EPFL

Electrical and Electronics Engineering

EE-518

Analog Circuits for Biochip

Master in Electrical and Electronics Engineering

EE-518: Analog Circuits for Biochip

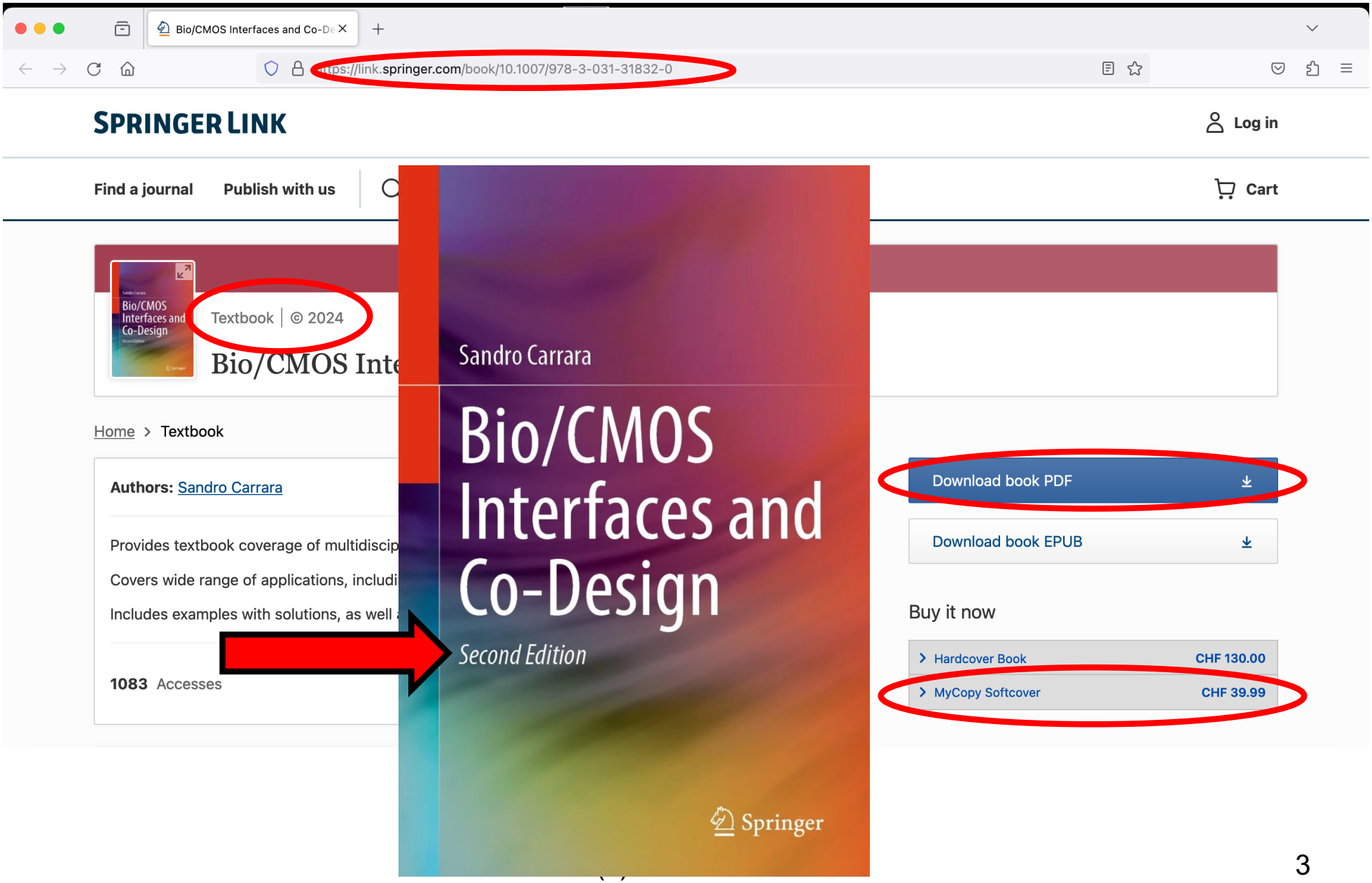
EPFL

Anja Skrivervik

Sandro Carrara

Alexandre Schmid

Get your copy of the Textbook (1st part)



Master in Electrical and Electronics Engineering

EE-518: Analog Circuits for Biochip

	Subject of the week	Chapter' paragraphs
Week 1	Biochips & Related Applications (Sandro)	§1.1-1.4*
Week 2	Equivalent Circuits for Bio/CMOS interfaces (Sandro)	§2.2-3,8-9; §4.4.2-3; §5.5.4; §10.2*
Week 3	Brain/Machine interfaces: Circuit for Electrical Stimulation/Sensing (Sandro)	Course slides (**)
Week 4	Circuits for Amperometric Potentiometric Chemical Sensing (Sandro)	§5.2-3; §10.1-6, and §12.1*
Week 5	Circuits for Capacitive & Impedimetric Chemical Sensing (Sandro)	§5.5 & Chap. 13*
Week 6	Architecture of wireless implantable systems (Alexandre, 3 hours lecture)	Course slides (**)
Week 7	Inductive links TX (power, data) (Alexandre, 2 hours lecture, 1 hour exercise)	Course slides (**)
Week 8	Inductive links RX (Alexandre, 2 hours lecture, 1 hour exercise)	Course slides (**)
18-23/04	EASTER HOLIDAY	
Week 9	RF telemetry TX, RX (power, data) (Alexandre, 2 hours lecture, 1 hour exercise)	Course slides (**)
Week 10	RF telemetry (Alexandre, 1 hour lecture, 2 hours exercises)	Course slides (**)
Week 11	Introduction to antennas and radiation regulations (Anja)	Course slides
Week 12	WBAN Antennas (Anja)	Course slides
Week 13	WBAN Antennas (Anja)	Course slides
Week 14	Review for final exam	-

S. Carrara

A. Schmid

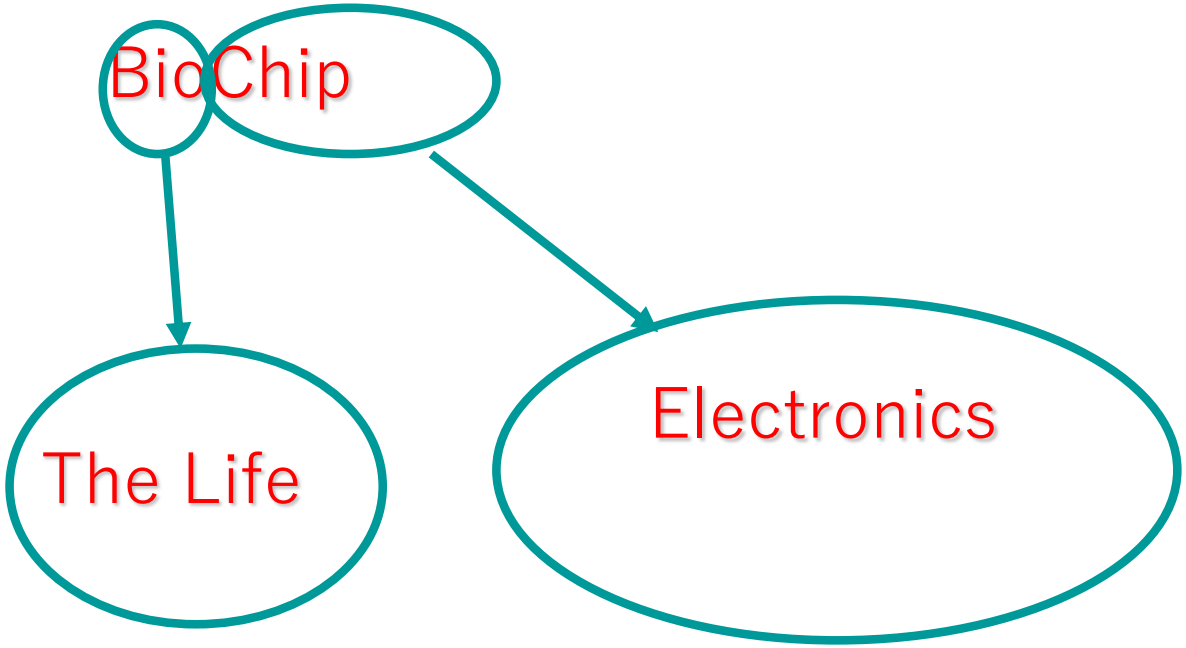
A. Skrivervik

* S. Carrara, Bio/CMOS interfaces and Co-Design, 2nd edition, Springer, 2024 – ** Supporting reading references announced in the slide set

Lecture #1

Biochips & Related Applications

What's about BioChip?



That means "electronics to cope with biological processes"

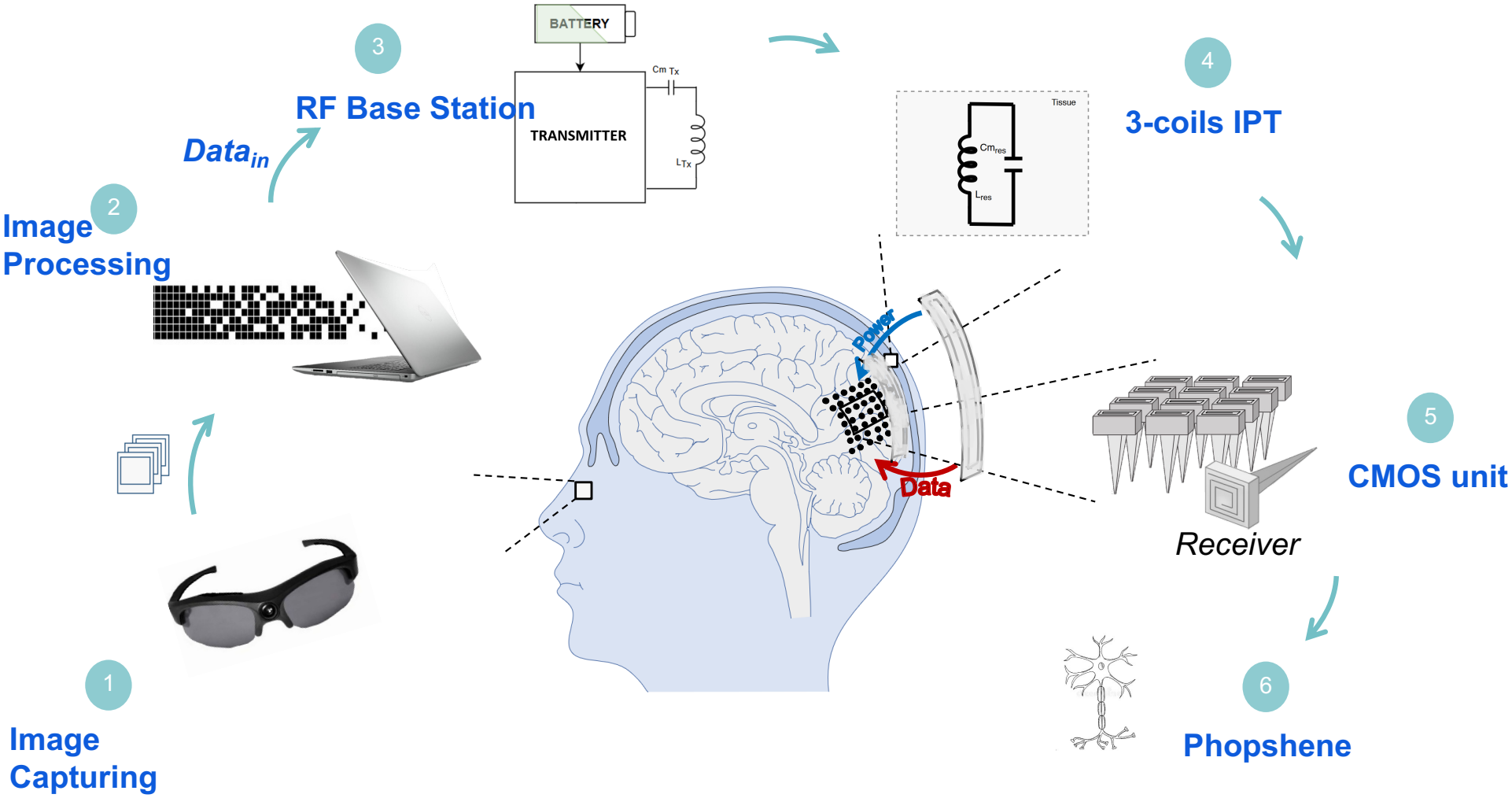
What's about BioChip?

BioChip = The Life ¨coupled¨ with Electronics

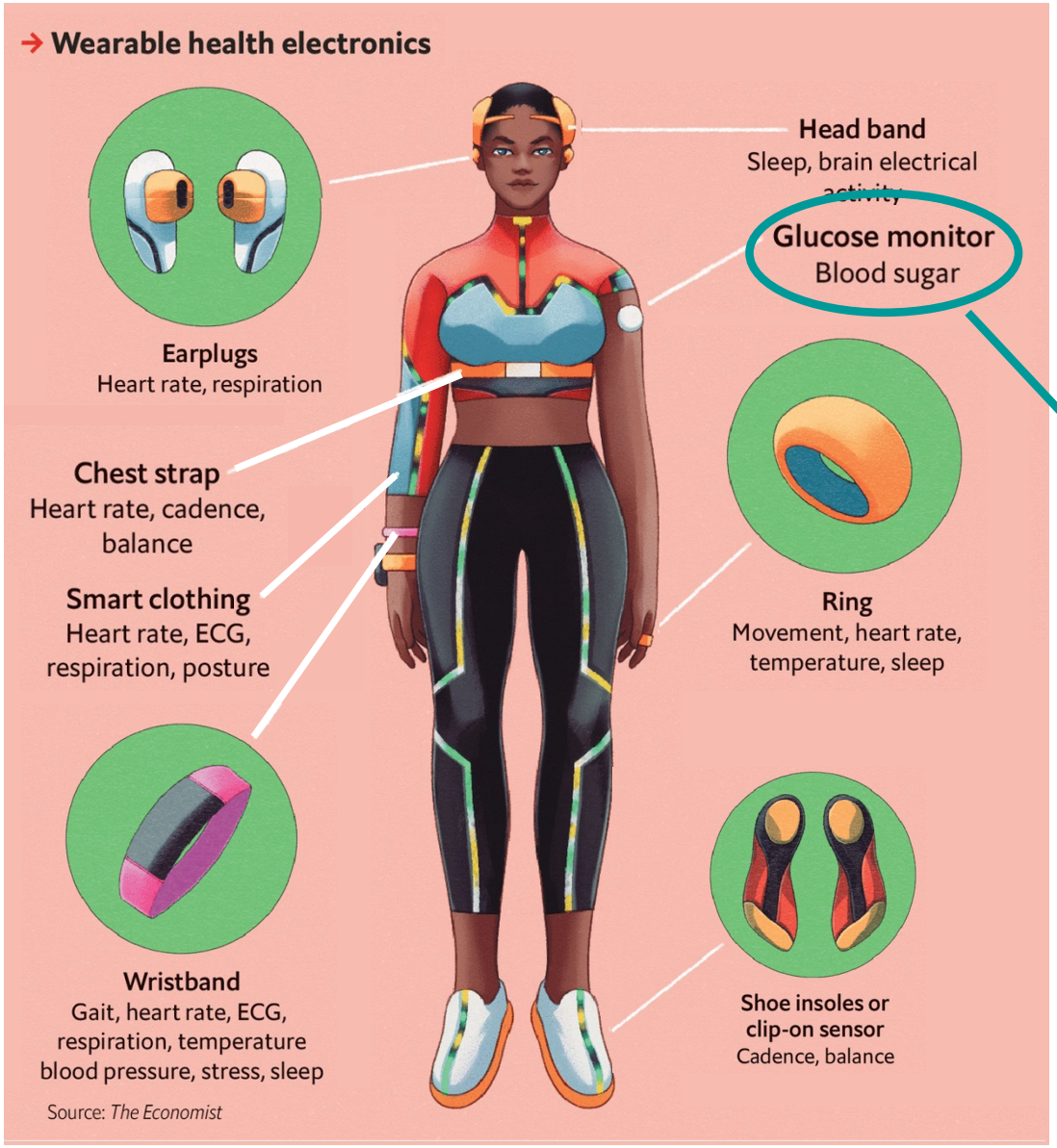
Bio/CMOS interfaces

That means also "biological systems coupled with electronics¨

Brain/Machine interfaces

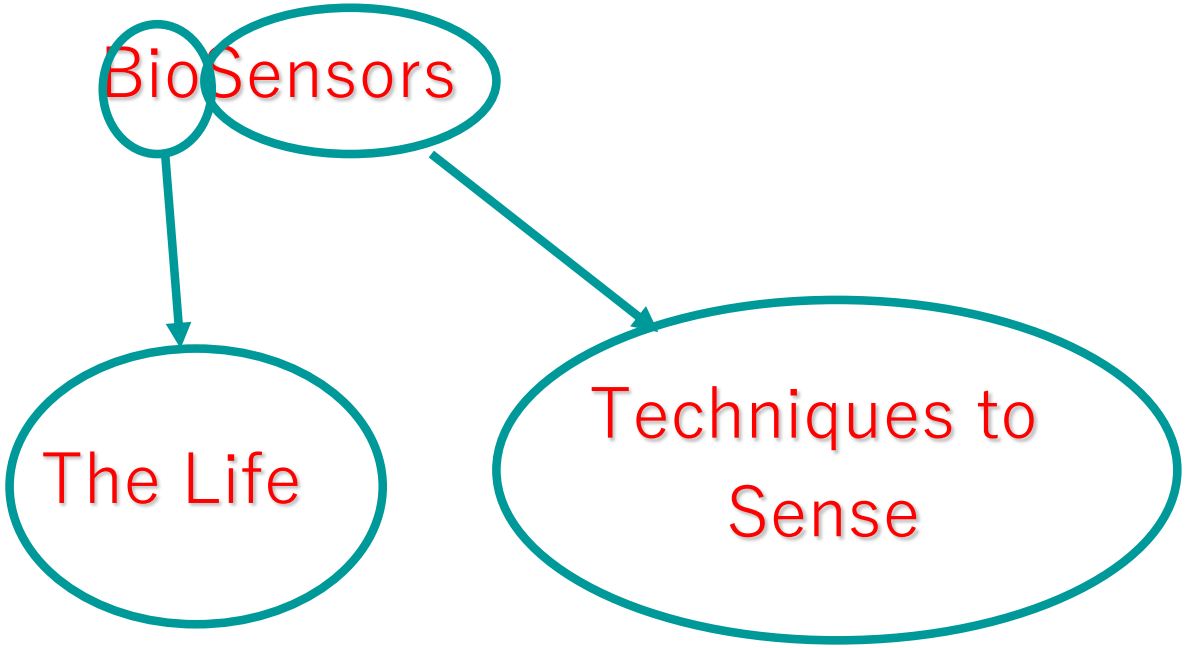


Wearable Devices



BioSensor

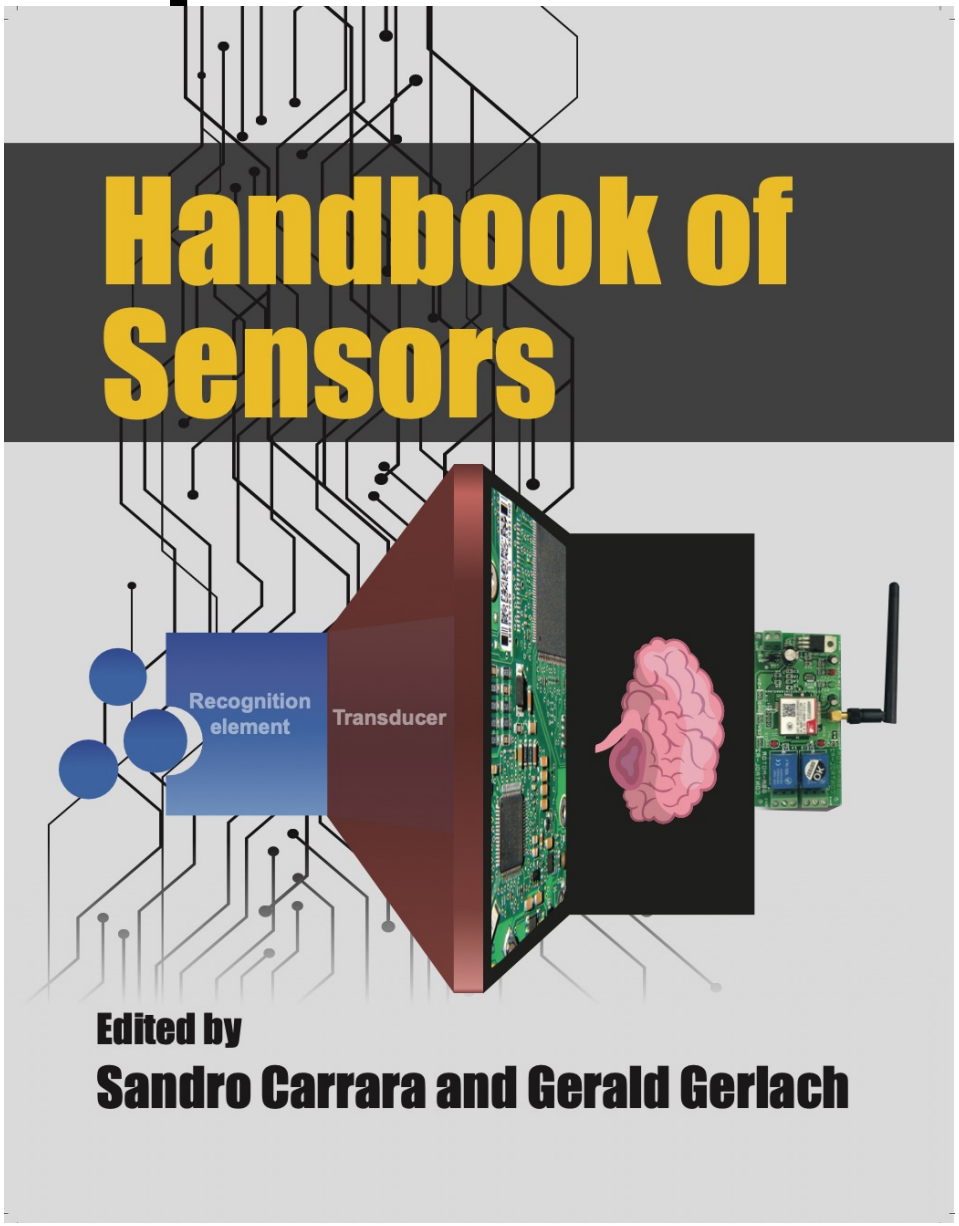
What's about BioSensors?



By definition, a biosensor is an analytical device combining a biological component with a physicochemical detector

[Reference to Turner, Anthony; Wilson, George; Kaube, Isao, *Biosensors: Fundamentals and Applications,* Oxford University Press, Oxford, UK, 1987]

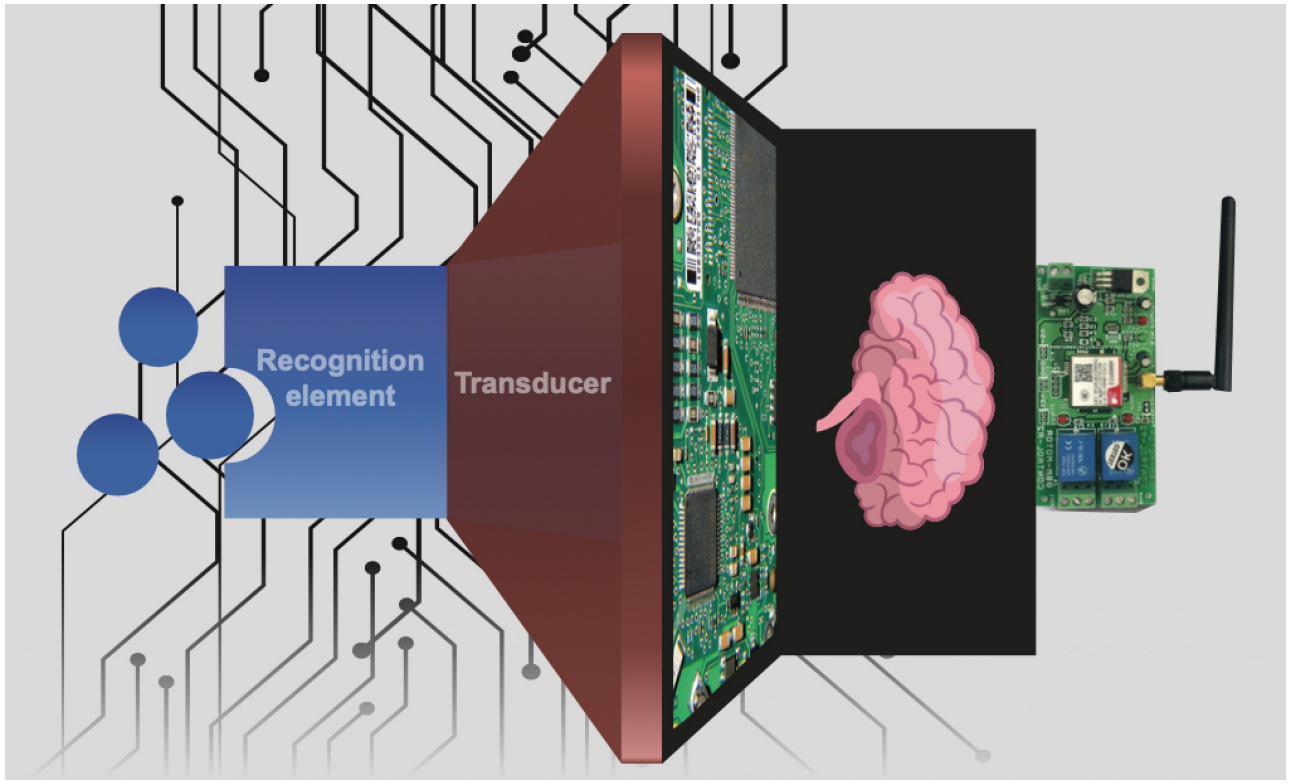
BioChip as BioSensors



BioSensors

EE-518 (Sandro's part)

EE-518 (Alex & Anja)



Lab versus Point-of-Care

- 100.000 $ (machinery)
- 1.000 $ the single µ-array

Labeled

Label-Free

- 50 $ (machinery)
- 0.05 $ the single strip

Bayer HealthCare

The Quicklab project by Siemens

Glucometer on iPhone

Glucometer on the Skin

Glucose Personal Diagnostics on our Skin

The Pancreas Functions

IN-put Signals

Bile aceids

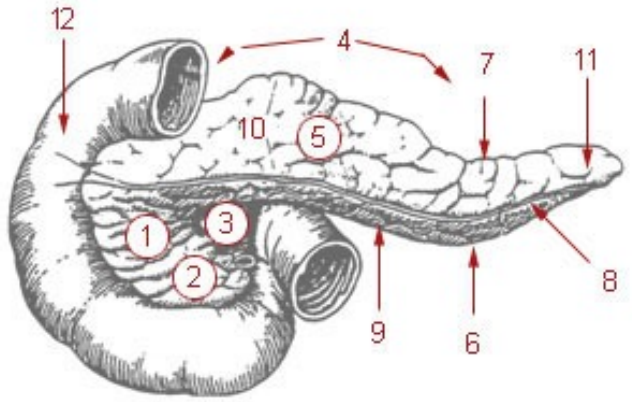
pH

Syrinic proteases

Glucose

Glycagone pancreatic

…….



OUT-put Signals

insulin

Lipase

Fospholipase A

Cholesterol estarase

Endopeptidase

Esopeptidase

Elastase

Ribonuclease

Enterochinase

…..

What to sense?

Simple Molecules	**Glucose (Diabetes)** **Cholesterol (heart attack)**
Proteins	**AFP (Hepato Carcinoma)** **PSA (Prostate)**
DNA sequences	**PC-1 gene (prostate cancer)** **p53 gene (Hepato Carcinoma)**

Bio-Markers may be simple molecules, proteins or genes

What else to sense?

Endogenous Metabolites	**Insulin (Diabetes)** **β-blockers (heart attack)**
Anti-cancer compounds	**Cyclophosphamide (Breast Cancer)** **Docetaxel (Prostate Cancer)**
Anesthetics	**Propofol (surgery)** **Midazolam (surgery)**

Endogenous and Exogenous Metabolites are usually simple molecules

What else to sense/actuate?

Electrical Signals (recording)	**Electromyography (EMG = measure of muscle response)** **Electroencephalogram (EEG = measure of brain activity)** **Electrocardiogram (ECG = measure of heart activity)**
Electrical Signals (stimulation)	**Alzheimer's disease** **Epilepsy** **Artificial Retina**
Chemical Signals	**Dopamine** **Glutamate** **Benzphetamine**

Signaling form the Nervous System, both Central and Peripheral

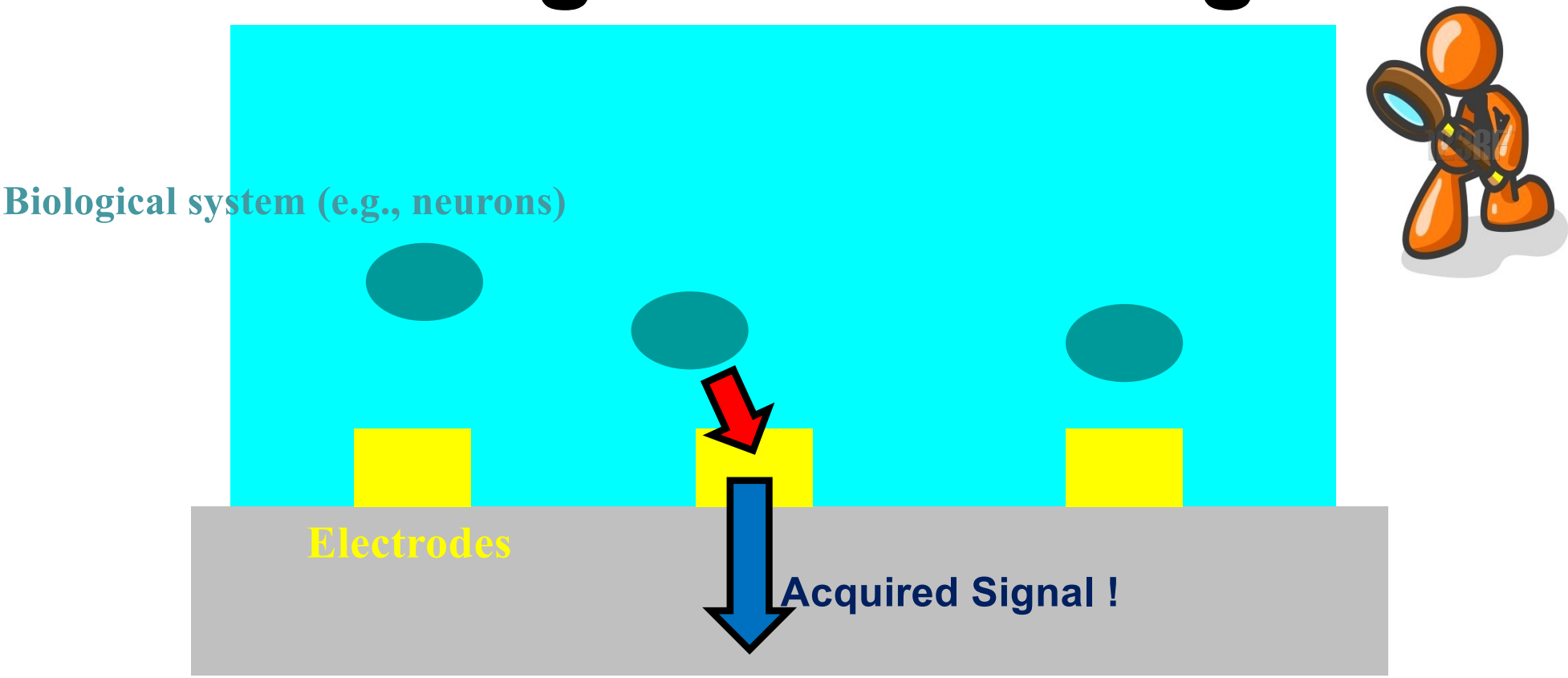
What to sense?

How to detect Bio-Markers?

Endogenous Chemical Signals	Glucose (Diabetes) Cholesterol (heart attack) PC-1 gene (prostate cancer)
Exogenous Chemical Signals	Propofol (Anesthetic) Docetaxel (Prostate Cancer) Cyclophosphamide (Breast Cancer)
Electrical Signals	Electrocardiogram (ECG = measure of heart activity) Electrocardiogram (ECG = measure of heart activity) Electroencephalogram (EEG = measure of brain activity)

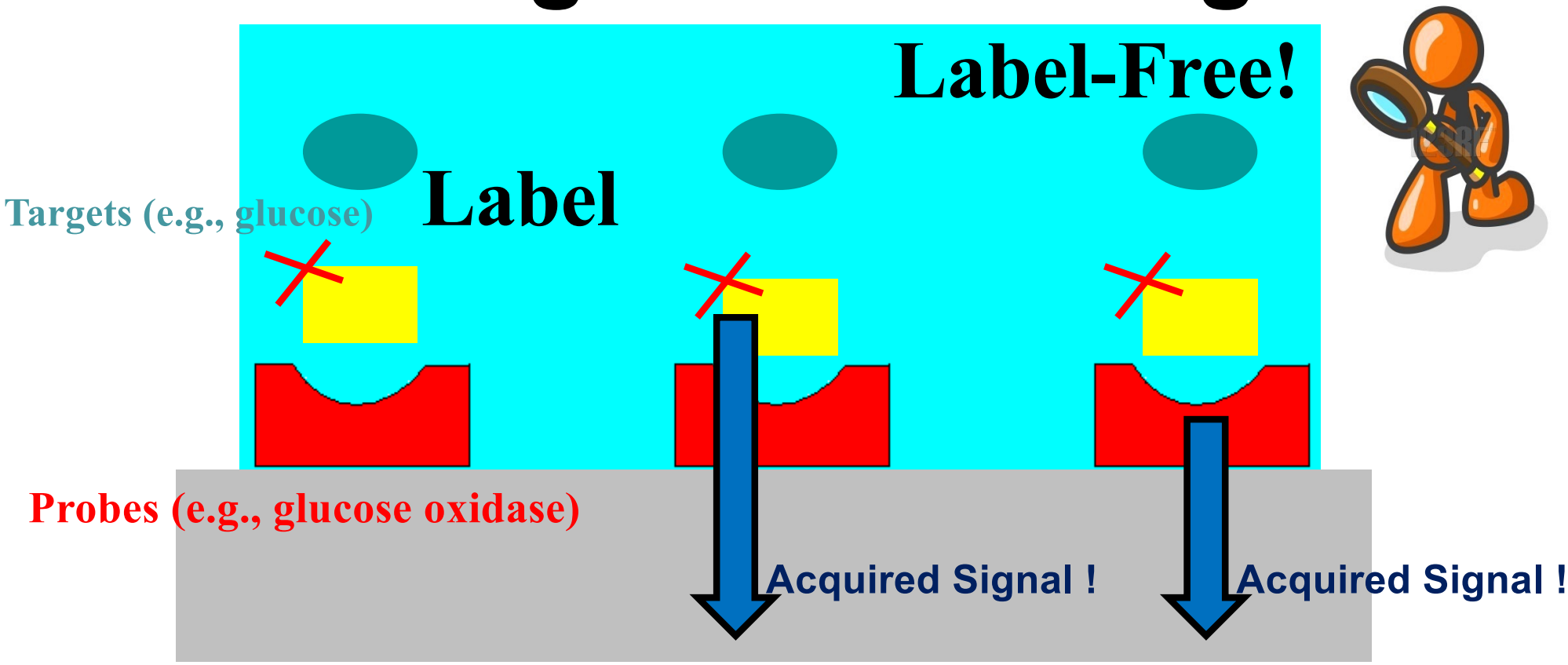
Bio-Markers may be electrical signals, simple molecules, proteins, or genes

Measuring Electrical Signals



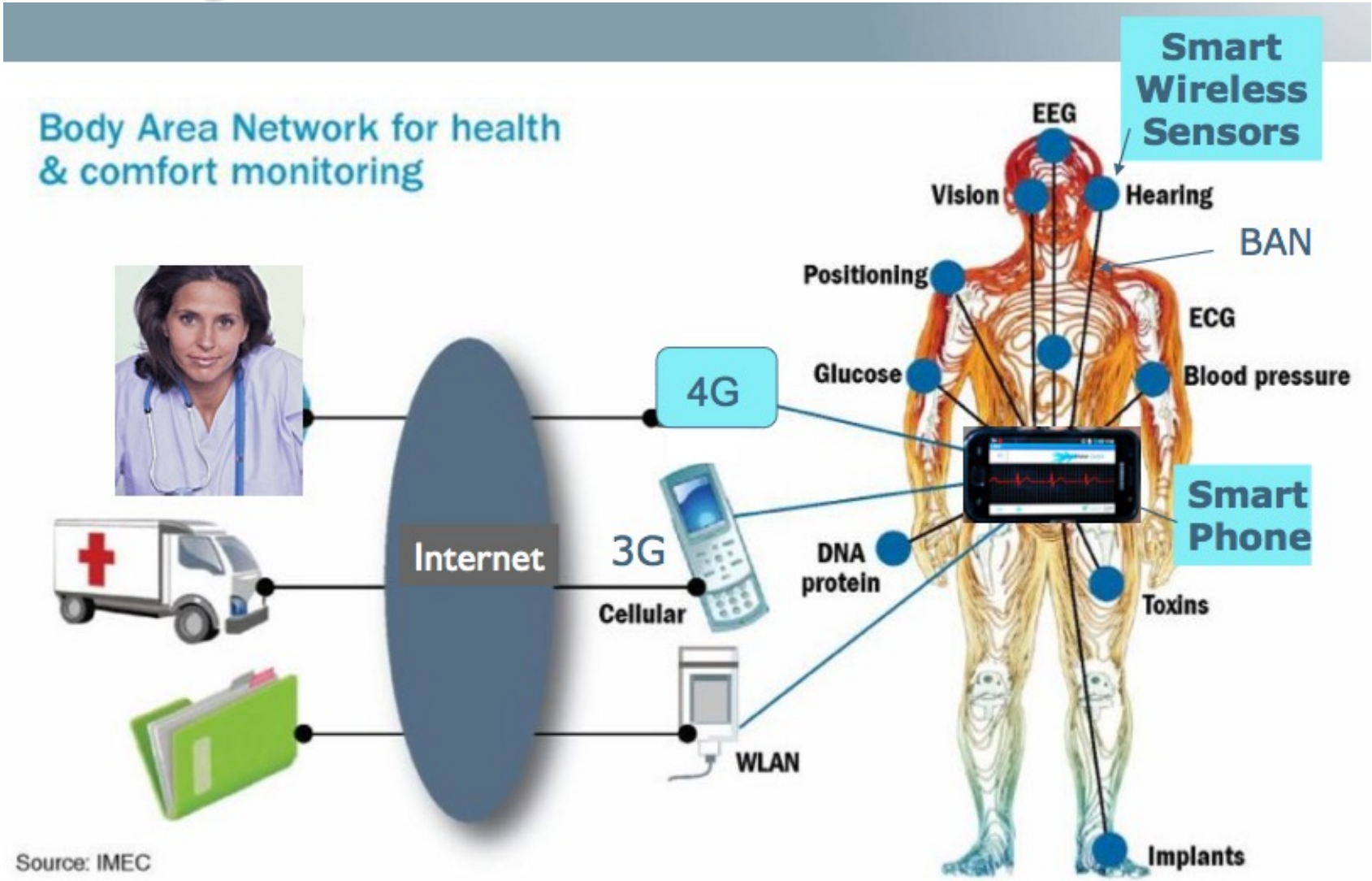
The Measure of electrical biomarkers may be performed with electronic readers

Measuring Molecular Signals



The Measure of molecular biomarkers may be performed in a labeled manner or in label-free mode

Fully-Connected Human++



Courtesy, Hugo De Man (IMEC)

The Time' forecast on Human++

[TIME, February 2011]

The Time' forecast on Human++

[TIME, September 2014]

Chips under the skin?

Under the skin: how insertable microchips could unlock the future

Volunteers in Melbourne have had microchips inserted for three months, designed to unlock doors and carry out other tasks. Will they really be any use?

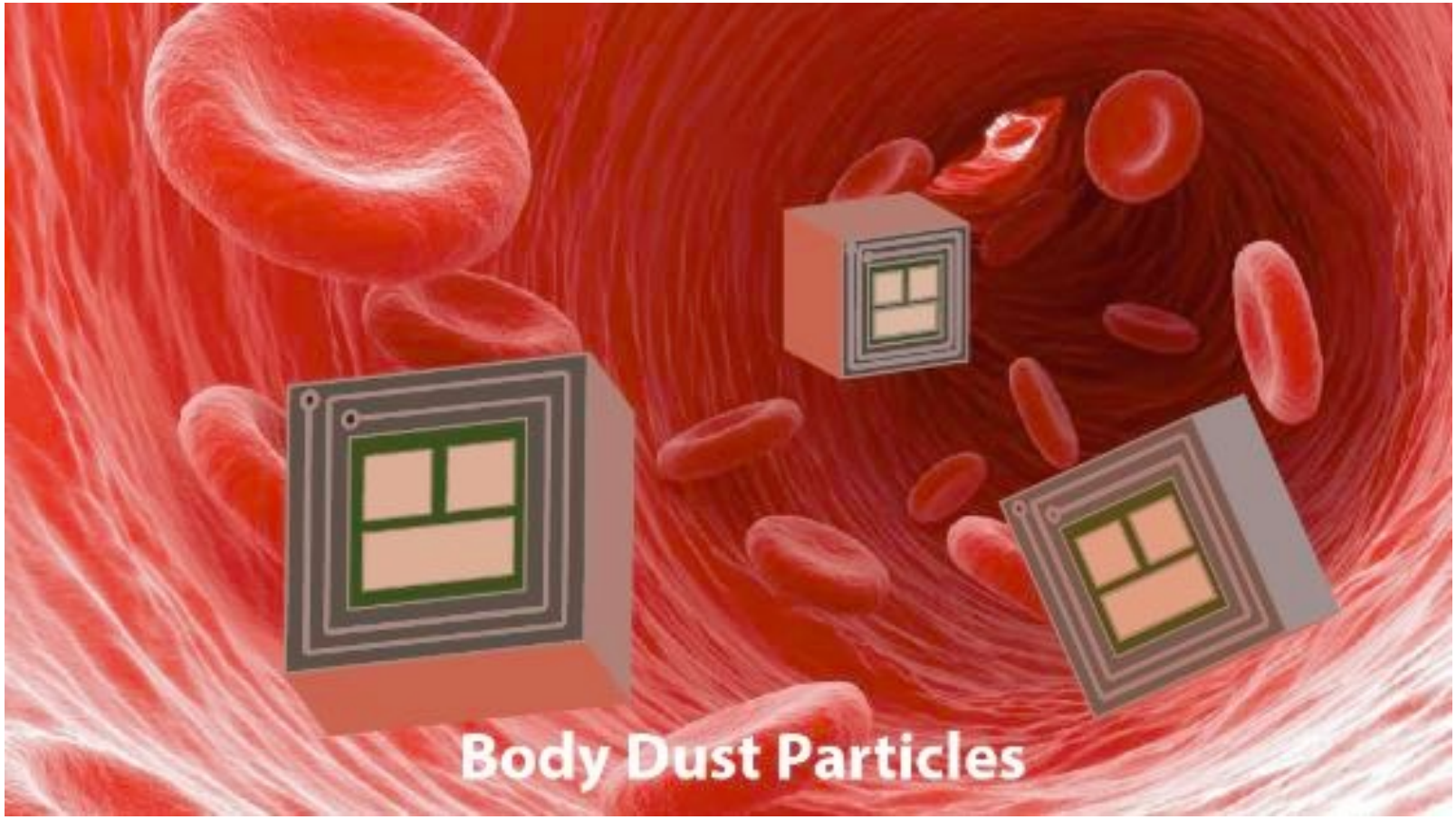
THEGUARDIAN.COM

[The Guardian, October 2017]

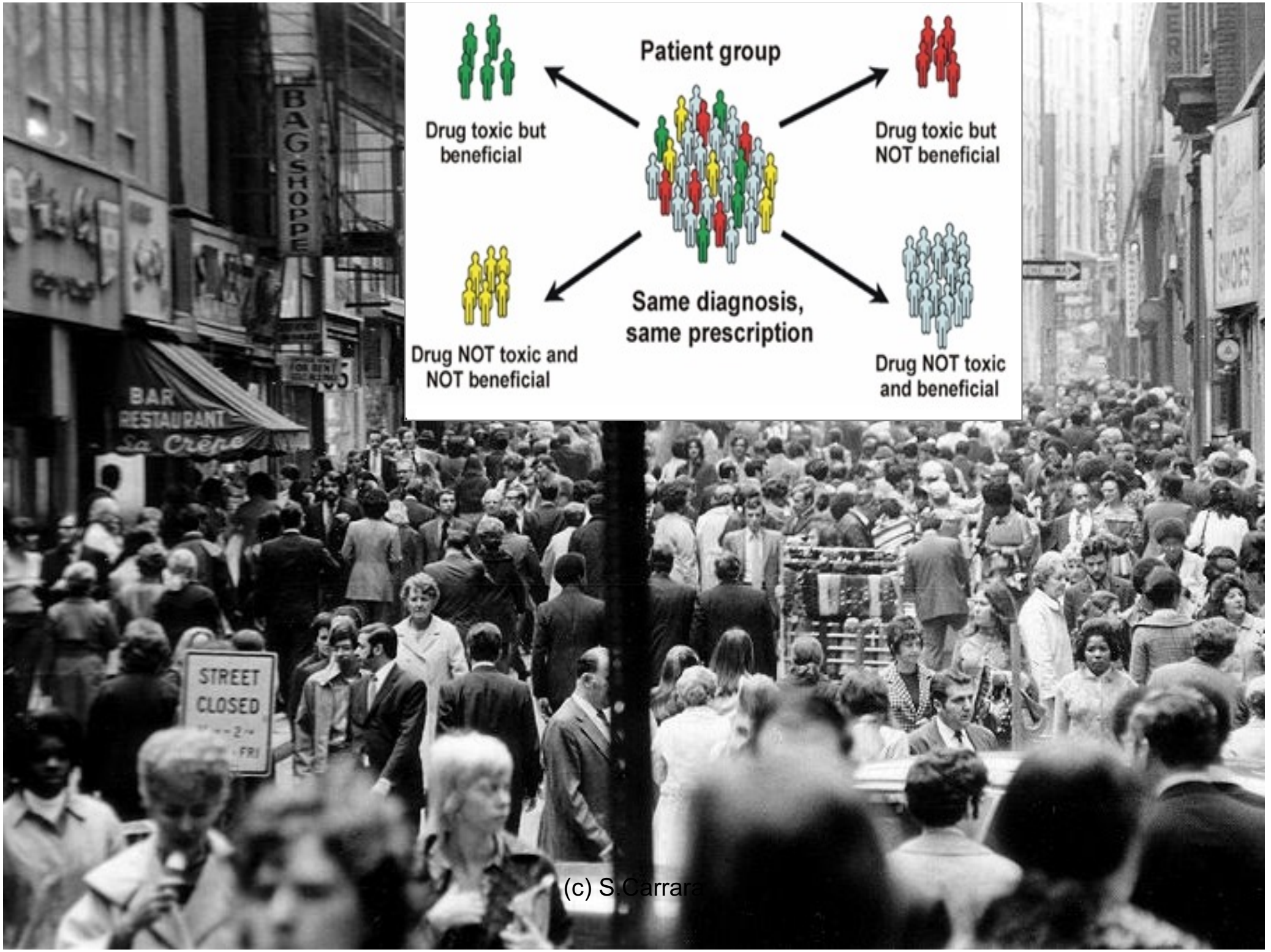
How small Chips under the skin?

[1966 Sci. Fi. movie titled “Fantastic Voyage”]

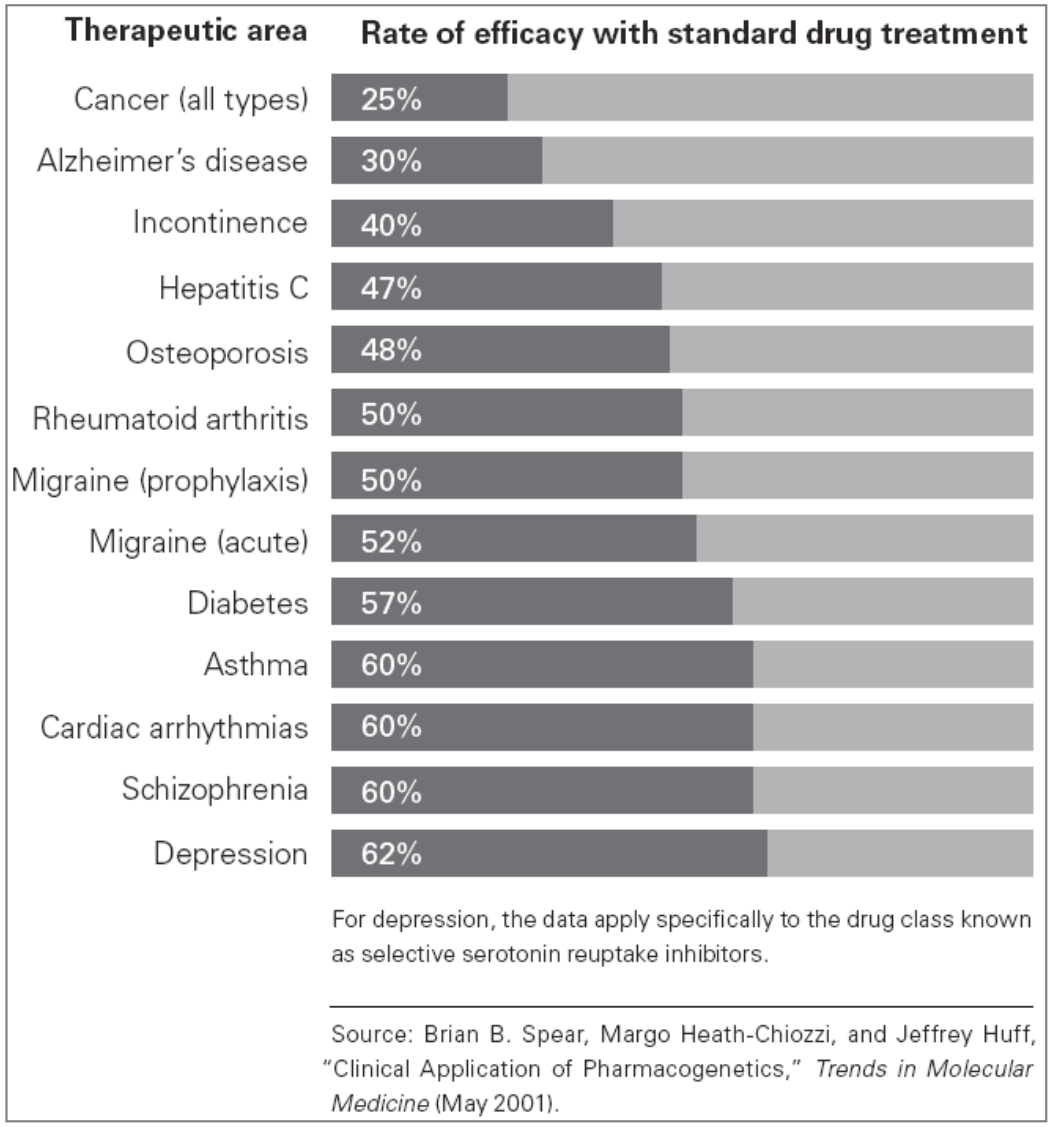
Body Dust:
Drinkable CMOS Bioelectronics



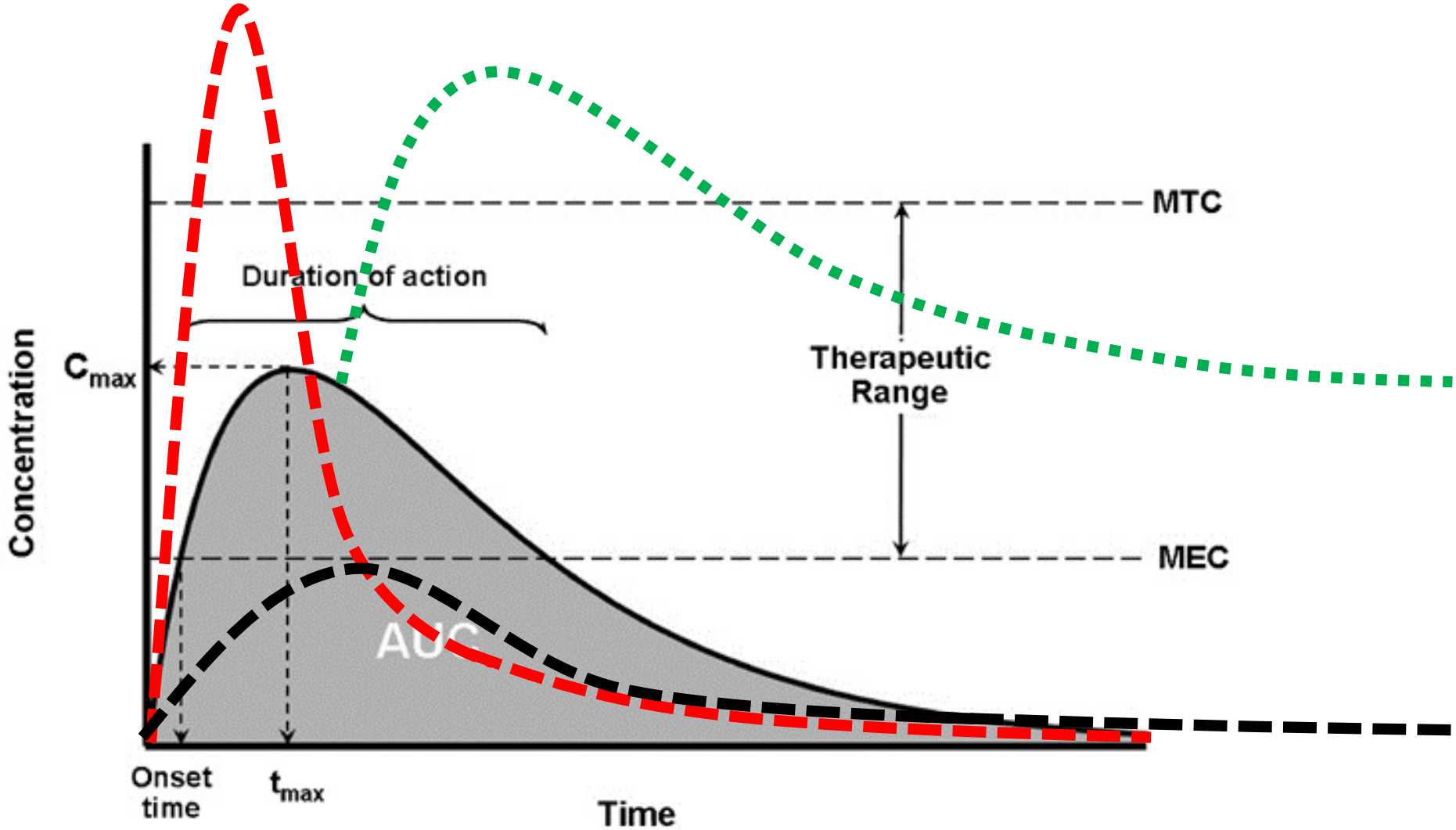
[ArXiv, May 2018]


Patient group
Drug toxic but beneficial
Drug toxic but NOT beneficial
Same diagnosis, same prescription
Drug NOT toxic and NOT beneficial
Drug NOT toxic and beneficial
BAG SHOPPE
BAR RESTAURANT
Sa Crêpe
STREET CLOSED

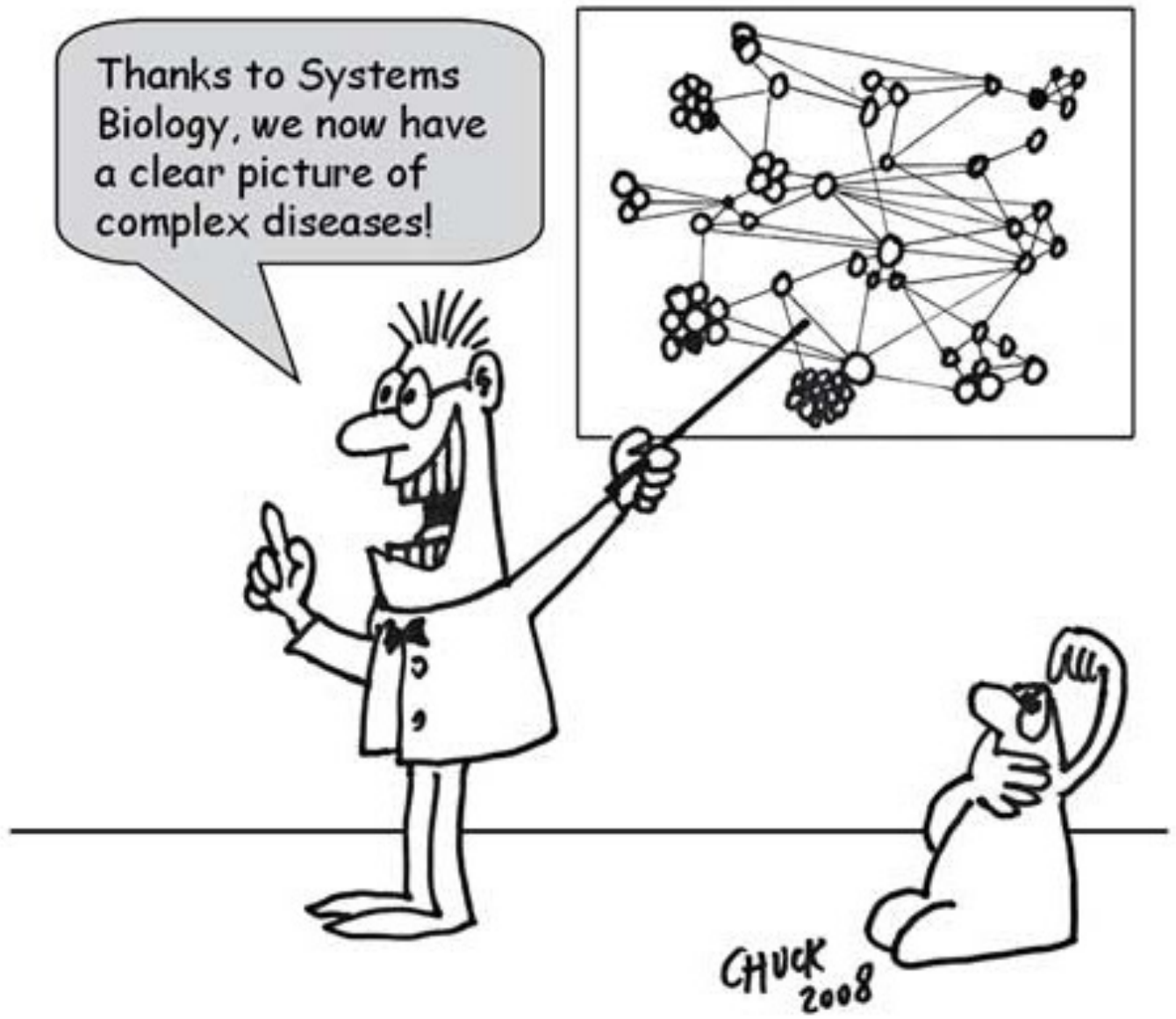
Low efficacy of used compounds



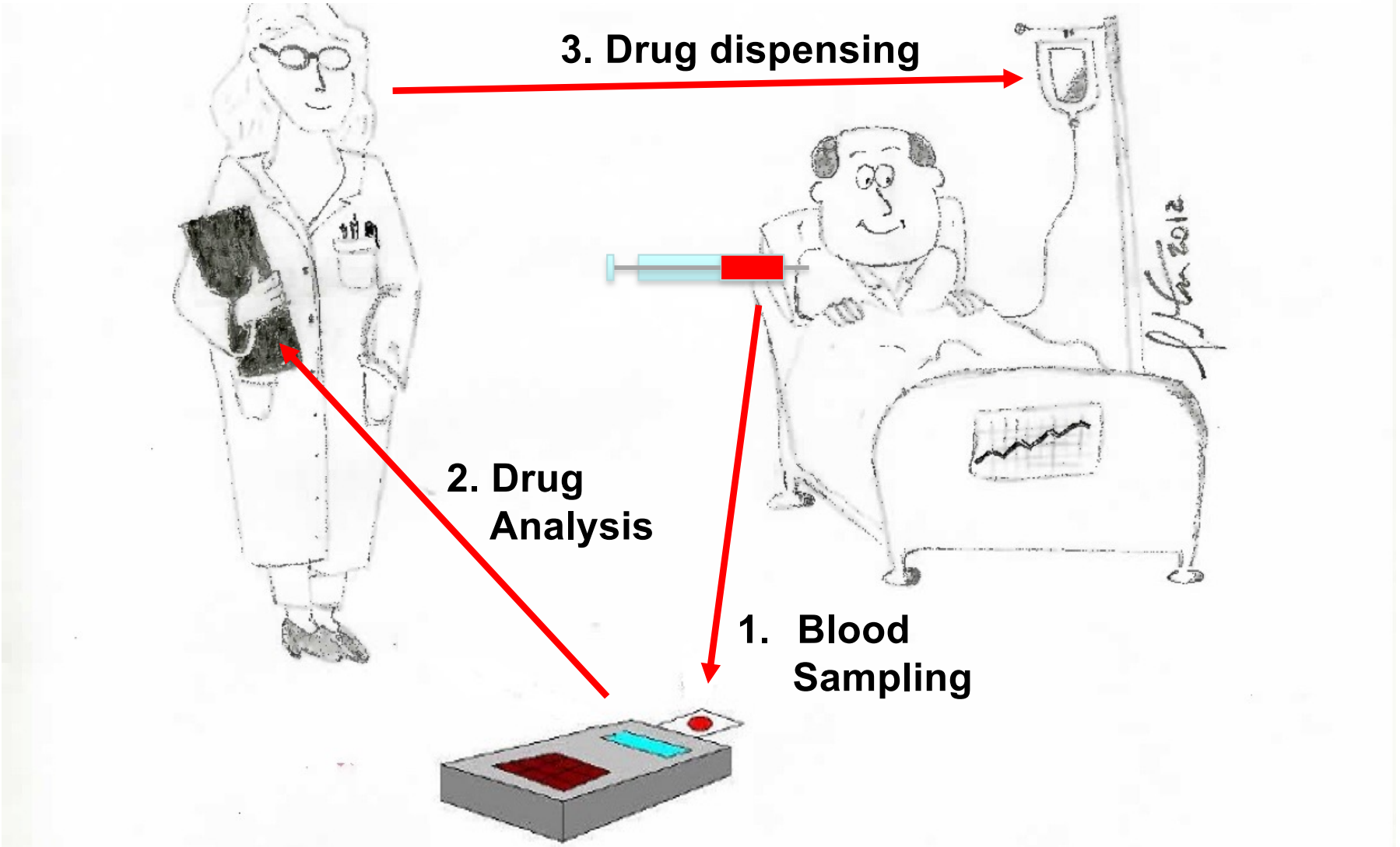
Personalized Therapy: the dose at the right moment!



System Biology is not enough



Personalized Therapy

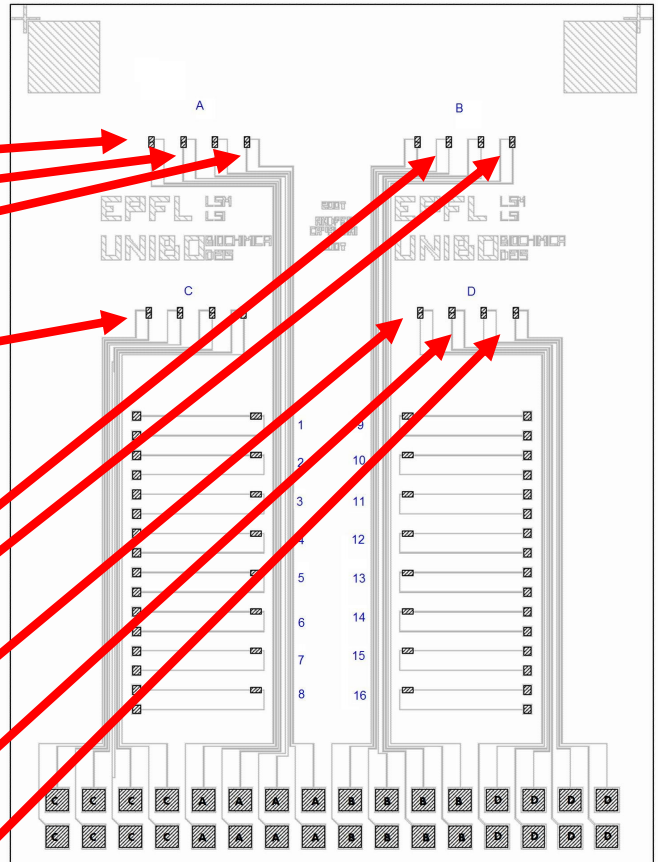


Drugs injection based on patient's pharmacokinetics

Need for new multi-panel systems

TARGETS

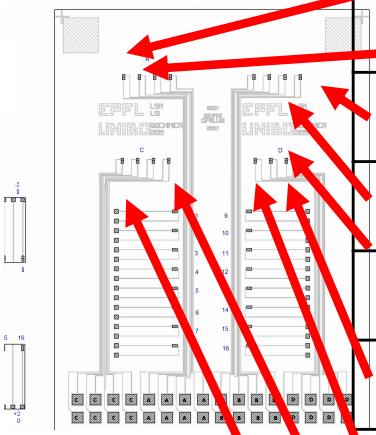
Endogenous metabolites	Exogenous metabolites
Glucose	
Lactate	
Glutamate	
Cholesterol	
	Benzphetamine
	Dextromethorphan
	Cyclophosphamide
	Flurbiprofen
	Naproxen



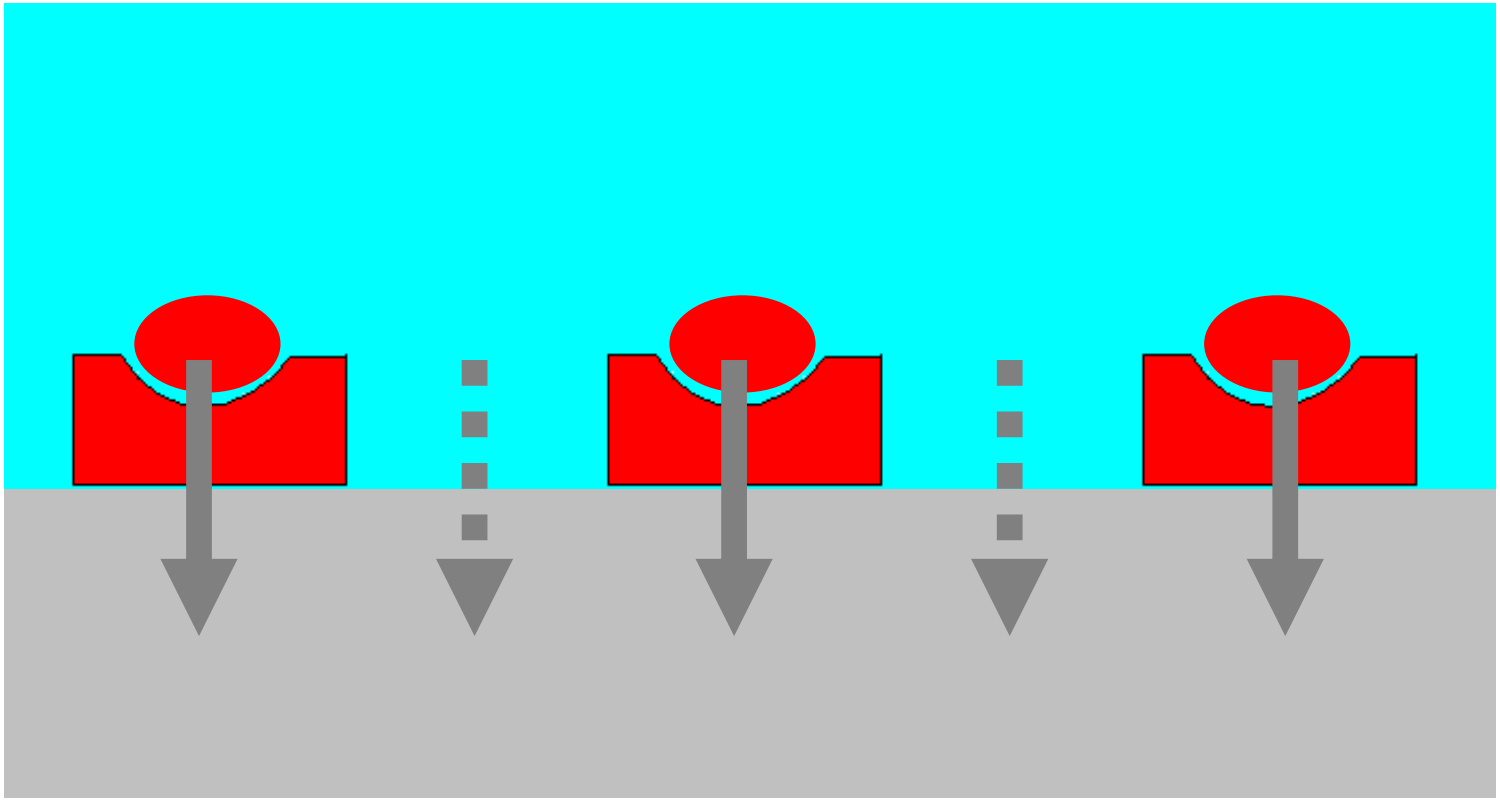
Bio-Probes for Label Free

TARGETS

Probe Enzymes	Endogenous metabolites	Exogenous metabolites
Glucose Oxidase	Glucose	
Lactate Oxidase	Lactate	
Glutamate Oxidase	Glutamate	
P450 11A1	Cholesterol	
P450 2B4		Benzphetamine
P450 3A4		Dextrometorphane
P450 3A4		Cyclophocphamide
P450 2C9		Flurbiprofene
P450 2C9		Naproxene

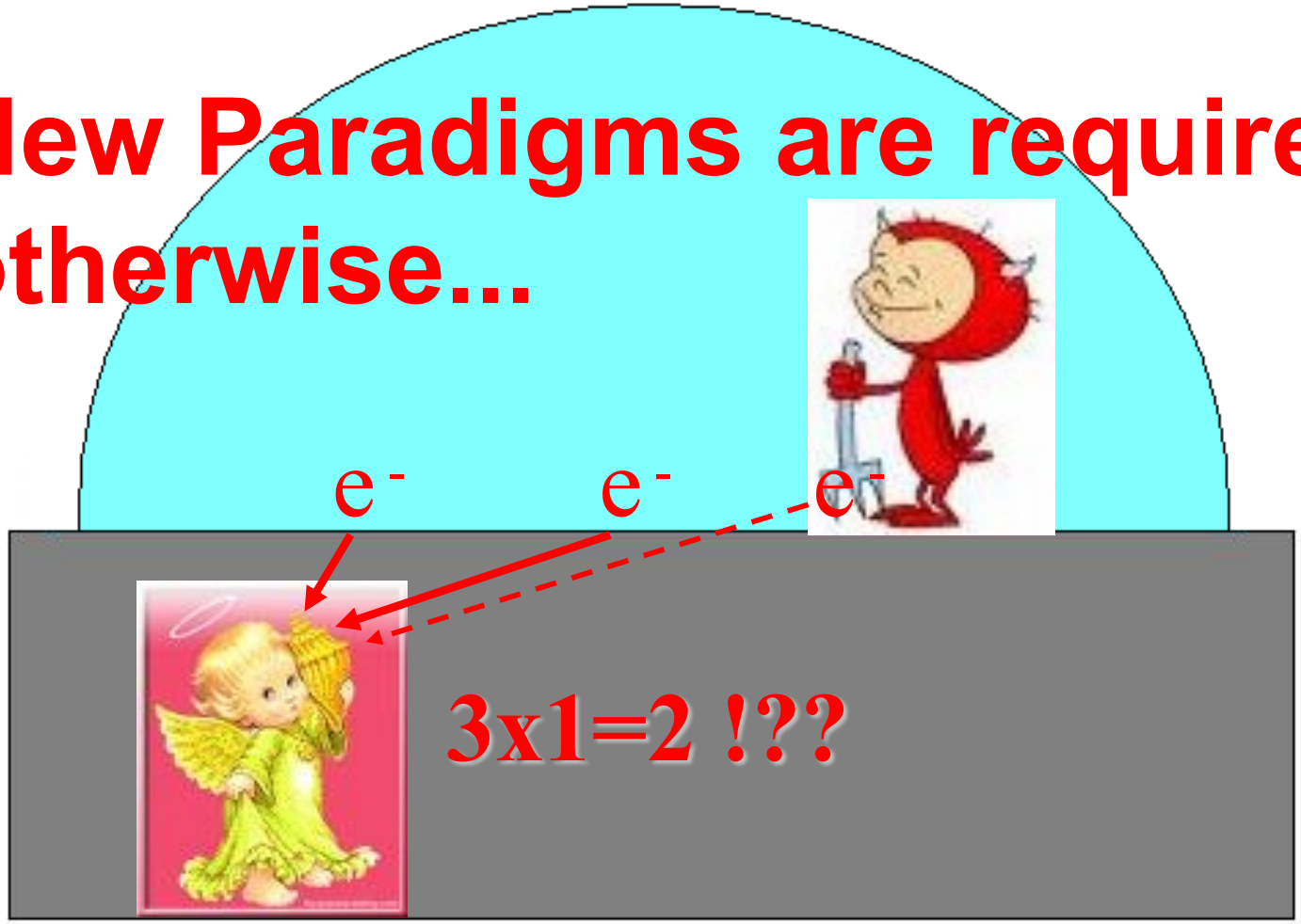


CMOS/Sample interface



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

New Paradigms are required otherwise...

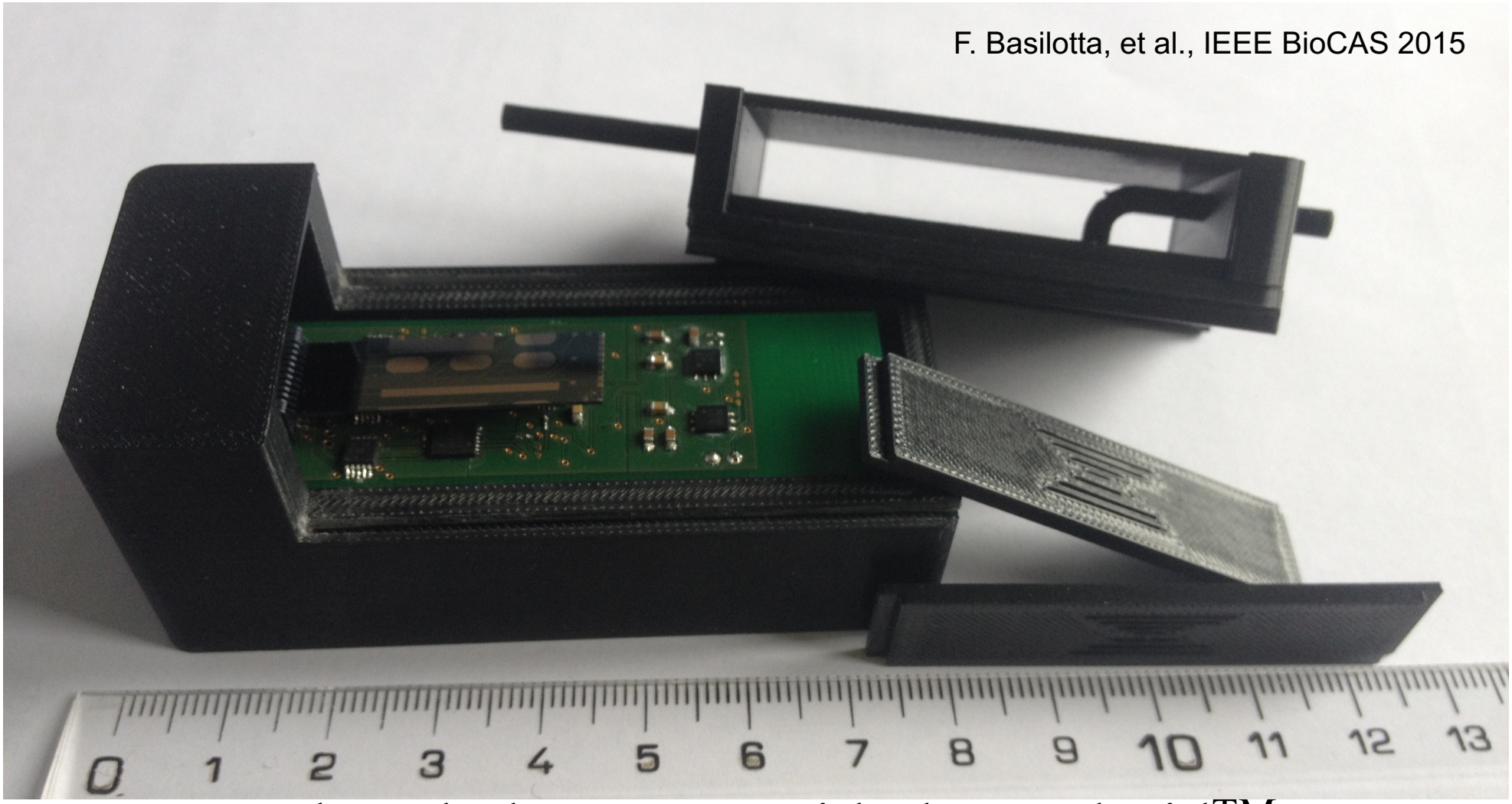


Excellent CMOS technology is not sufficient if molecules are not doing their own job at the Bio/CMOS interface!

Portable, Implantable, ‘n’ Wearable

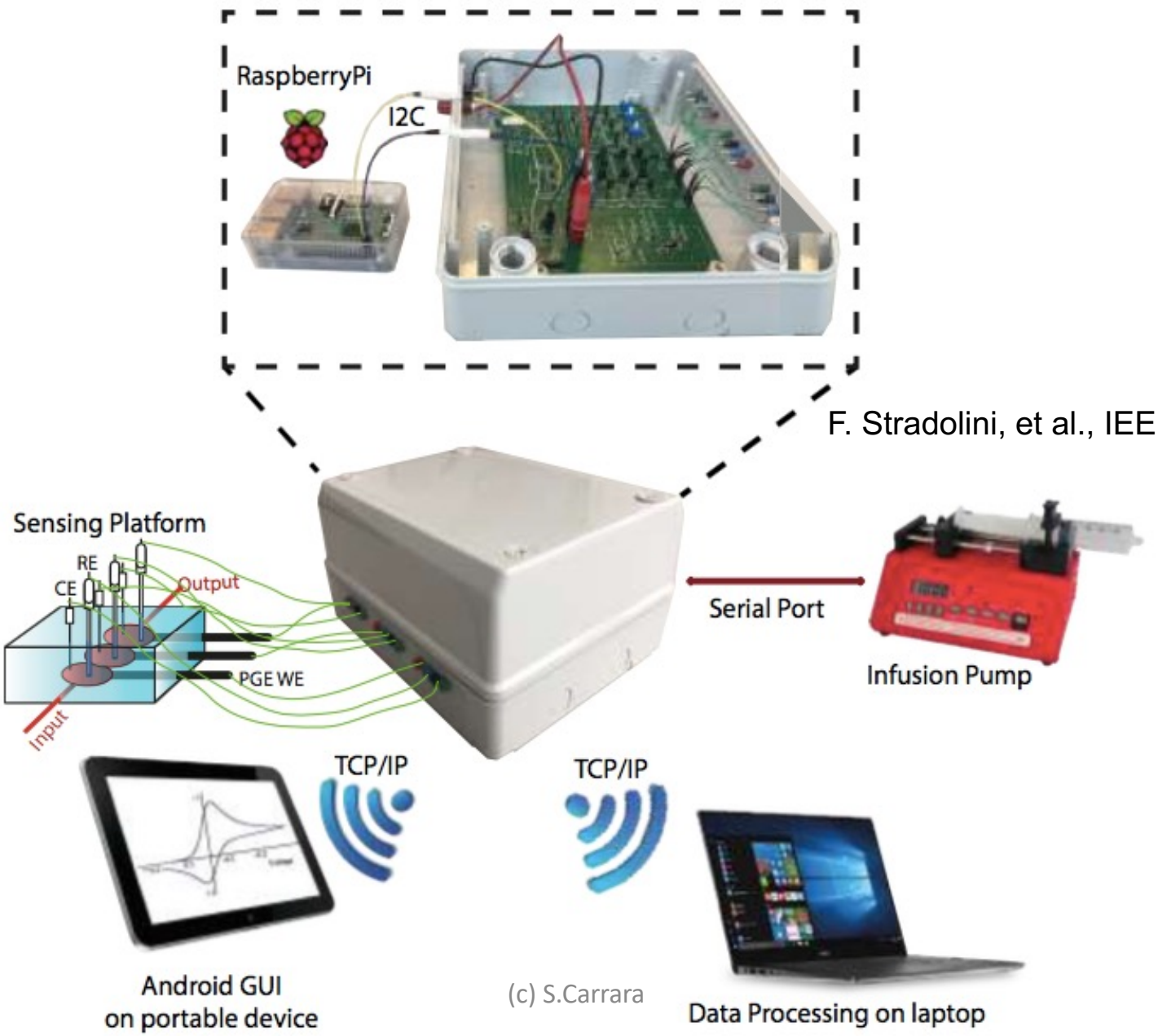
Monitoring scenarios

Monitoring in Intensive Care Units



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

Monitoring and Injection in Surgery

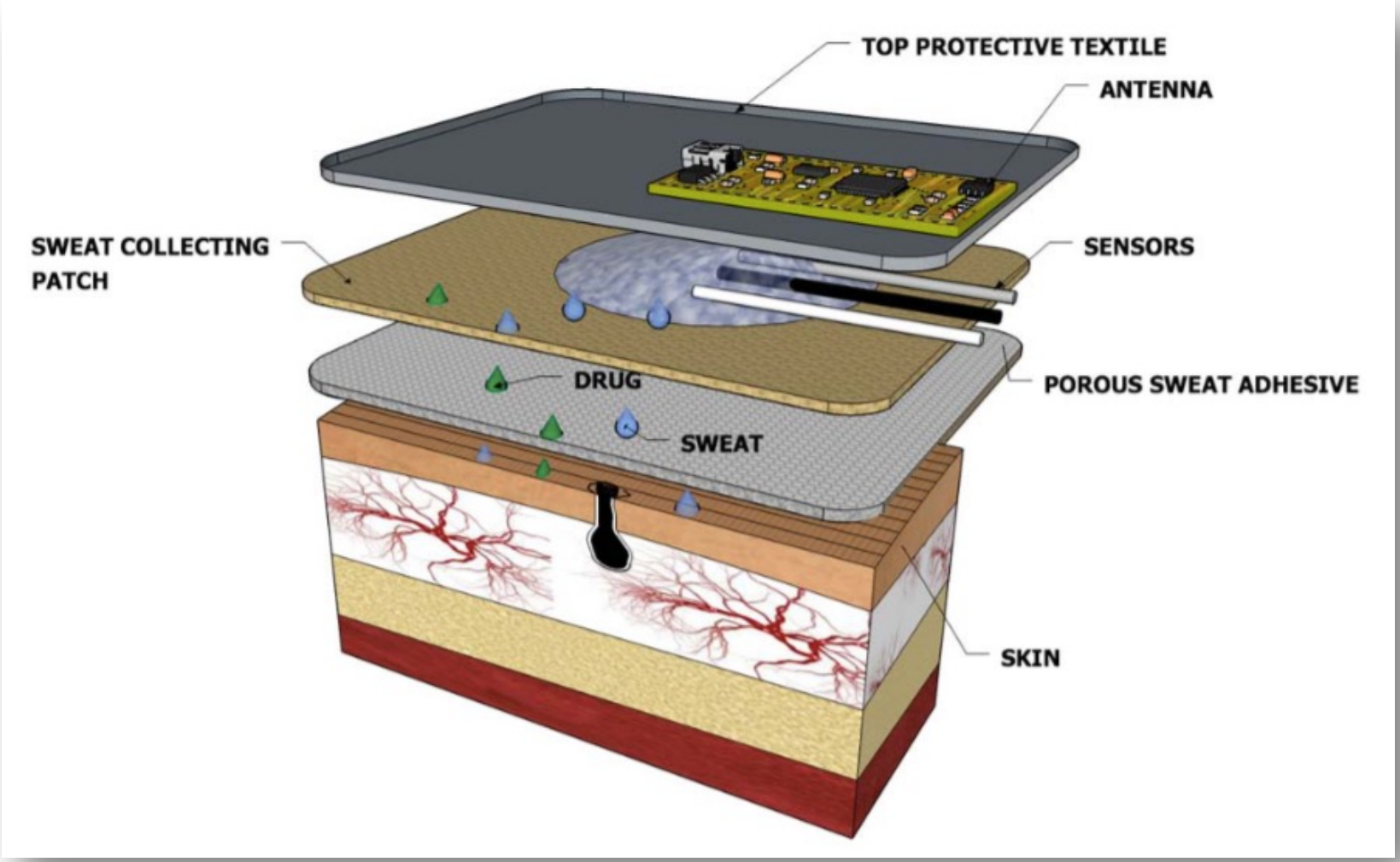


F. Stradolini, et al., IEEE NGCAS 2017

Monitoring Anaesthetics in Surgery

S. Aiassa, et al., Biosensors And Bioelectronics, 171(2021) 112666, 1-7 S. Aiassa, et al., IEEE MeMeA 2020
S. Aiassa, et al., IEEE TBCAS), 15(2021) 294 - 302 S. Aiassa, et al., IEEE Sensors Letters 3(2019) 1-4

Wearable Monitoring Devices



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

Metabolites Monitoring on the skin

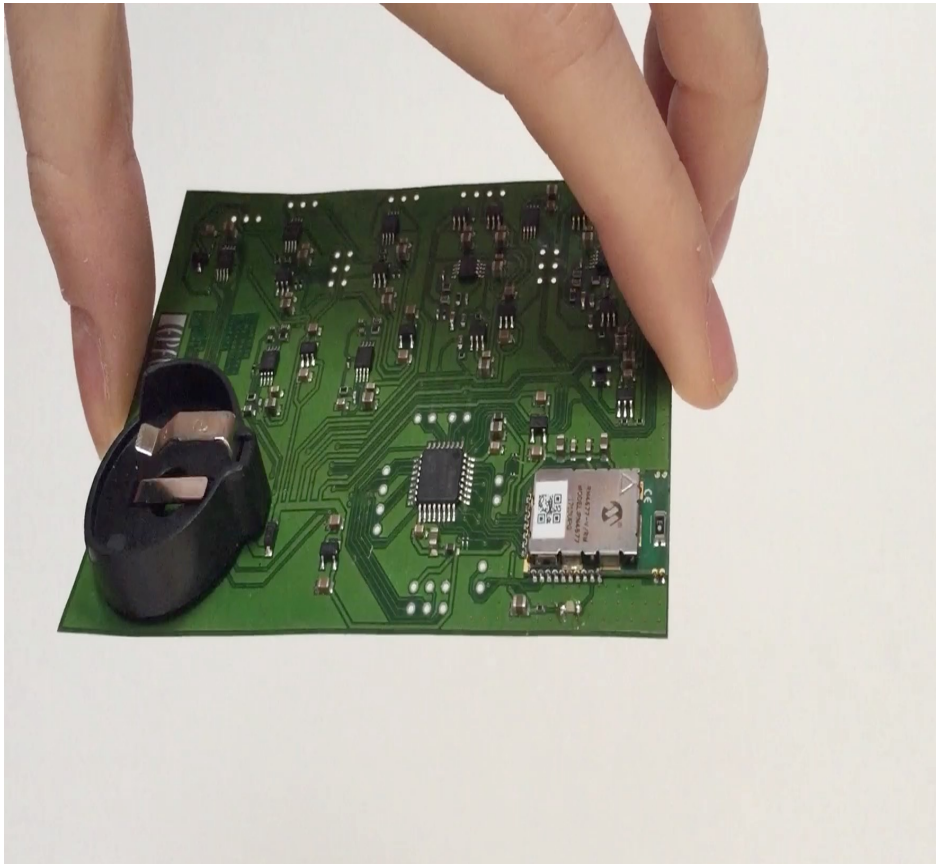
Wearable Monitoring Device Realized

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

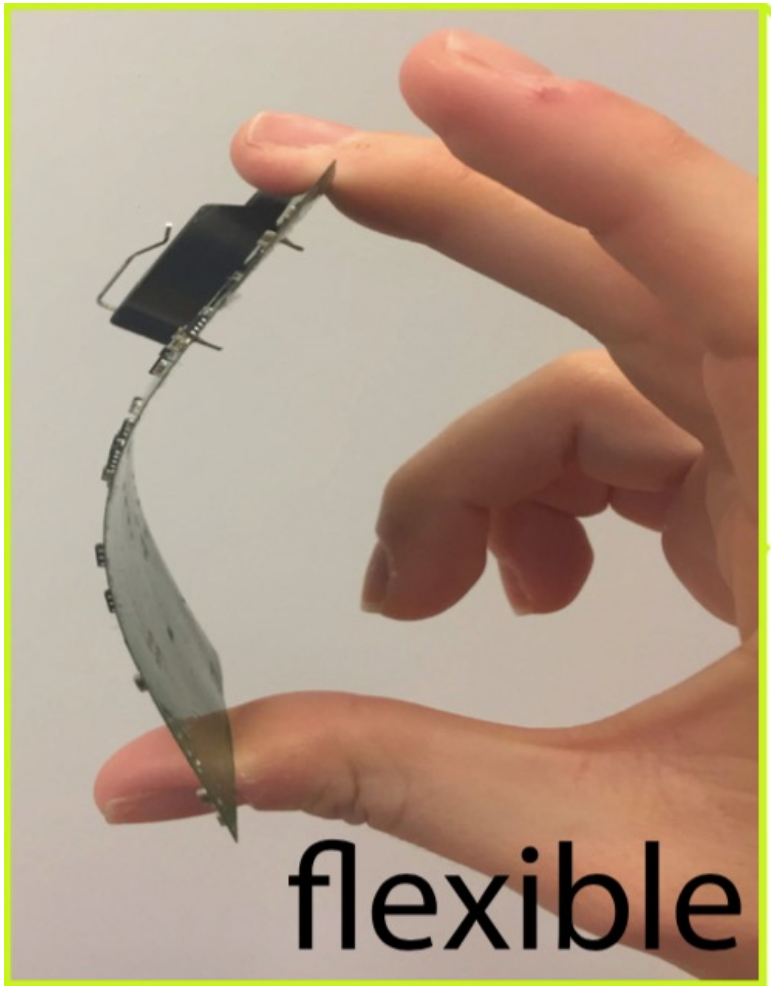
Wearable Electronics

Wearable Sensors

Flexible Instrumentation



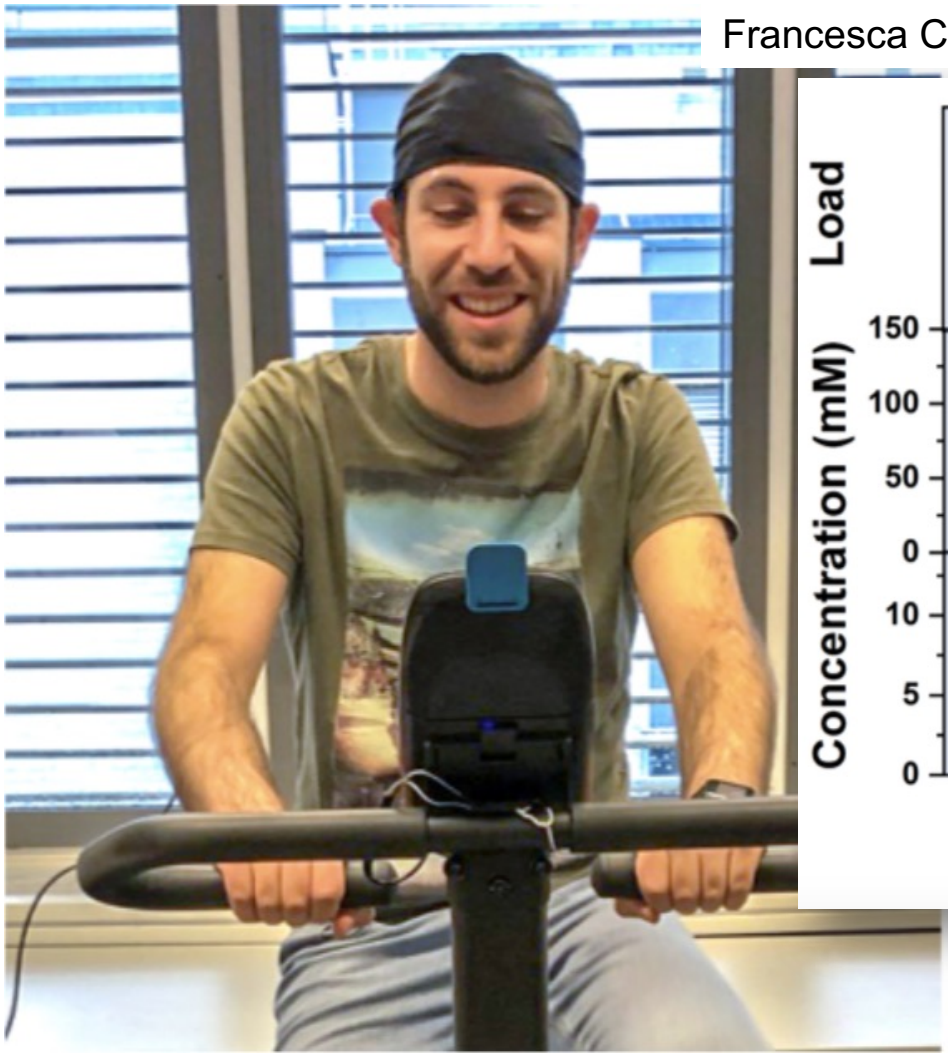
I.Ny Hanitra, et al., IEEE MeMeA 2018

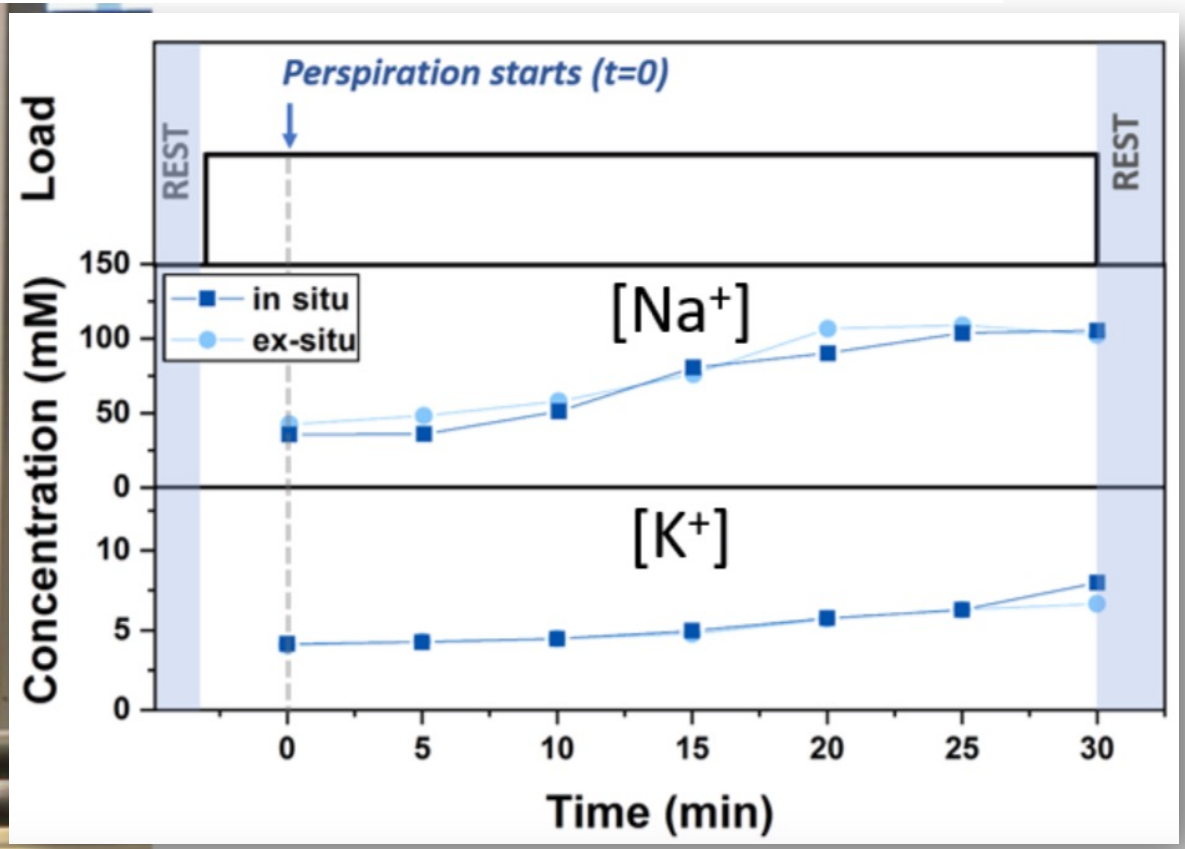


The Detection system has been realized
on flexible PCB

Na^+ & K^+ @ Wearable

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

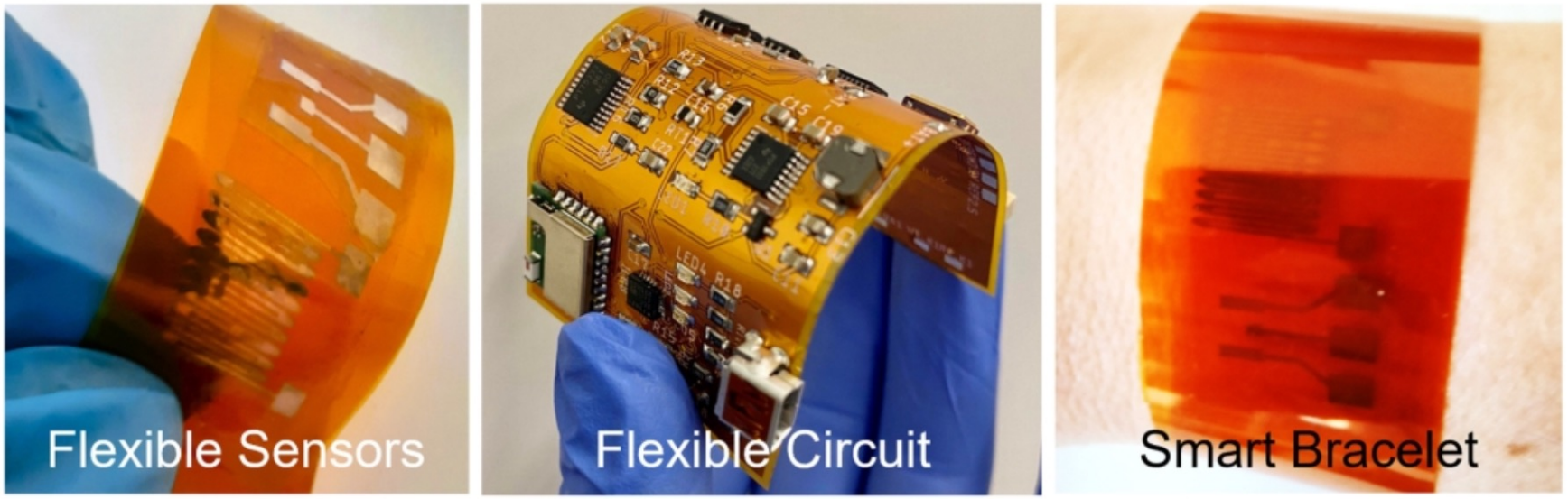




The Detection of ions in sportsmen

(c) S.Carrara

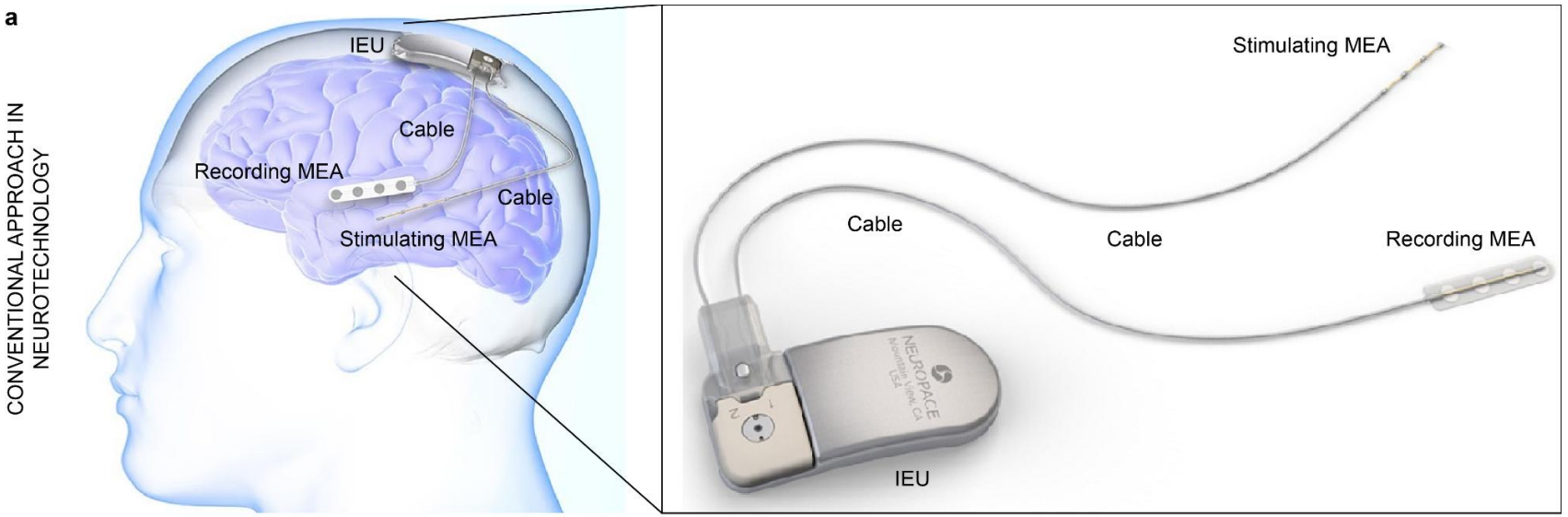
Smart Bracelet

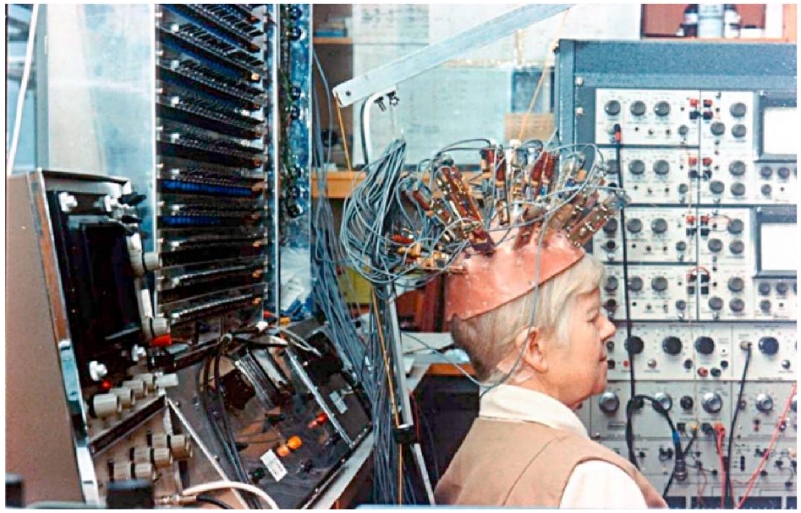


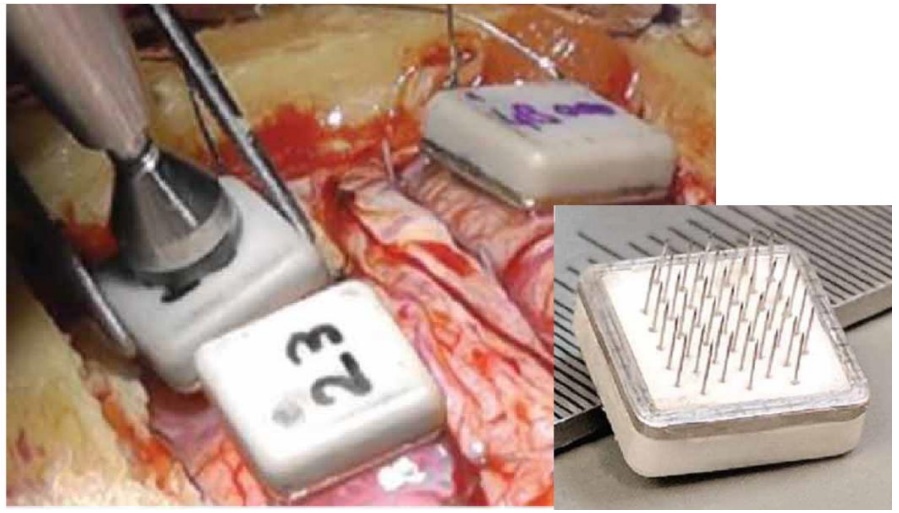
Ata Golpoarvar, al. et / IEEE FLEPS, 2023

The whole system fully integrated in a wearable light-bracelet

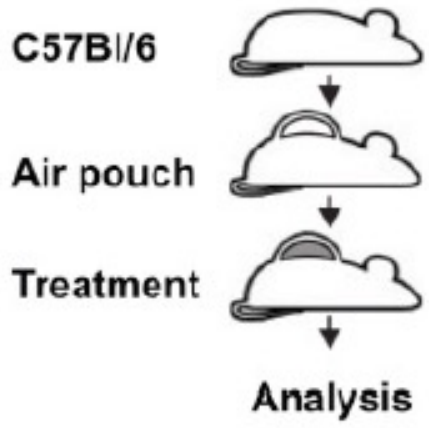
Neural Interfaces

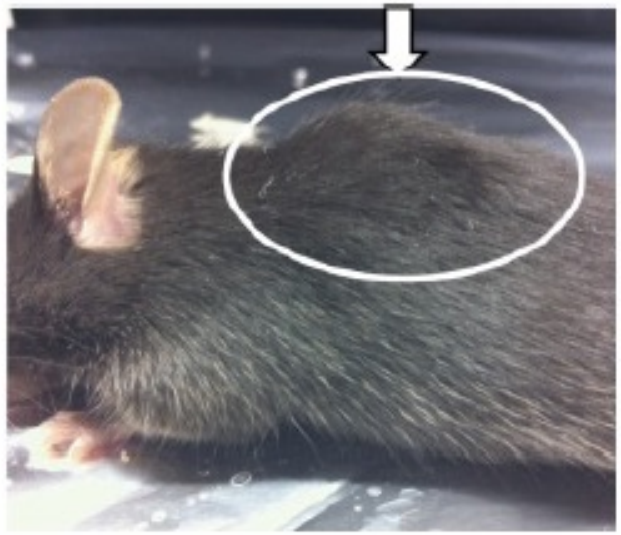






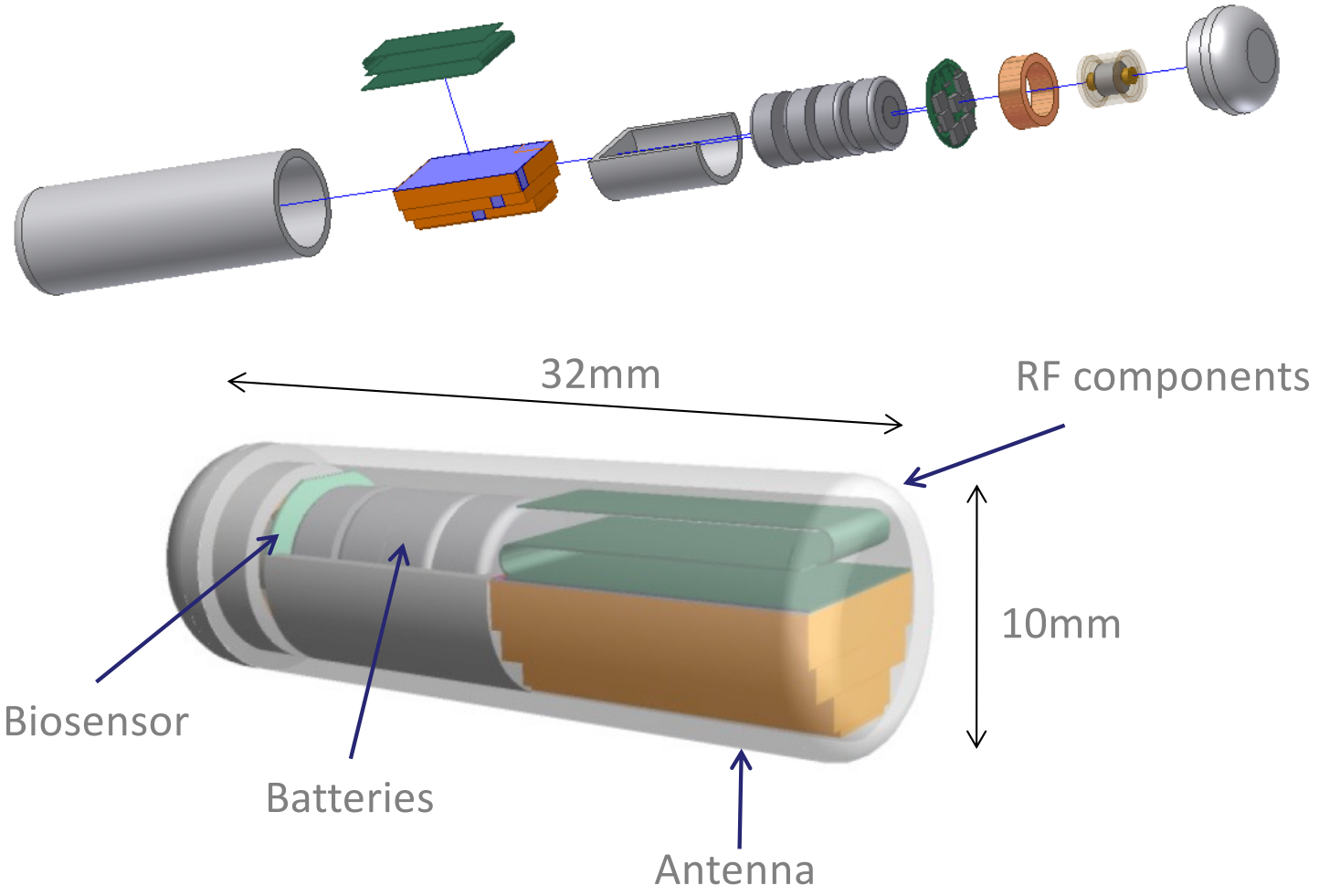
Biochips for Animals Monitoring



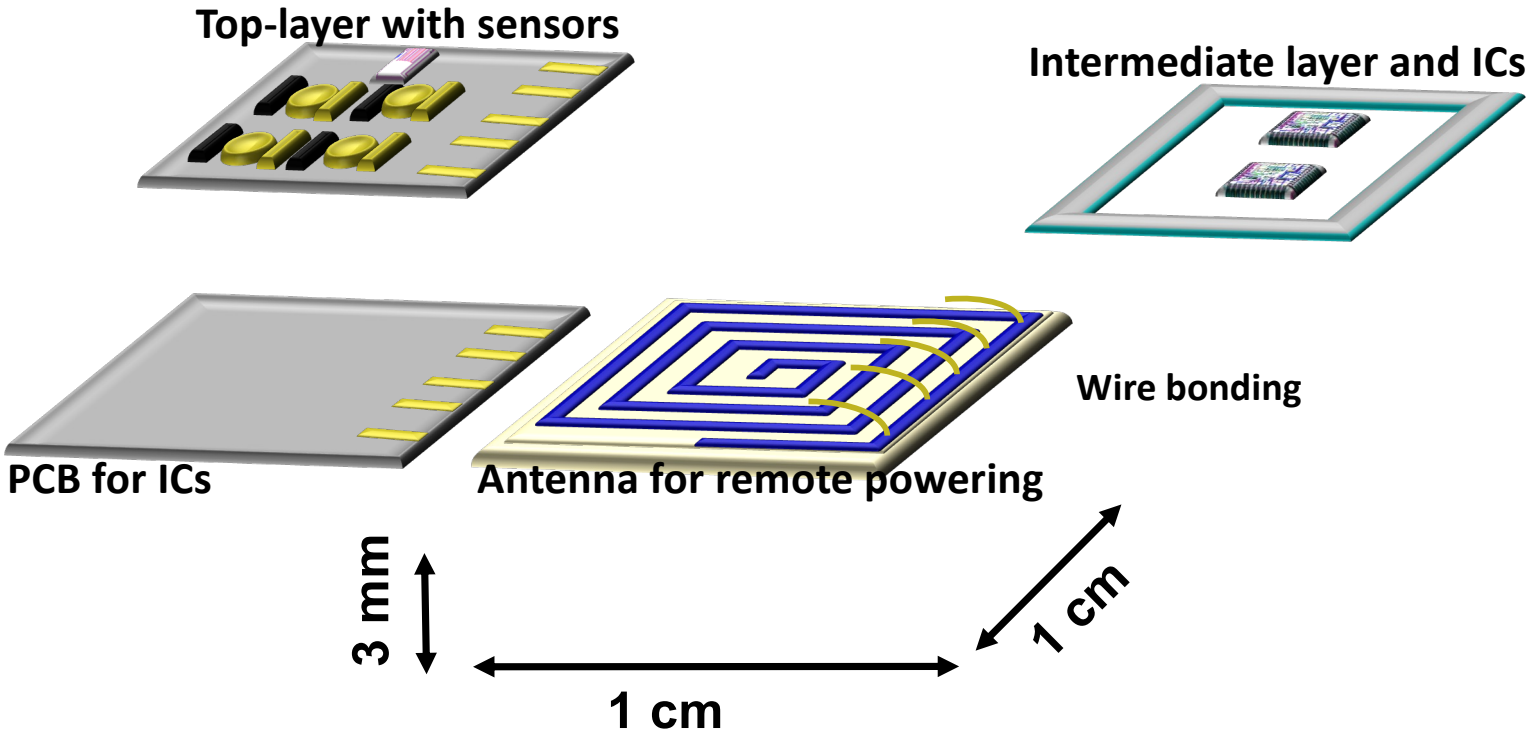


The Air Pouch Model in mice has been used to test the monitoring implants

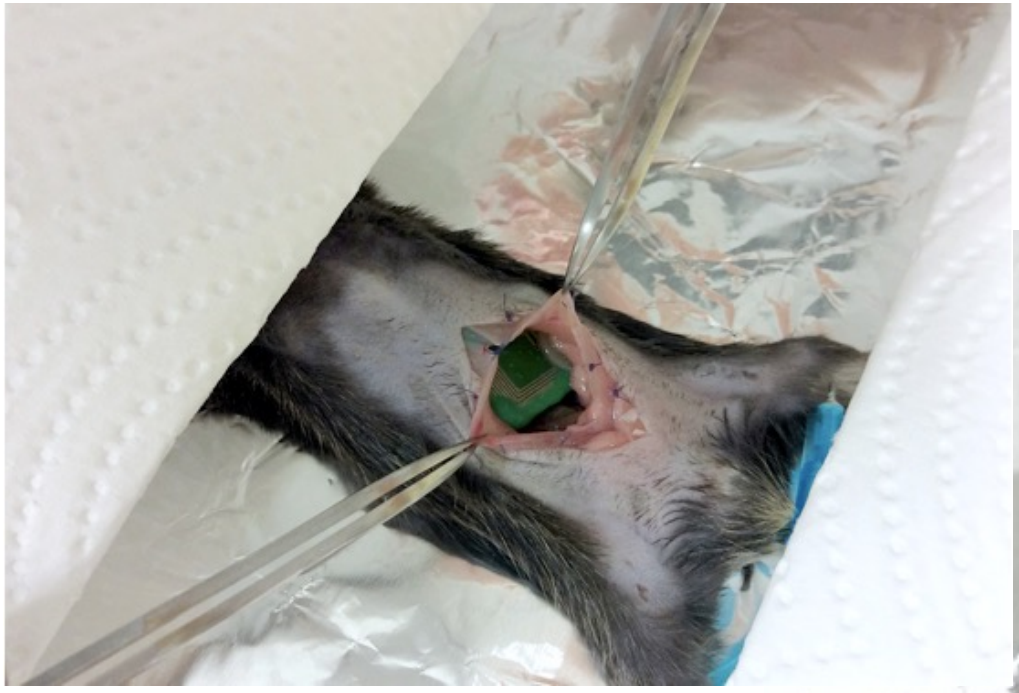
Full Biocompatible System Packaging

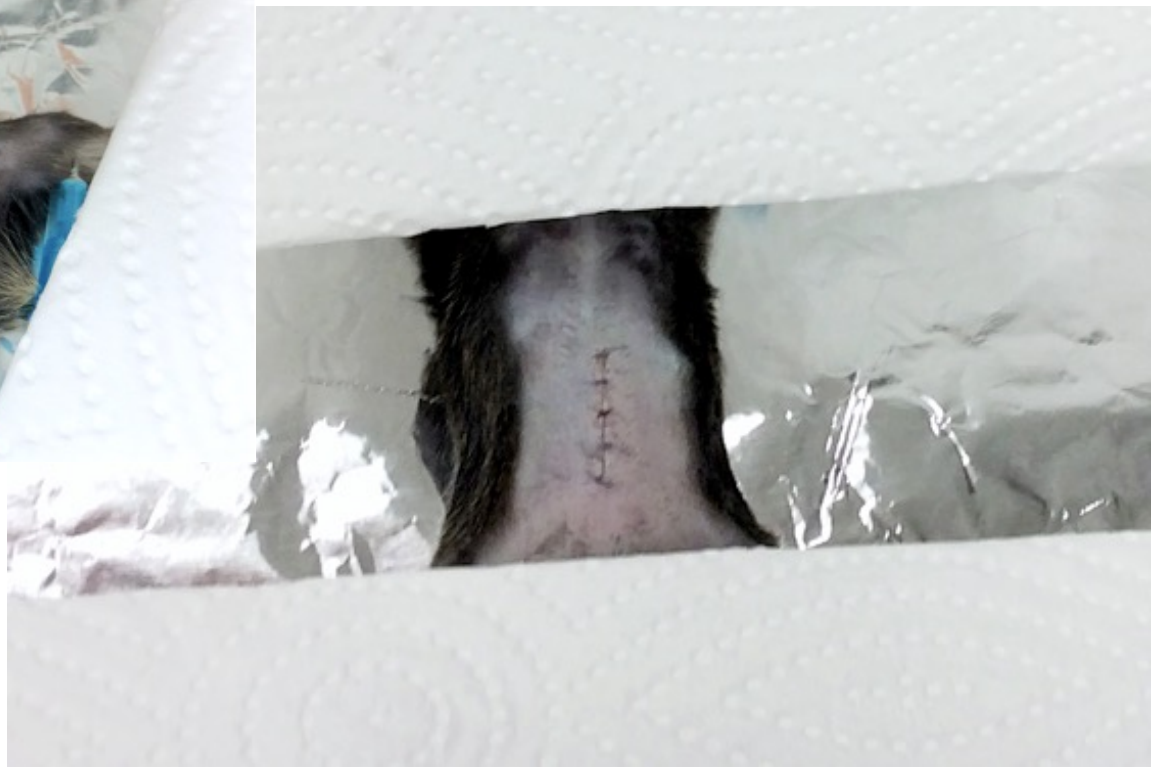


Under-the-Skin Device



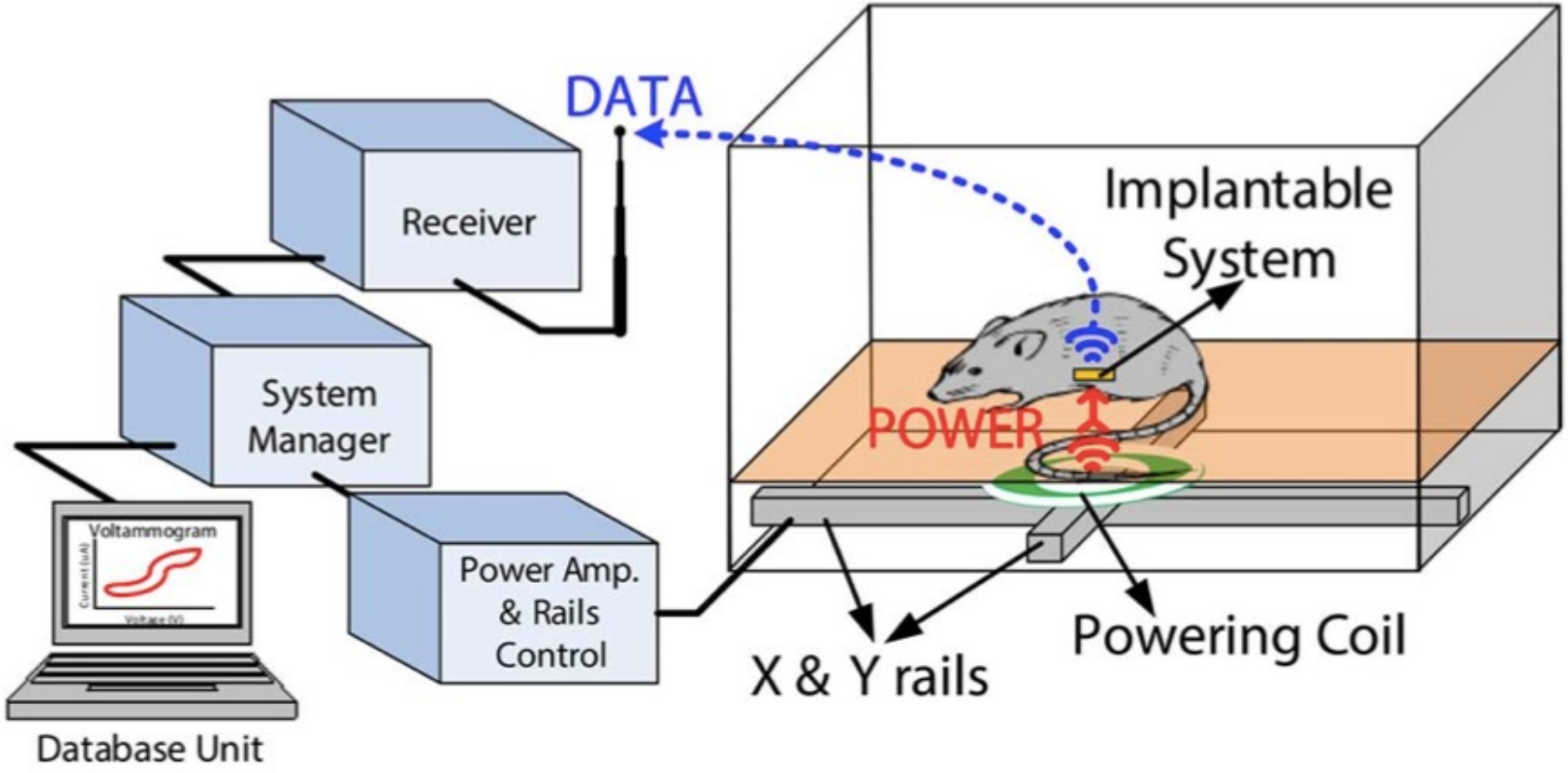
Under-the-Skin Device: implanted





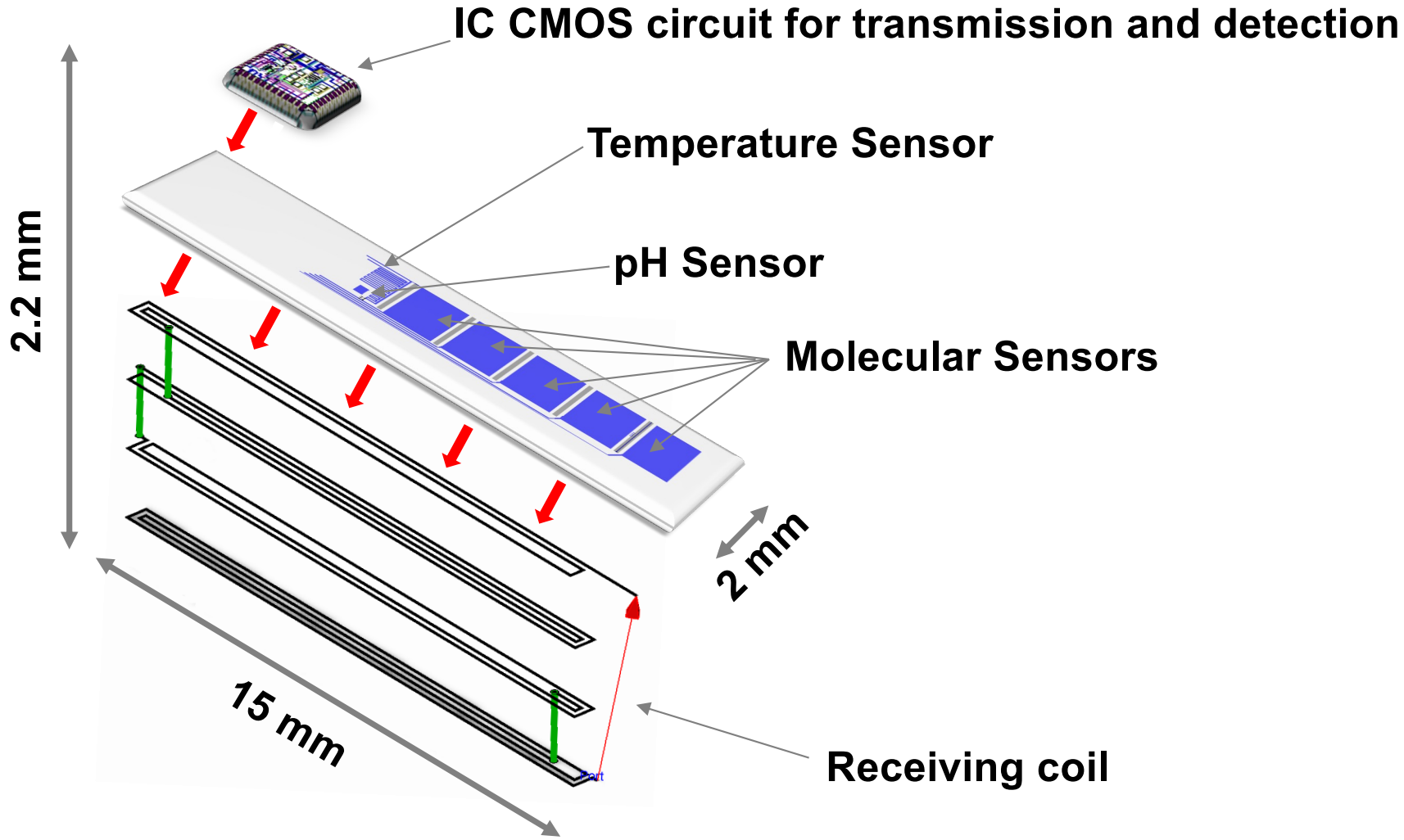
The whole device (with ARIC embedded) was implanted in the peritoneum of the animal and the suture after the surgery

Remotely Powered Implantable Devices for Animal Metabolism Telemetry



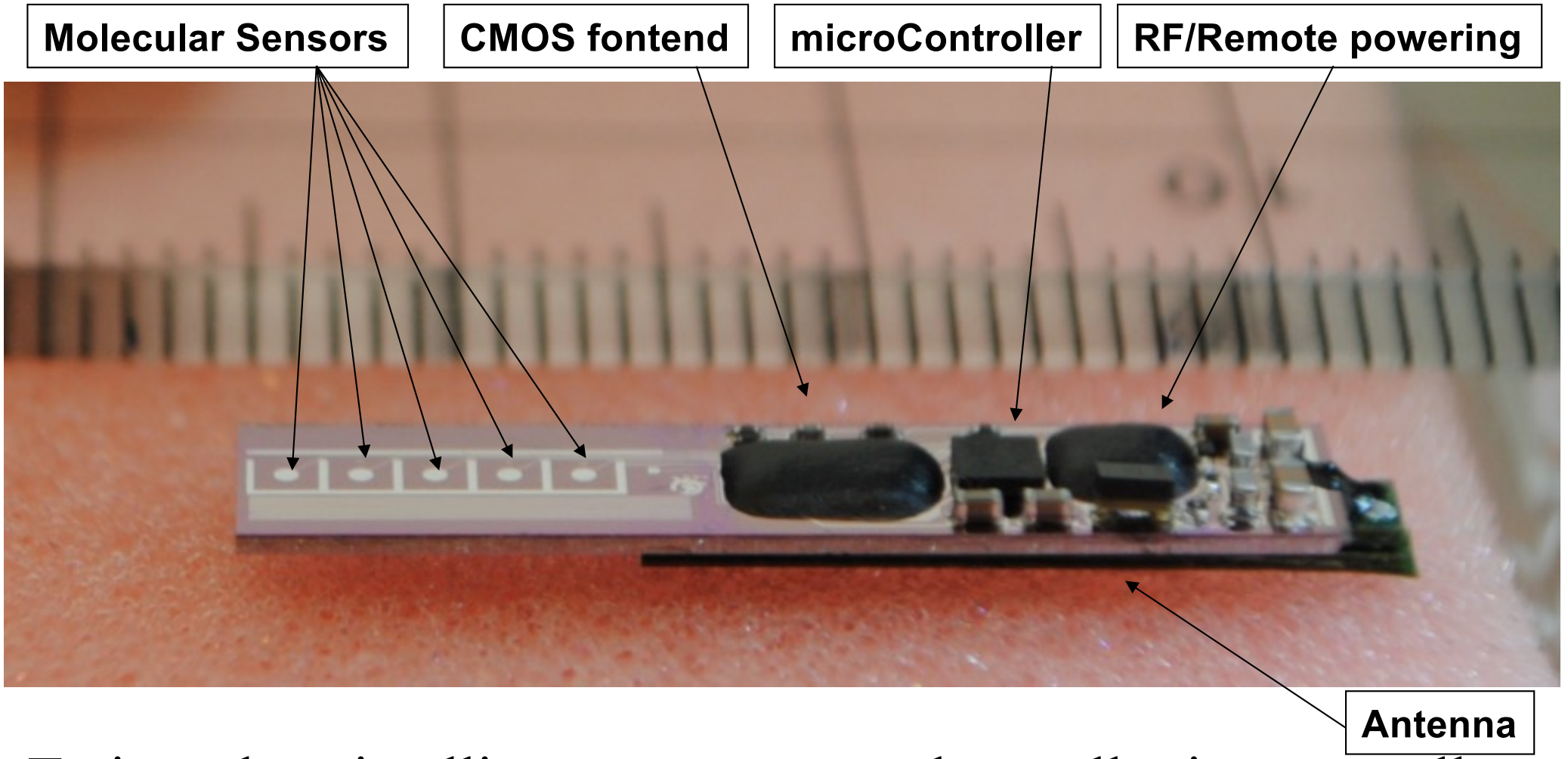
The design of remotely powered implantable systems for continuous monitoring of small-animal metabolism

Under-the-Skin Device



Minimally invasive with size within that of a surgery needle

Subcutaneous Biochip

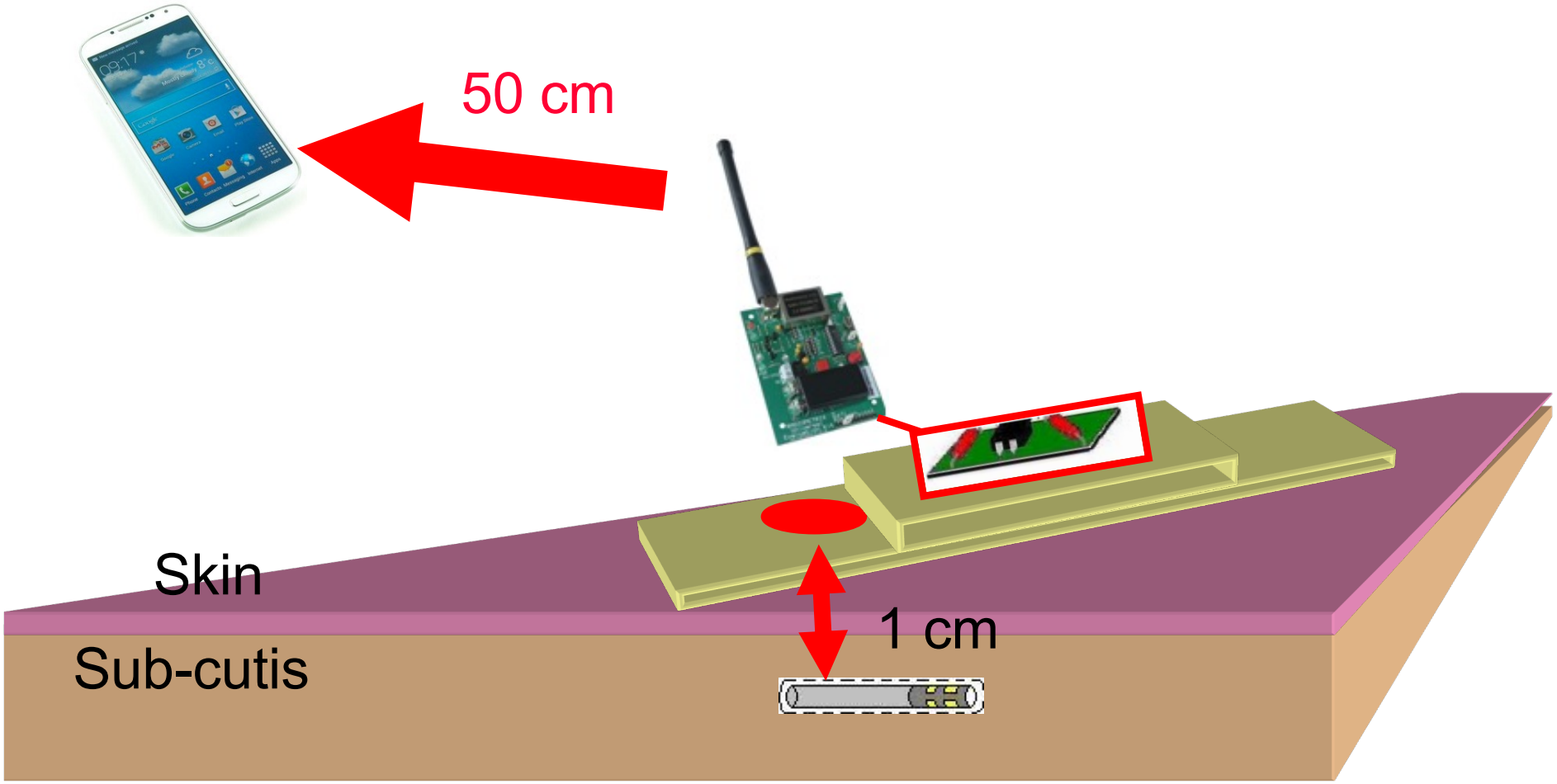


To introduce intelligence, an extremely small microcontrollers is introduced into the CMOS interface too

Injectable ECG monitoring by Medtronic

Mark Phelps by Medtronic, and the Reveal LINQ™ system

Under-the-Skin Devices with remote powering



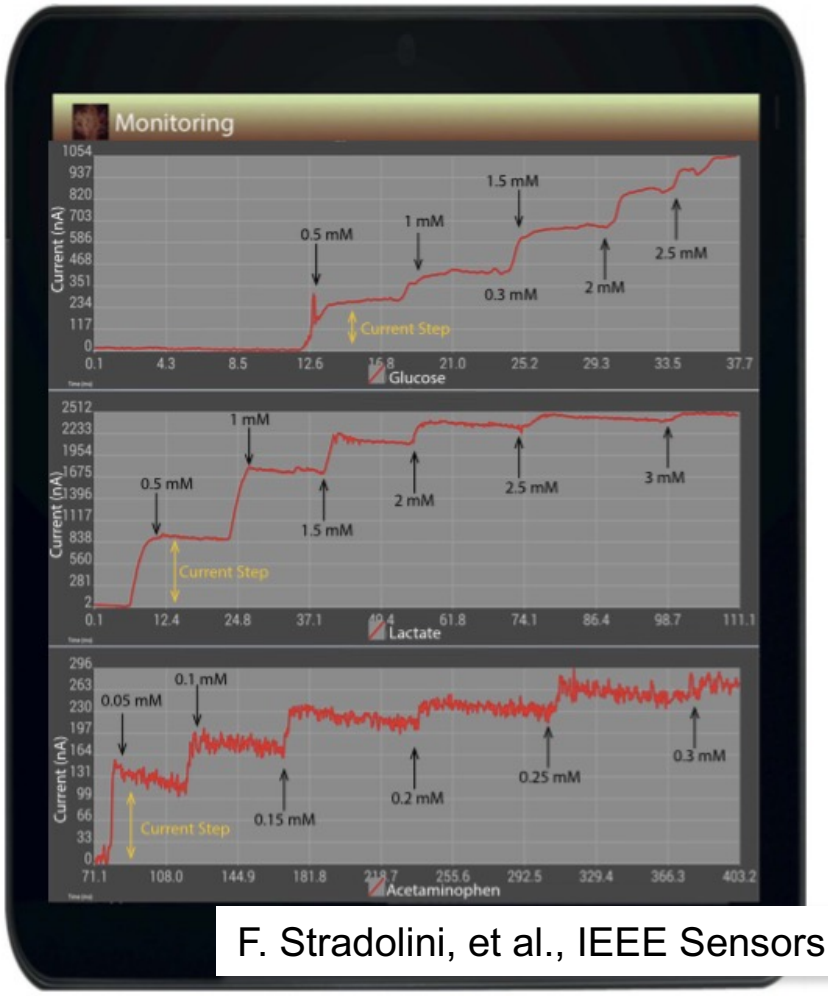
An antenna very close to the chip is required for the remote powering

Android Users Interface

Glucose →

Lactate →

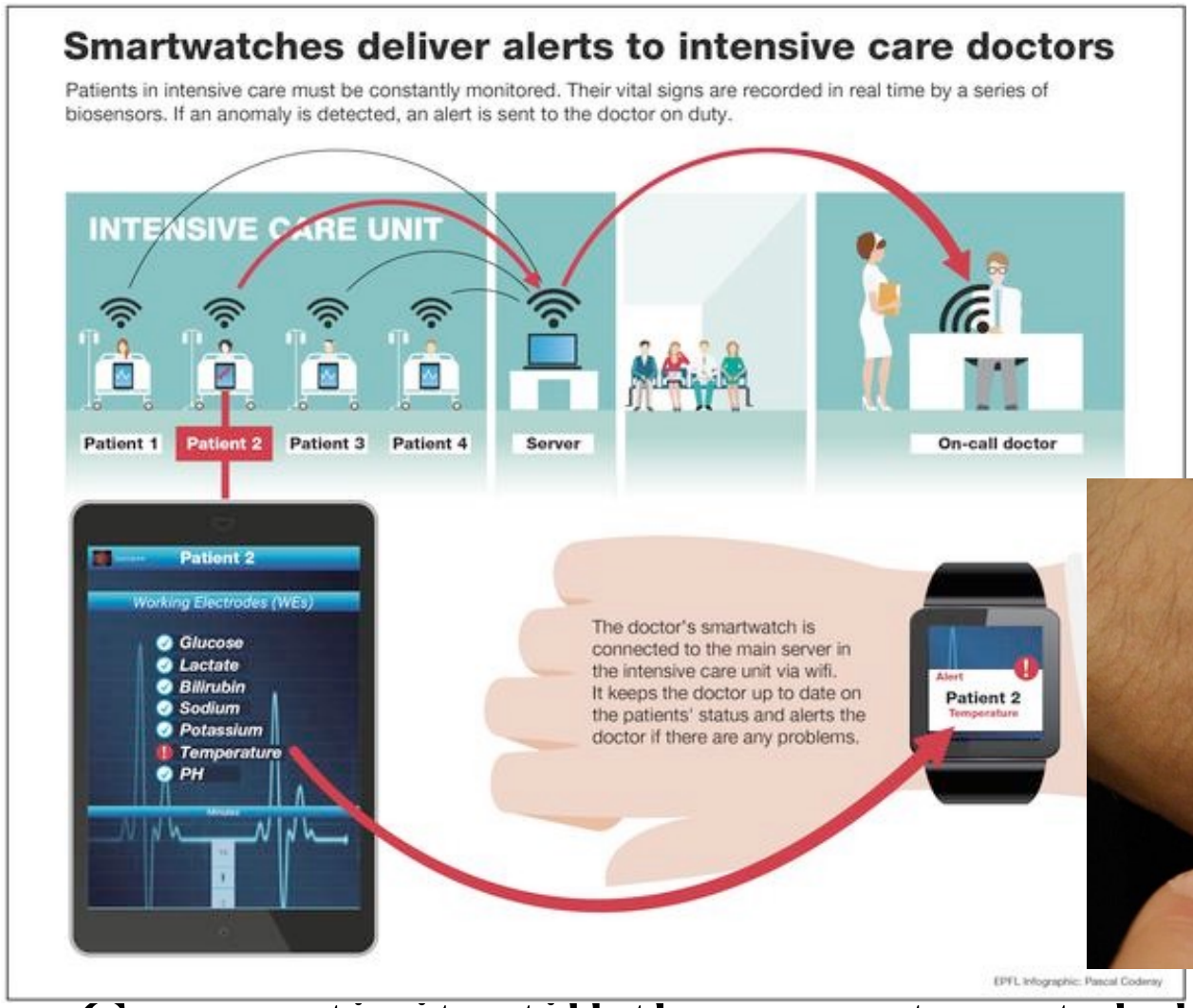
Paracetamol →



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

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

Connectivity with Smart-Watch



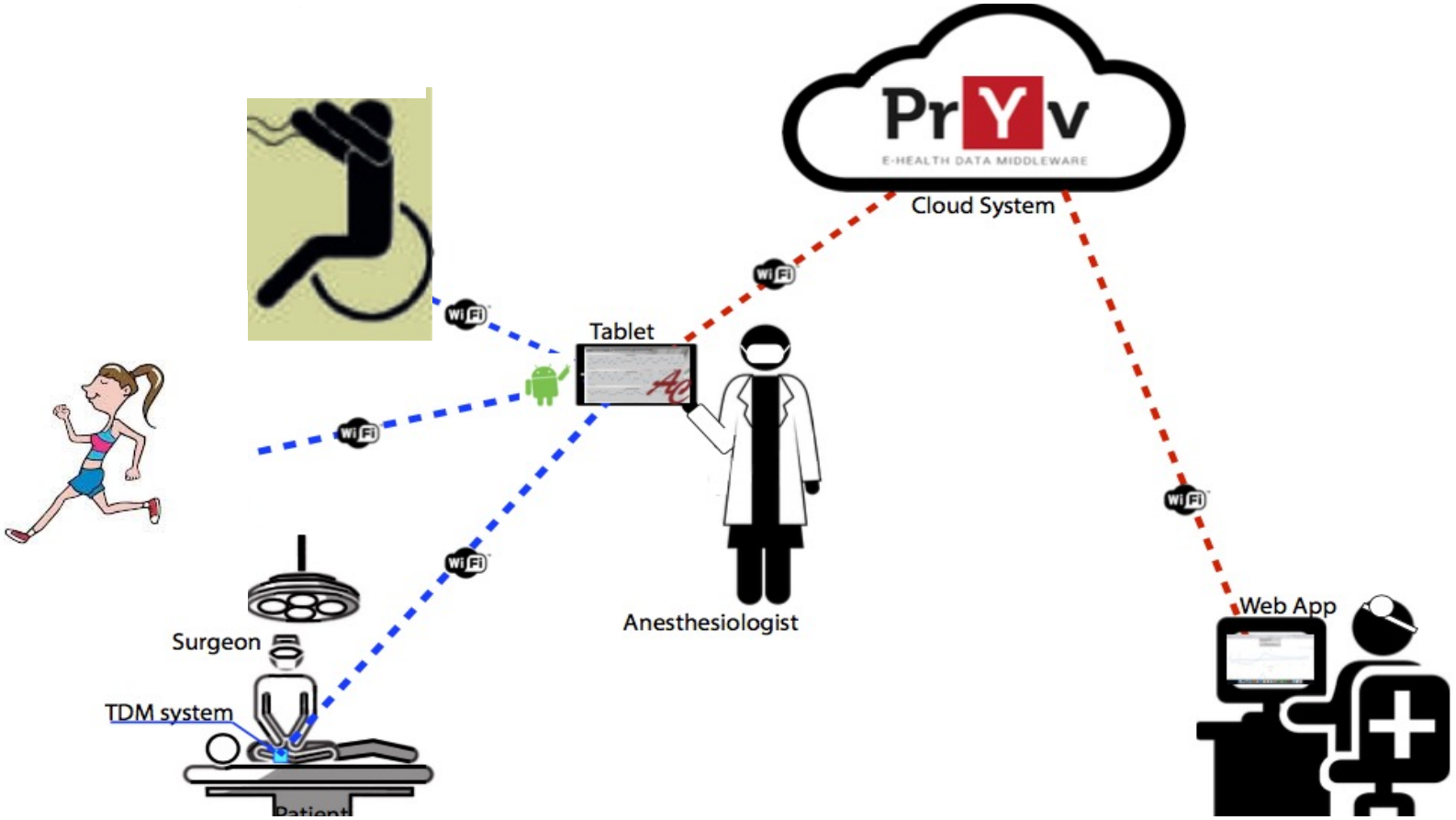
Live Demo @ BioCAS17

YouTube

F. Stradolini, et al., MOBILHEALTH 2016

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

Connectivity to the Cloud



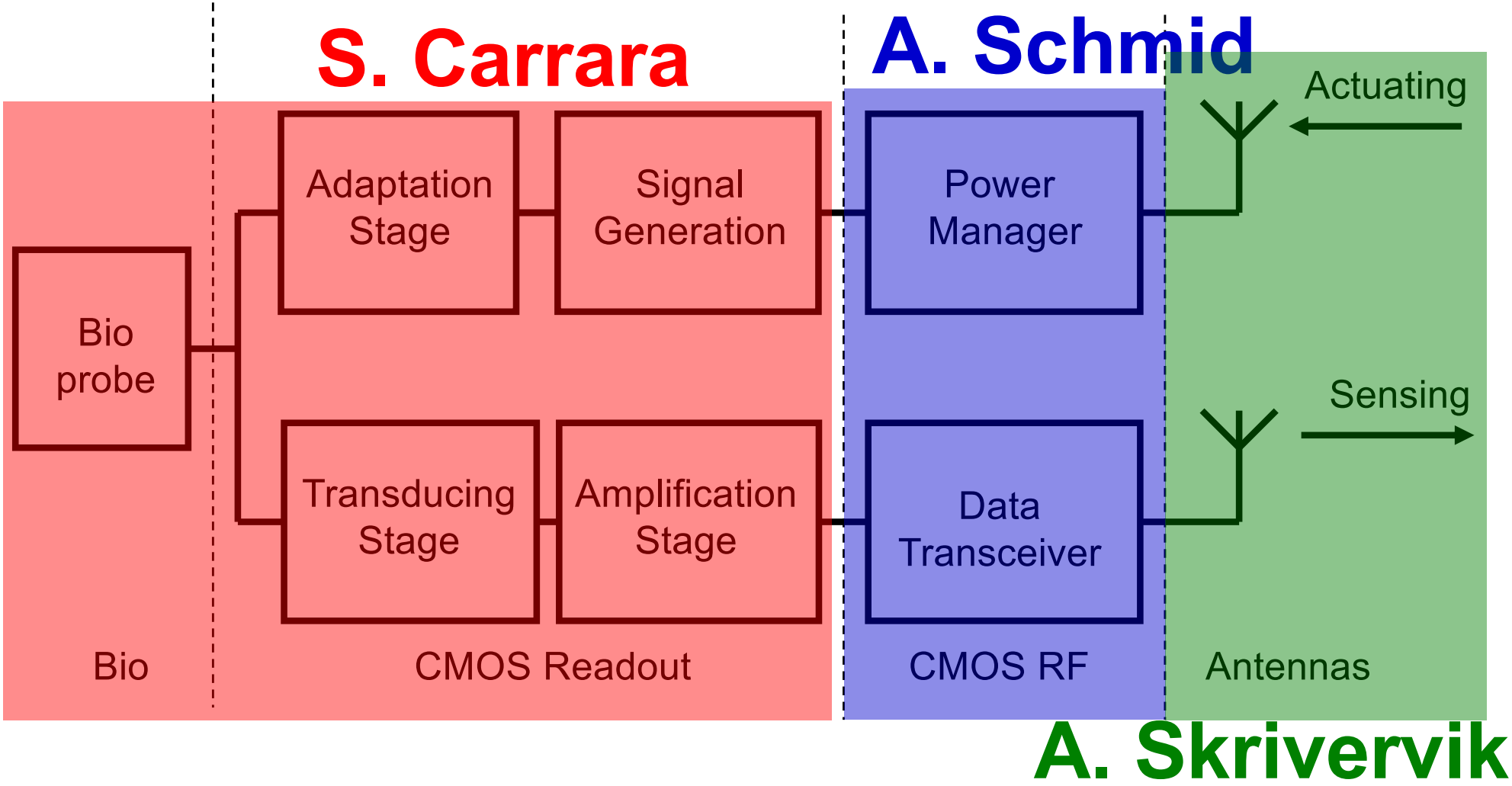
N.Tamburrano, et al., IEEE ISCAS 2018, invited paper

Connectivity by through the cloud has been successfully investigated too

In Summary

- **We can realize Bio/CMOS analog circuits for electrical and electrochemical measure in humans**
- **We can realize low-cost biochips based on CMOS technology, inject printing and other easy and low cost technologies, including microfluidics**
- **We can then provide reliable measures of many human parameters as biomarkers**
- **Automatic and continuous measurements of the humans health is actually feasible with our personal electronics and biochips, including Multisensory Platform !**

Designing Bio/CMOS interfaces



The Bio/CMOS interface