New concepts
In Remotely-Powered
Telemetry of the
Human Metabolism
GlucoDay® and GlucoMenDay® consist of a micro-pump and a biosensor coupled with a micro-dialysis system.
Human metabolism monitoring requires biochip array

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

Different enzymes sense different Human metabolites

- Glucose
- Lactate
- Cholesterol
- ATP
- Drugs

S. Carrara, EPFL Lausanne
(Switzerland)
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.

P450 for Drugs Monitoring

RH (e.g. benzphetamine)

O$_2$

2e$^-$

From electrode

Drugs detection!

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

$$f(E) = \frac{1}{1 + e^{\frac{E-E_F}{k_BT}}}$$

$$G = nG_0 = n\left(\frac{e^2}{2\hbar}\right)$$
Scanning Electron Microscopy clearly show the P450 wrapping onto each single Multi-Walled Carbon Nanotube

S.Carrara, EPFL Lausanne (Switzerland)
Cyclophosphamide (CP), an anti-cancer agent, is detected by P450 3A4 in its therapeutic range.
# Measurement in Serum

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Pharmacologic al range (µM)</th>
<th>P450 enzyme</th>
<th>Sensitivity (nA/µM*mm²)</th>
<th>Detection limit (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PBS</td>
<td>Serum</td>
<td>PBS</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>2.68-76.6</td>
<td>2B6</td>
<td>1.021</td>
<td>0.279</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>10-160</td>
<td>3A4</td>
<td>1.602</td>
<td>0.430</td>
</tr>
<tr>
<td>Ftorafur</td>
<td>1-10</td>
<td>1A2</td>
<td>8.832</td>
<td>3.469</td>
</tr>
<tr>
<td>Etoposide</td>
<td>33.98-101.94</td>
<td>-</td>
<td>73.73</td>
<td>9.142</td>
</tr>
</tbody>
</table>
Sensor array architecture

<table>
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<tr>
<th>Probe enzymes</th>
<th>ATP-ase</th>
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Different enzymes sense different target metabolites

- Glucose
- Lactate
- Cholesterol
- ATP
- Drugs

S. Carrara, EPFL Lausanne (Switzerland)
Working principle of Oxidases based detection

Glucose, or Lactate, or Cholesterol, etc …

Oxygen

Hydrogen peroxide

Oxidase

Product

2e-

Amperometric Detection !!!!!

S.Carrara, EPFL Lausanne (Switzerland)
Peroxide Based Detection

Carbon nanotubes also Enhance the peroxide based detection

S. Carrara, EPFL Lausanne (Switzerland)
Precise Current measurements

Time Based Potentiostat

\[ I_\text{WE} \rightarrow f_\text{counter} \]

Current-to-frequency converter

S. Carrara, EPFL Lausanne
(Switzerland)
Different working electrodes are multiplexed to the current-to-frequency converter.
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

$i \propto n F A D \left( \frac{nFvD}{RT} \right)^{1/2} C_r$

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

The switches also multiplex the T and pH measure

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Energy Scavenging Strategies

- Infrared Radiation (IR)
- Inductive Coupling
- Thermoelectric Effect
- Magnetic Coupling
- Kinetic
- Fuel Cells

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(Switzerland)
# Inductive Coupling

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Coil Area ($\lambda - 10 \ mm^2$)</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>5 mm</td>
<td>Air</td>
<td>Neural Recording System</td>
<td></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>25 mm</td>
<td>Water Bearing Colloids</td>
<td>Various</td>
<td></td>
</tr>
<tr>
<td>[10]</td>
<td>Tx: 13200 $\lambda$ Rx: 25.2 $\lambda$</td>
<td>1 MHz</td>
<td></td>
<td></td>
<td>150 mW</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></td>
<td>10 mW</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>Orthopaedic Implant</td>
<td></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 $\approx$ 19 mW in vivo</td>
<td>15 mm</td>
<td>Rabbit</td>
<td>Muscles</td>
<td></td>
</tr>
<tr>
<td>[14]</td>
<td>Tx: 196.3 $\lambda$ Rx: 3.5 $\lambda$</td>
<td>5 MHz</td>
<td>twd Int.: OOK twd Ext.: LSK</td>
<td>100 kbps</td>
<td>5 mW</td>
<td>40 mm</td>
<td></td>
<td>Neural Stimulator</td>
<td></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></td>
<td>0.14 mW</td>
<td>0.06%</td>
<td>15 mm</td>
<td>Bovine Muscle</td>
<td>Various</td>
</tr>
</tbody>
</table>

Reference:
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

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

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

Power consumption vs. Complexity

S.Carrara, EPFL Lausanne (Switzerland)
Near-Field Power Transmission

E.G. Kilinc, et al., SM2ACD 2010
Far-Field Power Transmission

- Antenna Placement to Bottom

Meandered-Slot Antenna

S. Carrara, EPFL Lausanne
(Switzerland)
The design of implantable/wearable systems for continuous monitoring of human metabolism is feasible

S.Carrara, EPFL Lausanne
(Switzerland)
Fully implanted system with fluidics, sensors, electronics, antenna, data processing and transmission

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

Future Perspective: Fully-new subcutaneous system are required
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:

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- Giovanni De Micheli

S.Carrara, EPFL Lausanne (Switzerland)
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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