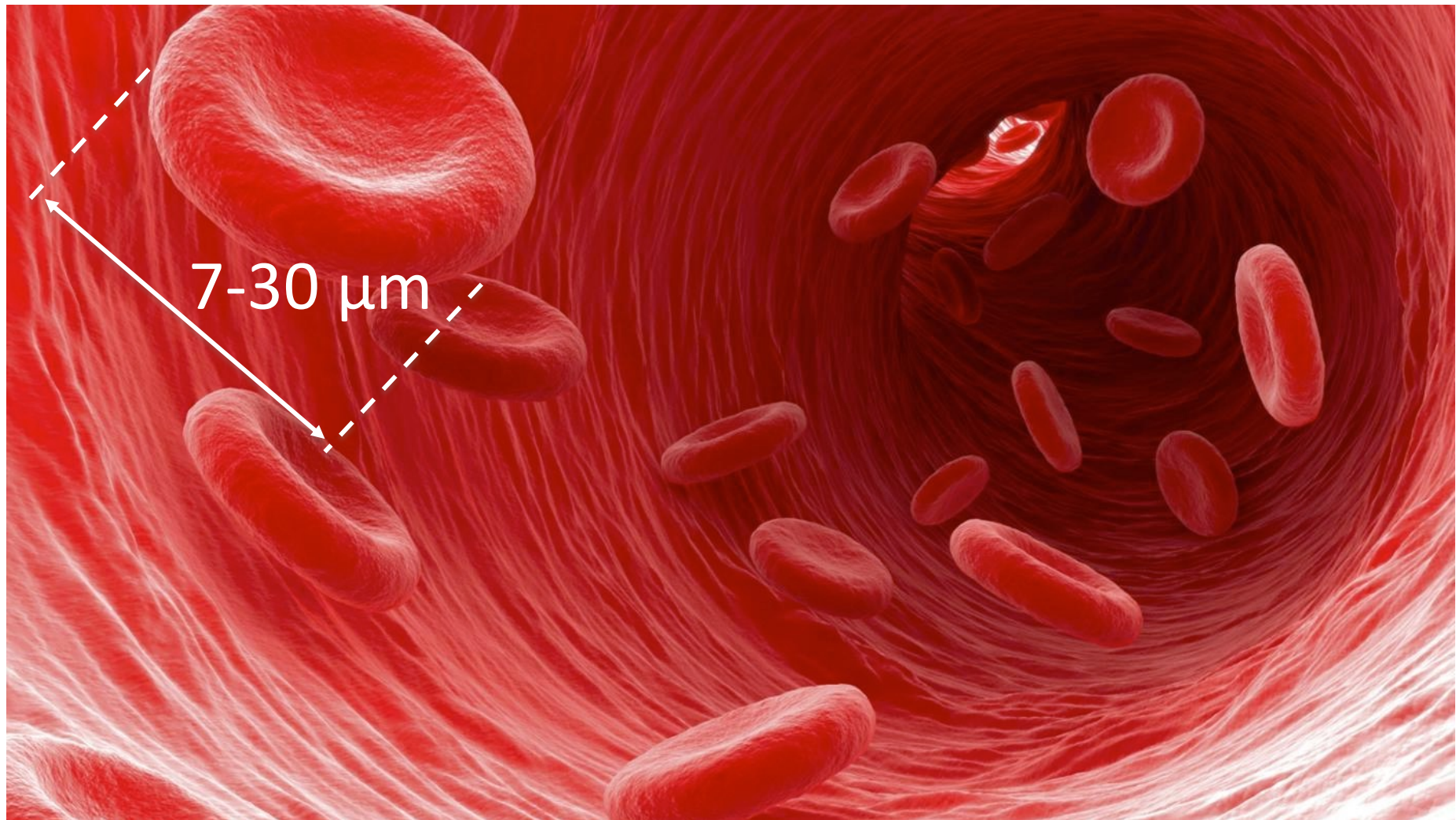


Credit: EPFL news pages

Tracking cancer-cell development
with “drinkable” electronic sensors

(c) S.Carrara

Body Dust: Dramatically Small



Credit: EPFL news pages

Drinkable electronics so small to be filtrated by liver and kidneys means sizes on the scale of a blood cell

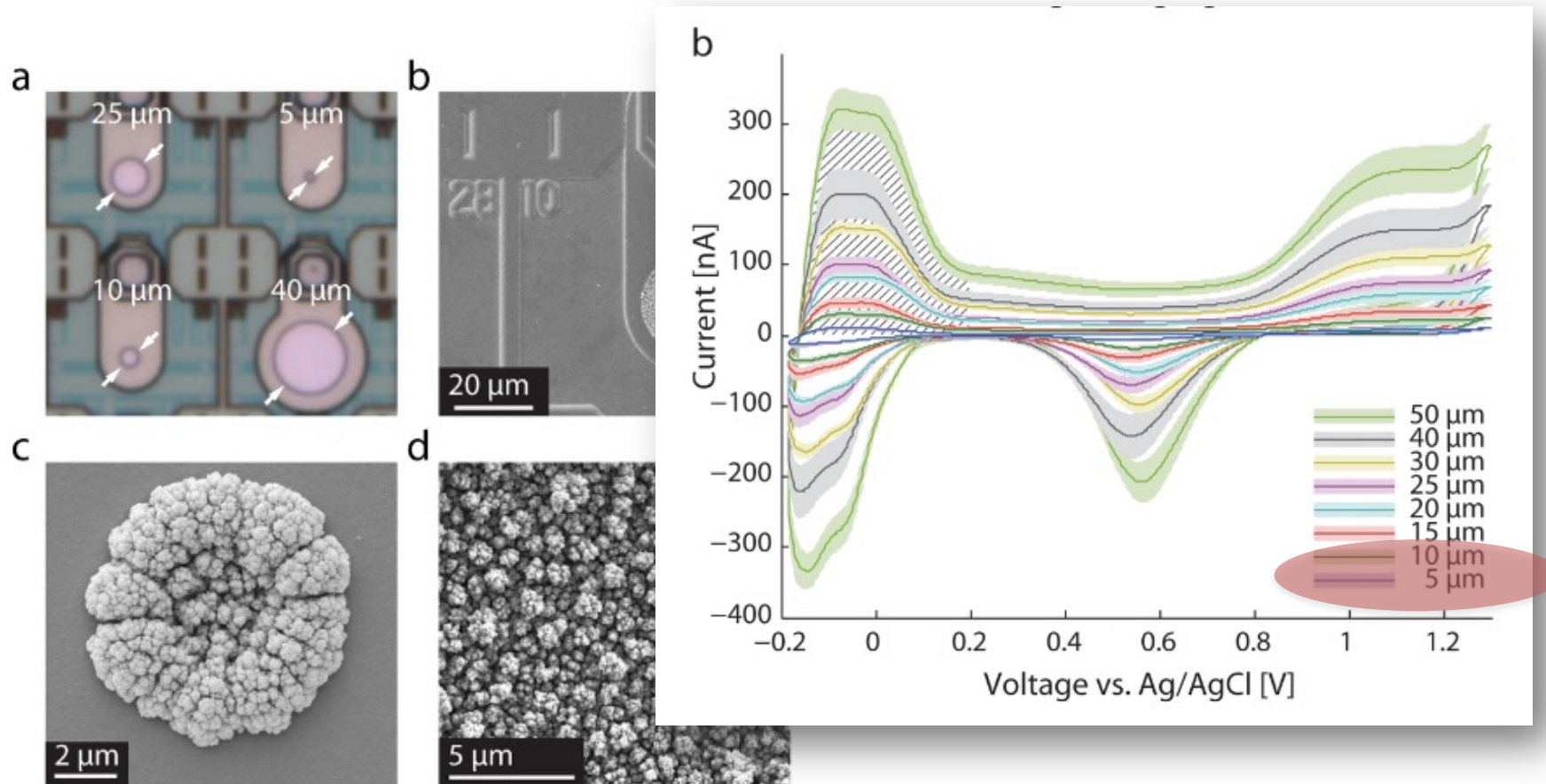
(c) S.Carrara

Body Dust: Challenges to address!

Sandro Carrara / IEEE Sensors Journal, 2021

- (i) Extremely small sensors;
- (ii) Extremely small and thin CMOS;
- (iii) Extremely small data-link;
- (iv) Powering approaches with extremely small power-receivers;
- (v) Demonstrating in-body applications by drinking

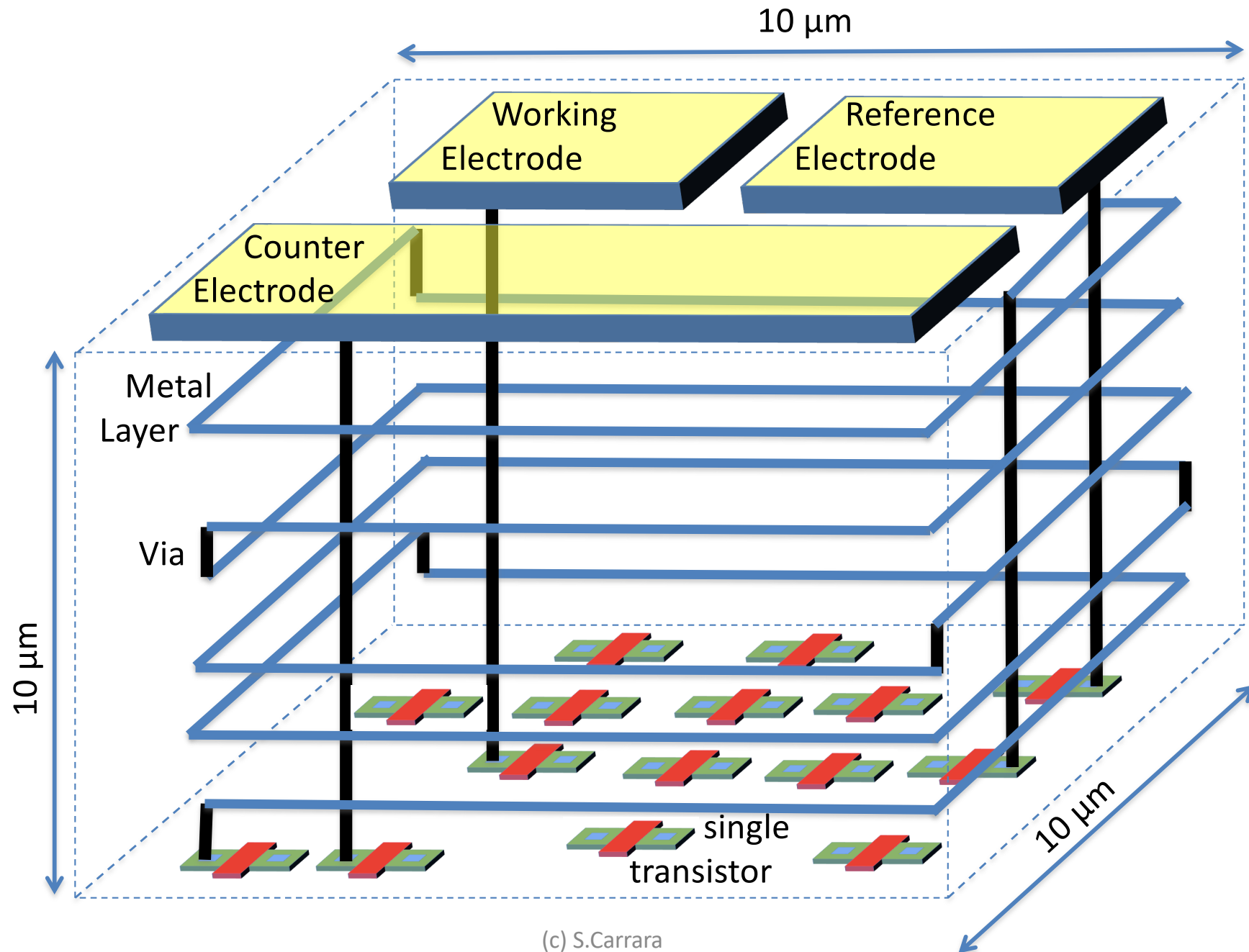
(i) Extremely small sensors;



Rothe, Joerg, et al. / Analytical chemistry 86.13 (2014): 6425-6432.

Imagine to drink a water that contain an electronic Dust that spread in your body and then provide diagnostics

(ii) Extremely small and thin CMOS;



(ii) Extremely small and thin CMOS; CMOS 0.18 μm within $10^2 \mu\text{m}^2$ possible?

CMOS Body Dust - Towards Drinkable Diagnostics

Jan Snoeijs¹, Pantelis Georgiou² and Sandro Carrara¹

IEEE BioCAS 2017

¹ EPFL, Lausanne, Switzerland ²Centre for Bio-Inspired Technology, Imperial College London, UK.

Email: sandro.carrara@epfl.ch

Abstract—In this paper we introduce the concept of CMOS Body Dust. Body dust, as we envisage is to be, is a swarm of physical micro-sensing systems designed in CMOS as a cube with the size of red blood cells such that they will be drink to deliver vital diagnosis the source of a disease therefore to discuss a CMOS architecture with factor, to be in the same have a diameter of around total size of less than

Keywords—Diagnostics,

TABLE IV. TOTAL AREA AND POWER CONSUMPTION TRADE-OFF

	Area [μm^2] (best case)	Power [μW]	Power [μW] (best case)	Area [μm^2]
Potentiostat	8.7	0.141	0.124	12
I to f conv.	22	0.836	0.836	22
Rectifier	28.44	9.655	9.655	28.44
Voltage regulator	15.9	18.170	5.7	24
Band-gap ref.	15.2	0.009	0.009	15.2
Pulse generator	10	—	—	10
Total	100.24	27.741	15.64	111.64

Yes!



(ii) Extremely small and thin CMOS; CMOS 0.18 μm within $10^2 \mu\text{m}^2$ possible?

Direct Digital Sensing Potentiostat targeting Body-Dust

IEEE BioCAS 2022

Roberto Rubino
DET

Sandro Carrara

Paolo Crovetto

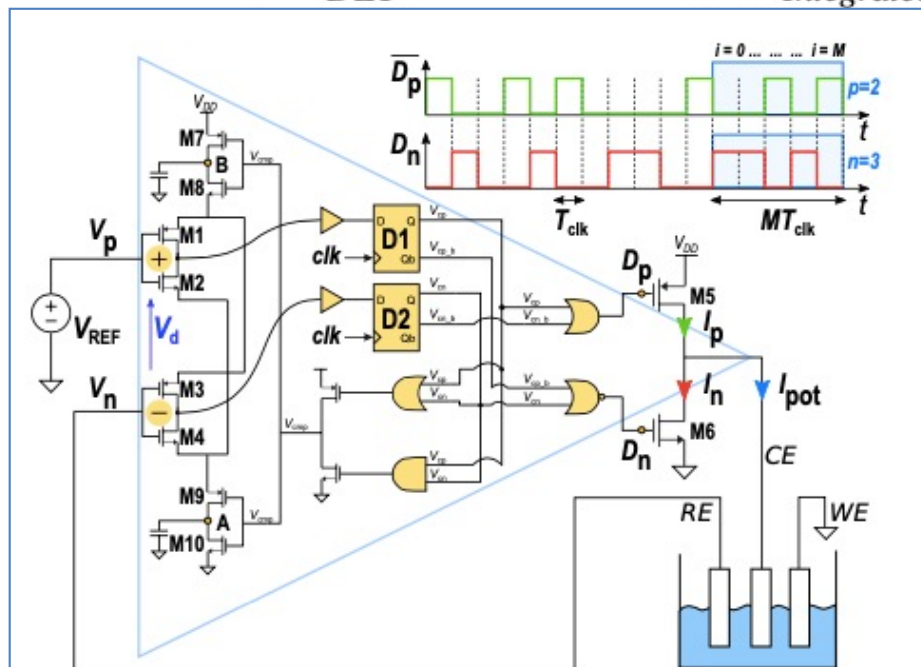


Fig. 3. Proposed digital-based potentiostat schematic and digital acquisition pulses.

Integrated Circuit

ique P
anne, S
o.carr

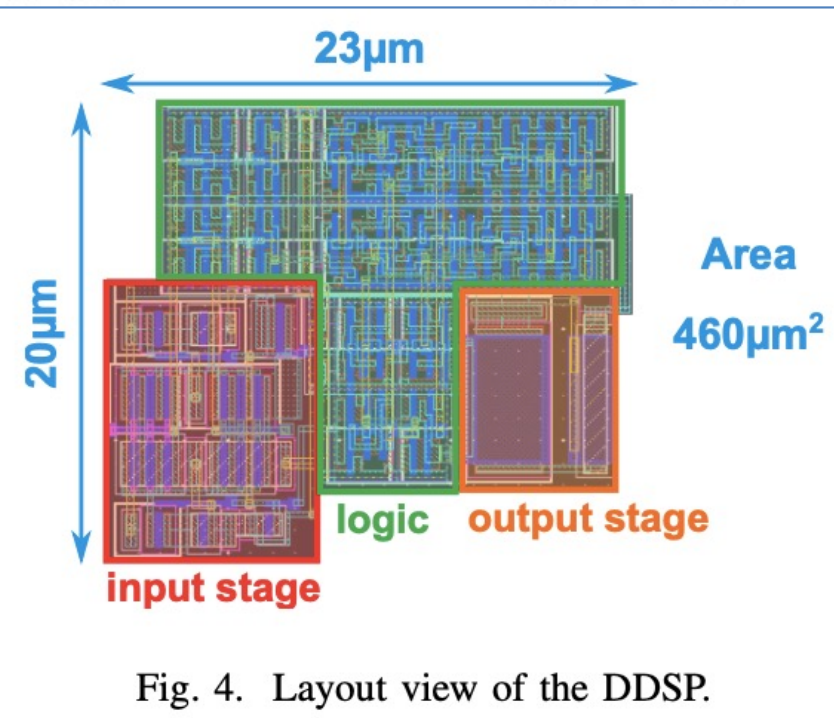


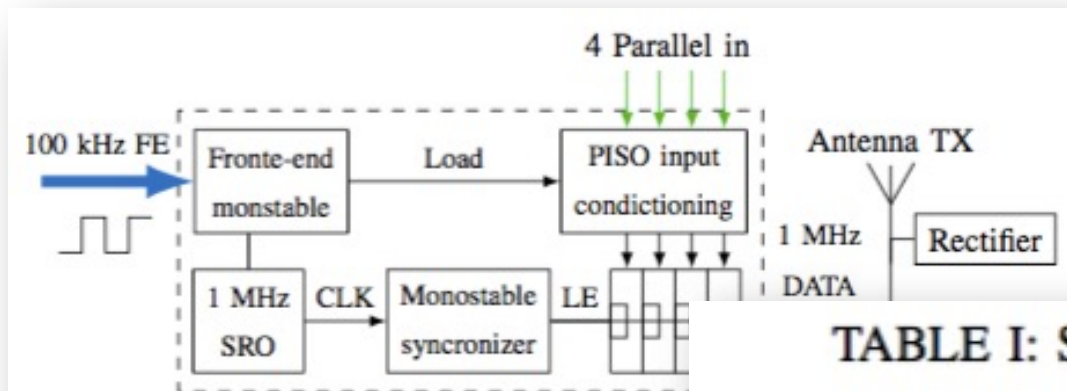
Fig. 4. Layout view of the DDSP.

(c) S.Carrara

(ii) Extremely small and thin CMOS; DATA 0.18 μm transmission within $10^2 \mu\text{m}^2$?

Body Dust: Ultra-Low Power OOK Modulation Circuit for Wireless Data Transmission in Drinkable sub-100 μm -sized Biochips

ArXiv, December 2019



ssa[†], Danilo Demarchi^{*†}, Sandro Carrara[†]
ns, Politecnico di Torino, Turin, Italy
l rale de Lausanne, Neuch tel, Switzerland
no di Tecnologia, Genova, Italy
aiassa@polito.it

TABLE I: SRO performance comparison.

	[12]	[13]	This work
CMOS technology	130 nm	130 nm	180 nm
Voltage supply (V)	3.3	3.3	1.8
External component	Yes	No	No
Frequency (MHz)	22.5-360	1	1
Power (μW)	1515 [*]	87	9.5
Area (mm^2)	0.05	0.054	0.00116

Almost: 34x34 μm^2 !

Fig. 1: System block diagram. The system is designed to be smaller than 100 μm in order to mimic the typical cell (diameter around 30 μm for white blood cells) and to facilitate the circulation of the cube in human tissue. The main challenge came from the low-power consumption required for the system. The energy provided by an external US wave is not sufficient to power the architecture for a data transmission. The system is implemented in a 0.18 μm CMOS process, with sub-10 μV and a total chip area of 43x44 μm^2 . The limits of the designed system and improvements toward real applications are discussed in the next section.

(ii) Extremely small and thin CMOS; DATA 0.18 μm transmission within $10^2 \mu\text{m}^2$?

Body Dust: Ultra-Low Power OOK Modulation Circuit for Wireless Data Transmission in Drinkable sub-100 μm -sized Biochips

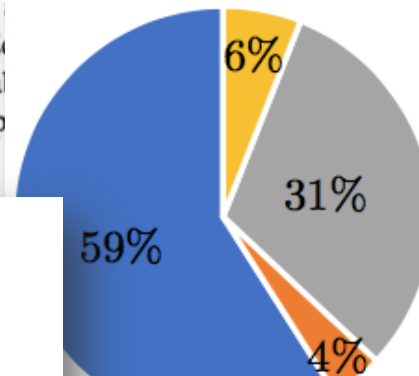
ArXiv, December 2019

Gian Luca Barbruni^{*†}, Paolo Motto Ros[‡], Simone Aiassa^{*†}, Danilo Demarchi^{*†}, Sandro Carrara[†]

^{*}Department of Electronics

[†]Integrated Circuits Laboratory, É

[‡]Electronic Design Lab
Corresp



Total area: 1980 μm^2

- Starved ring
- Monostable synchronizer
- PISO Register
- Front-end adaptor

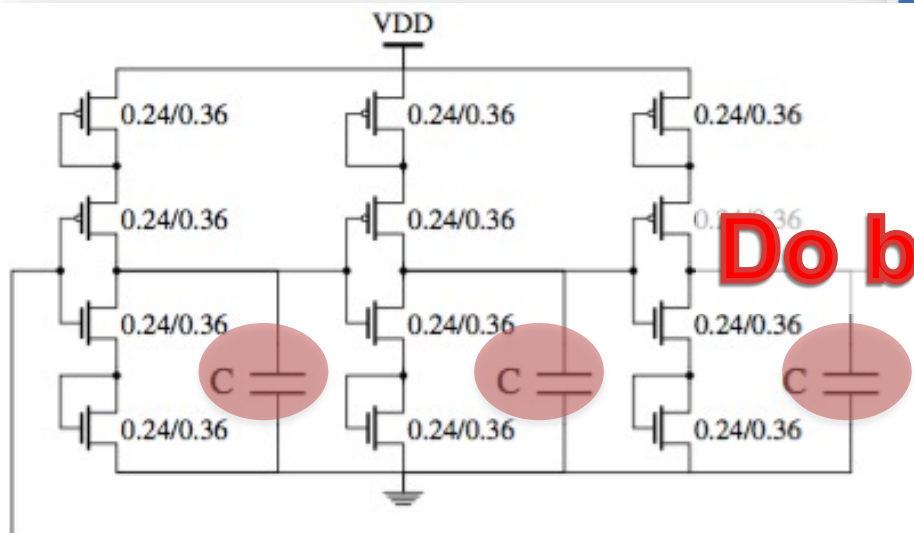


Fig. 2: Three stages starved Ring Oscillator (RO).

Do better: below 34x34 μm^2 !

with the
he results
design an
y using a
assumption
discusses
or further
agnostics.

c) S.Carrara

sensing approach [8], but in that case the architecture was quietly different: that proposed solution included three nodes (an external transceiver, a sub-dural one and the proper Neural Dust device) while in our design only two components are expected (the external base station that works both as power transmitter and data receiver and the body dust tags) and, secondly, in that architecture any communication circuit was

(ii) Extremely small and thin CMOS; DATA 28 nm transmission within $10^2 \mu\text{m}^2$?

From 0.18 μm to 28nm Scaling CMOS Technologies for Data Links in Body Dust Applications

IEEE SENSORS 2021

Gian Luca Barbruni^{†*‡}, Paolo Motto Ros,

Danilo Demarchi* and Sandro Carrara[†]

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Email: gianluca.barbruni@epfl.ch

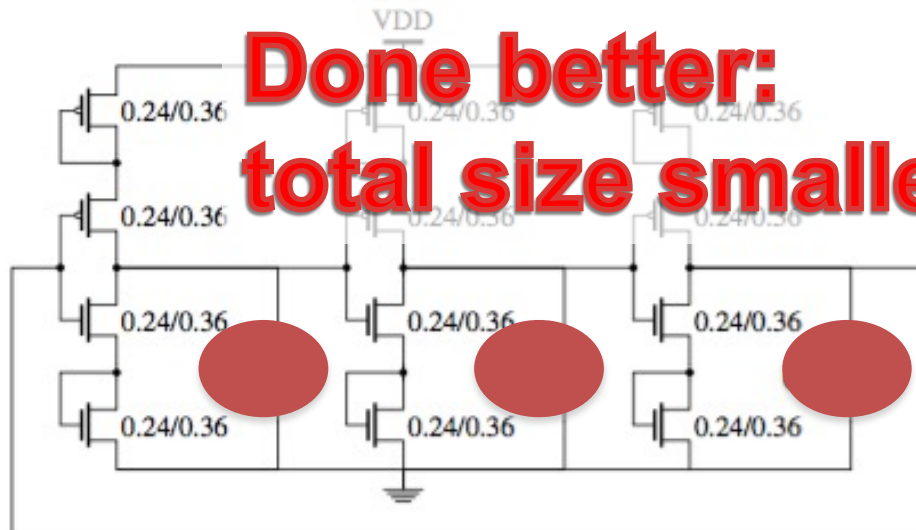
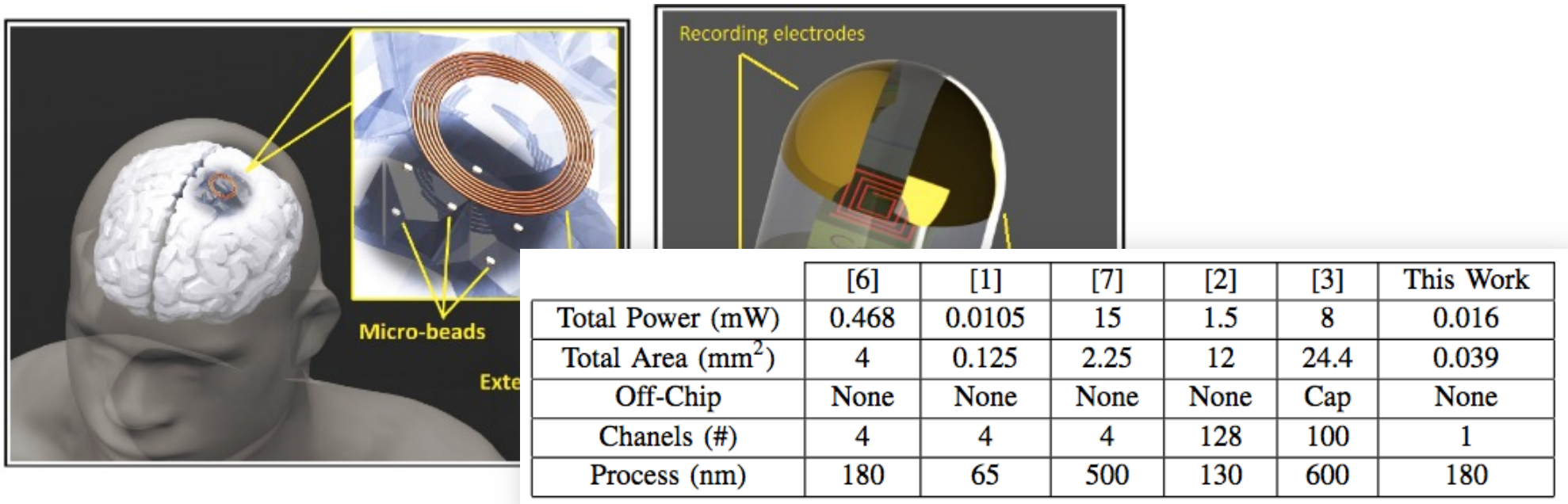


Fig. 2: Three stages starved Ring Oscillator (RO).

(c) S.Carrara

(iv) Powering approaches with extremely small power-receivers;

Khalifa, A., Zhang, et al. / 2016 IEEE ISCAS

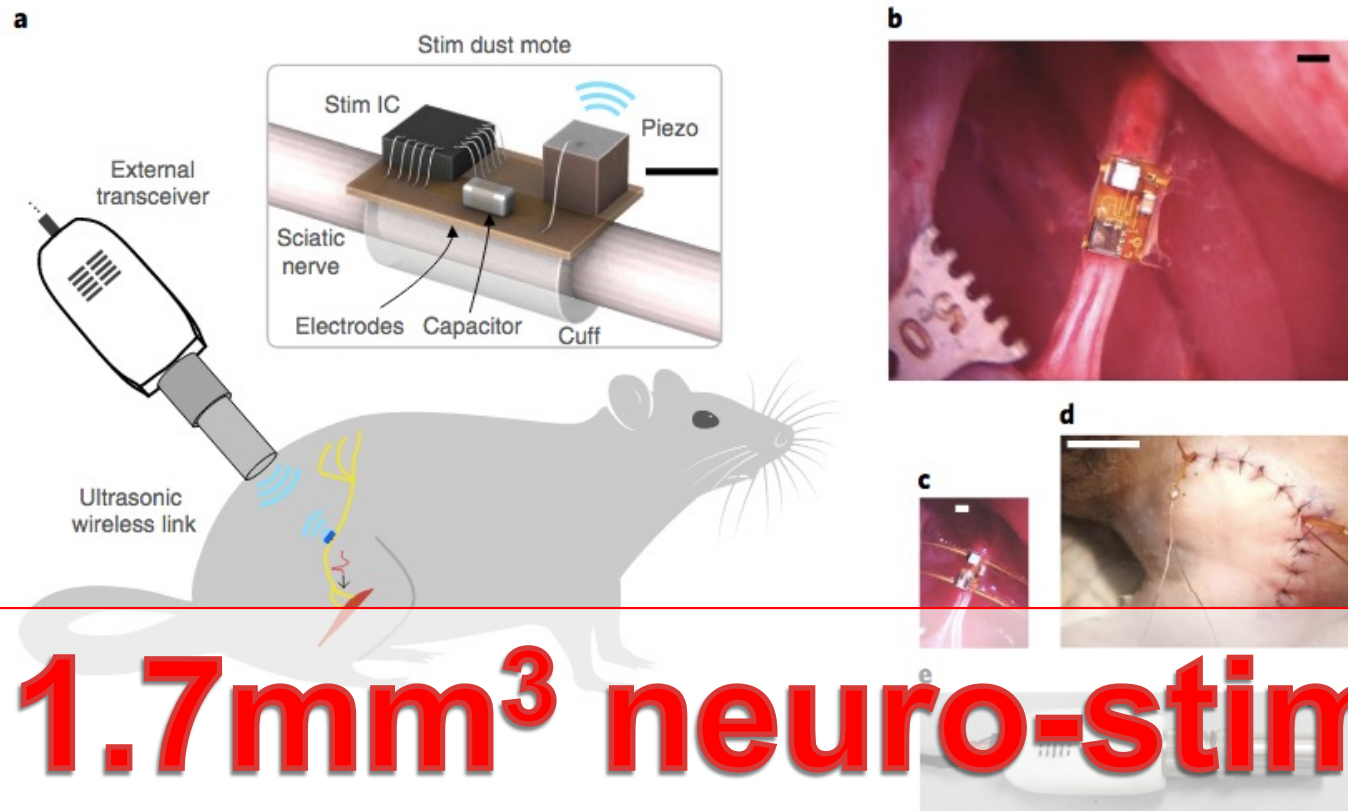


200μm x 200μm coil !

16 μW received to a 0.039 mm² area-coil
by inductive-link

(iv) Powering approaches with extremely small power-receivers;

D.K.Pietch, et al. / 2020 NATURE Biomedical Engineering



1.7mm³ neuro-stimulator!

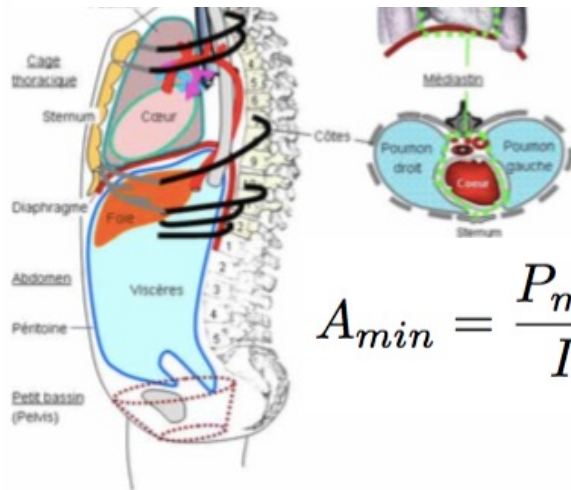
65 μ W received to a 1.7 mm³ volume-size transducer by ultra-sound

(iv) Powering approaches with extremely small power-receivers;

Three Scenarios



$$A_{min} = \frac{P_{min}}{I_d} = 1.98 \cdot 10^4 \mu m^2 \rightarrow \approx 140.81 \mu m$$



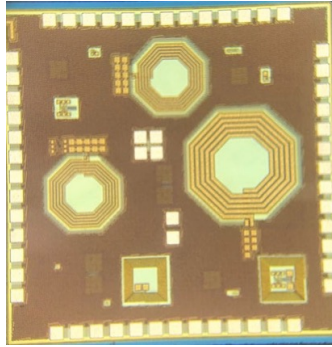
$$A_{min} = \frac{P_{min}}{I_d} = 4.22 \cdot 10^3 \mu m^2 \rightarrow \approx 65.6 \mu m$$

$$A_{min} = \frac{P_{min}}{I_d} = \frac{30 \cdot 10^{-6}}{1230 \frac{W}{m^2}} = 2.44 \cdot 10^4 \mu m^2 \rightarrow \approx 156 \mu m$$

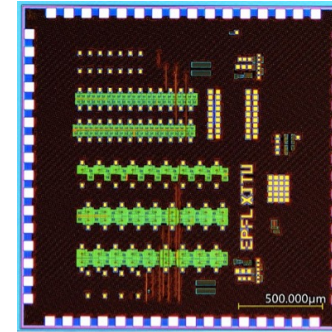
Almost!



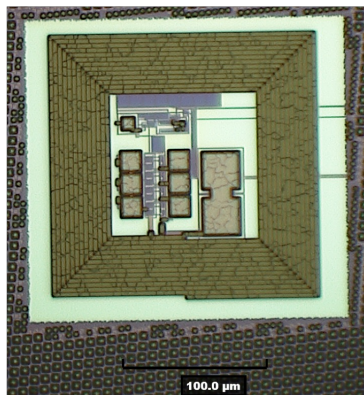
Some Recent Bio/CMOS interfaces



Chip # 5 TSMC 0.18
IEEE MOCAS, June 2022

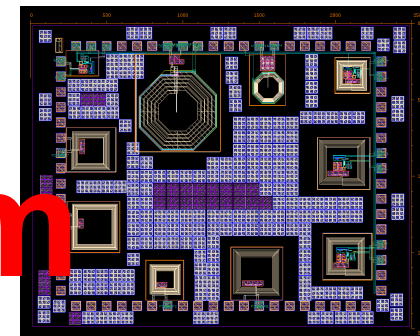


Chip # 6 TSMC 0.18
(arrived October 2022)



Chip # 7 TSMC 0.18
(arrived October 2022)

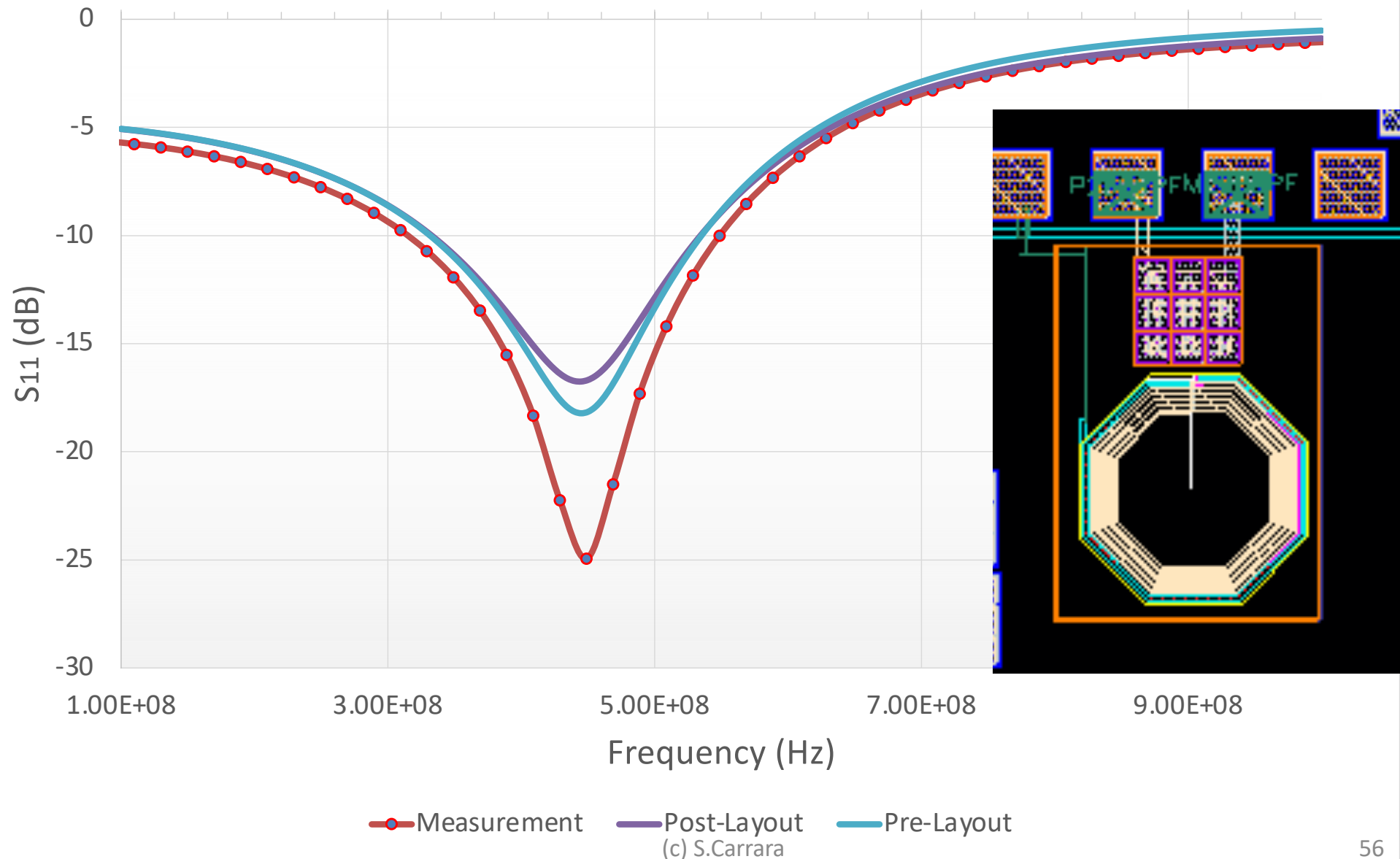
↑
150 μm
↓



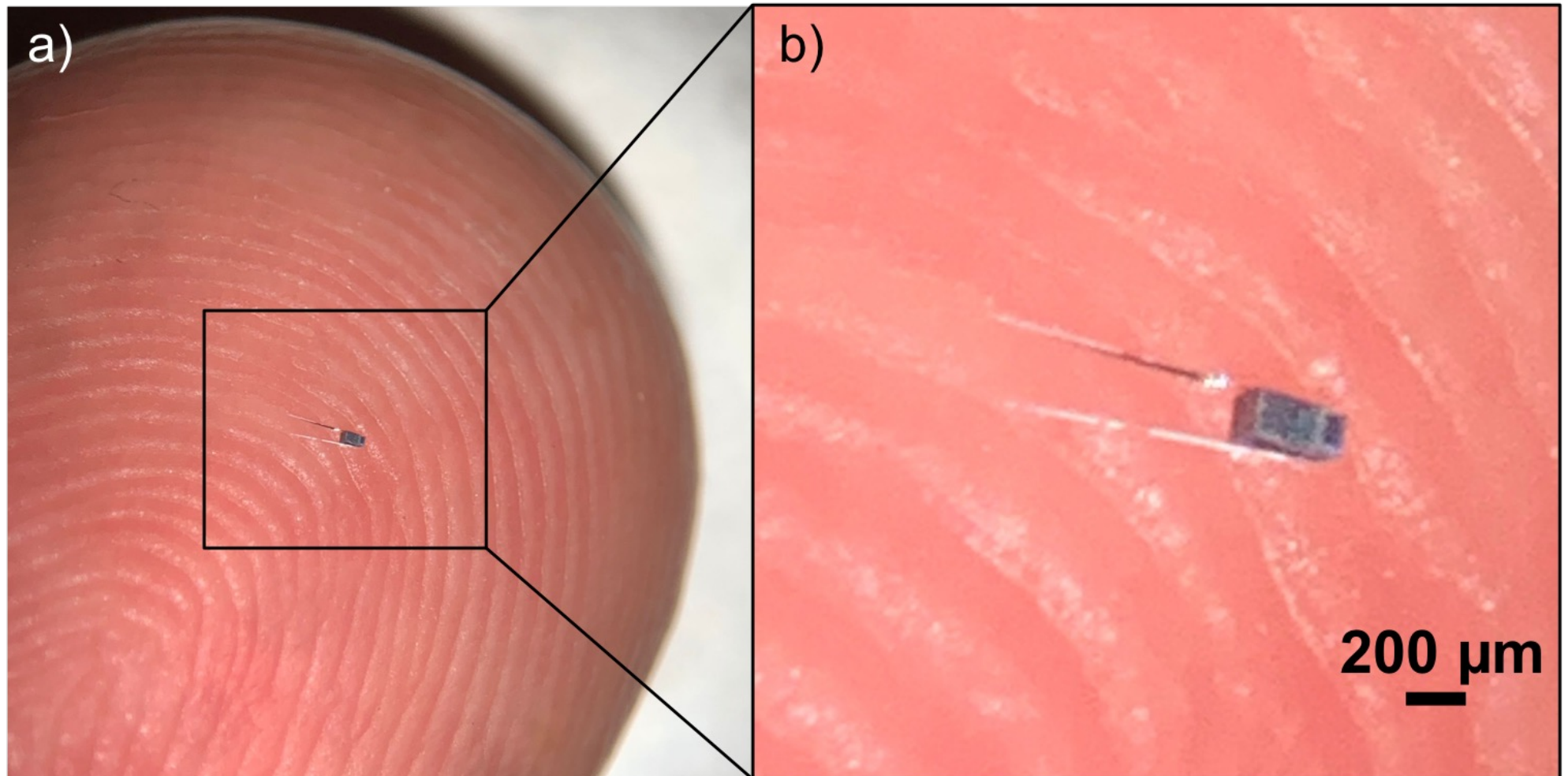
Chip # 8 TSMC 0.18
(Just arrived 2023)

Power Transfer to 150 μm -coil

200 μm On chip coil - Simulations VS Measurements



Smart Micron-sized Neural Dust



Barbruni Gian Luca, et al., PCT/IB2022/059944, 2022.

Body Dust: Challenges to address!

Sandro Carrara, al. et / IEEE Sensors Journal, 2021

- (i) Extremely small sensors;
- (ii) Extremely small and thin CMOS;
- (iii) Extremely small data-link;
- (iv) Powering approaches with extremely small power-receivers;
- (v) Demonstrating in-body applications by drinking

Conclusions

- CMOS ASICs design is still required for more reliable Bio/CMOS Interfaces and, especially, for electrochemical sensing for metabolism
- Special Biotech solutions are necessary to target the right selectivity in order to uniquely identify the right metabolic molecules
- Special Nanotech solutions are necessary to reach the right sensitivity and limit-of-detection in the ranges of concentrations on human tissues
- Automatic and continuous monitoring of the metabolism in humans is actually feasible from body tissues to our personal electronics, including **portable, wearable, implantable**, and may be one day also **spreadable** in the form of Diagnostic Dust!

Course outline

1. Probes and Targets Building Blocks
2. Probes/Target interactions (DNA & Ab)
3. Probes/Target interactions (Ox & P450)
4. Probes Detection Principles (DNA or Ox)
5. Probes Detection Principles (P450)
6. Probes immobilization
7. Checking Probes-layer quality (RR+SPR+SEM+AFM)
8. Nanotechnology to prevent Electron Transfer
9. Nanotechnology to enhance Electron Transfer
10. Nanotechnology for Memristive Biosensors
11. Circuits for metabolites detection in Fixed-Voltage
12. Circuits for metabolites detection in Scanning Voltage
13. Circuits for DNA Capacitance and Amperometric Detection
14. Circuits for metabolites detection with multi-panel systems
15. Summary on Bio/nano/CMOS interfaces co-design

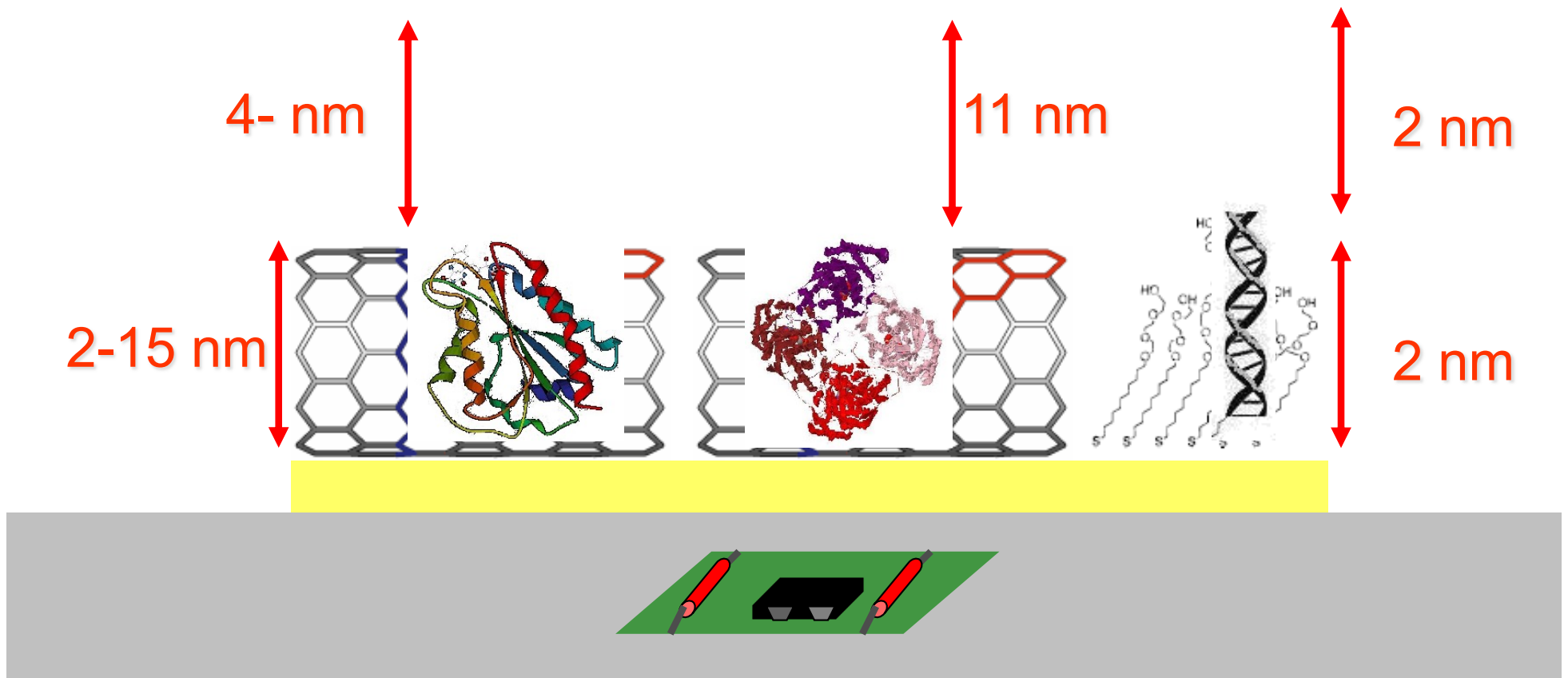
Summary

Bio

Nano

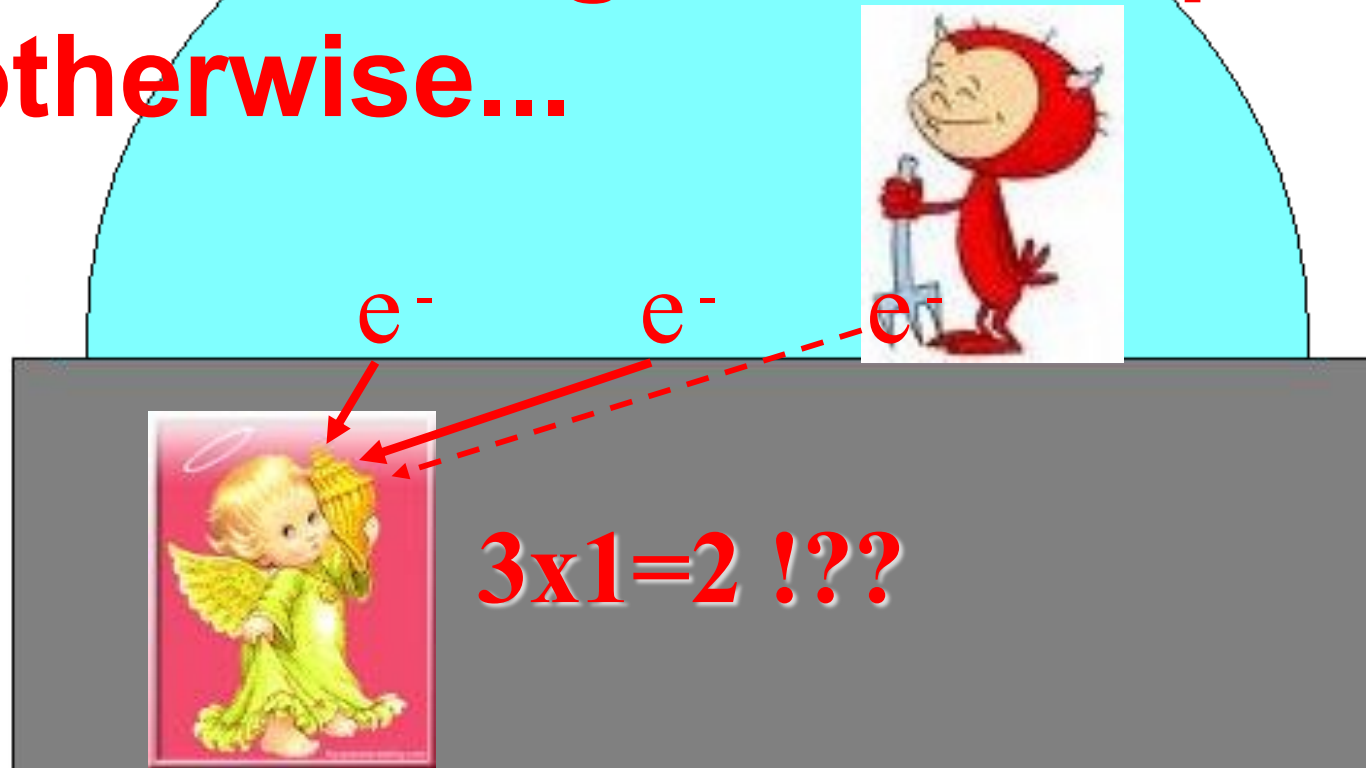
CMOS

Aim of the course



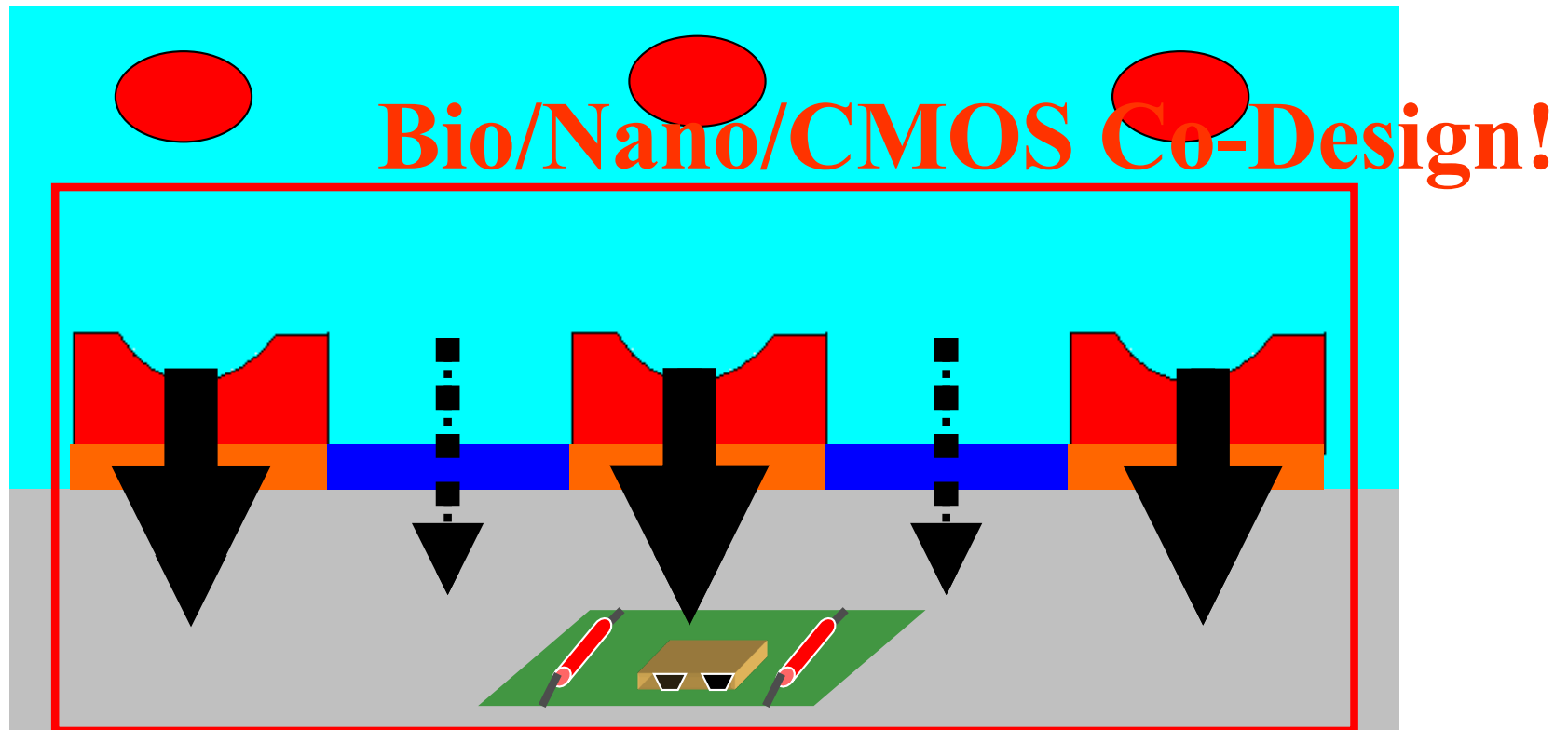
New paradigms for Nano-Bio-CMOS co-design are required to succeed in chip bio-sensing

**New Paradigms are required
otherwise...**



**Excellent CMOS technology is not sufficient if
molecules are not doing their own job at the
Bio/CMOS interface!**

CMOS/Sample interface



The interface between the CMOS circuit and the bio-sample needs to be deeply investigated and organized

Exercise' Solutions to get the Credit

Meeting Information - Zoom | EDOC Teaching | Day-15th-June - Dropbox | Course: Electrochemical nano- | +

← → ↻ 🏠 🔒 https://moodle.epfl.ch/course/view.php?id=14479 🔍 Search

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MICRO-614

- 👤 Participants
- 📅 Grades
- 📁 General
- 📁 Day 1 - Bio: Probe/Target Molecular interactions
- 📁 Day 2 - Bio: Electrochemical Sensing
- 📁 Day 3 - Nano: Probes-layer for Targets Detection
- 📁 Day 4 - Nano/CMOS: Memristors and CMOS Analog4Bio

Day 1 - Bio: Probe/Target Molecular interactions

- 📄 Bio/CMOS: present & future! (An introduction)
- 📄 Probe/Target interactions
- 📄 Sensing Principles with biomolecules
- 📄 APPENDIX 1: Building Blocks & Protein Structures
- 📄 APPENDIX 2: Binding Energy
- 🌐 Euronews about under-the-skin biochip

Read Chapter 2 in the Book for Conductive Solutions and the concept of pH, and Chapters 3 & 4 for Target/Probe biochemistry & interactions

Read also APPENDIX A in the Book for the concept of Molar Concentration

Solve the Exercise # 1 in page 28 of the Book (show computations)

Solve the Exercise # 9 in page 50 of the Book (justify the answer)

Solve the Exercise # 5 in page 85 of the Book (Solve the exercise by also

Final Work to get the Credit

To complete the work in order to get the grade, each student is finally required to critically read a paper from literature and analyse a paper with the perspective of the course. So, please, download the paper assigned to you by clicking on your name in the list below. Then, write a **Blog Article** in 4000 characters max (including spaces) by commenting about the "Bio", the "Nano", and the "CMOS" content of the paper assigned to you. If some of these system-layers is missing in the paper, please, elaborate your ideas about in order to suggest completing and improving the system proposed by the paper with all the three mentioned system' layers. The blog article needs to be then send by email in Microsoft/word format (editable).

The best written Blog Articles will be then published online, with permission by the authors...

Media Discussion group on Sensors

The screenshot shows the Facebook interface for the 'IEEE Sensors Journal' group. The left sidebar contains navigation links: Home, Community home, Overview, Admin tools (Community chats, Admin Assist, Badge requests, Pending approvals, Potential spam), and a '+ Create a chat' button. The main content area features a post by Marios Sophocleous, a Moderator and Top contributor, dated November 3, 2020. The post discusses a futuristic paper from the EIC about Smart Dust, mentioning its applications in human monitoring, brain applications (Neural Dust), and metabolism monitoring (Body Dust). Below the text is an illustration of red blood cells and small electronic components. The right sidebar includes an 'About' section with group rules, a 'Public' privacy setting, a 'Visible' group type, and a 'Popular topics in posts' section listing 'Q/A posts (18)', 'Sci.Publishing (7)', and 'Blog Articles (5)'. A 'Show more' button is at the bottom of the sidebar.

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Overview

Admin tools

Community chats
4 chat suggestions for your group

Admin Assist
0 actions, 0 criteria

Badge requests
0 new today

Pending approvals
0 new today

Potential spam
0 new today

+ Create a chat

IEEE Sensors Journal

+ Invite

Marios Sophocleous
Moderator Top contributor +1 · November 3, 2020 ·

A great futuristic paper from our EIC!

Over the last 20 years, the field of Smart Dust has been proposed and demonstrated. Almost in the same period, implantable and wearable sensors for human monitoring have been actually successfully introduced in the market. The present research about Smart Dust is actually in the field of Dust for brain applications (Neural Dust) or for metabolism monitoring (Body Dust). This feature article provides a review of all the developments pres... [See more](#)

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Where to find your paper to discuss

Go to main site < **EPFL** | MOODLE FR | EN Sandro Carrara Student

MICRO-614

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- Final work for the grade

Final work for the grade

To complete the work in order to get the grade, each student is finally required to critically read a paper from literature and analyze the paper with the perspective of the course. So, please, download the paper assigned to you by clicking on your name in the list below. Then, write a **Blog Article** in 4000 characters max (including spaces) by commenting about the "Bio", the "Nano", and the "CMOS" content of the paper assigned to you. If some of these system-layers is missing in the paper, please, elaborate your ideas about in order to suggest completing and improving the system proposed by the paper with all the three mentioned system' layers. The blog article needs to be then send by email in Microsoft/word format (editable). The **best written Blog Articles** will be then **published online, with permission by the author...**

- Ansaryan Saeid
- Ayar Dulabi Zahra
- Chen Junrui
- Ghadiani Bahareh
- Gilani Ali
- Kechris Christodoulos

Thank you to had chosen the **EPFL PhD course on Electrochemical Nano-Bio-Sensing and Bio/CMOS interfaces**



Coordinates

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