Outline

▲ Introduction
▲ Electronic implants: a lab under the skin
▲ Drug monitoring and administration
▲ Conclusions
The megatrends

▲ Relentless growth of computing, storage and communication technologies
  ▼ Inexpensive terminals providing ubiquitous services

▲ Biomedical science becoming more quantitative
  ▼ Societal need of better care at lower costs

▲ Big data issues fueling research and businesses
  ▼ Models, algorithms, architectures to tame data deluge
Cyberphysical systems

[Image: Diagram depicting the interrelation of Infrastructural Core, Sensory swarm, and Mobile access.]
The sensory interface

▲ The More than Moore revolution

[Courtesy: ST]  [Courtesy: Carrara EPFL]
What is health?

State of complex physical, mental and social well-being and not merely the absence of disease or infirmity.
Quantitative medicine

Sequencing

Personalized drugs

Human implants
The bio-information revolution

Genetic information

Medical records

Consenting informed educated patients

www.23andme.com

www.patientslikeme.com
E-health: objectives

▲ Bettering medicine with electronic means
▲ Bringing low-cost medicine to the people
▲ Exploiting electronic well-being as a lifestyle
▲ Opportunities
  ▼ Synergy of integrated electronic and sensing
  ▼ Platform-based design of sensors
  ▼ Mobile telephone as point of care
Outline

▲ Introduction

▲ Electronic implants: a lab under the skin
  ▼ Biosensing technology
  ▼ Platform-based design
  ▼ Low-power and energy

▲ Drug monitoring and administration

▲ Conclusions
Monitoring chronic patients

- Continuous real-time monitoring
- Current devices are external and limited to a single measurement
- Wireless, batteryless implant
- Tracking multiple metabolites
- Driver technology for a wide set of applications
Case study: implant

- Silicon chip for sensor read-out, control
- Wire bonding
- Soft biocompatible encapsulation
- Substrate with antenna for remote powering and data transmission
- Sensor platform component
- Porous biocompatible membrane
- Bio-sensors
- Bio-compatible bi-directional diffusion barrier

IC CMOS for RF and detection

- Temperature Sensor
- pH Sensor
- Molecular Sensors
- Inductive coil

Dimensions: 20 x 4.2 x 3 mm
Case study: external patch

FEATURES
Remote powering through inductive link
Short-range bidirectional communication
Long-range comm. with remote devices

ADVANTAGES
Improved wearability
Direct placement over implant area
Stand alone
Battery-powered
Android user interface

Target molecule detection
The sensing technology

CARBON NANOTUBES

CNTs + PROBE ENZYMES
The electrochemical sensing principle

- Peak position returns the type of chemical contained into the sample (target signature)
- Peak current returns the concentration of the target
- Different isoforms of the cytochrome P450 enable detection of different targets
The platform and its components

▲ Specific components
  ▼ Probes and electrodes
  ▼ Chambers and fluidic circuits

▲ Electronic components
  ▼ Transconductance amplifier and data conversion
  ▼ Transmission and powering

Diagram:
- Probes
- Electrodes
- Readout
- Potentiostat
- Signal processing
- Transmission
- Powering
Control and readout electronics

▲ A biosensing platform
▲ Small size, low power
▲ Remotely powered
▲ Flexible and programmable
▲ High accuracy

Layout of the fabricated IC (0.18um technology)
Low power/energy is key

▲ Implants must last long time without intervention
   ▼ Battery replacement
   ▼ Battery toxicity

▲ Dissipated heat must be minimal
   ▼ Particularly critical for brain implants

▲ Slow signal – low noise solutions
Powering by inductive link

- Wireless power transfer through inductive link
- Bidirectional data communication
Multi-layer receiving inductors

- Higher link efficiency (up to 35% higher)
- Higher voltage gain (up to one order of magnitude higher)
Power and data transmission

**Downlink**
- Bitstream: 100 kbps

**Uplink**
- Bitstream: 66.6 kbps

![Graph showing received power vs distance](image)

**Power**
- Received Power: 8.7 mW
- Amplifier Power: 246 mW
- Efficiency: 3.54%
- Received Power: 6.3 mW
- Amplifier Power: 230 mW
- Efficiency: 2.74%
- Received Power: 4.7 mW
- Amplifier Power: 217 mW
- Efficiency: 2.17%
- Received Power: 2.85 mW
- Amplifier Power: 206 mW
- Efficiency: 1.38%
- Received Power: 550 μW
- Amplifier Power: 192 mW
- Efficiency: 0.29%
- Received Power: 105 μW
- Amplifier Power: 188 mW
- Efficiency: 0.06%
- Received Power: 20 μW
- Amplifier Power: 189 mW
- Efficiency: 0.01%
- Received Power: 6 μW
- Amplifier Power: 192 mW
- Efficiency: <0.01%

**Data**
- **Downlink Bitstream**
  - 100 kbps
- **Uplink Bitstream**
  - 66.6 kbps
Lesson learned

▲ Co-design of electronics and sensing is key
  ▼ Achieve low-power consumption
  ▼ Achieve small footprint

▲ Electronic technology can be extended upwards
  ▼ Monolithic integration
  ▼ Silicon interposer technologies

▲ Platform-based design
  ▼ Modularity of design is key to reducing NREs
Outline

▲ Introduction
▲ Electronic implants: a lab under the skin
▲ Drug monitoring and administration
  ▽ Real-time measurements in patients and lab animals
  ▽ Machine learning prediction methods
  ▽ Drug administration support systems
▲ Conclusions
### Drug efficacy

<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.

What does this mean in practice?
Monitoring drugs in lab animals

INDUCTIVE LINK

EXTERNAL UNIT

3-Dimensional integrated sensor

SENSING PLATFORM

INTEGRATED CIRCUITS

COIL FOR POWER AND DATA TRANSMISSION
Operation and measurements

4 Independent cells
(3-electrodes)

GLUCOSE DETECTION

Injections of glucose 500μM

Current, nA

Time, s

DRUG DETECTION

Potential, mV

Current, nA

PBS
MTX 3 μM
MTX 200 μM
Therapeutic drug monitoring (TDM)

- ▲ TDM measures the real concentration values to estimate clinical parameters
- ▲ An *a posteriori* adaptation for patients’ parameters
Pharmacokinetic models

▲ Intravenous bolus dose

▽ One-compartment model

\[ C = \frac{\text{dose}}{V} \cdot e^{-k_{el} \cdot t} \]

- \( C \): concentration value
- \( V \): body volume
- \( k_{el} \): elimination rate

http://sepia.unil.ch/pharmacology/index.php?id=71
Pharmacokinetic models

▲ Oral dose

▽ Two-compartment model

\[ C = \frac{F \cdot \text{dose} \cdot k_a}{V \cdot (1 - \frac{k_{el}}{k_a})} \cdot \{e^{-k_{el} \cdot t} - e^{-k_a \cdot t}\} \]

- **C**: concentration value
- **F**: constant factor
- **V**: body volume
- **Ka**: absorption rate
- **Kel**: elimination rate

http://sepia.unil.ch/pharmacology/index.php?id=71
Blood samples are measured to adjust the parameters

\[
\min_{\{k_a, k_{el}, V\}} \left( \sum_{i=1}^{N_1} \frac{(C_{obs_i} - C_{calc_i})^2}{\text{variance}_i} + \sum_{j=1}^{N_2} \frac{(P_{pop_j} - P_{pop_j})^2}{\text{variance}_j} \right)
\]

Machine learning approaches

▲ A mathematical model that can ‘learn’ from data

▲ Advantages
  ▶ Accept any data type (continuous/discrete)
  ▶ Robust in various domains

▲ Limitation
  ▶ Training data can bias the model
Drug administration decision support system (DADSS)

▲ Train the SVM model based on previous patients’ data
Drug administration decision support system (DADSS)

▲ Train the SVM model based on previous patients’ data
▲ Compute the drug-concentration-to-time curve for a new patient
Drug administration decision support system (DADSS)

▲ Train the SVM model based on previous patients’ data

▲ Compute the drug-concentration-to-time curve for a new patient

▲ Compare concentration value according to the therapeutic range
Drug administration decision support system (DADSS)

▲ Train the SVM model based on previous patients’ data
▲ Compute the drug-concentration-to-time curve for a new patient
▲ Compare concentration value according to the therapeutic range
▲ Recommend dose and administration frequency to clinicians
General flow
The verification problem

▲ Verify that a therapeutical protocol is
  ▼ Consistent
  ▼ Complete

▲ Verify that a drug administration control unit
  is an *implementation* with the protocol
  ▼ Model checking
Formal model of Imatinib protocol
Advantages of formal models

▲ Reason about properties in a formal way
   ▼ Check for properties and invariants
▲ Synthesize optimal control policies for drug administration
▲ Golden model to verify hardware implementation
Lesson learned

- Very few protocols have a formal description
  - Corner cases are hazardous for patients
- Personalization of drug dosage is important
  - But used in still few cases
- Modeling human body reaction is critical
  - But often hard to achieve in deterministic way
Outline

▲ Introduction
▲ Electronic implants: a lab under the skin
▲ Drug monitoring and administration
▲ Conclusions
Back to megatrends

▲ Health care and systems
  ▷ Predictive medicine
  ▷ Participative medicine
  ▷ Personalized medicine
  ▷ Preventive medicine

▲ Strong need to generate relevant data (sensors) and to process big data

▲ Strong societal and economic push
Soft care – healthy individuals

▲ Health care of elderly and isolated persons
   ▼ Telemedicine

▲ Well-being of active persons
   ▼ Weight monitoring
   ▼ Sport activity monitoring
   ▼ Habits

▲ Potentially large market for selling devices, software and services
Opportunities and challenges

▲ E-health is an unstoppable life-changing trend with unlimited possibilities

▲ The market is articulated:
  ▼ Some areas are harder than others to penetrate
  ▼ Many problems are still not well understood
  ▼ Ethics and regulations play a major role

▲ Exciting field for researchers and developers
Nano-Tera.ch: Mission

Research, Design & Engineering of complex tera-scale systems using nano-scale devices and technologies

Foster research and crossbreeding of technologies

Main application domains are Health and Environment with transversal themes such as Energy and Security

- Develop new markets
- Improve living standards
- Better the quality of health and environment
- Foster a vision of engineering with social objectives
- Promote related educational programs
## Nano-Tera.ch: key figures

- **118** projects (19+25 RTD large projects)
- **30** MCHF/year (approximately 50% in cash + institutional matching)
- **36** Swiss research institutions involved (currently)
- **189** research groups (currently)
- **~700** researchers
- **~180** PhD thesis supported
- **~750** papers published
- **~1300** presentations
- **37** awards
- **24** patents

### Current reporting period (2012) vs. TOTAL since beginning of the program

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RTD 2009</td>
<td>48</td>
<td>69</td>
<td>117</td>
<td>144</td>
<td>133</td>
<td>277</td>
</tr>
<tr>
<td>RTD 2010</td>
<td>44</td>
<td>77</td>
<td>121</td>
<td>82</td>
<td>147</td>
<td>229</td>
</tr>
<tr>
<td>RTD add-on</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>NTF</td>
<td>6</td>
<td>10</td>
<td>16</td>
<td>14</td>
<td>36</td>
<td>50</td>
</tr>
<tr>
<td>SSSTC</td>
<td>6</td>
<td>9</td>
<td>15</td>
<td>6</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td><strong>105</strong></td>
<td><strong>168</strong></td>
<td><strong>273</strong></td>
<td><strong>247</strong></td>
<td><strong>328</strong></td>
<td><strong>575</strong></td>
</tr>
</tbody>
</table>
Conclusions

▲ New electronic health systems and services will be enabled by advances in biology and medicine – combined with progress in cyber-physical systems

▲ The rationalization of health care will provide advanced care to a broader audience at lower cost

▲ Human factors will still be central to decisions in medicine - decision support will be automated
Thank you