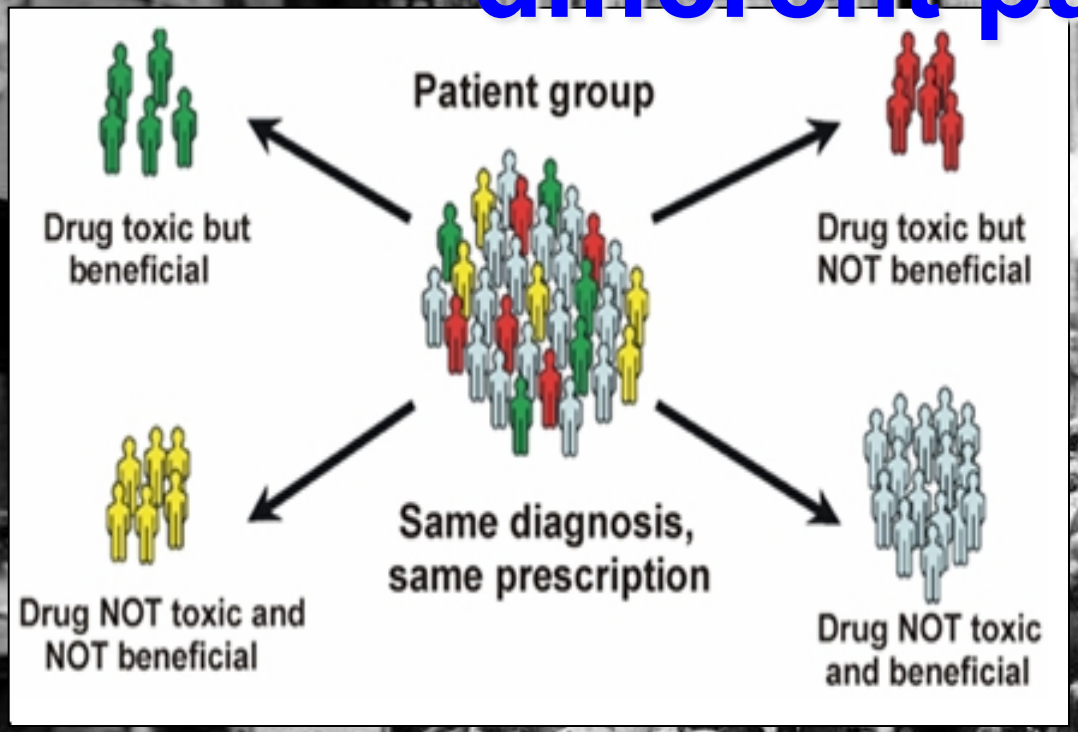
Workshop on Security and Privacy in Implantable Medical Devices
1 April 2011, EPFL Lausanne, Switzerland

Lausanne, April 1st, 2011

New concepts In Remotely-Powered Telemetry of the Human Metabolism

SANDRO CARRARA
Laboratoire des Systèmes Intégrés (LSI)
ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE
nano-tera.ch

Different outcomes for different patients

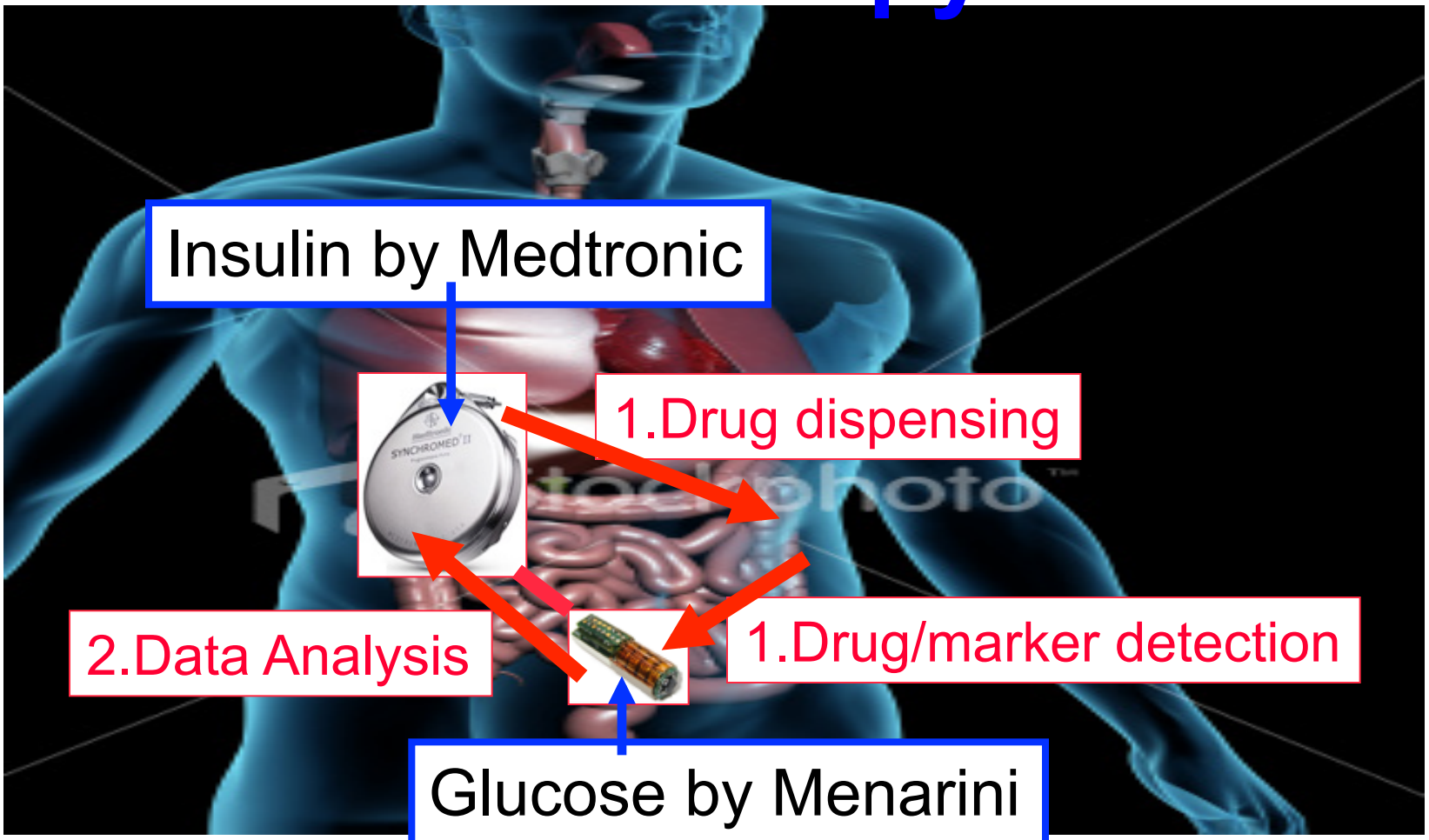


Therapeutic area	Rate of efficacy with standard drug treatment
Cancer (all types)	25%
Alzheimer's disease	30%
Incontinence	40%
Hepatitis C	47%
Osteoporosis	48%
Rheumatoid arthritis	50%
Migraine (prophylaxis)	50%
Migraine (acute)	52%
Diabetes	57%
Asthma	60%
Cardiac arrhythmias	60%
Schizophrenia	60%
Depression	62%

For depression, the data apply specifically to the drug class known as selective serotonin reuptake inhibitors.

Source: Brian B. Spear, Margo Heath-Chiozzi, and Jeffrey Huff, "Clinical Application of Pharmacogenetics," *Trends in Molecular Medicine* (May 2001).

Personalized Therapy and I.M.D.



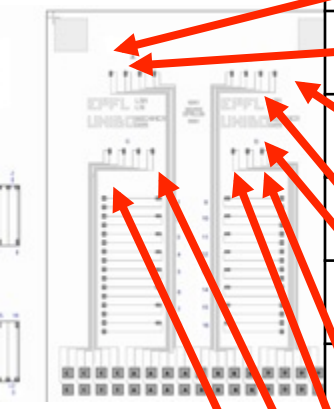
The Development of new Implantable Medical Devices is a key-factor for succeeding in Personalized therapy

S.Carrara, EPFL Lausanne
(Switzerland)

New development for the Nano-Bio-Sensors

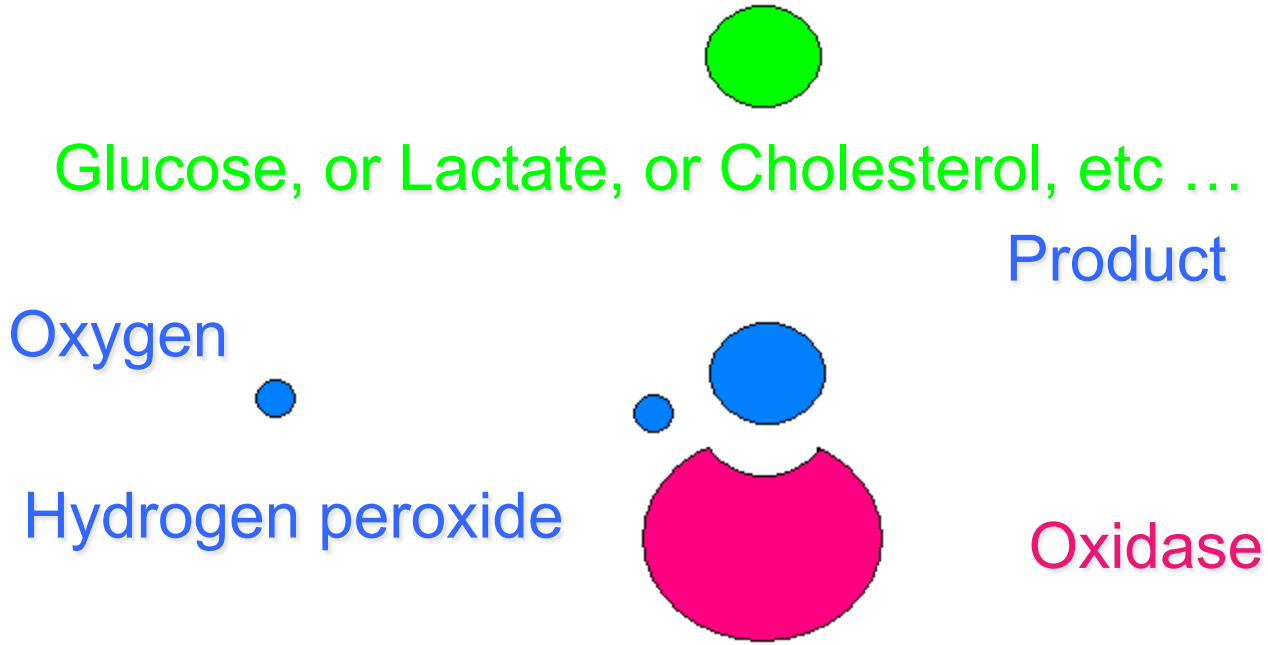
TARGETS

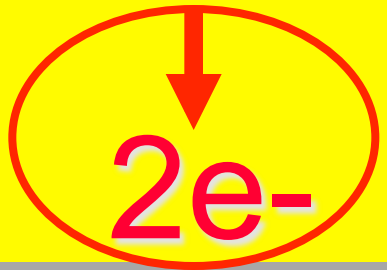
Probe Enzymes	Endogenous metabolites	Exogenous metabolites
Glucose Oxidase	Glucose	
Lactate Oxidase	ATP	
Glutamate Oxidase	Lactate	
P450 11A1	Cholesterol	
P450 2B4		Benzphetamine
P450 3A4		Dextrometorphane
P450 3A4		Cyclophocphamide
P450 2C9		Flurbiprofene
P450 2C9		Naproxene



S.Carrara, EPFL Lausanne
(Switzerland)

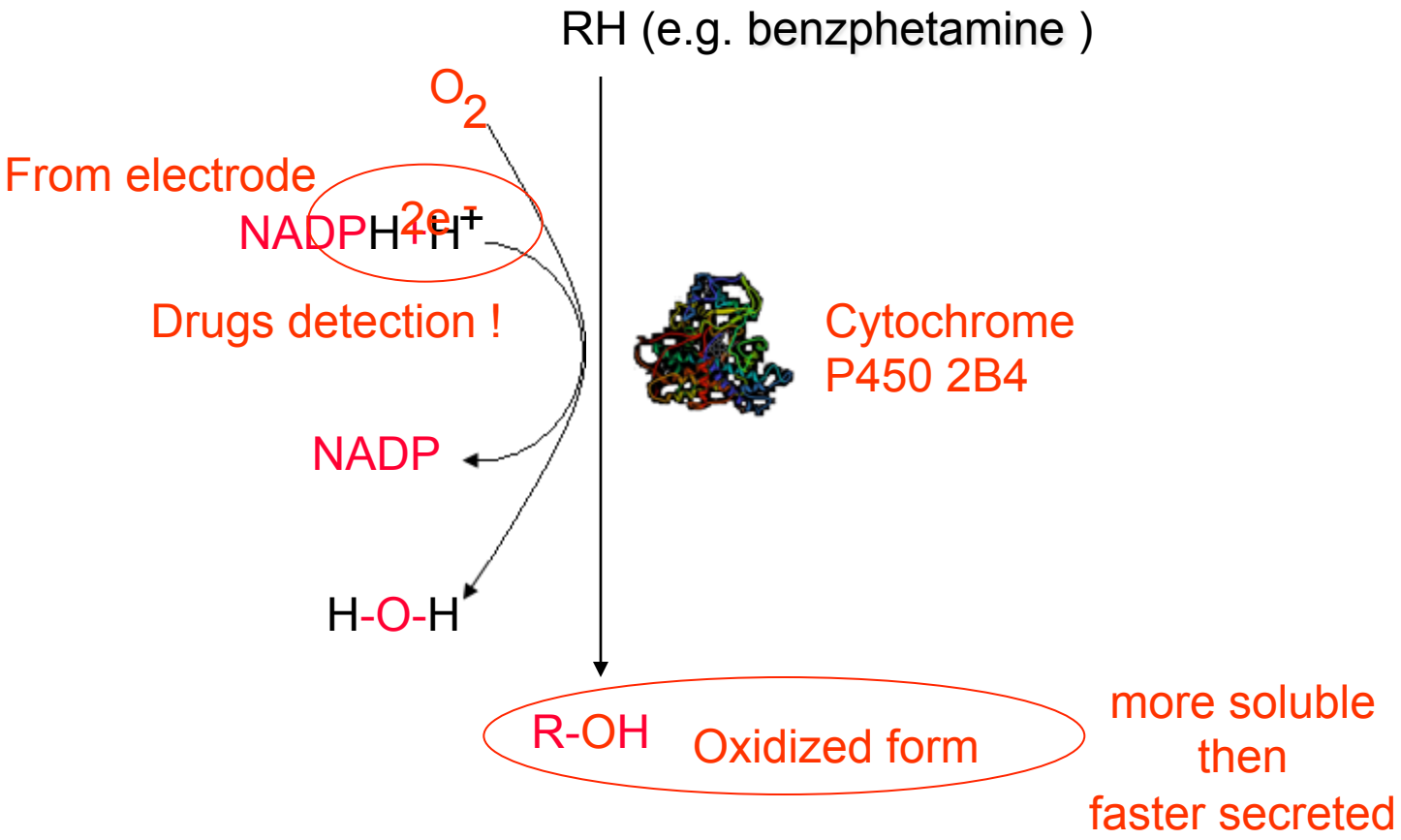
Oxidases for Biomarkers detection



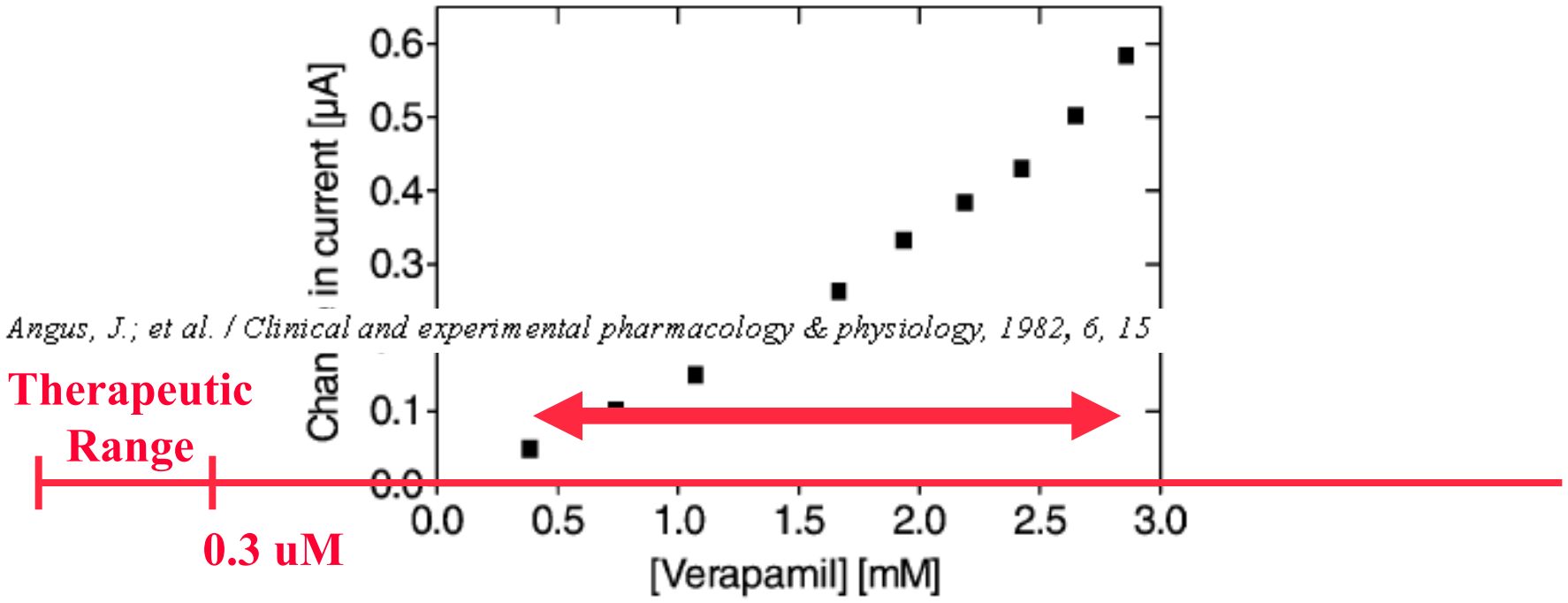


Amperometric Detection !!!!!

Cytochromes P450 for Drugs Detection

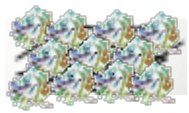


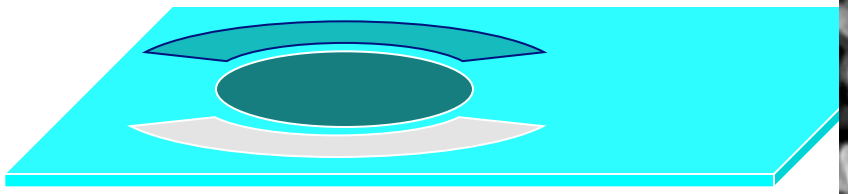
Problems on Detection Limits

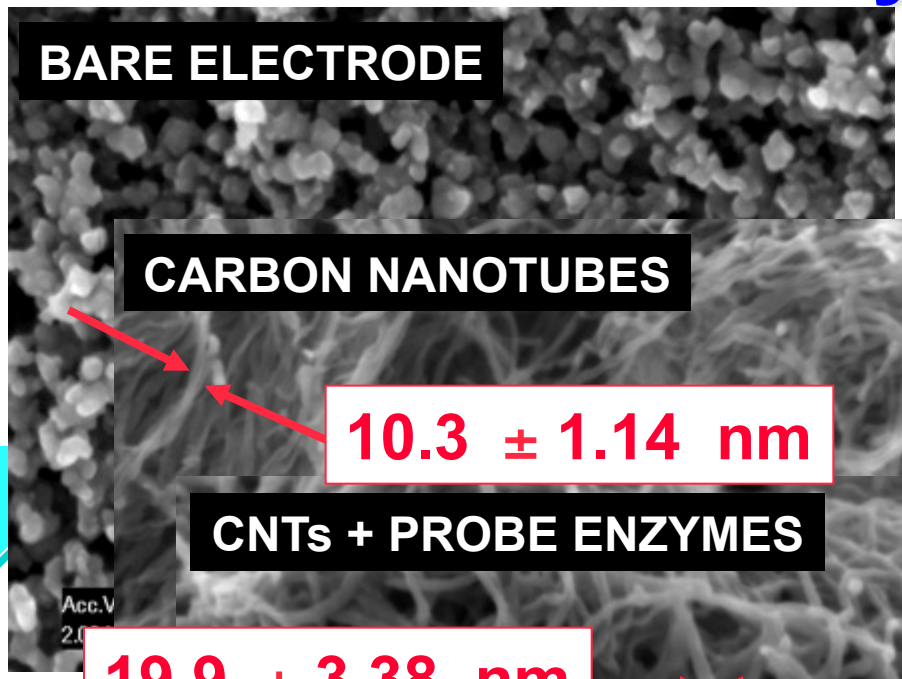


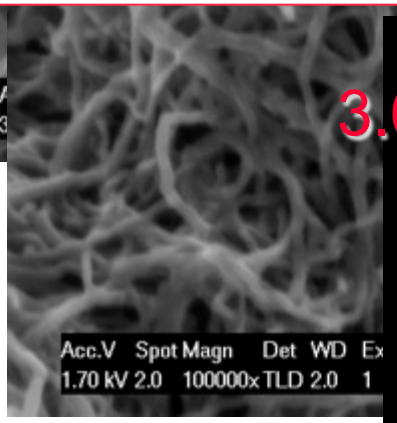
Detection of verapamil by 3A4, an antihypertensive drug, was from 400 µM to 3mM while its therapeutic range is below 0.3 µM

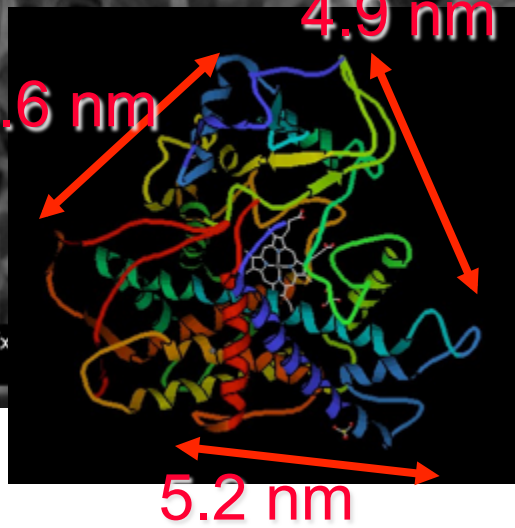
Nano-Bio-Sensors Macro-Assembly





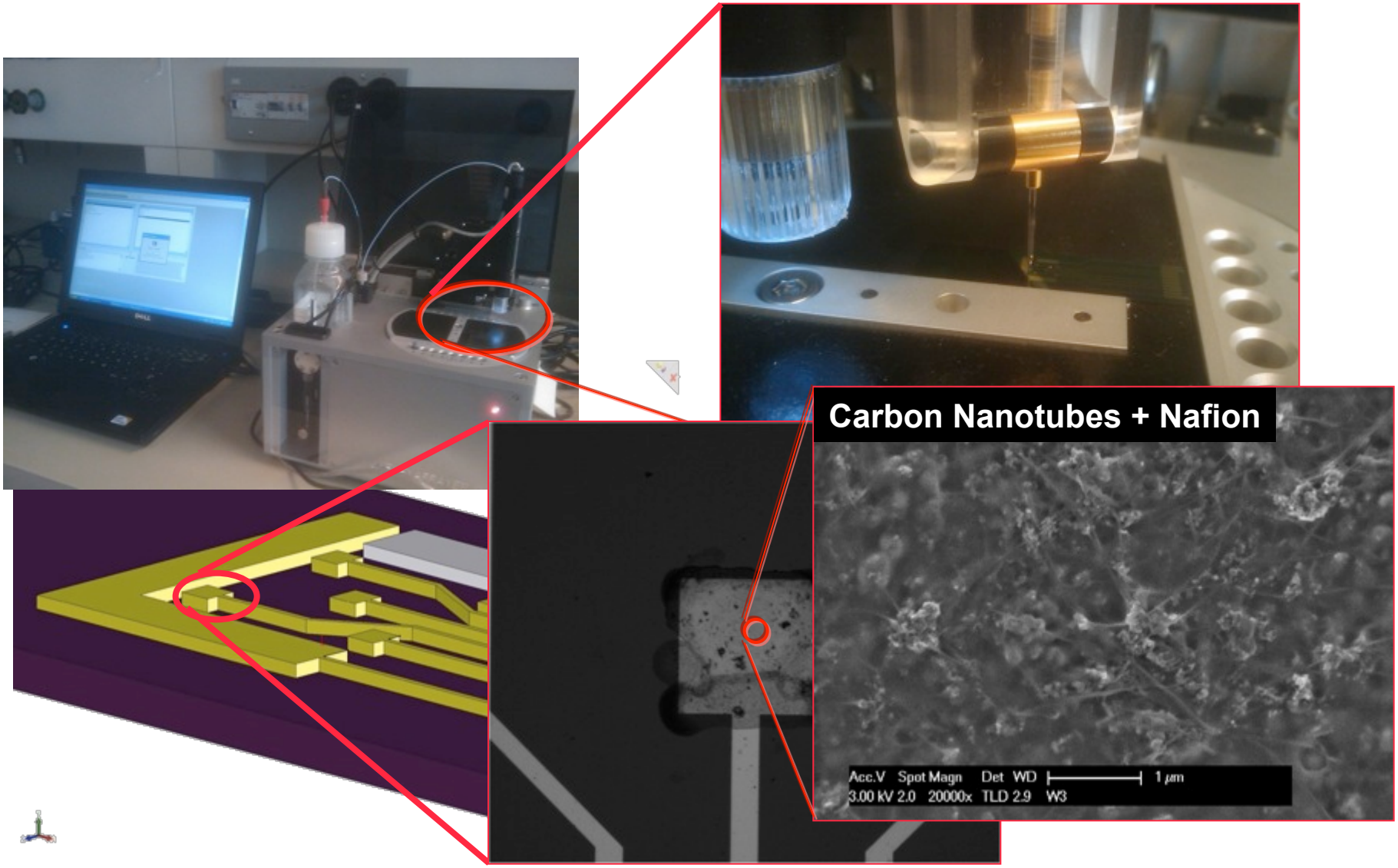






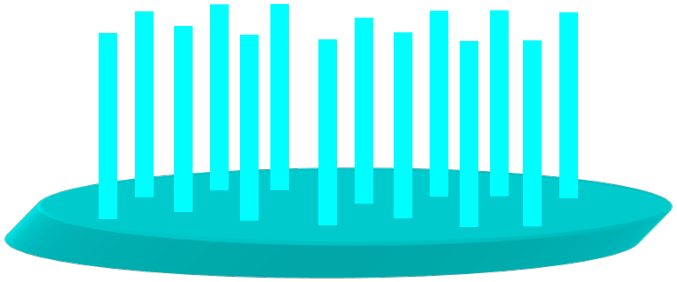
Boero et al. / IEEE PRIME 2009
Boero et al. / IEEE ICME 2010
Carrara et al. / Biosensors and Bioelectronics 2011

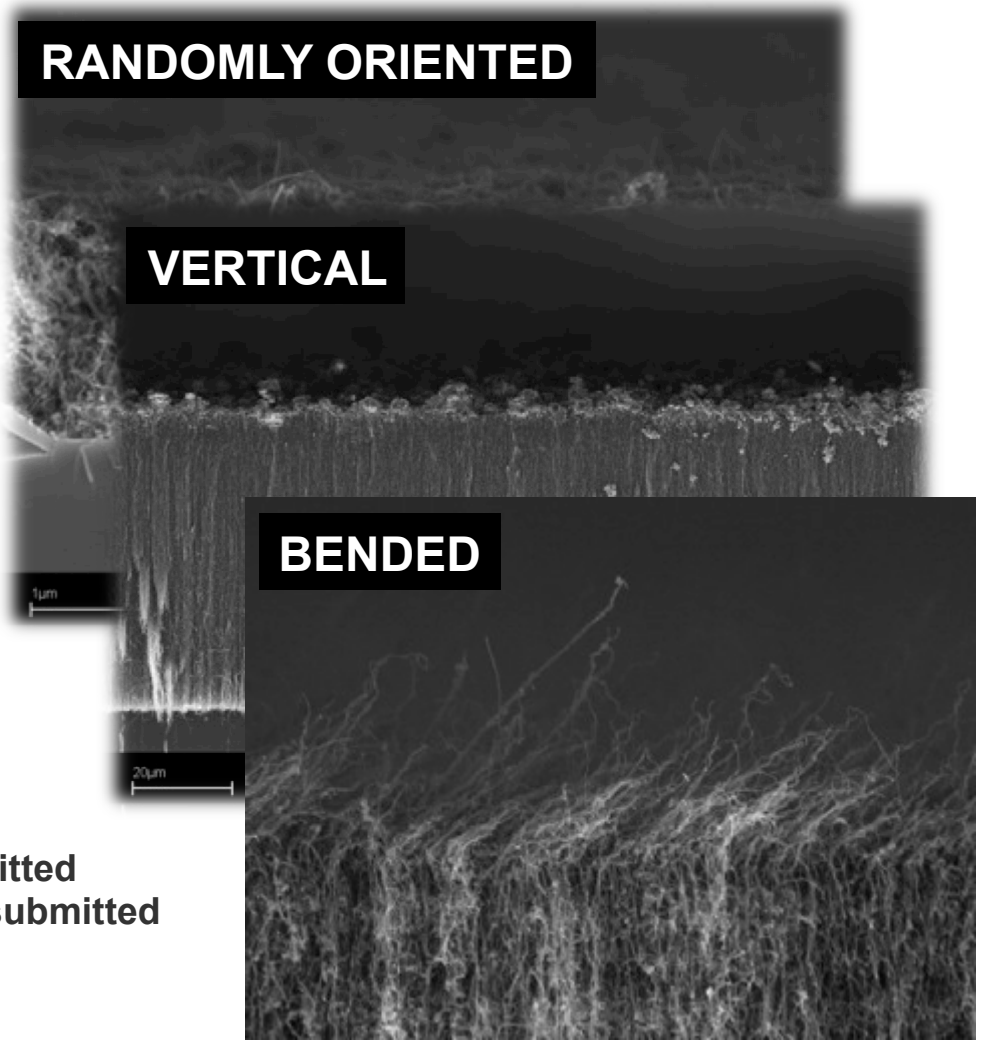
Nano-Bio-Sensors Micro-Spotting



S.Carrara, EPFL Lausanne
(Switzerland)

New Challenges on CNT integration directly onto Silicon chips





Taurino et al. / Electrochem. Comm./2011 submitted
Taurino et al. / Sensors and Actuators B, 2011 submitted

S.Carrara, EPFL Lausanne
(Switzerland)

Carbon Nanotubes contribute to Redox Reactions Efficiency

Nernst equation

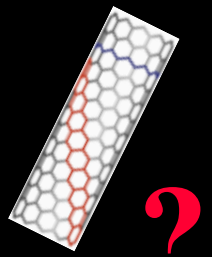
$$E = E^{0'} - \frac{RT}{nF}\ln\left(\frac{C_R(0,t)}{C_O(0,t)}\right)$$

Randles-Sevcik equation

$$i(0,t) = nFAD\left(\frac{nFv}{RT}\right)^{1/2} C(0,t)$$

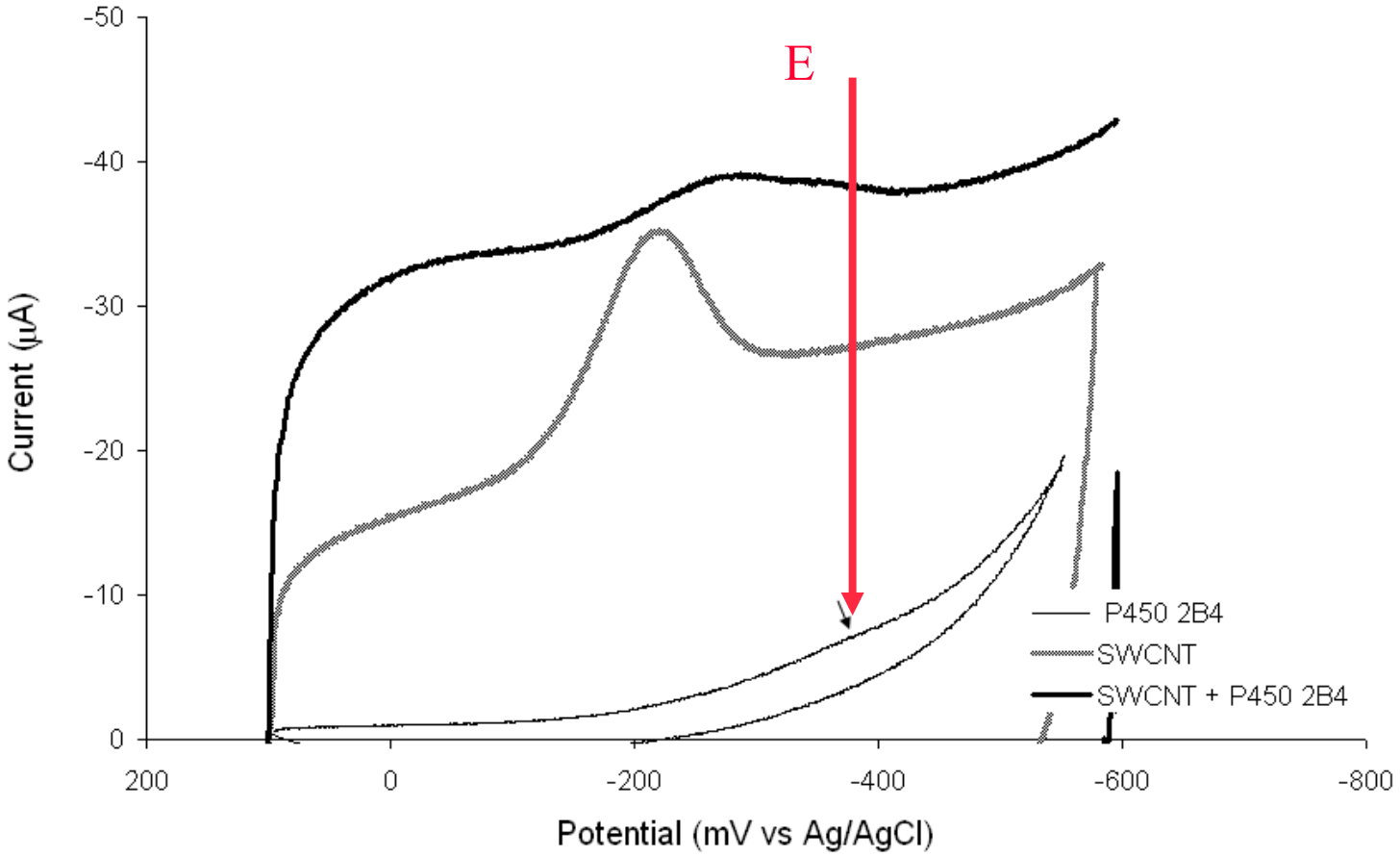
Cottrell equation

$$i(x,t) = \frac{nFAD^{1/2}C(x,t)}{\pi^{1/2}t^{1/2}}$$



?

Nernst Effect



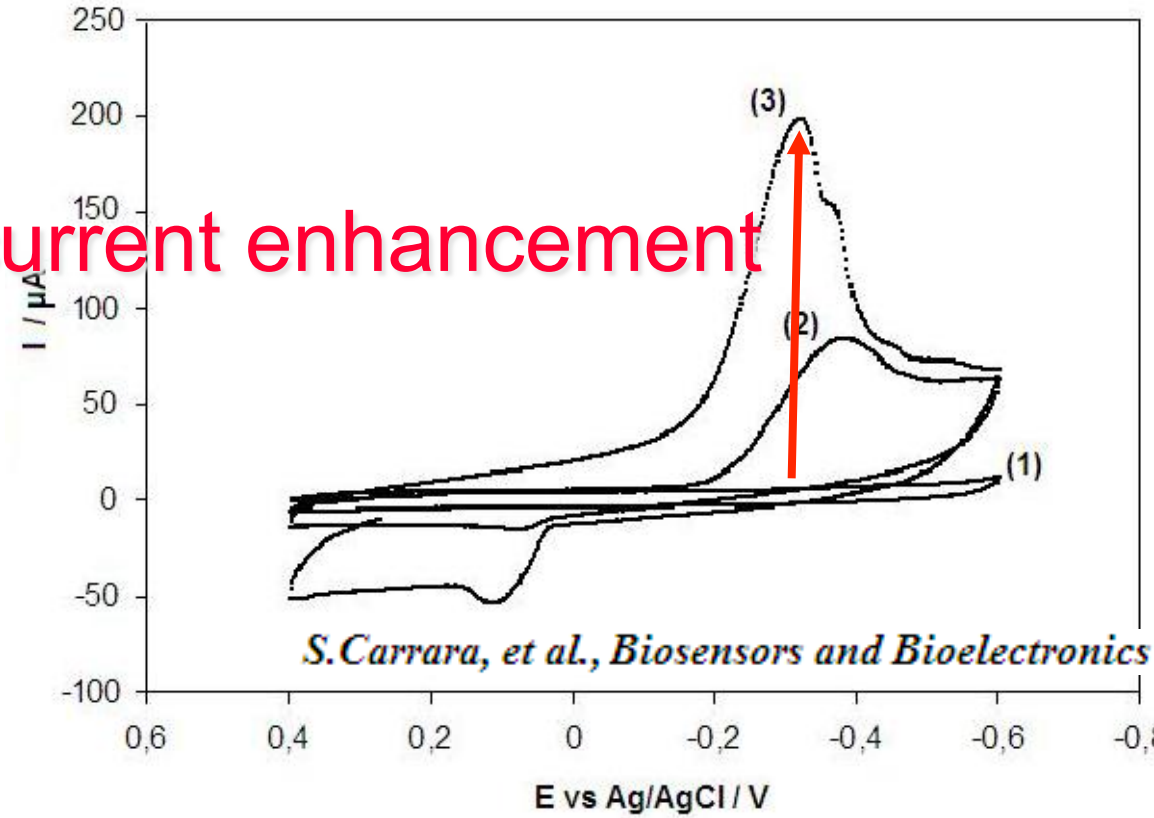
Benzphetamine detection by means of P450 2B4 immobilized onto Single Walled Carbon Nanotubes

S.Carrara, EPFL Lausanne
(Switzerland)

Randles-Sevcik Effect

Peak current enhancement

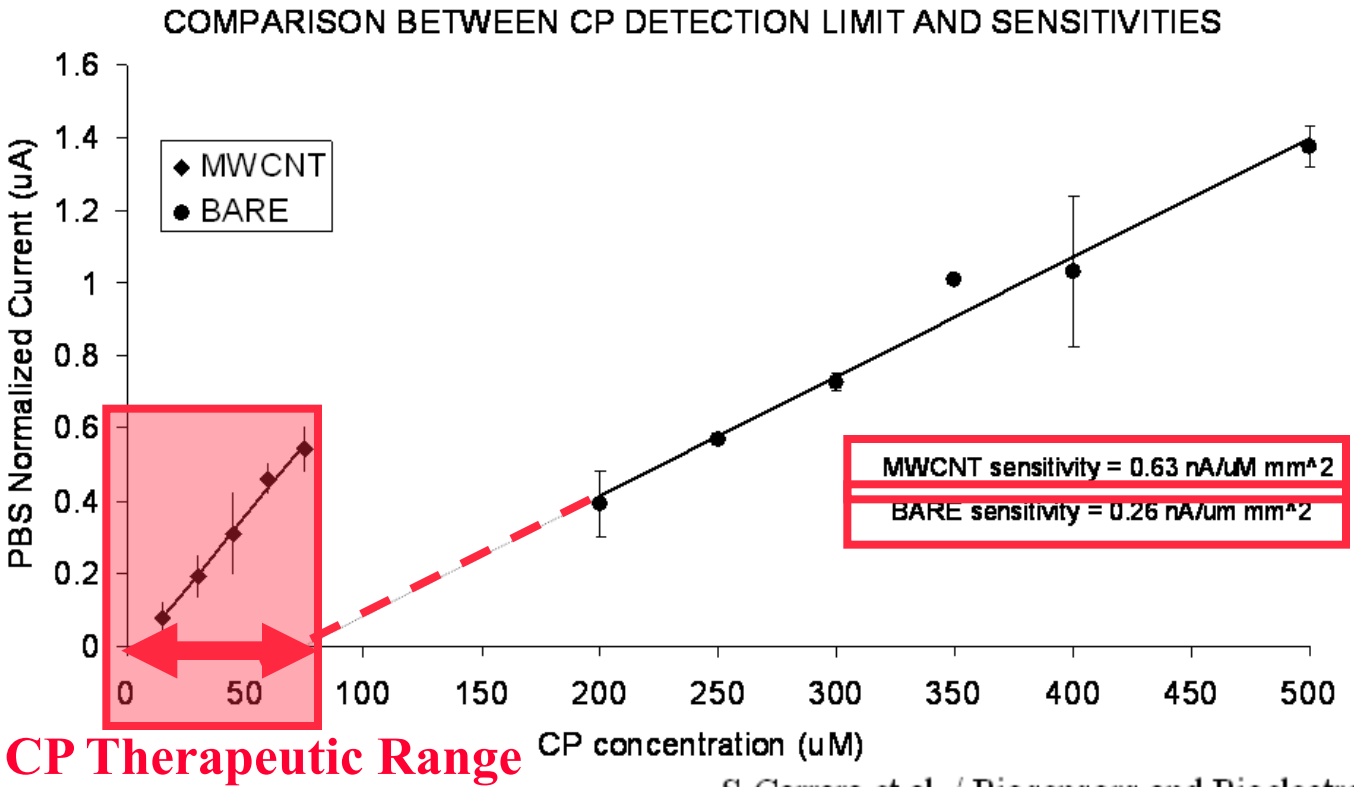
Figure 1



S.Carrara, et al., Biosensors and Bioelectronics 24 (2008) 148-150

Cholesterol detection by means of P450 11A1 immobilized onto Multi Walled Carbon Nanotubes

Improved Detection Limit in Drugs detection

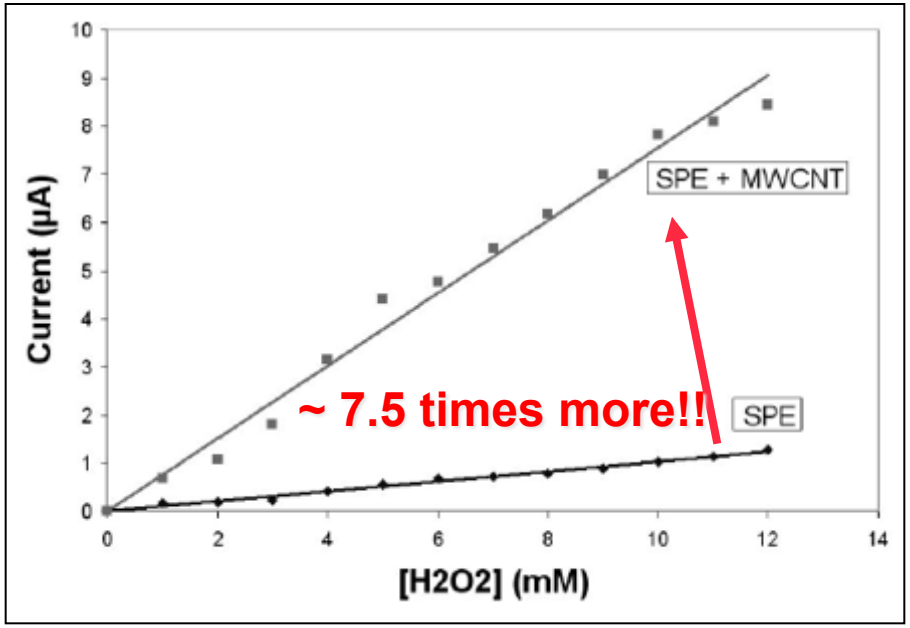


S.Carrara et al. / Biosensors and Bioelectronics, in press

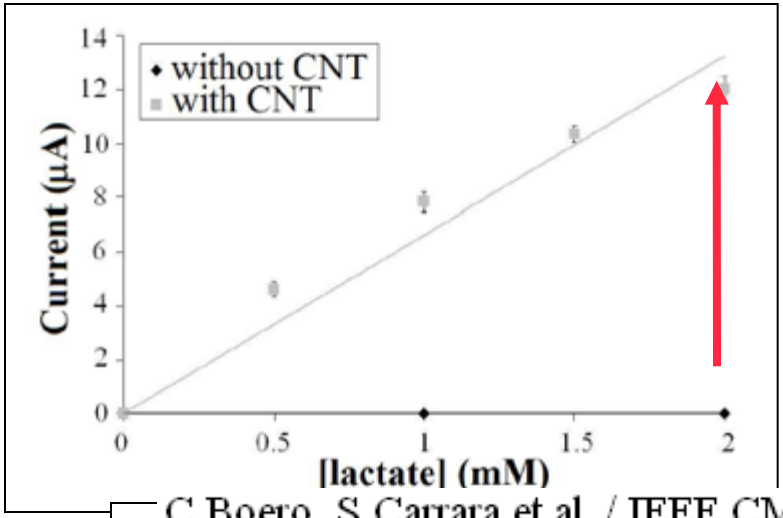
Cyclophosphamide (CP), an anti-cancer agent, detected by P450 3A4 onto MWCNT

S.Carrara, EPFL Lausanne
(Switzerland)

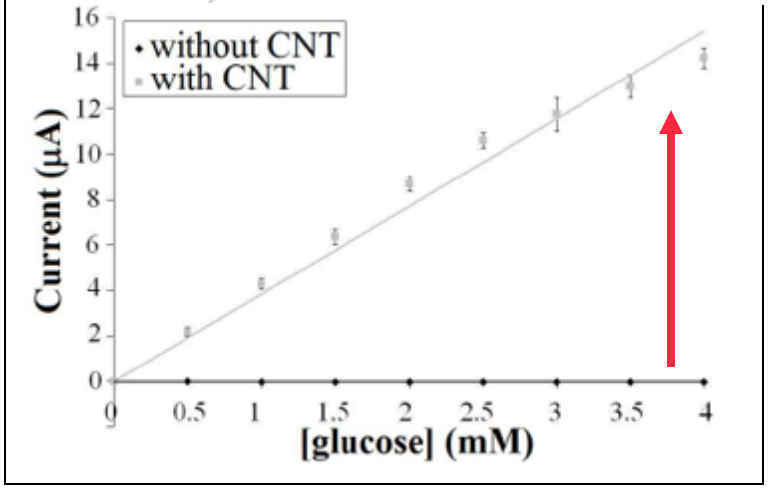
Improved Sensitivity in Peroxide Based Detections

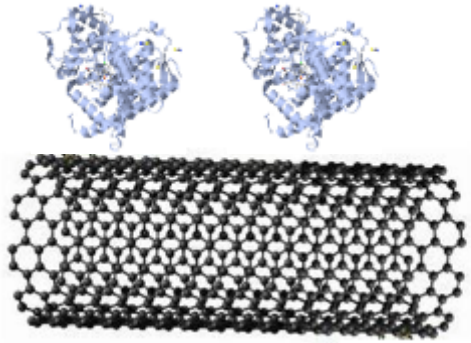


C. Boero, S.Carrara et al., IEEE PRIME, 2009



C.Boero, S.Carrara et al. / IEEE CME 2010





Oxidases onto MWCNT for Glucose and Lactate

S.Carrara, EPFL Lausanne
(Switzerland)

Drugs for treating Breast Cancer

Drugs	Pharmacologica	volved in drug metabolism
Cyclophosphamide[2],[3]	2,68-76,6 µM	
Etoposide[4],[5]	33,98-101,94 µM	3A4 1A2 (-)
Ifosfamide[2]	10-160 µM	3A4 2B6
Mitoxantrone[6]	1,84-3,31 µM	3A4 1B1 (-)
Tegafur[7] (contain Fluorouracil)	1 µM-10 µM	1A2 2A6

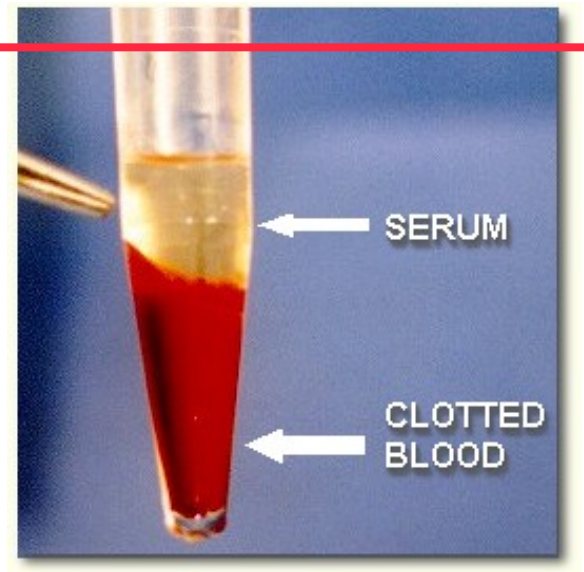
Good concentration ranges for the sensitivity of our technology !

The CYP in the table are sorted according to their importance in the drug metabolism.
The simbol (-) means that the CYP isoform is involved as the minor enzymatic components in the drug metabolic pathway.

S.Carrara, EPFL Lausanne
(Switzerland)

Measurement in Serum !

Drugs	Pharmacological range (μM)	P450 enzyme	Sensitivity (nA/ μM*mm²)		Detection limit (μM)	
			PBS	Serum	PBS	Serum
Cyclophosphamide	2.68-76.6	2B6	1.021	0.279	1.935	13.81
Ifosfamide	10-160	3A4	1.602	0.430	2.018	7.086
Ftorafur	1-10	1A2	8.832	3.469	0.646	0.957
Etoposide	33.98-101.94	-	73.73	9.142	0.046	0.476



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

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

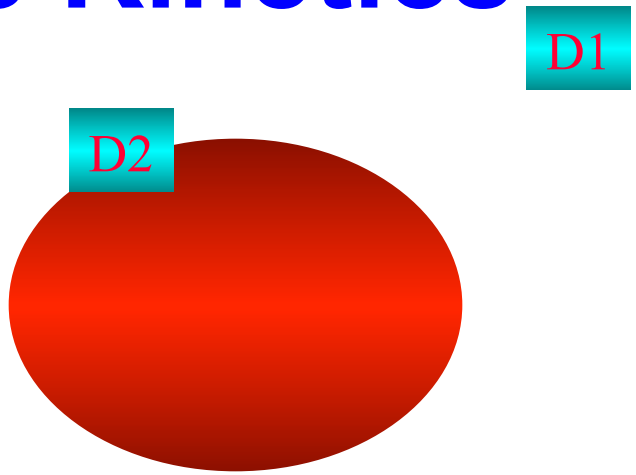
Charging current

Faradic currents

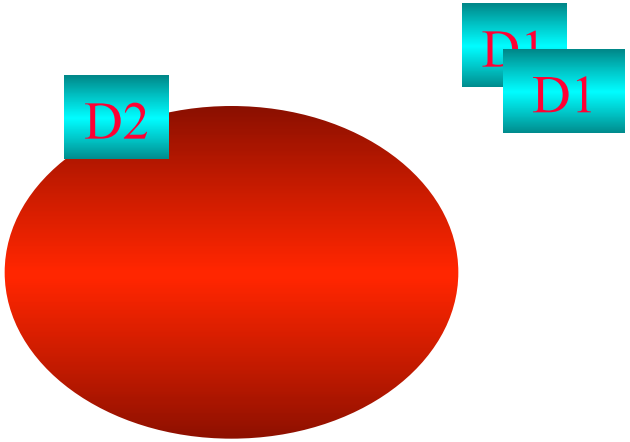
The cytochrome P450 2C9 presents peak shifts in the range of tens of mV by changing drug substrates

The Hetero-tropic Kinetics

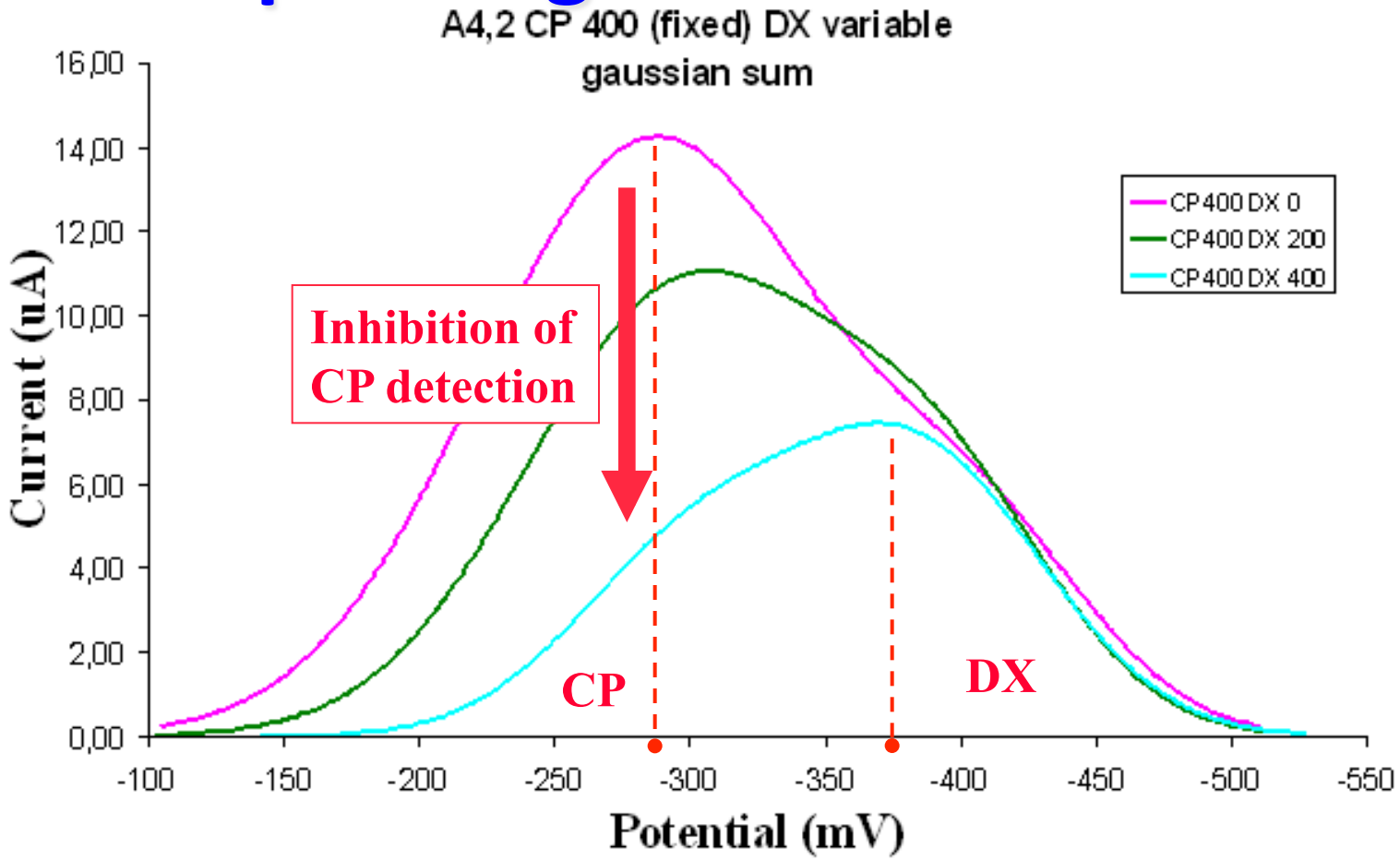
- **Enzyme ACTIVATION**



- **Enzyme INHIBITION**



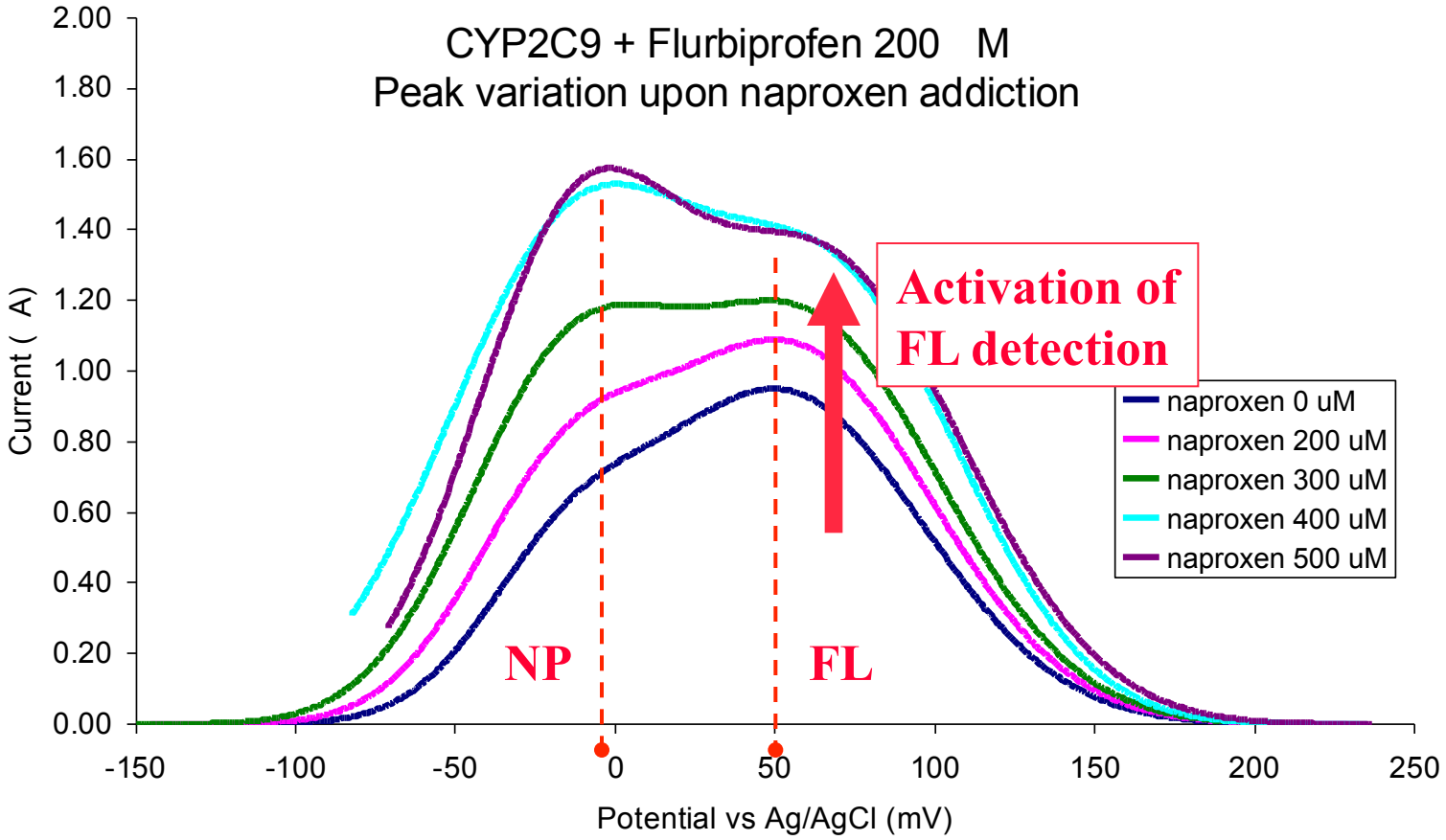
Multiple drugs detection: CYP3A4



Cyclophosphamide (CP) and Dextromethorphan (DX) detection by P450 3A4 onto MWCNT

S.Carrara, EPFL Lausanne
(Switzerland)

Multiple drugs detection: CYP2C9



Naproxen (NP) and Flurbiprofen (FL) detection by P450 2C9 onto MWCNT

S.Carrara, EPFL Lausanne
(Switzerland)

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	[illegible]

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

Dependence from the other drug concentrations

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

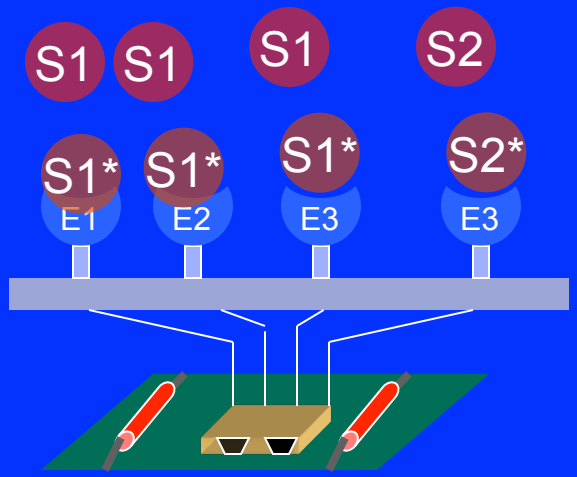
Charging current

Faradic currents

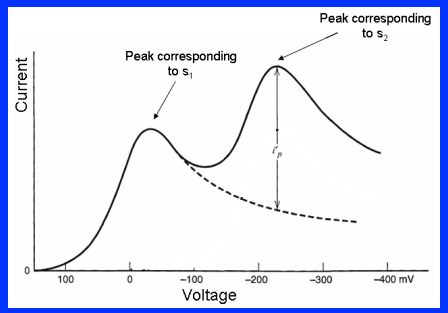
S.Carrara et al. / Biosensors and Bioelectronics, in press

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

The Problem of multi-panel arrays response



Bio-sensor

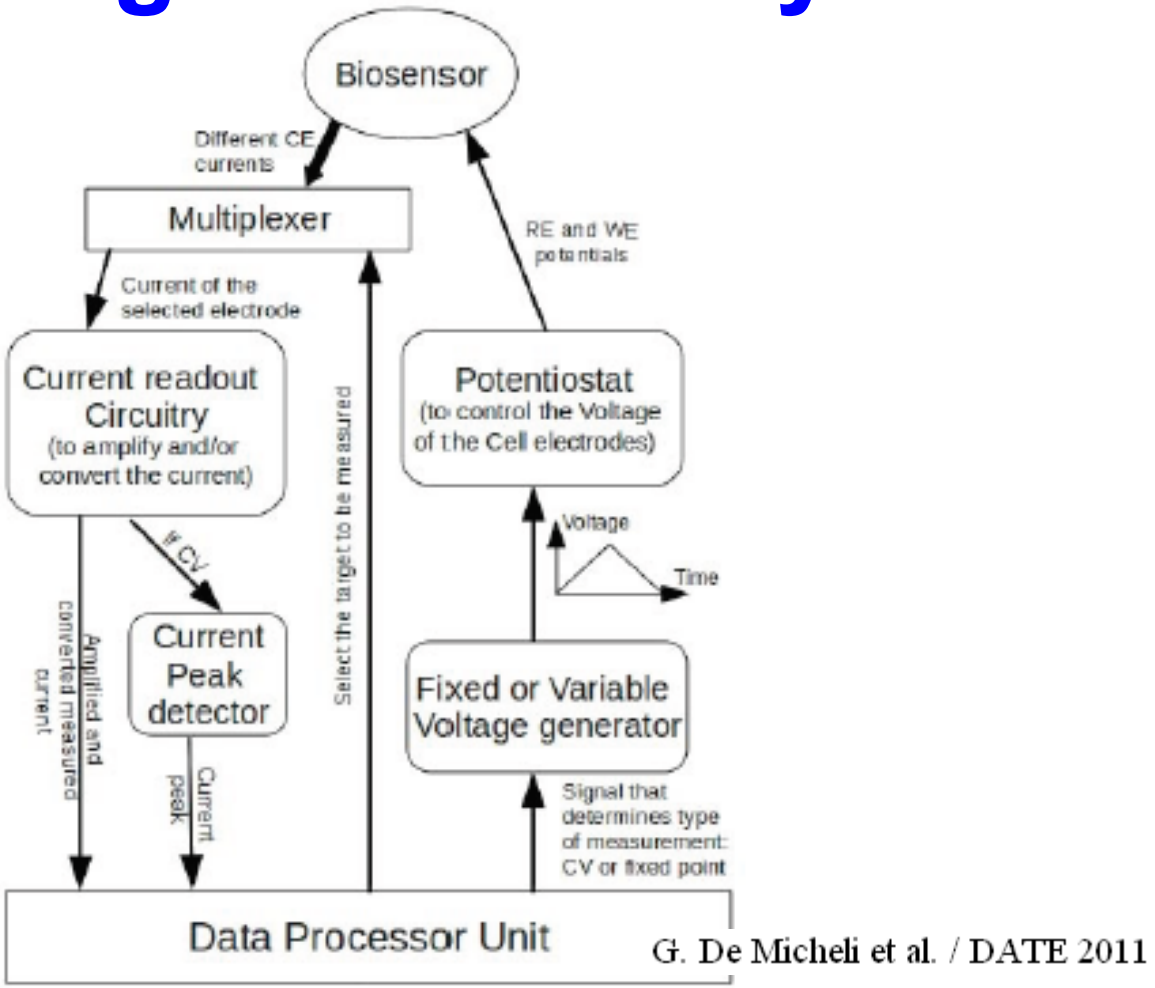


Voltammogram Plot

Intelligence

(Switzerland)

Developing of the full system

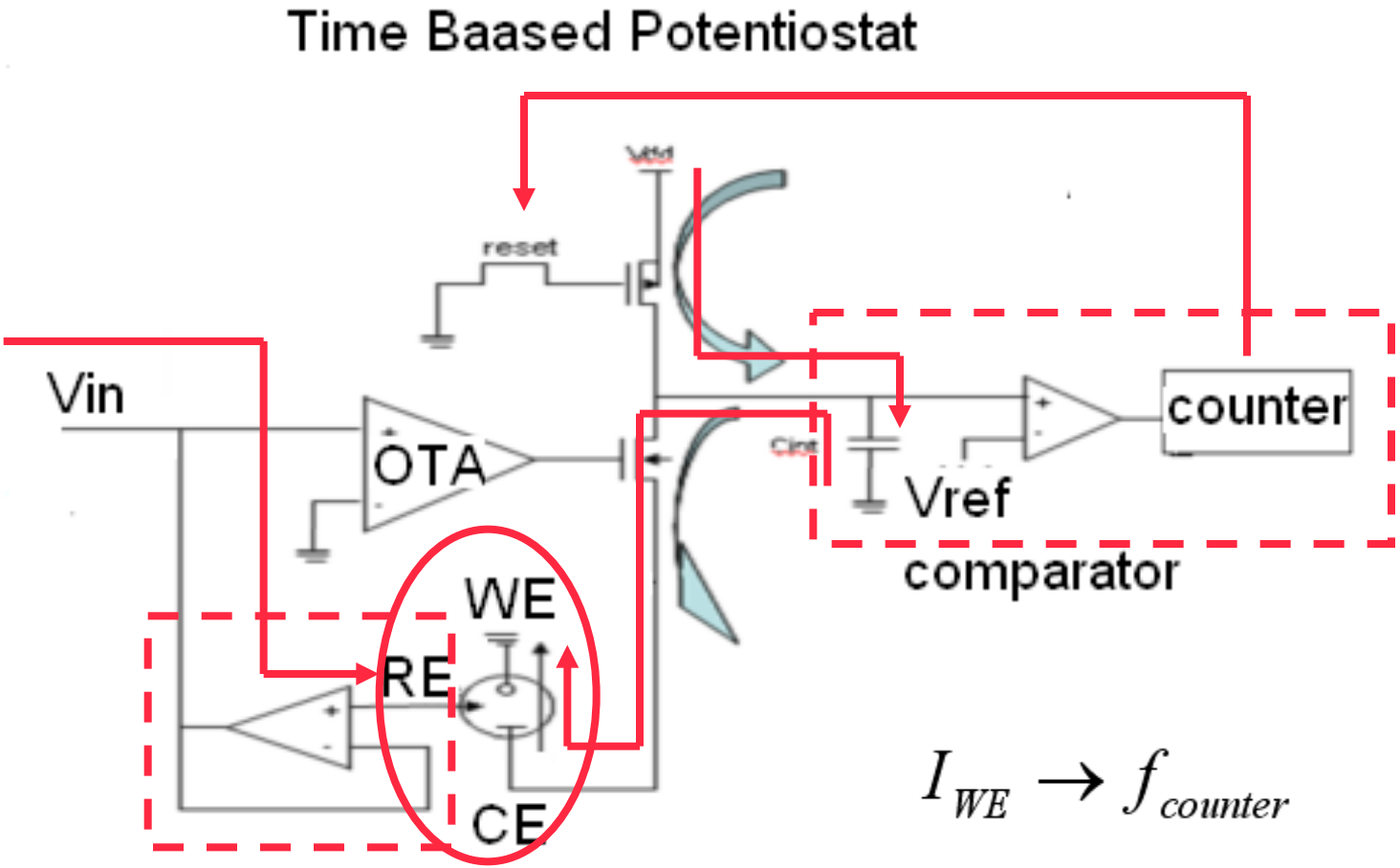


Building-block diagram for a biosensing platform

A reliable full system requires:

1. Precise Current measurements
2. Multiplexing for different molecules
3. Reliability in Temperature and pH
4. Multiplexing Molecular Detection with T and pH
5. Reliable in sweeping the Voltage
6. Security
7. Privacy

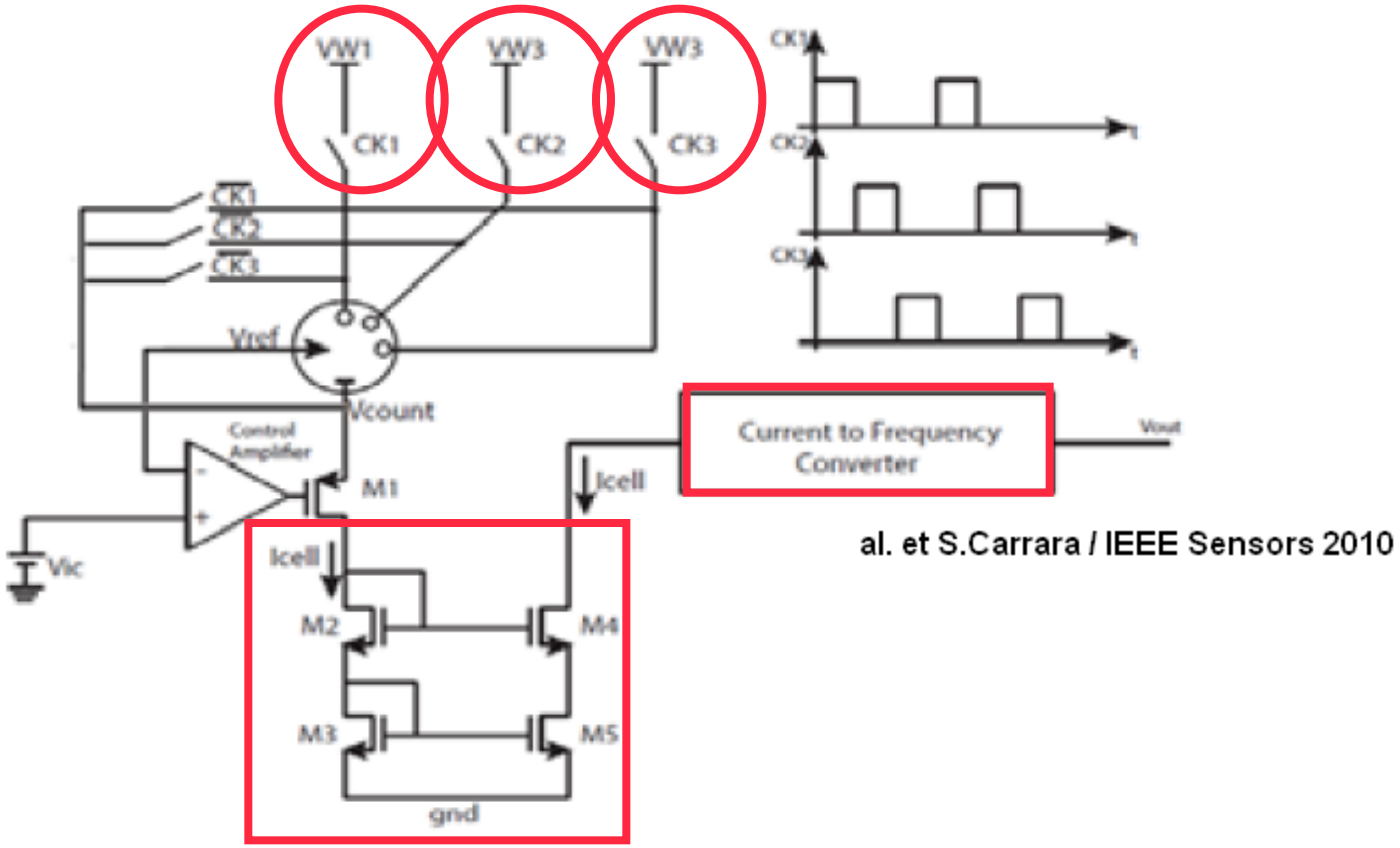
1. Precise Current measurements



NARULA AND HARRIS: IEEE SENSORS JOURNAL, VOL. 6, NO. 2, APRIL 2006

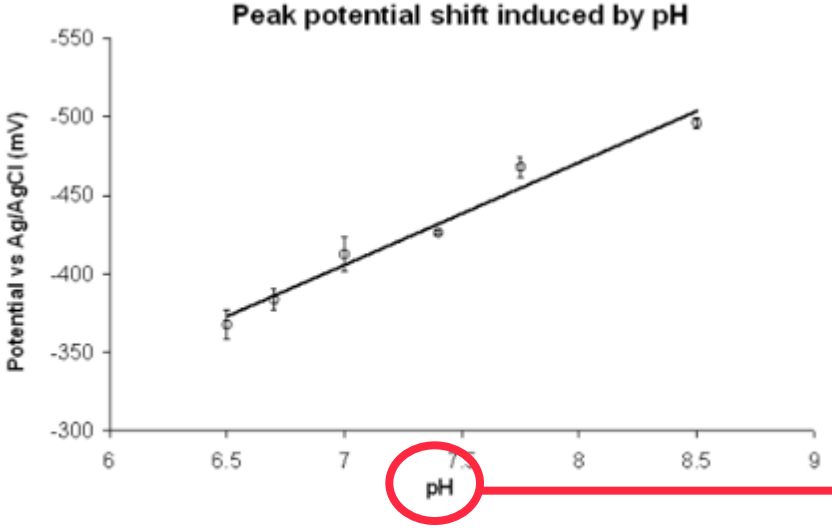
Current-to-frequency converter

2. Multiplexing Molecular Detection



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

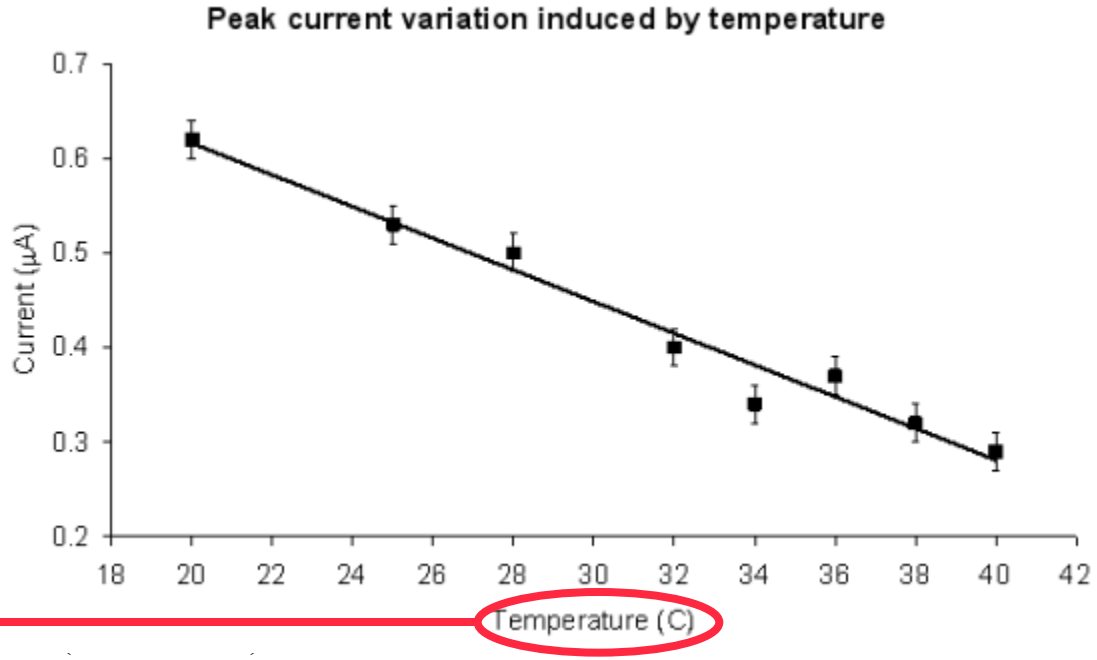
3. Reliability in Temperature & pH



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

Figure 2. .Peak Potential shift versus pH

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



S.

4. Multiplexing Molecular detection with T and pH

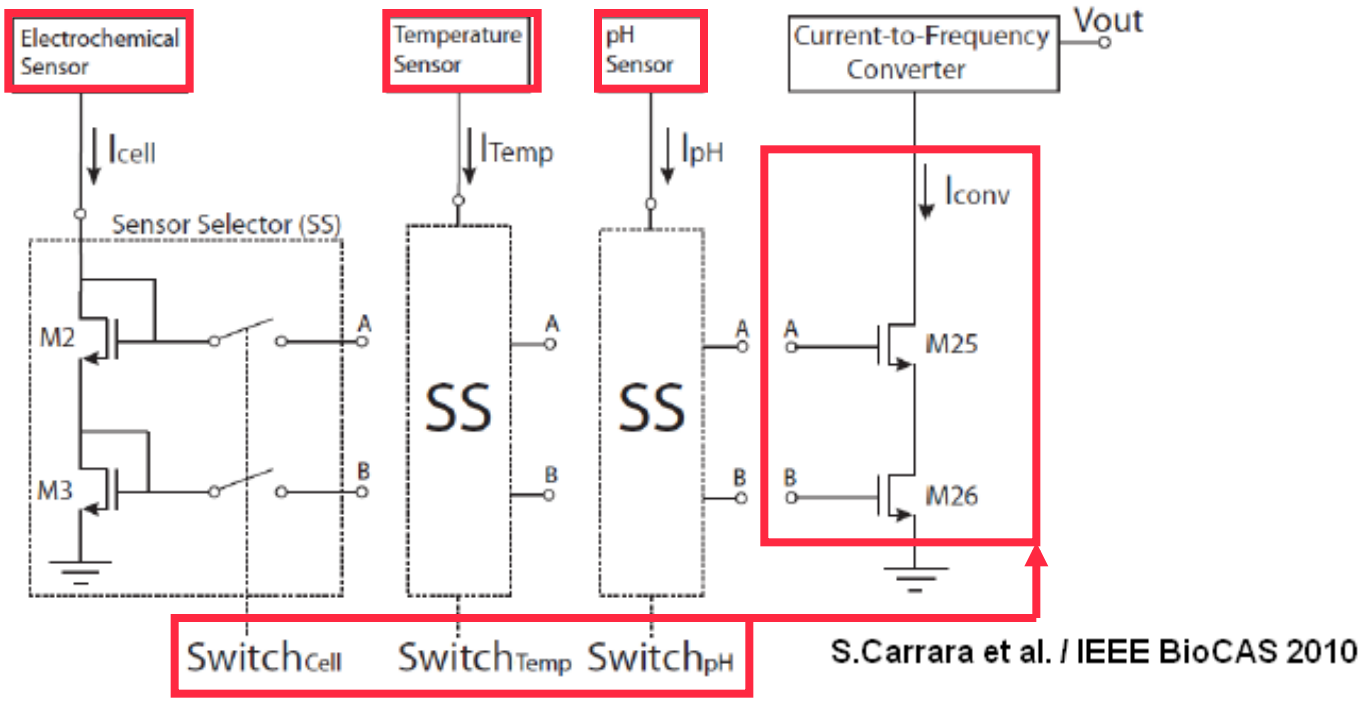
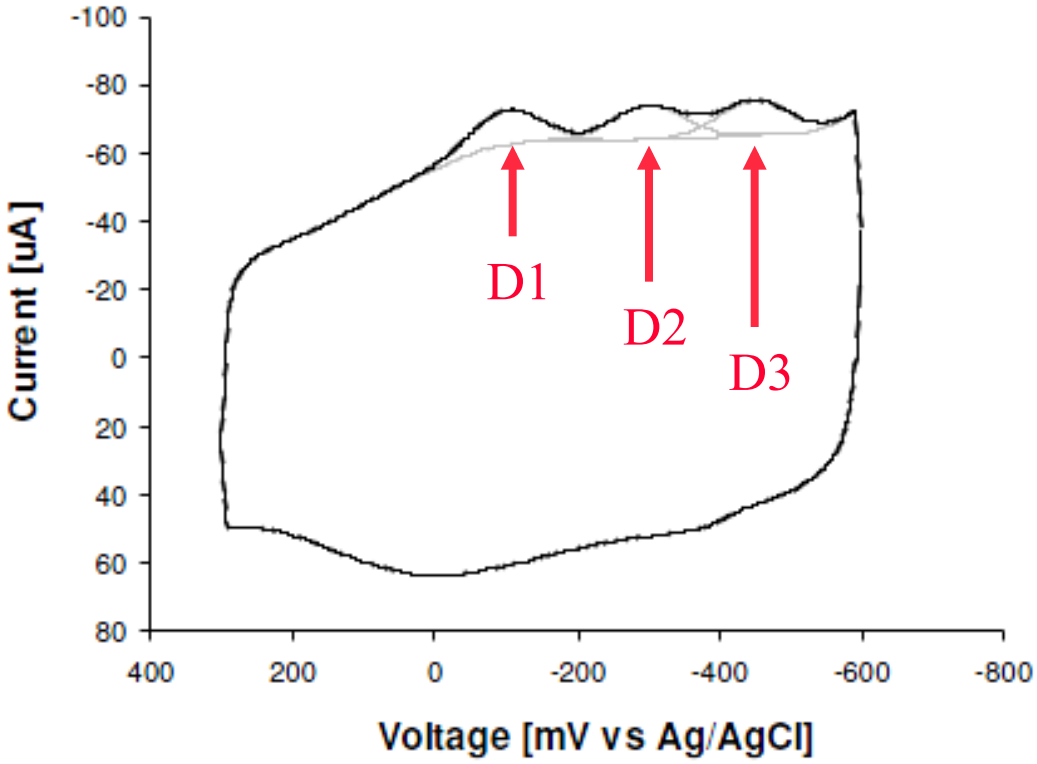


Figure 8. The bloks-scheme of the multiplexing

The switches also multiplex the T and pH measure

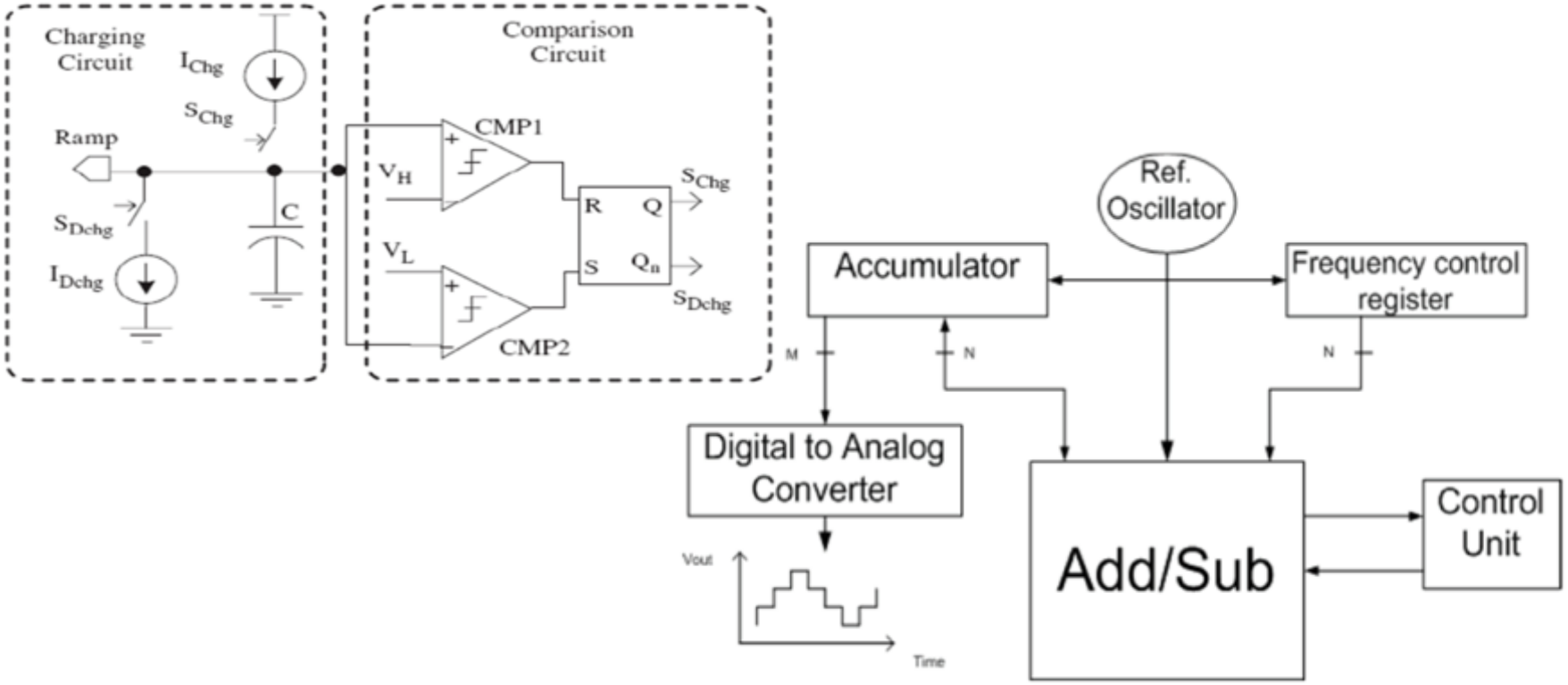
5. Reliable for Sweep in Voltage



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

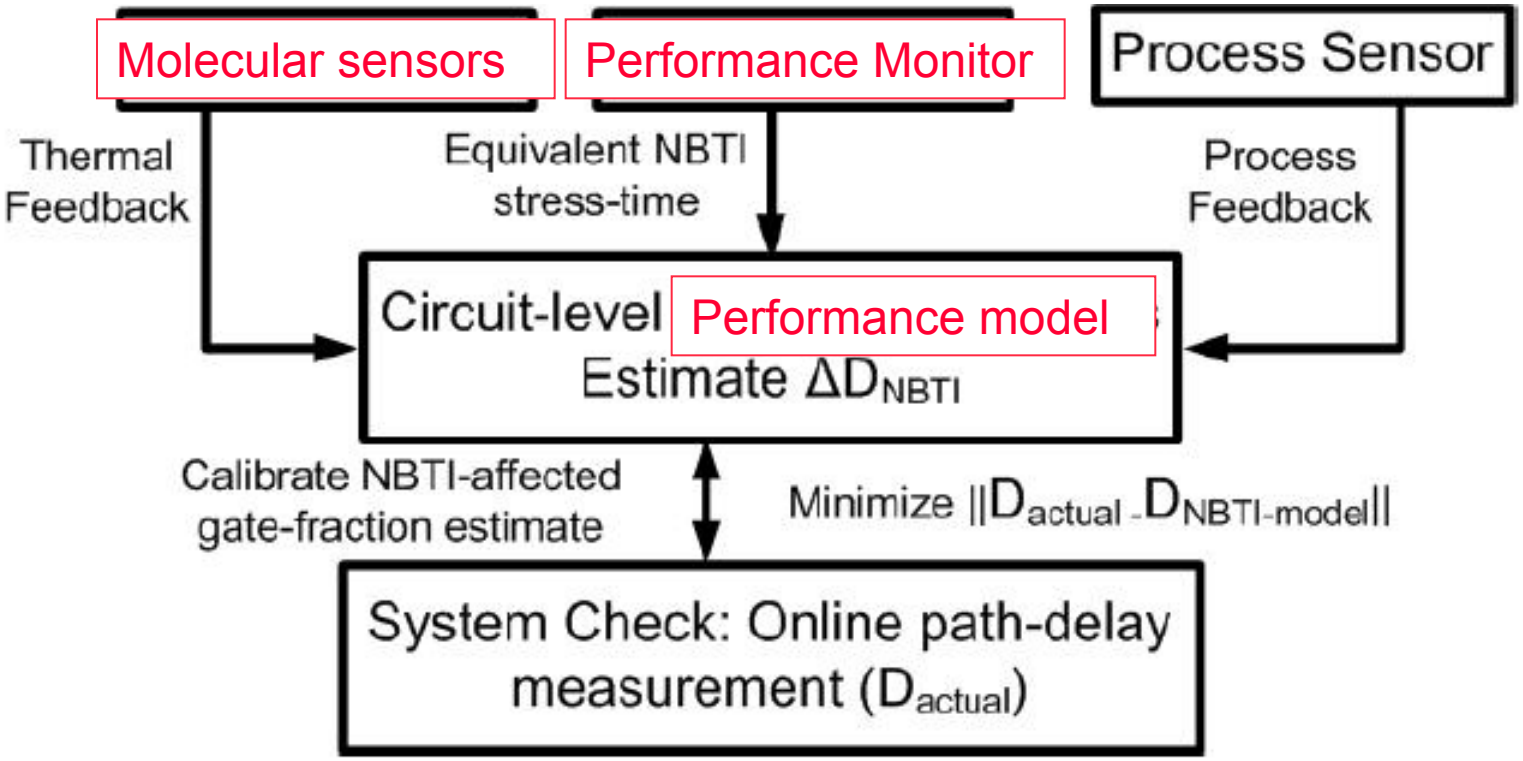
S.Carrara, EPFL Lausanne
(Switzerland)

5. Sweep in Voltage



The Direct Digital Synthesis (DDS) method to generate the triangular voltage waveform and based on Capacitor charging/discharging Method

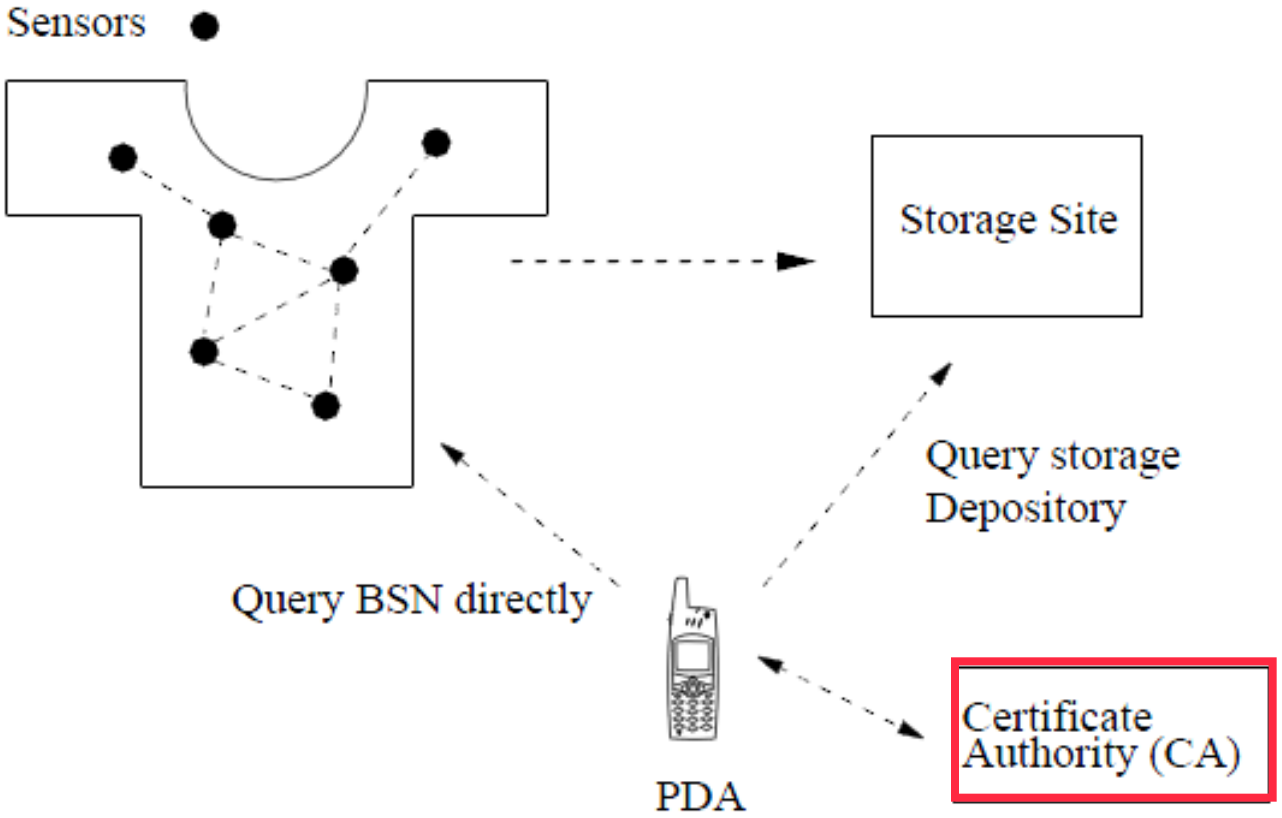
6. Security



B.Datta & W.Burleson, GLSVLSI 2010

On line reliability by novel collaborative monitoring frame-work to track circuit level performance degradation

7. Privacy



C.C. Tan et al., WiSec 2008

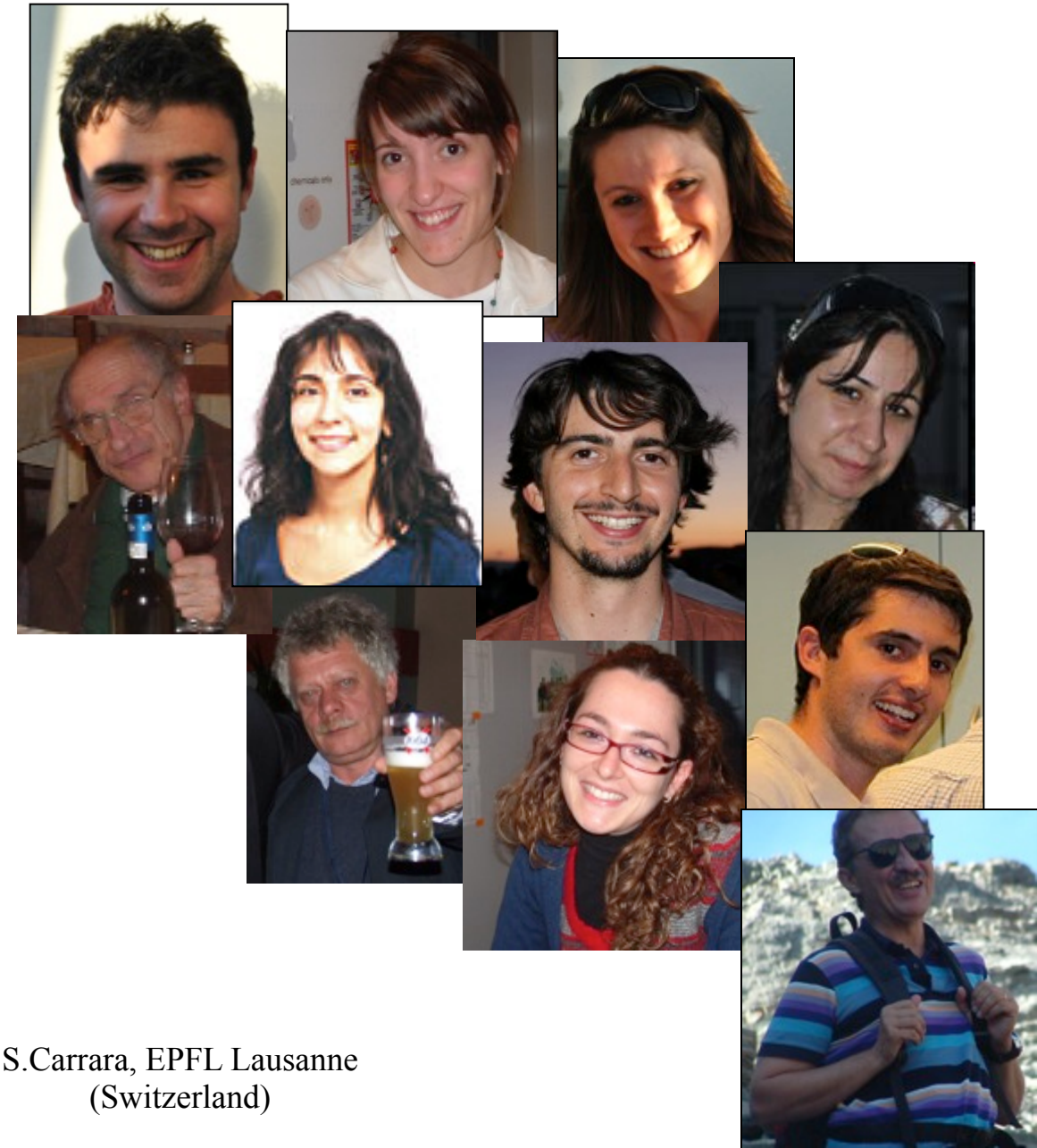
Lightweight identity-based encryption system

Conclusions

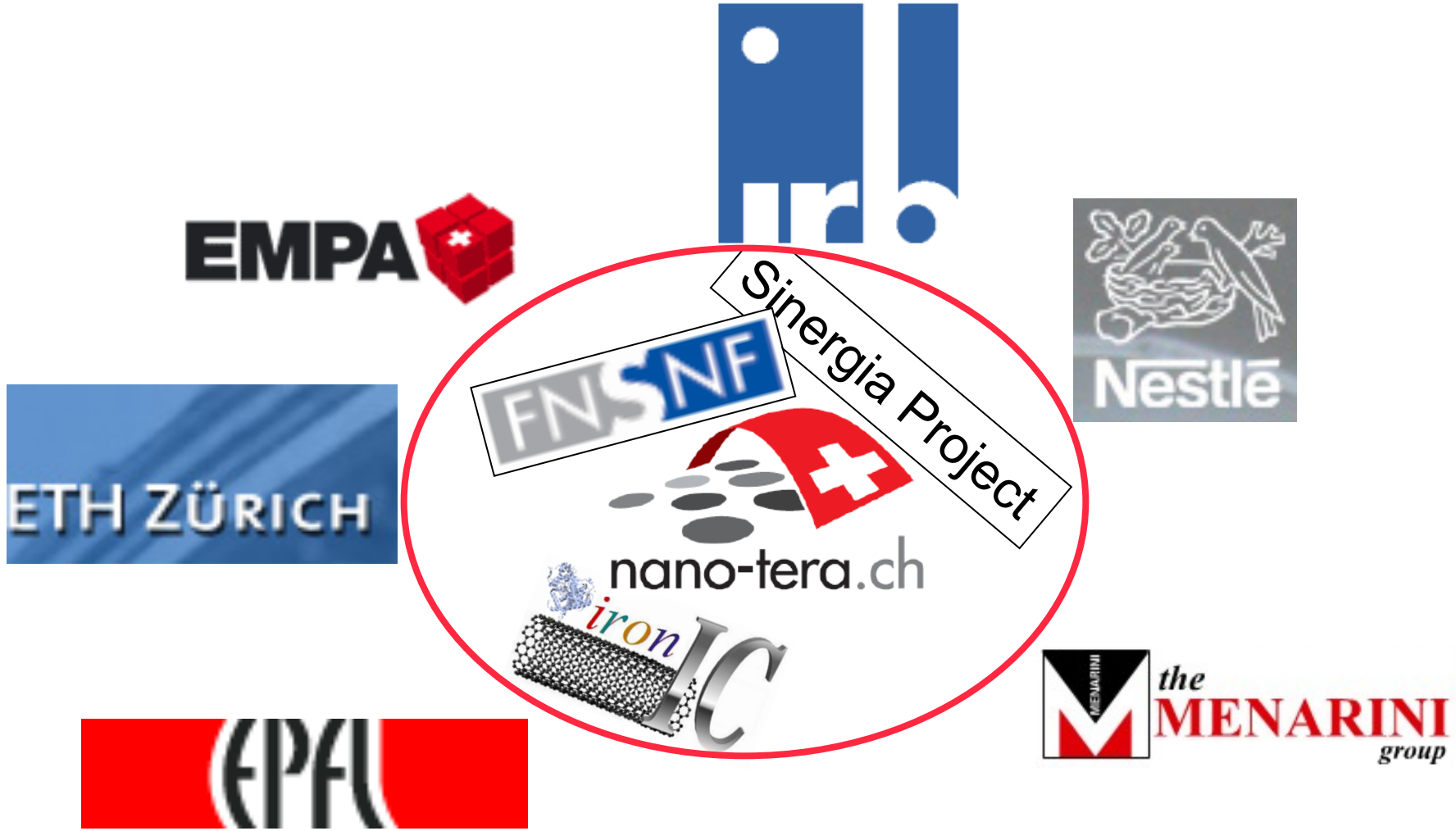
- **P450 Cytochromes are required to detect Exogenous metabolites (Drugs)**
- **Oxidases are required to detect endogenous metabolites (bio-markers)**
- **Carbon Nanotubes are required to improve sensitivity of electrochemical detection**
- **Data analysis is required to improve specificity on exogenous compounds**
- **New CMOS design is required to develop Dedicated systems for molecular detection**
- **New system architectures are required to improve and assure Security and Privacy**

Thanks to:

- *Andrea Cavallini*
- *Camilla Bai-Rossi*
- *Cristina Boero*
- *Sara Ghoreishizadeh*
- *Daniel Torre*
- *Daniela De Venuto*
- *Jacopo Olivo*
- *Irene Taurino*
- *Dino Giuseppe Albini*
- *Victor Erokhin*
- *Giovanni De Micheli*



Thanks to my Sponsors



Thank you for your attention!

Coordinates

Sandro Carrara Ph.D
EPFL - Swiss Federal Institute of Technology in Lausanne - Switzerland

Web: **http://si2.epfl.ch/~scarrara/**
email: **sandro.carrara@epfl.ch**

Related References :

1. Biosensors and Bioelectronics, (2011) in press
2. Proceedings of DATE 2011 and ISMICT 2011
3. Proceedings of IEEE/Bio-CAS 2010, and 2008
3. Proceedings of the IEEE/Sensors 2010
4. Proceedings of the IEEE/ICME 2009 & 2010
5. Proceedings of the IEEE/PRIME 2009 & 2010
6. Biosensors and Bioelectronics, 24(2008) 148-150
7. Sensors and Actuators B, 109(2005) 221-226