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IEEE SENSORS 2013

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Tutorials: November 3, 2013 Conference: November 4-6, 2013

Baltimore, November 3rd, 2013

Tutorial

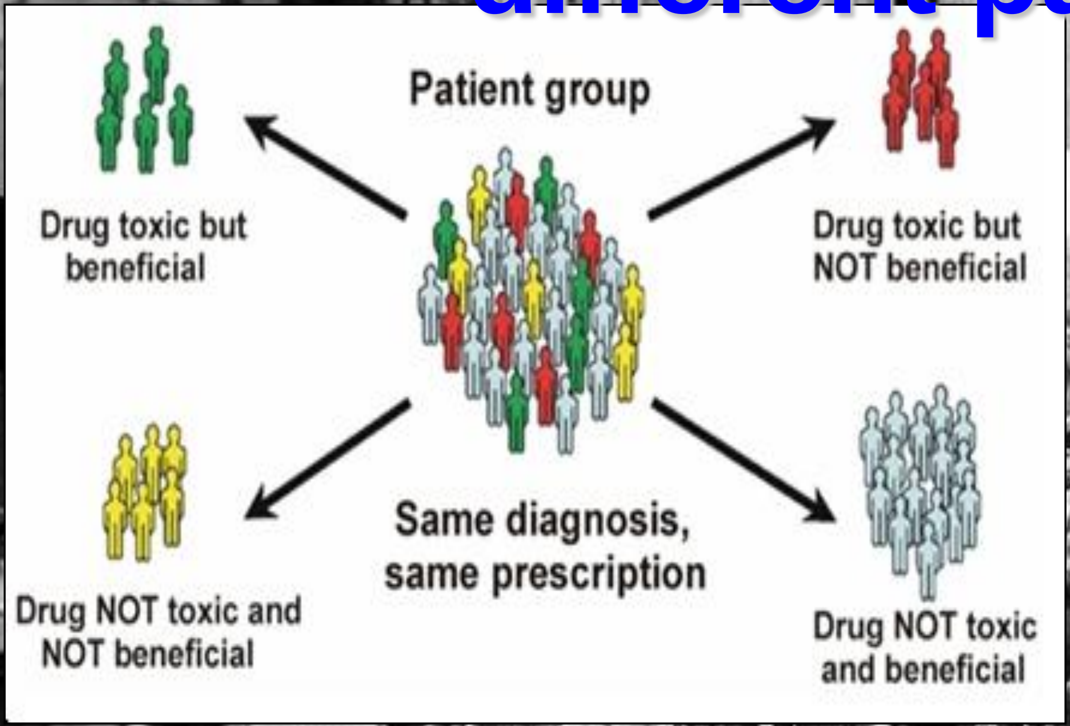
Technologies for an Implantable Nano-Bio-Sensing Laboratory

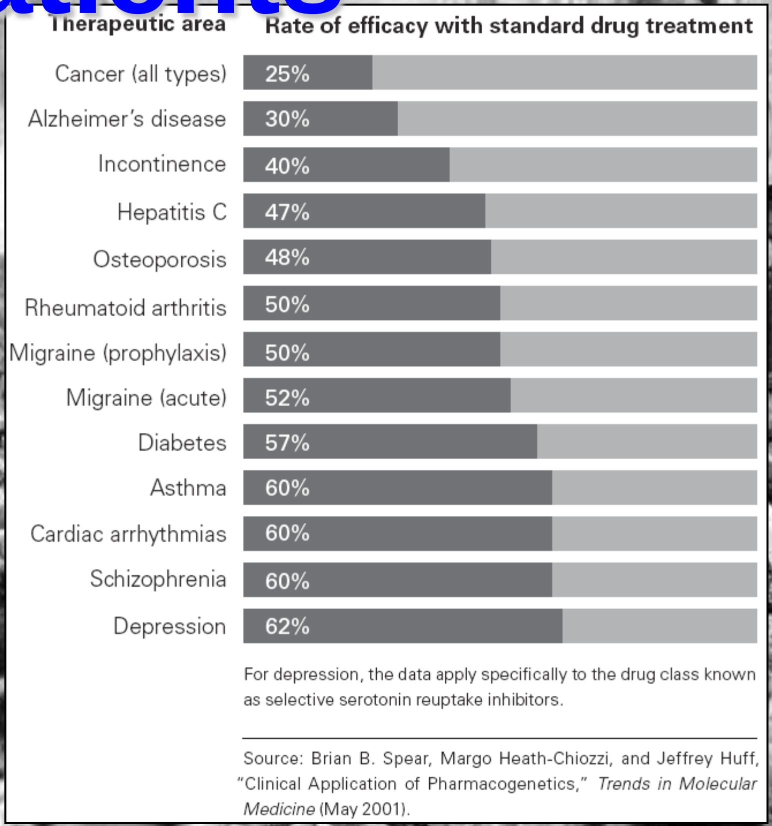
SANDRO CARRARA

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

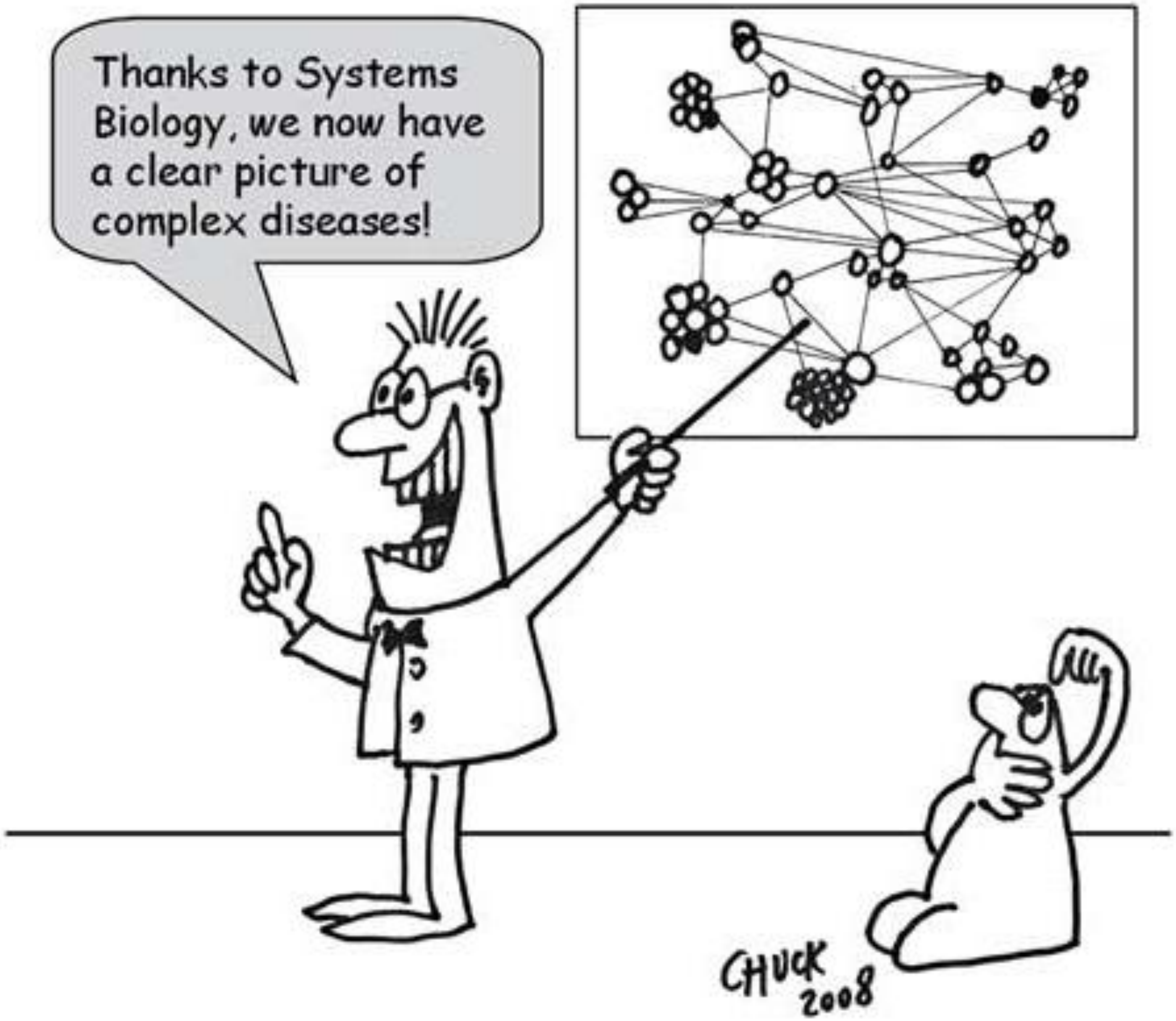
Laboratoire des Systèmes Intégrés (LSI)

Different outcomes for different patients

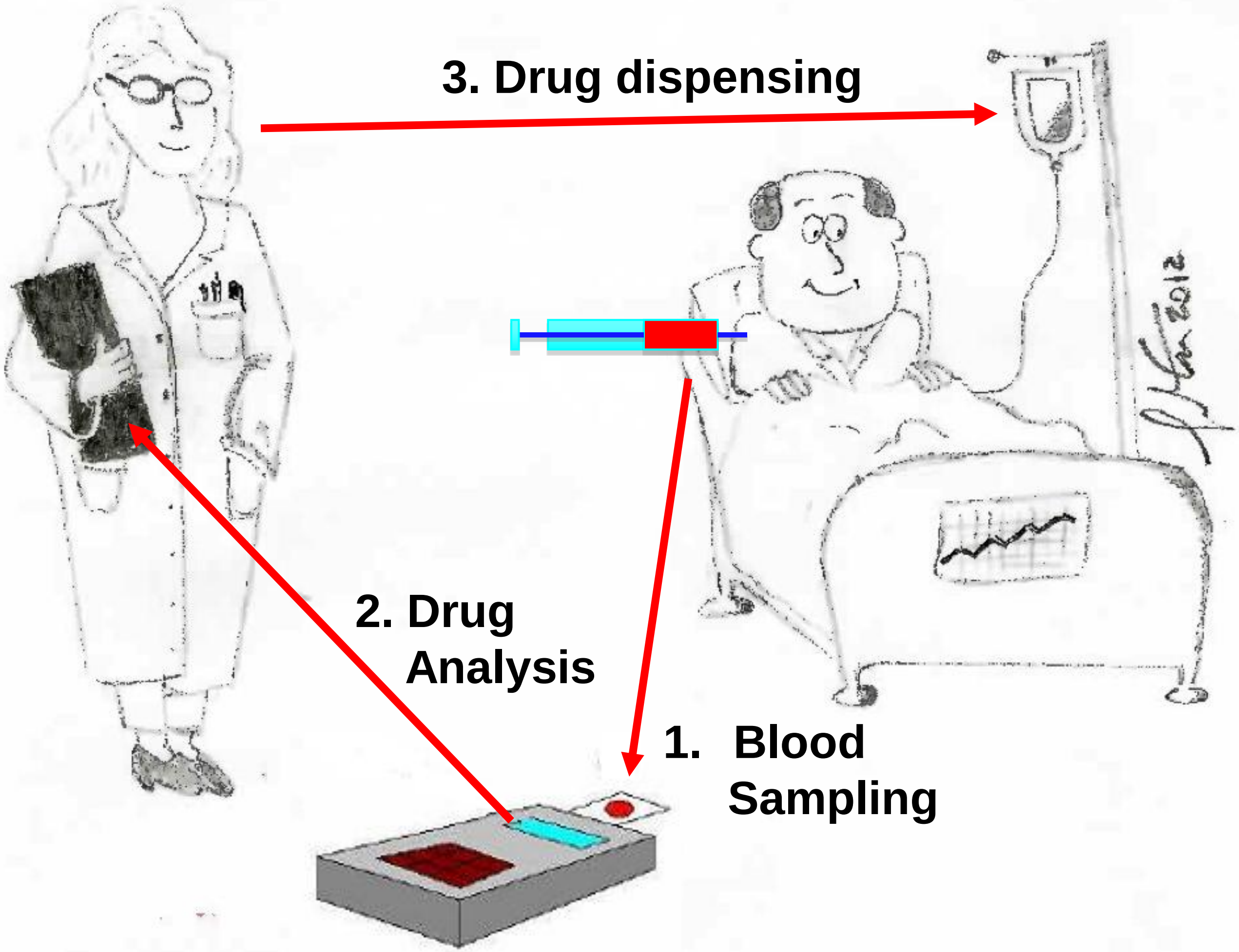




System Biology is not enough

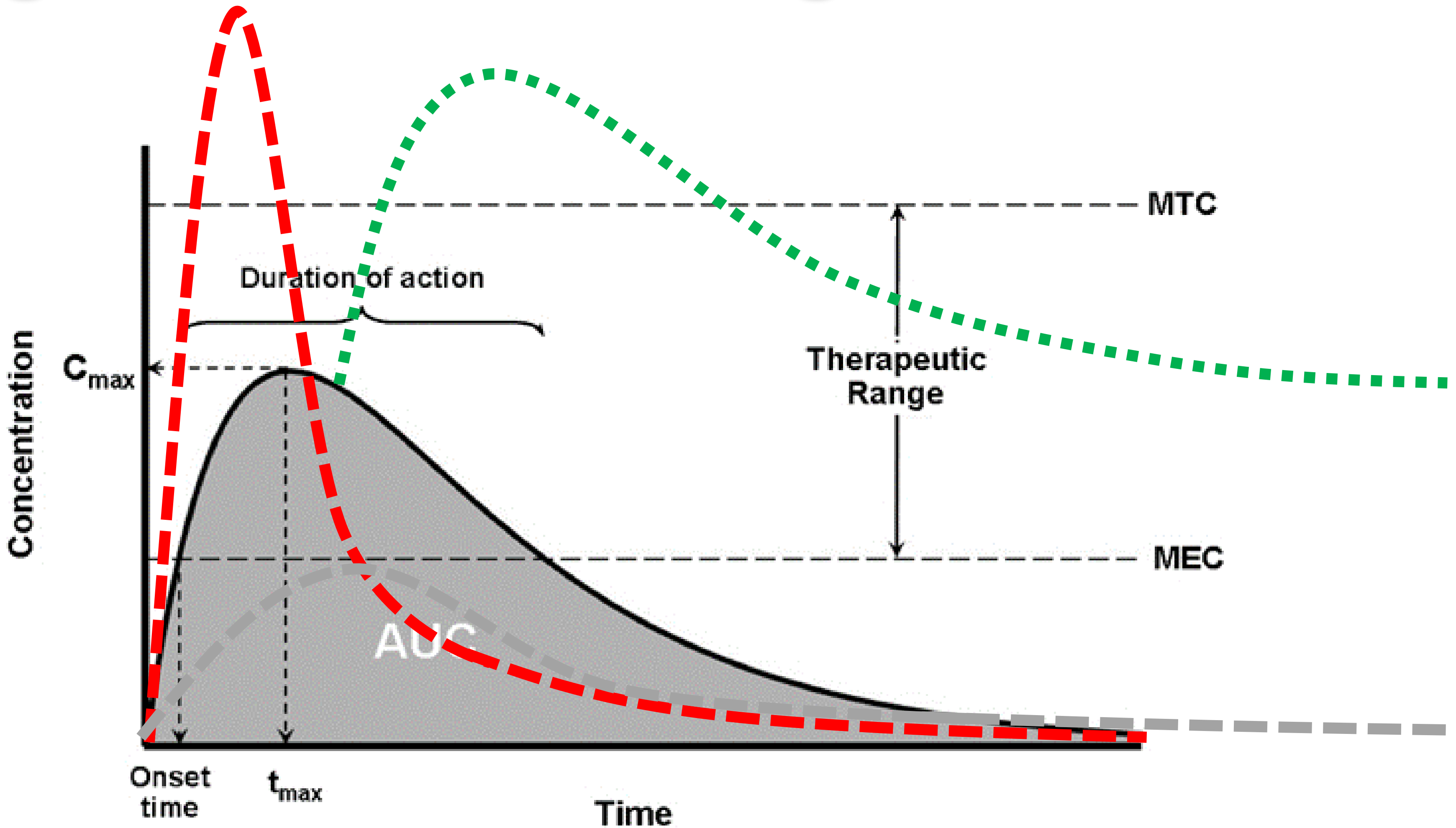


Personalized Therapy

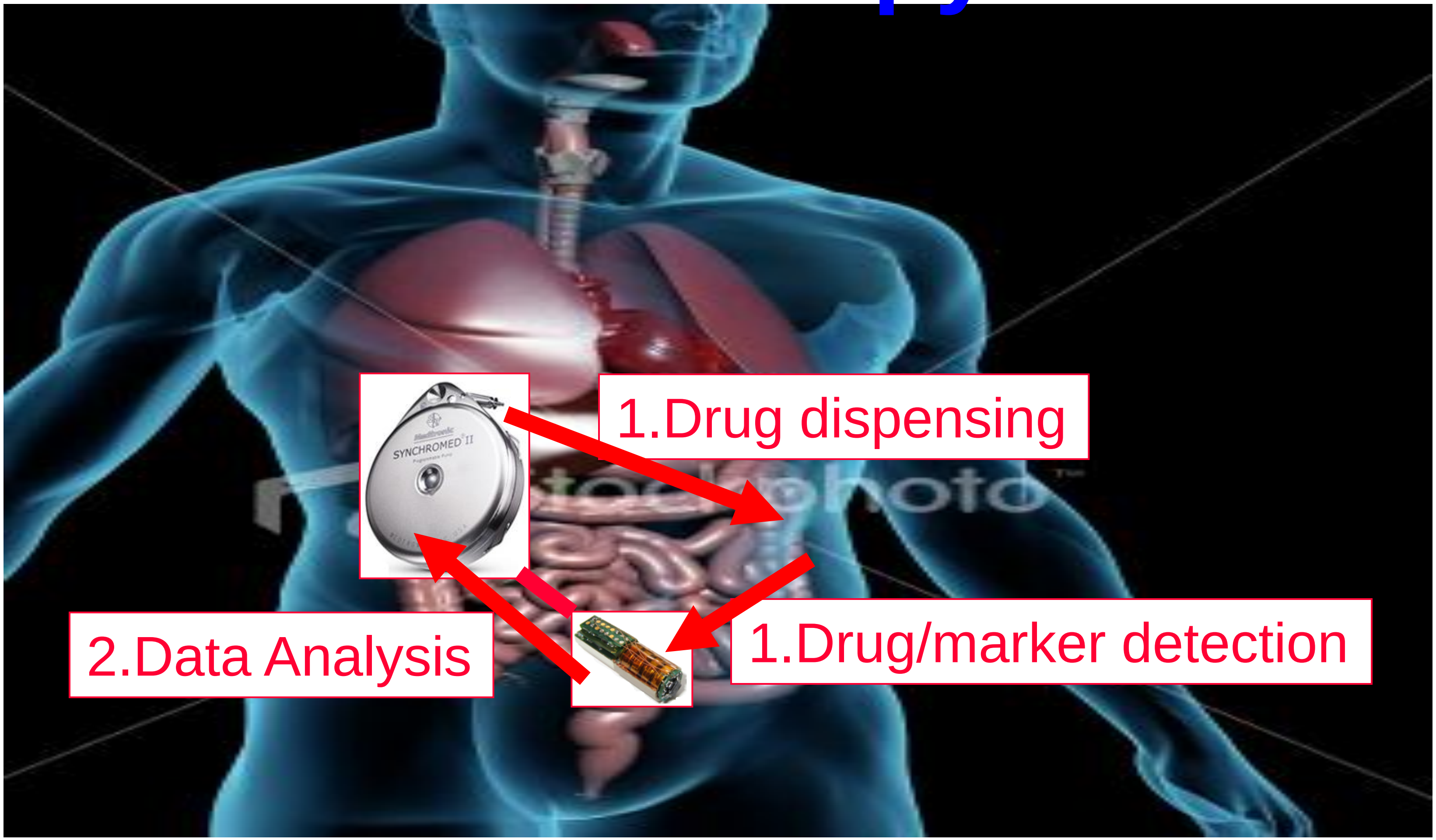


Development of Monitoring Point-of-Care Devices
is a key-factor for succeeding in Personalized Therapy

Personalized Therapy: the right dose in the right moment!

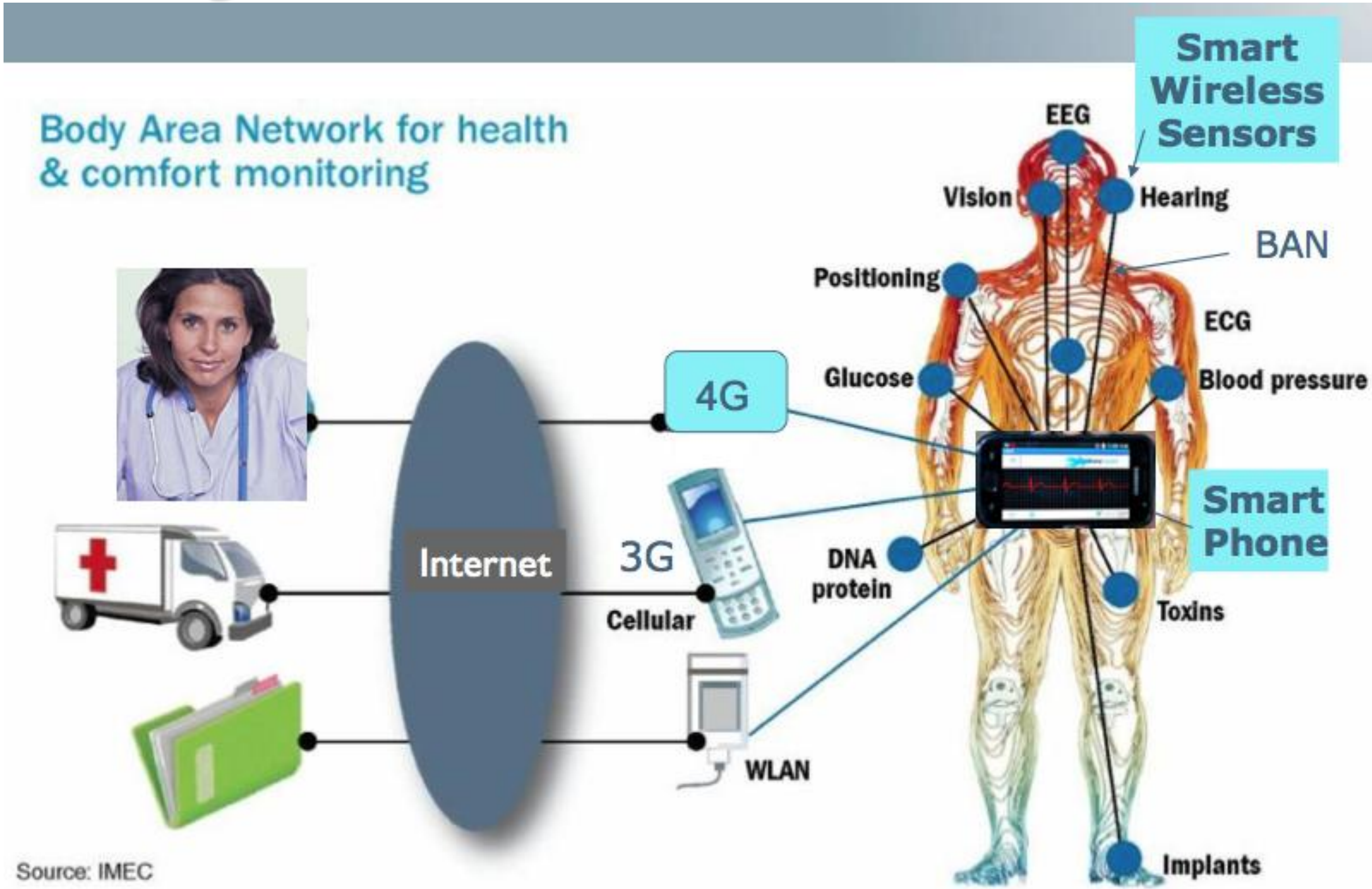


Personalized Therapy and I.M.D.



The Development of new Implantable Medical Devices is a key-factor for succeeding in Personalized therapy

Fully Connected Human++

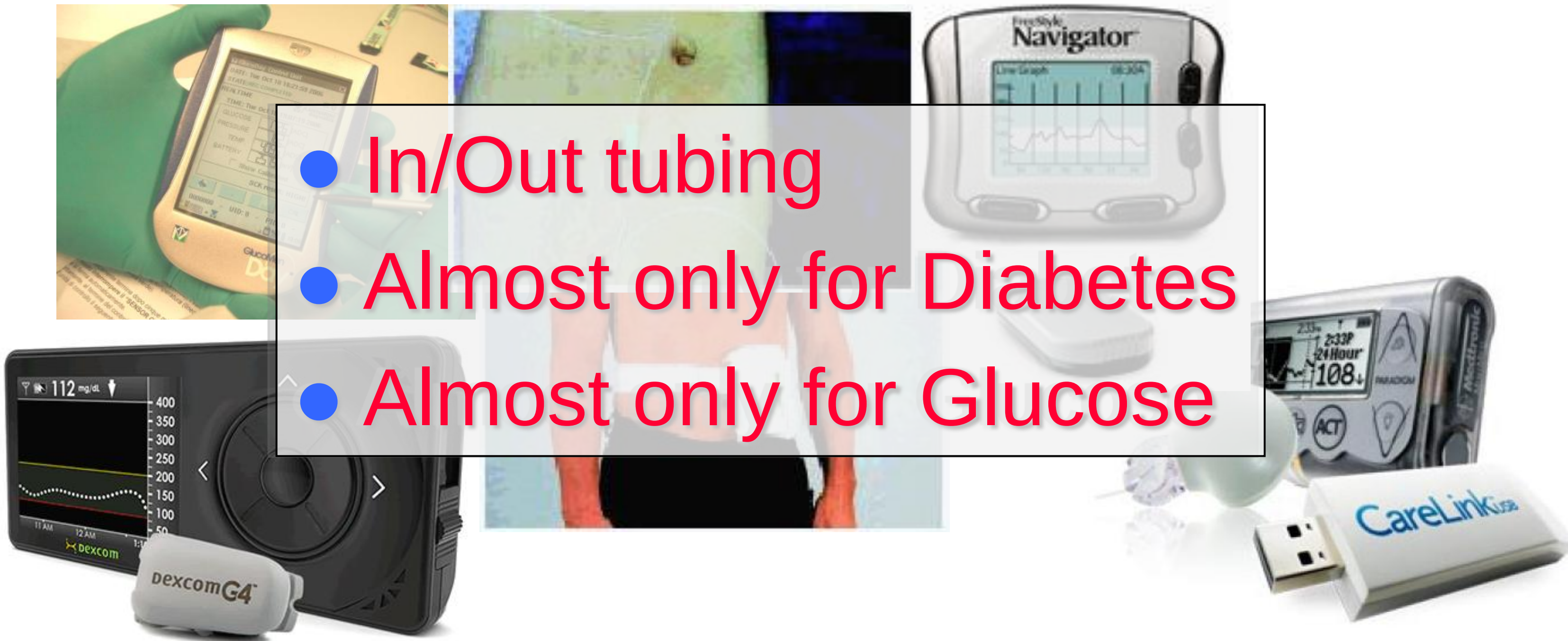


Courtesy, Hugo De Man

State-of-the-Art is limited

A. Menarini GlucoMenDay

Abbott FreeStyle Navigator



- In/Out tubing
- Almost only for Diabetes
- Almost only for Glucose

Dexcom SEVEN Plus

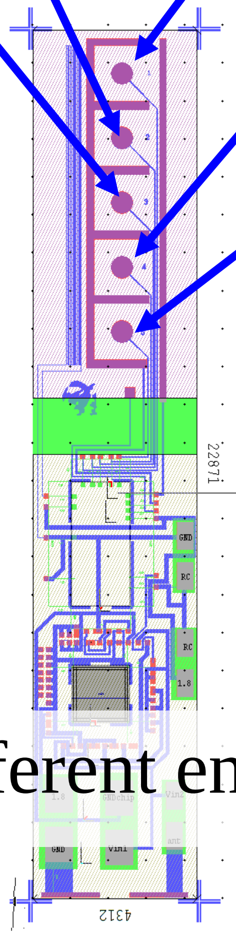
Medtronic MiniMed Guardian

Continuous Monitoring Systems typically consist of a biosensor coupled with a microdialysis sampling system

Multi-Panel Platforms for Human Metabolism

ATP-ase	Lactate oxidase	Glucose oxidase	Lipoxygenase
P450 11A1	P450 5A1	P450 4A11	Cholesterol oxidase

Probe enzymes



- Glucose
- Lactate
- Cholesterol
- ATP
- Drugs

Different enzymes sense different human metabolites

P450 for Drugs Monitoring

RH (e.g. benzphetamine)

O_2

From electrode

$2e^-$

NADPH + H^+

Drugs detection !

Cytochrome P450 2B4

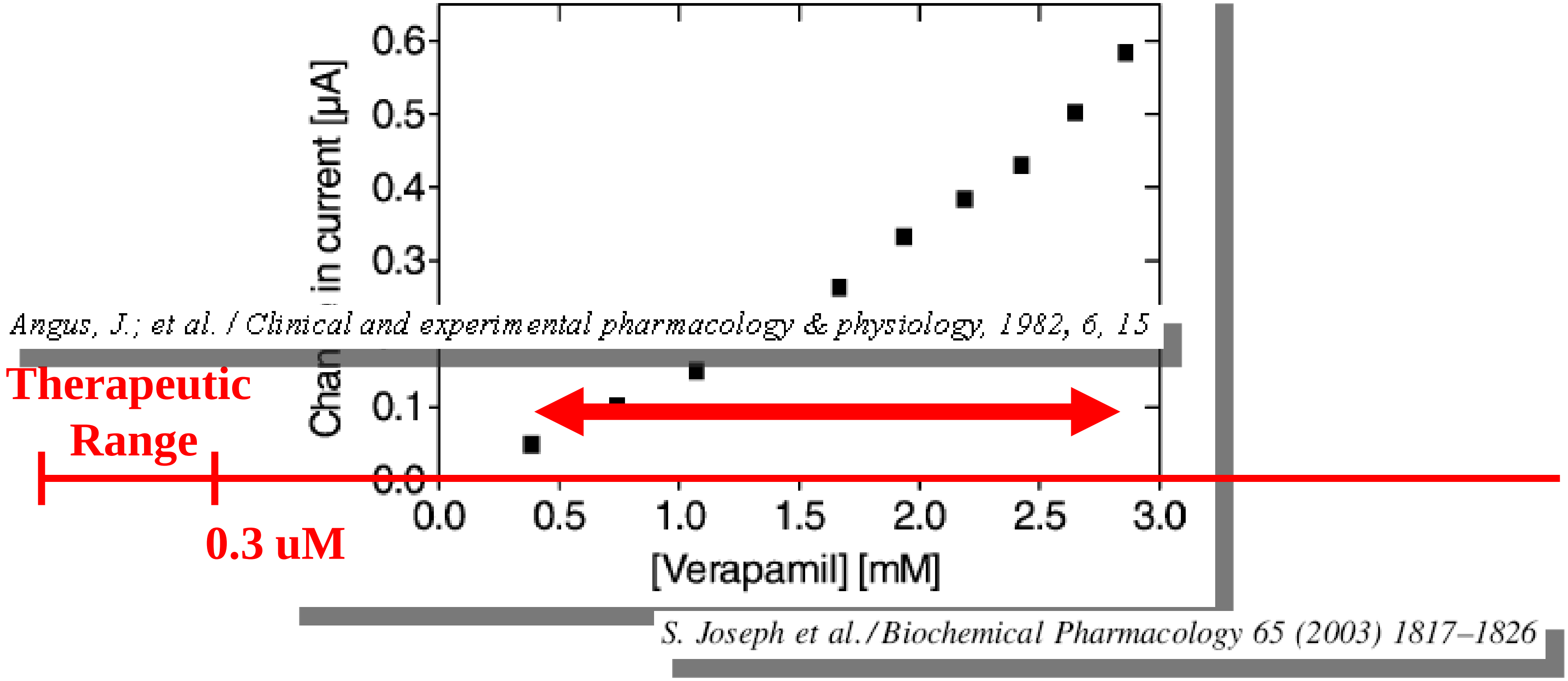
NADP

H-O-H

R-OH Oxidized form

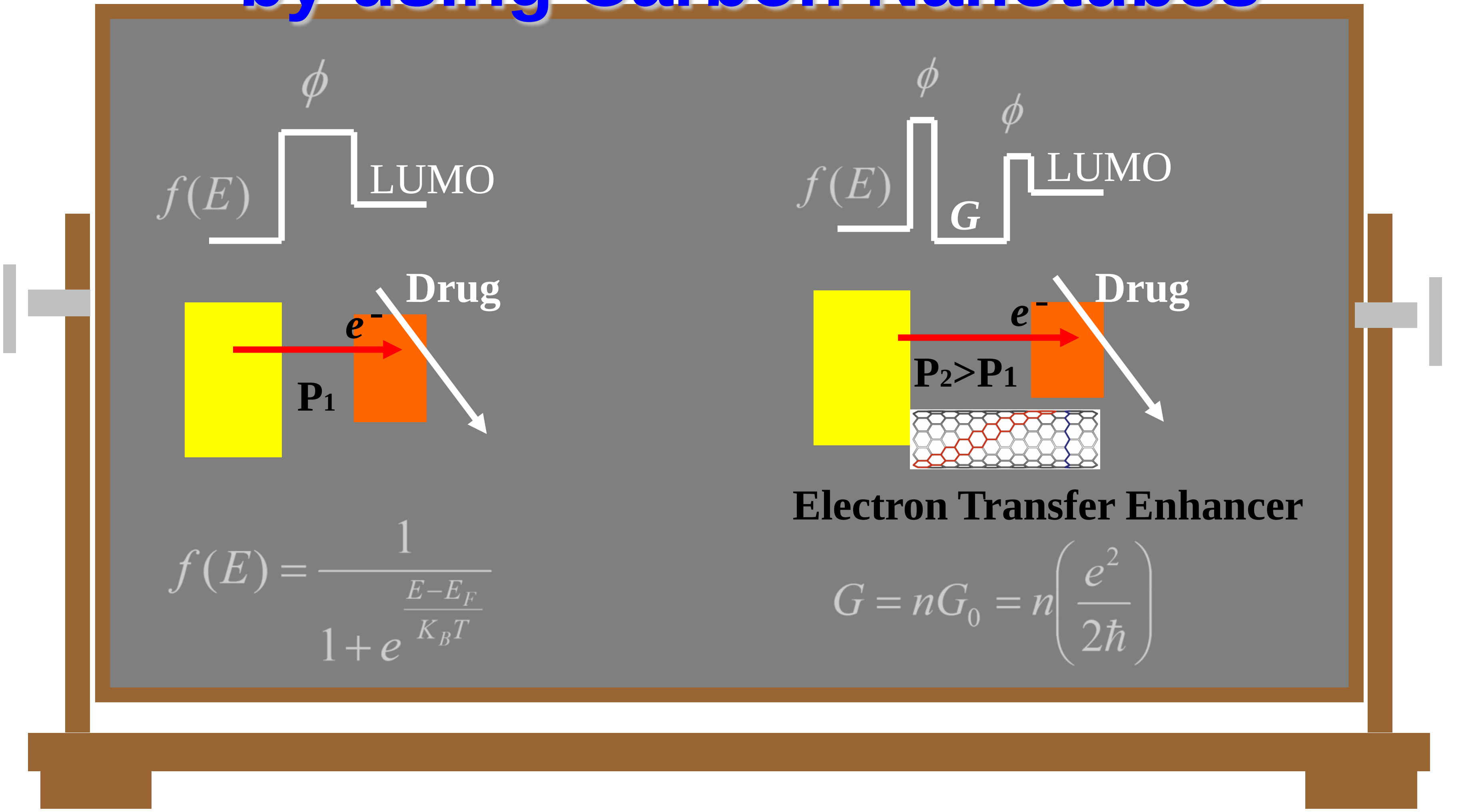
more soluble
then
faster secreted

Problems on Detection Limits

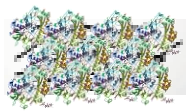


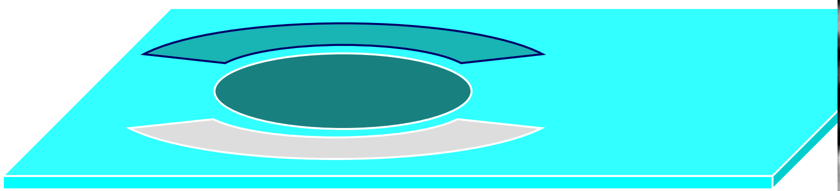
Detection of verapamil by 3A4, an antihypertensive drug, was from 400 µM to 3mM while its therapeutic range is below 0.3 µM

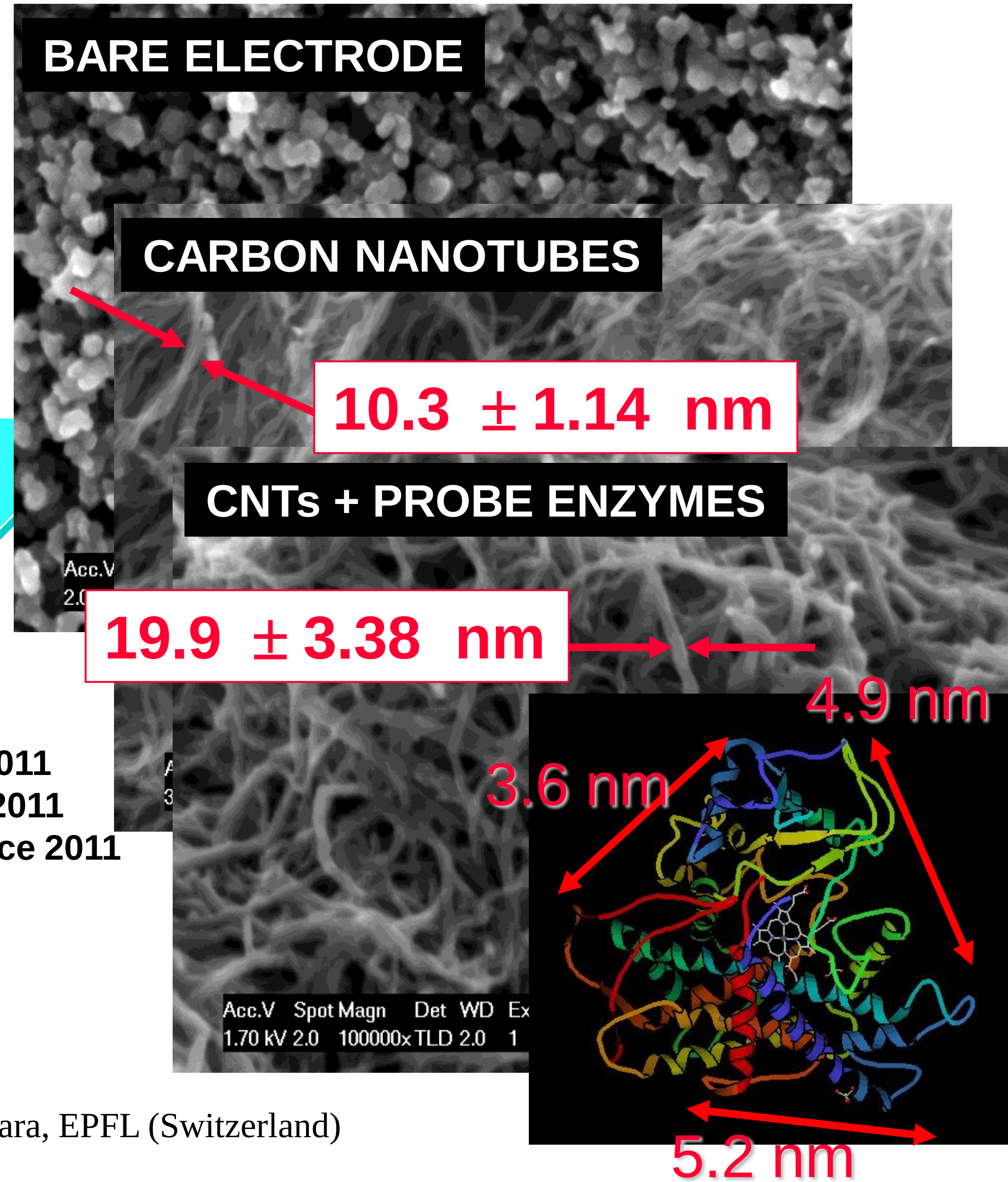
An improved P450/Electrode coupling by using Carbon Nanotubes



Nano-Bio-Sensors integration



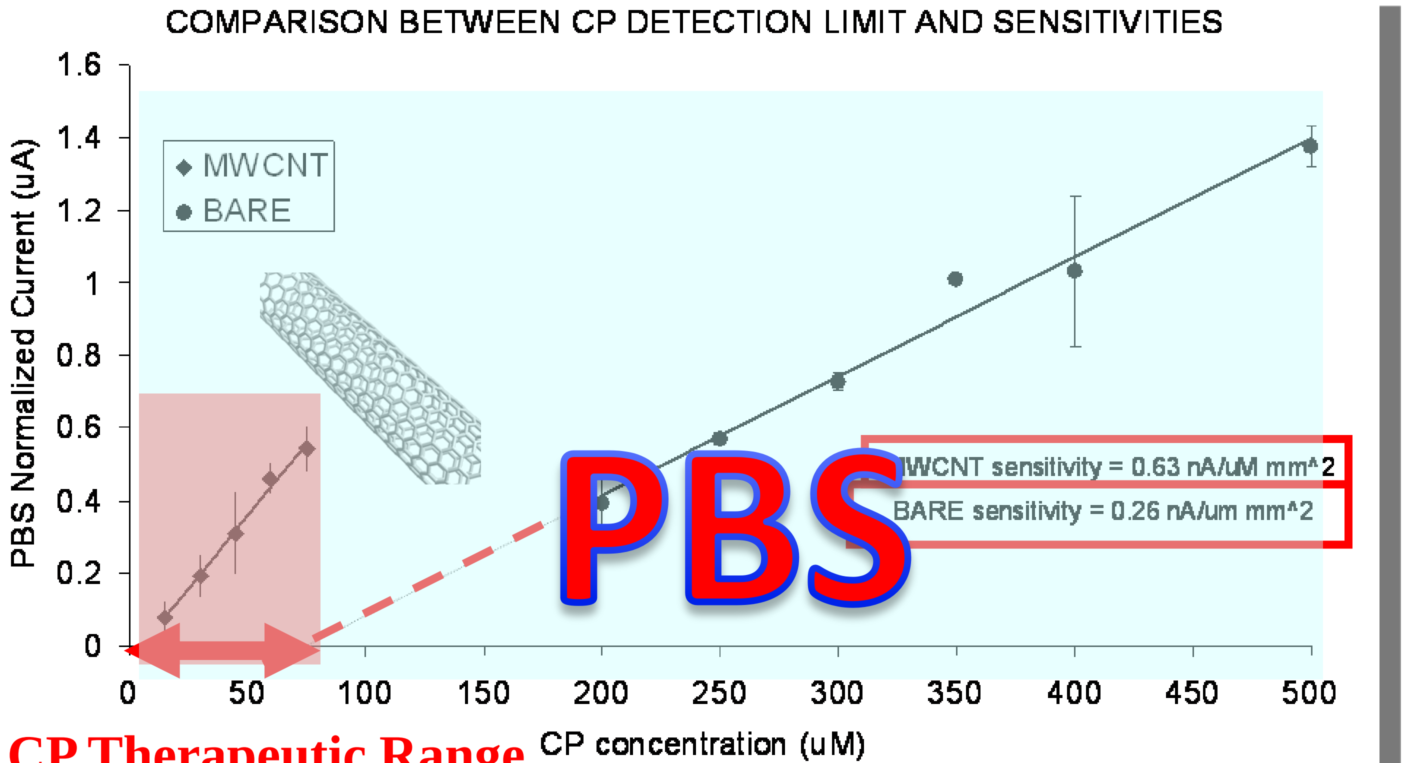




Boero, Carrara et al. / IEEE PRIME 2009
Boero, Carrara et al. / IEEE ICME 2010
De Venuto, al. et Carrara / IEEE Senors 2010
Boero, Carrara et al. / Sensors & Actuators B 2011
Carrara et al. / Biosensors and Bioelectronics 2011
Boero, Carrara et al. / IEEE T on NanoBioScience 2011

Improved Detection Limit

S. Carrara et al. / Biosensors and Bioelectronics 26 (2011) 3914–3919



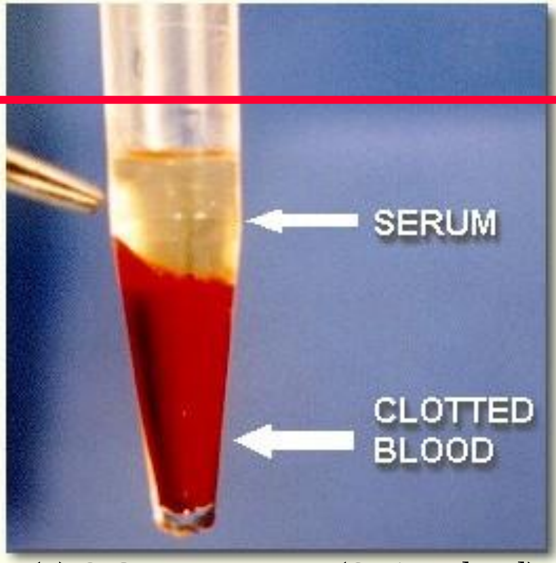
CP Therapeutic Range

Cyclophosphamide (CP), an anti-cancer agent, is detected by P450 3A4 in its therapeutic range

Detection of Several Drugs

C. Bay-Rossi, G. De Micheli, S. Carrara, *Sensors 2012, 12, 6520-6537*

Drugs	Pharmacological range (µM)	P450 enzyme	Sensitivity (nA/µM*mm²)		Detection limit (µM)	
			PBS	Serum	PBS	Serum
Cyclophosphamide	3-77	2B6	1	0.3	2	14
Ifosfamide	10-160	3A4	1.6	0.4	2	7
Ftorafur	1-10	1A2	8.8	3.5	0.6	1
Etoposide	34-102	-	74	9	0.05	0.5



(c) S.Carrara, EPFL (Switzerland)

Breast cancer drugs cocktail

- cyclophosphamide, methotrexate, and fluorouracil (CMF)[8][11];
- fluorouracil, doxorubicin, and cyclophosphamide (FAC)[8];
- cyclophosphamide, doxorubicin and 5-fluorouracil (CAF)[9];
- fluorouracil, epirubicin, and cyclophosphamide (FEC)[8][11][12];
- fluorouracil, doxorubicin, and cyclophosphamide [11][12];
- Ifosfamide, Carboplatin, Etoposide (ICE)[9];
- ifosfamide , metho- trexate and 5-fluorouracil (IMF)[9];
- cyclophosphamide, mitoxantrone, and etoposide[12].

[8] New England Journal of Medicine, The [0028-4793] Hortobagyi yr:1998 vol:339 iss:14 pg:974
GABRIELN. HORTOBAGYI, M.D.
[9] Cancer Chemother Pharmacol (1999) 44 (Suppl): S26±S28
A.Y. Chang, L. Hui, R. Asbury, L. Boros, G. Garrow, J. Rubins
[10] *Journal of Clinical Oncology*, Vol 22, No 12 (June 15), 2004: pp. 2284-2293
M. Ayers, W.F. Symmans, J. Stec, A.I. Damokosh, E. Clark, K. Hess, et al.
[11] *Journal of Clinical Oncology*, Vol 21, Issue 13 (July), 2003: 2600-2608
Manfred Kaufmann, Gunter von Minckwitz, Roy Smith, Vicente Valero, et al
[12] The Lancet [0140-6736] Weiss yr:2000 vol:355 iss:9208 pg:999
Raymond B Weiss, Robert M Rifkin, F Marc Stewart, Richard L Theriault, et al.

Different Drugs give peaks in different positions

Substrate/inhibitor of CYP2C9	K_m (μM)	K_i (μM)	CYP2C9 (mV)	E_{mid} CYP2C9 + substrate (mV)
Torsemide (s)	11.4		−41	−19
Diclofenac (s)	6.8		−41	−41
Tolbutamide (s)	120[a]		−41	−37
S-Warfarin (s)	6[b]		−41	−36
Sulfaphenazole (i)		0.1[c]	−41	−41
$CO_{(g)}$			−41	8

D.L. Johnson et al. / Biochemical Pharmacology 69 (2005) 1533–1541

$$i(V) = i_C(V) + \sum_{\forall k} A_k e^{-\frac{(V-V_k)^2}{\sigma_k^2}}$$

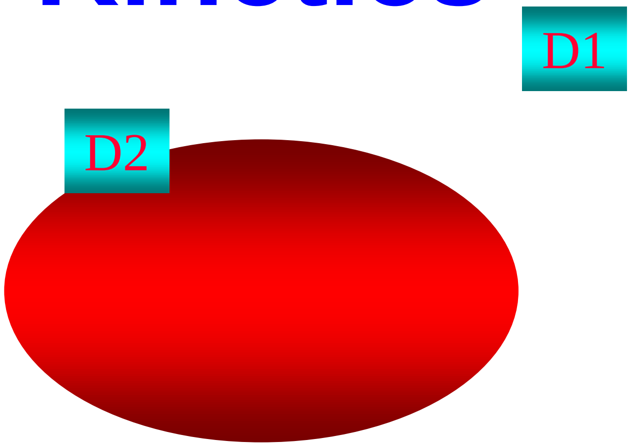
Charging current

Faradic currents

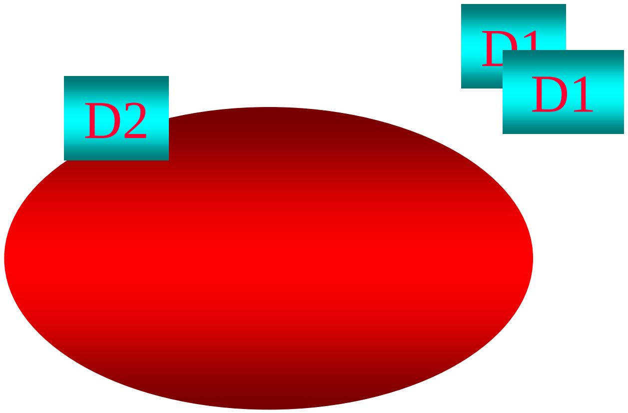
The cytochrome P450 2C9 presents peak shifts in the range of tens of mV by changing drug substrates

The Heterotropic Kinetics

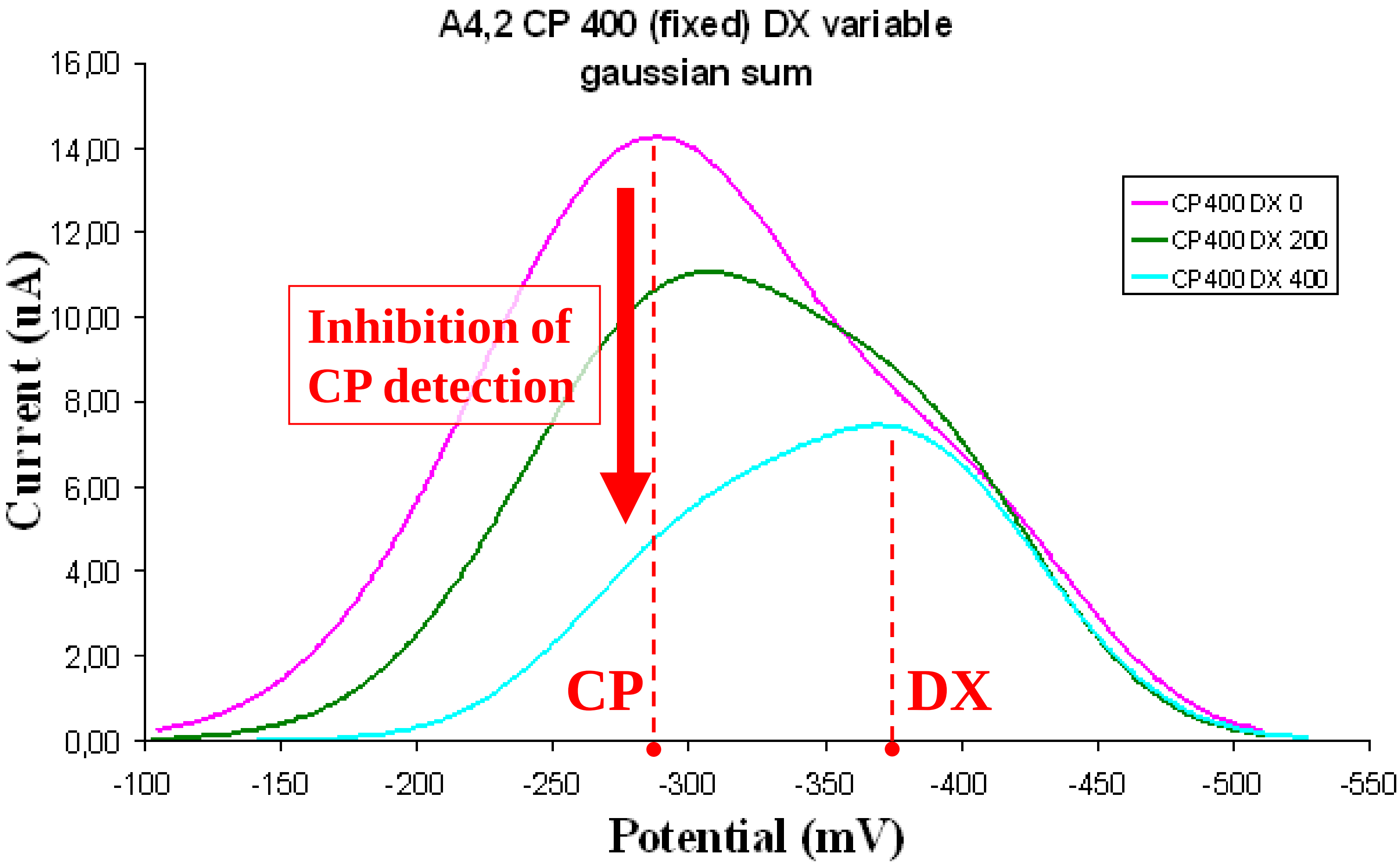
- **HETERO ACTIVATION**



- **PARTIAL INHIBITION**



Multiple drugs detection: CYP3A4

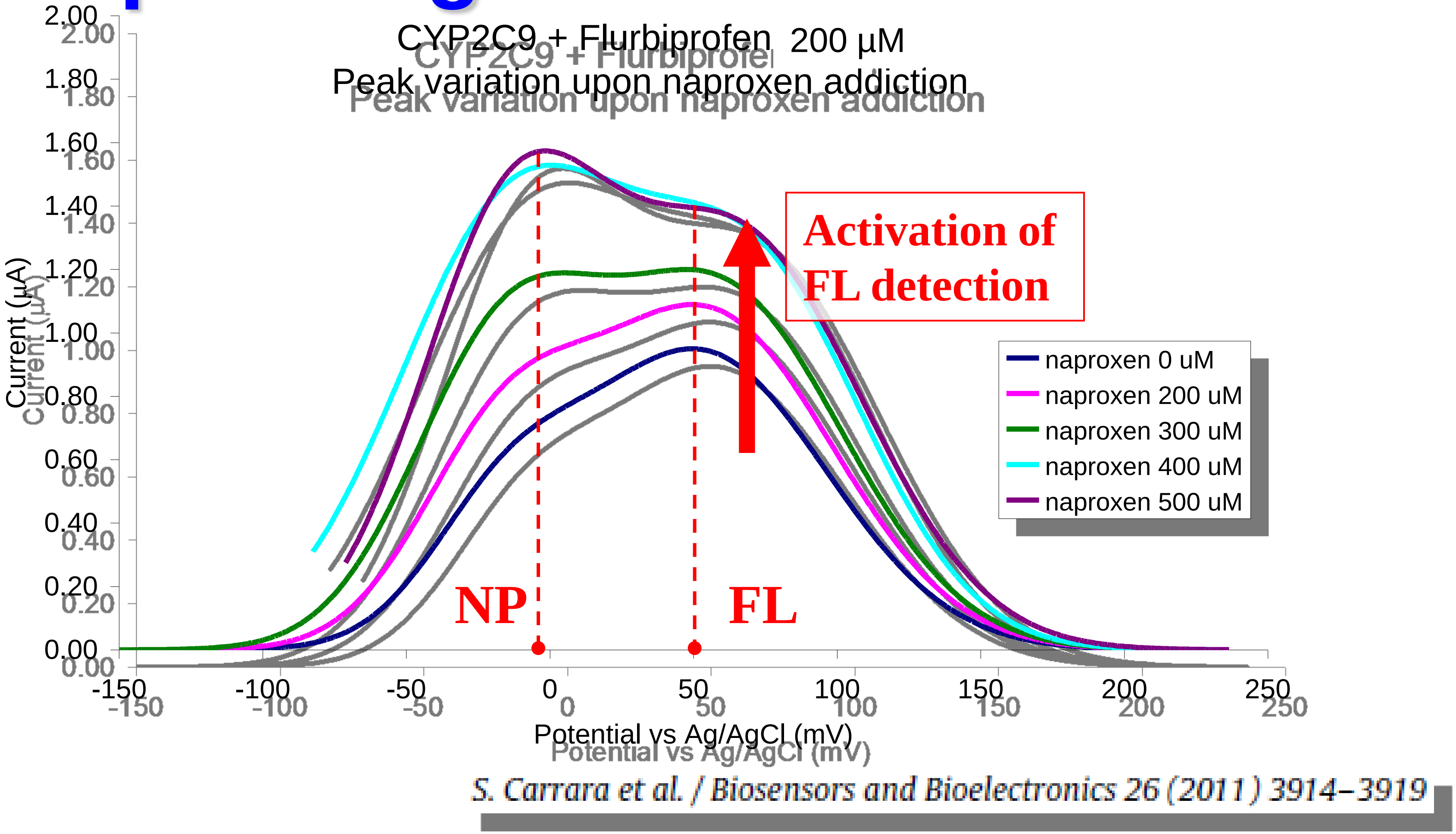


S. Carrara et al. / Biosensors and Bioelectronics 26 (2011) 3914–3919

Different amounts of CP and DX result in

two very-well defined peaks once detected by P450 3A4

Multiple drugs detection: CYP2C9



Naproxen (NP) and Flurbiprofen (FL) also result in two very-well defined peaks once detected by P450 2C9

Peaks Amplitude is affected by the other drugs

Substrate/inhibitor of CYP2C9	K_m (μM)	K_i (μM)	CYP2C9 (mV)	E_{mid} CYP2C9 + substrate (mV)
Torsemide (s)	11.4		−41	−19
Diclofenac (s)	6.8		−41	−41
Tolbutamide (s)	120[a]		−41	−37
S-Warfarin (s)	6[b]		−41	−36
Sulfaphenazole (i)		0.1[c]	−41	−41
$CO_{(g)}$			−41	8

D.L. Johnson et al. / Biochemical Pharmacology 69 (2005) 1533–1541

Dependence from the other drug concentrations

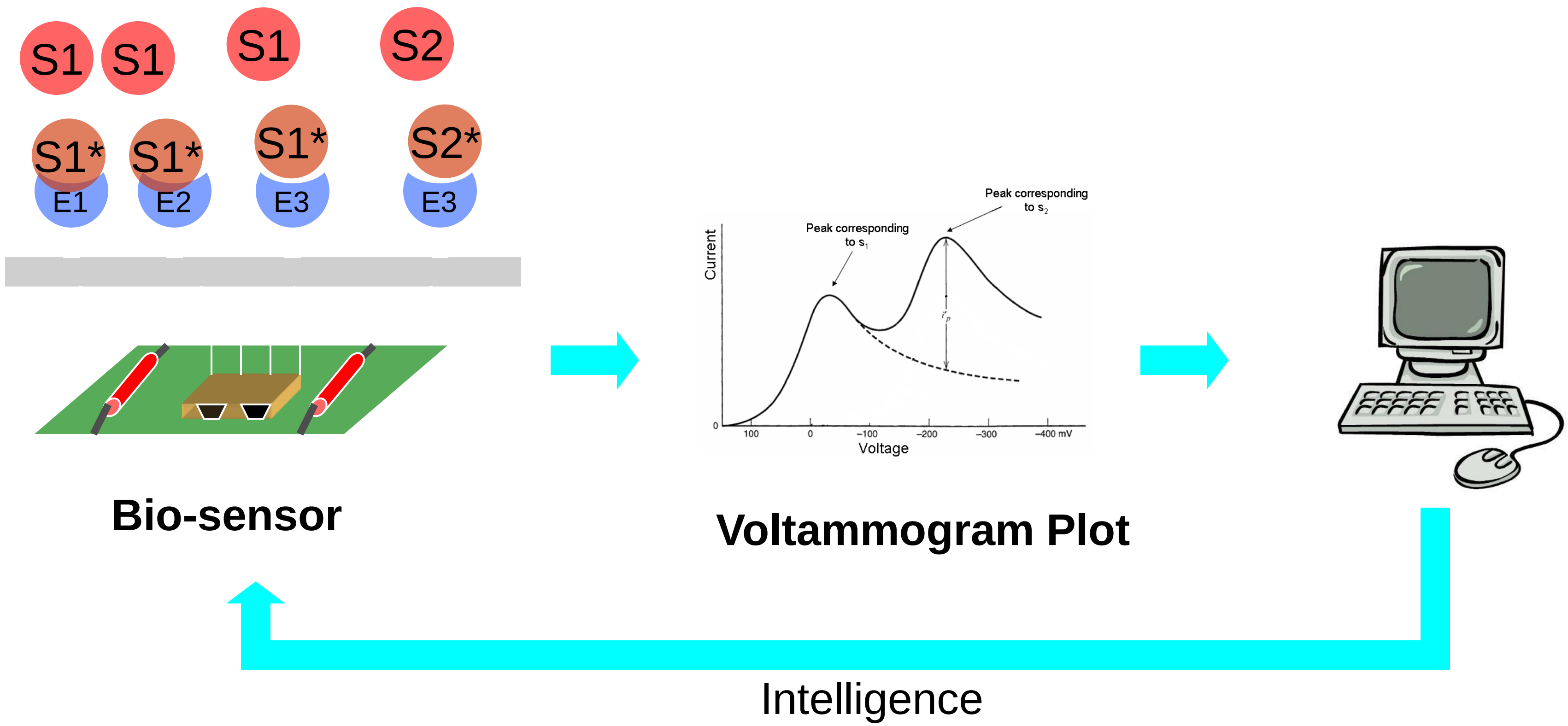
$$i(V) = i_C(V) + \sum_{\forall k} \prod_{\forall j \neq k} A_k\left(\left[C_j\right]\right)$$

Charging current

Faradic currents

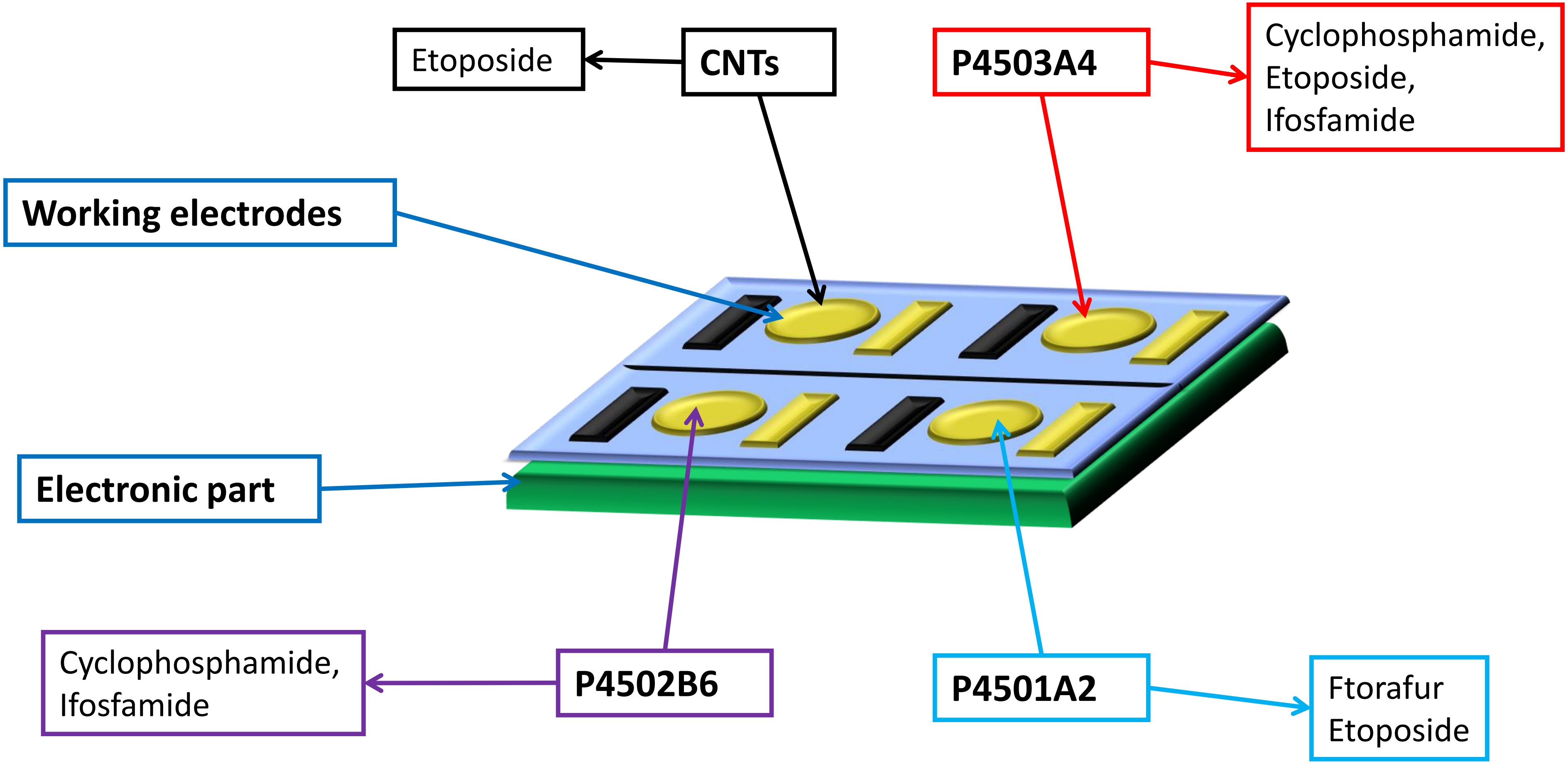
The Gaussian decomposition in cytochrome P450 based detection has to account for the heterotropic kinetics

The Problem of multi-panel arrays response

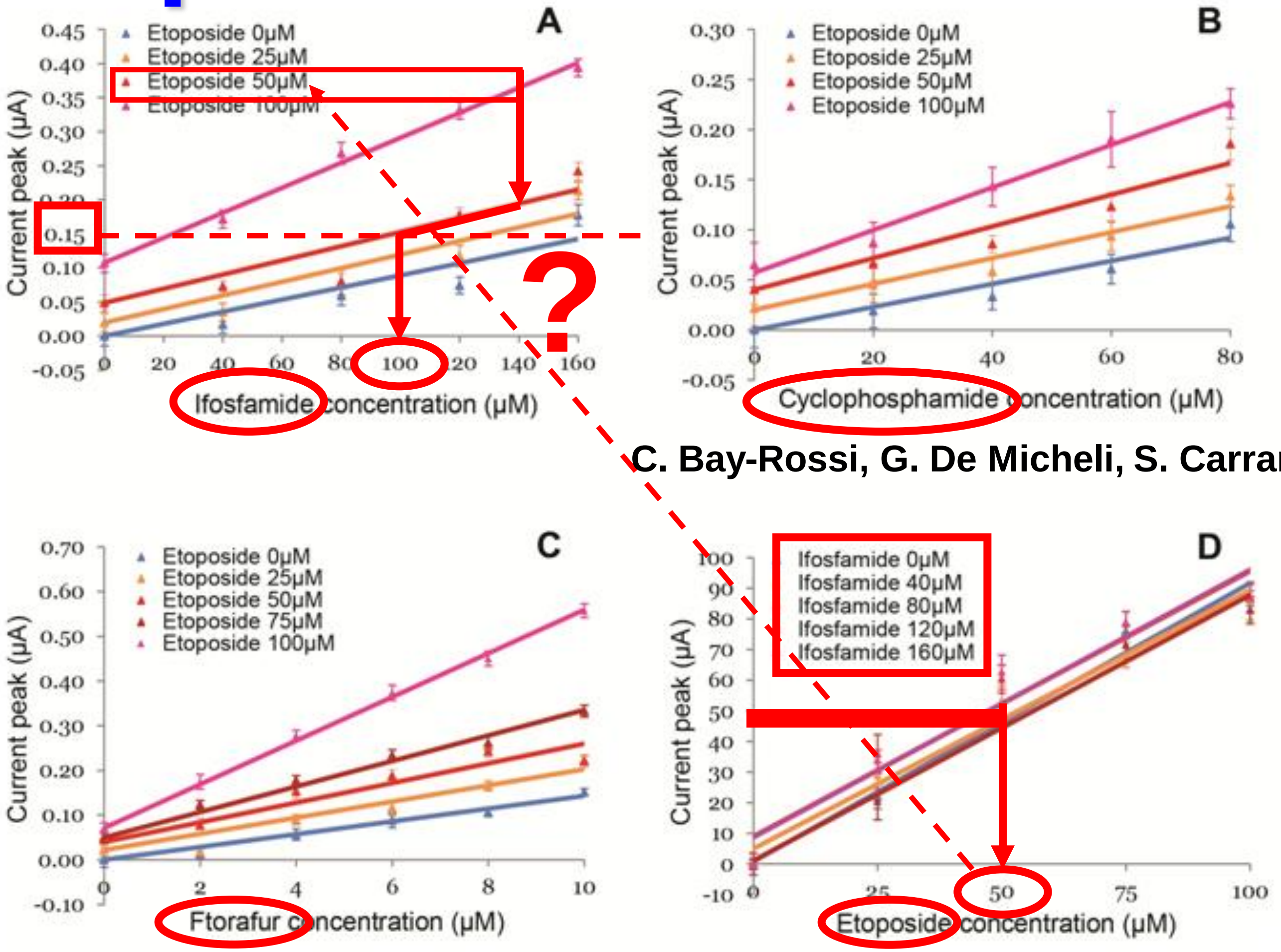


Multi-Platform design

Four working electrodes differently functionalized



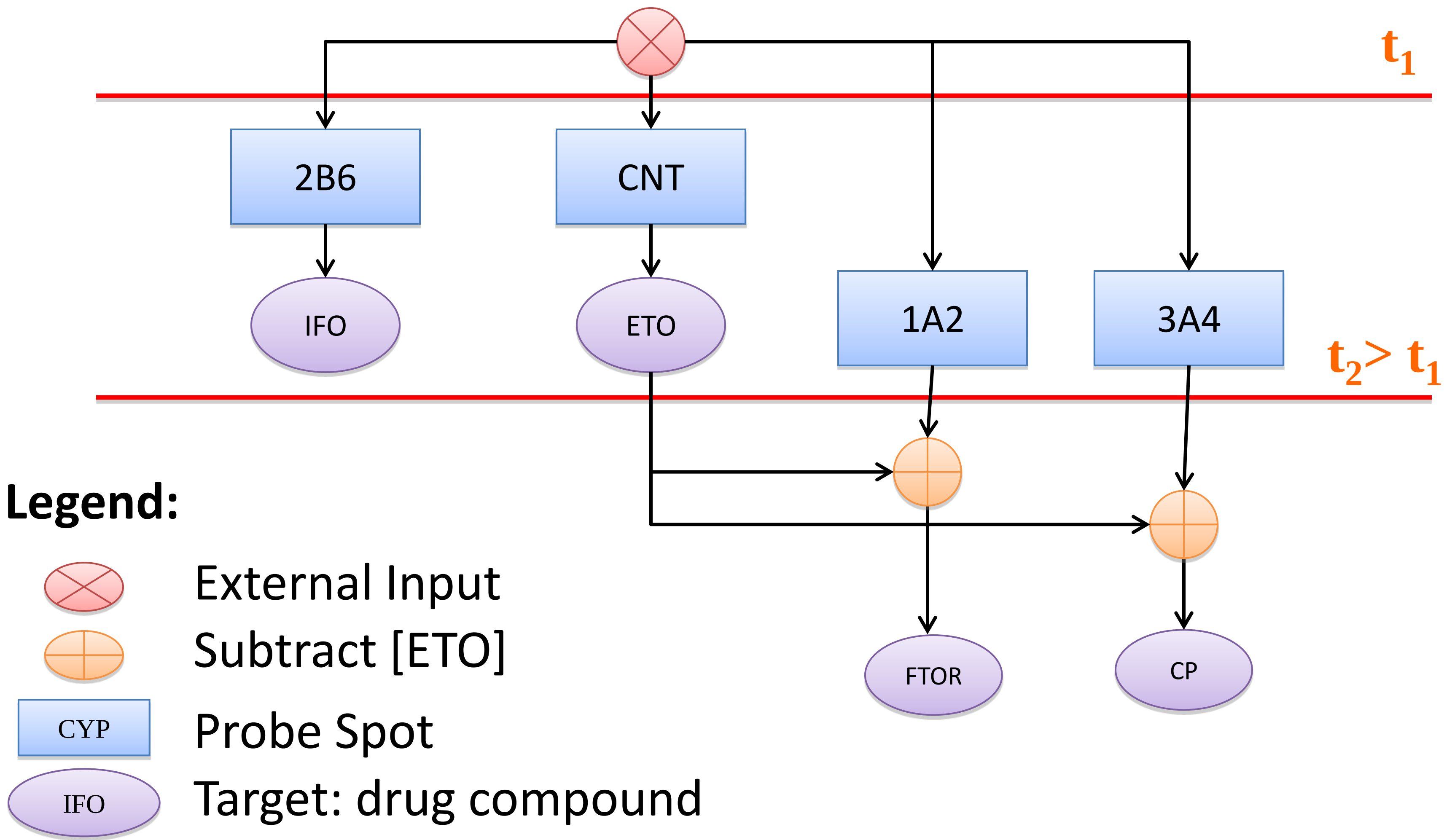
Multiple Calibration Curves



C. Bay-Rossi, G. De Micheli, S. Carrara, Sensors 2012

Deal with Calibration Curves Family allow us to improve specificity at system level

Sensors Query in Time

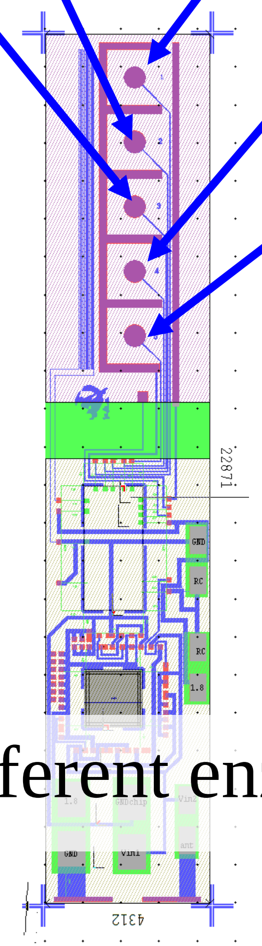


(c) S. Carrara, EPFL (Switzerland)

Multi-Panel Platforms for Human Metabolism

ATP-ase	Lactate oxidase	Glucose oxidase	Lipoxygenase
P450 11A1	P450 5A1	P450 4A11	Cholesterol oxidase

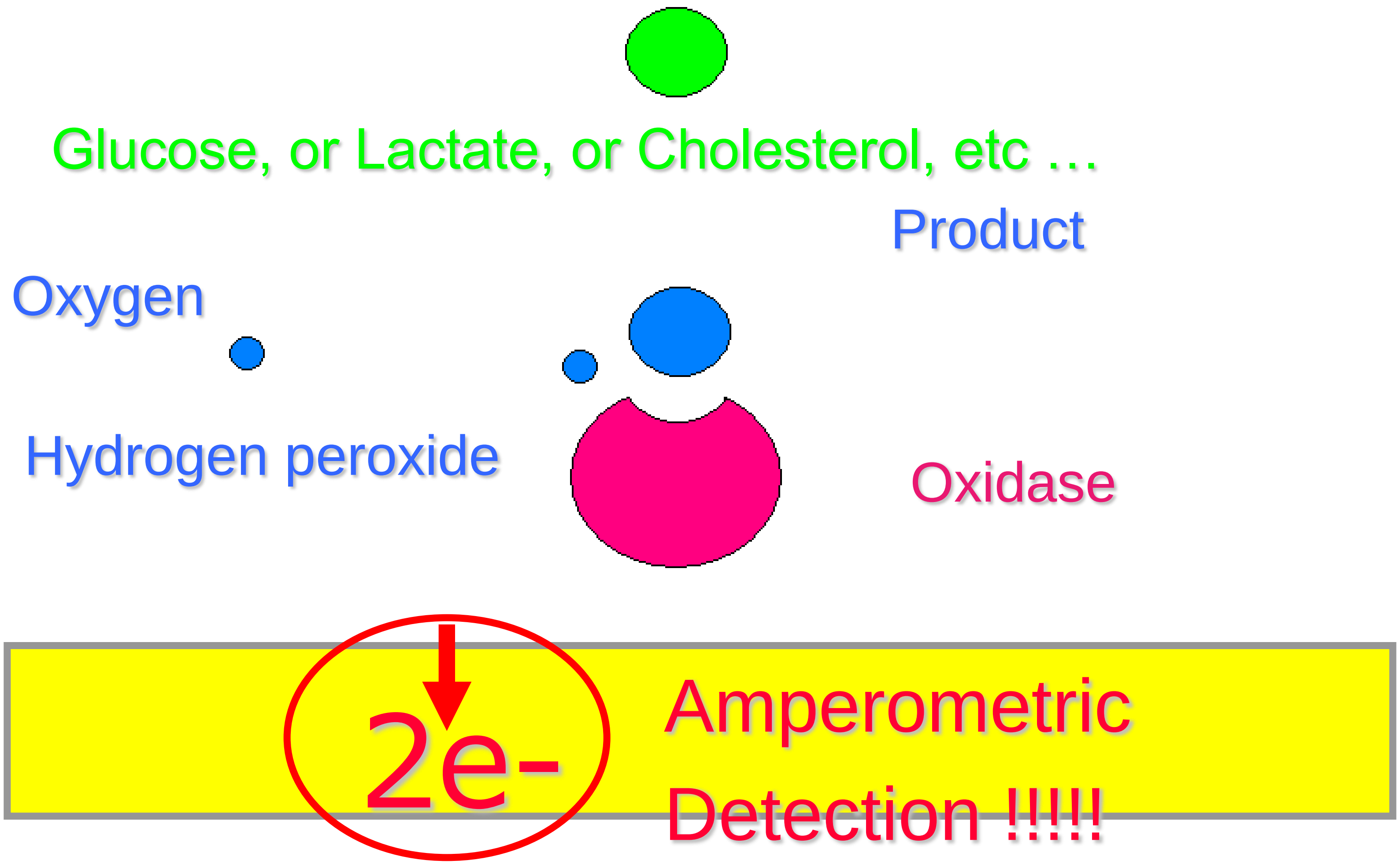
Probe enzymes



- Glucose
- Lactate
- Cholesterol
- ATP
- Drugs

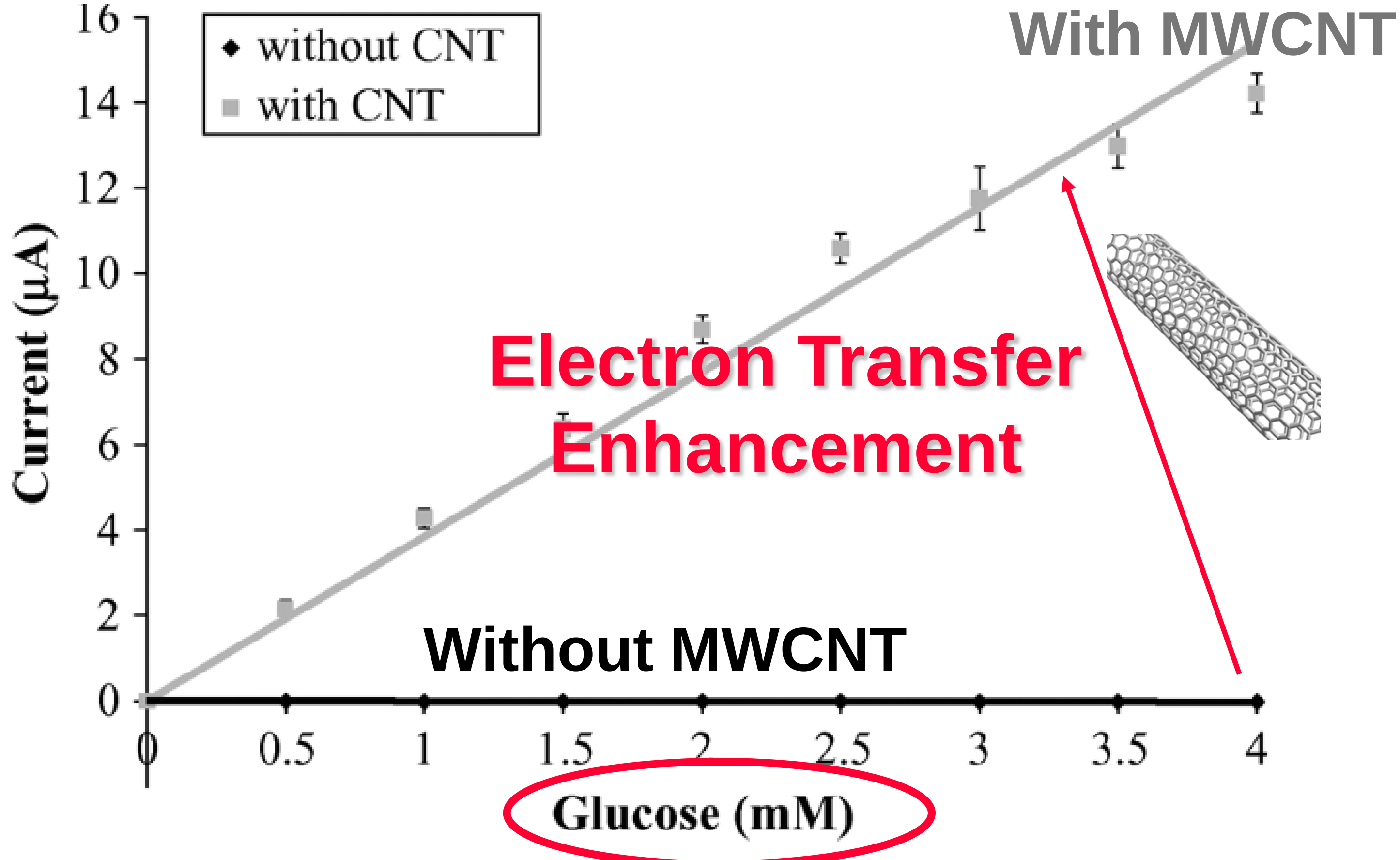
Different enzymes sense different human metabolites

Oxidases for Markers Monitoring



Cottrell Effect

BOERO *et al.*: HIGHLY SENSITIVE CARBON NANOTUBE-BASED SENSING
IEEE TRANSACTIONS ON NANOBIOSCIENCE, VOL. 10, NO. 1, MARCH 2011

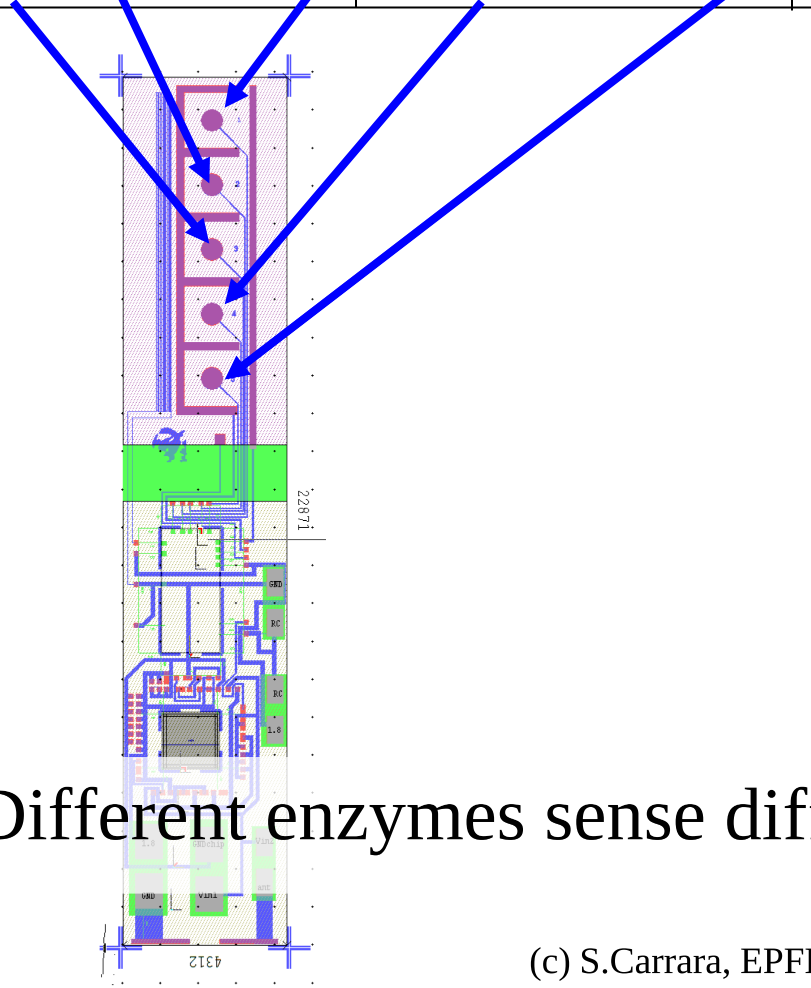


The performance in detecting Glucose is Highly-Enhanced by using MWCNT

Multi-Panel Platforms for Human Metabolism

ATP-ase	Lactate oxidase	Glucose oxidase	Lipoxygenase
P450 11A1	P450 5A1	P450 4A11	Cholesterol oxidase

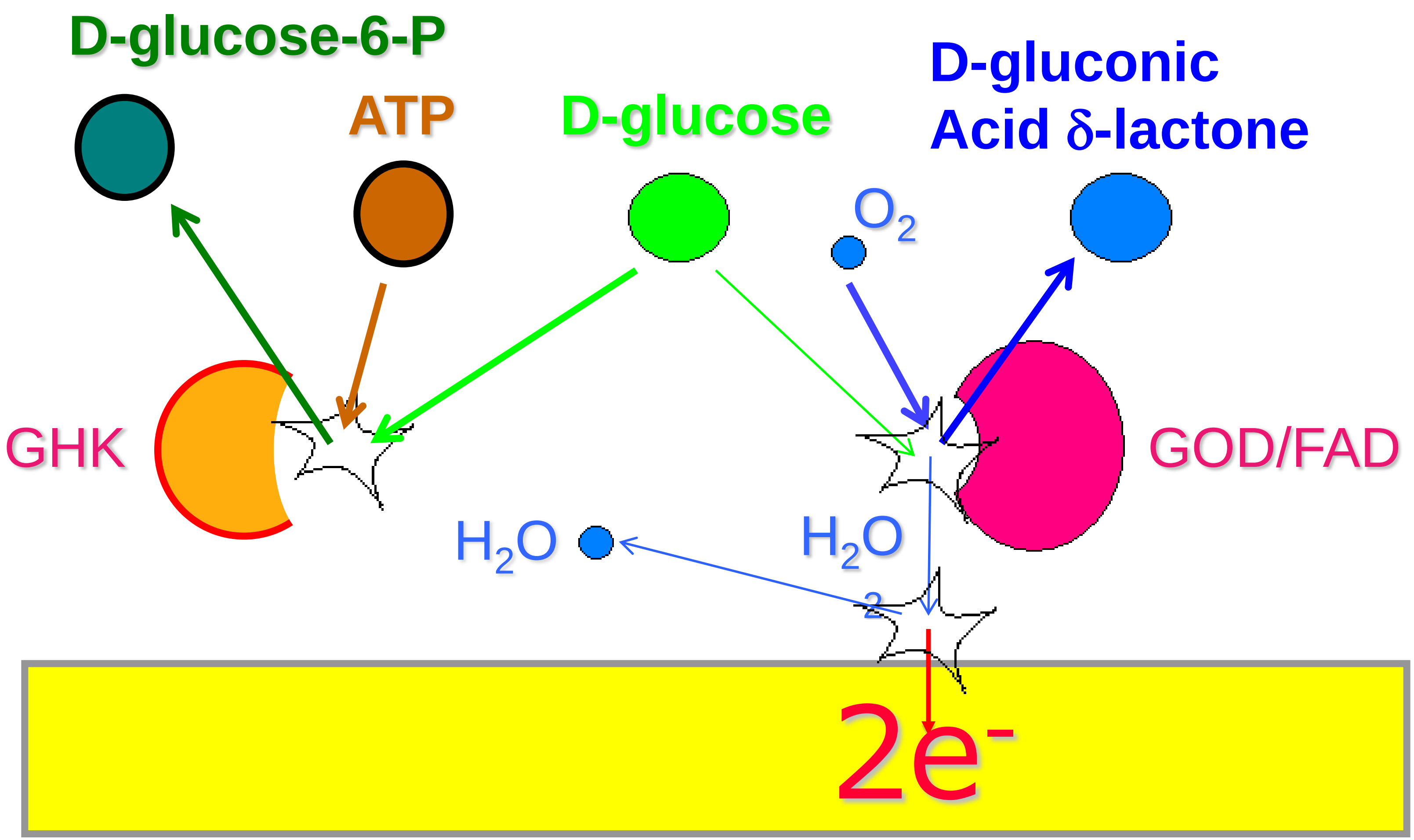
Probe enzymes



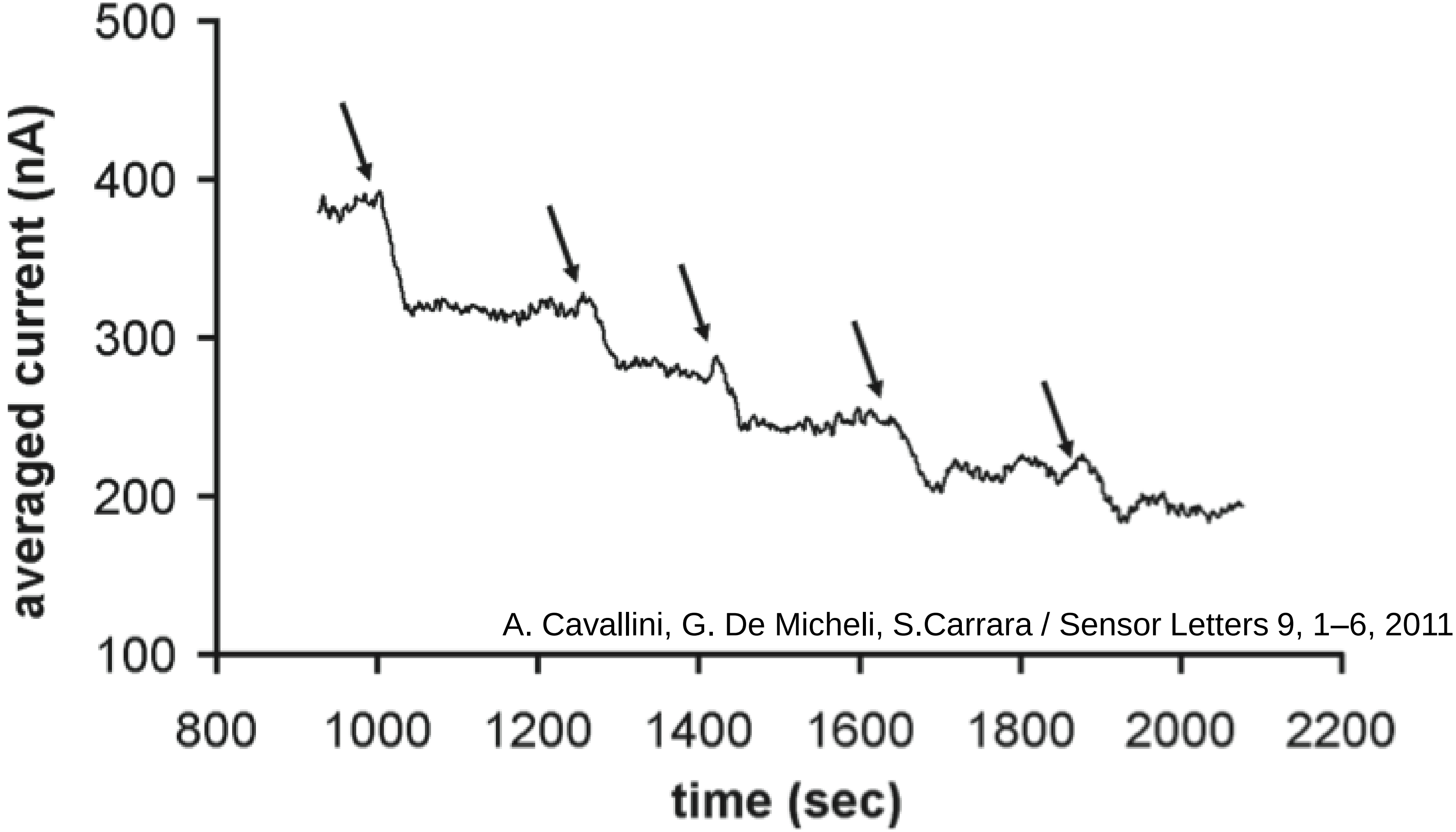
- Glucose
- Lactate
- Cholesterol
- ATP
- Drugs

Different enzymes sense different human metabolites

ATP detection

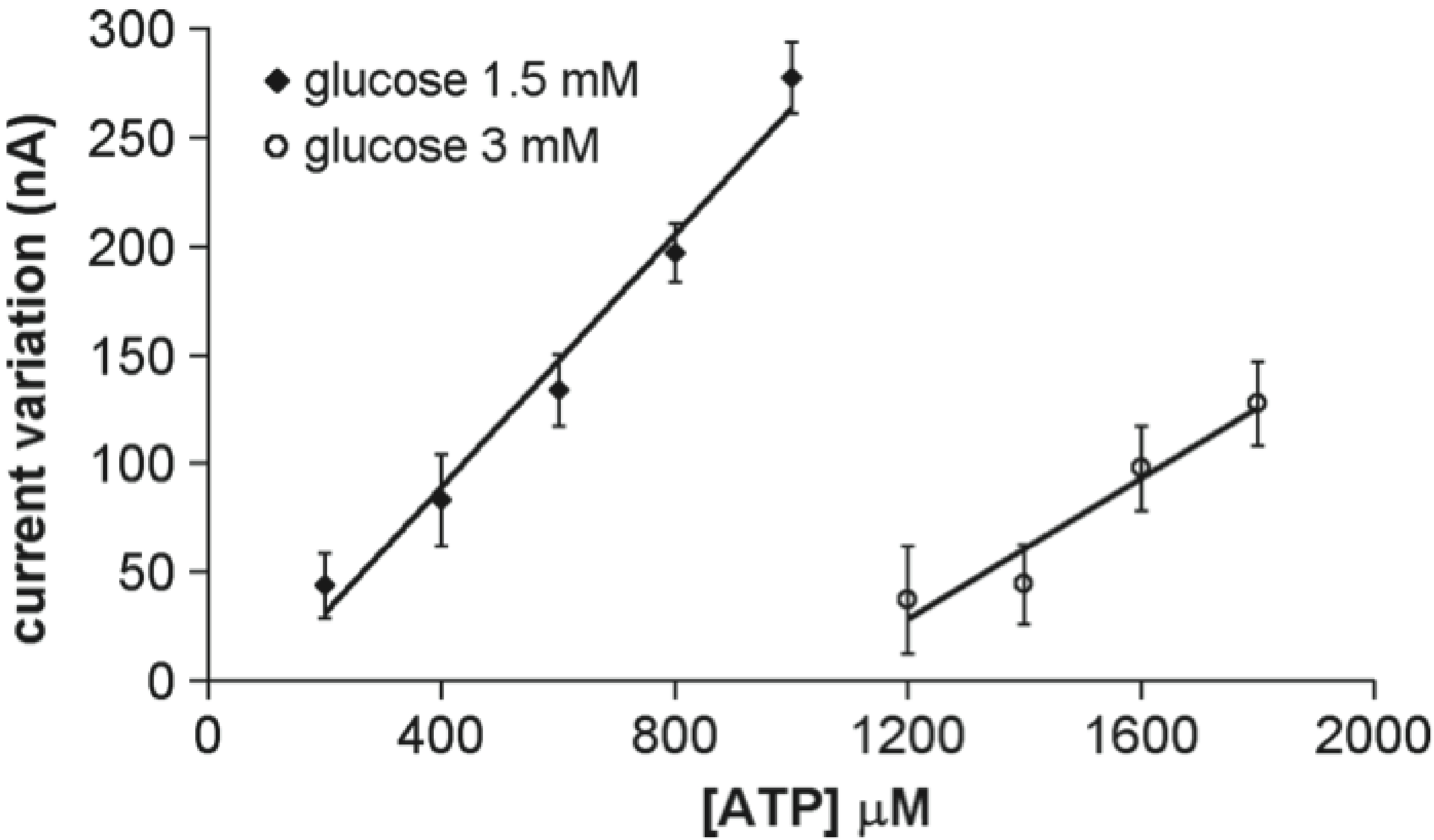


Indirect ATP Detection



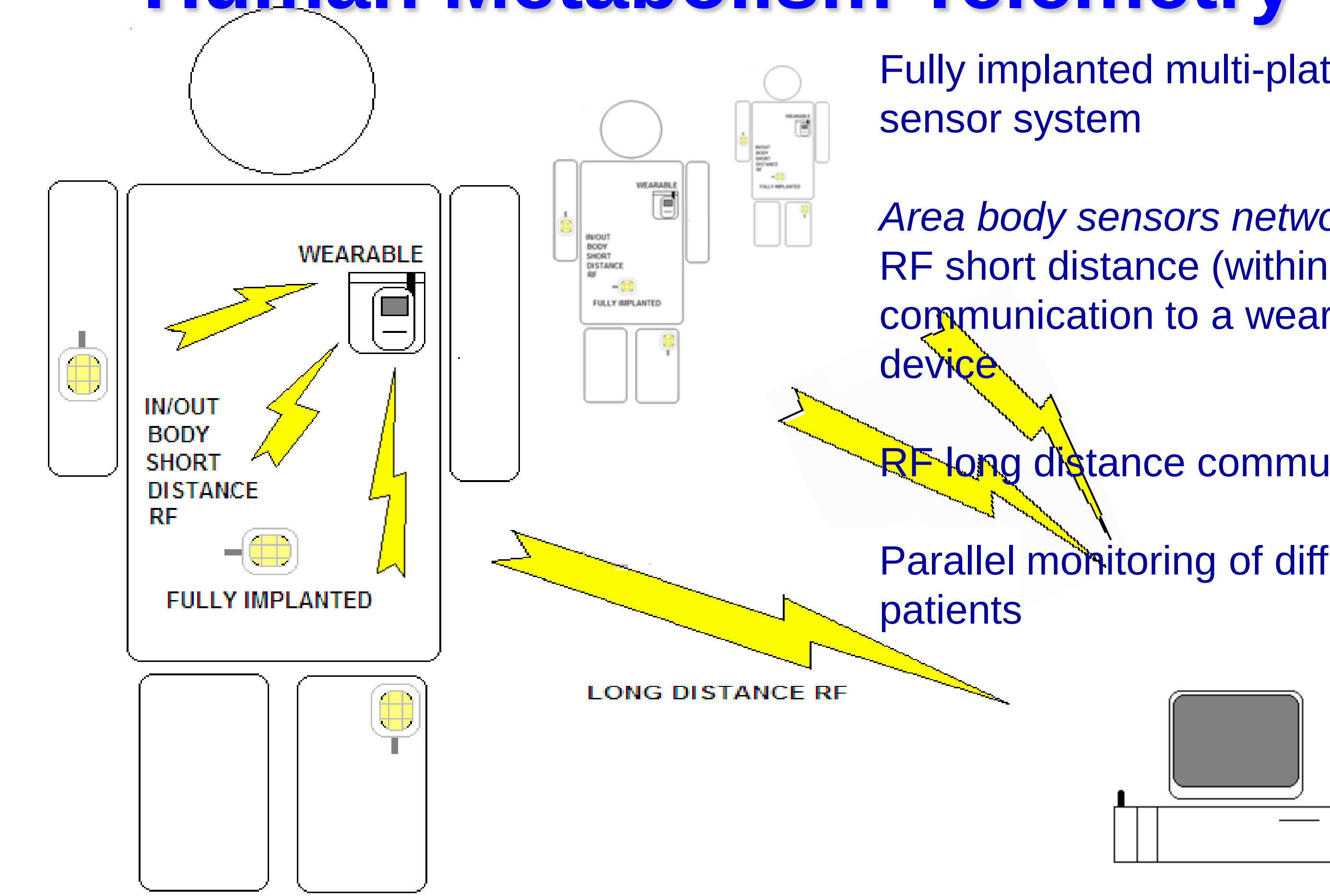
ATP is detected by a decreasing current at the interface

Indirect ATP Detection



ATP detection is affected by different values of glucose

New Concept in Human Metabolism Telemetry



Fully implanted multi-platform sensor system

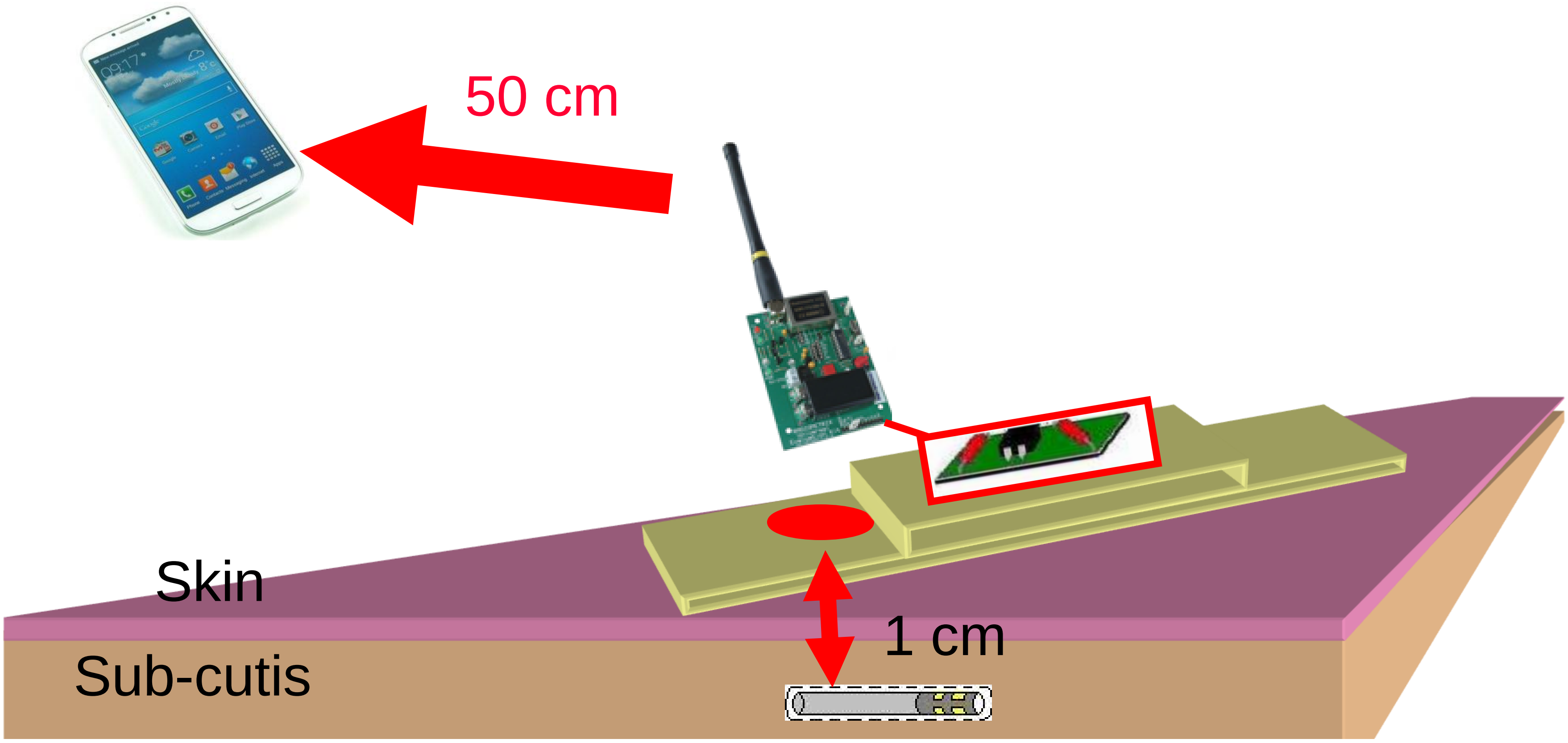
Area body sensors network with RF short distance (within 50 cm) communication to a wearable device

RF long distance communication

Parallel monitoring of different patients

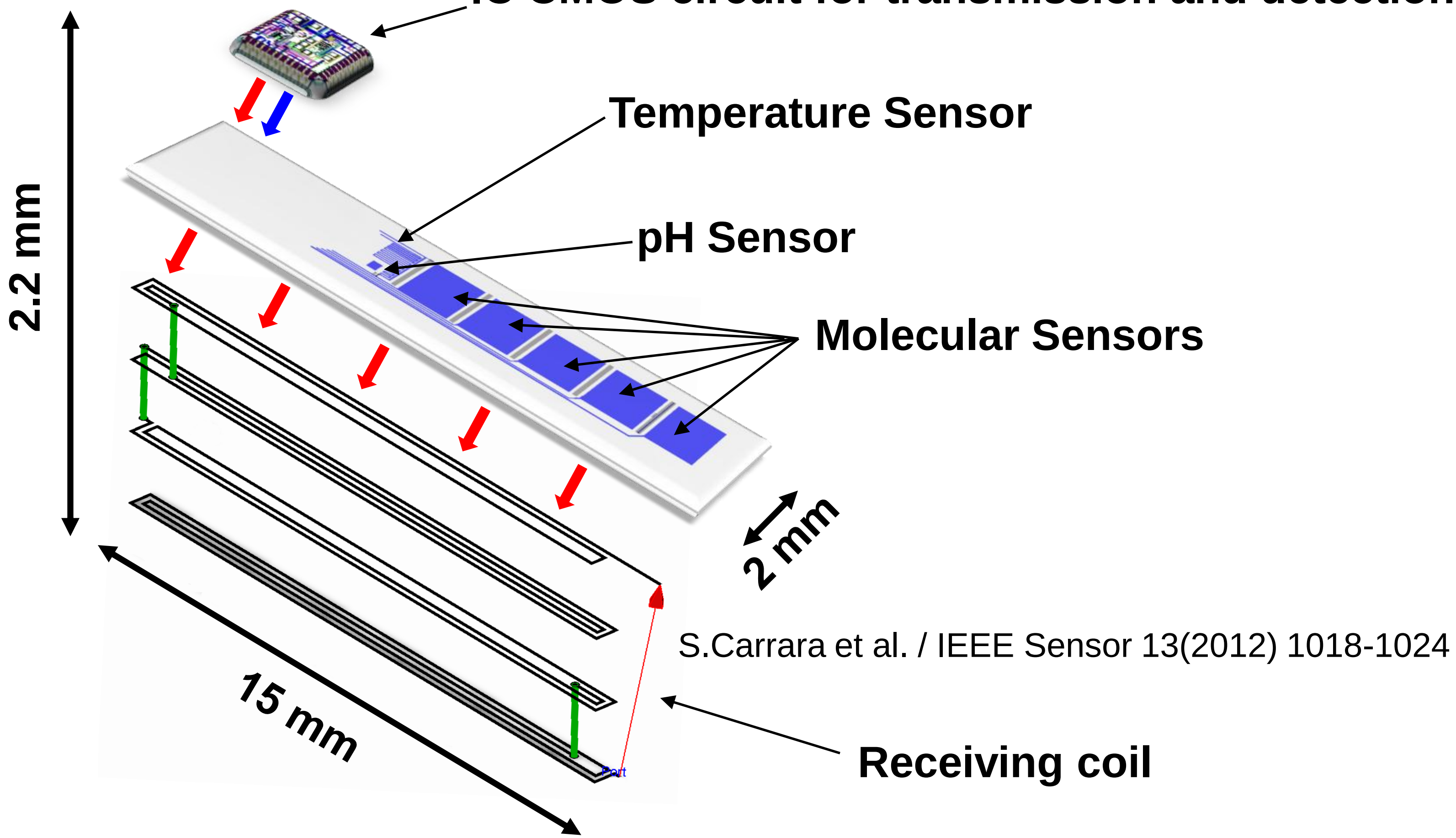
The design of implantable/wearable systems for continuous monitoring of human metabolism is feasible

Under-the-Skin Device & Wearable Patch



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

Under-the-Skin Device



S.Carrara et al. / IEEE Sensor 13(2012) 1018-1024

Minimally invasive with size within that of a surgery needle

A reliable system requires:

1. CNT-Biochip fully integration
2. Precise Current measurements
3. Multiplexing for different molecules
4. Reliability in Temperature and pH
5. Multiplexing Molecular Detection with T and pH
6. Reliability for Voltage Sweep
7. Remote Powering

A reliable system requires:

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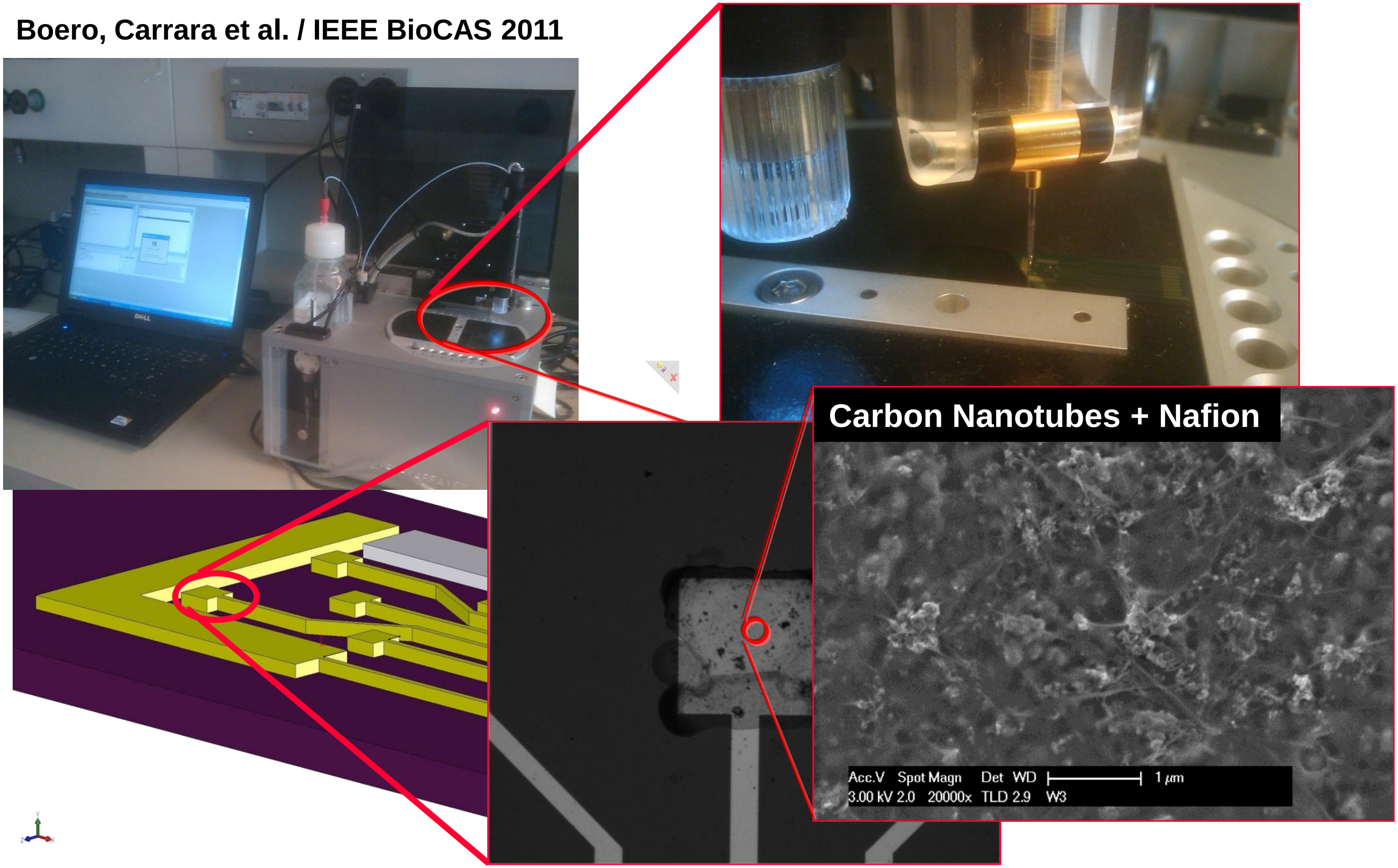
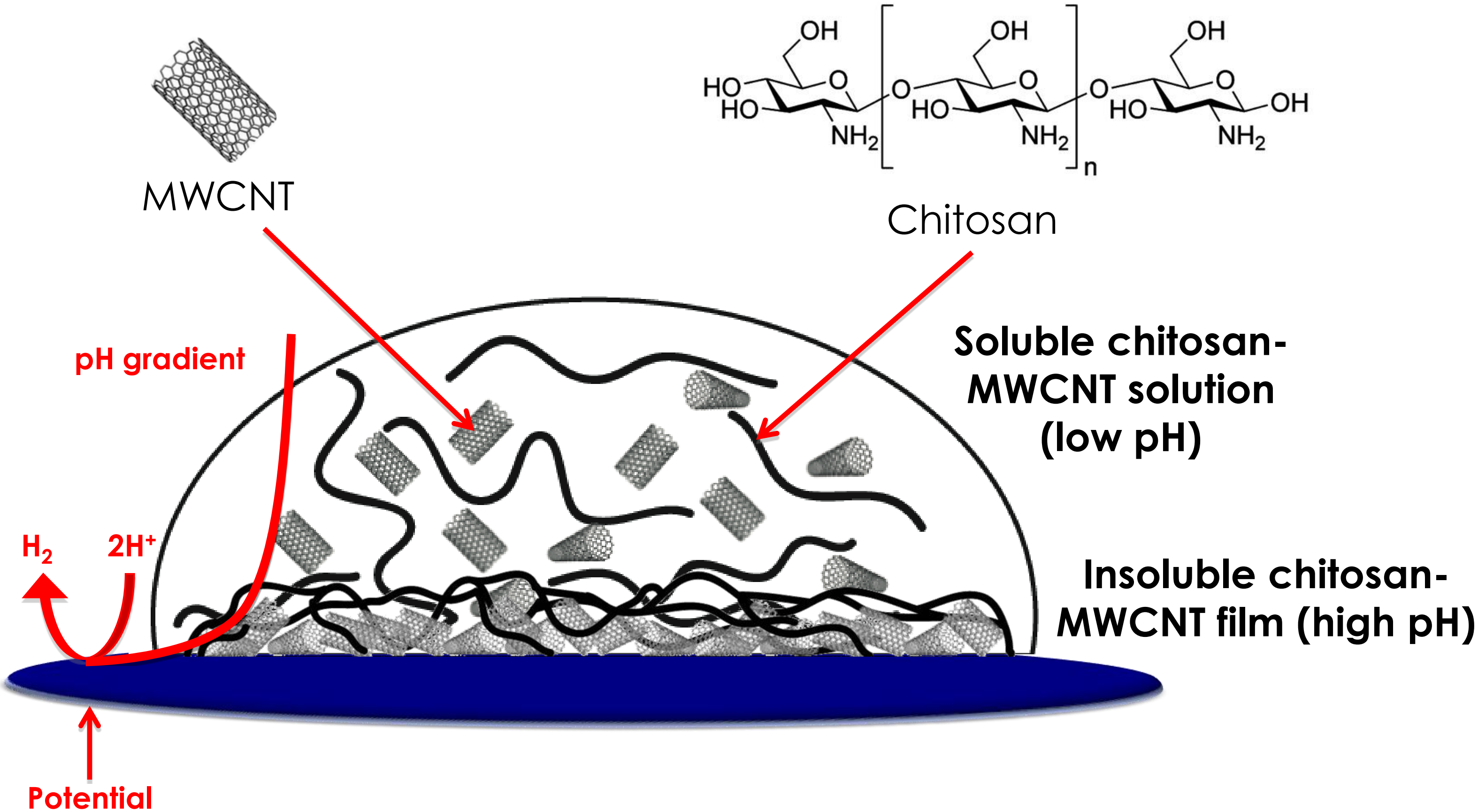
6. Reliability for Voltage Sweep
7. Remote Powering

1. Nano-Bio-Sensors Micro-Spotting

Boero, Carrara et al. / IEEE BioCAS 2011

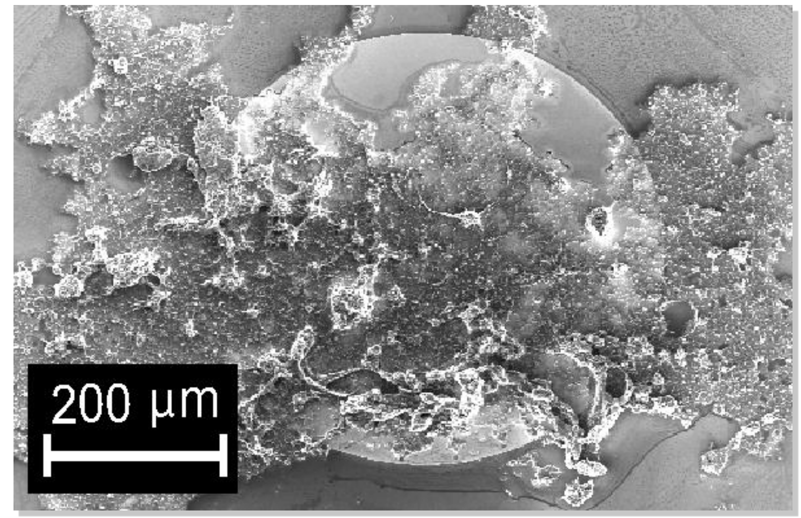


1b. Nano-Bio-Sensors by Electrodeposition

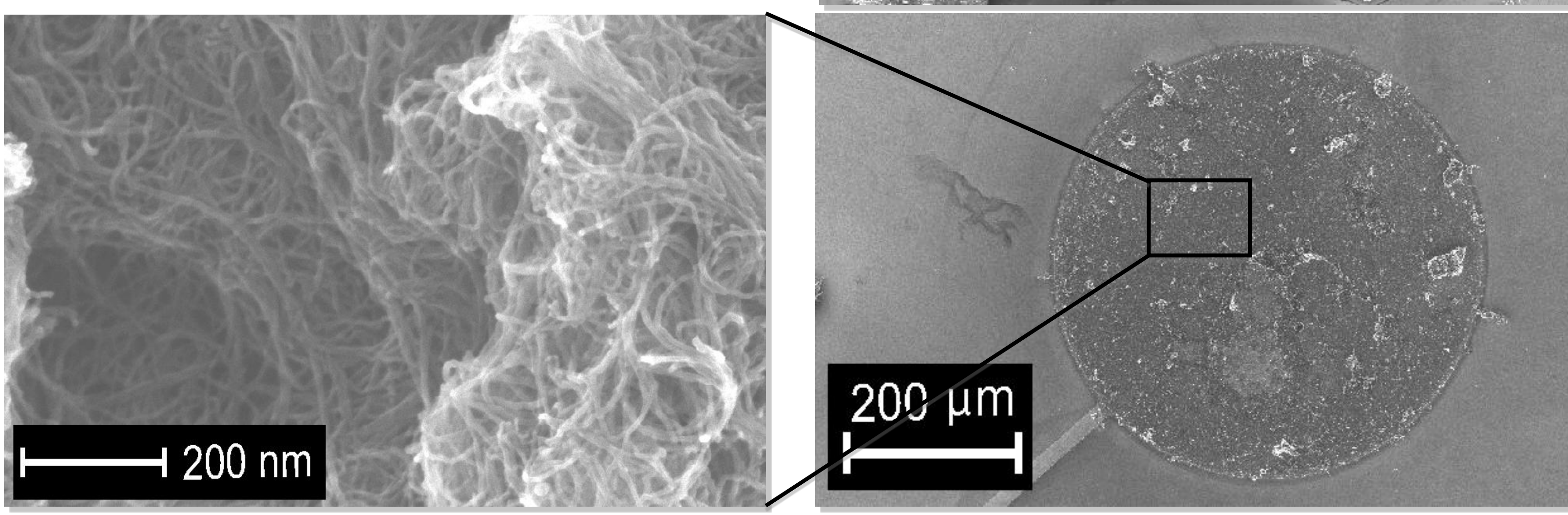


1b. Nano-Bio-Sensors by Electrodeposition

DROP-CASTING



Results



(c) S.Carrara, EPFL (Switzerland)

ELECTRODEPOSITION

1c. Nano-Bio-Sensors by CVD

Integration by Direct Growth

Step I Catalyst electrodeposition

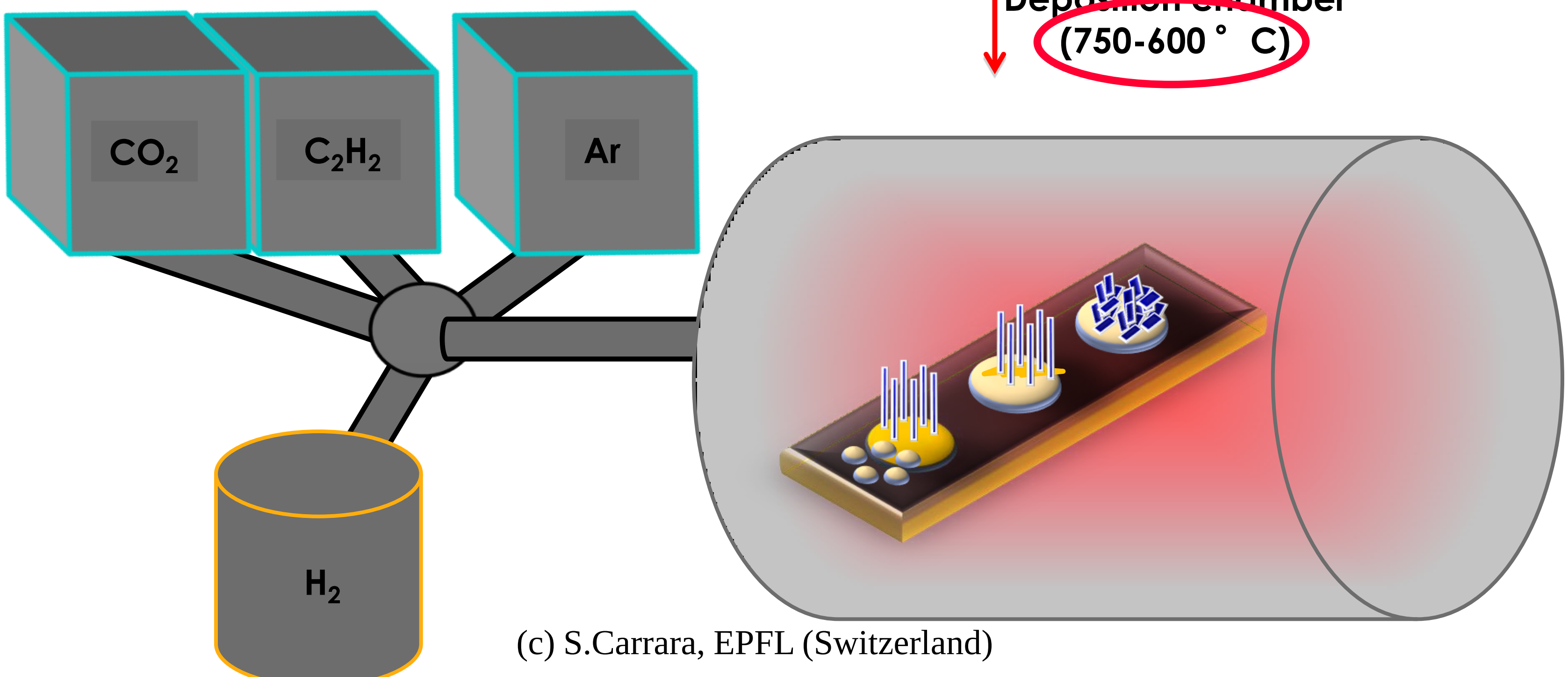
Step II Annealing (3-10 minutes)

Step III Deposition (CO_2 and C_2H_2 flow)

Taurino, Carrara et al. / UE Patent 2013

Down now till 450 ° C
To be fully CMOS-compatible

Deposition chamber
(750-600 ° C)



1c. Nano-Bio-Sensors by CVD

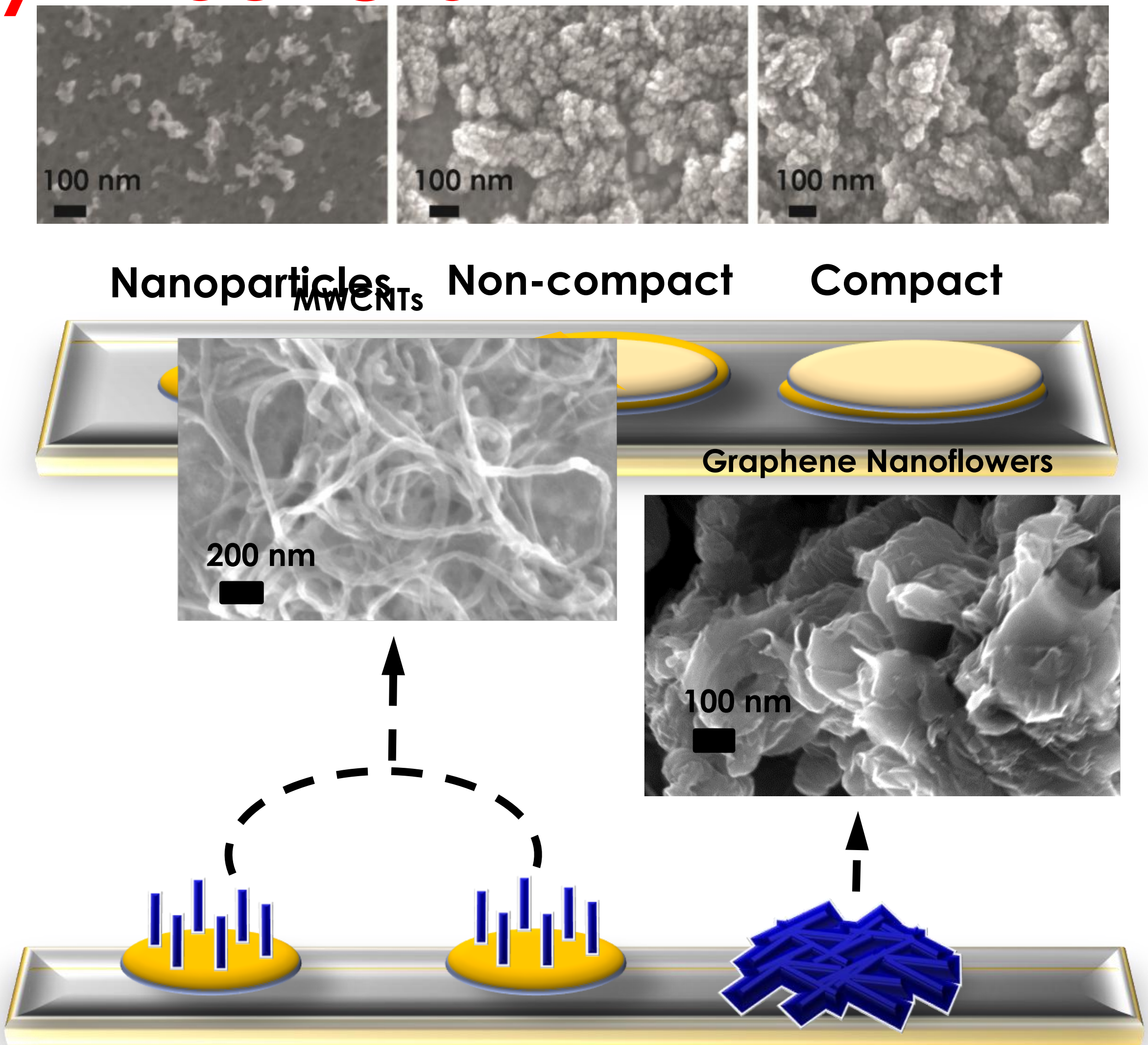
Integration by Direct Growth

Results

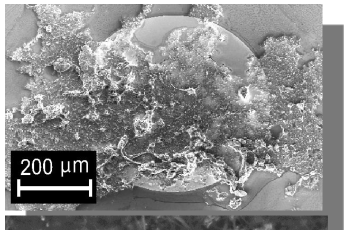
1.Fe electrodeposition

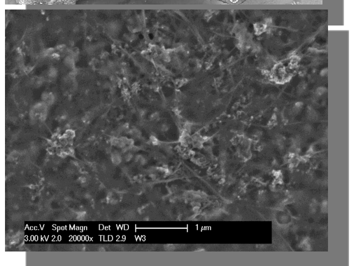
2.Deposition

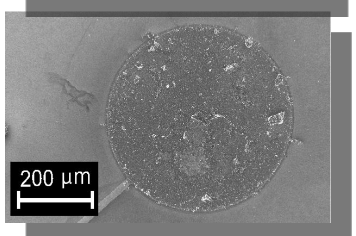
- ***10 min annealing***
- ***5 min deposition***
- ***750 ° C***
- ***0.25 l/h C_2H_2 flow***
- ***0.25 l/h CO_2 flow***

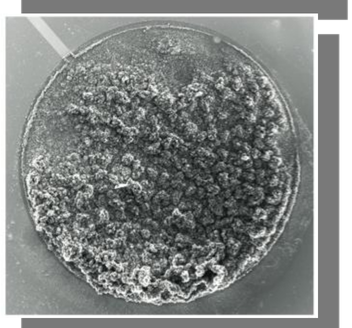


1d. Four different techniques









	Sensitivity * [µA/(mM*cm^2)]	Limit of Detection * (LOD) [µM]
DROP CASTING	27.7 ± 0.1	73 ± 1
MICRO SPOTTING	0.46 ± 2	115 ± 1
ELECTRO DEPOSITION	63 ± 15	8 ± 2
CVD growth	111.2 ± 0.3 (5703 ± 566	0.745 ± 0.005 3.5 ± 1.3) #

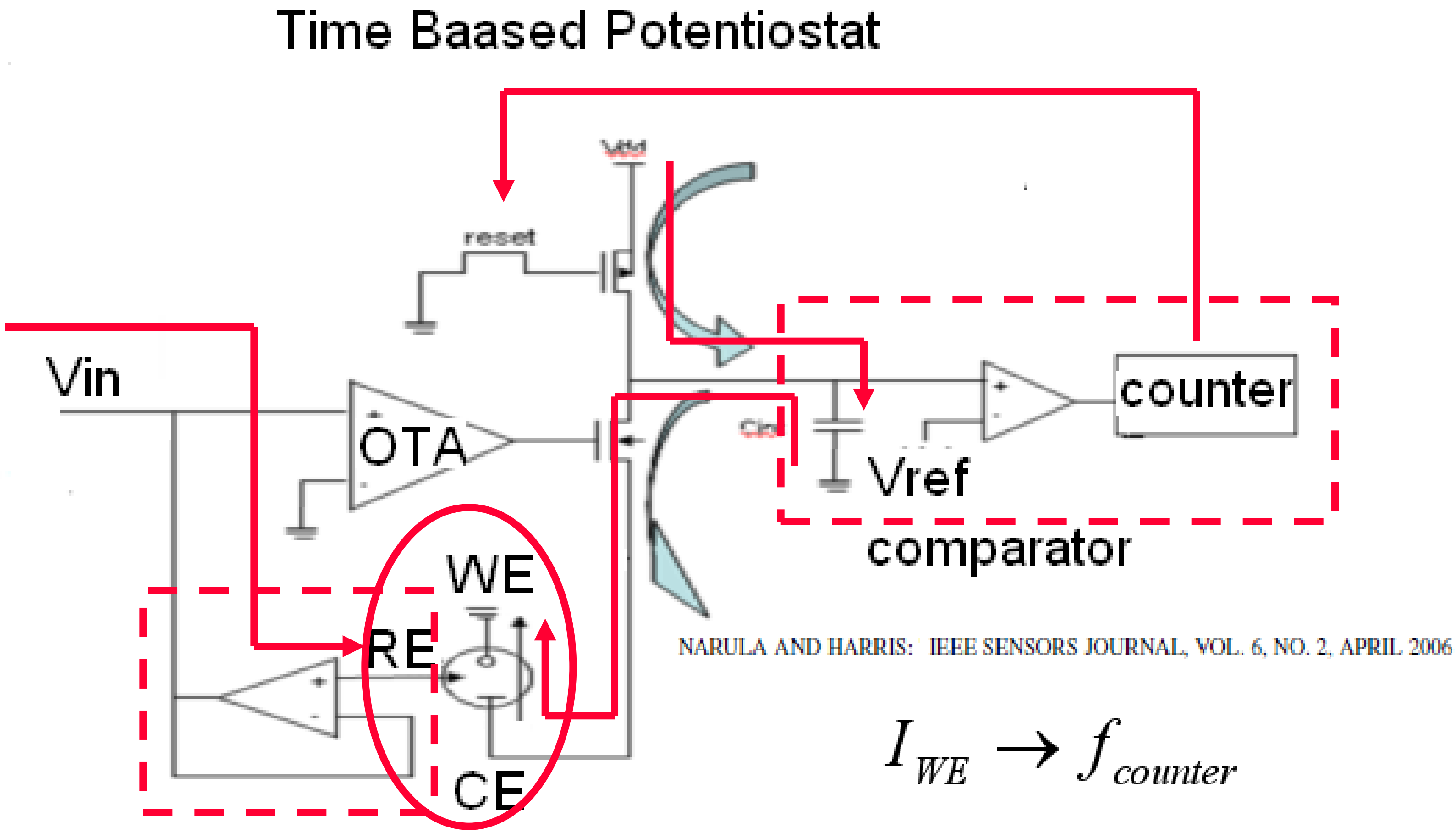
* on Glucose detection

\# on Uric Acid detection

A reliable system requires:

1. CNT-Biochip fully integration
2. **Precise Current measurements**
3. **Multiplexing for different molecules**
4. **Reliability in Temperature and pH**
5. **Multiplexing Molecular Detection with T and pH**
6. **Reliability for Voltage Sweep**
7. **Remote Powering**

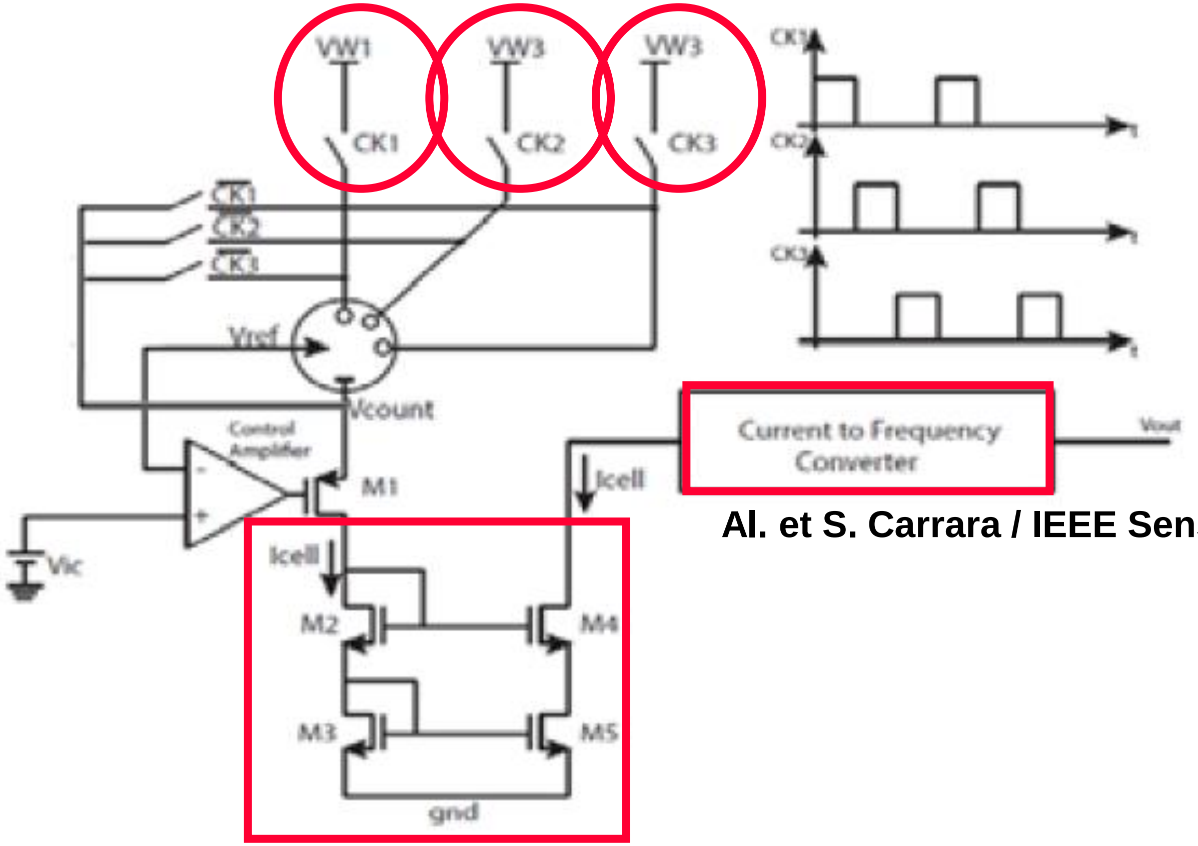
2. Current Measurements Front-End



$$I_{WE} \rightarrow f_{counter}$$

Current-to-frequency converter

3. Multiplexing Molecular Detection



Al. et S. Carrara / IEEE Sensors Conf. 2010

Different working electrodes are multiplexed to the current-to-frequency converter

4. Reliability in Temperature & pH

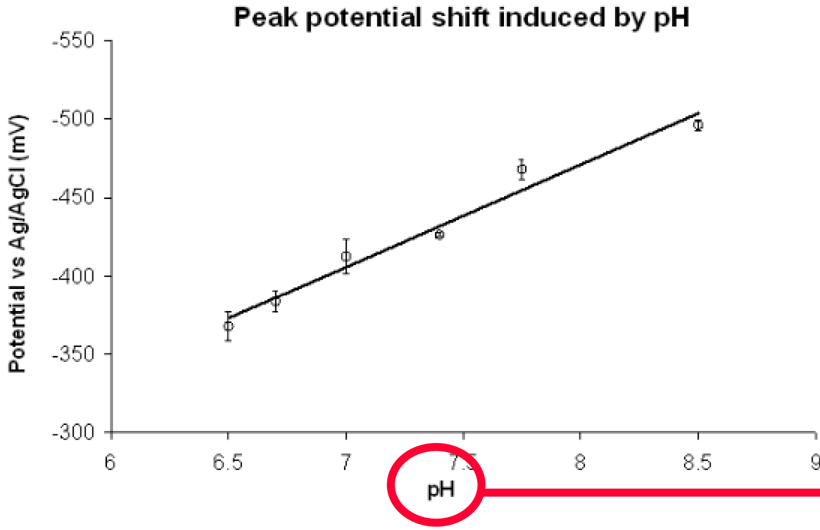
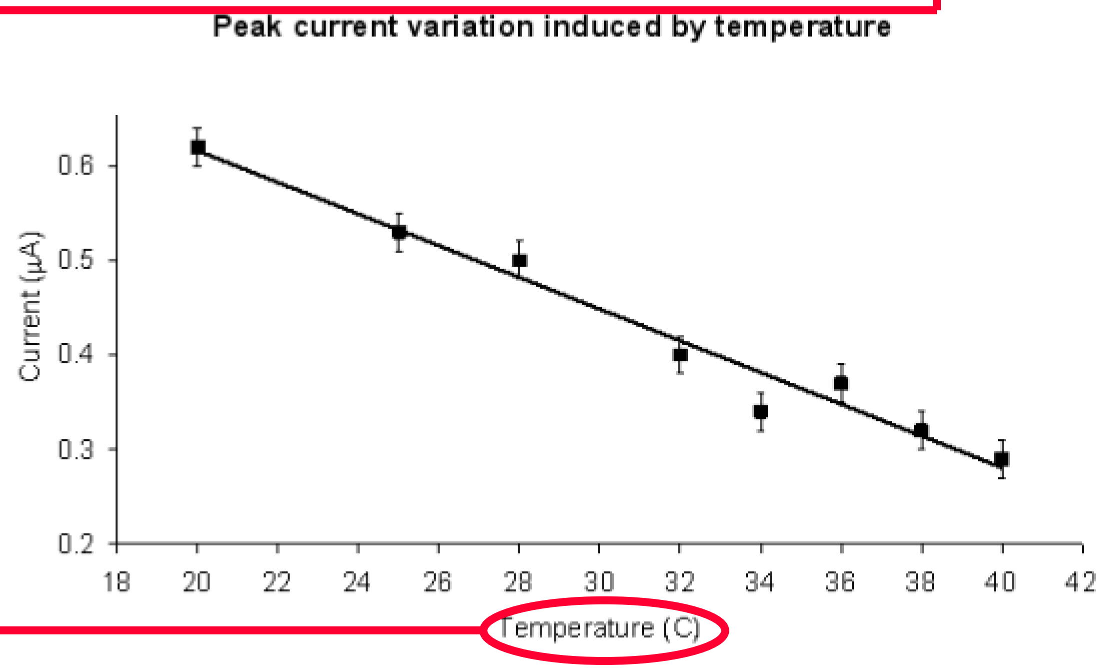


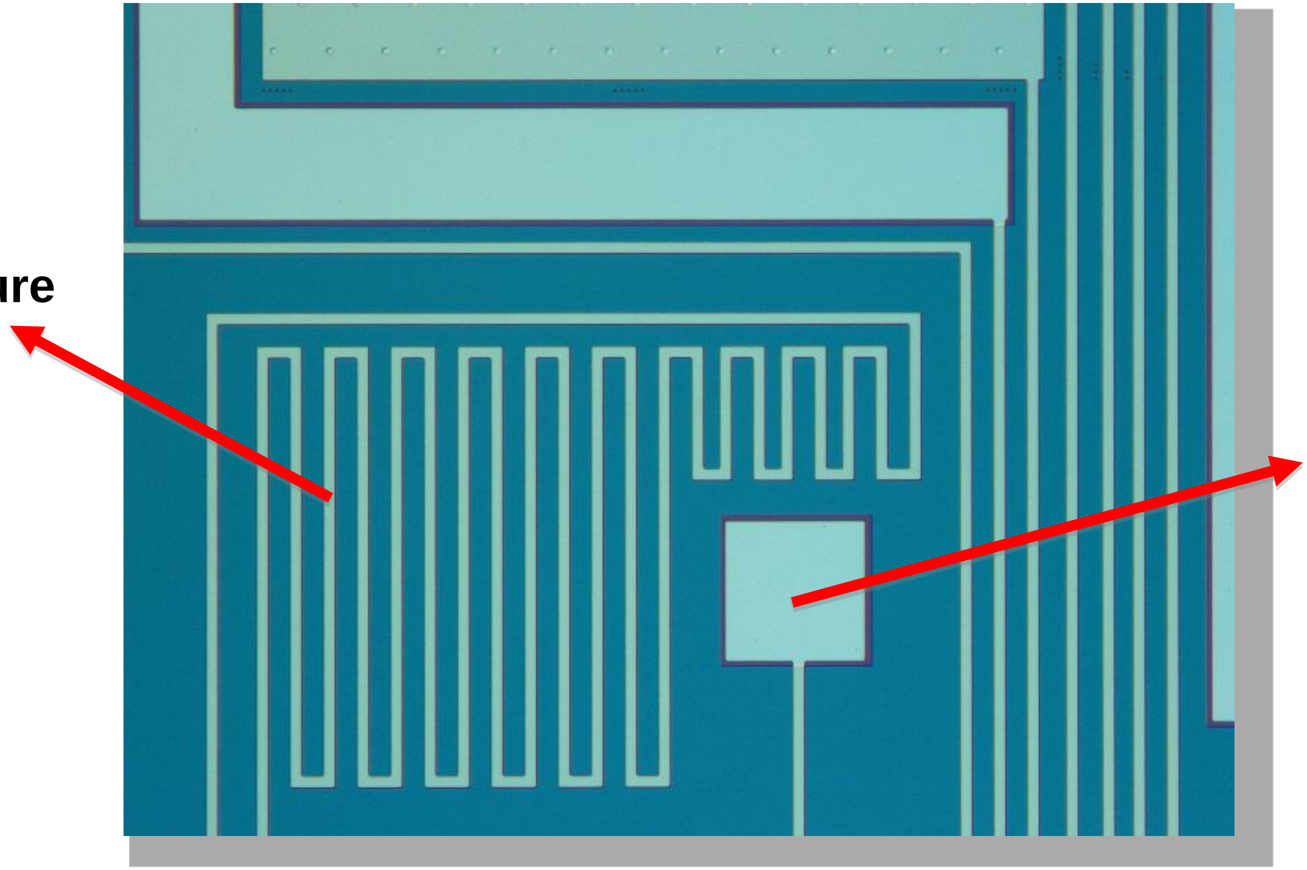
Figure 2. .Peak Potential shift versus pH

$$E = E^0 - \frac{RT}{nF}\ln\left(\frac{C_r}{C_o}\right) - \frac{RT}{F}pH$$



$$i \propto nFAD\left(\frac{nF\nu D}{RT}\right)^{1/2} C_r$$

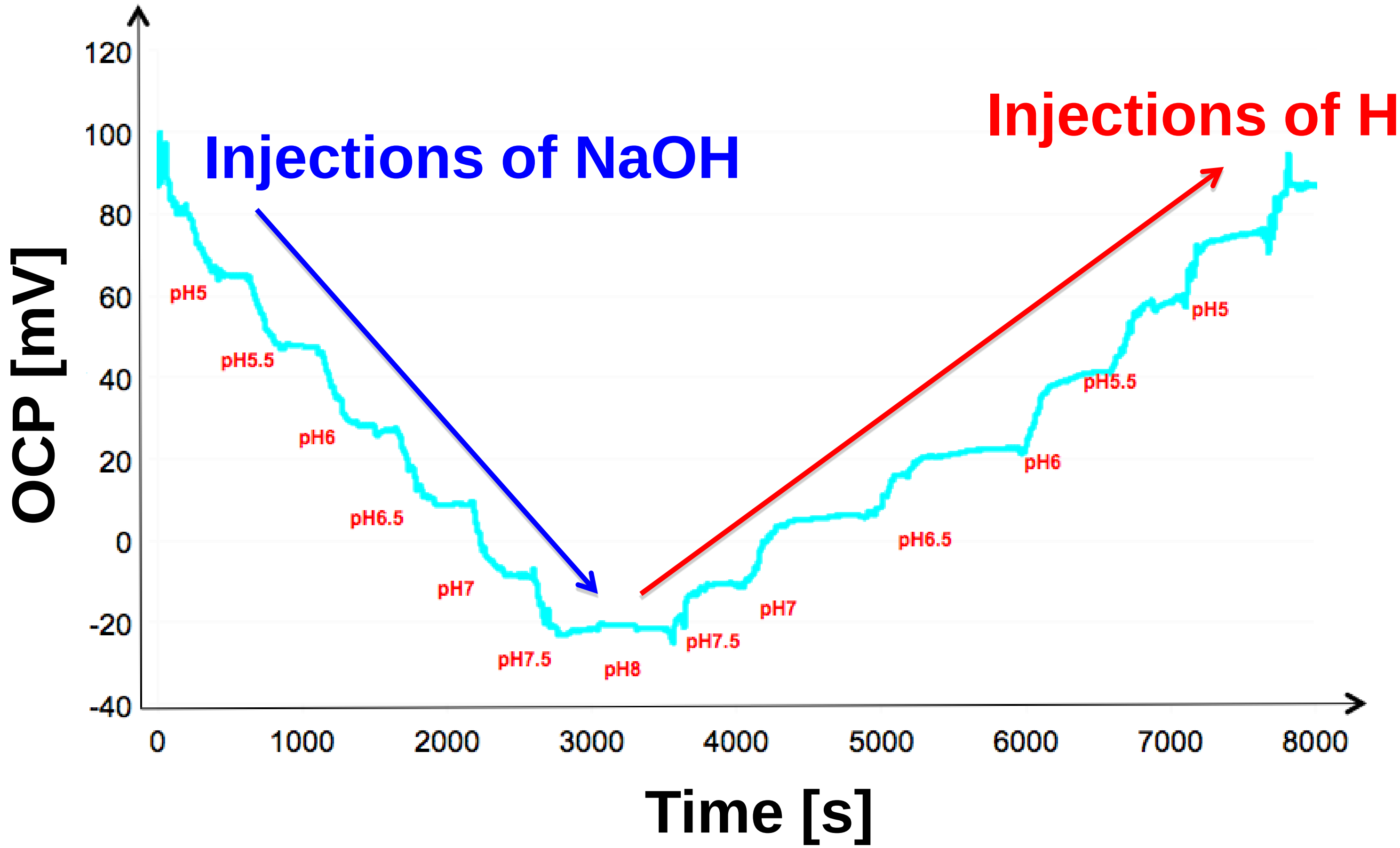
4. Reliability in Temperature & pH



A. Cavallini, al et, S. Carrara / IEEE BioCAS, 2012.

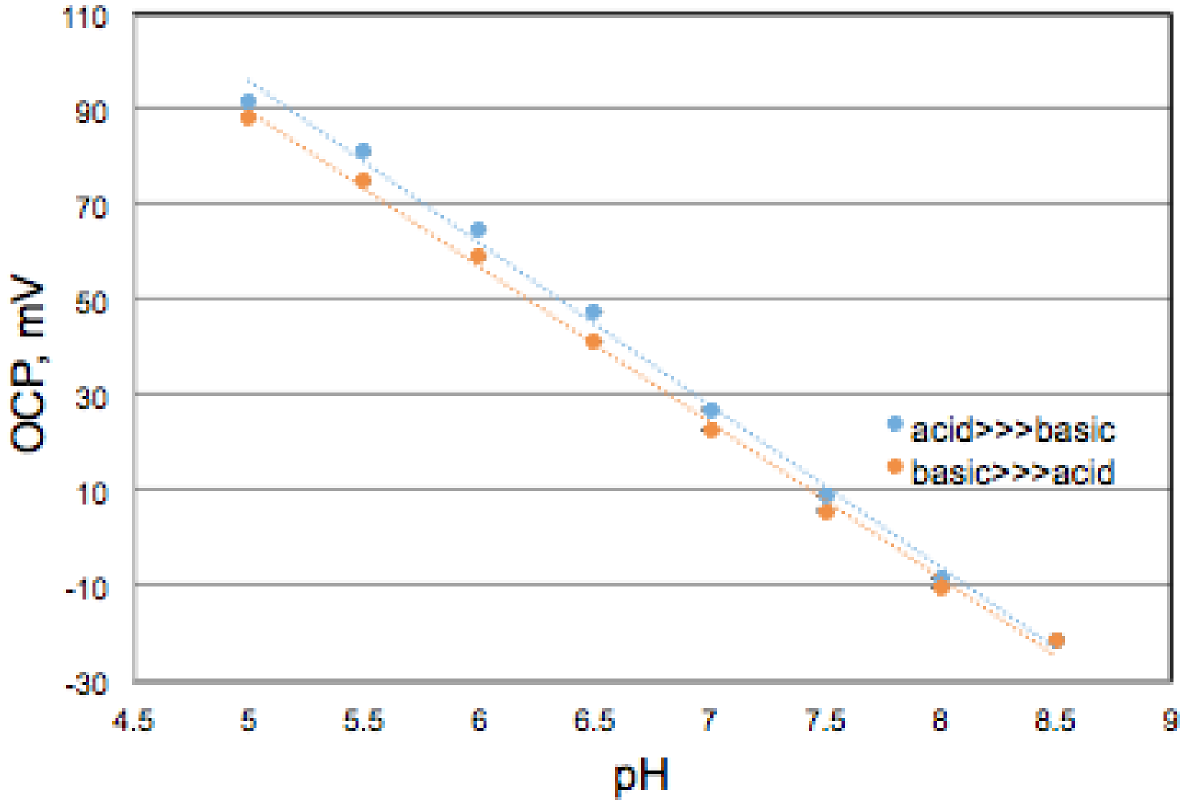
Thin-film technology for pH and Temperature sensors

4. Reliability in pH: OCP vs time



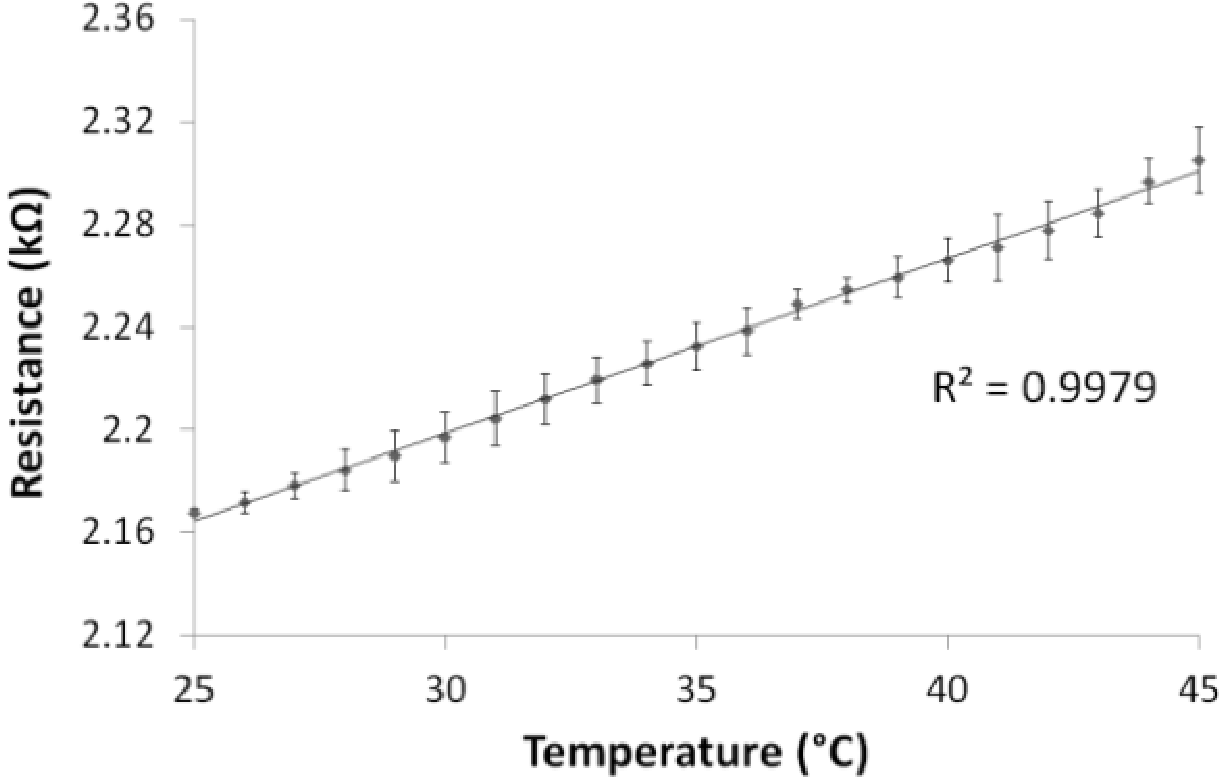
Measure of Open Circuit Potential (OCP)
during pH changes in time

4. Reliability in pH: OCP vs time



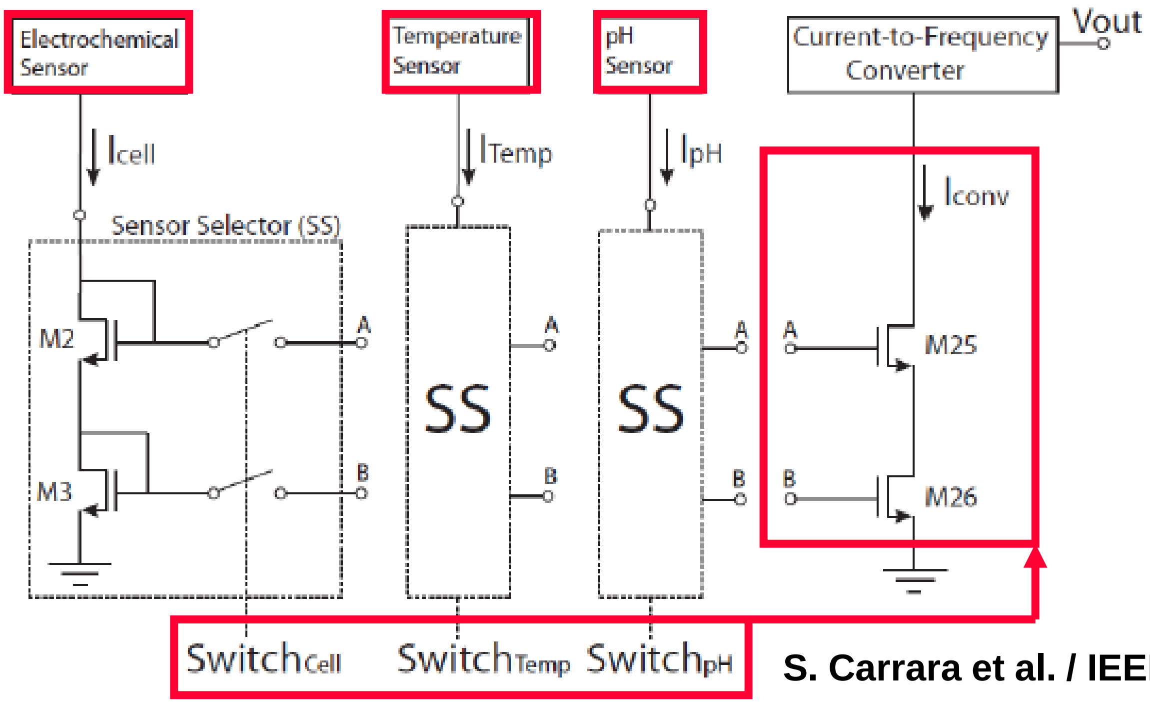
Measure of Open Circuit Potential (OCP) vs pH

4. Reliability in T



Measure of the Resistance vs Temperature

5. Multiplexing Molecular detection with T and pH

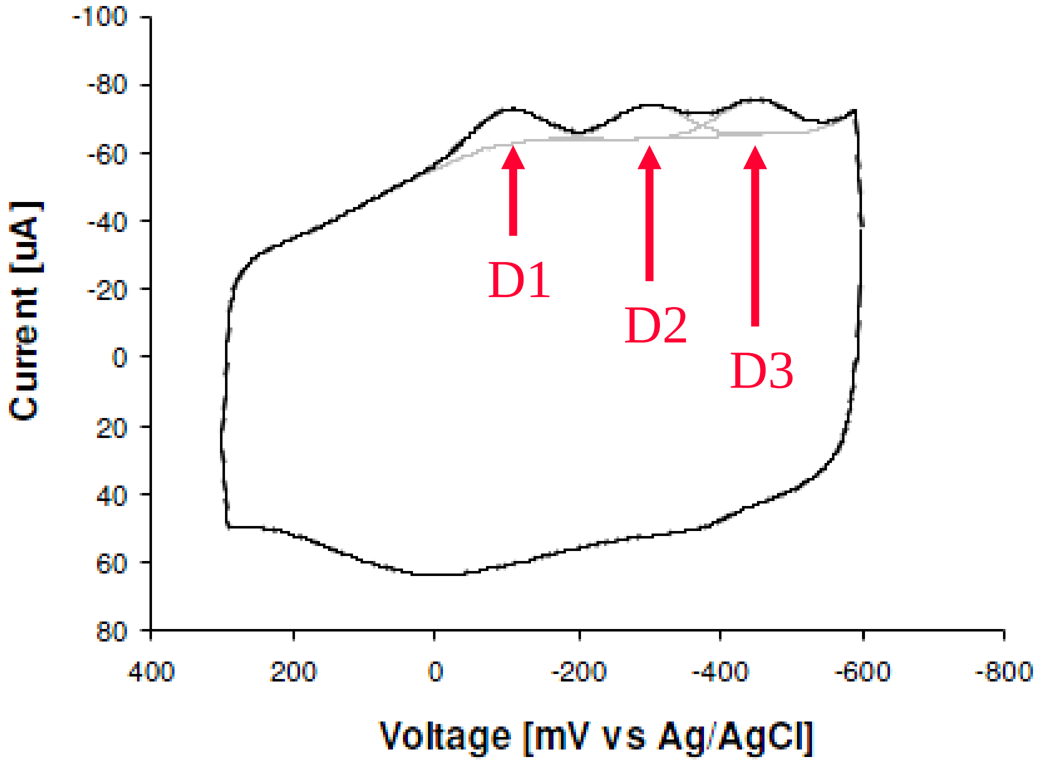


S. Carrara et al. / IEEE BioCAS. 2010

Figure 8. The bloks-scheme of the multiplexing

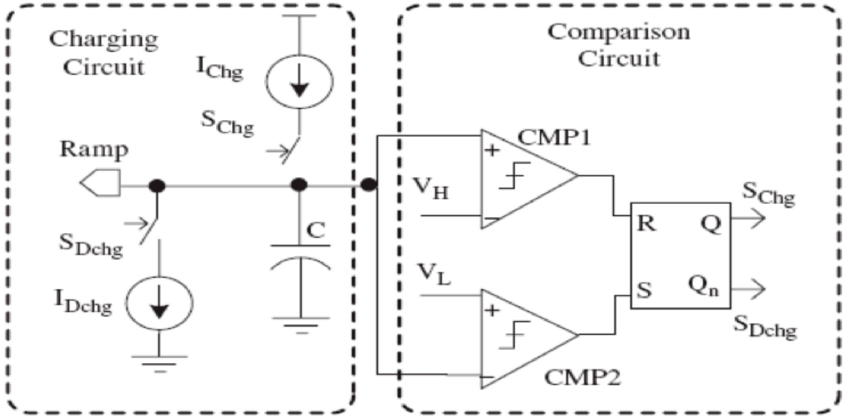
The switches also multiplex the T and pH measure

6. Reliability for Voltage Sweep



Sweeping the voltage is definitely required to distinguish each single drug contribution in the Voltammogram

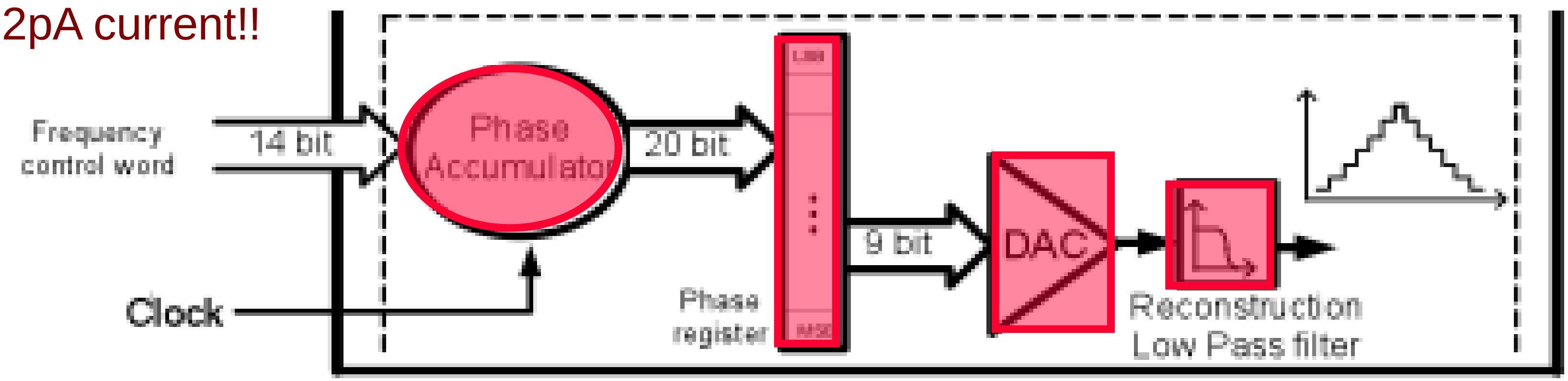
6. Reliability for Voltage Sweep



The conventional way to generate a ramp voltage

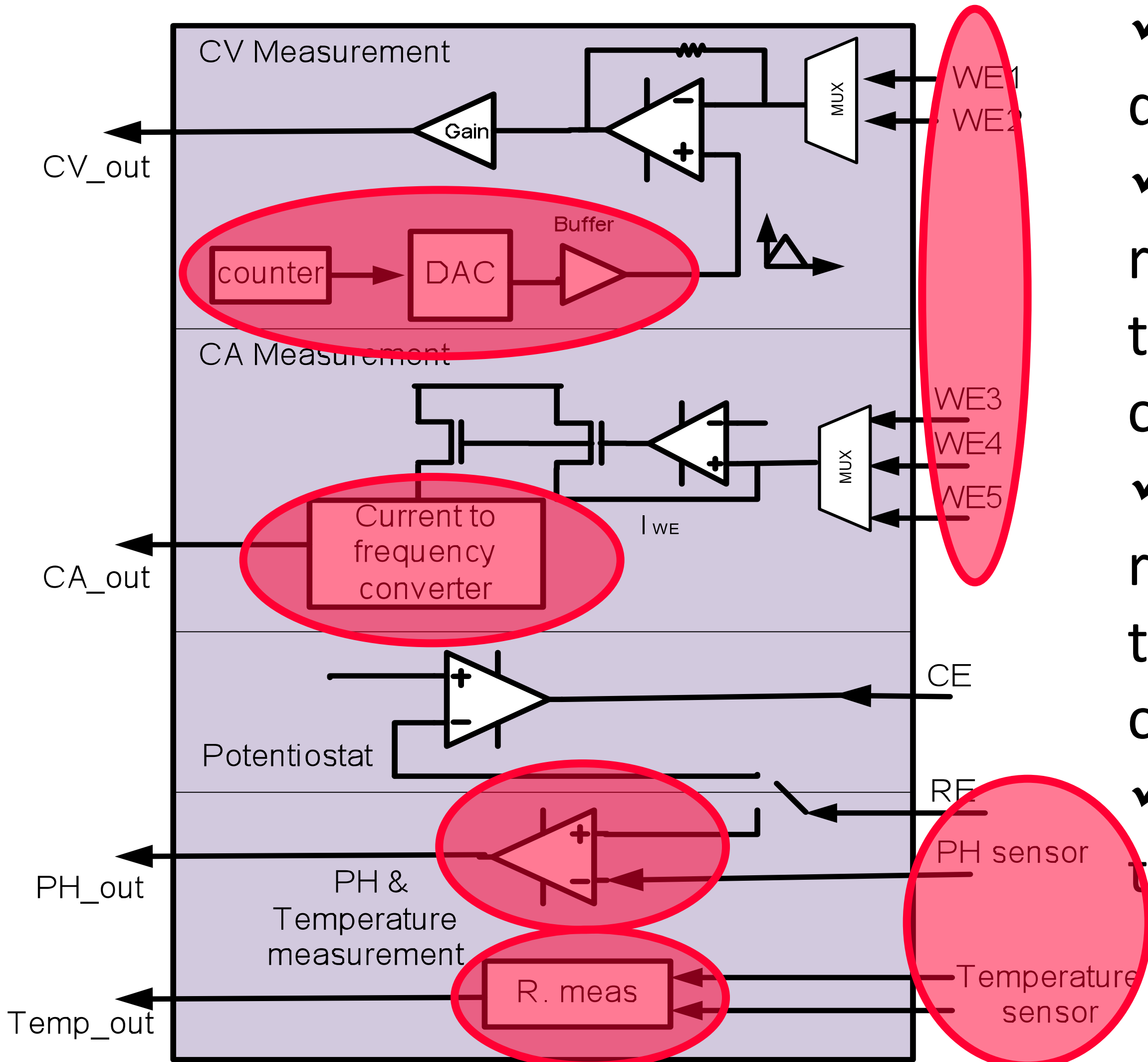
direct digital synthesizer (DDS) to generate A very slow ramp*

The slope is about 20 mV/s means 2pA current!!



al et S. Carrara, et al, IEEE LiSSA 2011

The Chip Frontend; 2nd prototype

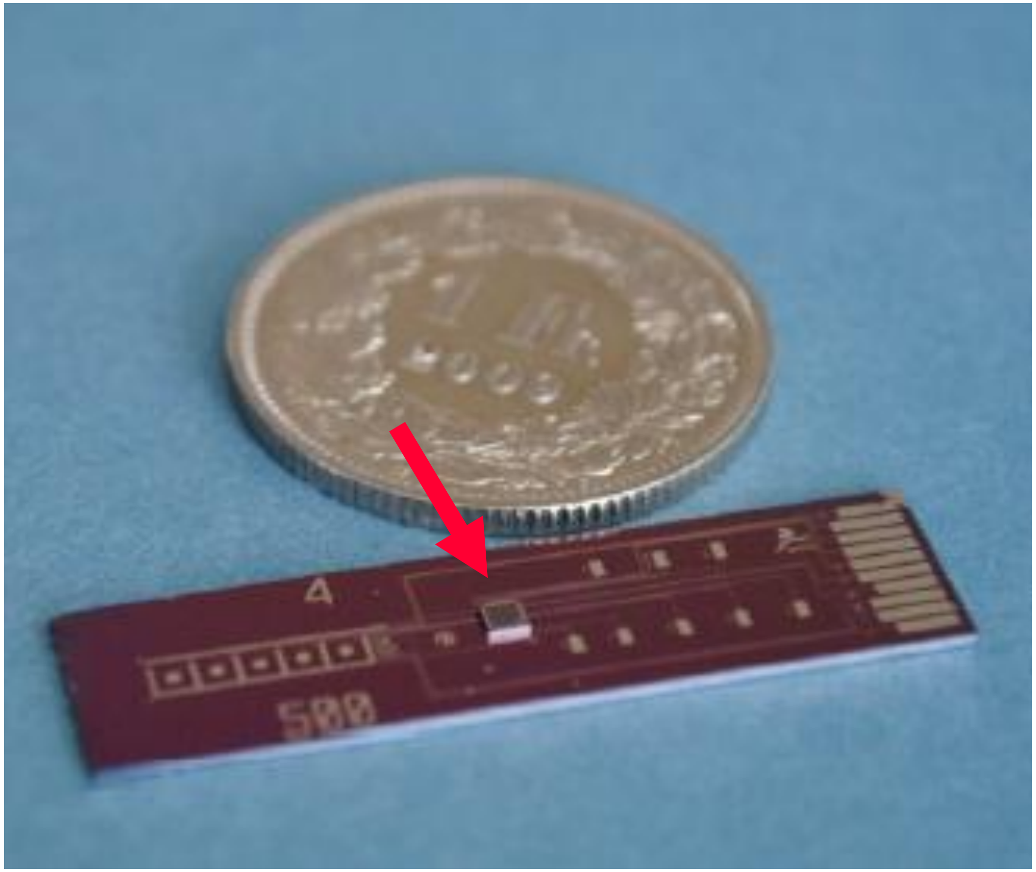


- ✓ up to 5 different target detection
- ✓ CV actuation and readout for up to 3 targets with sub µA current
- ✓ CA initiation and readout for up to 2 targets with sub µA current
- ✓ Embedded PH and temperature sensing

S. Ghoreishizadeh, S. Carrara et al. / IEEE TBCAS 2013, submitted

IC interfaced to the passive platform

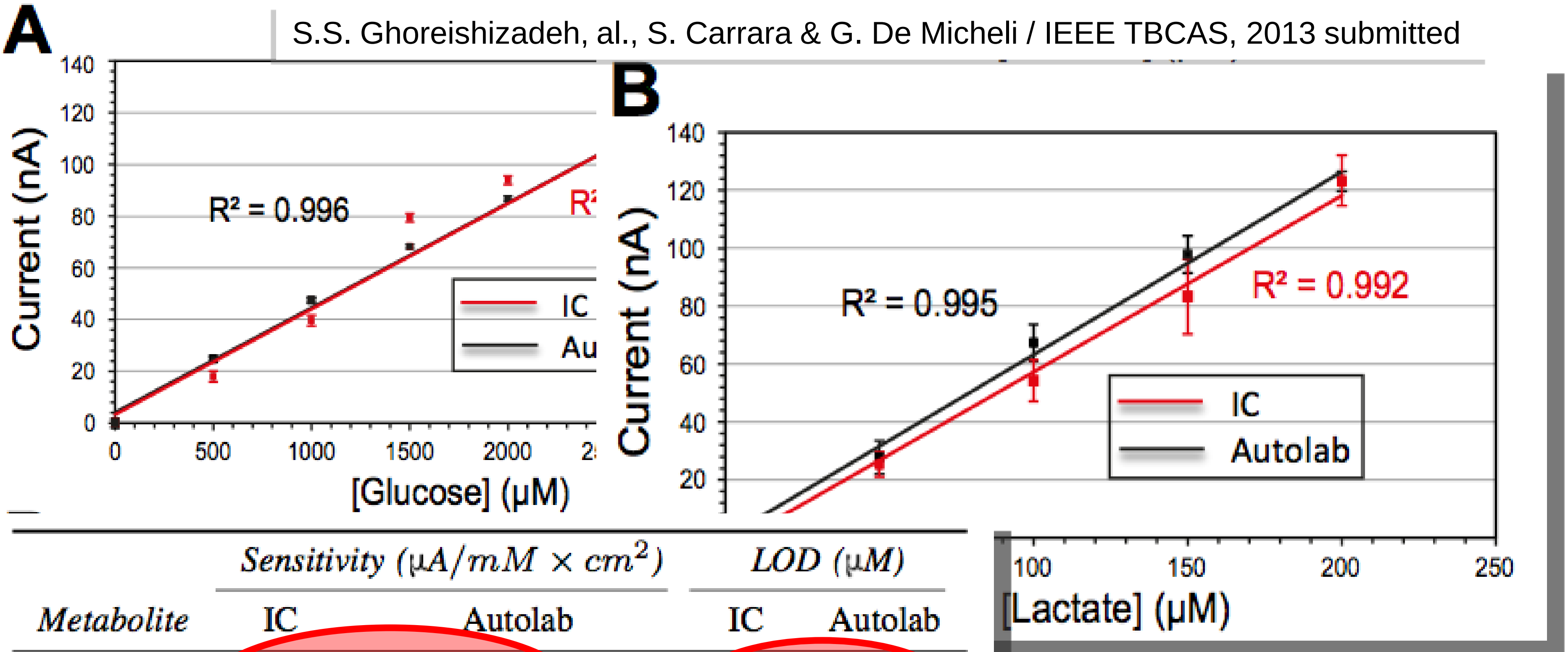
S. Carrara et al. / IEEE Sensors Conf. 2012



The IC has been fabricated in UMC 0.18 technology and interfaced to the passive multi-panel platform

The IC Potentiostat

S.S. Ghoreishizadeh, al., S. Carrara & G. De Micheli / IEEE TBCAS, 2013 submitted

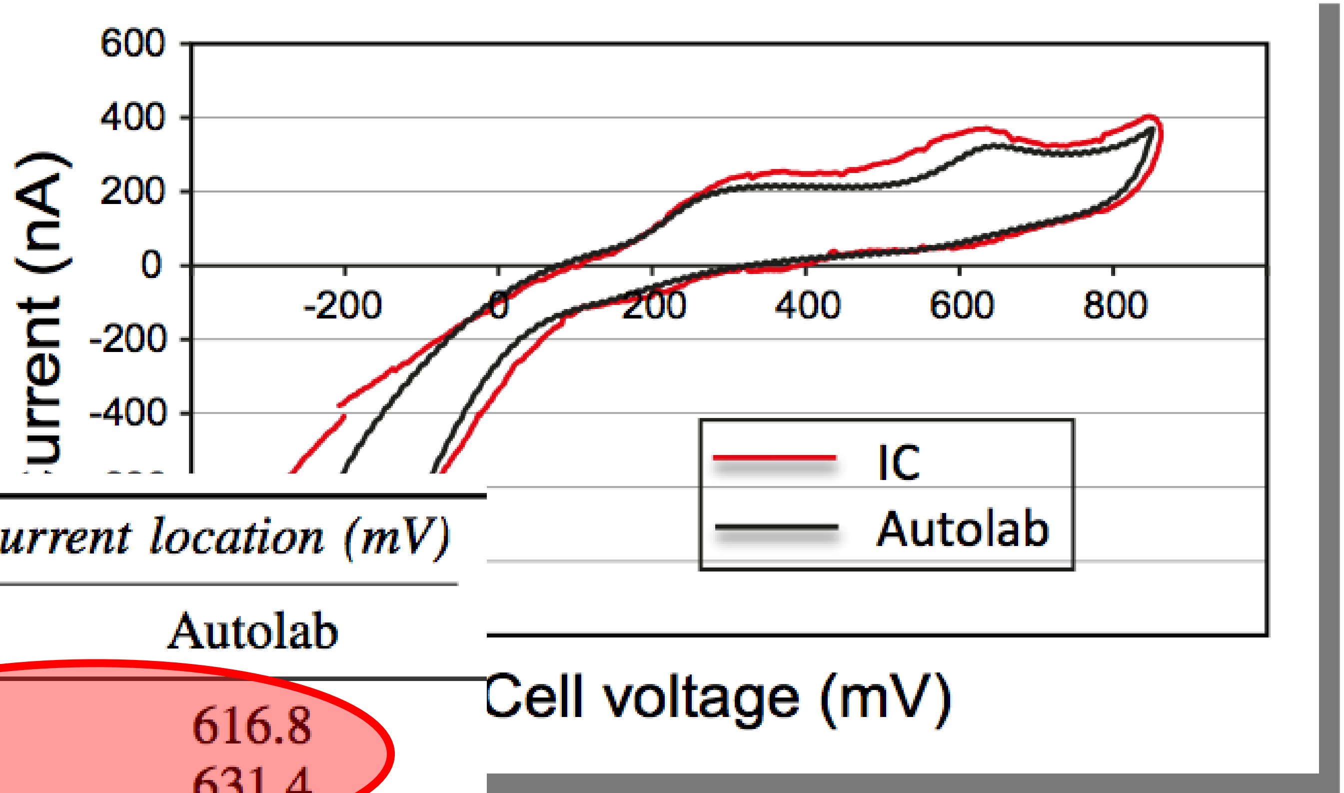


	Sensitivity ($\mu A/mM \times cm^2$)		*LOD* (μM)	
Metabolite	IC	Autolab	IC	Autolab
Glucose	27.2	27.3	87.9	17.5
Lactate	285.7	391.3	21.4	4.1

The integrated potentiostat works quite well with respect the well-know and costly lab-one by Autolab

The IC Potentiostat

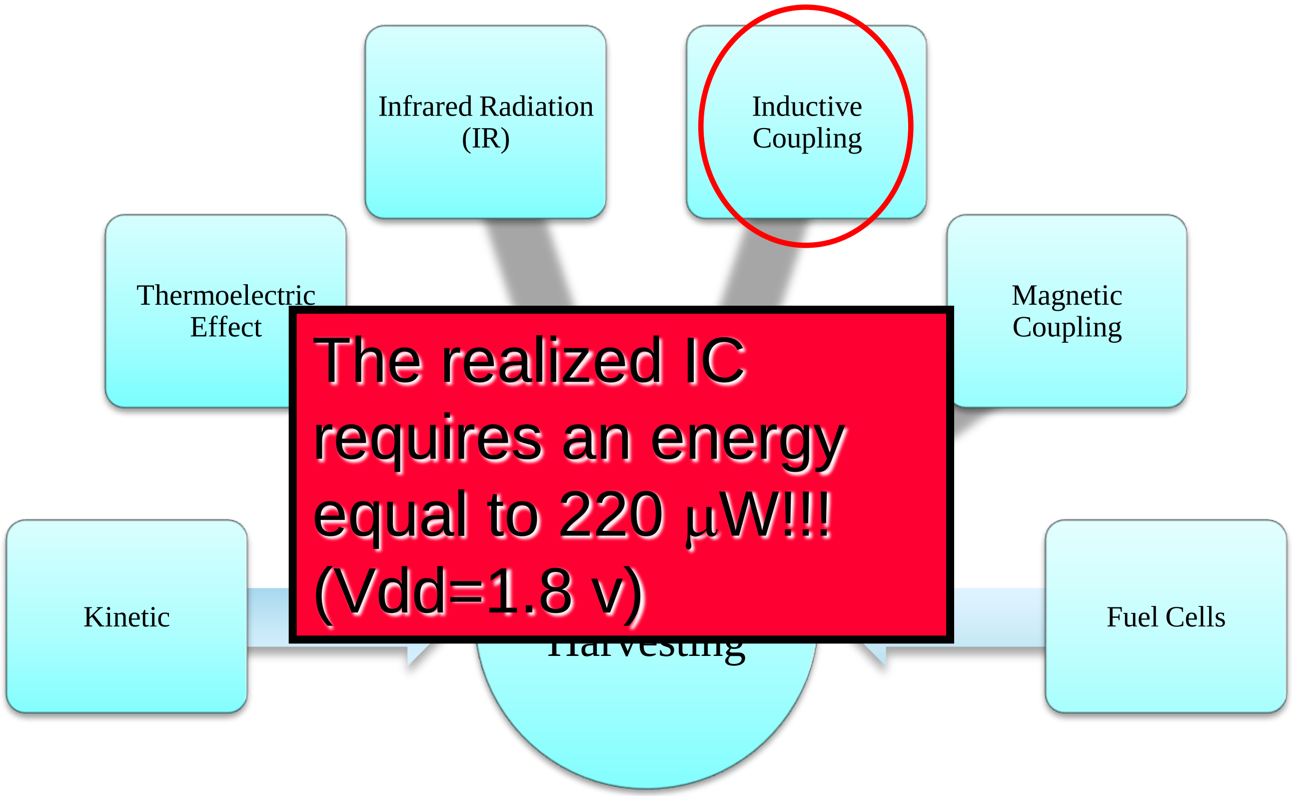
S.S. Ghoreishizadeh, al., S. Carrara & G. De Micheli / IEEE TBCAS, 2013 submitted



	Peak current location (mV)	
[Etoposide]	IC	Autolab
200 μM	612.5	616.8
400 μM	609.5	631.4

The integrated potentiostat works quite well with respect the well-know and costly lab-one by Autolab

7. Energy Scavenging Strategies



The realized IC requires an energy equal to 220 μW!!! (Vdd=1.8 v)

Inductive Coupling

Ref.	Coil Area (λ = 10 mm²)	Carrier Frequency	Data Transmission	Bit Rate	Power Consumption	Efficiency	Distance	Measurement Site	Implantation Site
[8]	Tx: 7.8 λ Rx: 1.7 λ	4 MHz	twd Int.: PWM-ASK twd Ext.: ASK	twd Ext.:125 kbps	10 mW		5 mm	Air	Neural Recording System
[9]	Tx: 196.3 λ Rx: 31.4 λ	4 MHz	twd Ext.: LSK	5 kbps	6 mW		25 mm	Water Bearing Colloids	Various
[10]	Tx: 13200 λ Rx: 25.2 λ	1 MHz			150 mW	1% (min)	205 mm	PVC Barrel	Stomach
[11]	Tx: 184.9 λ Rx: 10 λ	1 MHz			10 mW	18.9% (max)	5 mm	Air	Cerebral Cortex
[12]	Tx: 282.7 λ Rx: 31.4 λ	0.7 MHz	twd Int.: ASK twd Ext.: LSK	twd Int.: 60 kbps twd Ext.: 60 kbps	50 mW	36% (max)	30 mm		Orthopaedic Implant
[13]	Tx: 31.4 λ Rx: 5 λ	10 MHz	twd Int.: ASK twd Ext.: BPSK	twd Int.: 120 kbps twd Ext.: 234 kbps	22.5 mW in vitro ≈ 19 mW in vivo		15 mm	Rabbit	Muscles
[14]	Tx: 196.3 λ Rx: 3.5 λ	5 MHz	twd Int.: OOK	100 kbps	5 mW		40 mm		Neural Stimulator
[15]	≈ Rx: 112.5 λ	6.78 MHz	twd Int.: OOK twd Ext.: LSK	twd Ext.:200 kbps	120 mW	20% (max)	25 mm	Dog Shoulder	Muscolar Stimulator
[18]	Tx: 40 λ Rx: 0.4 λ	915 MHz			0.14 mW	0.06%	15 mm	Bovine Muscle	Various

!

[8] T.Akin et al., "A wireless implantable multichannel digital neural recording system for a micromachined sieve electrode", *IEEE J. Solid-State Circ.*, vol.33, pp. 109-118, Jan 1998

[9] C.Sauer et al., "Power Harvesting and Telemetry in CMOS for Implanted Devices", *IEEE Trans on Circuits and Systems*, vol.52, n.12, pp.2605-2613, 2005

[10] B. Lenaerts et. al., "An inductive power link for a wireless endoscope", *Biosensors and Bioelectronics*, vol.22, pp. 1390-1395, 2007

[11] K.M. Silay et. al., "Load Optimization of an Inductive Power Link for Remote Powering of Biomedical Implants", *IEEE Proc. of International Symposium on Circuits and Systems 2009*, pp. 533-536, May 2009.

[12] B. Lenaerts et. al., "An inductive power system with integrated bi-directional data-transmission", *Sensors and Actuators A*, vol. 115, pp.221-229, 2004

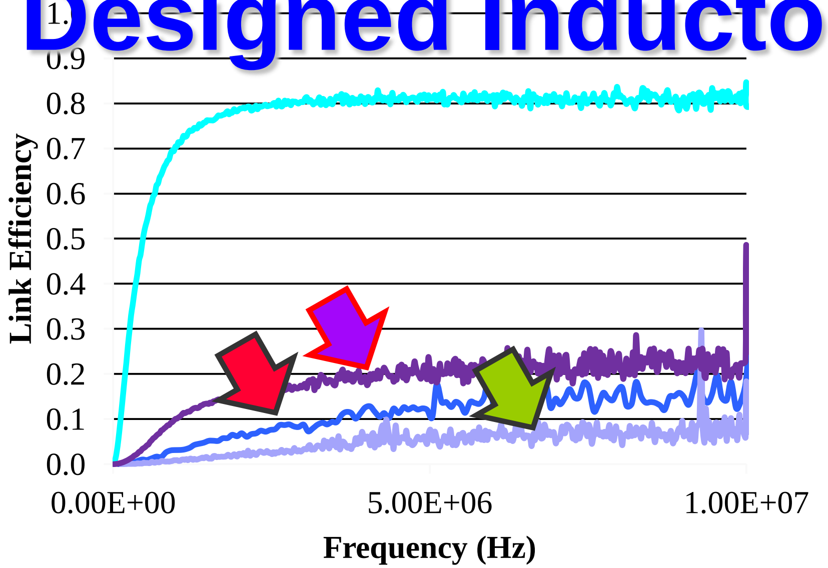
[13] J. Parramon et al., "ASIC-based batteryless implantable telemetry microsystem for recording purposes", *Eng. In Med. and Bio. Soc.*, in *Proc. of the 19th Annual Int. Conf.*, vol.5, pp. 2225-2228, 1997.

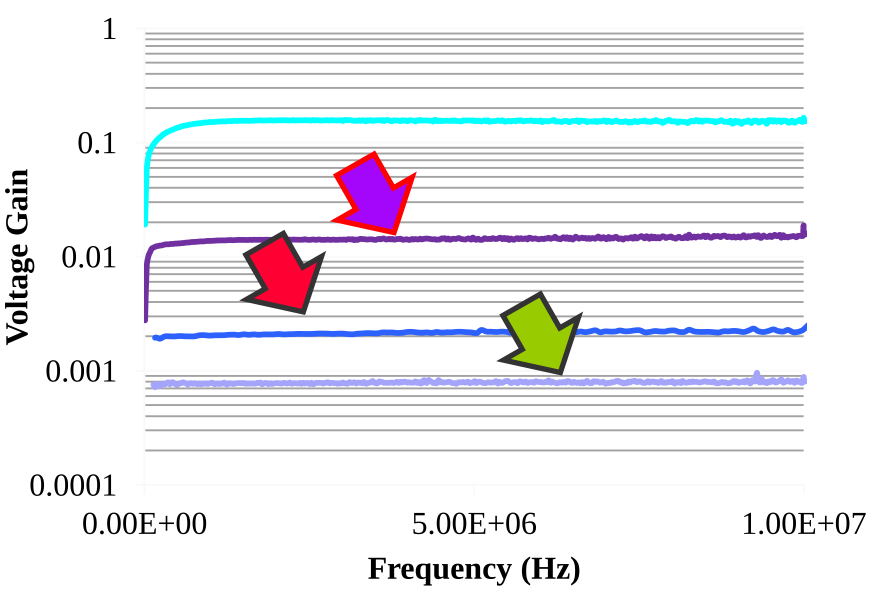
[14] G. Gudnason et al., "A Chip for an Implantable Neural Stimulator", *Analog Integrated Circuits and Signal Processing*, vol.22, pp.81-89, 1999

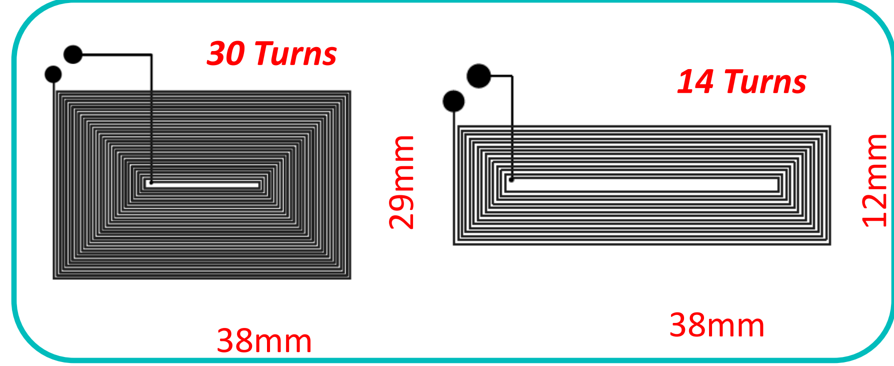
[15] B. Smith et al., "An externally powered, multichannel, implantable stimulator-telemeter for control of paralyzed muscle", *IEEE Trans. on Biomed. Eng.*, vol.45, pp.468-475, 1998

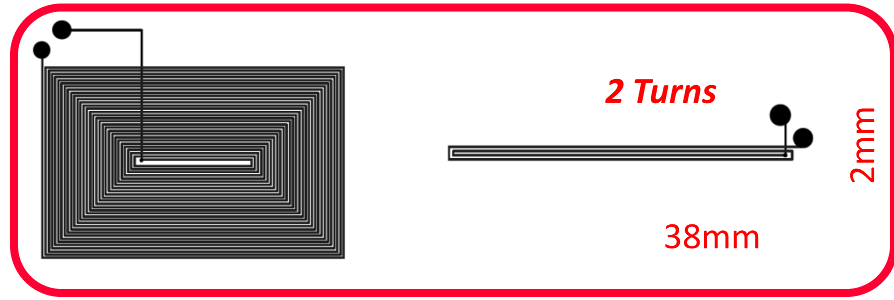
[18] A.S.Y. Poon et al., "A mm-sized Implantable Power Receiver with Adaptative Link Compensation", Stanford University

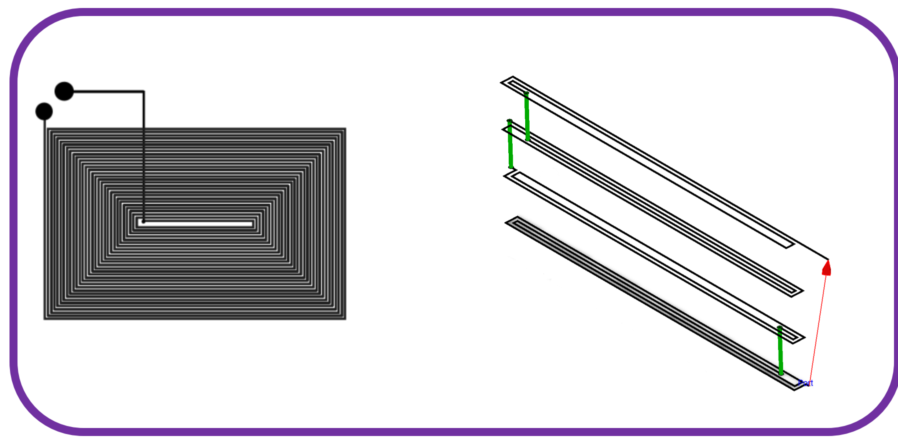
Measures on the Designed Inductors

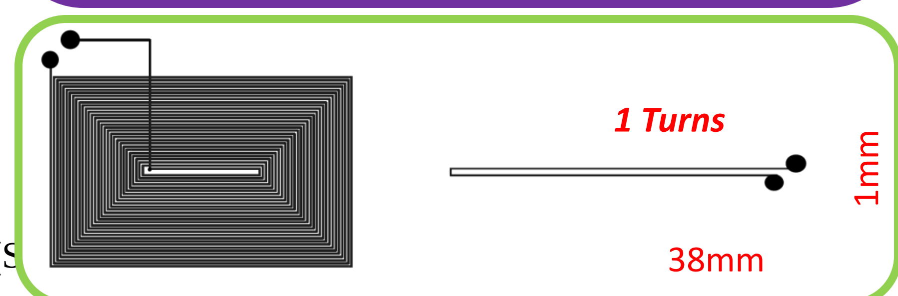




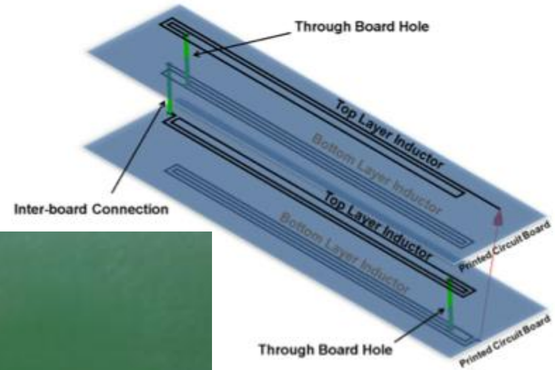




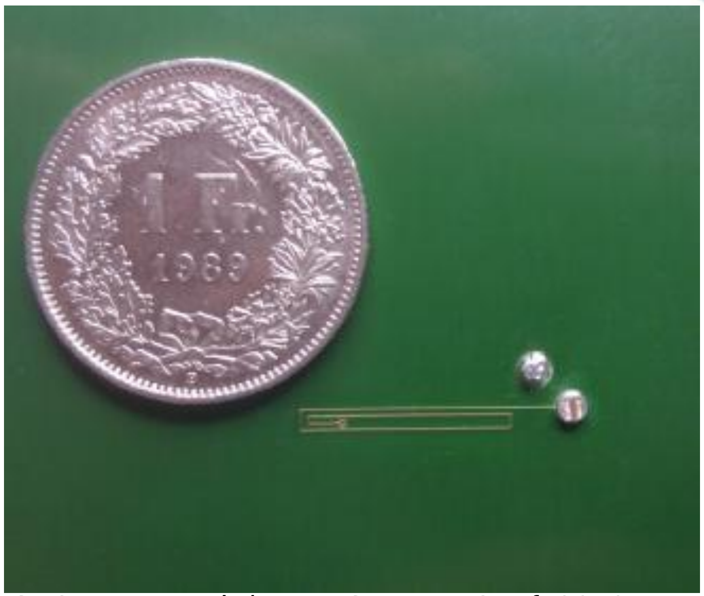




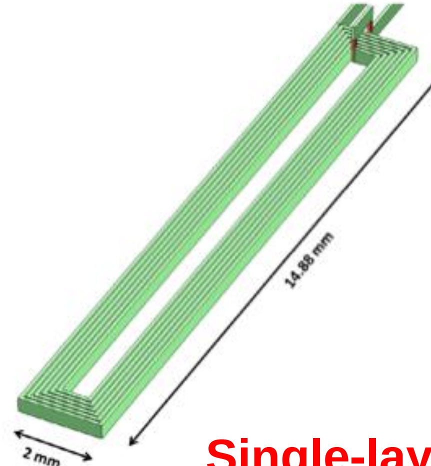
The Tiny Spiral Inductors



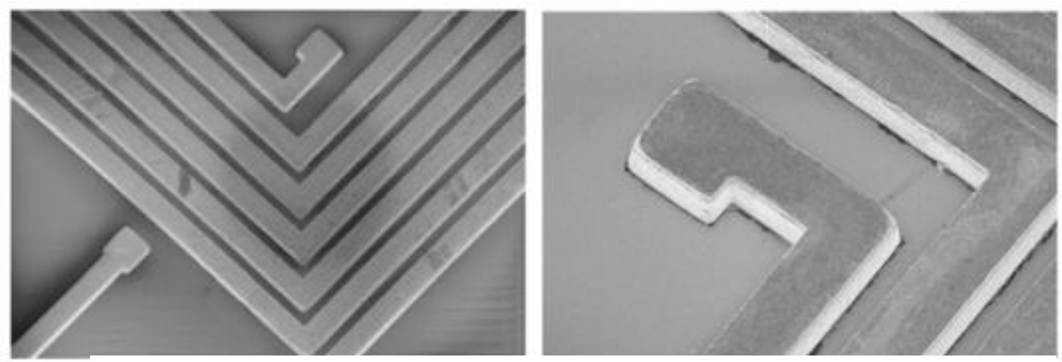
Multi-layer on PCB



S. Carrara et al. / IEEE Sensors Conf. 2012



Single-layer on Si

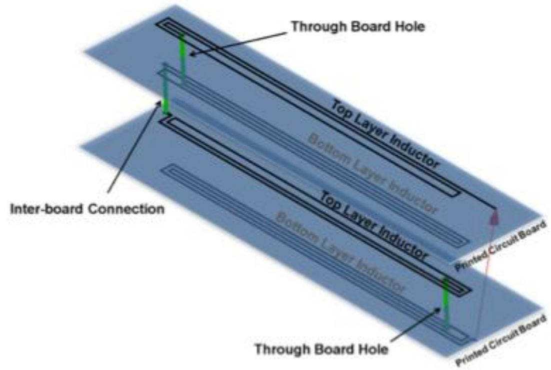


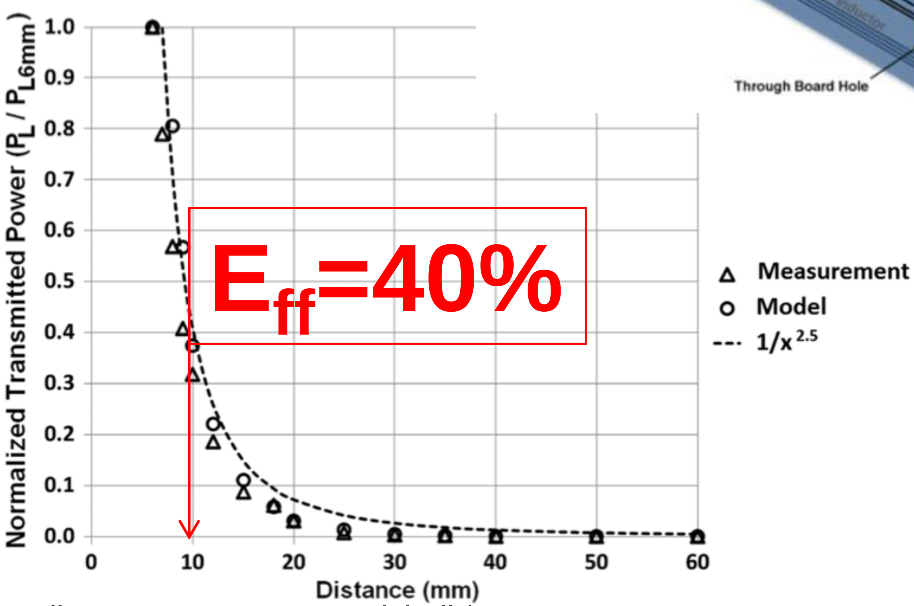
J. Olivo et al. / Microelectronic Engineering 113 (2014) 130–135

Two versions of the antenna have been fabricated and tested

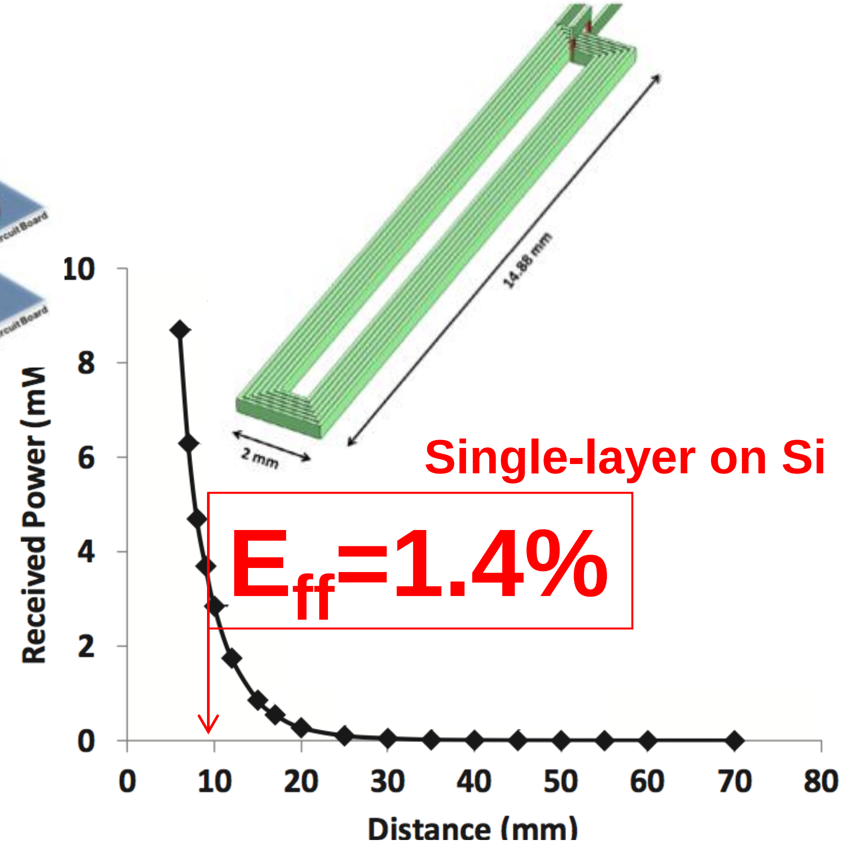
The Tiny Spiral Inductors on Air

Multi-layer on PCB





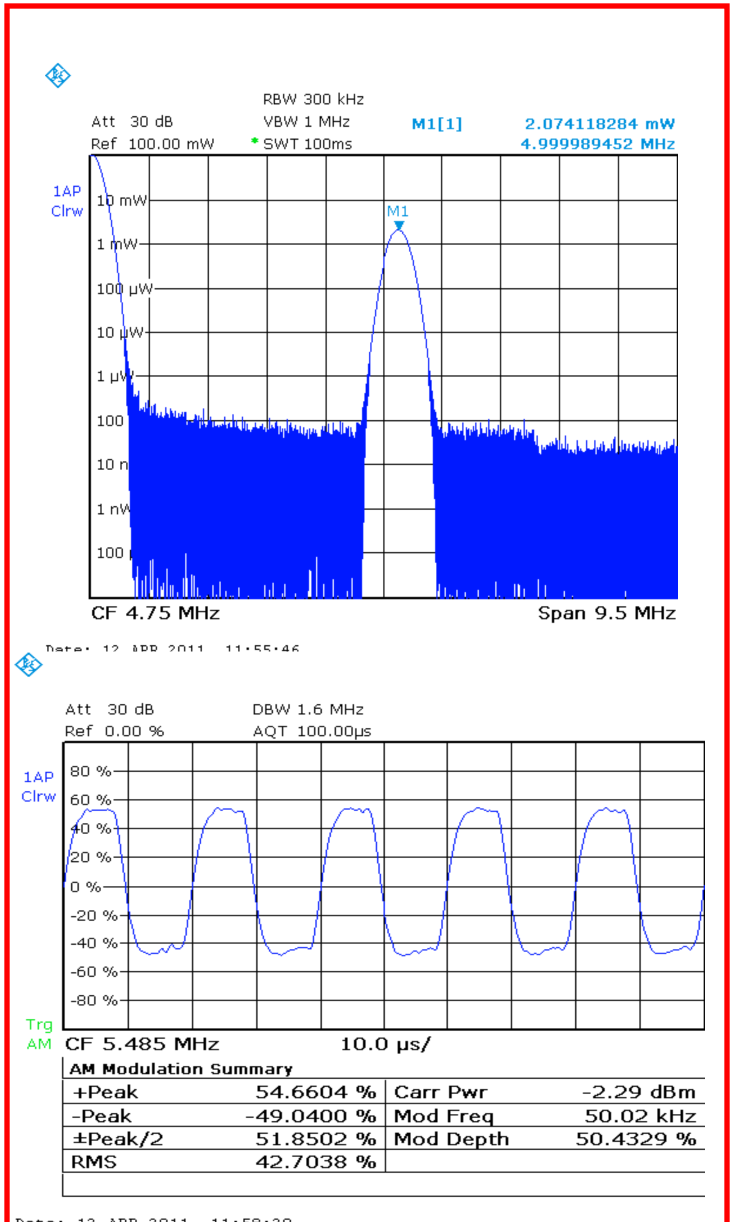
J.Olivo, S. Carrara, G.Demicheli / IEEE TBCAS 2013

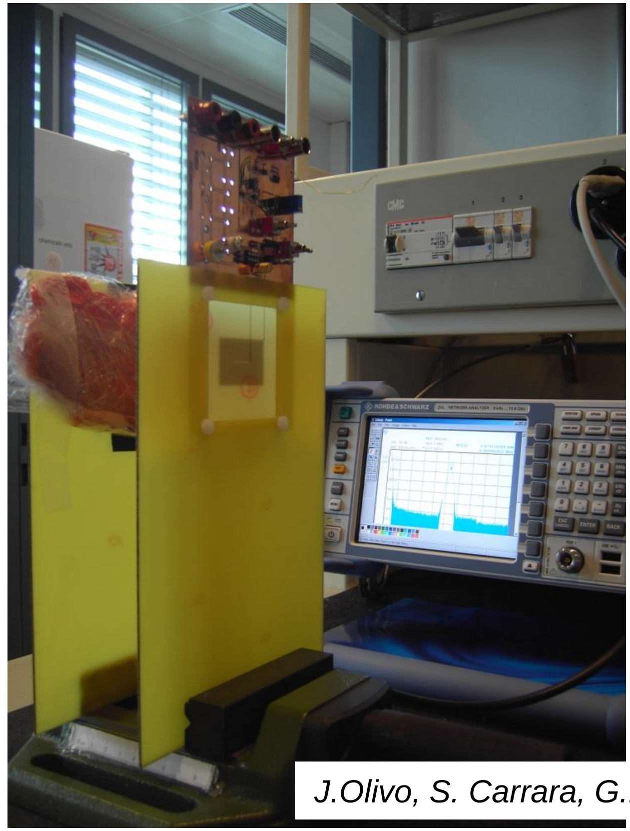


J. Olivo et al. / Microelectronic Engineering 113 (2014) 130–135

Two versions of the antenna have been fabricated and tested

The Multi-layer Inductor on Tissue

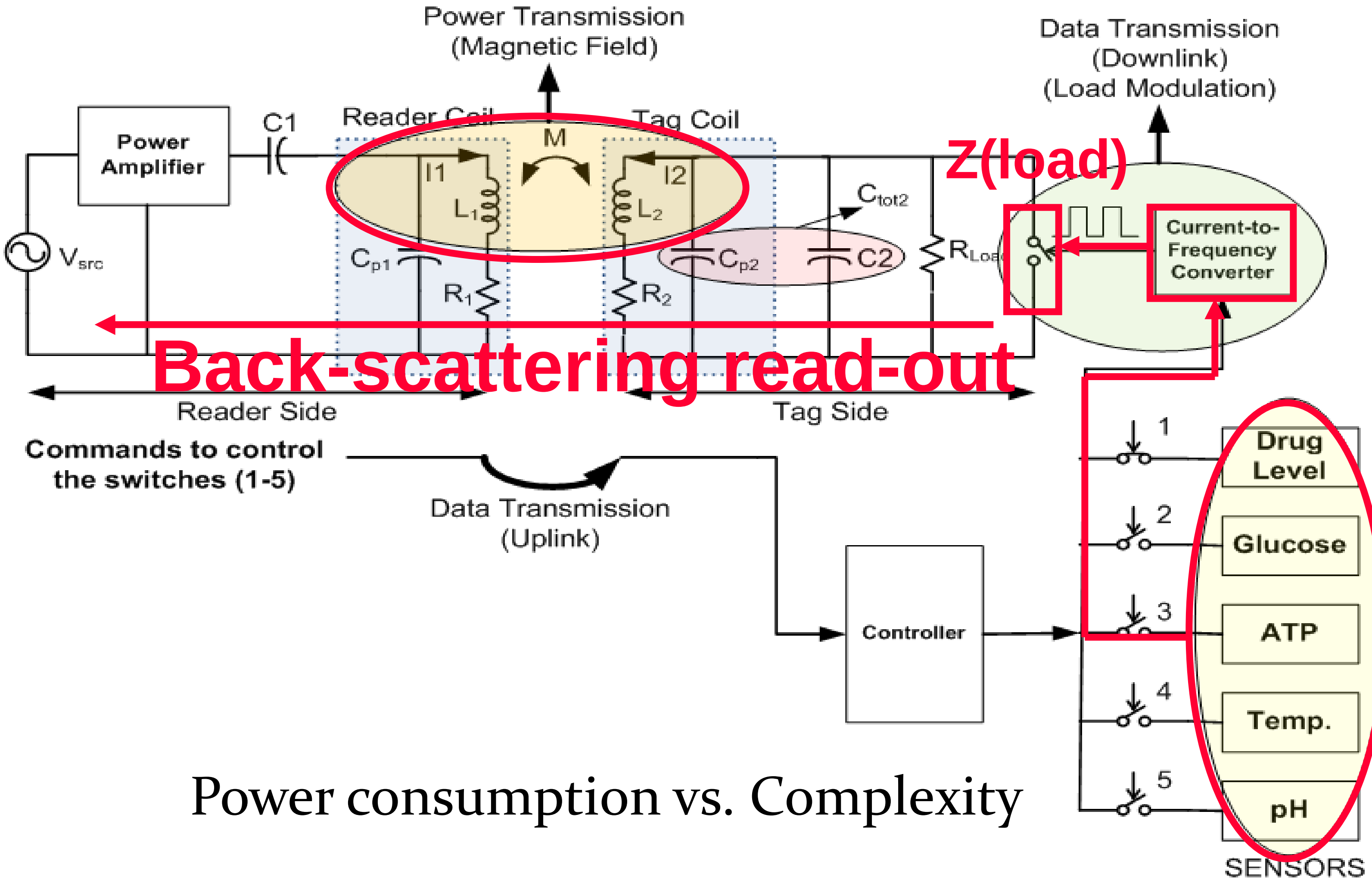




J.Olivo, S. Carrara, G.Demicheli / IEEE TBCAS 2013

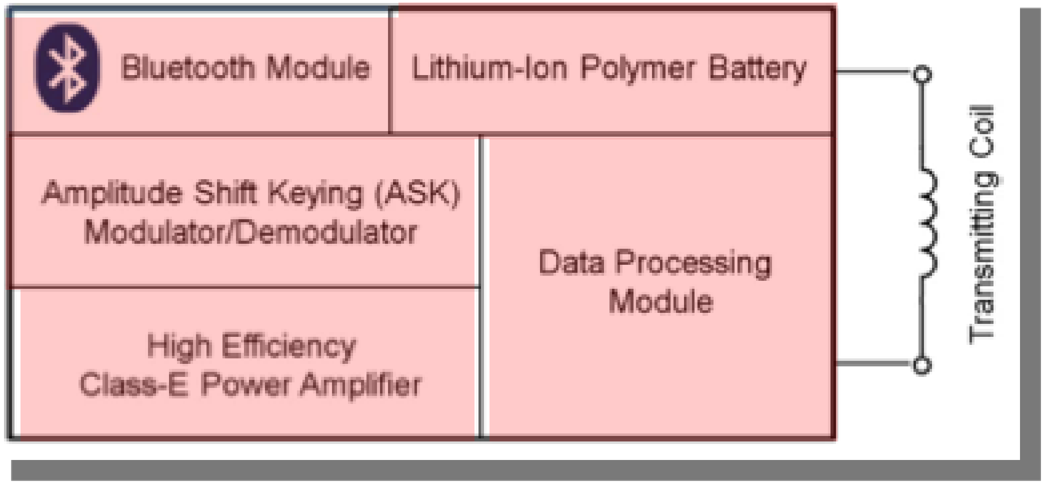
- 2.09 mW (25mm – Bovine Tissue) - THD 2.08%
- 3.6 mW (14mm – Bovine Tissue) - THD 2.27%
- Communication is achieved at 100 kbps

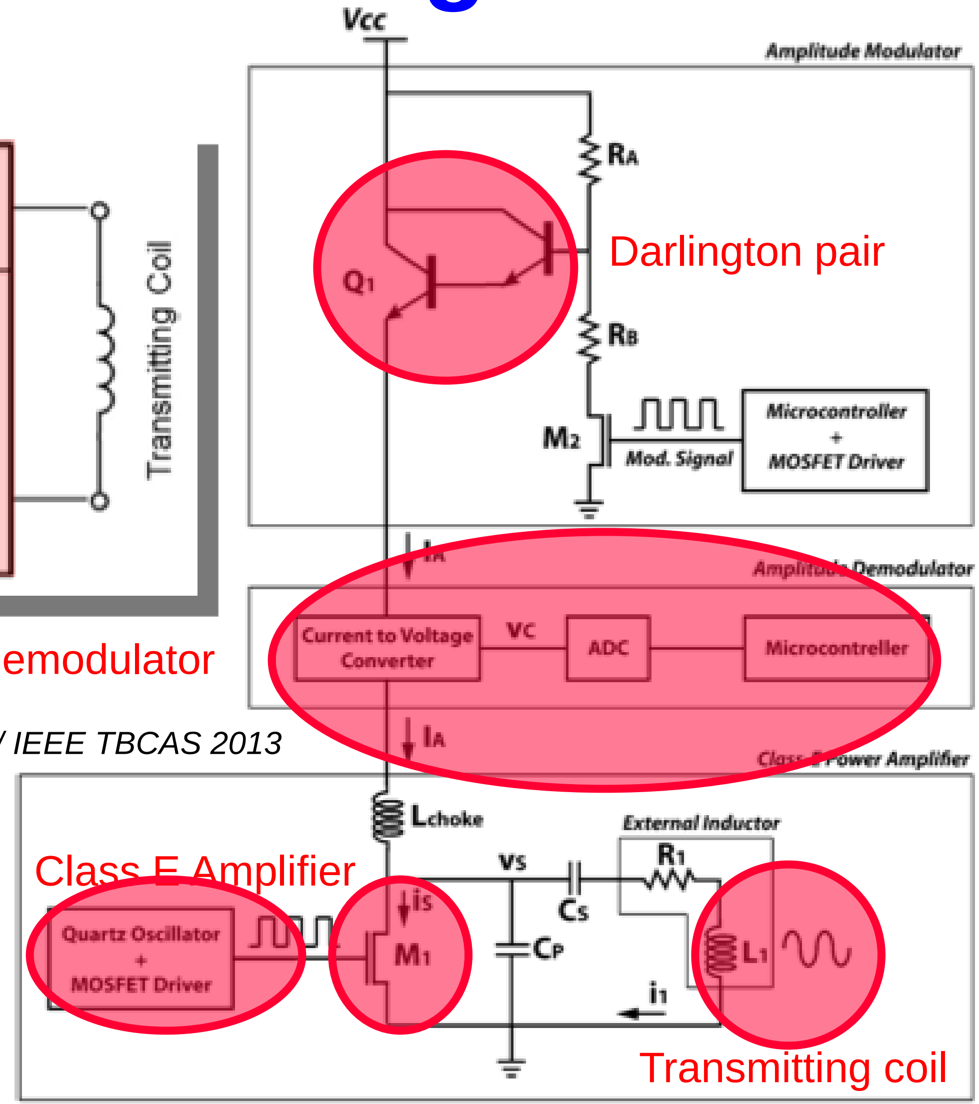
Data Transmission



Power consumption vs. Complexity

The Patch Design

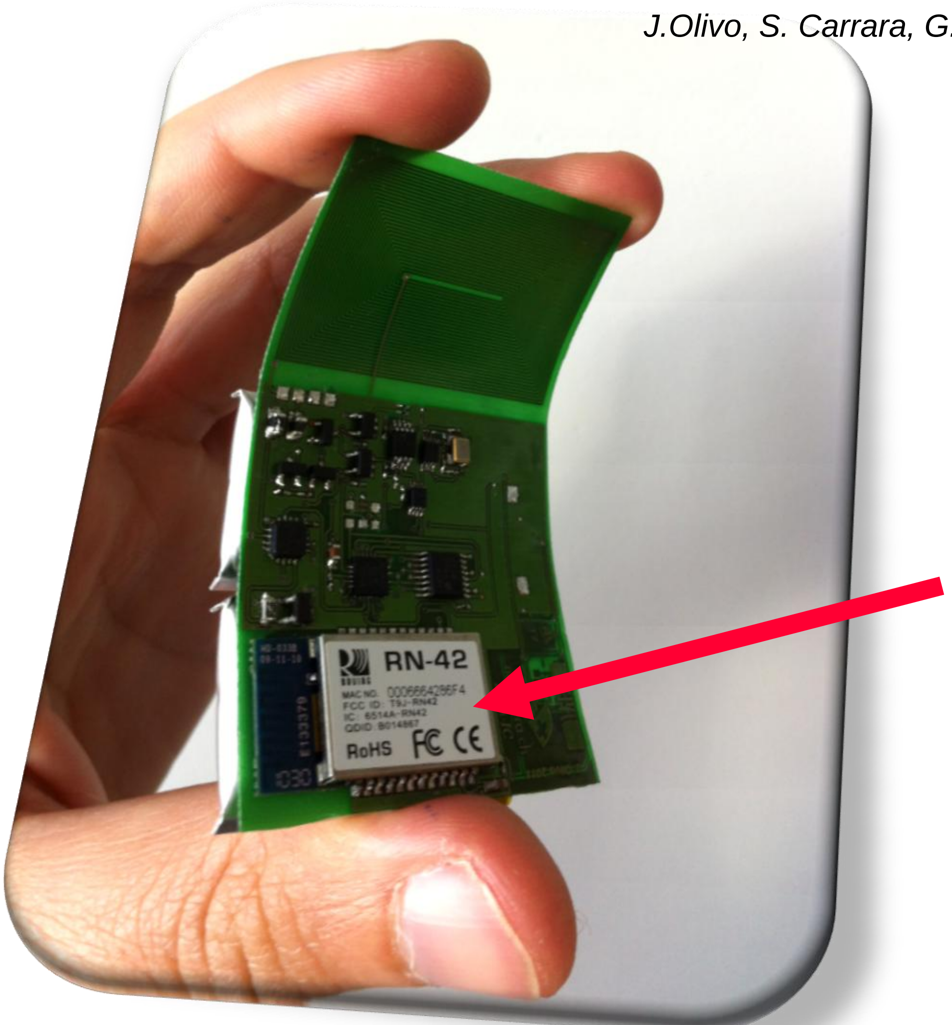




J.Olivo, S. Carrara, G.De Micheli / IEEE TBCAS 2013

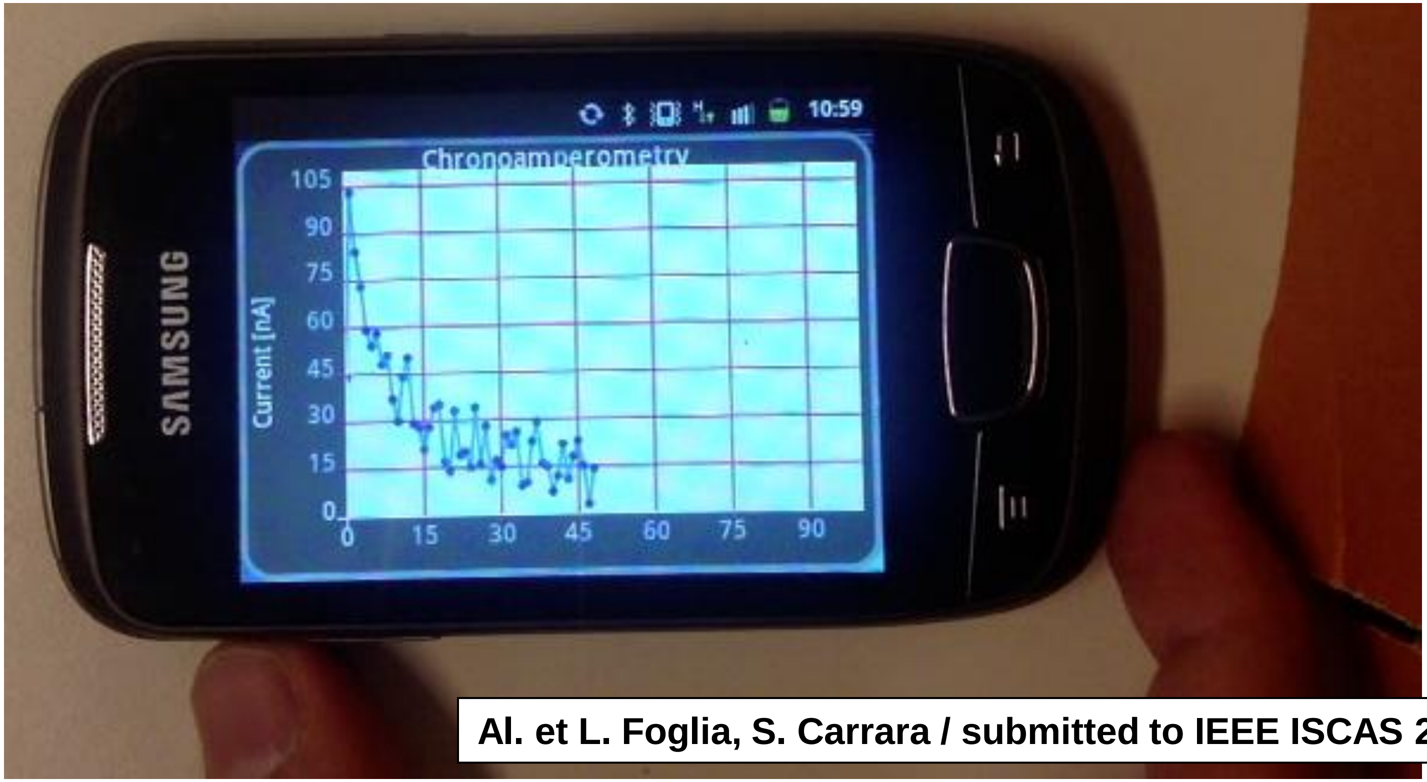
The Realized Remote Powering Patch

J.Olivo, S. Carrara, G.De Micheli / IEEE TBCAS 2013



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

The Android interface



Al. et L. Foglia, S. Carrara / submitted to IEEE ISCAS 2014

The Bluetooth® Interface for android smartphones as well as for iPads has been already developed

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20 March 2013 Last updated at 01:49 GMT

4.3K Share

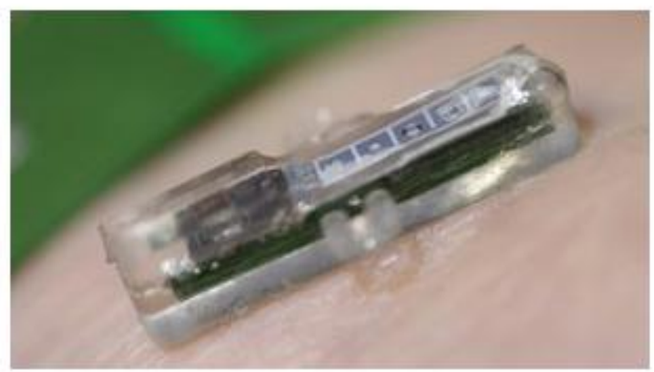
'Under the skin' blood-testing device developed

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.

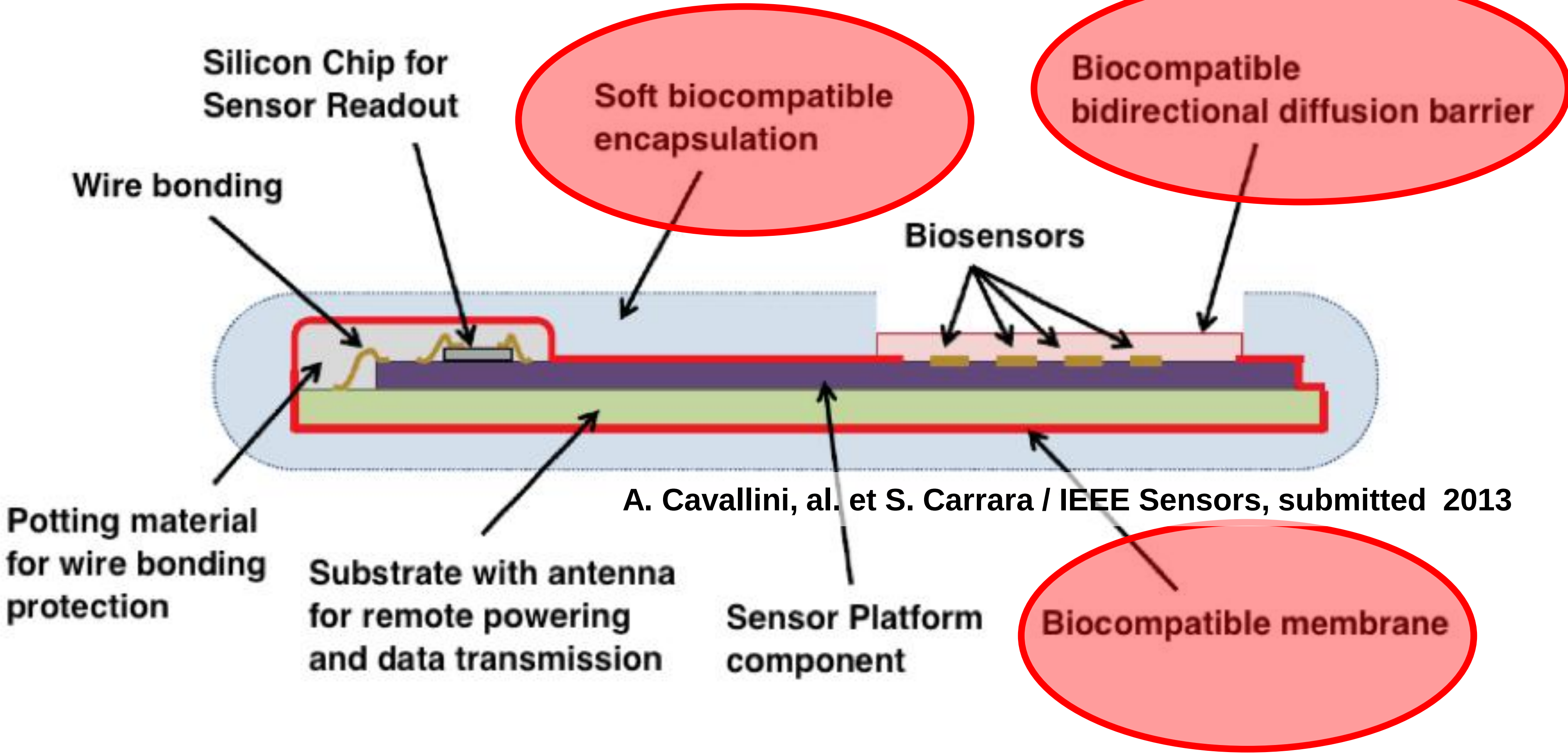


The device sits under the skin and takes multiple readings

Biocompatible Packaging

Biocompatible Silicon to create the shape

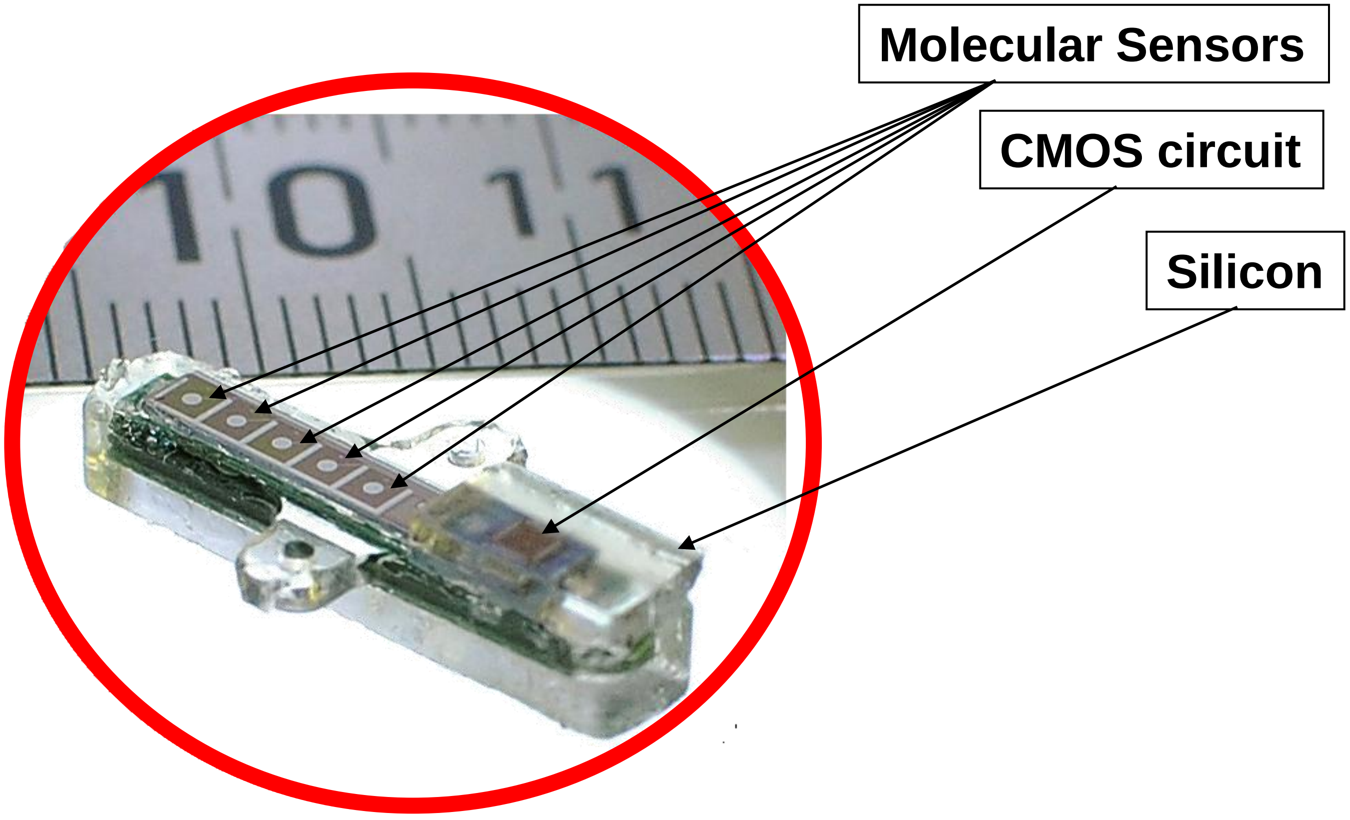
Polycarbonate for metabolites diffusion



A. Cavallini, al. et S. Carrara / IEEE Sensors, submitted 2013

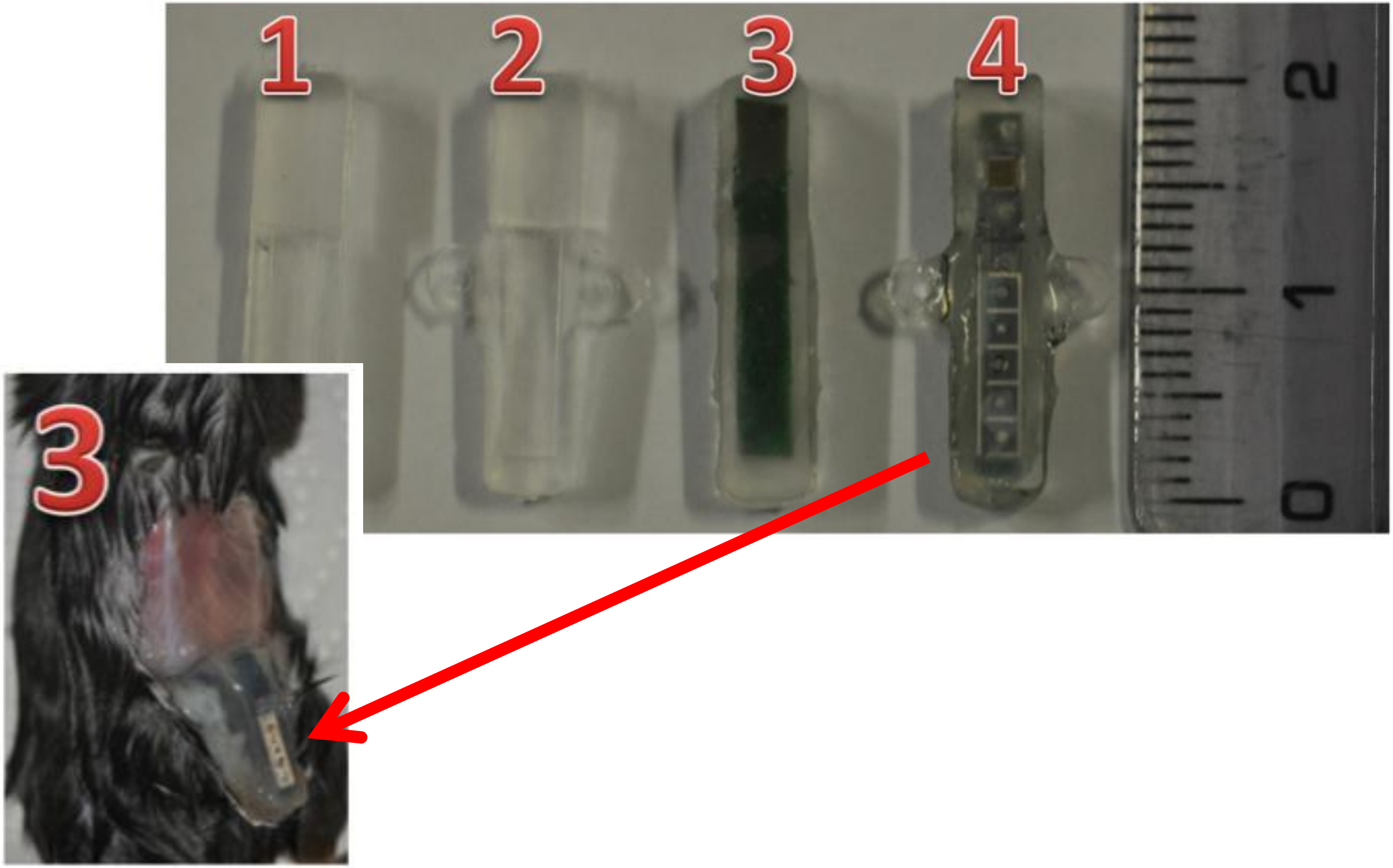
Parylene-C to protect the electronics

The Biocompatible Integration



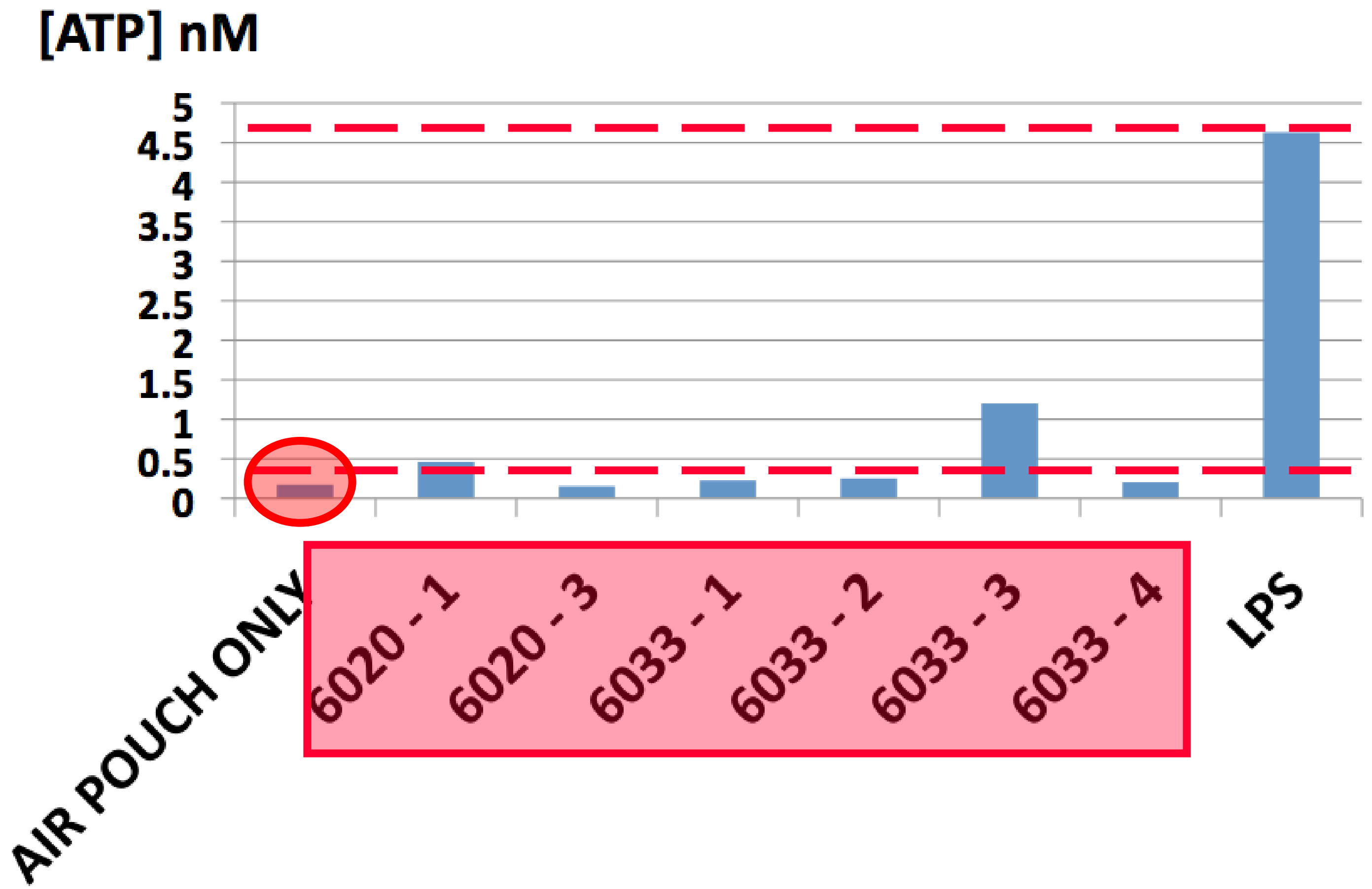
Already tested in animal models

Biocompatibility tests on mice



(c) S.Carrara, EPFL (Switzerland)

System Biocompatibility

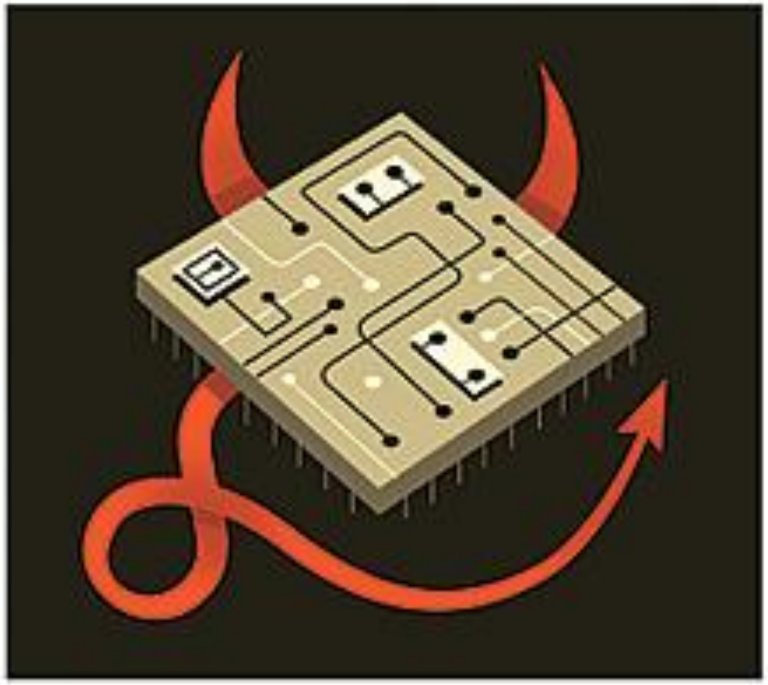


Tests of inflammation induced in mouse by the implanted Bio-Nano-Sensor and the wear remote system

Summary

- **P450 Cytochromes are required to detect Exogenous metabolites (Drugs)**
- **Oxidases are required to detect endogenous metabolites (bio-markers)**
- **Carbon Nanotubes are definitely required to improve sensitivity of molecular detection**
- **Dedicated CMOS design is required for a reliable electrochemical sensing of human metabolites**
- **Remote Powering is required for minimally invasive Under-the-Skin Devices**
- **Telemetry of human metabolism on our smartphones is actually feasible**

Conclusion:
Learning to Hate Big Tech



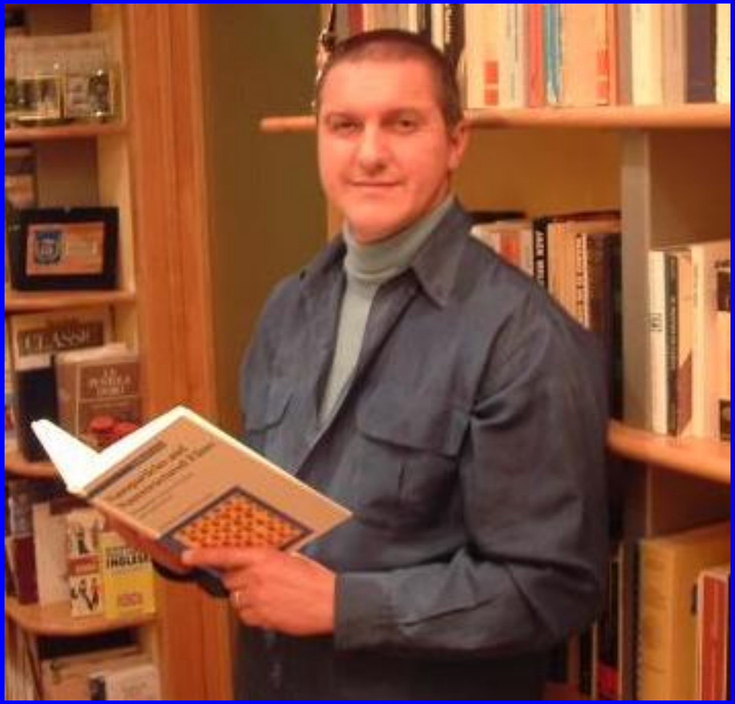
By TIME, May 14, 2012

By being more corporate and less cool,
IT firms are becoming as popular as banks

Thanks to:

- *Andrea Cavallini*
- *Camilla Bai-Rossi*
- *Cristina Boero*
- *Sara Ghoreishizadeh*
- *Daniel Torre*
- *Daniela De Venuto*
- *Irene Taurino*
- *Arnaud Magrez*
- *Dino Giuseppe Albini*
- *Victor Erokhin*
- *Jacopo Olivo*
- *Onur Kazanç*
- *Enver Gürhan Kilinç*
- *Catherine Dehollain*
- *Maaike Op de Beeck*
- *Giovanni De Micheli*

Thank you for your attention!



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email: sandro.carrara@epfl.ch