Technologies and Platforms for Biomedical Systems

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Outline

- **Introduction**
- Electronic implants: a lab under the skin
- Drug monitoring and administration
- Conclusions

The megatrends

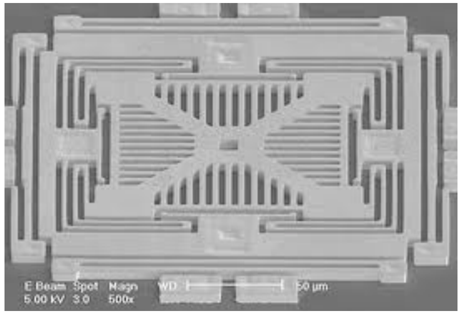
- Relentless growth of computing, storage and communication technologies
  - Inexpensive terminals providing ubiquitous services
- Biomedical science becoming more quantitative
  - Societal need of better care at lower costs
- Big data issues fueling research and businesses
  - Models, algorithms, architectures to tame data deluge

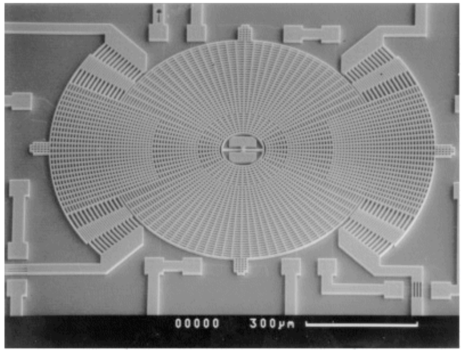
Cyberphysical systems

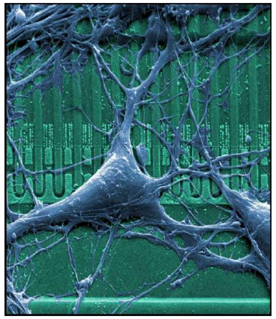
 [Courtesy: J. Rabaey]

The sensory interface

▲The *More than Moore* revolution







[Courtesy: ST]

[Courtesy: Carrara EPFL]

What is health?

World Health Organization

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

www.23andme.com

Genetic information

www.patientslikeme.com

Medical records

Consenting informed educated patients

E-health: objectives

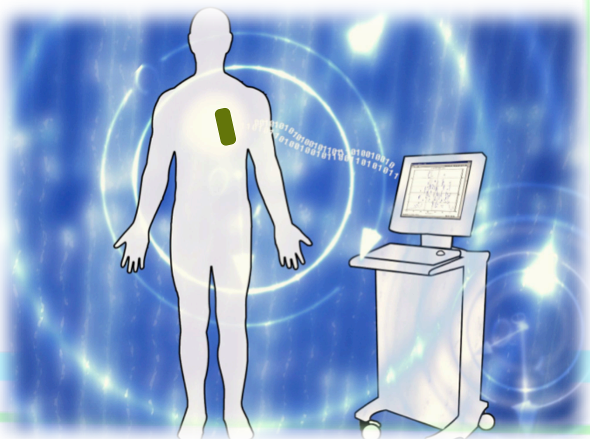
- Bettering **medicine** with electronic means
- Bringing **low-cost** medicine to the people
- Exploiting electronic **well-being** as a **lifestyle**
- Opportunities
  - Synergy of integrated electronic and sensing
  - Platform-based design of sensors
  - Mobile telephone as *point of care*

Outline

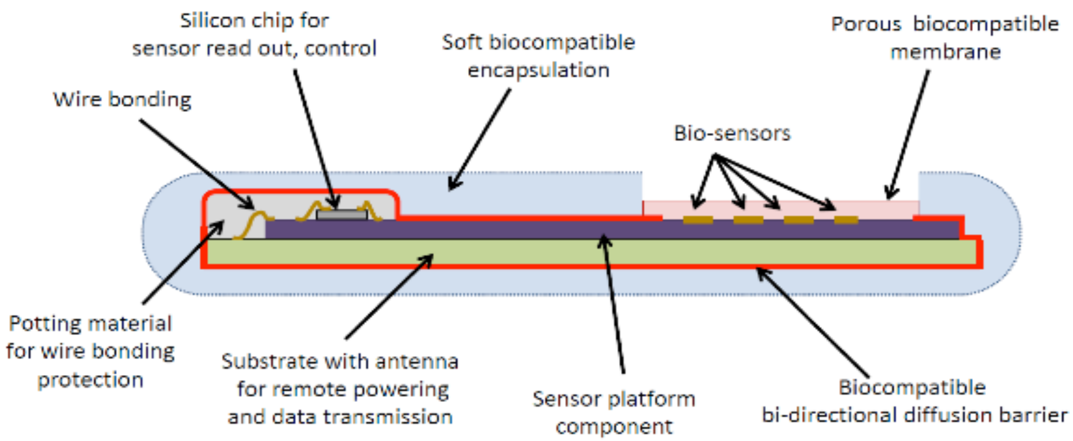
- ▲Introduction
- ▲**Electronic implants: a lab under the skin**
  - ▽**Biosensing technology**
  - ▽**Platform-based design**
  - ▽**Low-power and energy**
- ▲Drug monitoring and administration
- ▲Conclusions

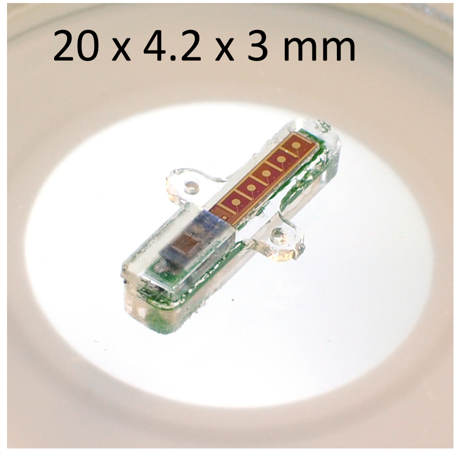
Monitoring chronic patients

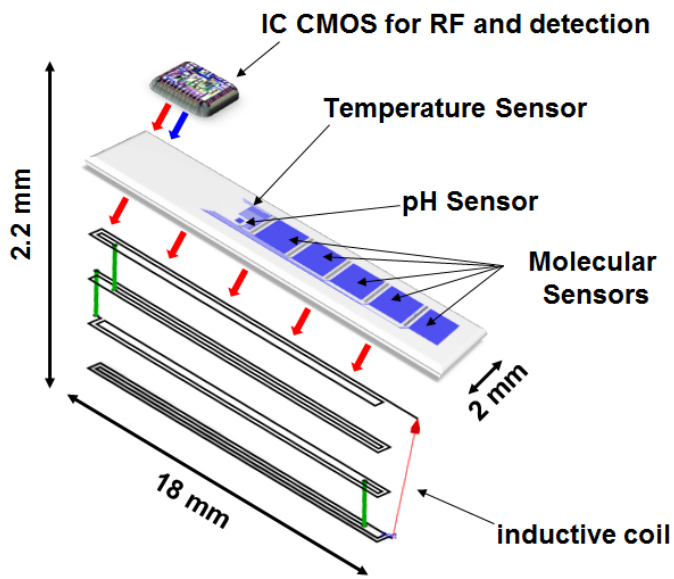
- Continuous real-time monitoring
- Current devices are external and limited to a single measurement
- Wireless, batteryless implant
- Tracking multiple metabolites
- Driver technology for a wide set of applications

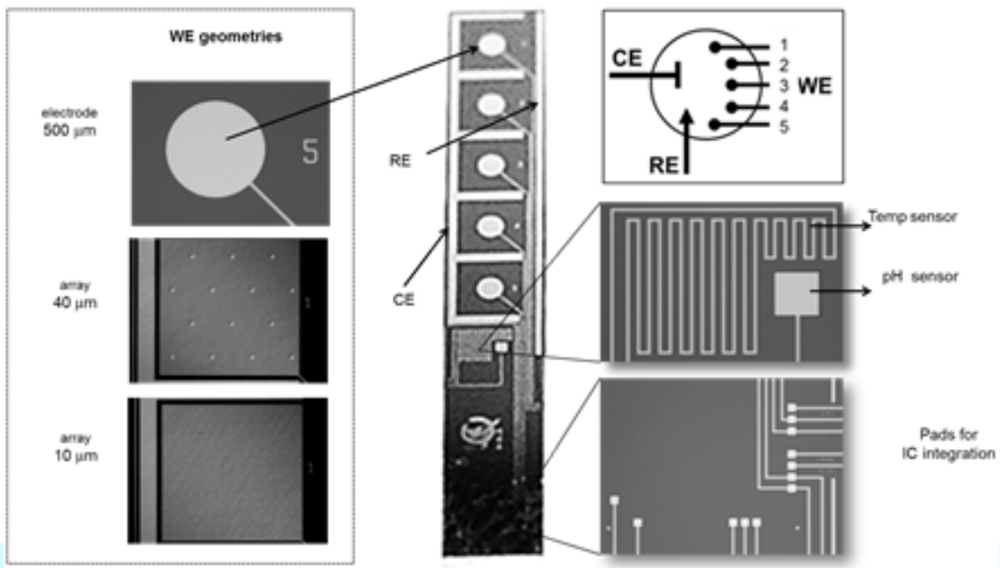


Case study: implant









Case study: external patch

FEATURES

Remote powering through inductive link

Short-range bidirectional communication

Long-range comm. with remote devices

ADVANTAGES

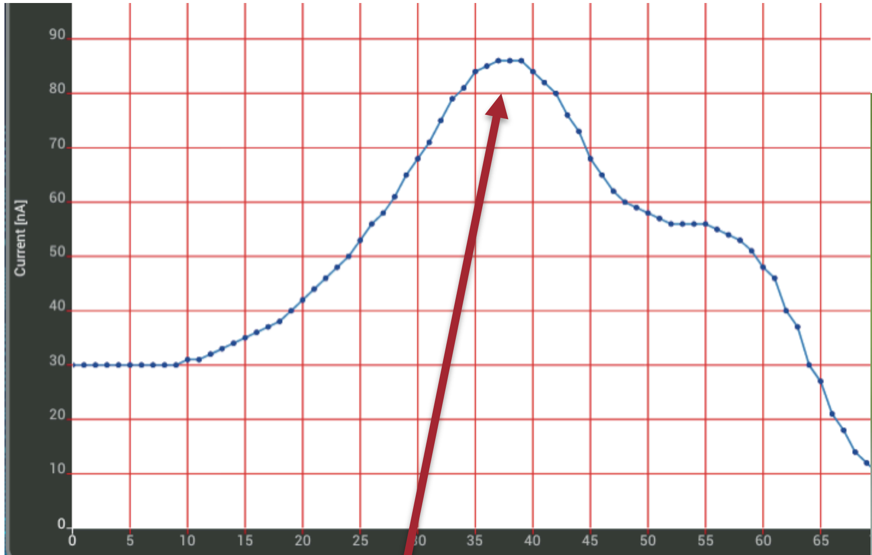
Improved wearability

Direct placement over implant area

Stand alone

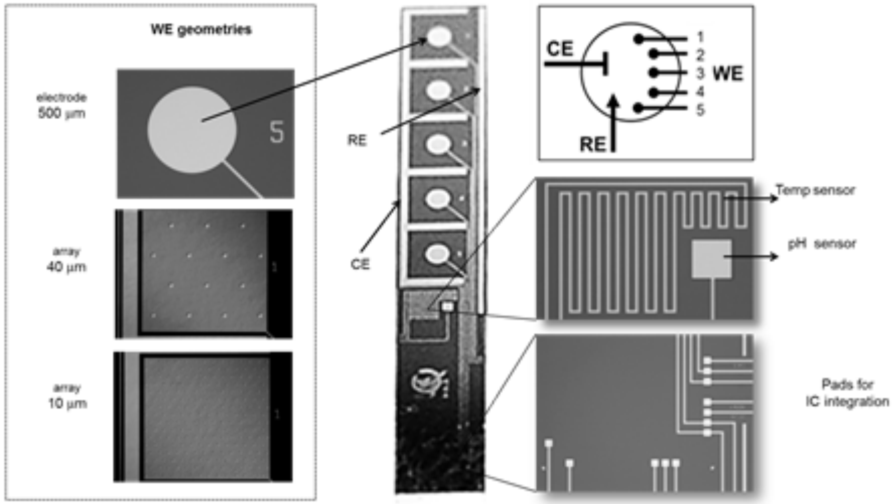
Battery-powered

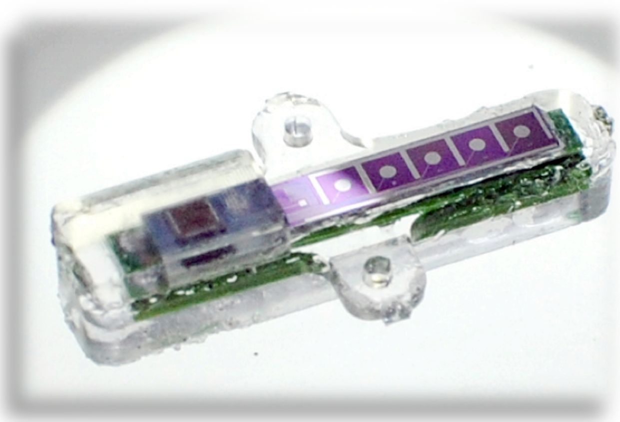
Android user interface

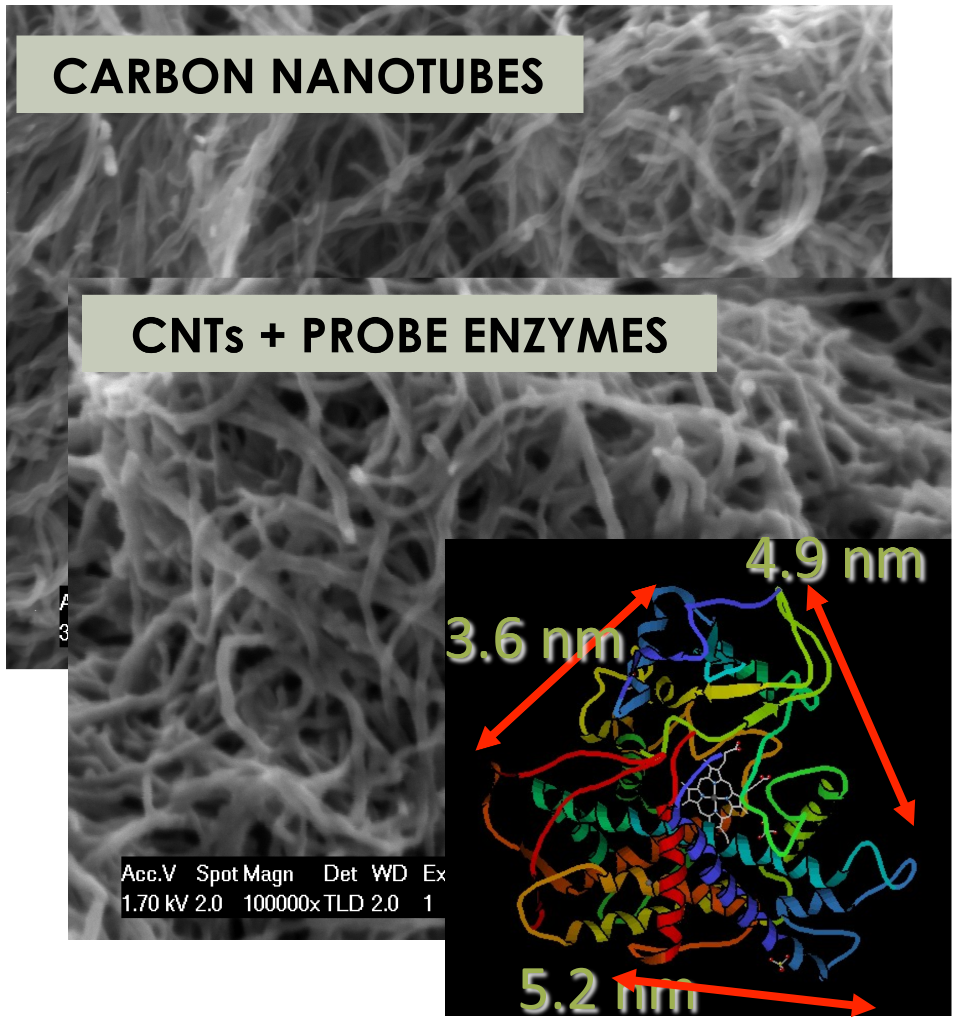


Target molecule detection

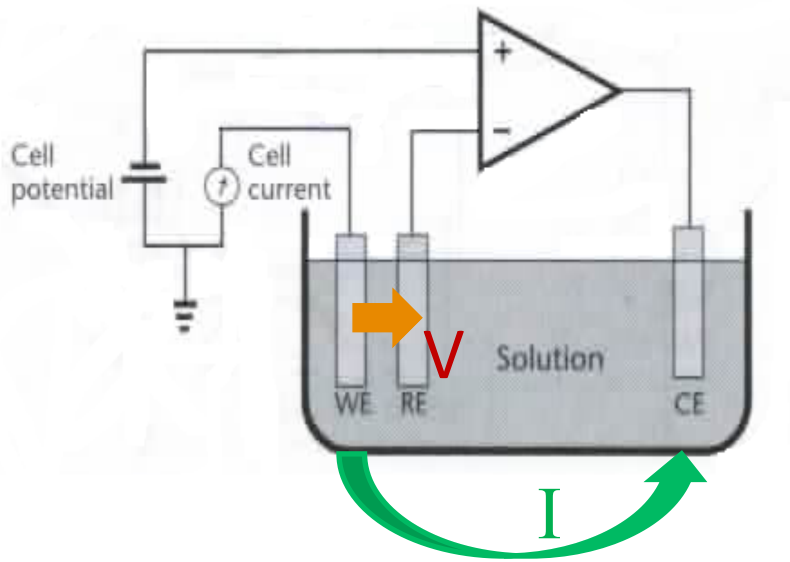
The sensing technology

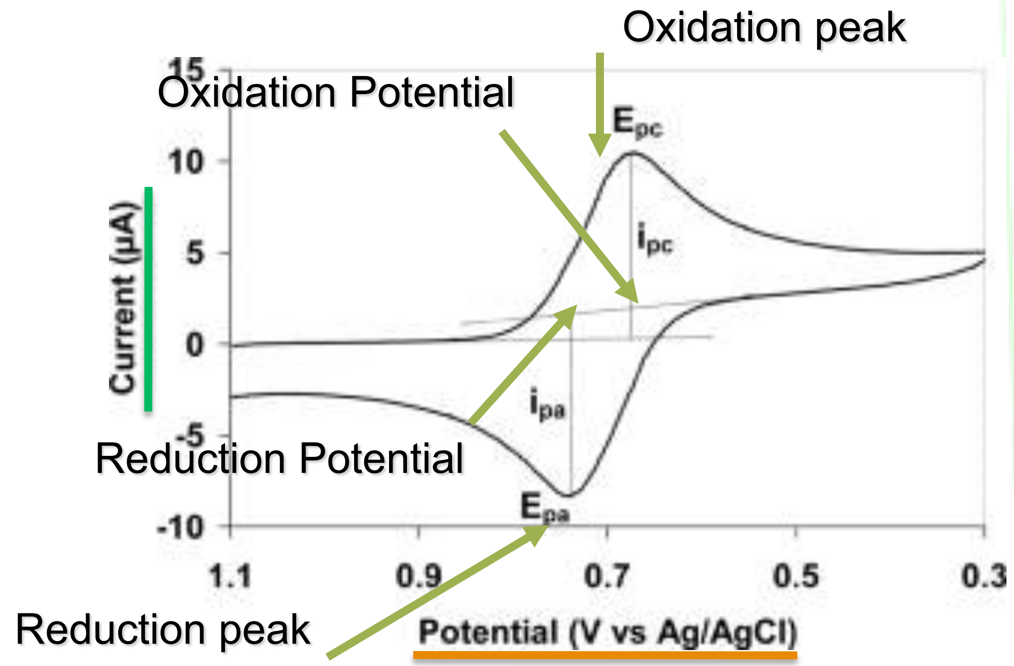






The electrochemical sensing principle

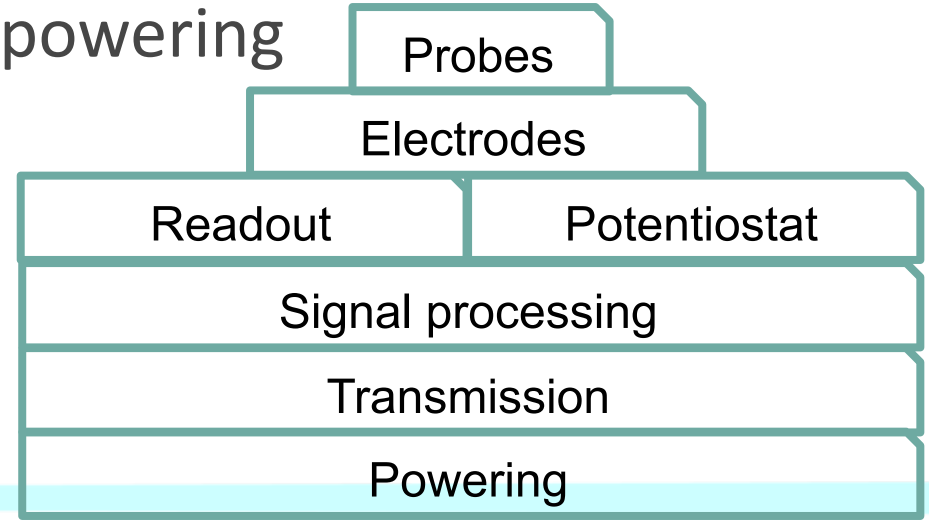




- Peak position returns the type of chemical contained into the sample (target signature)
- Peak current returns the concentration of the target
- Different isoforms of the cytochrome P450 enable detection of different targets

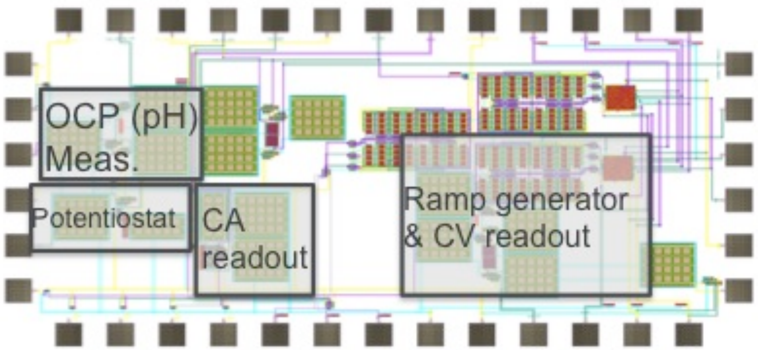
The platform and its components

- Specific components
  - Probes and electrodes
  - Chambers and fluidic circuits
- Electronic components
  - Transconductance amplifier and data conversion
  - Transmission and powering

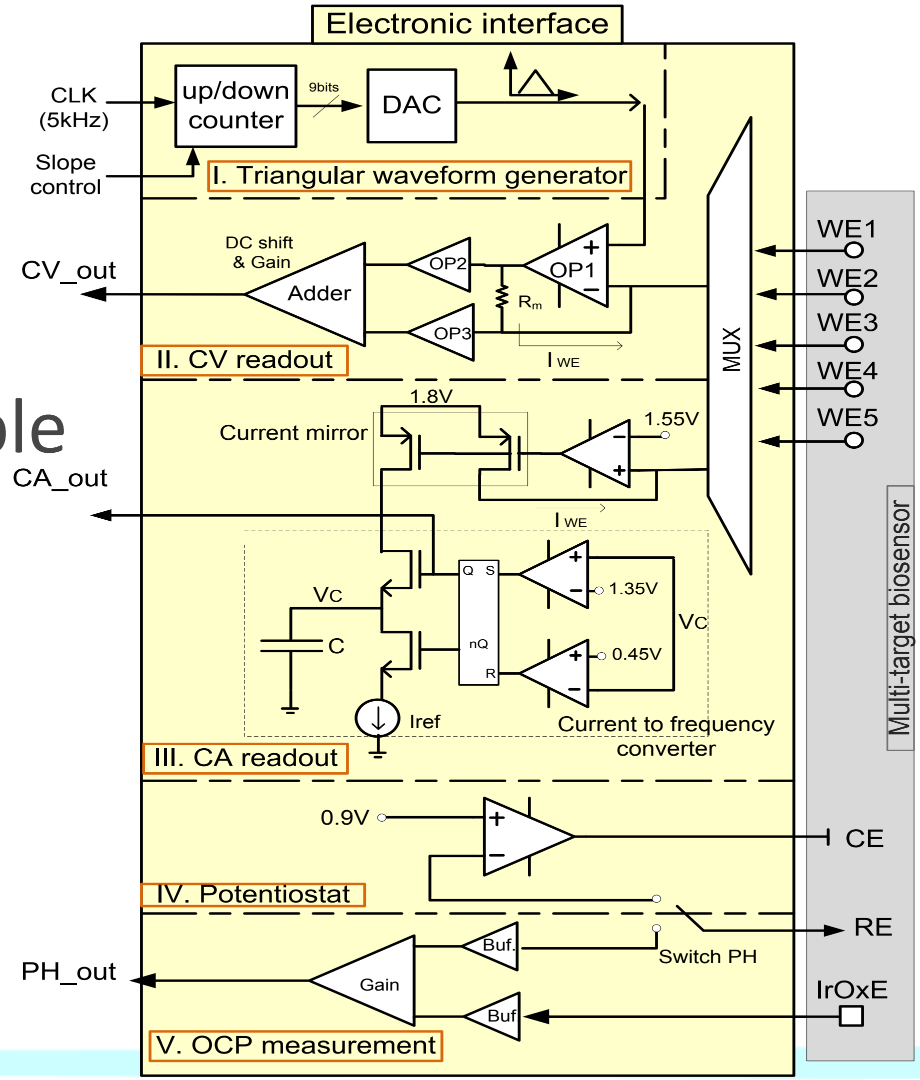


Control and readout electronics

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



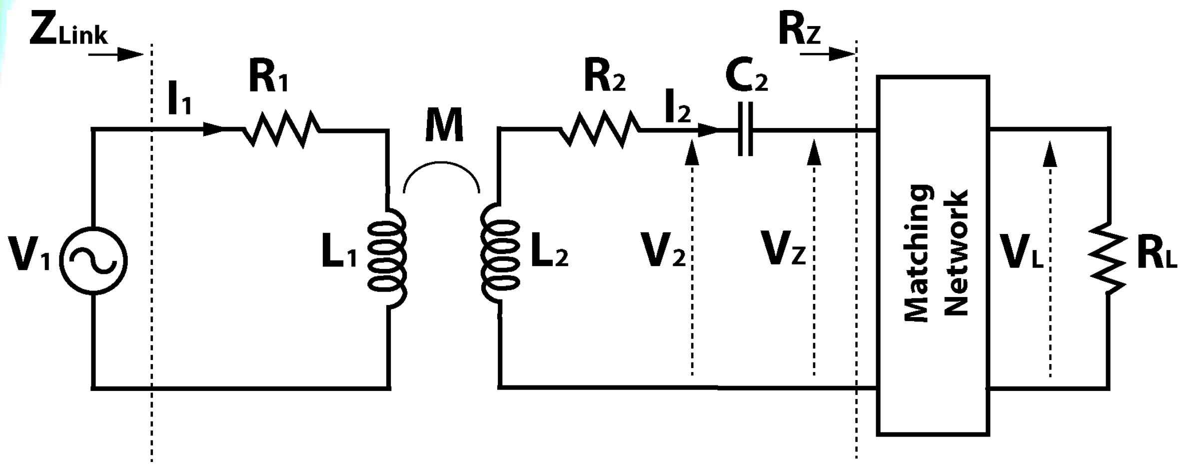
Layout of the fabricated IC
(0.18um technology)



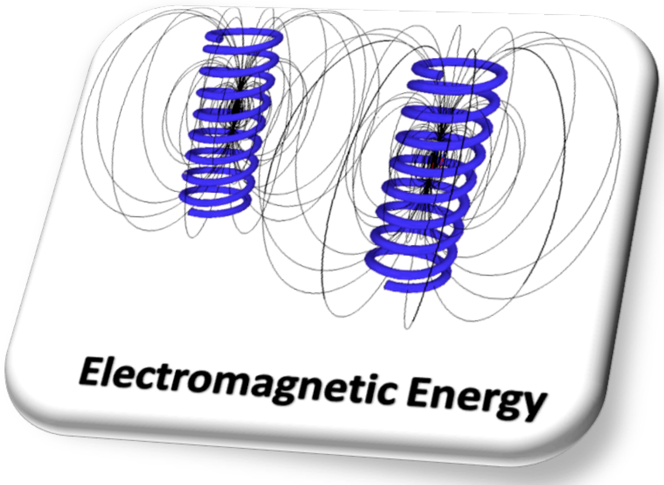
Low power/energy is key

- 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

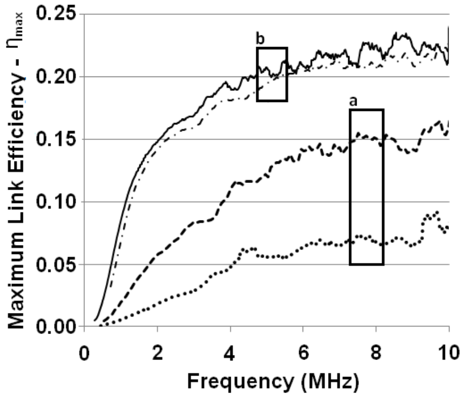
Powering by inductive link

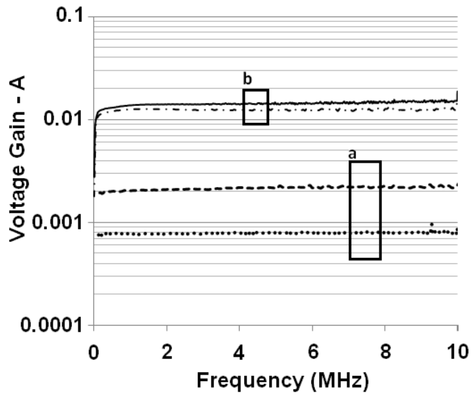


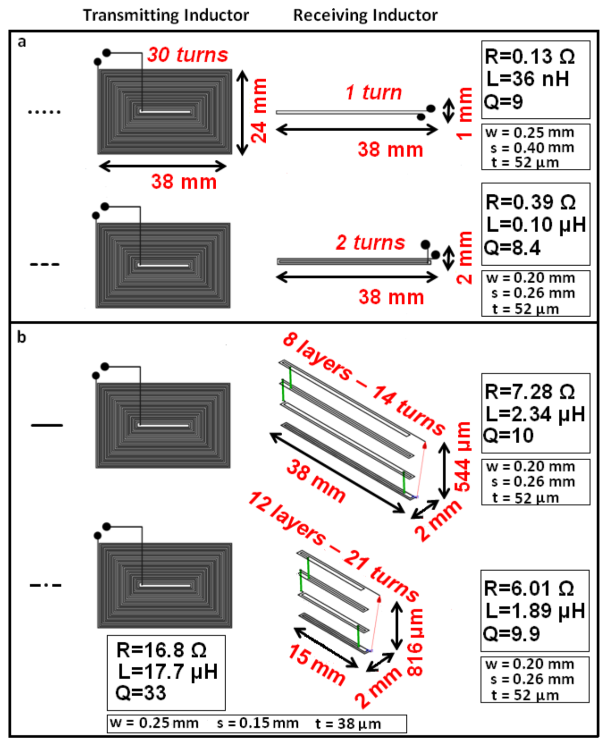
- Wireless power transfer through inductive link
- Bidirectional data communication

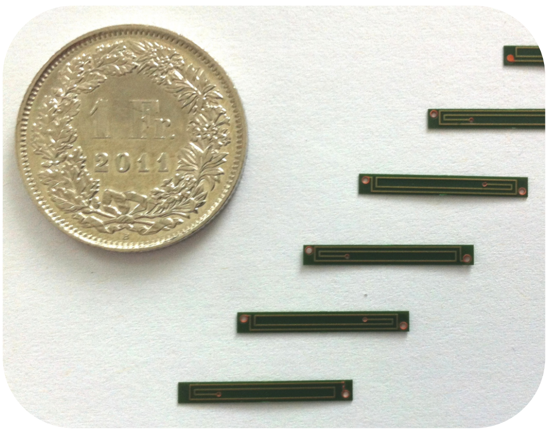


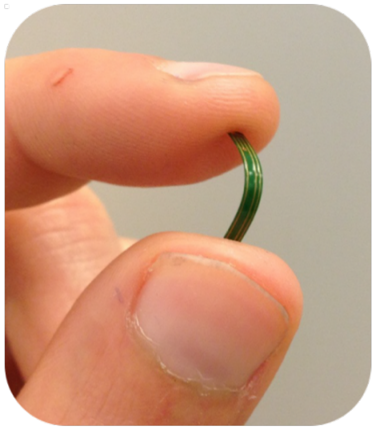
Multi-layer receiving inductors





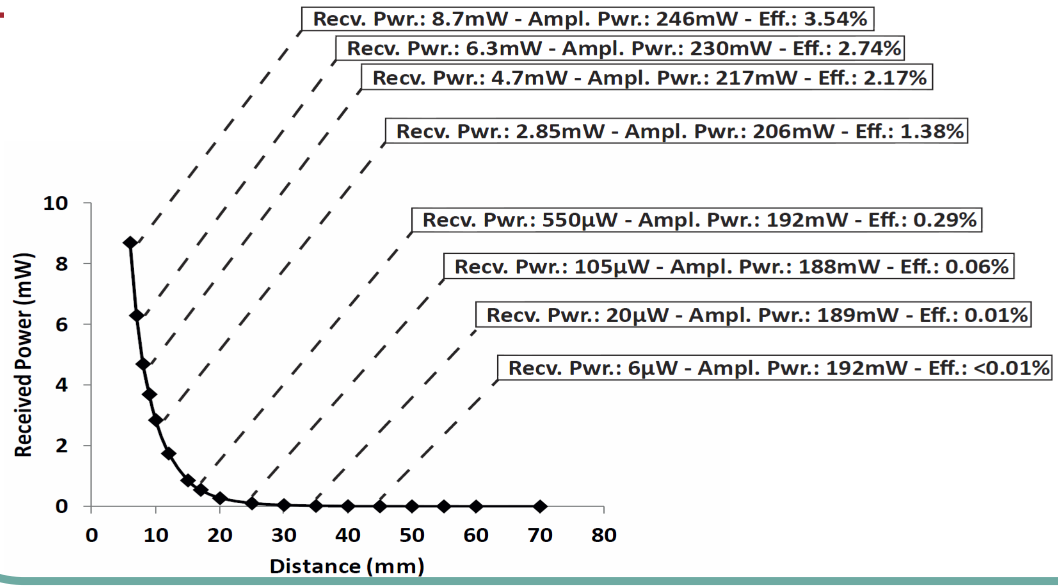




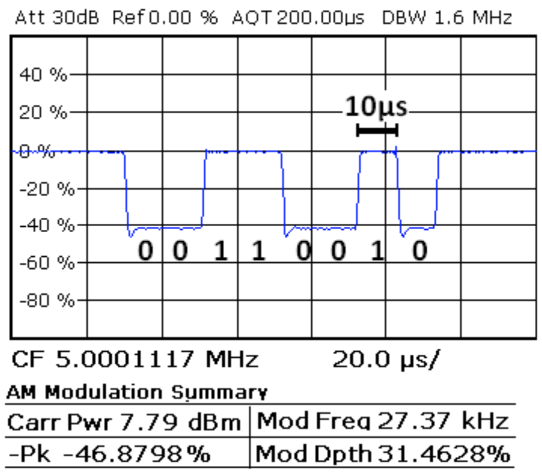


- Higher link efficiency (up to 35% higher)
- Higher voltage gain (up to one order of magnitude higher)

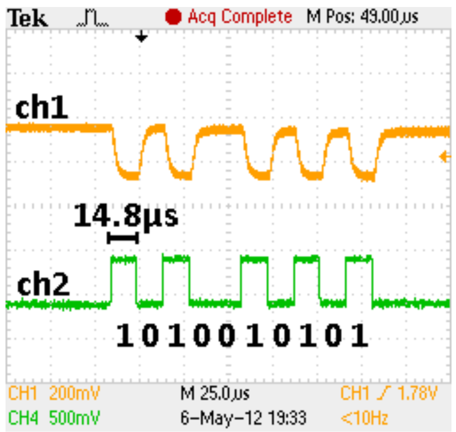
Power and data transmission



Power



Downlink Bitstream – 100 kbps



Uplink Bitstream – 66.6 kbps

Data

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

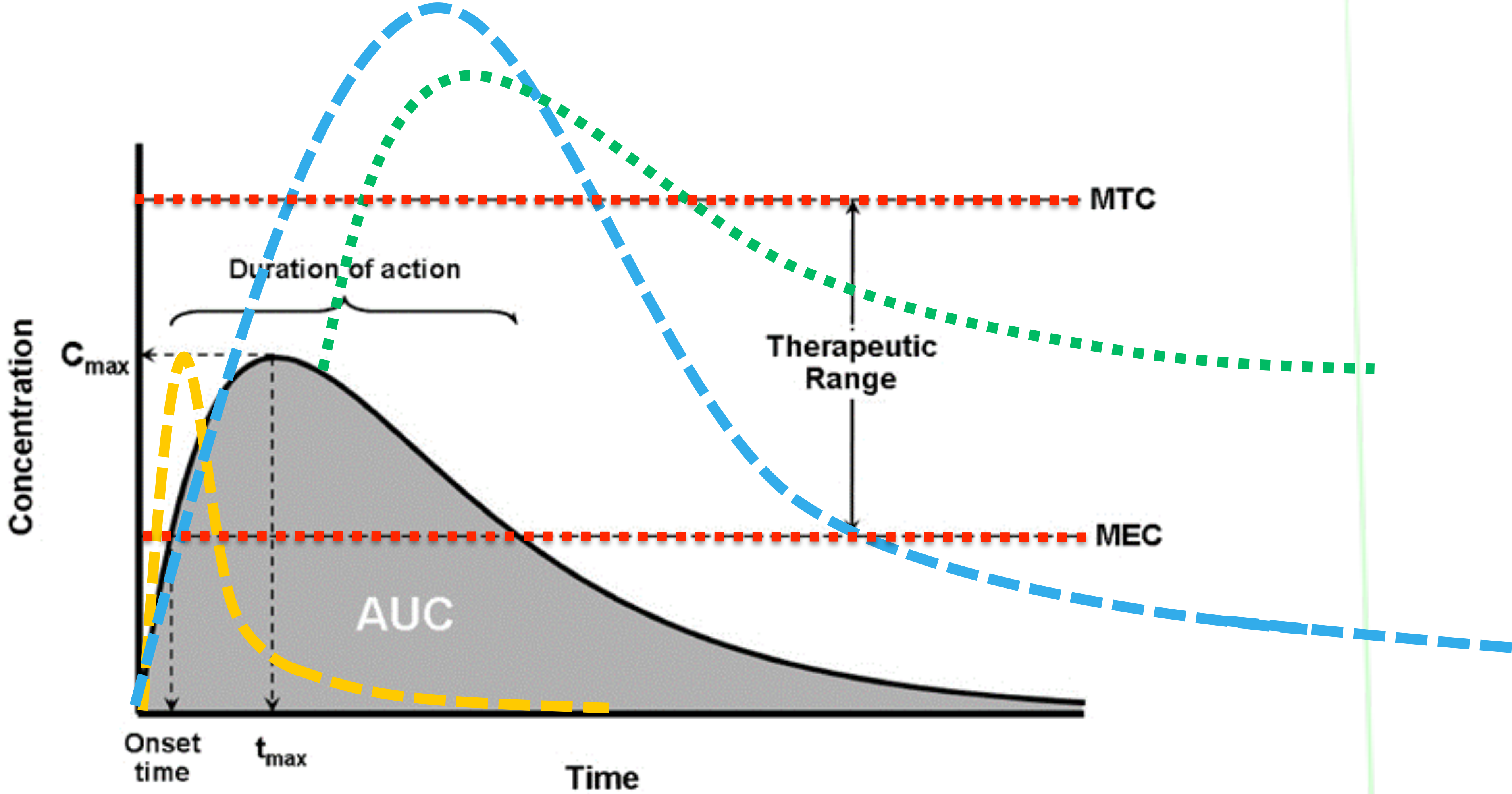
Drug efficacy

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.

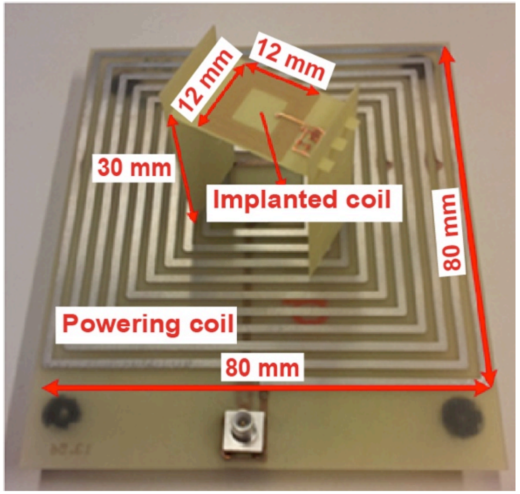
Source: Brian B. Spear, Margo Heath-Chiozzi, and Jeffrey Huff, "Clinical Application of Pharmacogenetics," *Trends in Molecular Medicine* (May 2001).

What does this mean in practice?

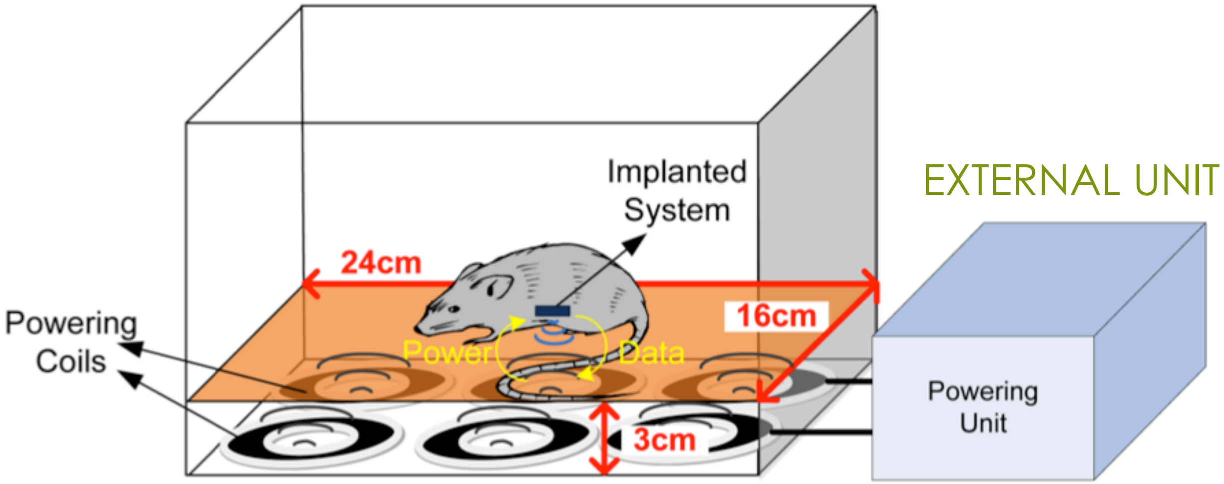


Monitoring drugs in lab animals

INDUCTIVE LINK

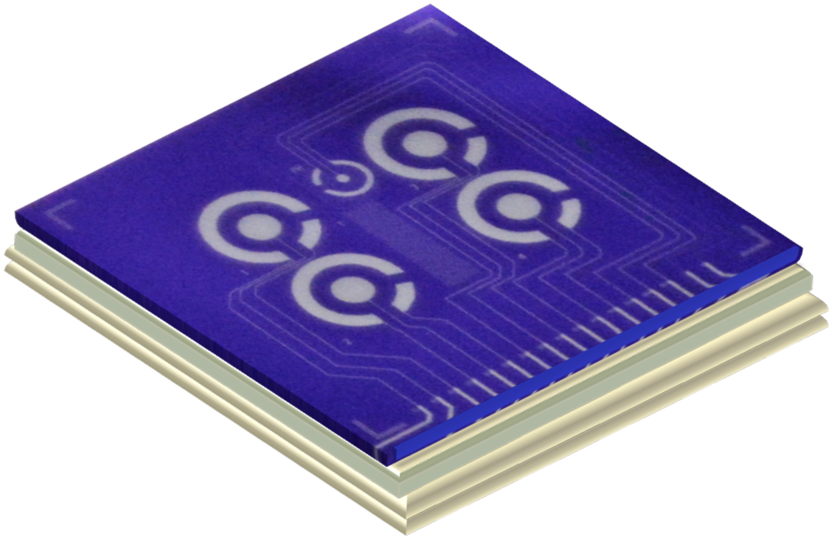


EXTERNAL UNIT



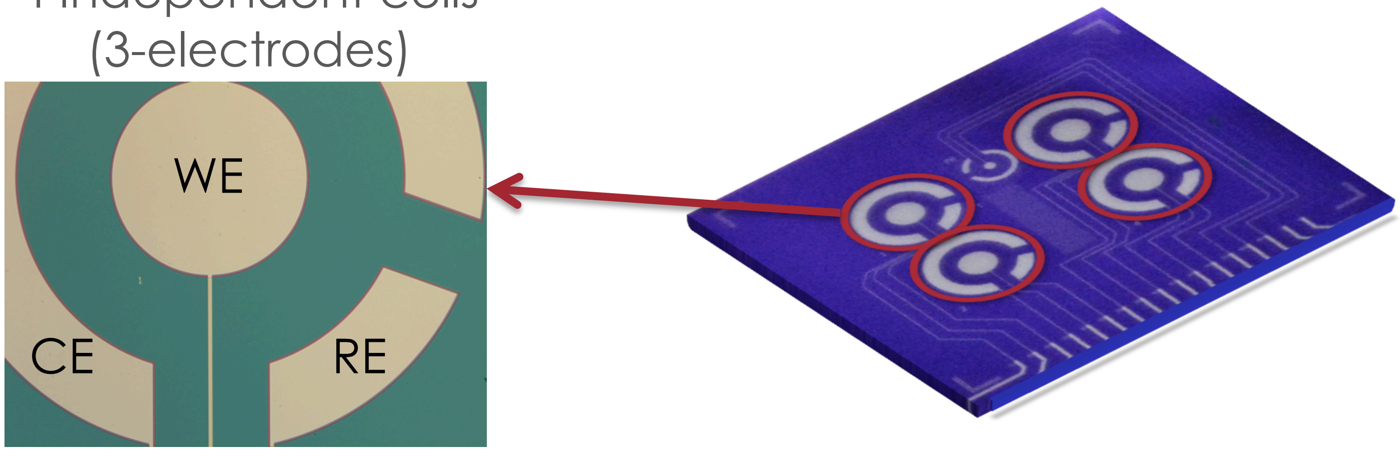
Kilinc, Enver G., et al. / *New Circuits and Systems Conference, 2013 IEEE 11th International. IEEE,* 2013.

3-Dimensional integrated sensor

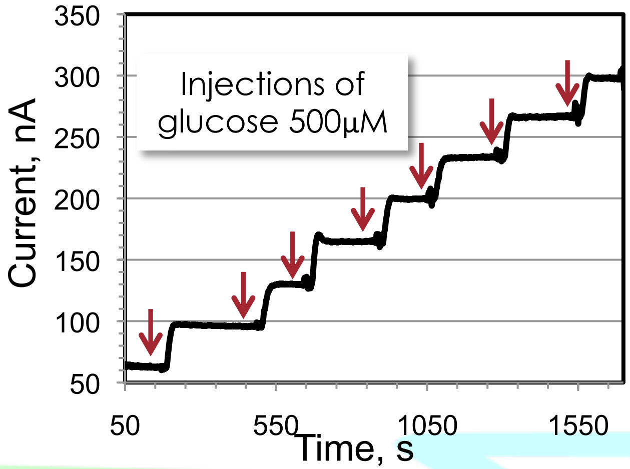


Operation and measurements

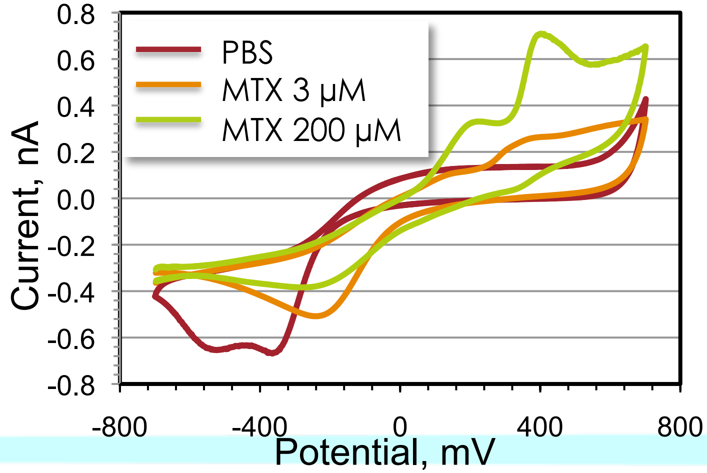
4 Independent cells
(3-electrodes)



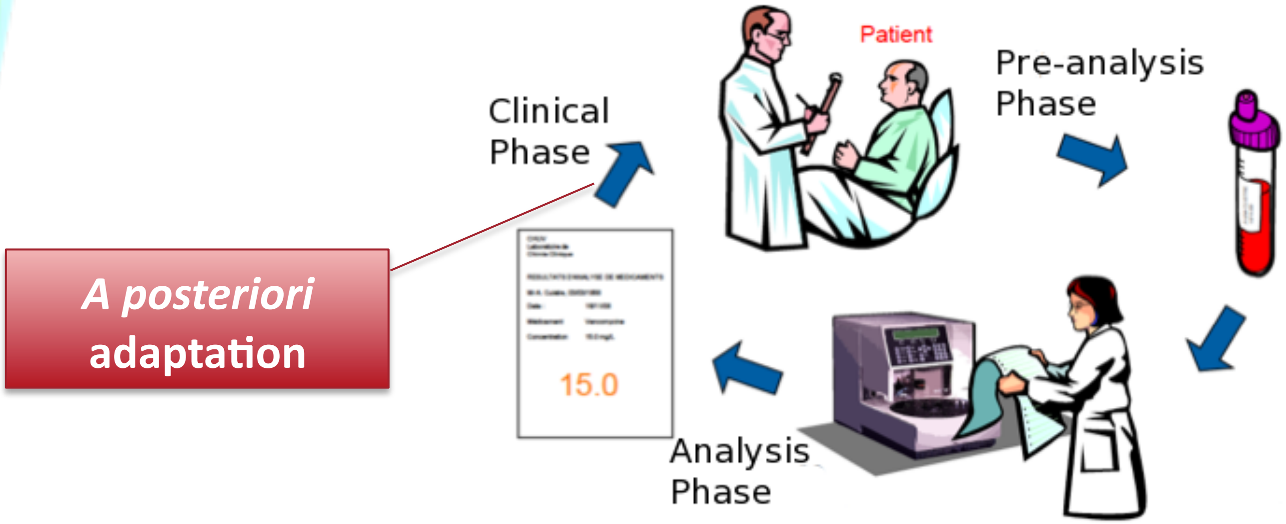
GLUCOSE DETECTION



DRUG DETECTION



Therapeutic drug monitoring (TDM)

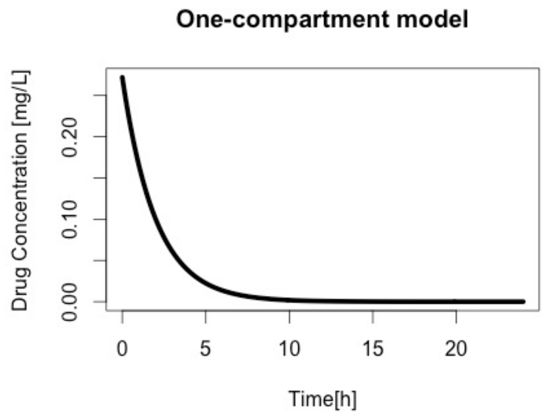


- TDM measures the real concentration values to estimate clinical parameters
- An *a posteriori* adaptation for patients' parameters

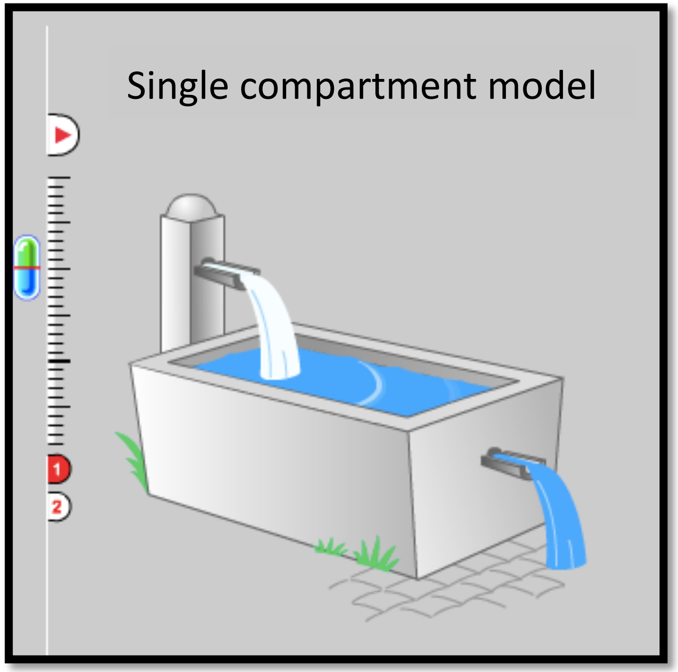
Pharmacokinetic models

- Intravenous bolus dose
  - One-compartment model

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



C: concentration value
V: body volume
Kel: elimination rate

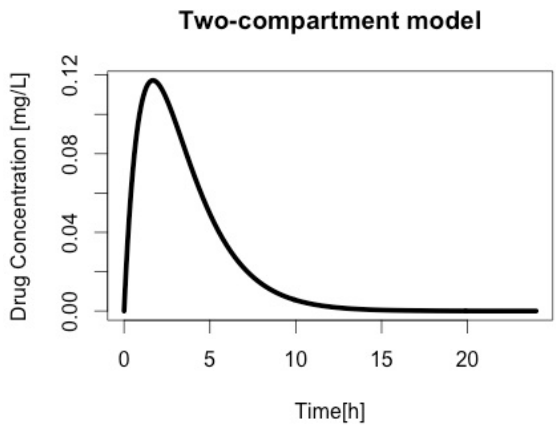


http://sepia.unil.ch/pharmacology/index.php?id=71

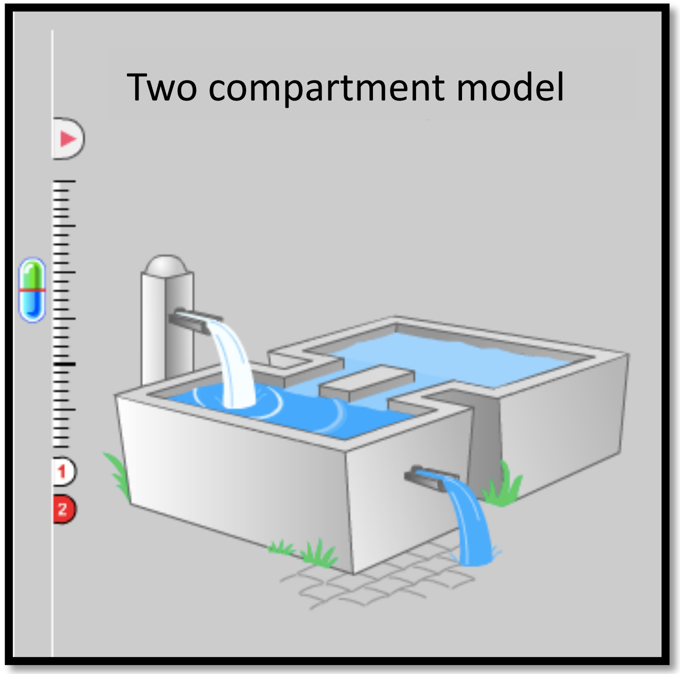
Pharmacokinetic models

- Oral dose
  - Two-compartment model

$$C = \frac{F\cdot \mathrm{dose}\cdot k_a}{V\cdot(k_a - k_{el})}\cdot\{e^{-k_{el}\cdot t} - e^{-k_a\cdot t}\}$$

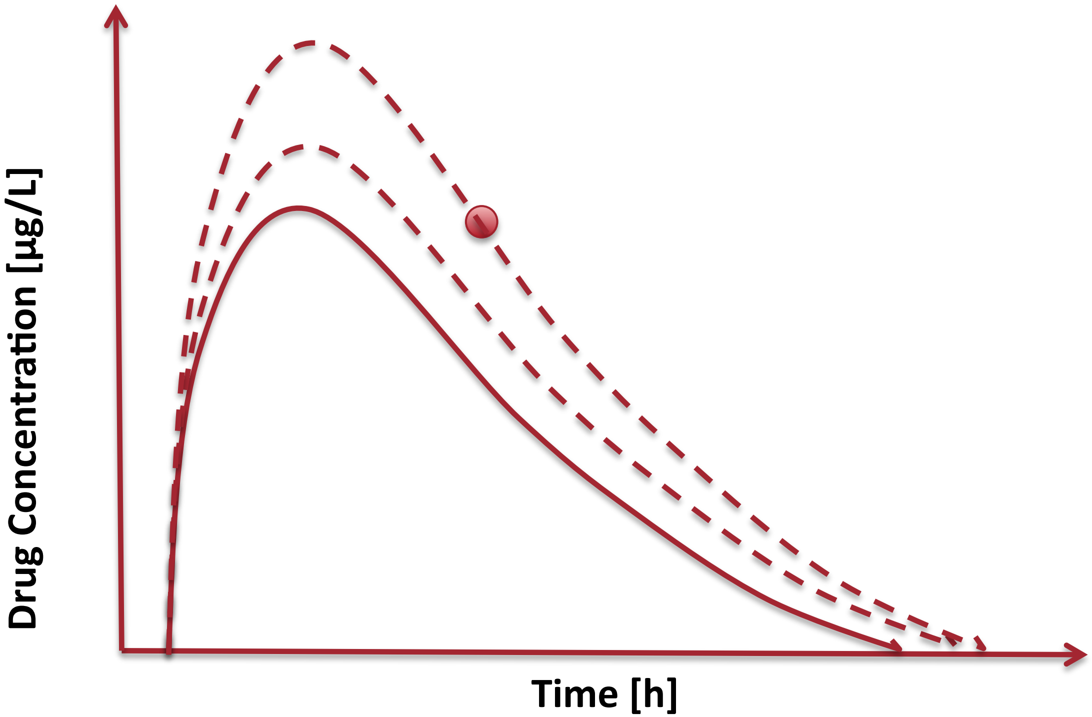


C: concentration value
F: constant factor
V: body volume
Ka: absorption rate
Kel: elimination rate



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

Bayesian approach



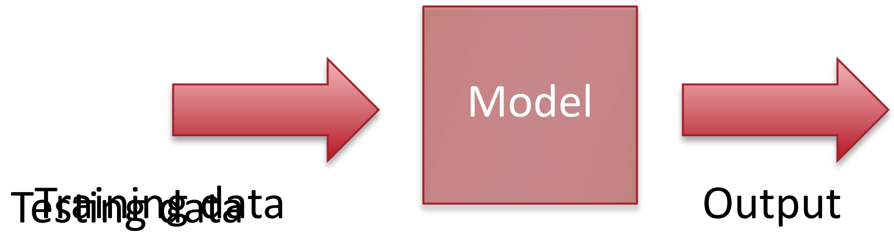
- Blood samples are measured to adjust the parameters

$$\min_{\{k_a, k_{el}, V\}} \left(\sum_{i=1}^{N_1} \frac{(C_{\text{obs}_i} - C_{\text{calc}_i})^2}{\text{variance}_i} + \sum_{j=1}^{N_2} \frac{(P_{\text{pop}_j} - P_{\text{pop}_j})^2}{\text{variance}_j} \right)$$

[1] N. Widmer, L.A. Decosterd, C. Csajka, S. Leyvraz, M. A. Duchosal, A. Rosselet, B. Rochat, C. B. Eap, H. Henry, J. Biollaz, T. Buclin, 'Population Pharmacokinetics of Imatinib and the Role of **1**-Acid Glycoprotein', Br J Clin Pharmacol 2006; 62:1 pp.97-112

Machine learning approaches

- A mathematical model that can ‘learn’ from data

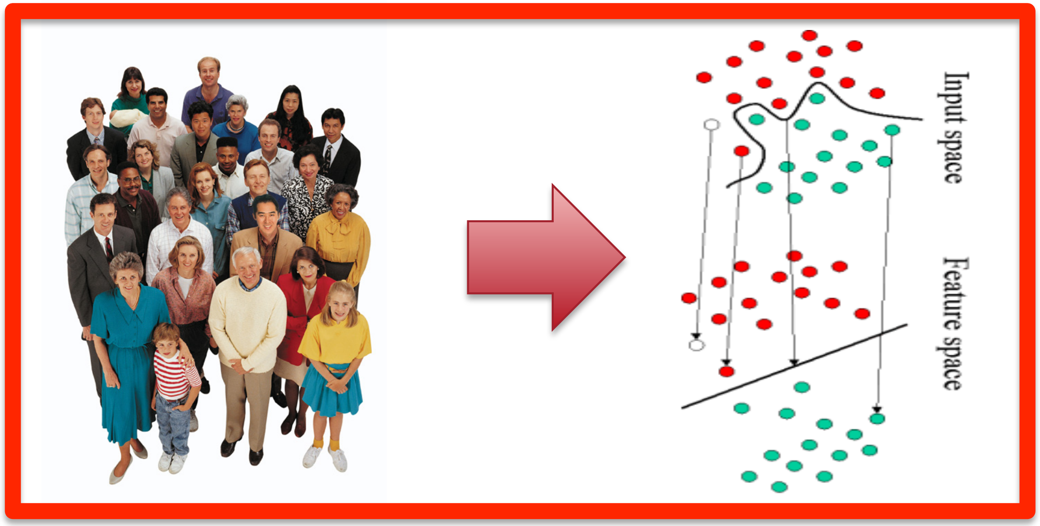


Supervised learning cases

- Advantages
  - Accept any data type (continuous/discrete)
  - Robust in various domains
- Limitation
  - Training data can bias the model

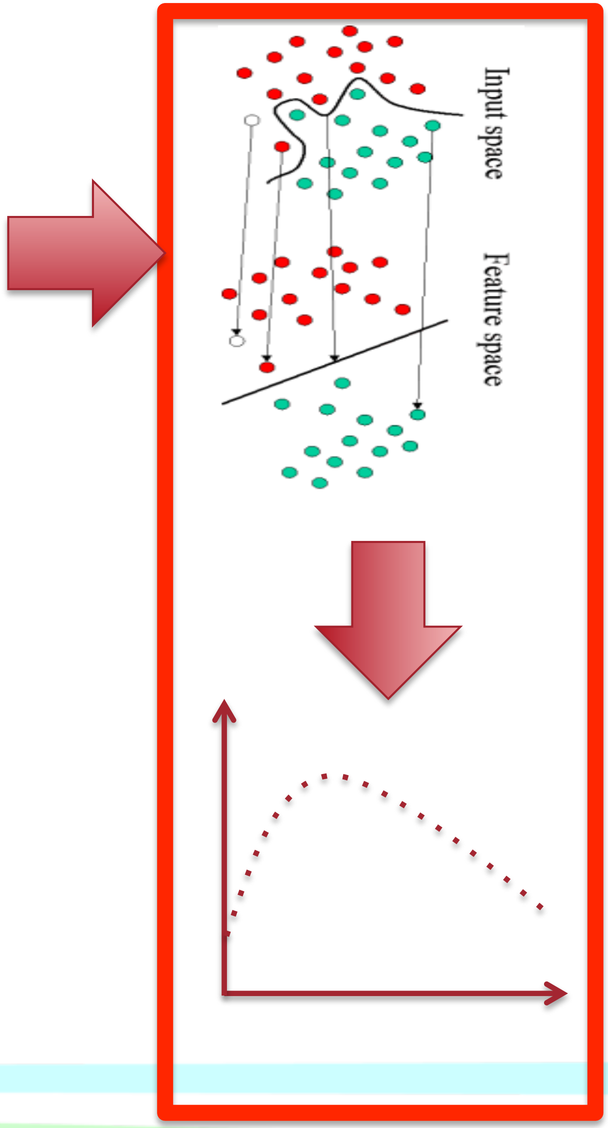
Drug administration decision support system (DADSS)

- Train the SVM model based on previous patients' data



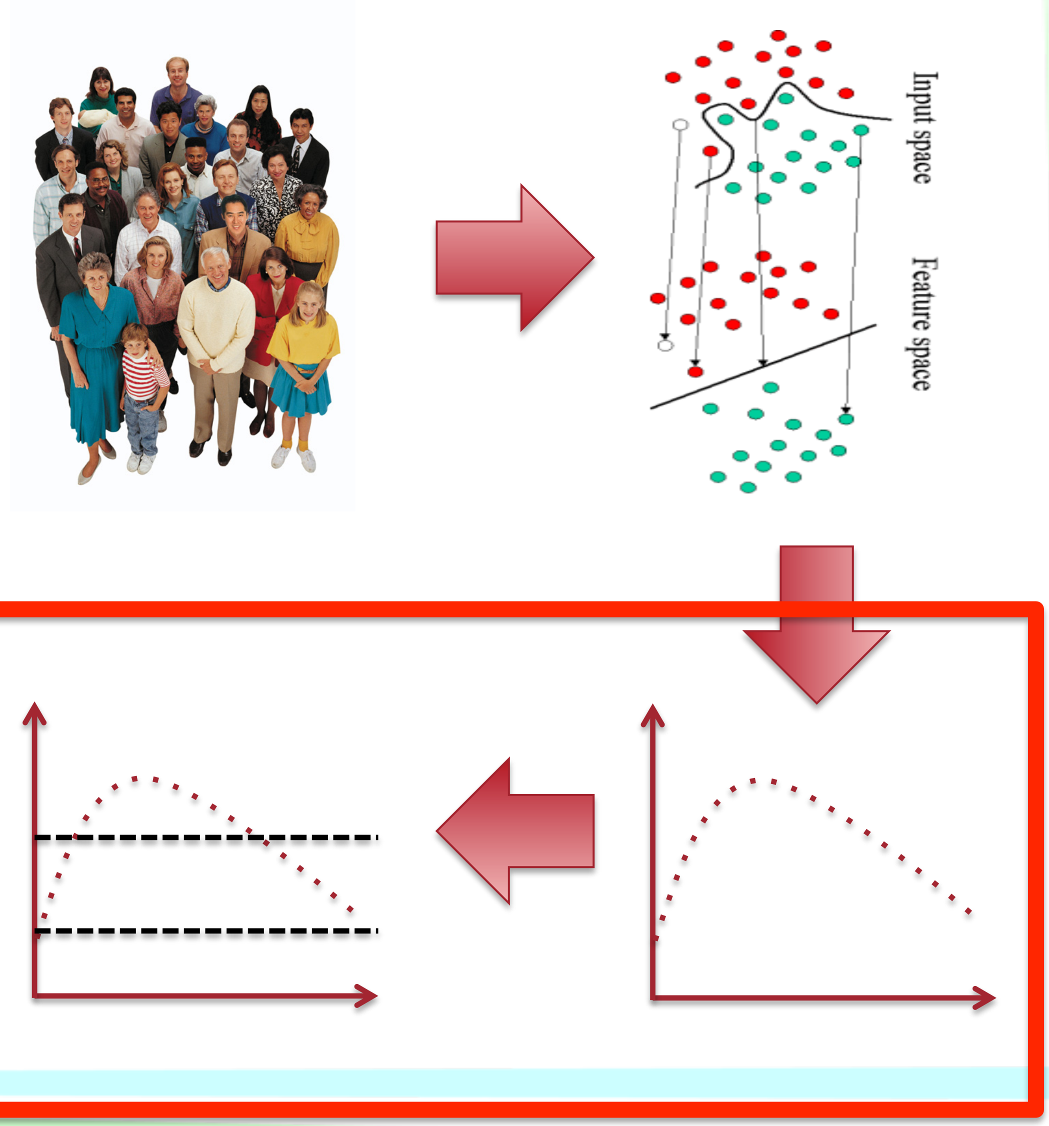
Drug administration decision support system (DADSS)

- Train the SVM model based on previous patients' data
- Compute the drug-concentration-to-time curve for a new patient



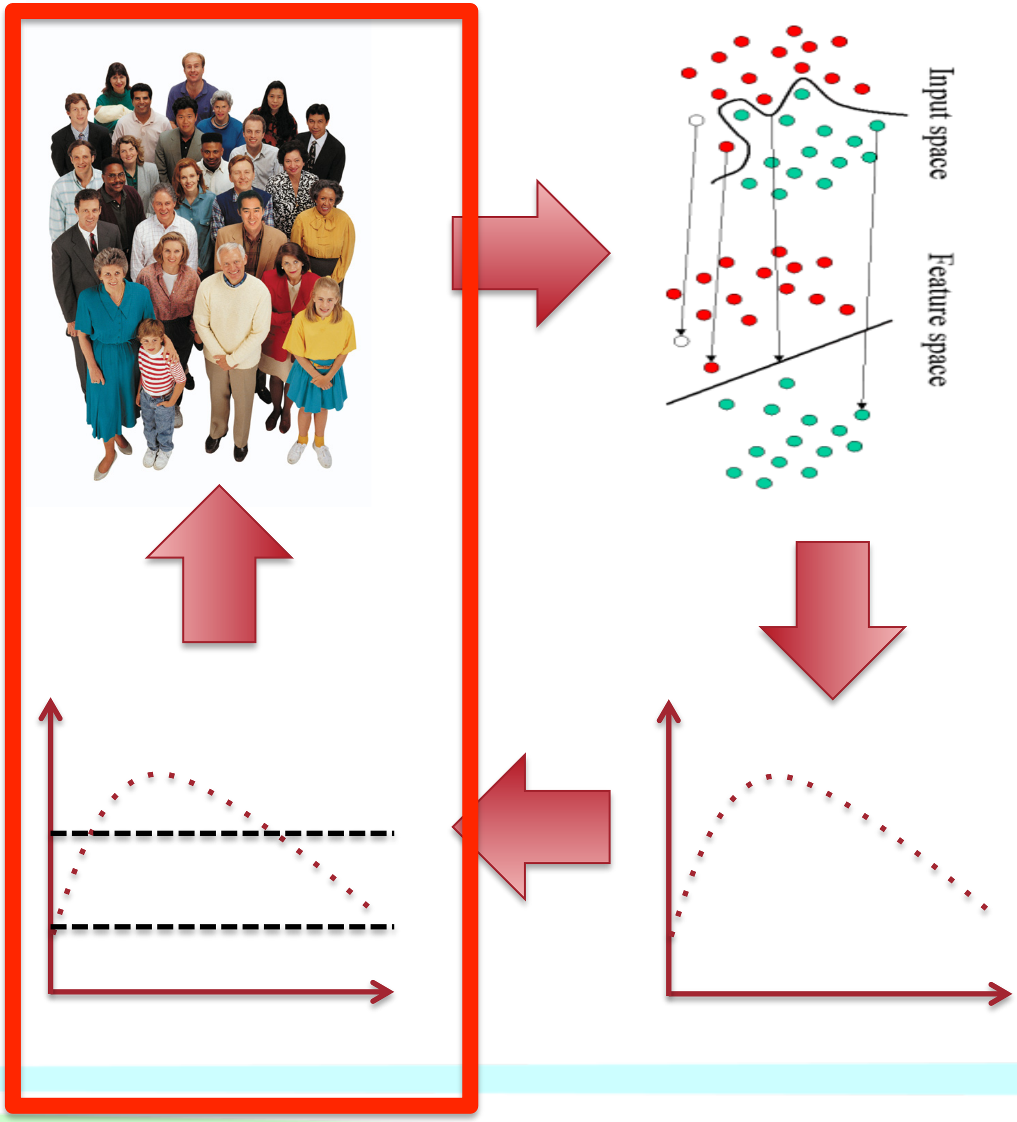
Drug administration decision support system (DADSS)

- 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

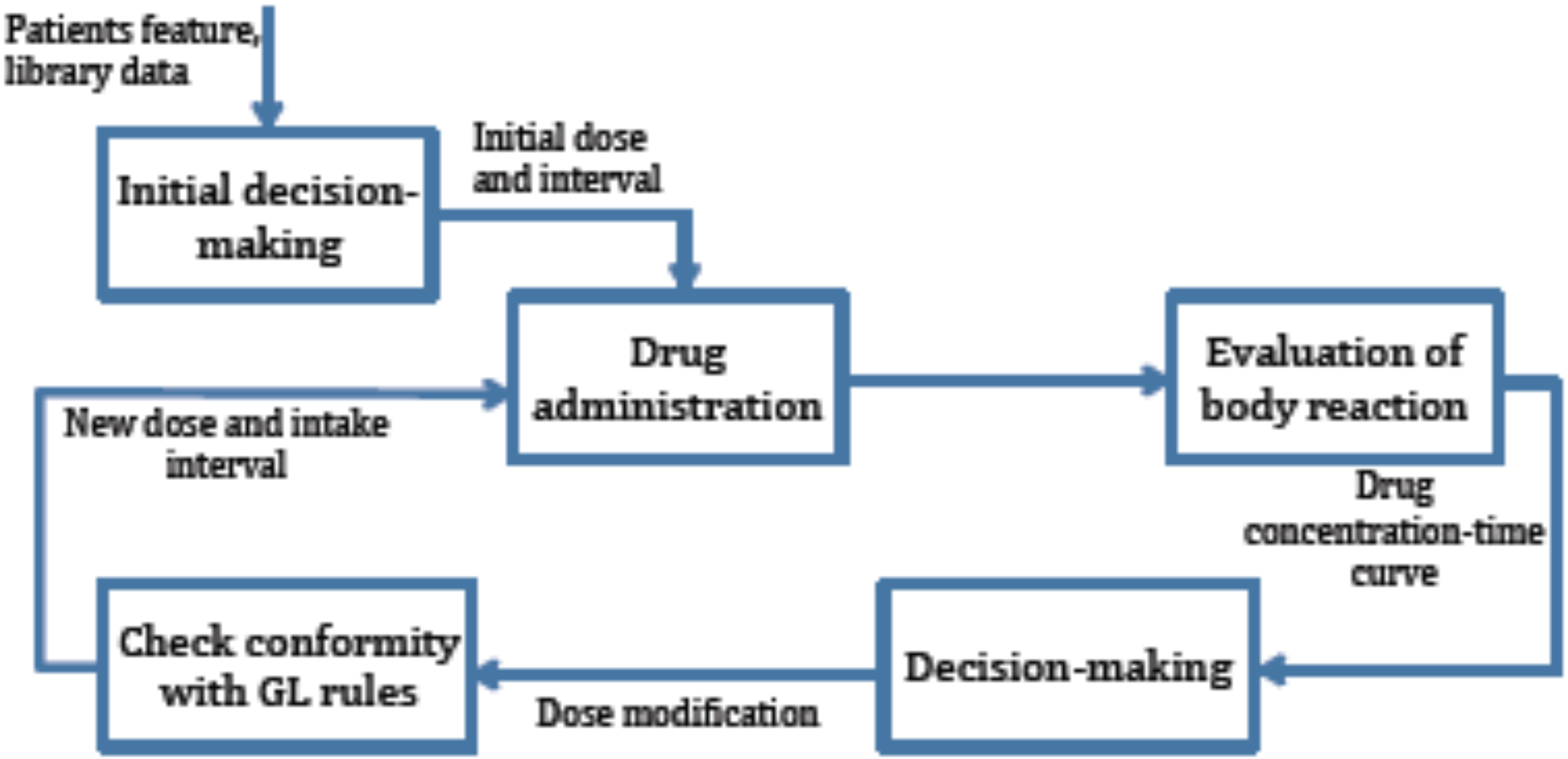


Drug administration decision support system (DADSS)

- 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



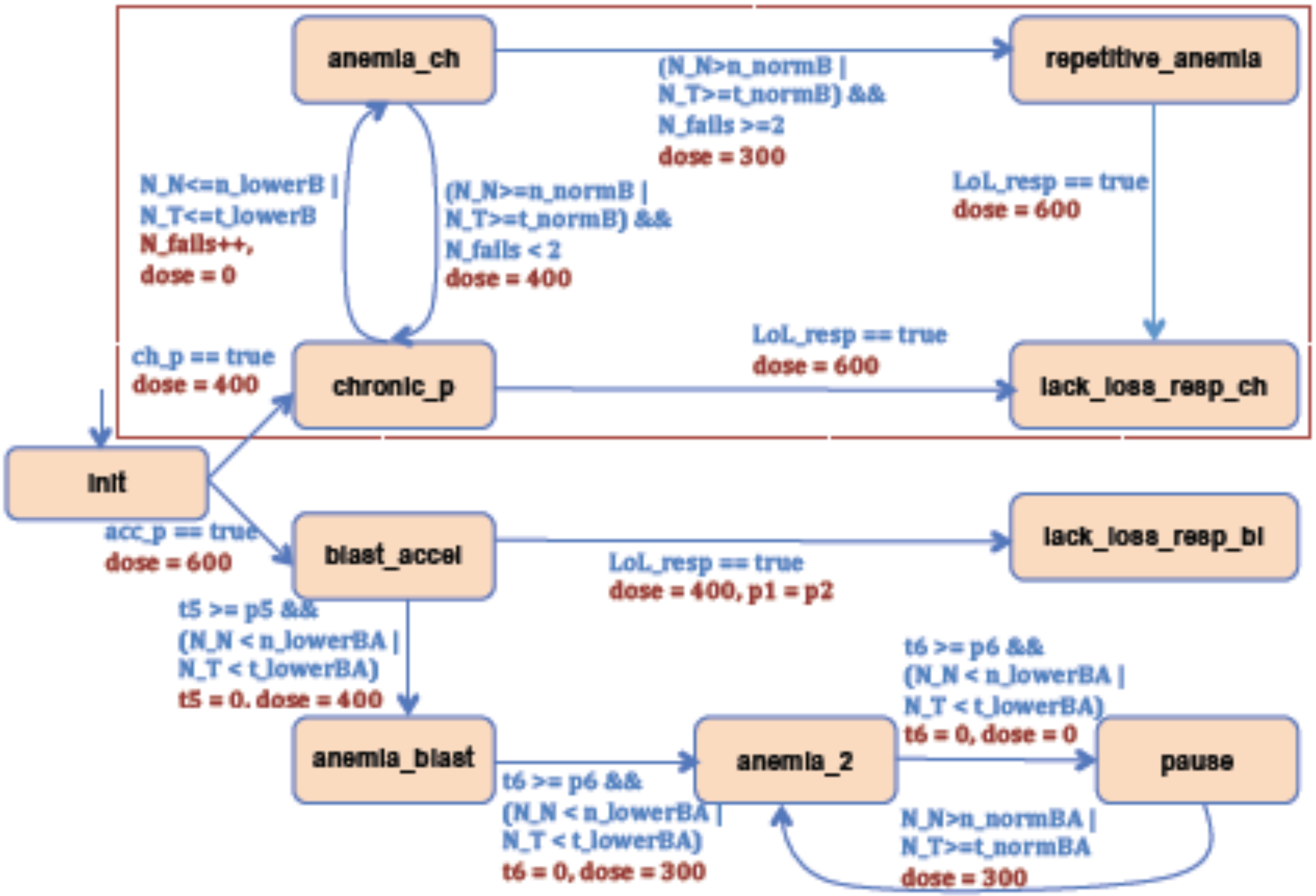
General flow



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

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- 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 educationl programs

nano-tera.ch

Nano-Tera.ch: key figures

- **118** projects (19+25 RTD large projects)
- **30** MCHF/year (approximatively 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)			TOTAL since beginning of the program		
	Journals, books	Conf. Proceedings	Total	Journals, books	Conf. Proceedings	Total
RTD 2009	48	69	**117**	144	133	**277**
RTD 2010	44	77	**121**	82	147	**229**
RTD add-on	1	3	**4**	1	3	**4**
NTF	6	10	**16**	14	36	**50**
SSSTC	6	9	**15**	6	9	**15**
	105	168	**273**	247	328	**575**

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