ultrasponder workshop

Montreux, March 30th, 2011

New concepts In Remotely-Powered Telemetry of the Human Metabolism

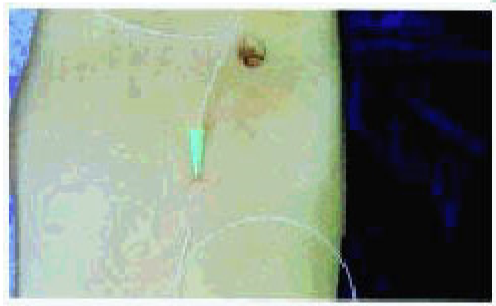
ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

SANDRO CARRARA

Laboratoire des Systèmes Intégrés (LSI)

State-of-the-Art

F.Valgimigli et al., J.Dabetes S&T, 2010



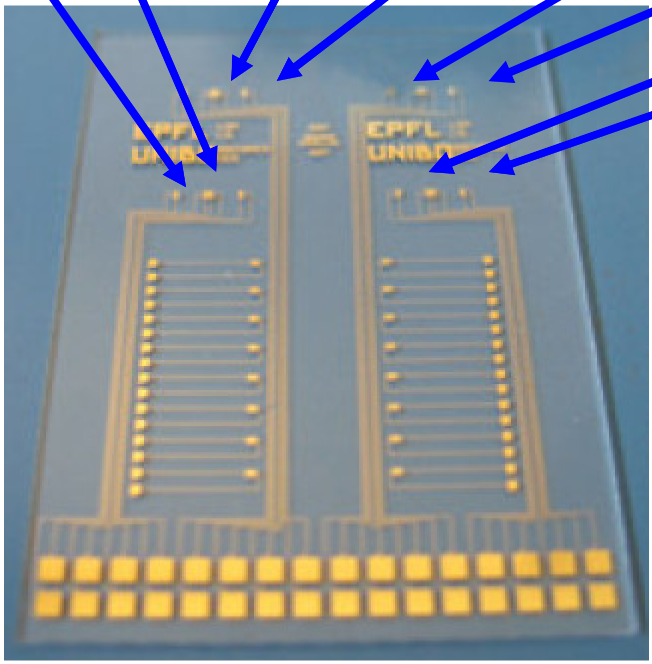
- In/Out tubing
- Almost only for Diabetes
- Almost only for Glucose

GlucoDay® and GlucoMenDay® consist of a micro-pump and a biosensor coupled with a micro-dialysis system

Human metabolism monitoring requires biochip array

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

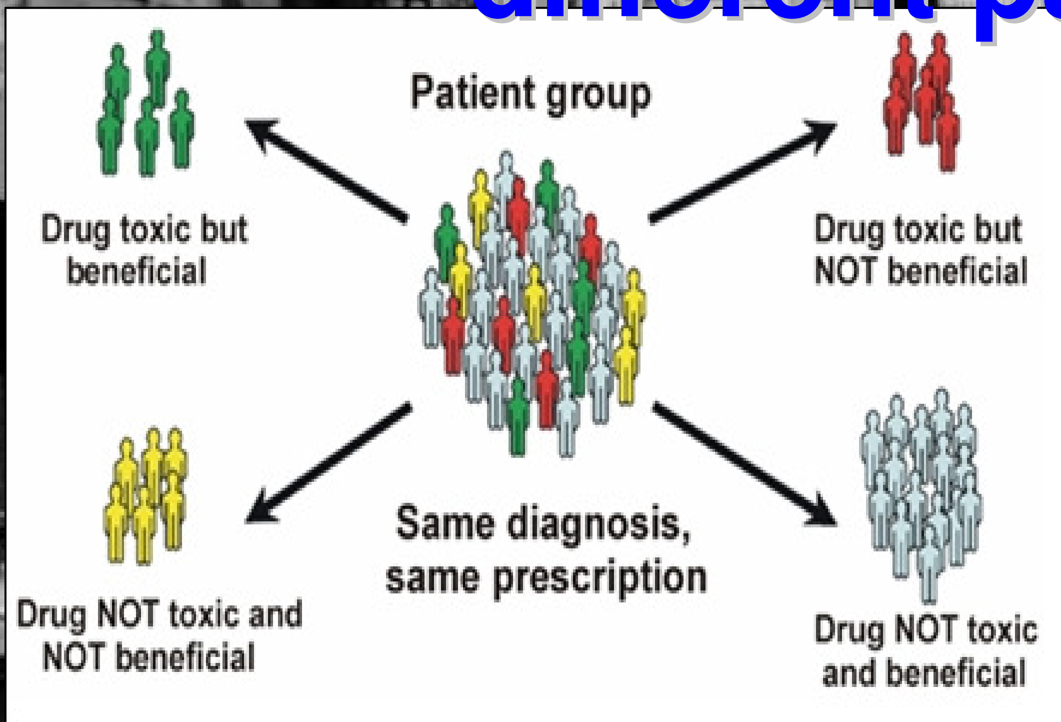
Probe enzymes

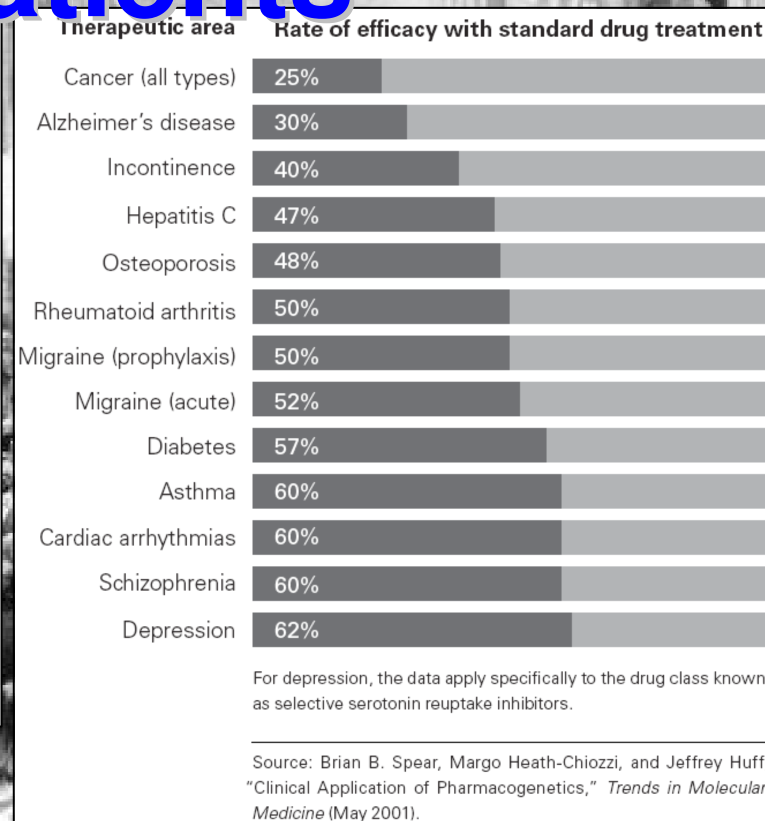


- Glucose
- Lactate
- Cholesterol
- ATP
- Drugs

Different enzymes sense different Human metabolites

Different outcomes for different patients





P450 for Drugs Monitoring

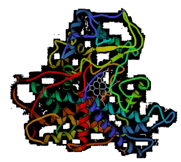
RH (e.g. benzphetamine)

O_2

From electrode

$2e^-$

Drugs detection !



Cytochrome
P450 2B4

NADP

H-O-H

R-OH Oxidized form

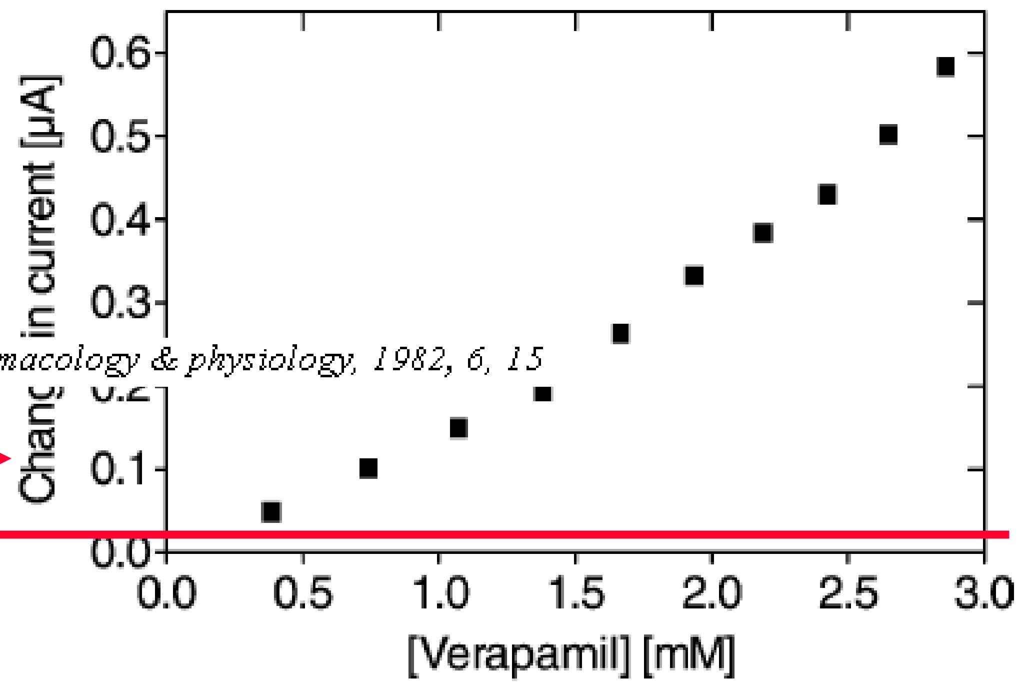
more soluble
then
faster secreted

Problems on Detection Limits

Angus, J.; et al. / Clinical and experimental pharmacology & physiology, 1982, 6, 15

Therapeutic Range

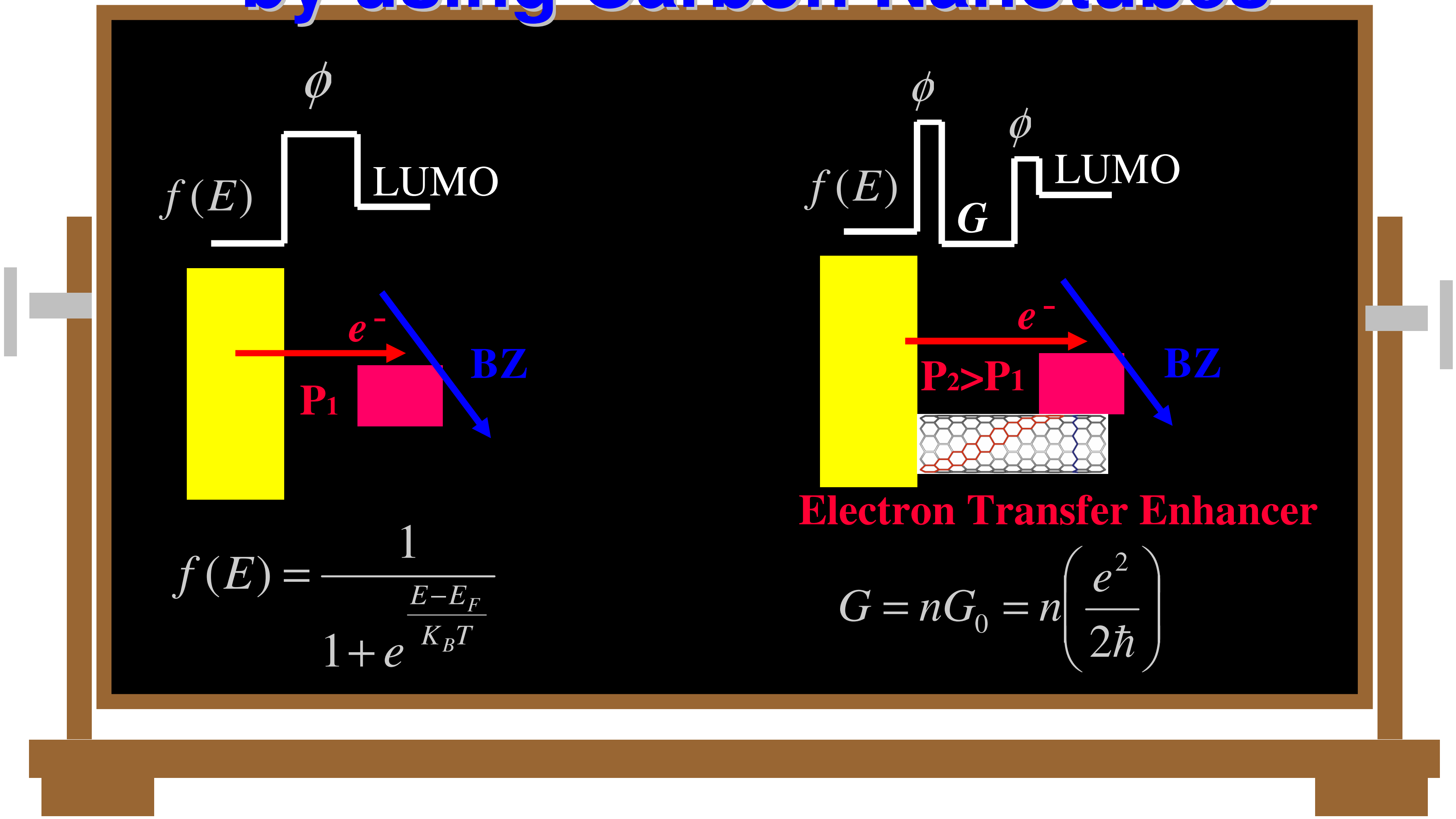
0.3 uM



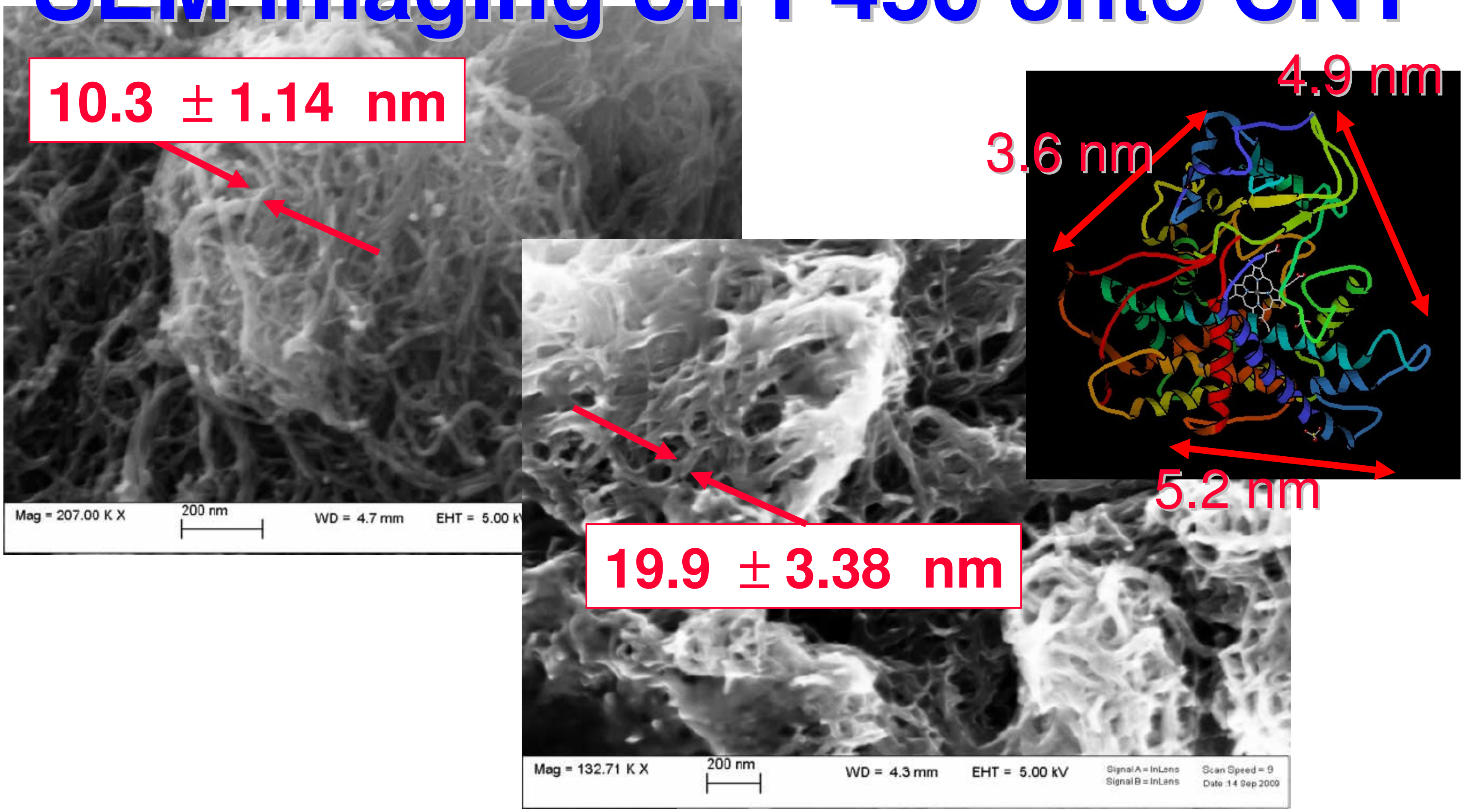
S. Joseph et al. / Biochemical Pharmacology 65 (2003) 1817–1826

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



SEM imaging on P450 onto CNT

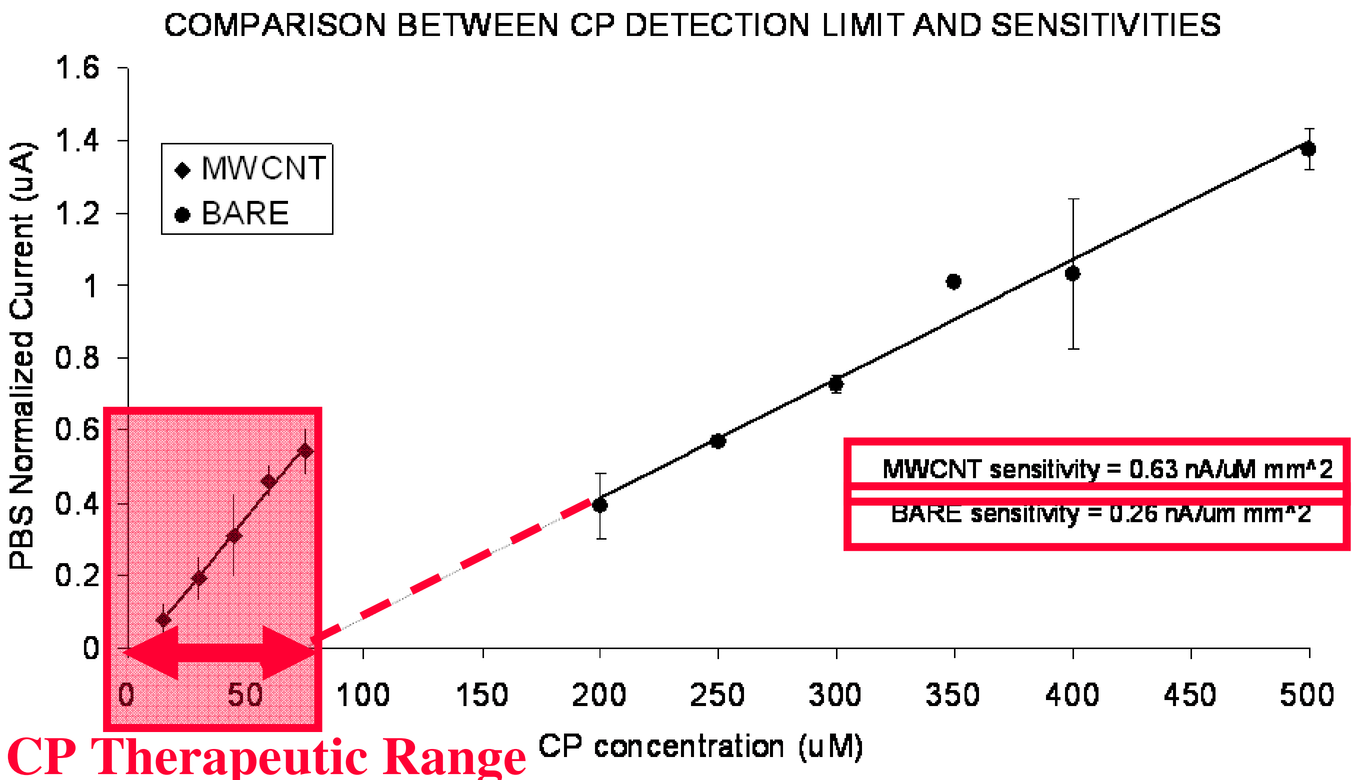


S.Carrara et al. / Biosensors and Bioelectronic, 2011, in press

Scanning Electron Microscopy clearly show the P450 wrapping onto each single Multi-Walled Carbon Nanotube

S.Carrara, EPFL Lausanne
(Switzerland)

Improved Detection Limit on Drugs detection

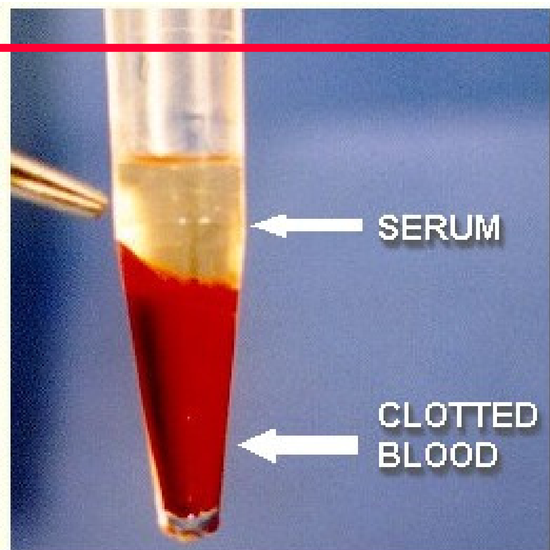


S.Carrara et al. / Biosensors and Bioelectronic, 2011, in press

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

Measurement in Serum

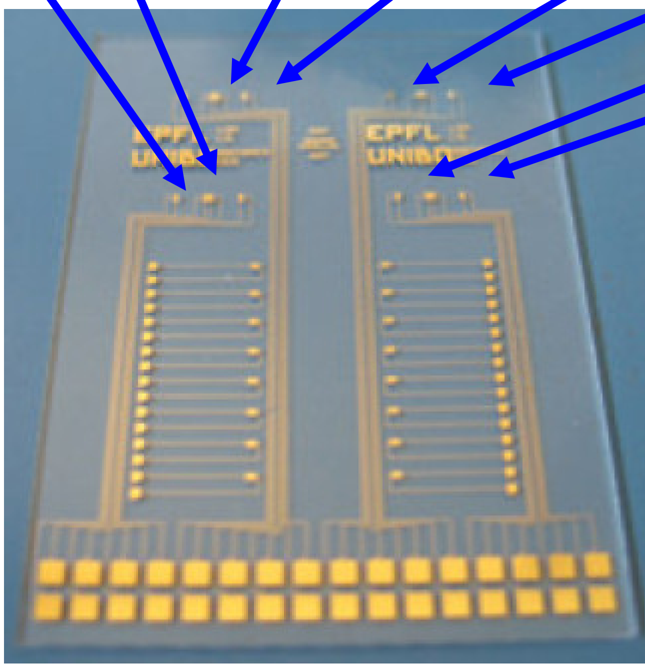
Drugs	Pharmacological range (μM)	P450 enzyme	Sensitivity ($nA/\mu M*mm^2$)		Detection limit (μM)	
			PBS	Serum	PBS	Serum
Cyclophosphamide	2.68-76.6	2B6	1.021	0.279	1.935	13.81
Ifosfamide	10-160	3A4	1.602	0.430	2.018	7.086
Ftorafur	1-10	1A2	8.832	3.469	0.646	0.957
Etoposide	33.98-101.94	-	73.73	9.142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



Sensor array architecture

Probe enzymes

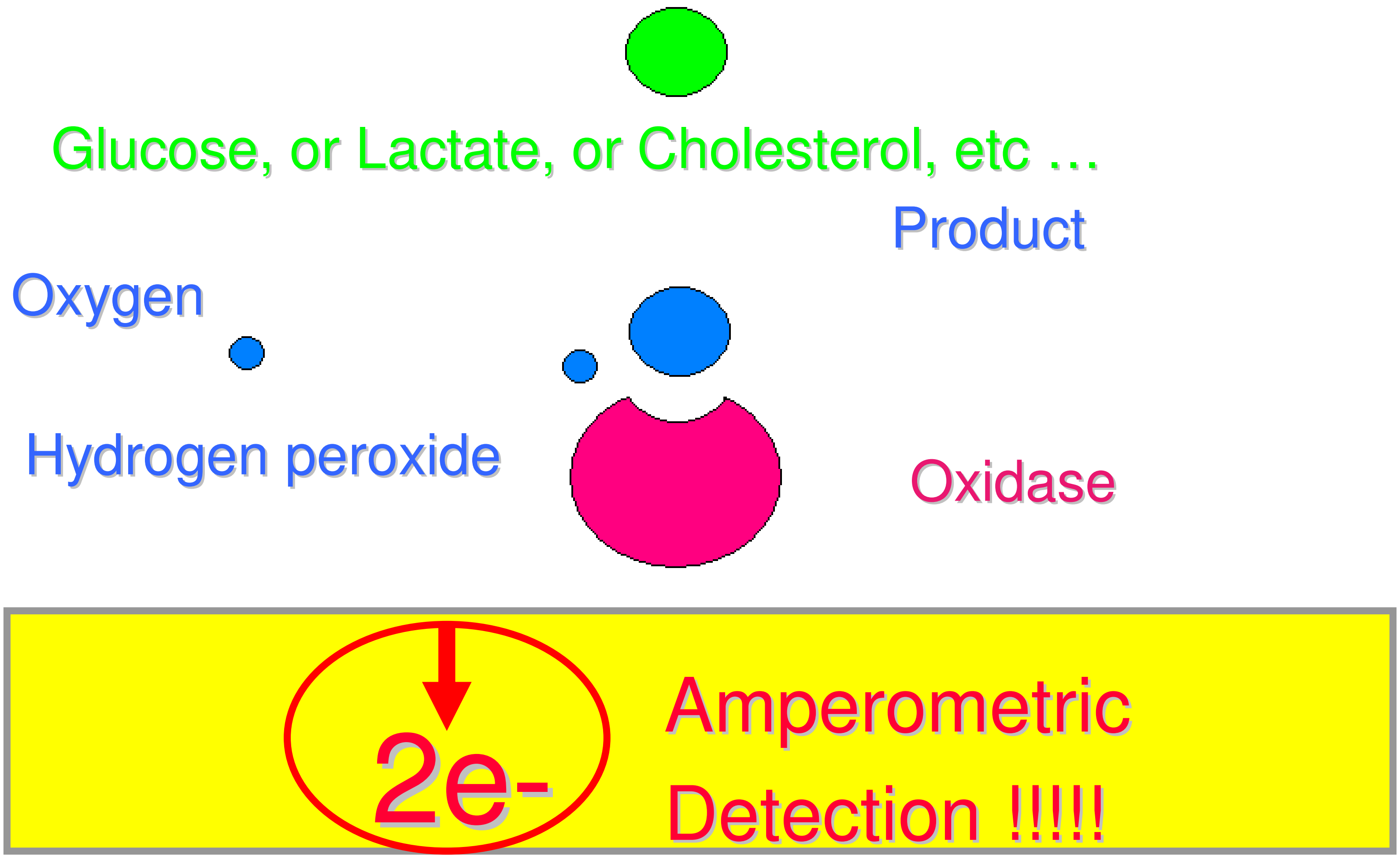
ATP-ase	Lactate oxidase	Glucose oxidase	Lipoxygenase
P450 11A1	P450 5A1	P450 4A11	Cholesterol oxidase



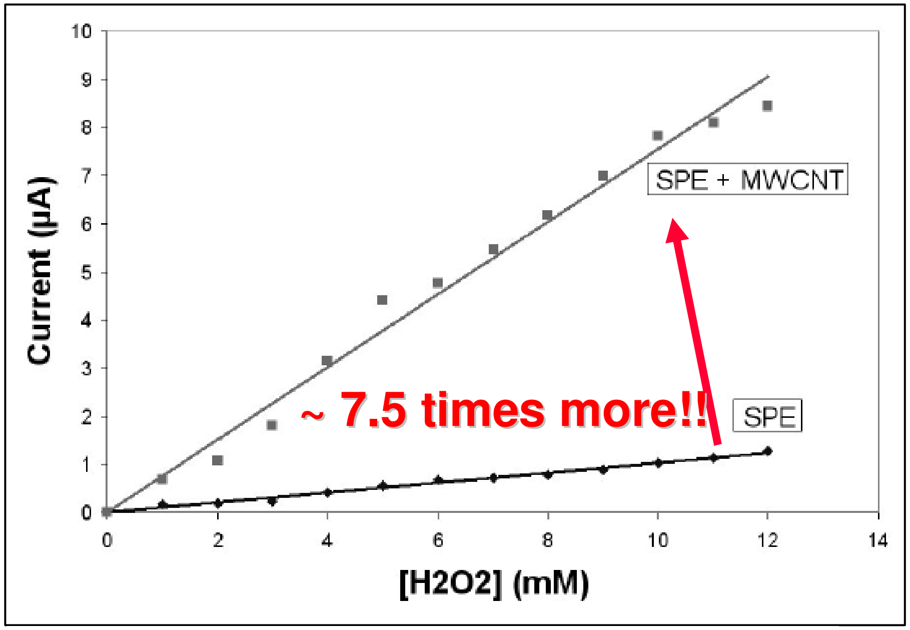
- Glucose
- Lactate
- Cholesterol
- ATP
- Drugs

Different enzymes sense different target metabolites

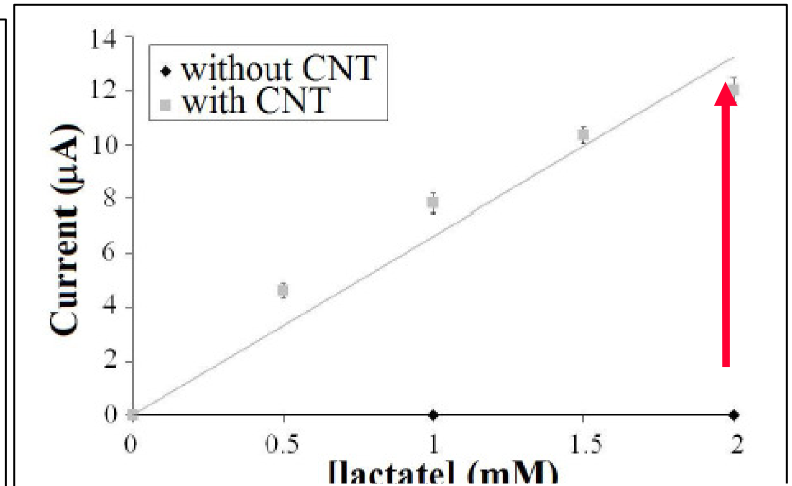
Working principle of Oxidases based detection



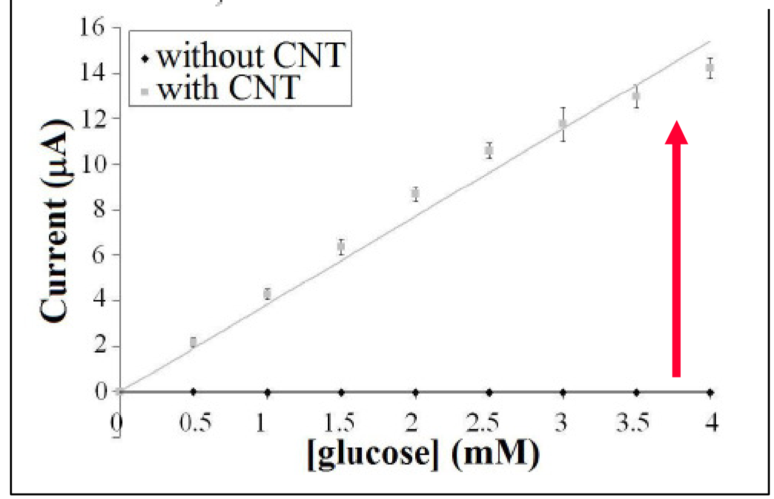
Peroxide Based Detection

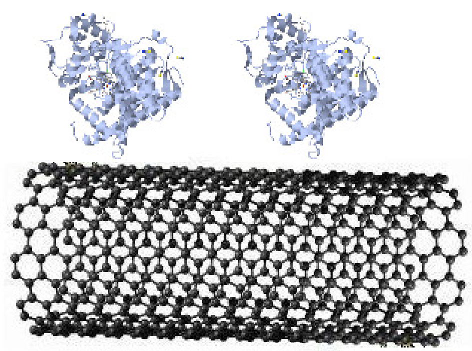


C. Boero, S.Carrara et al., IEEE PRIME, 2009



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





Carbon nanotubes also Enhance the peroxide based detection

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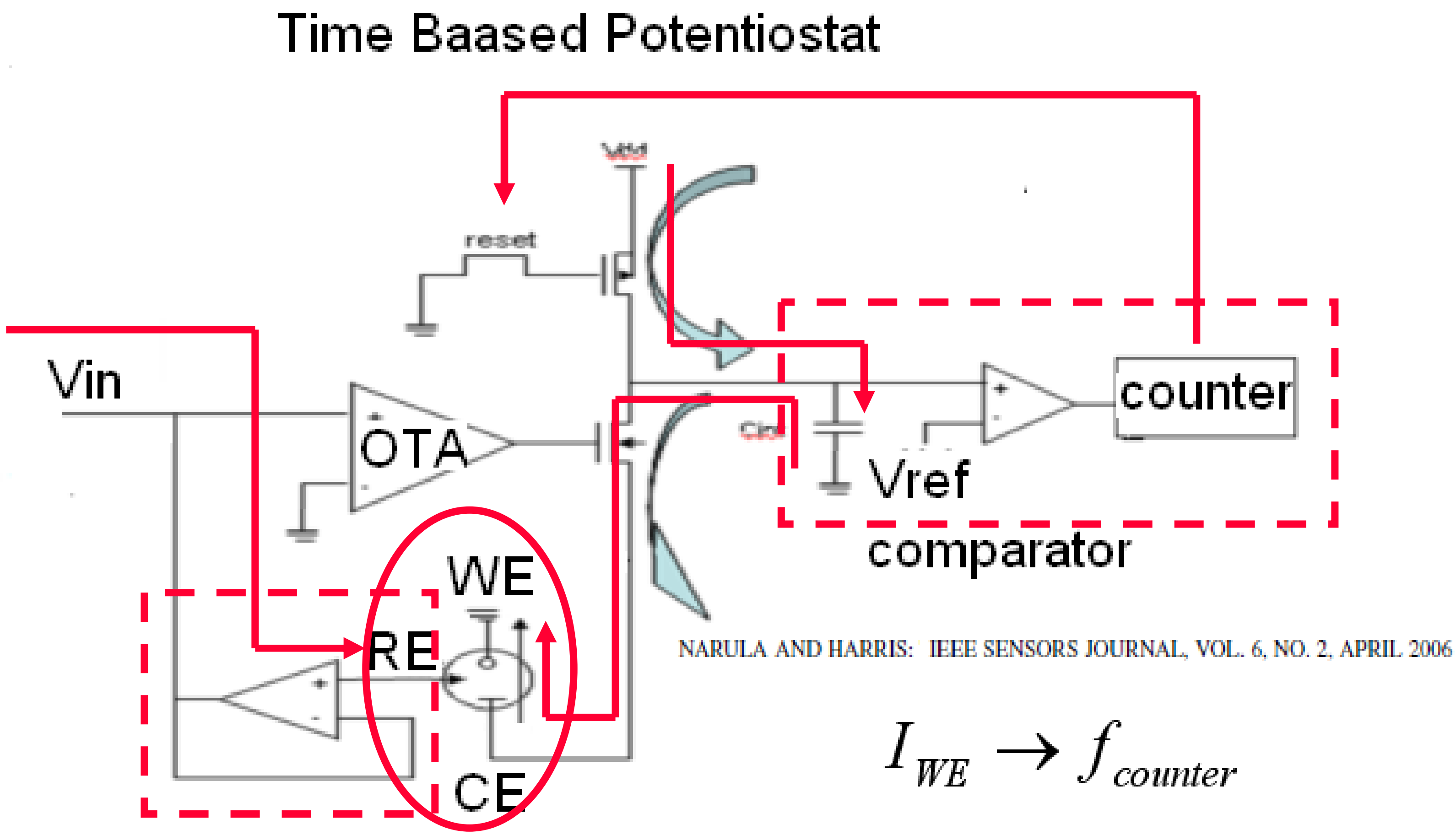
(Switzerland)

Precise Current measurements



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

Current-to-frequency converter

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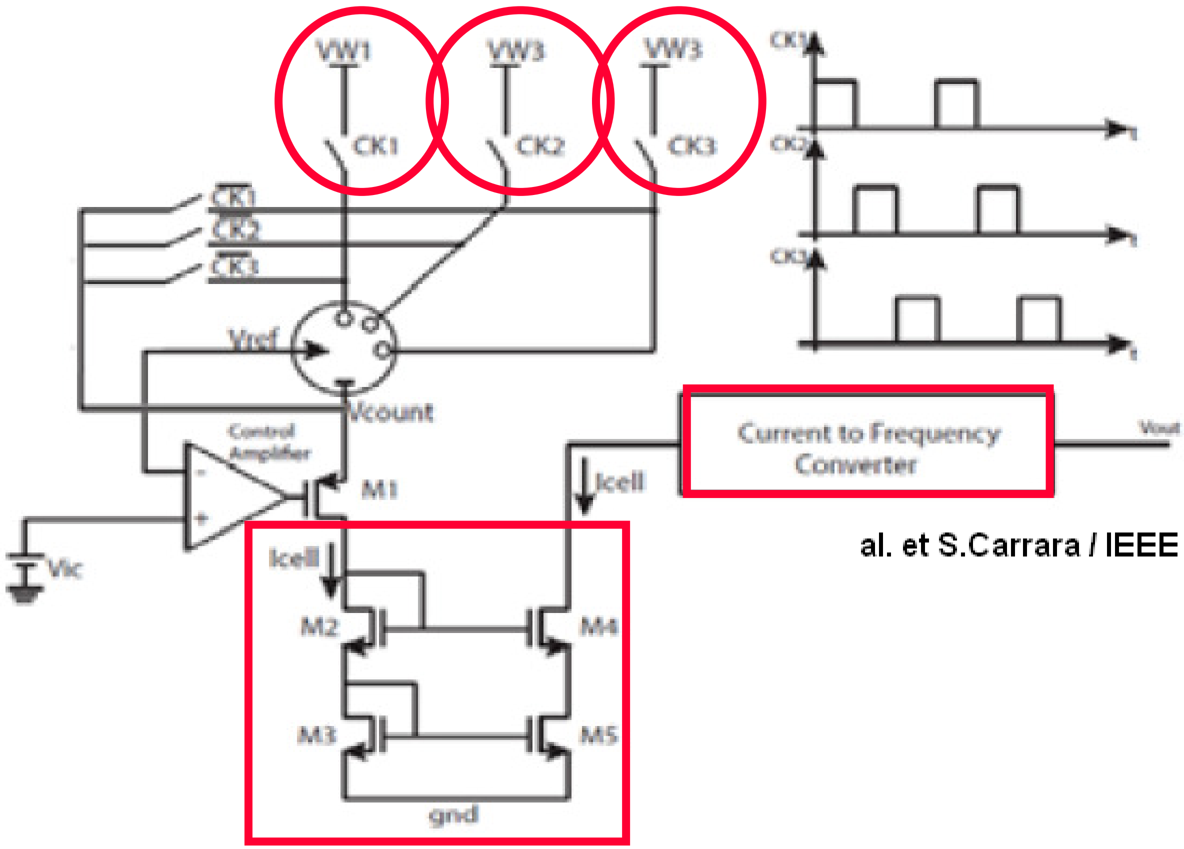
Multiplexing Molecular Detection



al. et S.Carrara / IEEE Sensors 2010

Different working electrodes are multiplexed

to the current-to-frequency converter

Reliability in Temperature & pH

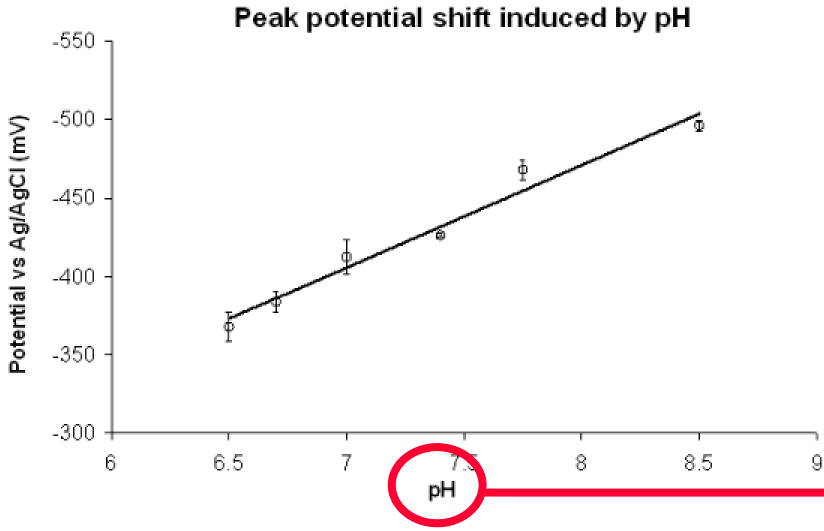
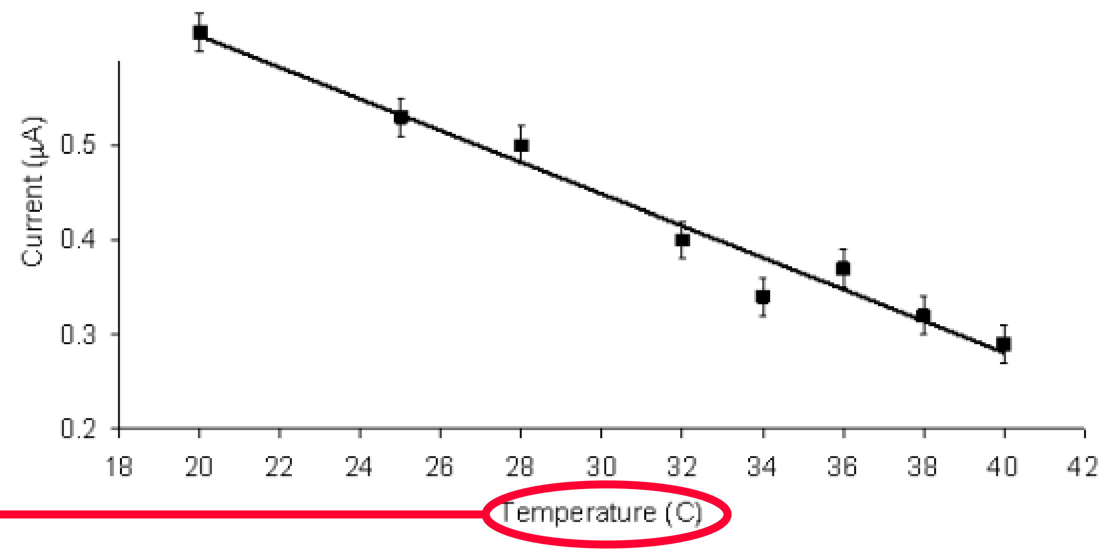


Figure 2. .Peak Potential shift versus pH

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

Peak current variation induced by temperature



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

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Multiplexing Molecular detection with T and pH

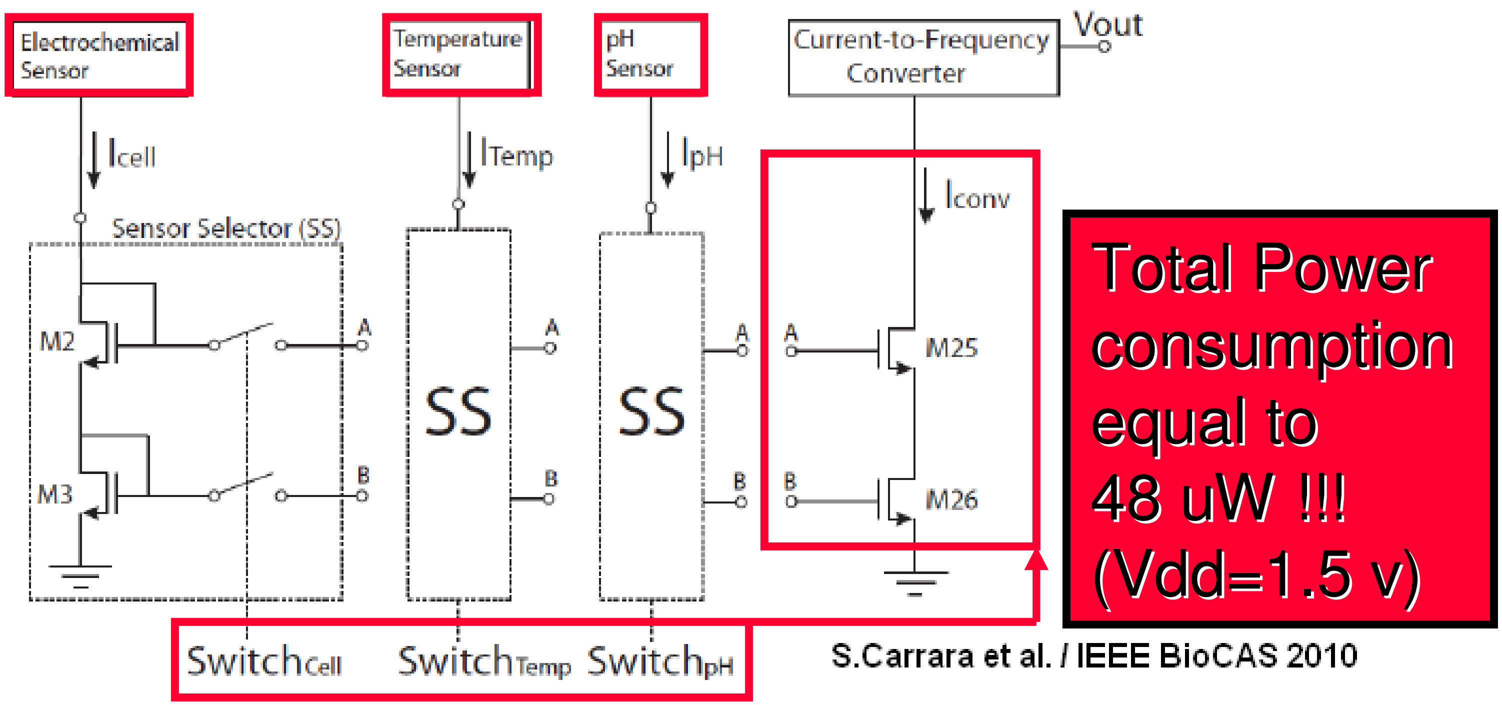
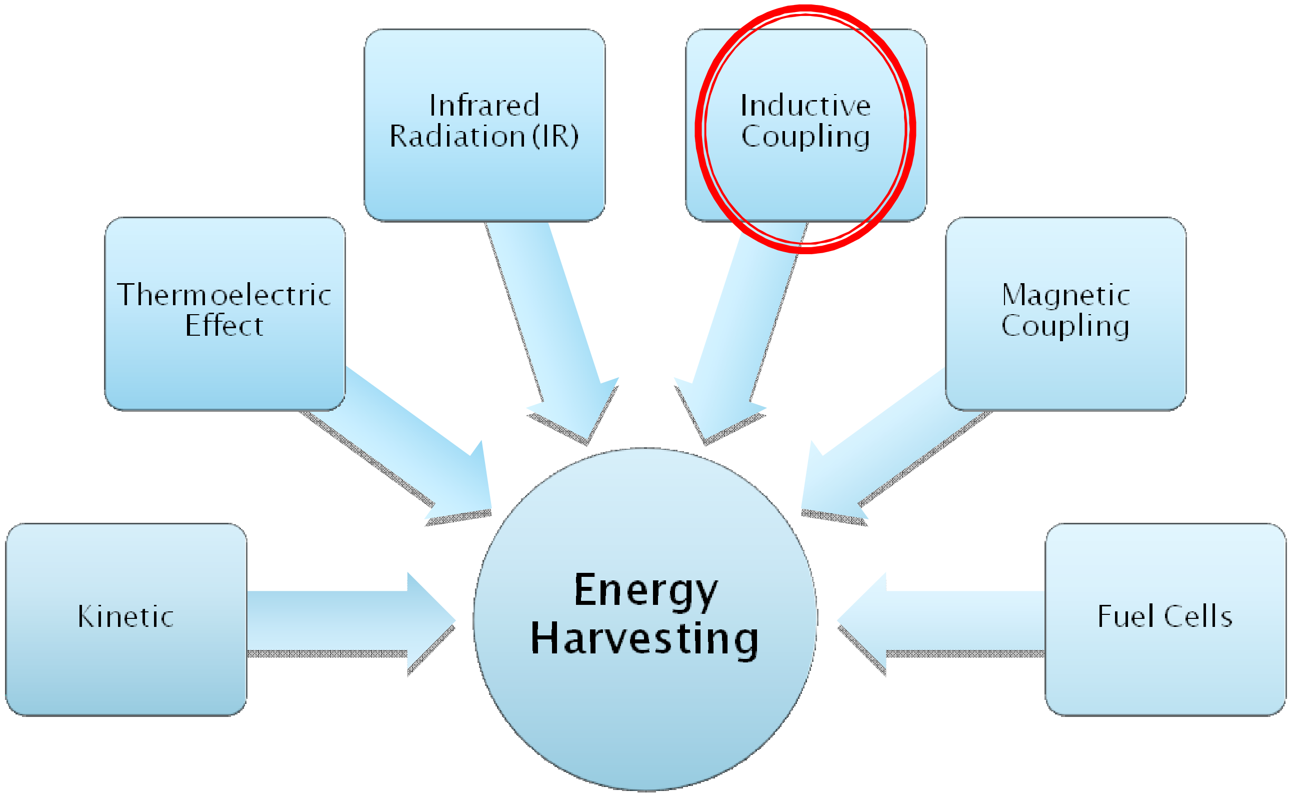


Figure 8. The bloks-scheme of the multiplexing

The switches also multiplex the T and pH measure

Energy Scavenging Strategies



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.2605-2618, 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

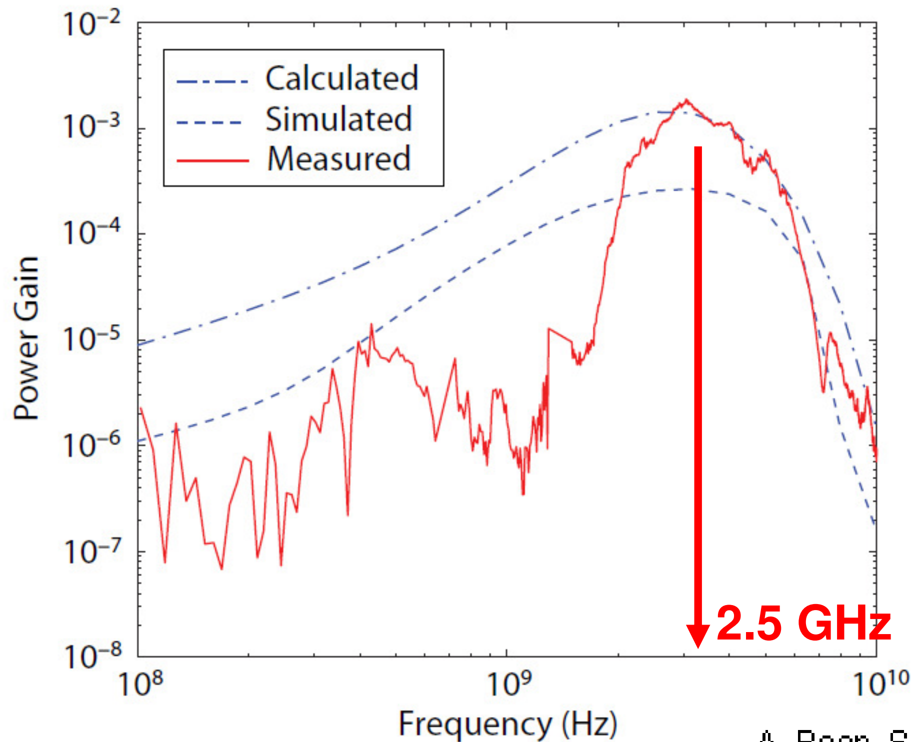
[13] J. Parramon et al., "ASIC-based batteryless implantable telemetry microsystem for recording purposes", *Eng. In Med. and Bio. Soc.*, In *Proc. of the 19th Annual Int. Conf.*, vol.5, pp. 2225-2228, 1997.

[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.463-475, 1998

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

High Frequency for Inductive Links



External Coil = 4mm²

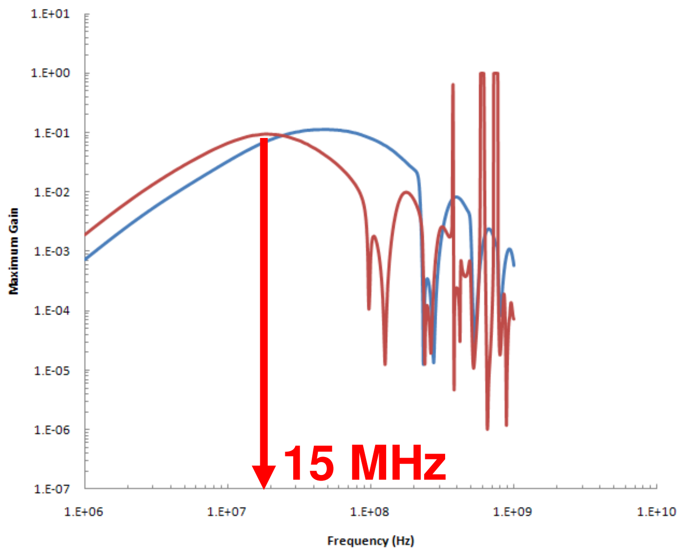
Internal Coil = 4mm²

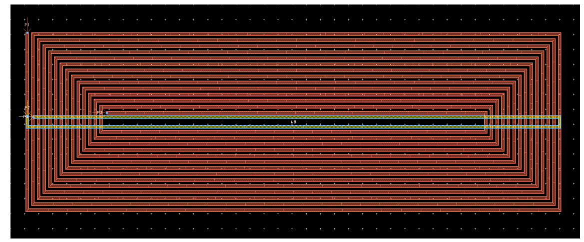
Optimum Frequency: 2.5 GHz

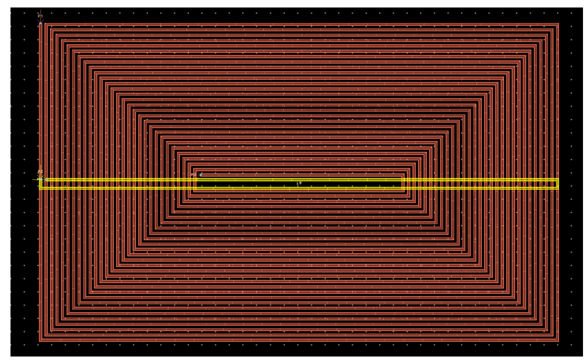
High Frequency:
- Better tolerance to misalignment
- Higher data rate

A. Poon, S. O'Driscoll, and T. Meng, IEEE EMBS, pp. 5673–5678, 2007.

Multiple Turns External Coil



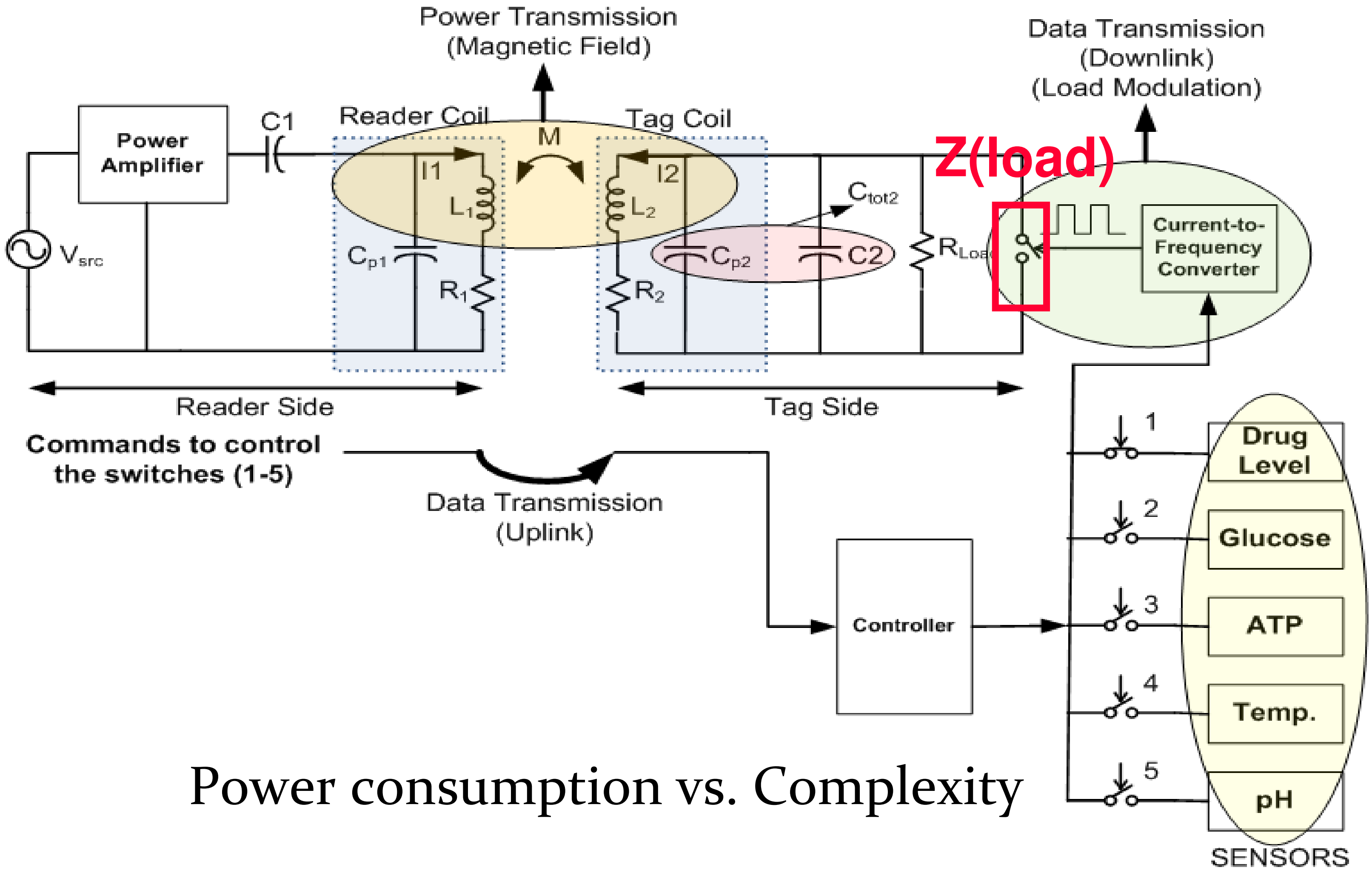




J.Olivo, S.Carrara et al. / IEEE Sensors 2010b

Multiple turns of the external coil shift the optimum frequency into a safe range.

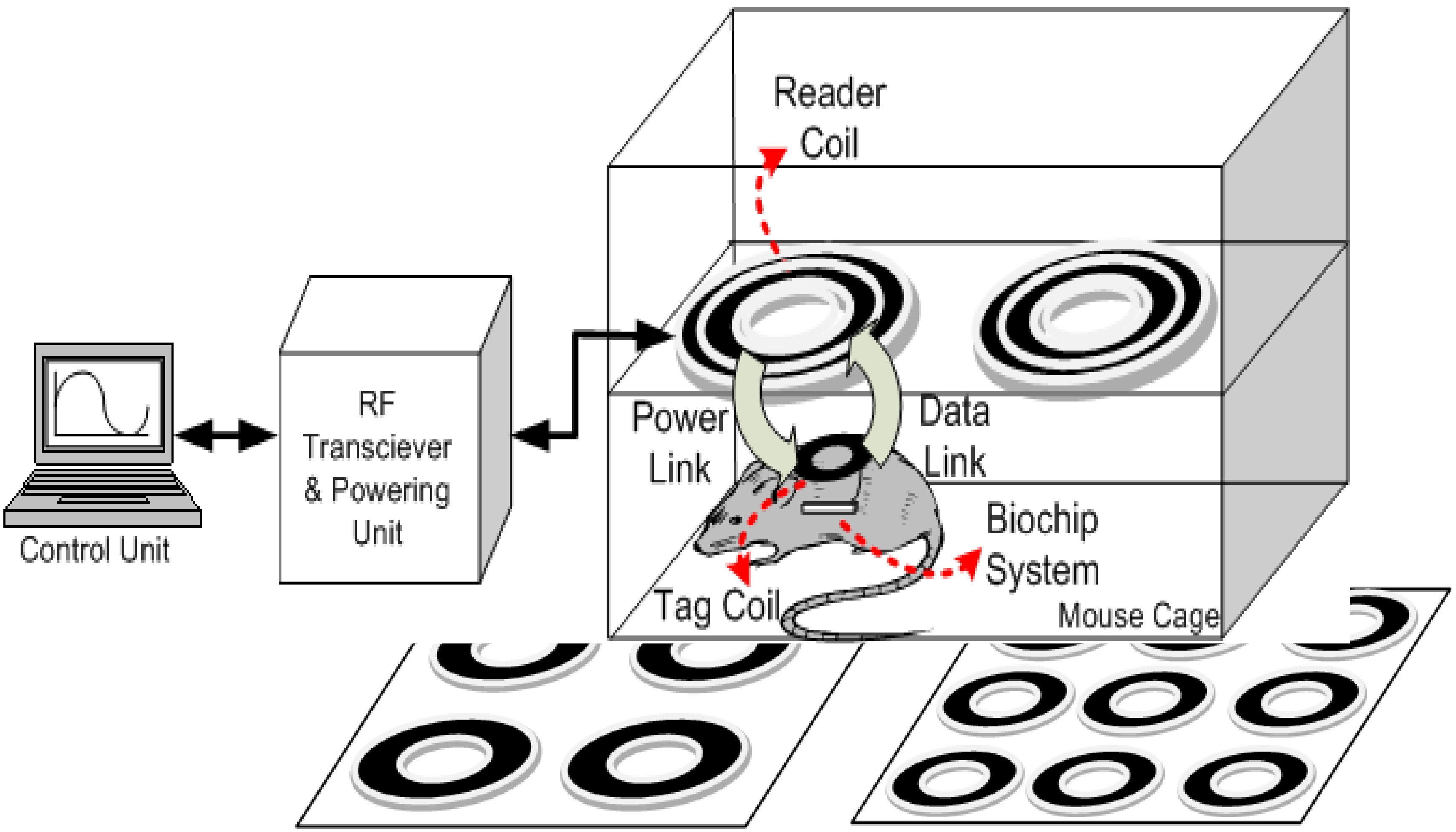
Data Transmission



Power consumption vs. Complexity

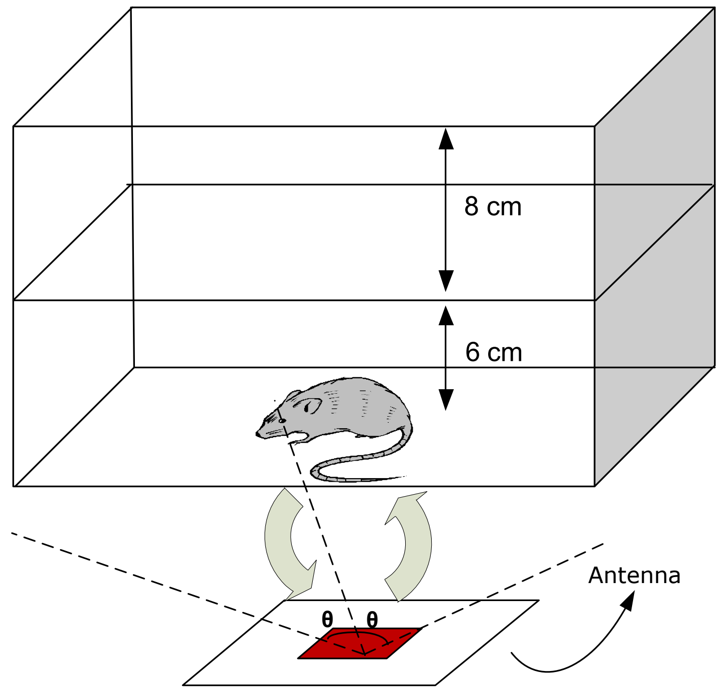
Near-Field Power Transmission

E.G.Kilinc, et al., SM2ACD 2010



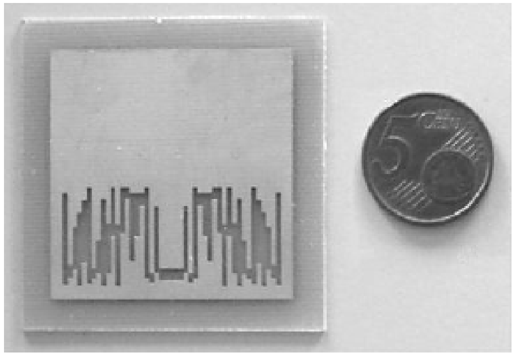
Far-Field Power Transmission

- Antenna Placement to Bottom

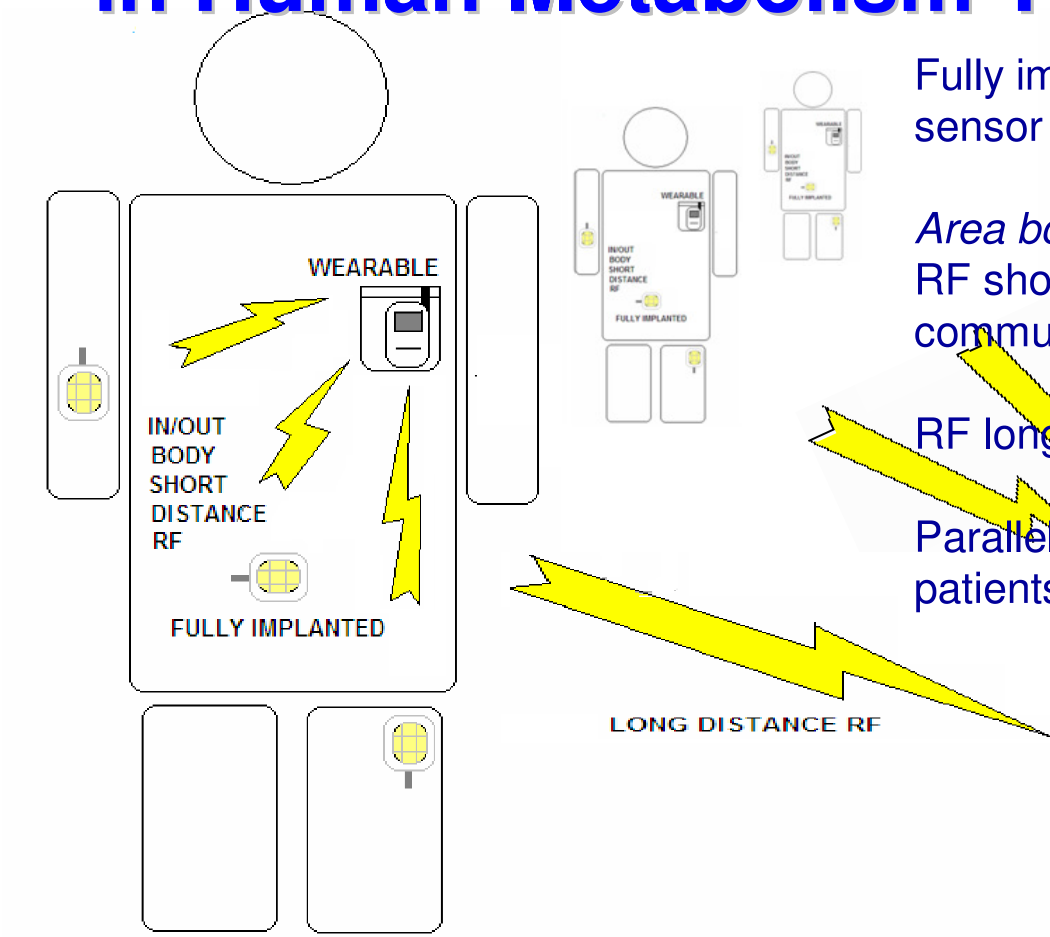


Meandered-Slot Antenna

Onour et al., ISMICT 2011



Future Perspective: New Concepts in Human Metabolism Telemetry

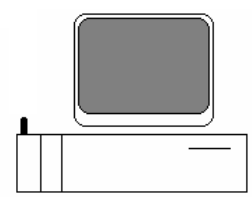


Fully implanted multi-platform sensor system

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

RF long distance communication

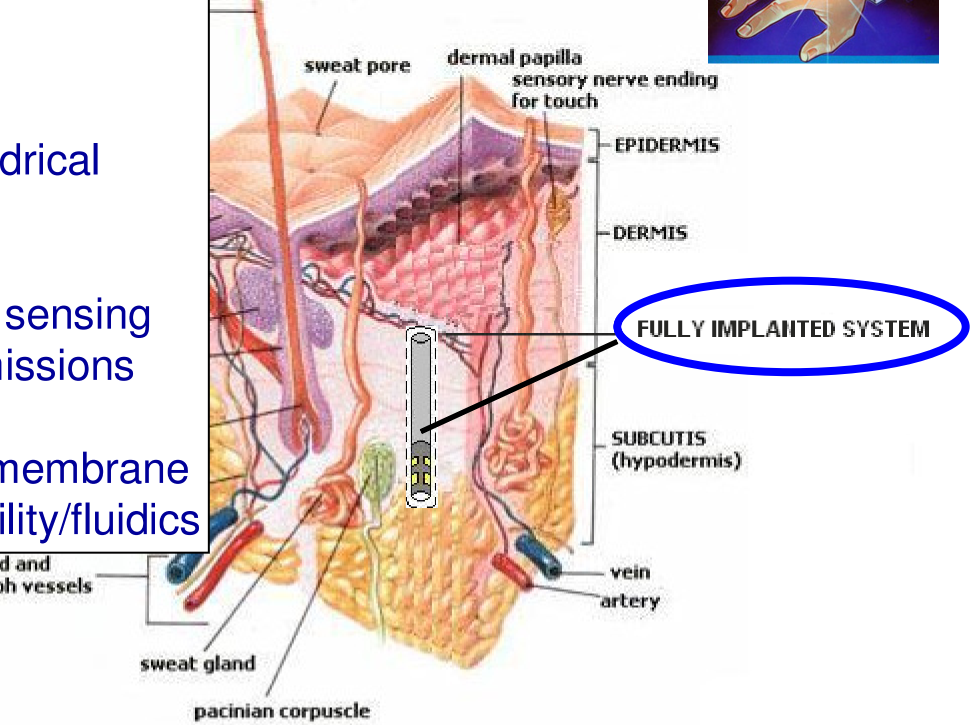
Parallel monitoring of different patients



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

Future Perspective: Fully-new sub-cutaneous system are required

- Cylinder: 1-2 mm in diameter
- Below 2 cm in length
- Chip packaging in cylindrical shape
- Implanted chip only for sensing and short range transmissions
- Porous MEMS/NEMS membrane to ensure bio-compatibility/fluidics



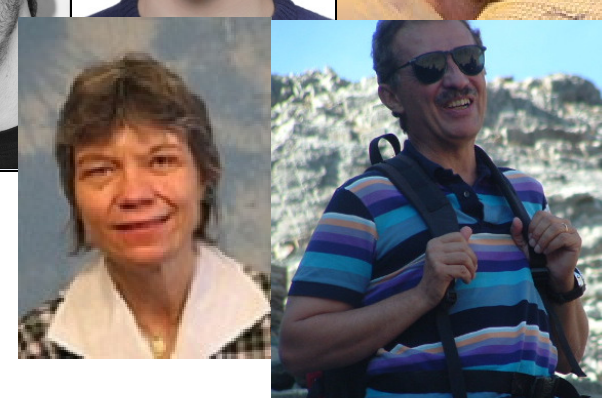
Fully implanted system with fluidics, sensors, electronics, antenna, data processing and transmission

Summary

- **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**
- **Remote Powering by inductive coupling is required for needle-shaped devices**
- **Fully-implantable Telemetry of human metabolism is feasible**

Thanks to:

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



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Thanks to my Sponsors

EMPA

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Sinergia Project

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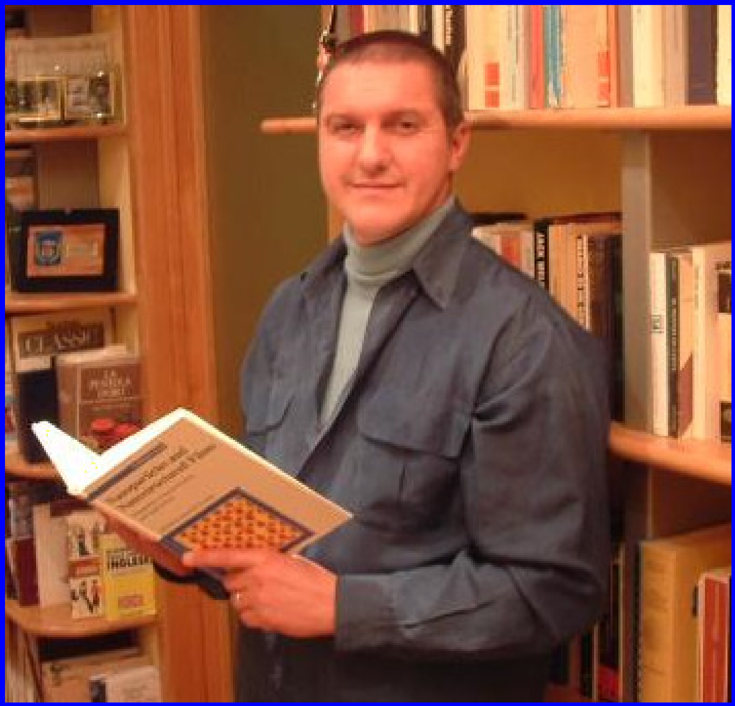
the MENARINI group

Thank you for your attention!



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