New frontiers in biomedical VLSI on implantable systems to monitor human metabolism including remote powering of the systems.
Different outcomes for different patients

<table>
<thead>
<tr>
<th>Therapeutic area</th>
<th>Rate of efficacy with standard drug treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer (all types)</td>
<td>25%</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>30%</td>
</tr>
<tr>
<td>Incontinence</td>
<td>40%</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>47%</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>48%</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>50%</td>
</tr>
<tr>
<td>Migraine (prophylaxis)</td>
<td>50%</td>
</tr>
<tr>
<td>Migraine (acute)</td>
<td>52%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>57%</td>
</tr>
<tr>
<td>Asthma</td>
<td>60%</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>60%</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>60%</td>
</tr>
<tr>
<td>Depression</td>
<td>62%</td>
</tr>
</tbody>
</table>

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

System Biology is not enough

Thanks to Systems Biology, we now have a clear picture of complex diseases!

S.Carrara, EPFL Lausanne
(Switzerland)
Personalized Therapy

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

S.Carrara, EPFL Lausanne (Switzerland)
The Motivation

- 100,000 $ (machinery)
- 1,000 $ the single μ-array
- 50 $ (machinery)
- 0.05 $ the single strip

S. Carrara, EPFL Lausanne
(Switzerland)
The Development of new Implantable Medical Devices is a key-factor for succeeding in Personalized therapy.

S. Carrara, EPFL Lausanne (Switzerland)
New Frontier in Human Metabolism Telemetry

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

S. Carrara, EPFL Lausanne (Switzerland)
New Frontier: Fully-implanted 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

S. Carrara, EPFL Lausanne
(Switzerland)
State-of-the-Art

A. Menarini Diagnostics, Florence

- 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

S.Carrara, EPFL Lausanne
(Switzerland)
Human metabolism monitoring requires biochip array.

Different enzymes sense different human metabolites:

- Glucose
- Lactate
- Cholesterol
- ATP
- Drugs

<table>
<thead>
<tr>
<th>ATP-ase</th>
<th>Lactate oxidase</th>
<th>Glucose oxidase</th>
<th>Lipoxigenase</th>
</tr>
</thead>
<tbody>
<tr>
<td>P450 11A1</td>
<td>P450 5A1</td>
<td>P450 4A11</td>
<td>Cholesterol oxidase</td>
</tr>
</tbody>
</table>

S. Carrara, EPFL Lausanne
(Switzerland)
Detection of Endogenous Metabolites

Glucose, or Lactate, or Cholesterol, etc …

Oxygen

Hydrogen peroxide

Oxidase

Product

2e−

Amperometric Detection !!!!!

S.Carrara, EPFL Lausanne
(Switzerland)
Detection of Exogenous Metabolites

RH (e.g. benzphetamine)

From electrode

Drugs detection!

O$_2$

2e$^-$

NADP

H-O-H

Cytochrome P450 2B4

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.

S. Carrara, EPFL Lausanne (Switzerland)

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

An improved P450/Electrode coupling by using Carbon Nanotubes

Electron Transfer Enhancer

$G = nG_0 = n\left(\frac{e^2}{2\hbar}\right)$
The Peak Current is larger when the Protein Activity is mediated by Multi Walled Carbon Nanotubes

S. Carrara, EPFL Lausanne
(Switzerland)
The P450 11A1 performance in detecting Cholesterol is Enhanced by a factor 10x by using MWCNT

S.Carrara, EPFL Lausanne
(Switzerland)
Improved Detection Limit on Exogenous Cyclophosphamide (CP), an anti-cancer agent, is detected by P450 3A4 in its therapeutic range.
# Multi-panel System for Human Metabolism

S. Carrara, EPFL Lausanne (Switzerland)

## Targets

### Probe Enzymes
- Glucose Oxidase
- Lactate Oxidase
- Glutamate Oxidase
- P450 11A1
- P450 2B4
- P450 3A4
- P450 2C9
- P450 2C9

### Endogenous metabolites
- Glucose
- Lactate
- Glutamate
- Cholesterol

### Exogenous metabolites
- Benzphetamine
- Dextrometormhane
- Cyclophosphamide
- Flurbiprofene
- Naproxene


---

Already Measured by us in Human Serum within the pharmacological ranges, too.
Heterogeneous integration on IC

- Components
  - Probes and electrodes
  - Chambers and fluidic circuits
  - Transconductance amplifier and data conversion
  - Transmission and powering

How to integrate all of this into an active Biochip?

S. Carrara, EPFL Lausanne
(Switzerland)
A reliable full 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. Reliable in sweeping the Voltage
7. Remote-Powering
1. Nano-Bio-Sensors Macro-Assembly

BARE ELECTRODE

CARBON NANOTUBES

10.3 ± 1.14 nm

CNTs + PROBE ENZYMES

19.9 ± 3.38 nm

4.9 nm

3.6 nm

5.2 nm

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

S. Carrara, EPFL Lausanne
(Switzerland)
1. Nano-Bio-Sensors Micro-Spotting
1. New Challenges on CNT integration directly onto Silicon chips

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

S.Carrara, EPFL Lausanne
(Switzerland)
2. Current Measurements Front-End

Current-to-frequency converter

\[ I_{WE} \rightarrow f_{\text{counter}} \]
Different working electrodes are multiplexed to the current-to-frequency converter.

S. Carrara, EPFL Lausanne
(Switzerland)
4. Reliability in Temperature & pH

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

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

Figure 2. Peak Potential shift versus pH

S. Carrara, EPFL Lausanne (Switzerland)
5. Multiplexing Molecular detection with T and pH

The switches also multiplex the T and pH measure

S. Carrara, EPFL Lausanne
(Switzerland)
6. Voltage Sweep for Multiple detection

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

S. Carrara, EPFL Lausanne (Switzerland)
6. Reliability for Voltage Sweep

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

S.Carrara, EPFL Lausanne (Switzerland)
Implantable prototype – 2.2 x 15 mm

- uE array for the specific Bio-Detection
- Reference electrode
- counter electrode
- pH electrode (platinum/Iridium Oxide)
- Pt thermal Sensing device
- Slot for IC circuit Location

S.Carrara, EPFL Lausanne (Switzerland)
The VLSI Integration

IC sent for fabrication in the 0.18 um technology

Sweep in voltage

I-to-f conversion

Multiplexing

CMOS Total Power consumption less than 530 uW!!! (Vdd=1.5 v)

al. et S. Carrara / submitted to BioCAS 2011

IC sent for fabrication in the 0.18 um technology

S.Carrara, EPFL Lausanne
(Switzerland)
7. Energy Scavenging Strategies

S.Carrara, EPFL Lausanne
(Switzerland)
## Inductive Coupling

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

References:

High Frequency for Inductive Links

- Optimum Frequency: 2.5 GHz
- Better tolerance to misalignment
- Higher data rate

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

S.Carrara, EPFL Lausanne
(Switzerland)
Measures on the Designed Inductors

- **30 Turns**
  - 29mm
  - 12mm

- **14 Turns**
  - 38mm

- **2 Turns**
  - 38mm
  - 2mm

- **1 Turn**
  - 38mm
  - 1mm

Graphs showing link efficiency and voltage gain over frequency range.
Transferred Power through Tissues

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

S.Carrara, EPFL Lausanne
(Switzerland)
Data Transmission

Power consumption vs. Complexity

S. Carrara, EPFL Lausanne
(Switzerland)
An antenna very close to the chip is required for the remote powering.

S. Carrara, EPFL Lausanne
(Switzerland)
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
- Dedicated CMOS design is required for a reliable electrochemical detection of metabolites
- Remote Powering by inductive coupling is required for minimally invasive devices
- Fully-implantable Telemetry of Human Metabolism is feasible

S. Carrara, EPFL Lausanne (Switzerland)
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
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