Closing the loop with hybrid (living/artificial) systems

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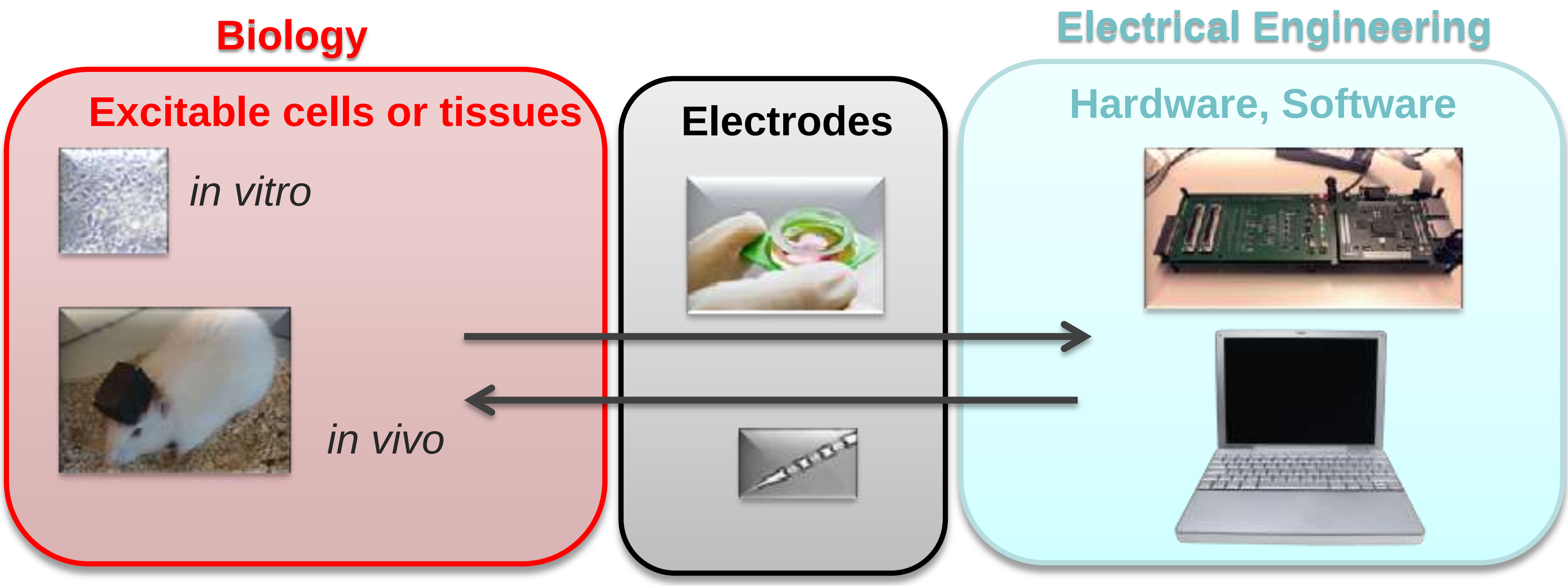
closing the loop ?

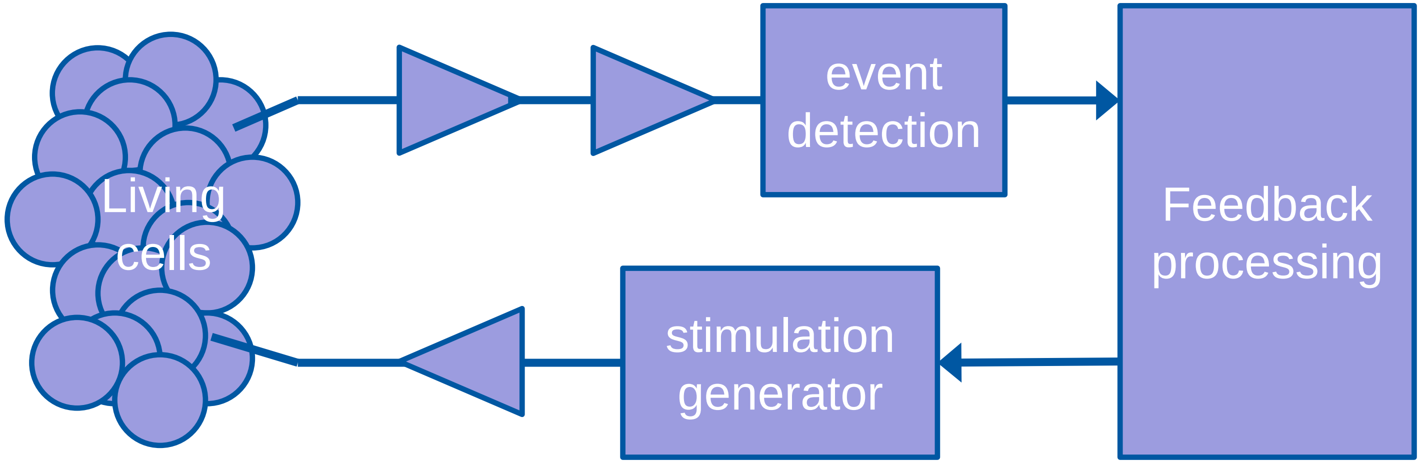


What can we learn from this interaction?

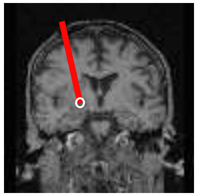
- *Explore unknown mechanisms*
- *Propose innovative therapeutical devices*

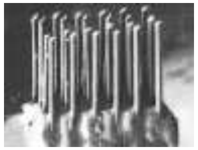
A closed loop setup

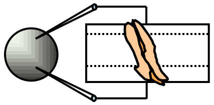
✓ principles of a closed loop setup (shematic)



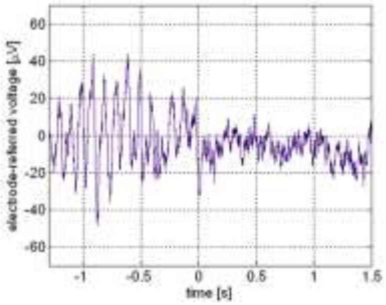
Electrodes (overview)







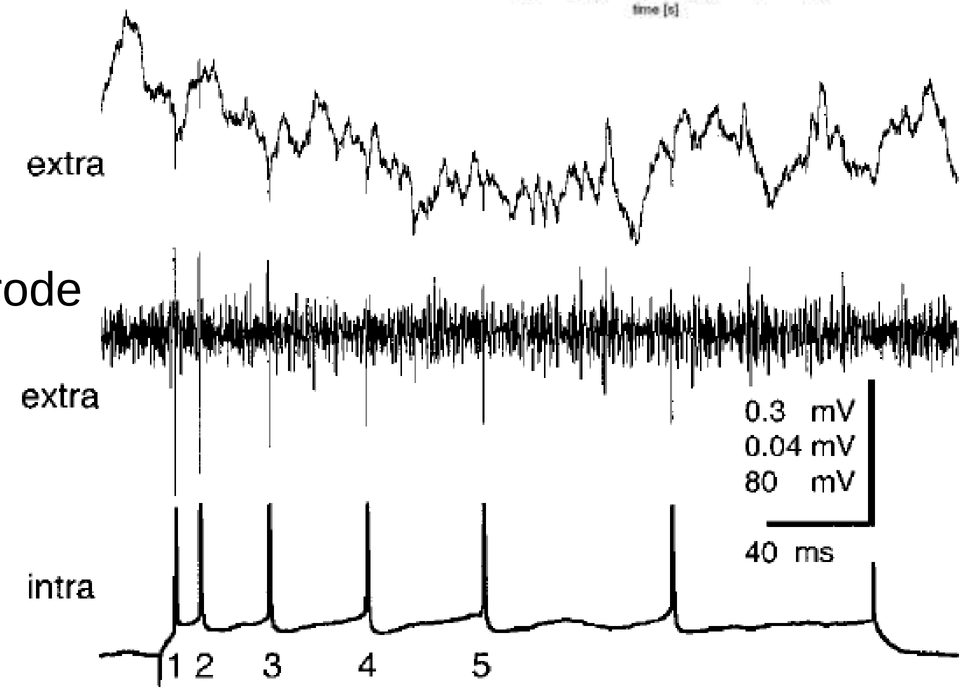
Surface electrodes



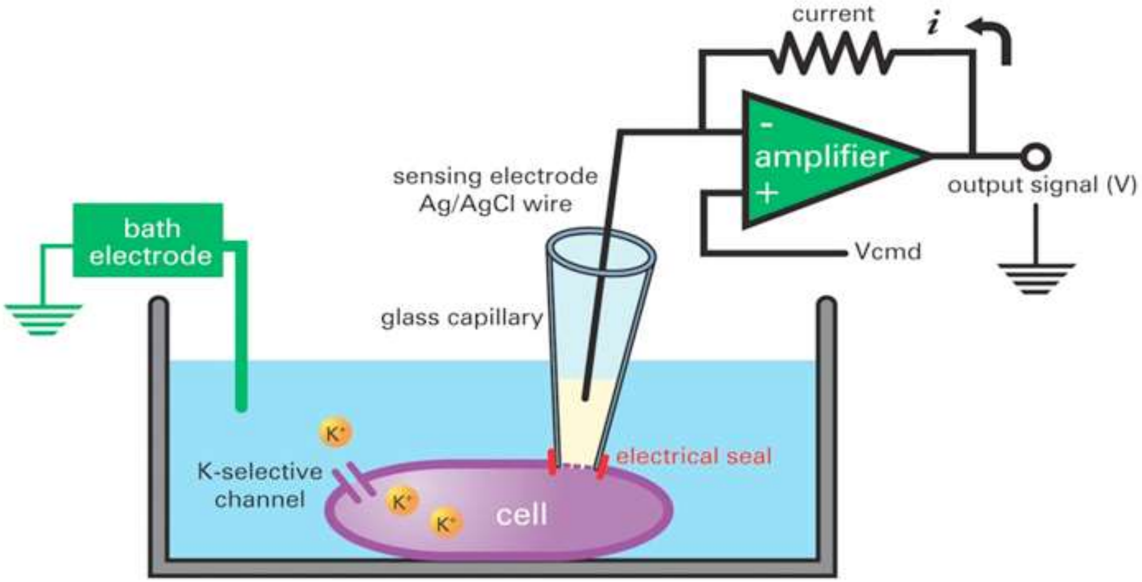
Macro-electrodes

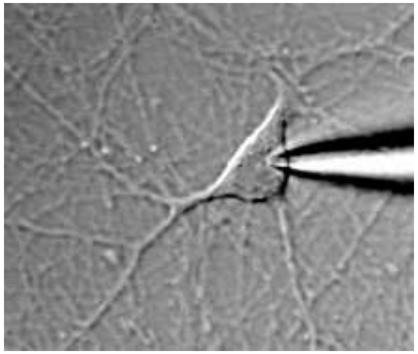
Extracellular microelectrode

Intracellular

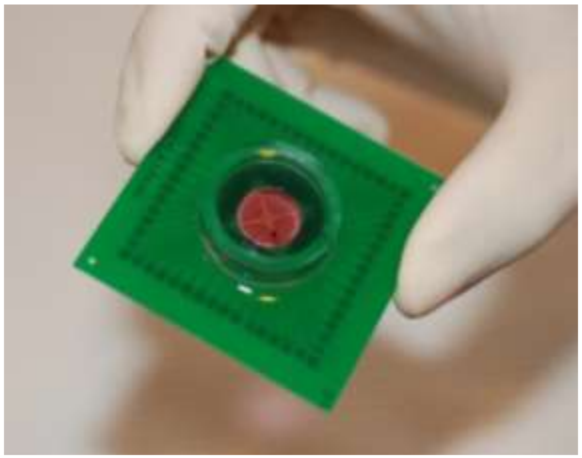


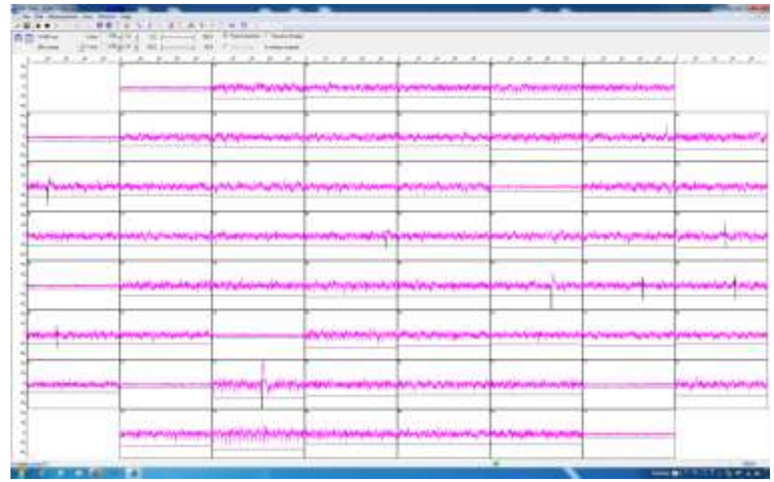
Electrodes : intracellular

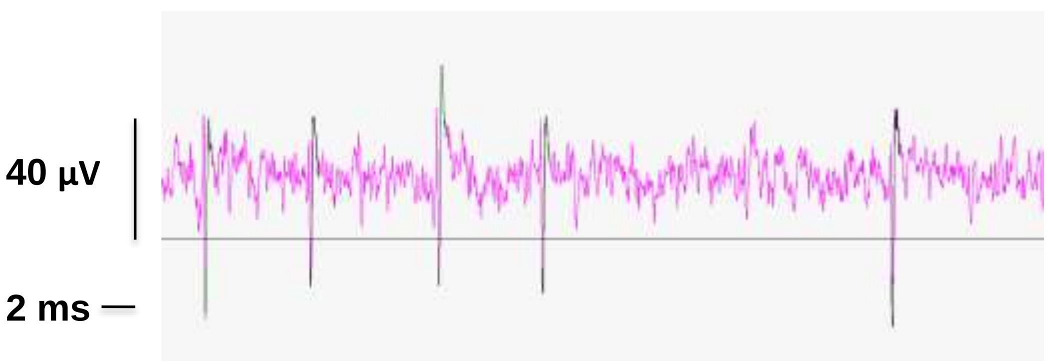




Electrodes : MEA

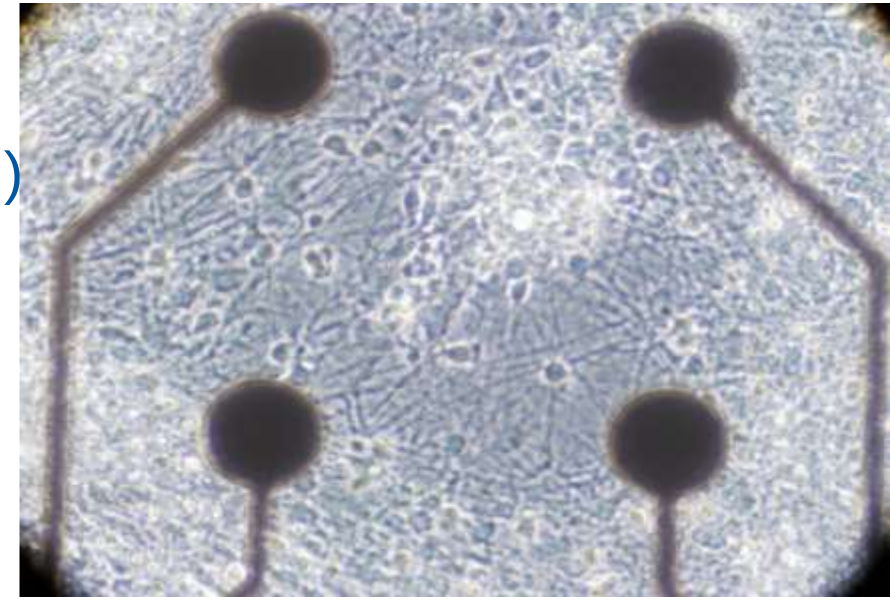






High storage needs :
from 1 to 3 MB/s

Electrodes : MEA



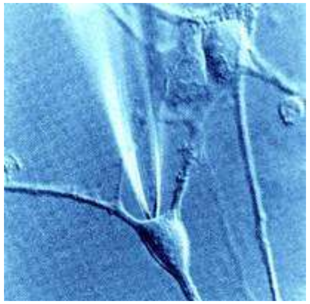
- Hundreds of electrodes
- Diameter : 10µm to 100µm (40µm)
- Pitch : 30µm to 1mm (200µm)
- metal :

  Gold / Titanium / indium / carbon nanotubes

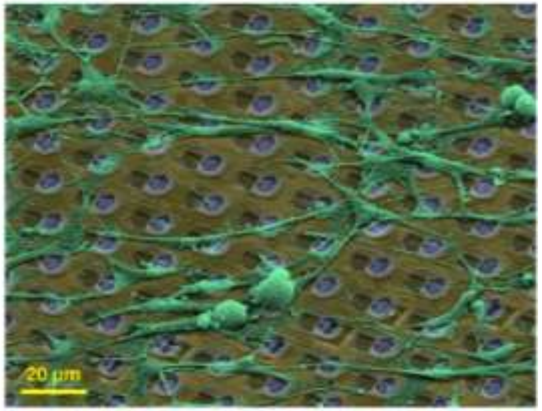
- substrate :
  - Glass (microscopy)
  - Silicon (for integration)

- impedence is a key parameter

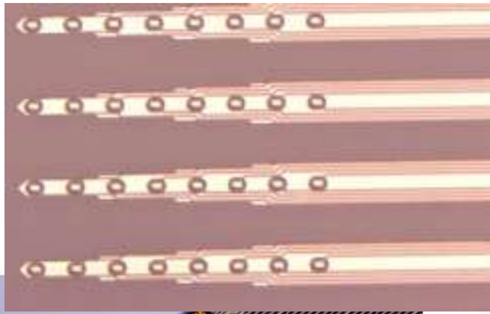
Electrodes (*exhibit*)

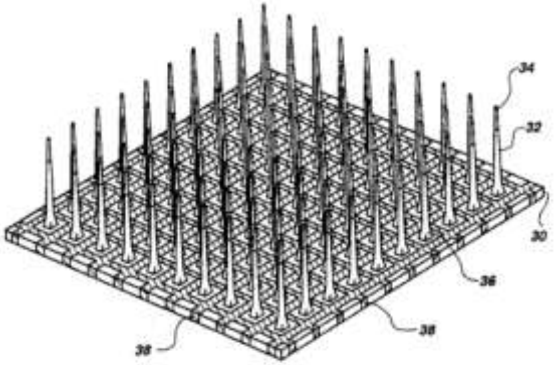


Microelectrode for Patch-clamp

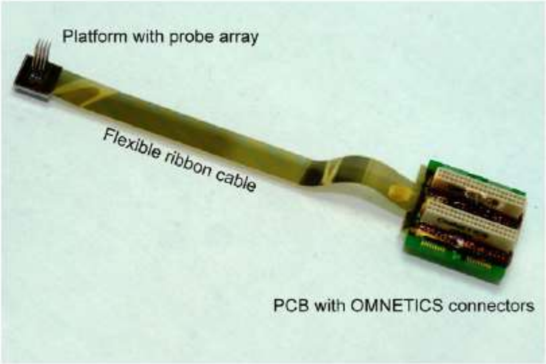


Hierlemann et al

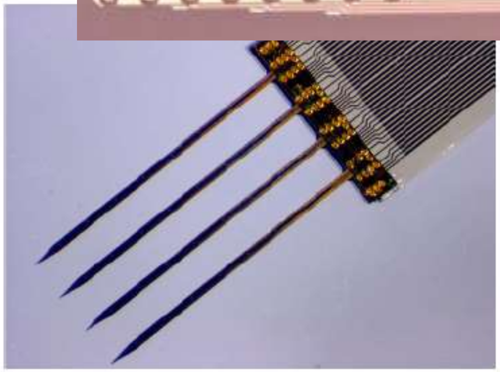




3D Electrode array (ECE Lab, U. Utah)

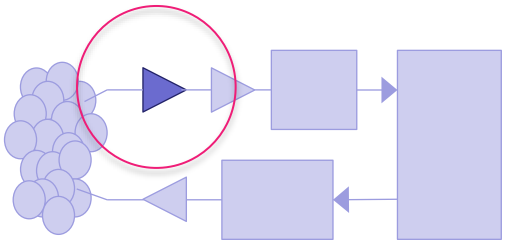


Complete system assembly



Single-comb assembly

preamplifier

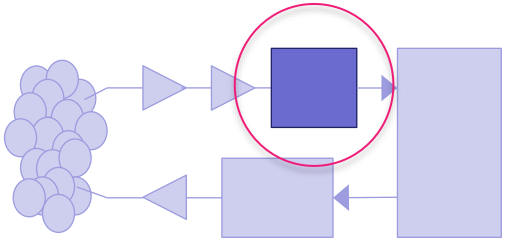


- ✓ Electrode impedance is not negligible
- ✓ Standard amplifiers are not sufficient

- ✓ Characteristics
  - ❖ very high input impedance
  - ❖ low output impedance
  - ❖ low noise
  - ❖ x4 to x10 amplification

- ✓ Need to be connected as close as possible to the electrodes

feature extraction

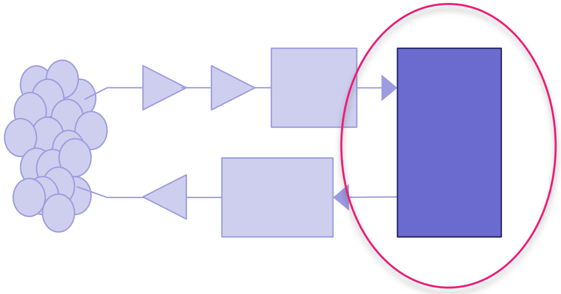


- ✓ Often : Spike detection
- ✓ Purpose :
  - ❖ feed the next computation module with events

- ✓ May also include higher level analysis
  - ❖ burst detection
  - ❖ inactivity detection
  - ❖ similarities

- ✓ can be totally different (frequency detection, …)

Computation



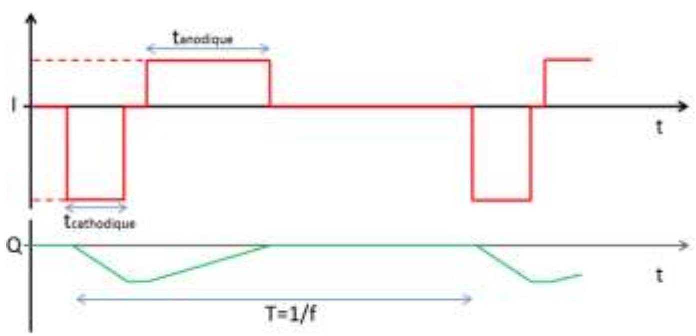
- input interpretation
  - produce a stimulation ?
  - what amount ?

- From simple thresholding …
- … to heavy pattern matching / correlation …
- … or spike based computing

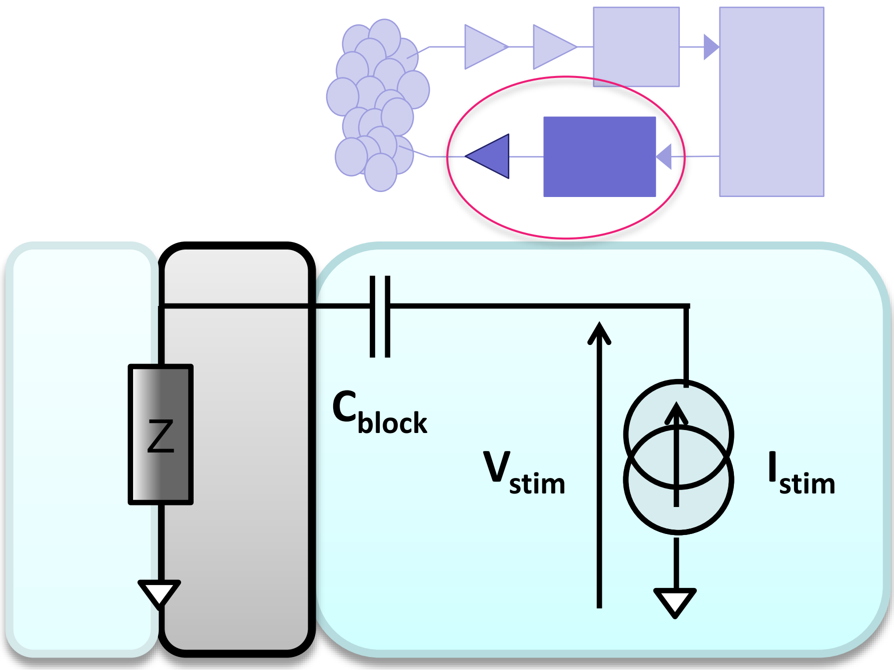
- Event production to trigger stimulation

(electrical) stimulation

- ✓ Safe stimulation (*in vivo*)
  - ❖ Biphasic current pulse



$$Q = \int_T I.dt = 0$$



I_{stim} = 100 mA
Z = 100 kΩ
=> V_{stim} = 10 V

- ✓ Main challenges
  - ❖ High voltage IC design
  - ❖ Embedded programmability
  - ❖ Low weight, low volume (portable or implantable)

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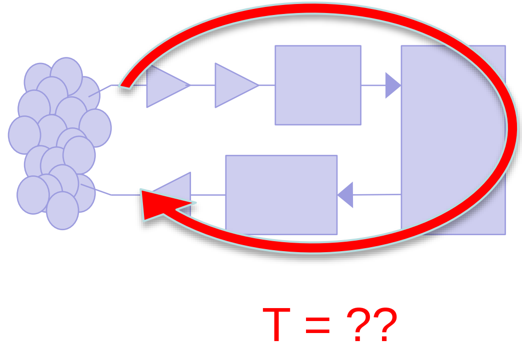
Timing constraints

- how to deal with the timings ?
  - computation power
  - latency issues



- Signal causality

- which kinds of computation for closed loop ?
  - on the fly / online
  - Soft real-time
  - Hard real-time

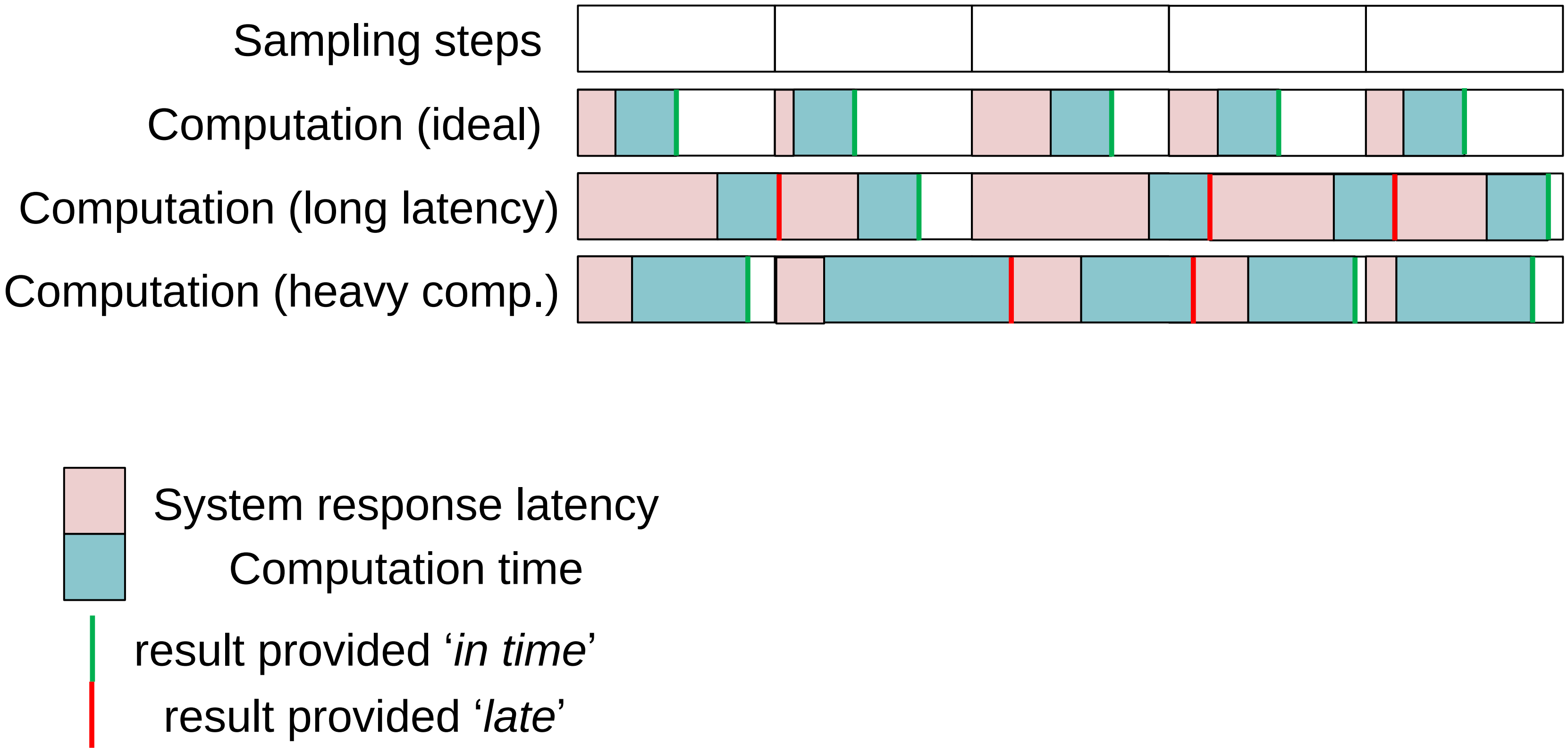
Causality

- ✓ Online computation

- ✓ features must be detected as soon as possible
  (not knowing data to come next)
- ✓ Even better if processing is stationary
  (independant from the sample number)

Online computing

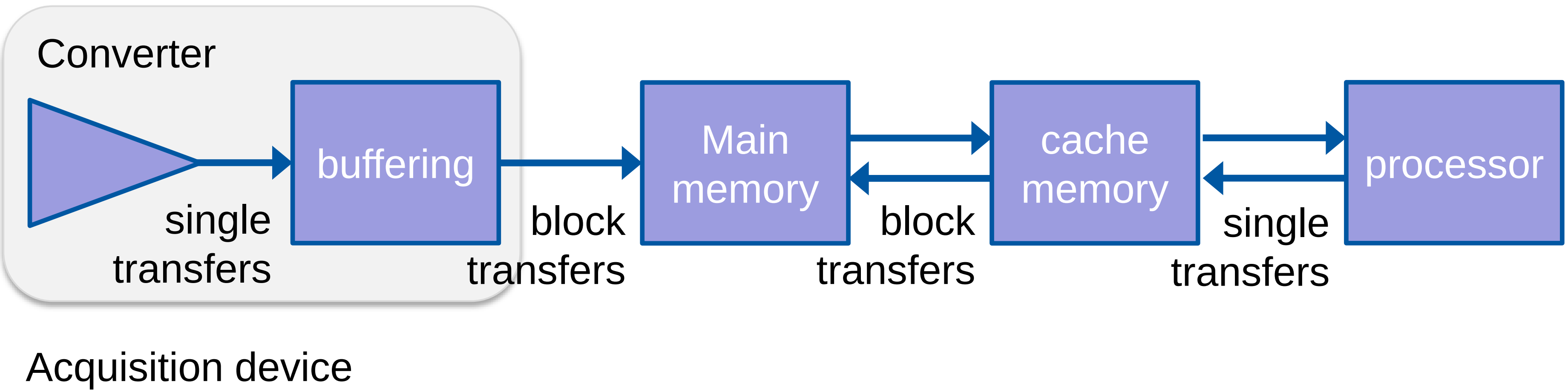
✓ The loop robustness only relies on computer performance



Online computing

- ✓ Computer achitectures are designed for high transfer rates, not for low latency data accesses.

(simplified) computer data flow architecture :



- ✓ A block transfer requires some µs of dead time before transfer
  - Negligible for very large blocks
  - kills performance for transfers of few bytes

Online computing

- ✓ Online computing is only powerful for computation of large data blocks.
  - ❖ ☺ easy to provide a user interface / monitoring / storage
  - ❖ ☺ suitable for high level, slow phenomenon
  - ❖ ☹ not possible to get spike-scale latency
  - ❖ ☹ system performance must be checked after each software change

Soft real time

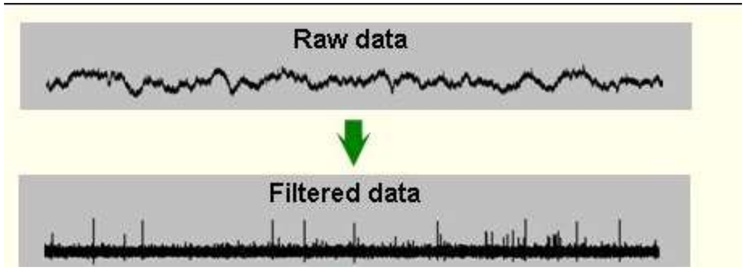
- A specific operating system feature bounds the response latency.
  - ☺ garanteed latency < 1ms achievable
  - ☺ system warnings when computation is too heavy
  - ☺ possibility to dedicate cores to the real time tasks
  - ☹ hardware architecture still not efficient for few bytes transfers
  - ☹ no possibility to gather computers in clusters

Hard real-time

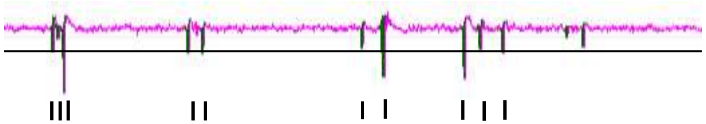
- ✓ Computation is performed on specific hardware platforms (Microcontrollers / DSP / FPGA / Analog ICs / …)
- ✓ No (or minimal) operating system
  - ❖ ☺ system is designed to respect timing constraints
  - ❖ ☺ (better) energy efficiency
  - ❖ ☺ ready for wearable devices
  - ❖ ☹ requires electrical engineering skills
  - ❖ ☹ costly (men-month, prototype production, development tools)
  - ❖ ☹ low flexibility (except if anticipated)

What to compute ?

Spike detection



Spike detection



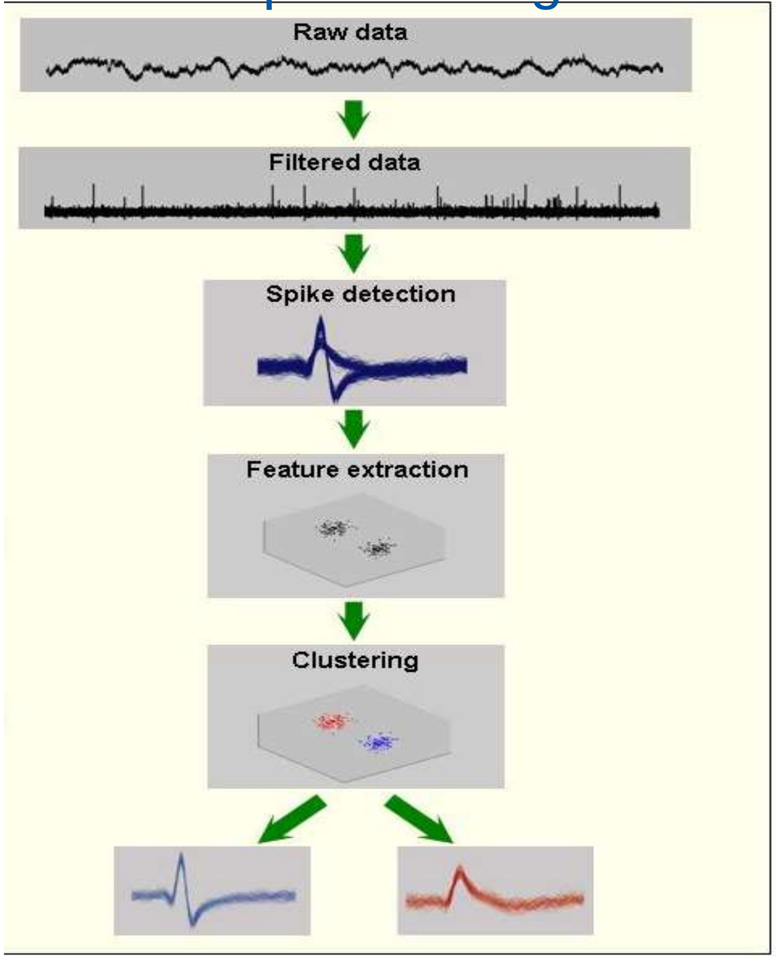
Spike Timestamps

$[t_1, t_2, t_3, t_4, t_5, t_6, t_7, t_8, t_9, t_{10}, t_{11}]$

Main metrics :

- Spike rate (FR, MFR)
- Inter Spike Interval (ISI)
- Burst rate (BR, MBR)

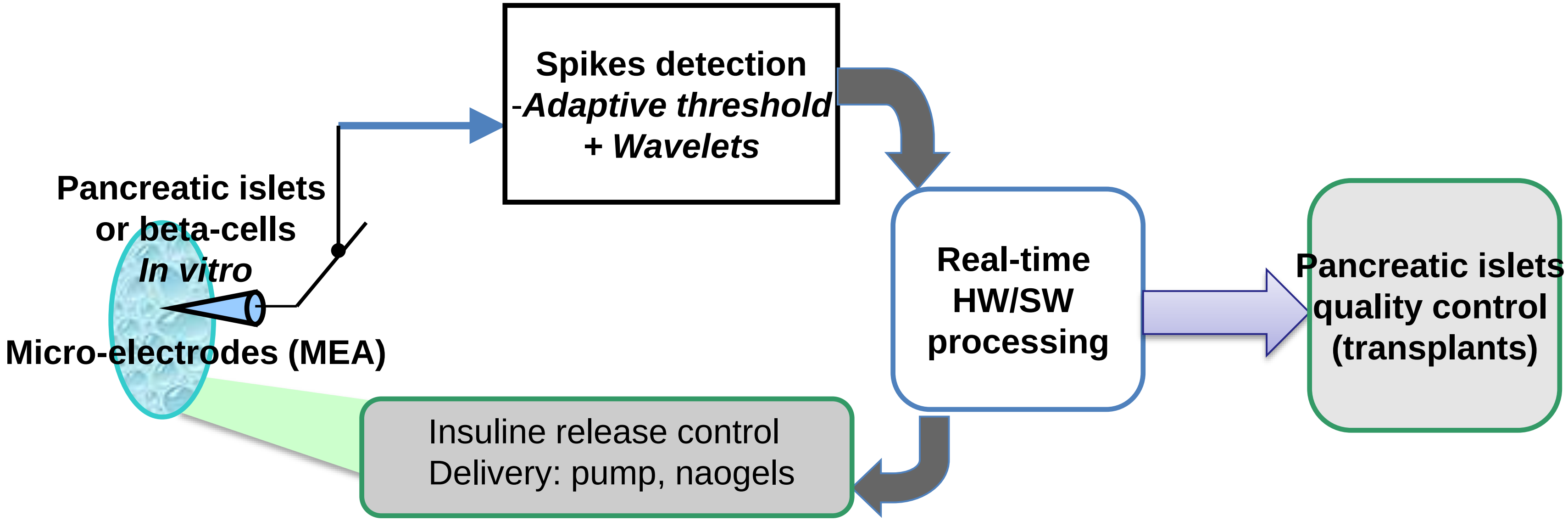
Spike sorting



Spikes are only a part of the story

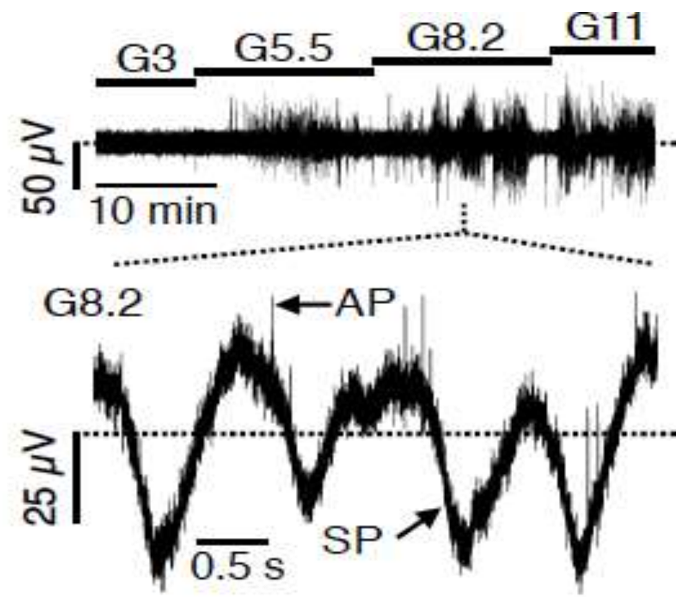
Signature of insulin need in diabetes therapy:

Pancreatic endocrine cells as electrical sensors of glucose, hormones and drugs, to control insulin delivery



Spikes are only a part of the story

- ✓ Pancreatic cells produce spikes,
  - ❖ gathered in micro-organs
  - ❖ low frequency (<1Hz) specific activity at the micro-organ scale



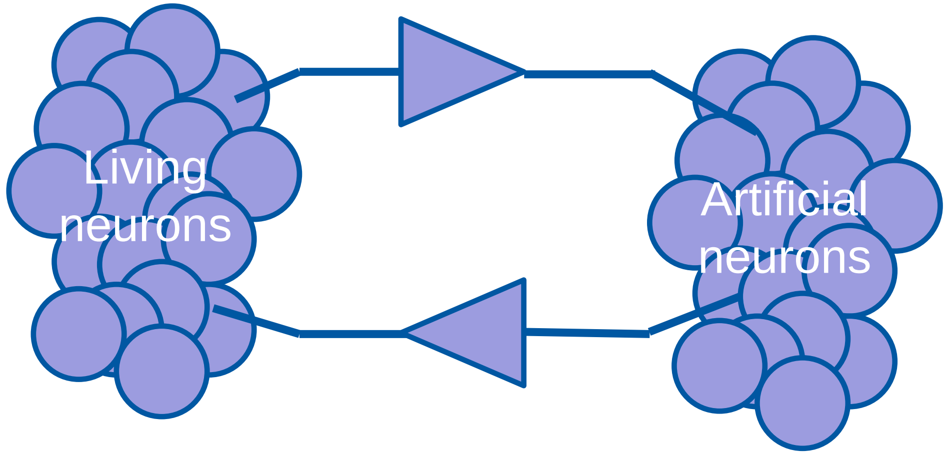
- ✓ Trust existing structures in cultured cells.
- ✓ Less computation
  - ❖ Higher amplitude => better Signal/noise ratio
  - ❖ detection based on '*simpler'* signal processing
  - ❖ lower frequency => more time to compute

closed-loop is automation

- ✓ Feedback loop stability has models
  - ❖ Specific field of electrical engineering
  - ❖ theory is based on transfer functions
    - each part of the loop has one input and one output
  - ❖ closed-loop experiments provide several inputs
    - how to avoid oscillations if models don't fit ?
    - positive or negative feedback ?
    - hypothesis : living tissues adapt to stabilize the loop

- ✓ individual 'open-loop' models must be gathered to form the 'closed-loop' model

How to use a closed loop ?



- ✓ Brainbow EU project :
  - ❖ Hybrid neural network for rehabilitation
  - ❖ All parts of the loop are actually working well
- ✓ Issues :
  - ❖ for *i* input electrodes and *j* artificial neurons there is potentially $i \times j$ connections to setup for input
  - ❖ even more if we have burst detection / pattern identification / correlation
  - ❖ each feedback stimulation produces an artifact that temporarilly blinds the system
    - stimulation events are limited vs time
  - ❖ how to choose the stimulation triggers and locations ?

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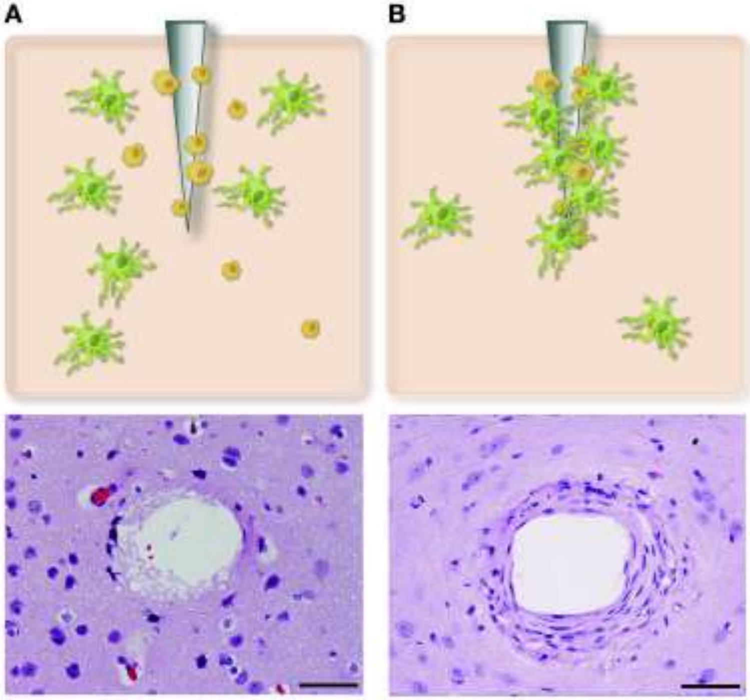
Dealing with *in vivo* devices



- ✓ Implanted devices
  - ❖ active
    - cardiac stimulator
    - Neuro stimulator
  - ❖ passive
    - stents
- ✓ Fibrosis phenomenon
  - ❖ body reaction against a foreign body
  - ❖ Alteration of tissue/implant interface
  - ❖ implant looses functionnality
- ✓ requires (at least) electrode impedance monitoring

Dealing with *in vivo* devices

- In vivo means implanted or portable devices :
  - size / weight / consumption constraints
  - portable : need to get signals from the body
    - wireless : low signal quality => heavy signal processing
    - wired : long term infection issues
  - implanted : heat dissipation limited by tissue tolerence

- animal experiments :
  - constraints are stronger than for humans
  - mechanical robustness
  - device monitoring / data recording

Closing the loop : conclusion

- ✓ No universal system (constraints are applications specific)
- ✓ Modelling needs :
  - physiological
  - behavioral
  - automated help for experiments / parameter reduction

Closing the loop : perspectives

- Promising for symptomatic cure or rehabilitation
- Demanding in lots of fields
  - biology / physics / implementation / modelling / automation …
- Improves knowledge of physiological phenomenon
- Ethical issues
  - improved human
  - hybrid systems invovling animal cells

That's all folks…

Thank you for you attention…