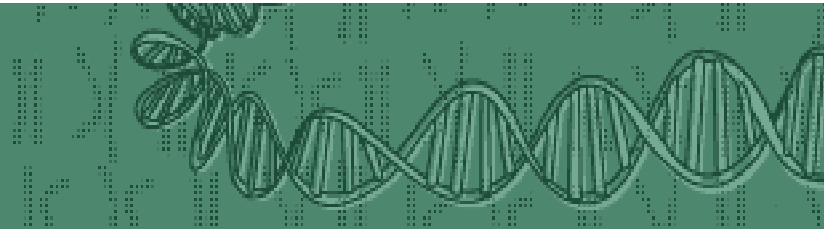
Autonomous Micron-scale system for *in vivo* cell monitoring

Carlotta Guiducci, Ph.D.

Department of Electronics, Informatics and Computer Science

University of Bologna

Trends in microsystems for *in vivo* monitoring



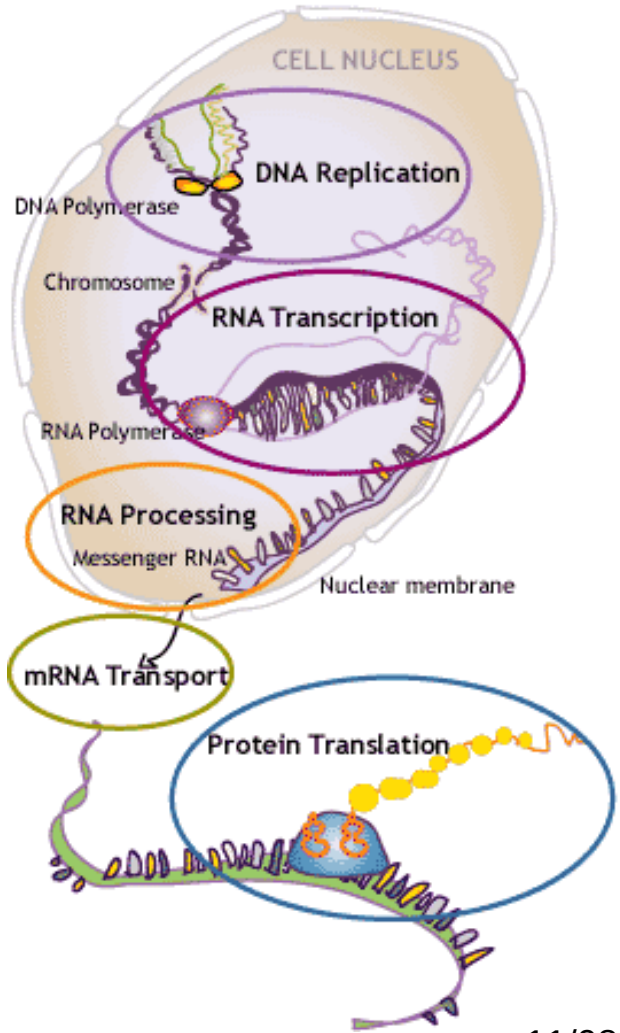
Node	Maturity	Power (W)	Size(m^3)
Obtrusive	Commercial	$1\text{-}10^{-1}$	10^{-3}
Parasitic	Prototype/Comm.	10^{-2} -10^{-3}	10^{-6}
Symbiotic	Research/Protot.	10^{-5} – 10^{-6}	10^{-9}
Bio-hybrid	Concept/Research	< 10^{-7}	10^{-15}

Molecular targets for *in vivo* monitoring of the cell

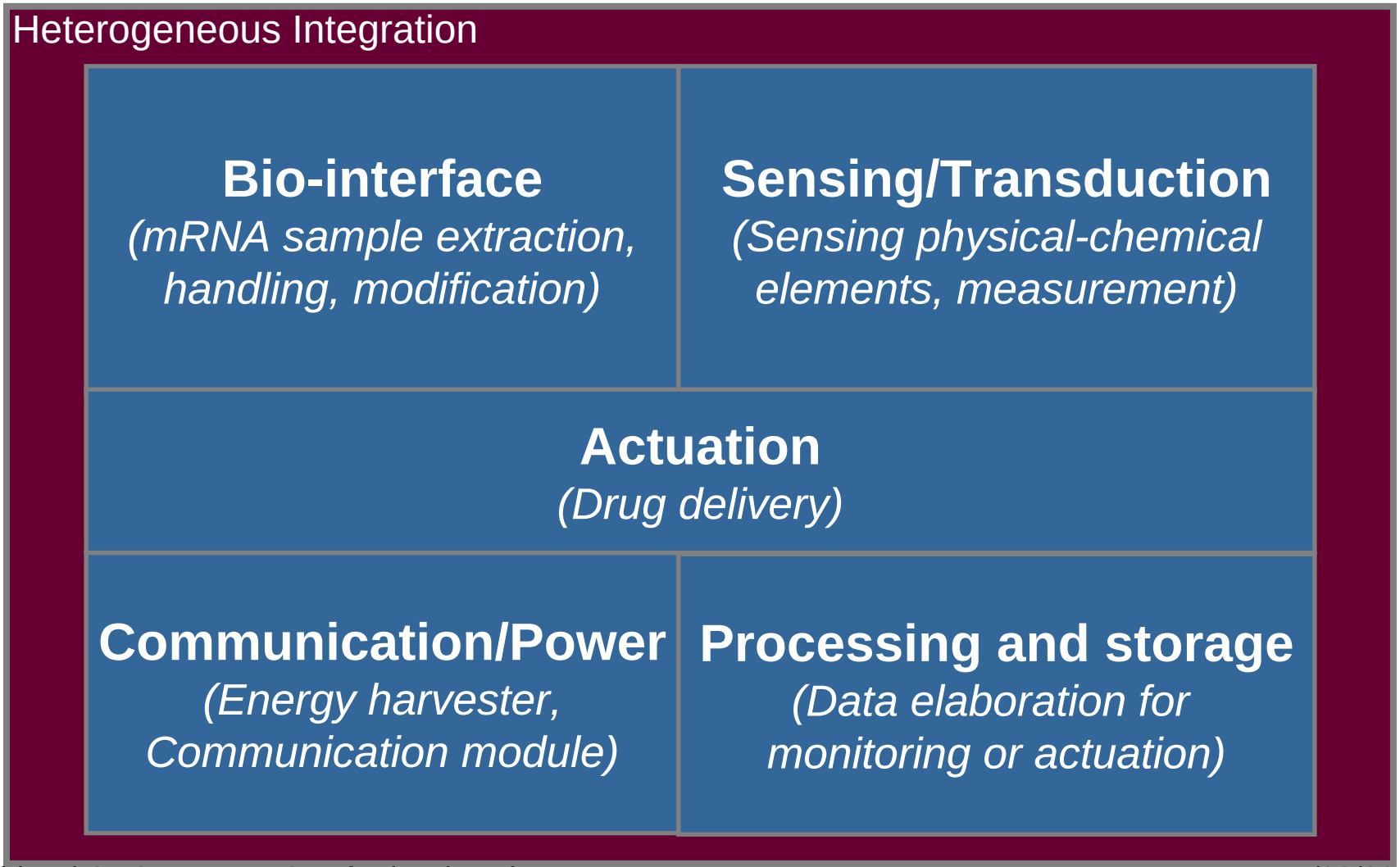
Extract **mRNA** to monitor **genetic expression** is the most powerful way to be able to address complex questions on the cell state.

Micron-Scale System for *in vivo* genetic expression analysis and drug delivery

- *symbiotic* to *bio-hybrid* node
- multi-site
- heterogeneous integration



Components of an autonomous micro-system for *in vivo* cell expression



Bio-interface. mRNA extraction

mRNA extraction from cells

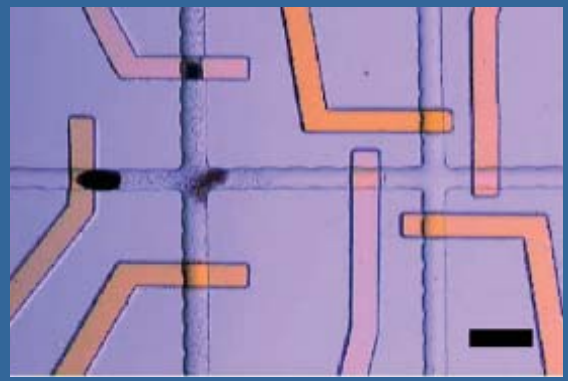
Cell isolation

↓

Cell lysis

↓

mRNA purification



J.W. Hong *et al., Nature Biotechnology, (2004) 22-4, pp. 435-439.*

- ***Device:*** PDMS by soft lithography.
- ***Sample processing:*** Pressure and reagents
- ***Biological sample:*** Measurable RNA was extracted from down to 28 cells processed in a 0.4 nl volume.
- ***Time for processing:*** several minutes

Bio-interface. mRNA extraction

Scaling trade-off
mRNA extraction and analysis from SINGLE CELL?

- Technically feasible, but

- Single cell $\Rightarrow$ Single molecules. The minimum quantity of final mRNA depends on the sensor performance.

- This limit can be relaxed by the integration of an **Amplification Reactor**

Bio-interface. Amplification

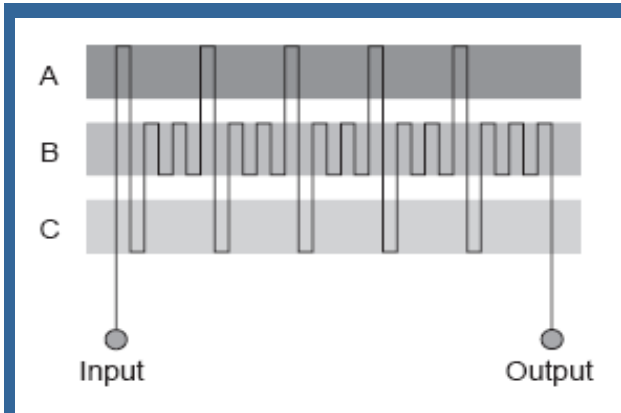
Polymerase Chain Reaction

Thermal cycling between Ts. A, B, C (95°C, 77°C, 60°C).

A - 95°C Separation of original molecules

B – 77° C Strands binds to suitable primers for targeted amplification.

C - The polymerase enzyme extends “builds” double strands from single elements



M.U. Koop *et al., Science (1998), 280, pp1046-1047*

- ***Device:*** Glass and copper
- ***Sample processing:*** reagents (enzymes, primers, oligonucleotides)
- ***Biological sample:*** few nl, 2^{20} amplification factor.
- ***Time for processing:*** 18 min

Bio-interface. Amplification

Heat management

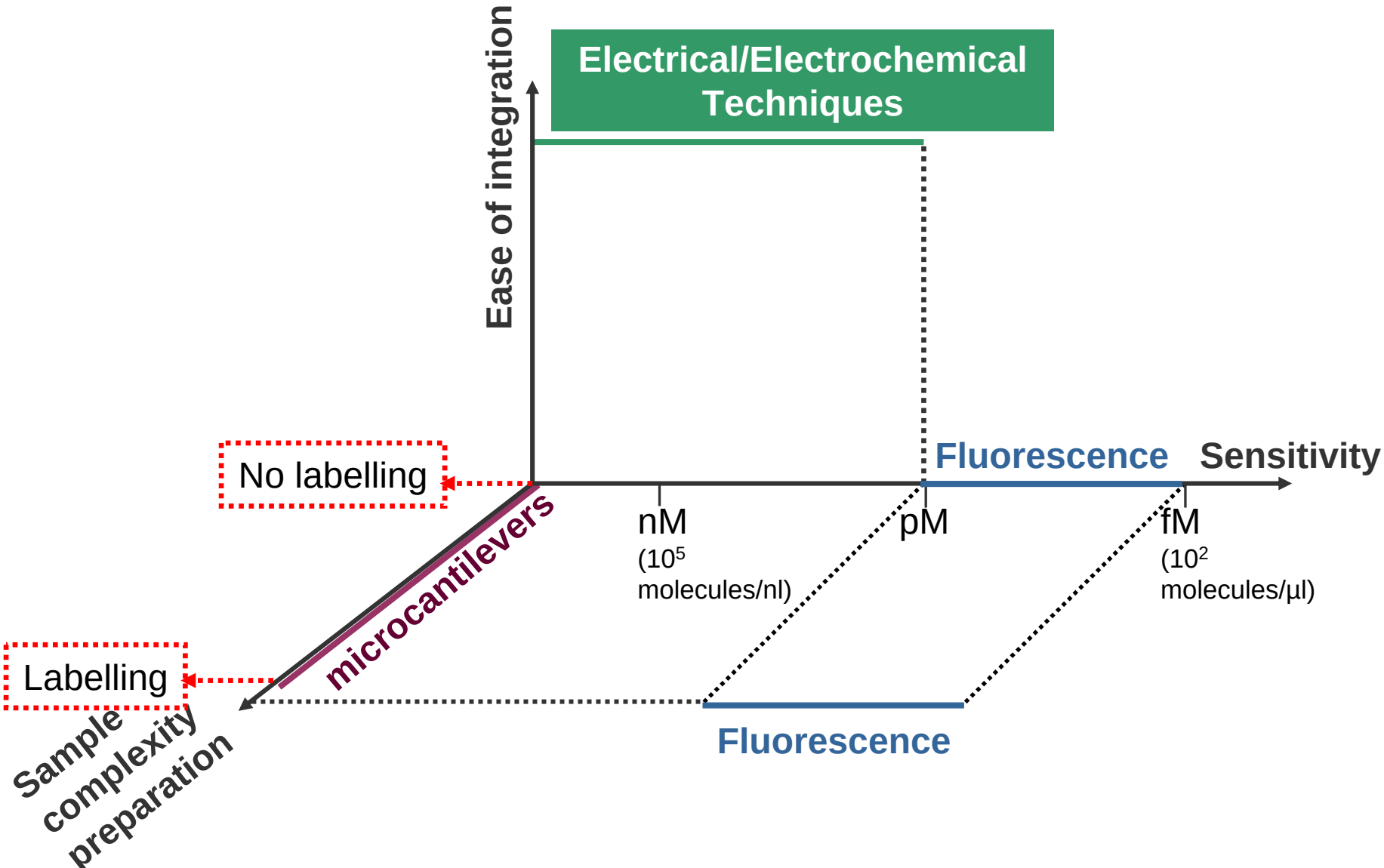
- Low thermal mass of the sample and high surface-to-volume ratio allows for rapid temperature cycling between temperature setpoints.
- Heating and cooling time are each less than 100ms (90µm × 40µm channels in glass and copper heaters).
- Thermal coatings may impact cooling schedule.

Energy costs

Costs of thermal cycling on chip

- Power consumption for heating can be estimated to be 1-10mW for a flow rate 100 nl/sec. (D.J. Saldler, *IEEE Trans. On Components and Pack. Tech. (2003), 26-2, pp. 309-316*)

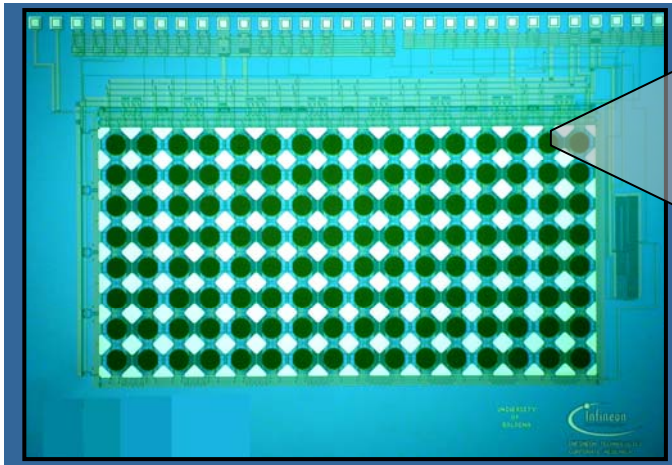
Sensing/Transduction. Techniques



Sensing/Transduction.
Electrical Technique based on capacitance measurements

128-site CMOS chip

- Capacitance measurement by capacitance to frequency conversion.
- Fully digital output
- Reduced number of pads by on chip addressing



C. Stagni *et al., IEEE J. of Solid-State Circuits (2006) 41-12, pp. 2956-2964*

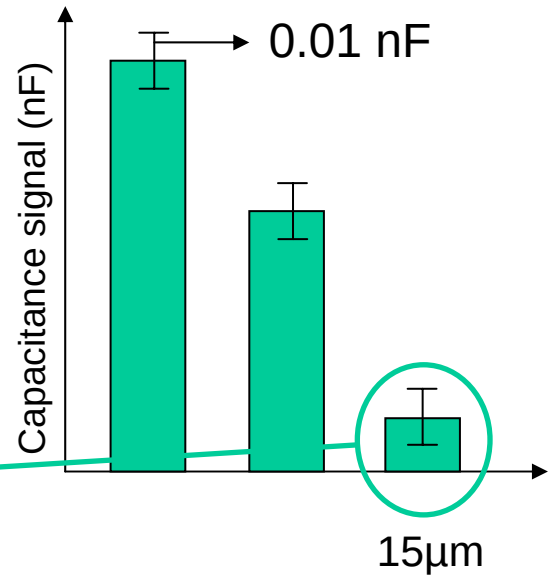
- ***Device:*** Gold on CMOS standard process
- ***Sample processing:*** hybridization reaction at RT
- ***Time for processing:*** 15 min (biochemical reaction)
- ***Biological sample:*** 500 nl of 10nM (10^7 molecules per site)

Sensing/Transduction.
Electrical Technique based on capacitance measurements

Scaling Trade-off
Minimum dimension of the spot

- Capacitance signal for a 200µm spot and 10^2 molecules/µm^2: 0.9 nF ± 0.01 nF (30 fF/µm^2).

- Limit of the spot size for 6dB SNR capacitance signal → 15 µm



Energy costs
Cost of measurement per site

- Input generation: 10 mV · 1 mA = 10 µW

- Measurement: 100 µW (for low power amplifiers). Need for on-chip multiplexing strategies.

Sample rate: 1Hz, 1 sec per site

Processing.
Electrical Technique based on capacitance measurements

Energy costs
Cost of the data processing for sensing output

- 1000 instructions per site to perform averages and thresholding.

- 1MIPS microprocessor. Power consumption range from ultra low power to standard:
[2.6 pJ/instr – 20 pJ/instr] $\rightarrow$
[2.6 nW per site – 20 nW per site].

- In case of 1000 site the power consumption ranges from [2.6 µW – 20 µW].

Communication

Communication

Wireless data communication for monitoring purposes

- Energy cost per site
  - 12 bit/site per second (1 site per second)
  - down to 10^{-7}J/bit with RF systems (J. Ammer, *IWWAN'06*)
  - $\Rightarrow$ 1 µW per site

- In case of 1000 site the power consumption for communication is 1 mW.

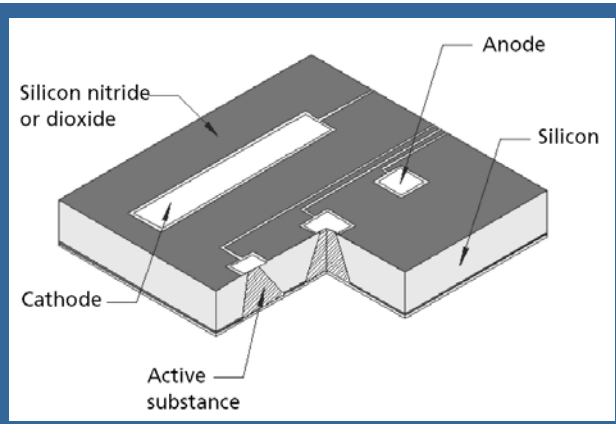
Actuation

Local delivery of controlled quantity of drugs

- Array of reservoirs in an electrolyte impermeable substrate

- Gold membranes (300nm) that close the reservoirs are anodes and other gold electrodes are cathodes. Surface of membranes: 50 × 50 μm^2

- Membranes dissolve at specific potential applied 1.04 V and 3 µA. P = 3 µ W



J.T. Santini, *Angewandte (2000), 39, pp. 2396-2407*

- ***Device:*** Bulk micromachining of Si process.

- ***Sample processing:*** drug release one well at a time.

- ***Time for processing:*** 30 sec per well

- ***Biological sample:*** 25 nl

Total Energy costs for a node with monitoring purposes.

- Bio-interface: 10mW, determined by PCR amplification reaction.

- **Power cost per site** for signal generation and communication
  - 110 µW. Sensing and transduction, determined by amplifier consumption.
  - 10 nW. Processing.
  - 1 µW. Communication

- **Power cost for 1000 sites** for signal generation and communication
  - › 110 mW without multiplexing strategies.

Bottle neck: PCR and analog measurement circuit without multiplexing strategies.

Total Energy costs for a node for monitoring and actuation

- Bio-interface (non PCR-free)

	Bio-interface	Signal Transduction	Processing	Communication	Actuation
Per site	1-10mW	110µW	10nW	1µW	10µW
100 sites	1-10mW	11mW	1µW	100µW	10µW
1000 sites	1-10mW	110mW	10µW	1mW	10µW

- Processing for control generation non critical

Wireless Power Delivery

- Standard UHF RFID energy trasfer is about 40 µW
- More advanced implementation can reach up to 1mW (Powercast) at 1 m distance.
  - Suitable for PCR free, serial-mode or low parallelism analysis devices

- Inductive power coupling up to hundreds of mW.
  - Suitable for PCR-based, parallel-mode systems