“Hybrid neural networks : biology/electronics interactions ”

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http://neuromorphic.ims-bordeaux.fr

The story ….

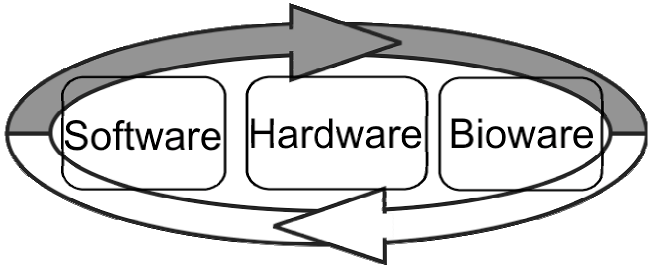
« hybrid (bio-artificial) systems at the neuron (cell) level: when neuroengineers get involved»

- ✓ Neuro-electronics interfaces
- ✓ A closed-loop approach
- ✓ Single-cell level interactions
- ✓ Network scale level interactions
- ✓ Multi-modal systems

The keywords….

(remember the talk title:
"Hybrid neural networks :biology/electronics interactions ")

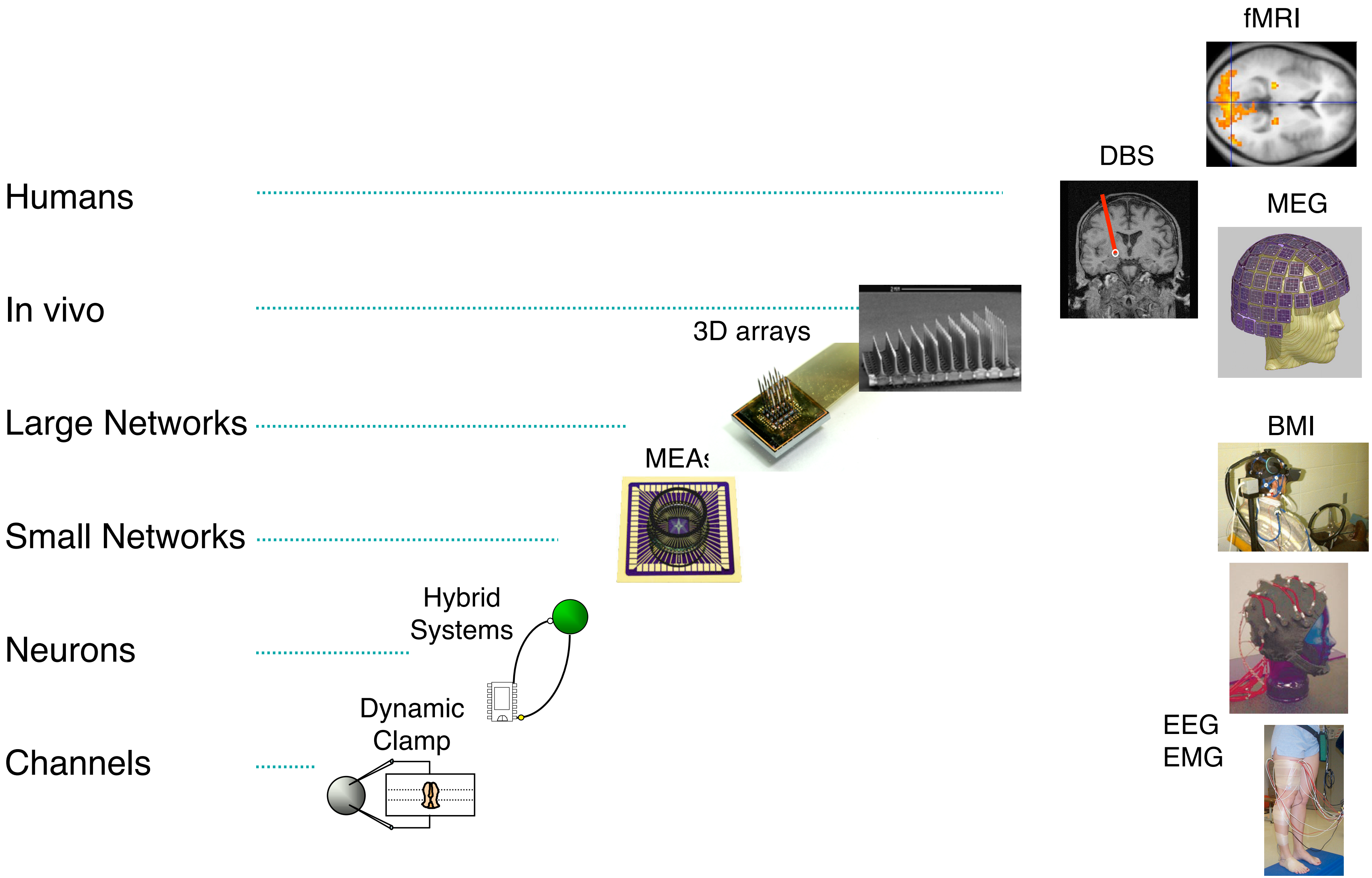
✓ INTERACT :



✓ ELECTRONICS: electrical signals (currents, voltages)
from direct measurements or using sensors/transducers

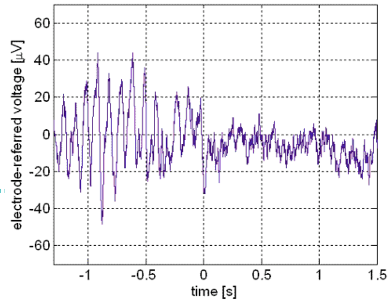
✓ BIOLOGY: ionic channels, cells, networks, systems

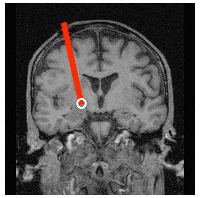
Different levels of investigation = Different interfaces



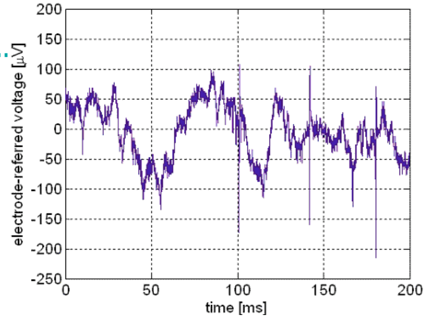
Different levels of investigation = Different signals

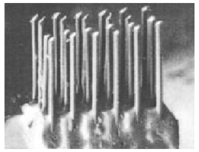
Electro-encephalo/myo-graphs

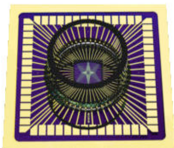




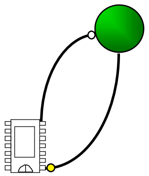
Local field potentials

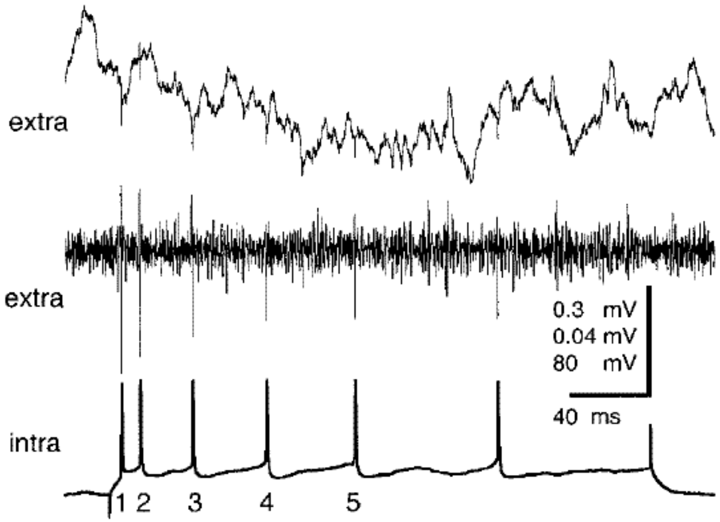




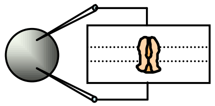


Extracellular



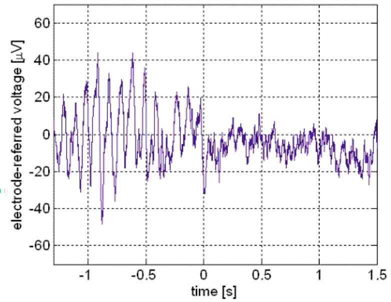


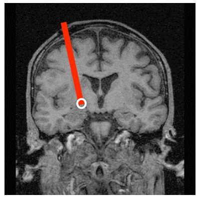
Intracellular



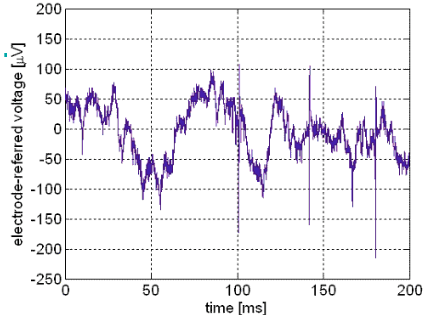
Different levels of investigation = Different signals

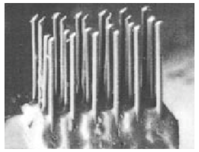
Electro-encephalo/myo-graphs

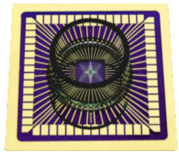




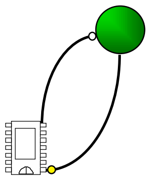
Local field potentials

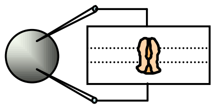




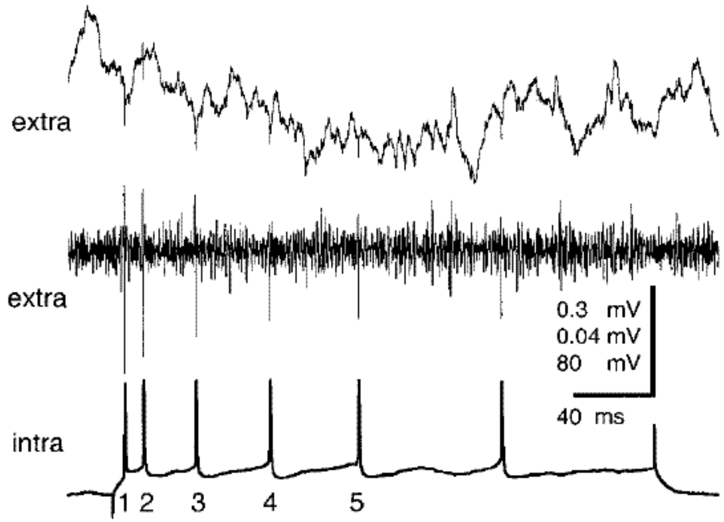


Extracellular



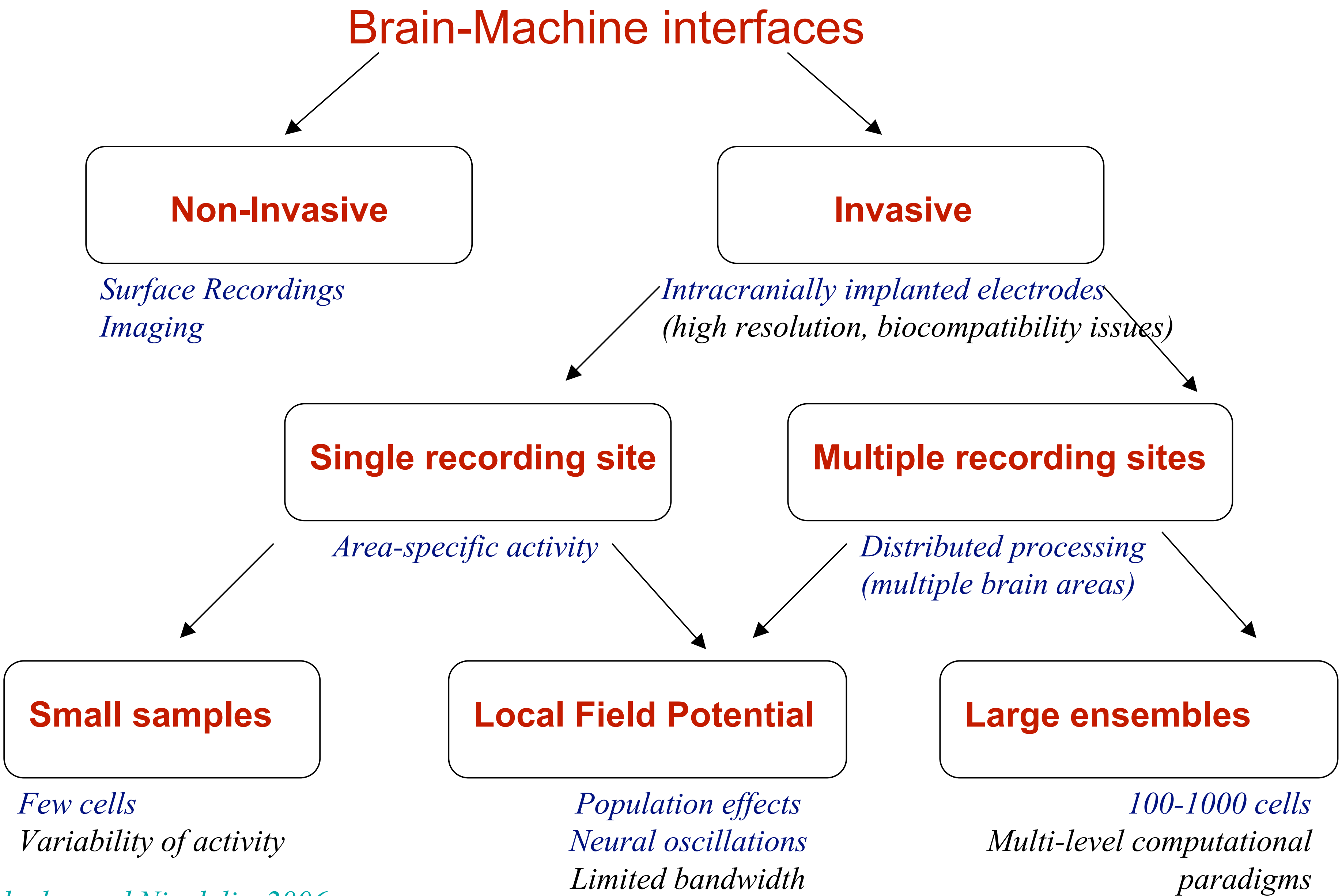


Intracellular



In-vivo
/
In vitro

And what about BMI (in vivo) ?



Lebedev and Nicolelis, 2006

And what about BMI (in vivo)?

Brain-Machine interfaces

Non-Invasive

Surface Recordings
Imaging

Invasive

Intracranially implanted electrodes
(high resolution, biocompatibility issues)

Single recording site

Area-specific activity

Multiple recording sites

Distributed processing
(multiple brain areas)

This talk

Small samples

Few cells
Variability of activity

Local Field Potential

Population effects
Neural oscillations
Limited bandwidth

Large ensembles

100-1000 cells
Multi-level computational paradigms

Lebedev and Nicolelis, 2006

And what about BMI (in vivo)?

Brain-Machine interfaces

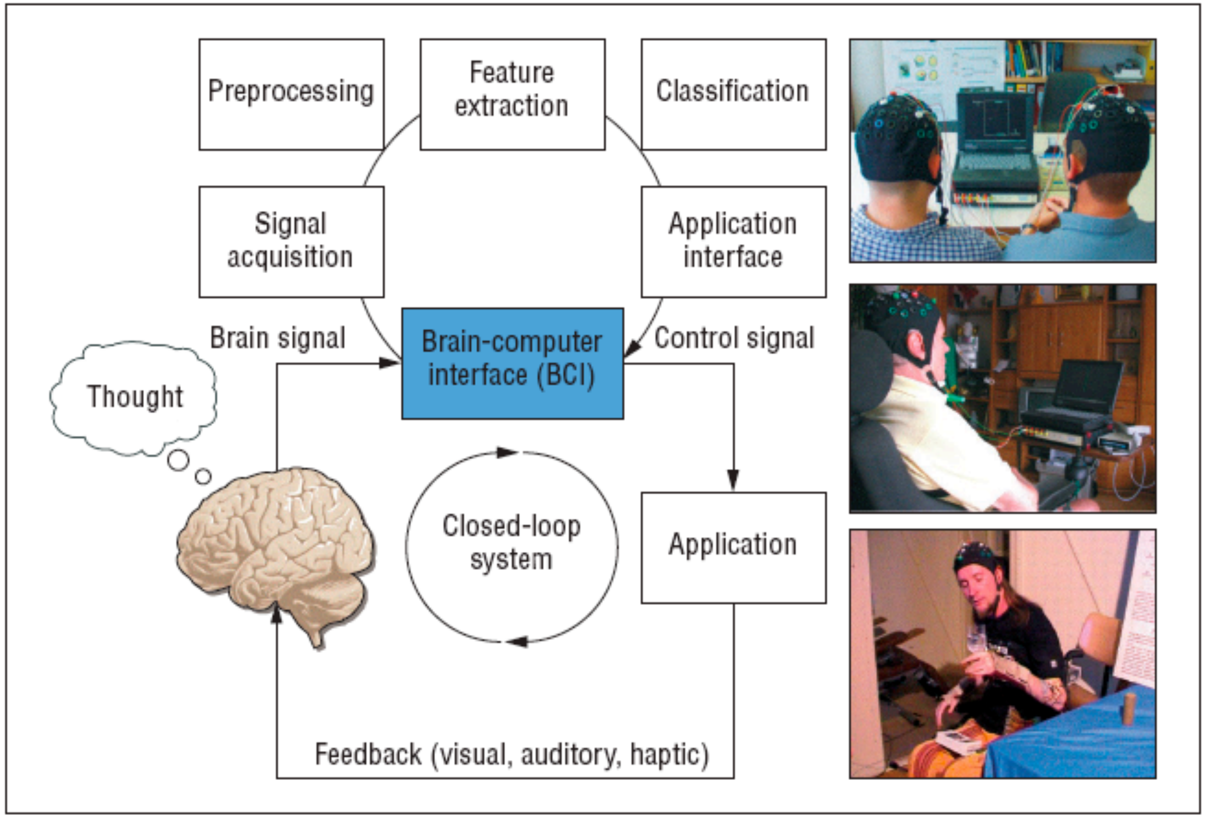
Non-Invasive

but:
EEG=Limited bandwidth
Limited resolution
"Surface" analysis (2 cortical layers)

Lebedev and Nicolelis, 2006

BCI = High-level features

« Brain-computer interfacing: schematic of the principal components » *



** A. Nijholt and D. Tan, Brain-Computer interfacing for intelligent systems, 2008, IEEE Intelligent systems, 23(3):72-79*

This talk is finally about….

Electronics processing **electrical** cellular or cellular-induced signal

for investigating
low-level neural features (cell, small network)

or
low-level **induced** neural features

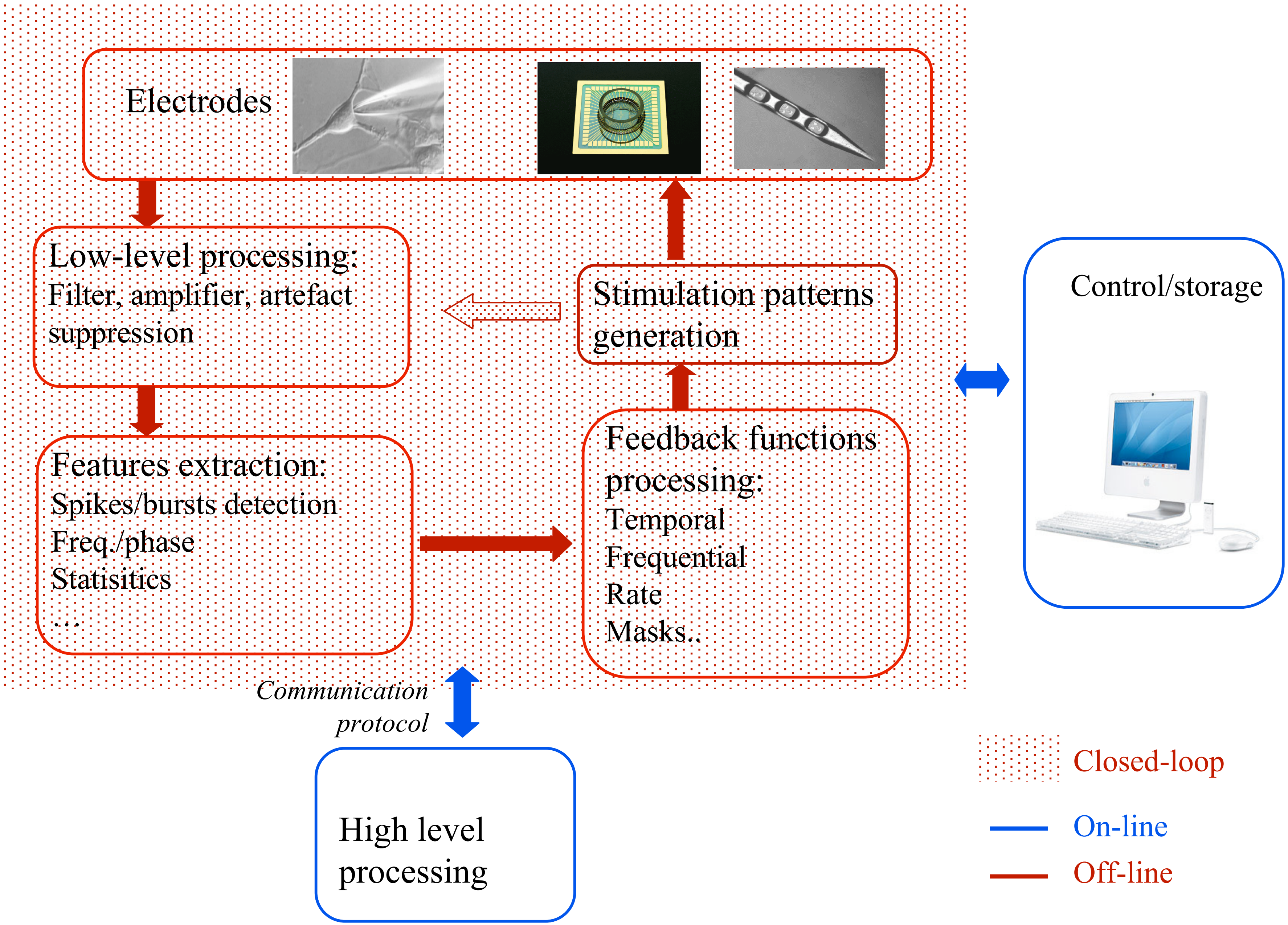
in
in-vitro / in vivo **closed-loop** configurations

with
electrically-induced **feedback**.

The story ….

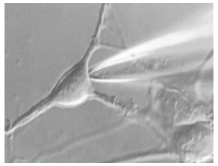
- ✓ Neuro-electronics interfaces
- ✓ The closed-loop approach
- ✓ Single-cell level interactions
- ✓ Network scale level interactions
- ✓ Multi-modal system

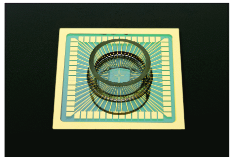
A modular closed-loop

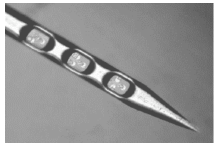


Closed-loop : biology ➔ artificial

Electrodes







Low-level processing:
Filter, amplifier, artefact suppression

Features extraction:
Spikes/bursts detection
Freq./phase
Statisitics …

Communication protocol

(High level) processing

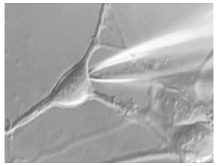
Control/storage

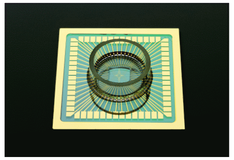
On-line

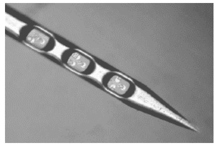
Off-line

Closed-loop : artificial ➔ biology

Electrodes







Stimulation: electrical, mechanichal, chemical

Control/trigger:
- from inputs (sensors)
- from high level proc.
- patterned

-- …

Control/storage

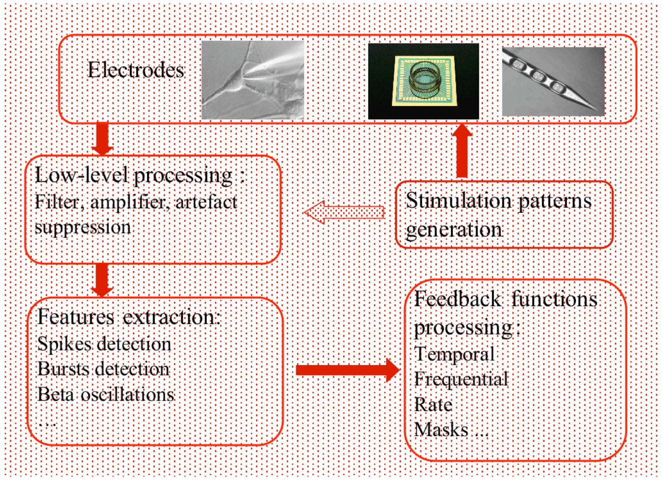
Communication protocol

High level processing

On-line

Off-line

Closed-loop : a modular approach



• Process « neural information »
What is information?
Which processing? bio-inspired? task-inspired?

• Process data in « biological real-time »:
Define « real-time »?

• Processing material:
Hardware?
Software?
Mixed?

Closed-loop : a modular approach

• Process « neural information »
What is information?
Which processing?

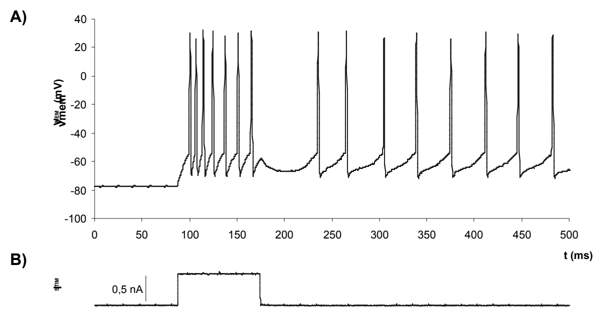
Temporal Coding

Discrete Time, Discrete Signal

1	*0*	*0*	*1*	*1*	*0*	*0*	*0*	*0*	*1*

Continuous Time, Discrete Signal

Continuous Time, Continuous Signal



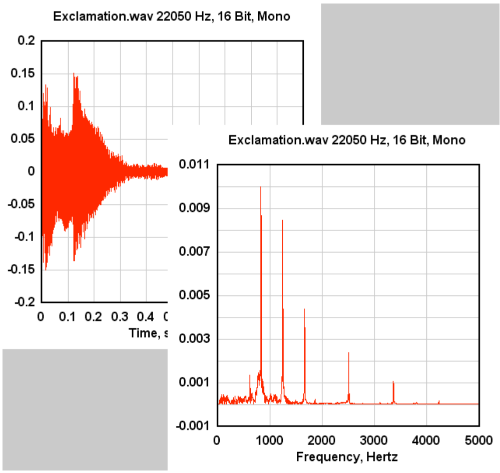
Sarpeshkar, Neural Computation, 1998

Closed-loop : a modular approach

• Process « neural information »

What is information?

Which processing?

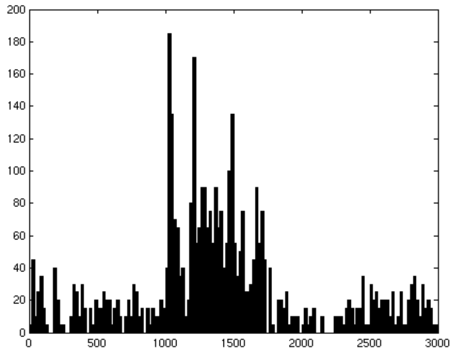


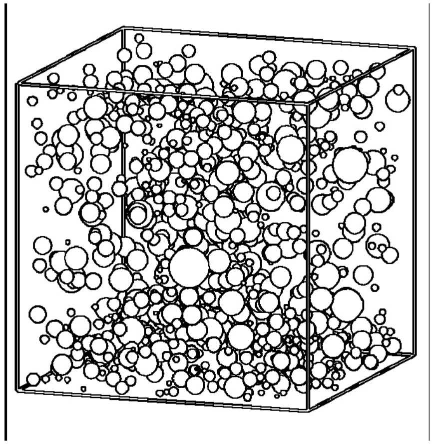
✓ *Bio-mimetic neural network…*

✓ *Frequency analysis….*

✓ *Time-frequency analysis (frequency-varying signals)…..*

✓ *Statistics, classification (spatial)….*





Closed-loop : a modular approach

• Process data in « biological real-time »

What is real-time?

✓ *Temporal processing:*

. Analog HW: identical kinetics

. Digital HW, SW:

- fix the sampling rate, process data between 2 samples;

- average real-time over a fixed period

✓*Other processing methods;*

. Define the maximum feedback delay

Need for specifications…

Closed-loop : a modular approach

Processing material: the implementation issues

- *Software: on-line, off-line*

- *Hardware: on-line*

  - ❖ *digital*
  - ❖ *analog*
  - ❖ *mixed*

  - ✓ *single-chip*
  - ✓ *multi-chips*

✓ *Embedded*
✓ *Discrete modules*

Need for specifications…

- *Configurability*

The story ….

- ✓ Neuro-electronics interfaces
- ✓ The closed-loop approach
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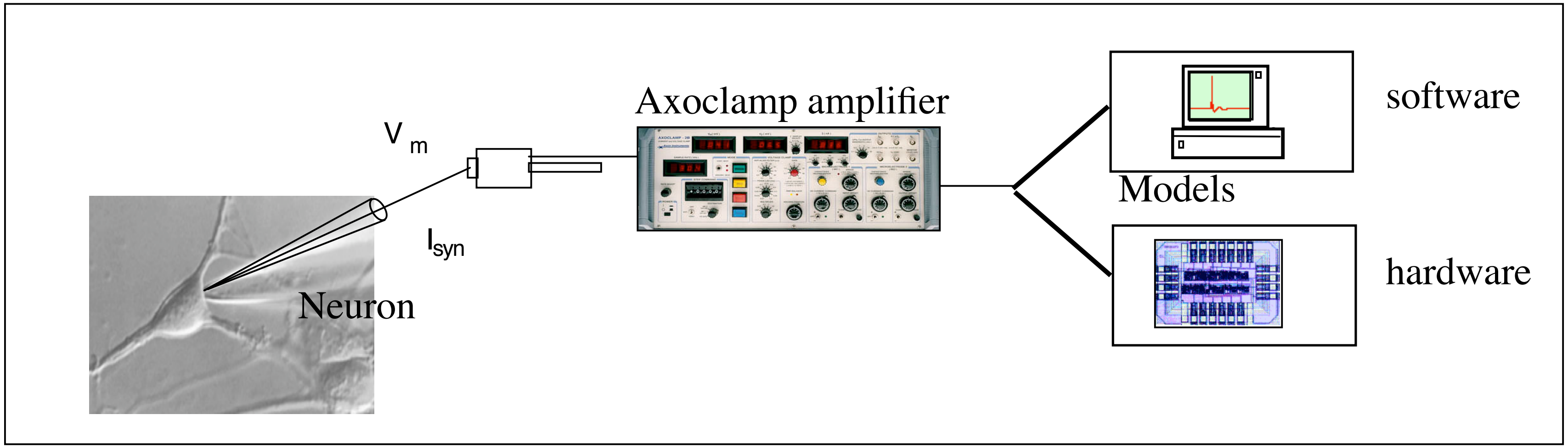
Hybrid networks at the single cell level

Dynamic clamp or hybrid neural networks (conductance-based models)

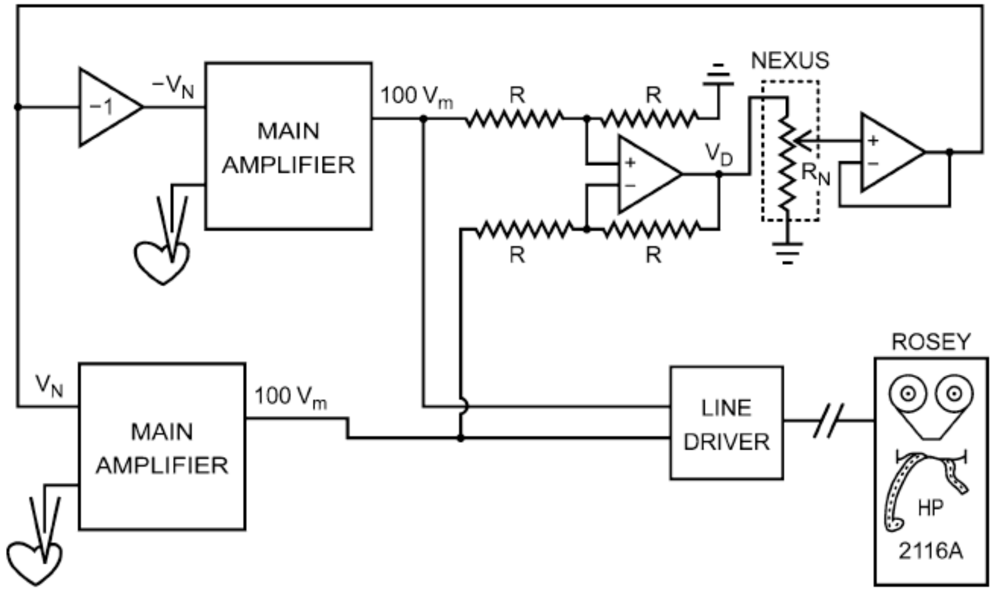
Synaptic connections (computed on HW or SW):

- from artificial to living: $I_{syn1} = g_{syn1}(V_{pre}) \cdot (V_{post} - V_{equi})$
- from living to artificial: $I_{syn2} = g_{syn2}(V_{pre}) \cdot (V_{post} - V_{equi})$



A. Sharp, E. Marder, Brandeis U.
G. Le Masson, INSERM Bx

Back in time: The first dynamic clamp

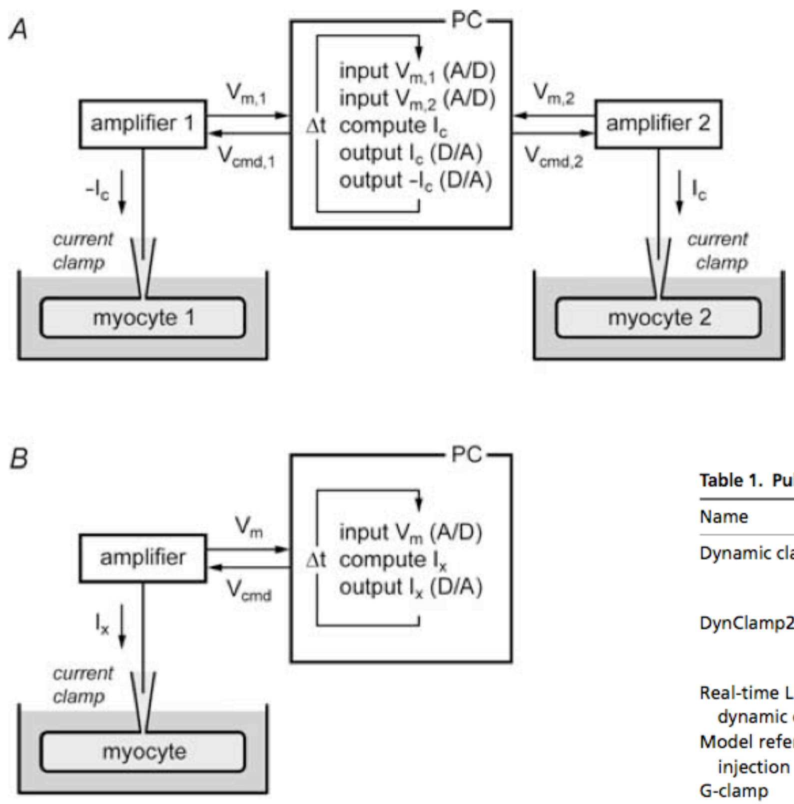


Block diagram of the first « dynamic clamp » set-up (from Scott, 1979): Synchronisation of 2 small clusters (100 μm) of spontaneously active embryonic chick ventricular cells. The analog circuit generates positive and negative command potentials proportional to the difference of membrane potentials between the 2 clusters. These command potentials are sent to the main amplifiers to let them inject a « nexus current » so that they are coupled by an equivalent « nexus resistance ».The HP « minicomputer » only records the 2 membrane potentials.

Nexus = link, tie

R. Wilders, 'Dynamic clamp' in cardiac electrophysiology, J Physiol. 2006; 576; 349-3599

Now: Dynamic clamp software



Standard dynamic clamp configurations

Software solutions compatible with custom or commercial hardware (any excitable cell)

Table 1. Publicly available dynamic clamp software

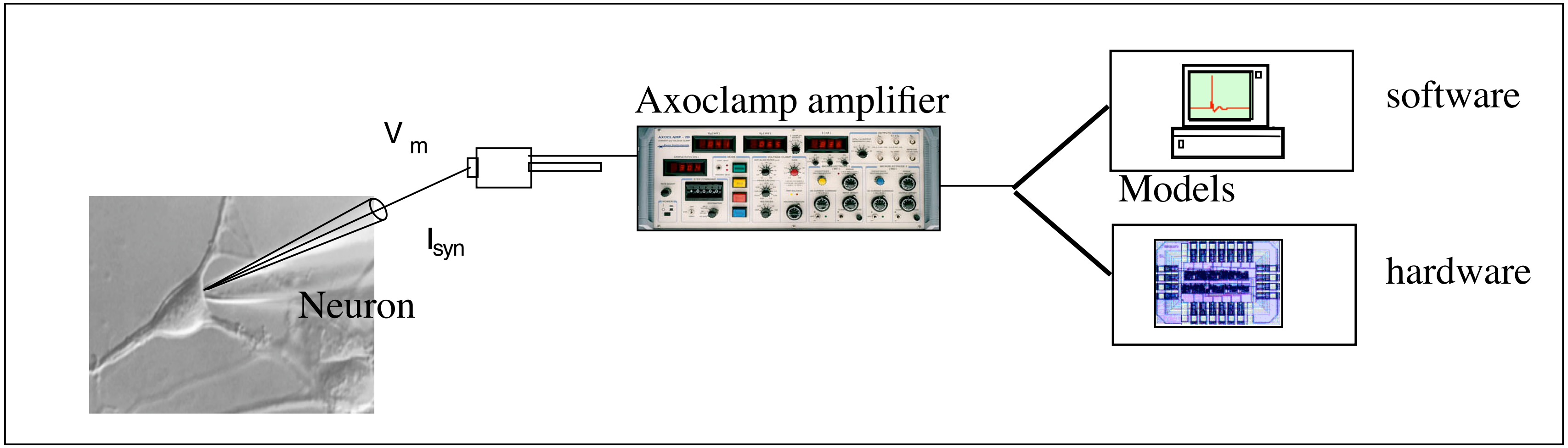
Name	Reference	Configuration*	Platform	Notes
Dynamic clamp	Manor & Nadim (2001)	A,B	Windows	Available at http://stg.rutgers.edu/ Requires National Instruments data acquisition board
DynClamp2	Pinto *et al.* (2001)	A,B	Windows	Available at http://inls.ucsd.edu/~rpinto/ Requires Axon Instruments Digidata 1200A data acquisition board
Real-time Linux dynamic controller (RTLDC)	Dorval *et al.* (2001)	B	RT-Linux	Available at http://www.bu.edu/ndl/
Model reference current injection (MRCI)	Butera *et al.* (2001), Raikov *et al.* (2004)	B	RT-Linux	Available at http://www.neuro.gatech.edu/mrci/
G-clamp	Kullman *et al.* (2004)	B	Windows	Available at http://hornlab.neurobio.pitt.edu Requires National Instruments LabVIEW-RT hardware and software components
Advanced dynamic clamp	Muñiz *et al.* (2005)	B	RT-Linux	Available at http://www.ii.uam.es/~gnb/adclamp
DynaClamp	Berecki *et al.* (2005, 2006)	C	RT-Linux	Available at http://www.physiol.med.uu.nl/dynaclamp/

*A, B and C refer to the dynamic clamp configurations of Fig. 2*A*, *B* and C, respectively.

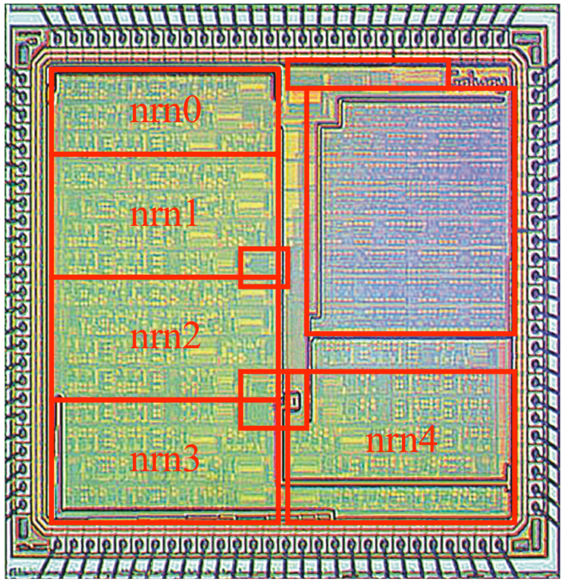
R. Wilders, 'Dynamic clamp' in cardiac electrophysiology, J Physiol. 2006; 576; 349-3599

Hybrid networks at the single cell level

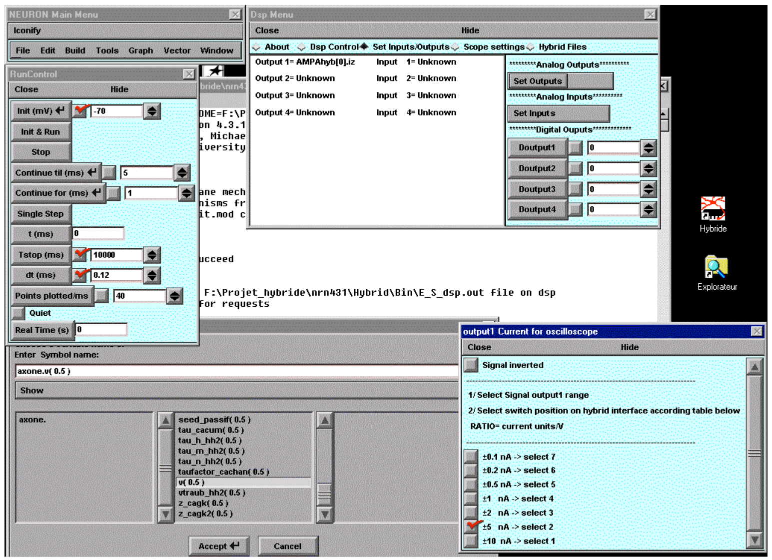
Dynamic clamp or hybrid neural networks (conductance-based models)



Configurable HH-neuron ASIC



RT-Neuron software *(M. Hines)*



Hybrid networks at the single cell level - Example 1

Investigation of rythmic pattern generation

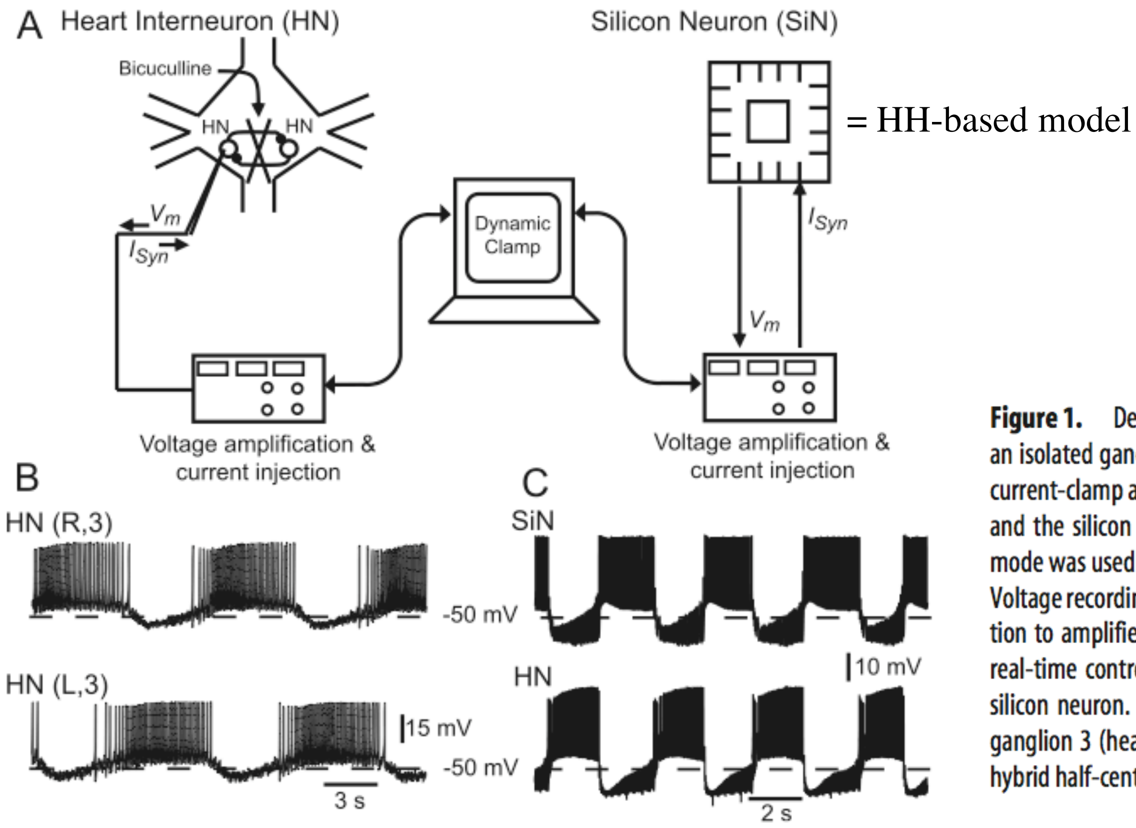
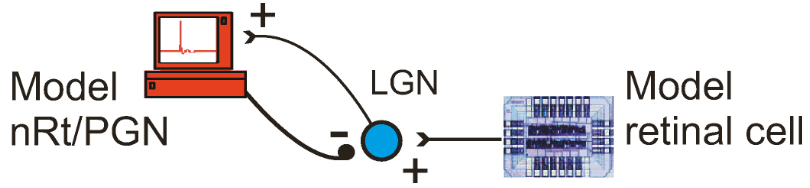


Figure 1. Design and activity of hybrid half-center oscillator. *A*, Heart interneurons (HN), in an isolated ganglion preparation, were pharmacologically isolated with bicuculline. Voltage/current-clamp amplifiers were used for recording and current injection into heart interneurons and the silicon neuron (SiN). A single sharp microelectrode in discontinuous current-clamp mode was used for voltage recording and current injection into an isolated heart interneuron. Voltage recording and current injection into the silicon neuron were provided by direct connection to amplifier headstages (two-electrode current-clamp mode). Dynamic clamp provided real-time control signals to create artificial synapses between a heart interneuron and the silicon neuron. *B*, Activity of a living heart interneuron half-center oscillator in an isolated ganglion 3 (heart interneurons indexed by body side and ganglion number). *C*, Activity of a hybrid half-center oscillator.

M. Sorensen, S. DeWeerth, G. Cymbaliuk,R. Calabrese , Using a hybrid neural system to reveal reguation of neuronal activity by an intrinsic current, J Neuroscience. 2004; 24(23); 5427-5438.

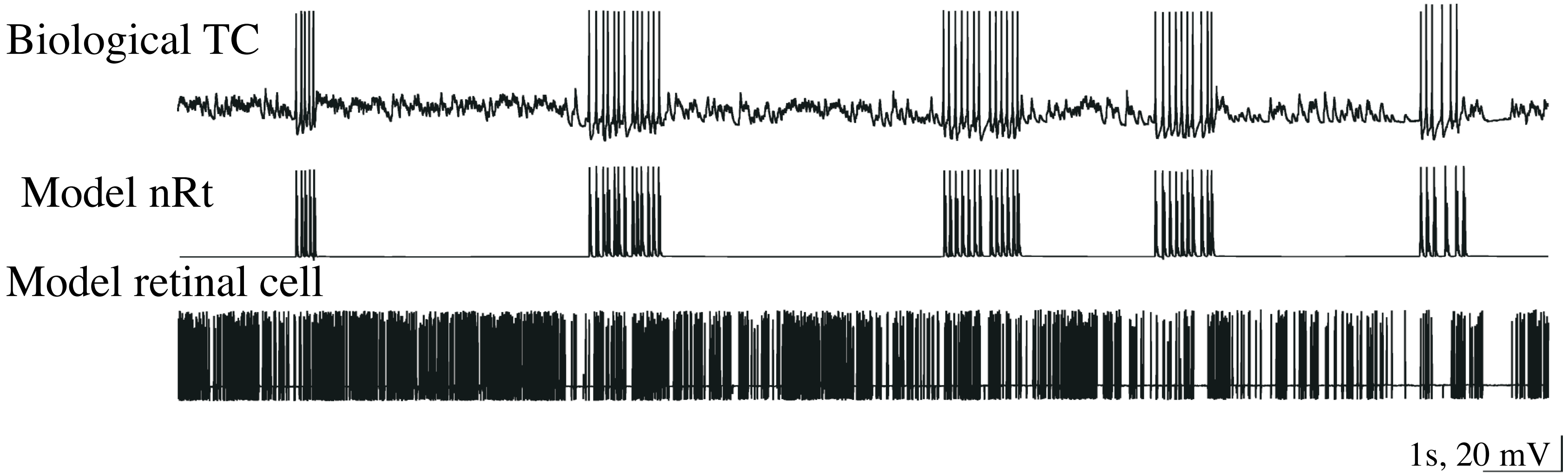
Hybrid networks at the single cell level - Example 2

Artificial = Software AND Hardware



« A retinal cell spike induces an EPSP in the TC cells, which triggers itself bursts of spike in the nRt/relay cells »

Le Masson and al, Nature (INSERM Bx, UNIC Gif/Yvette)



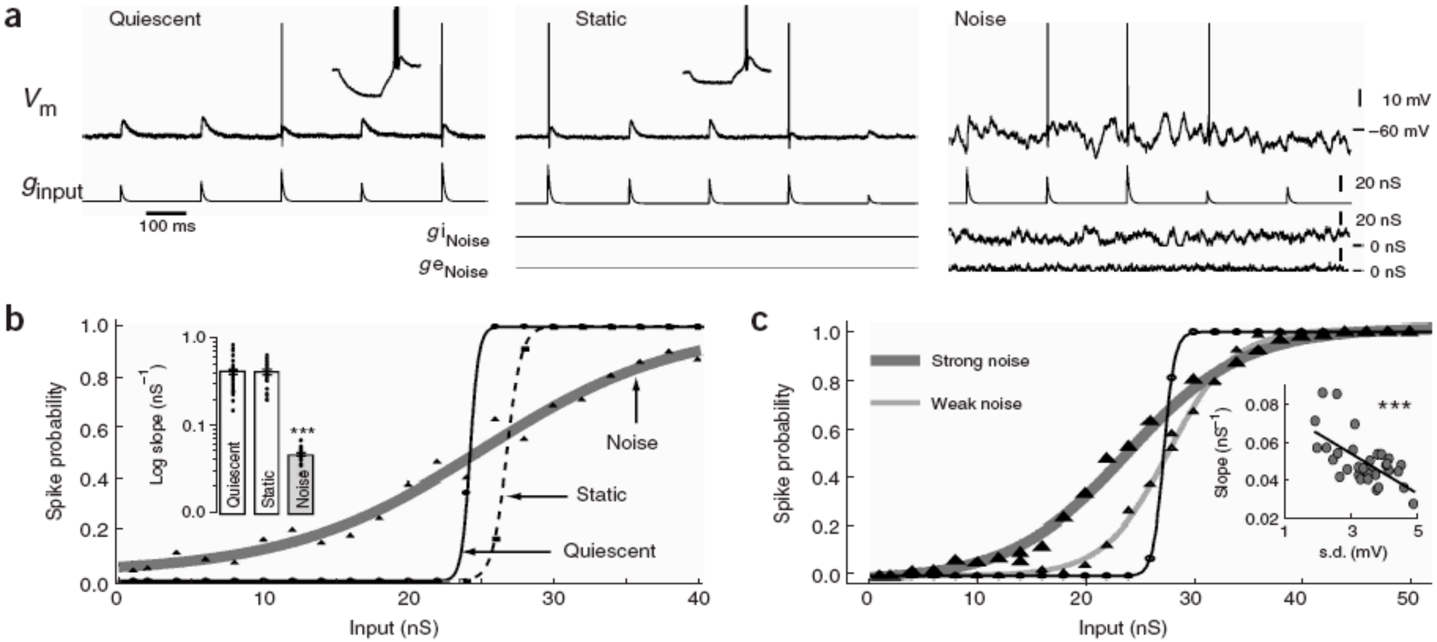
« Synaptic background activity controls spike transfer from thalamus to cortex »

Wolfart and al, J.Physiol.

Hybrid networks at the single cell level - Example 3

<u>Hypothesis:</u>
Thalamocortical feedback exerts its function by using a separate channel of modulatory information: the variance of background synaptic input (originating from cortex).

Dynamic clamp set-up (RT-Neuron software+DSP)



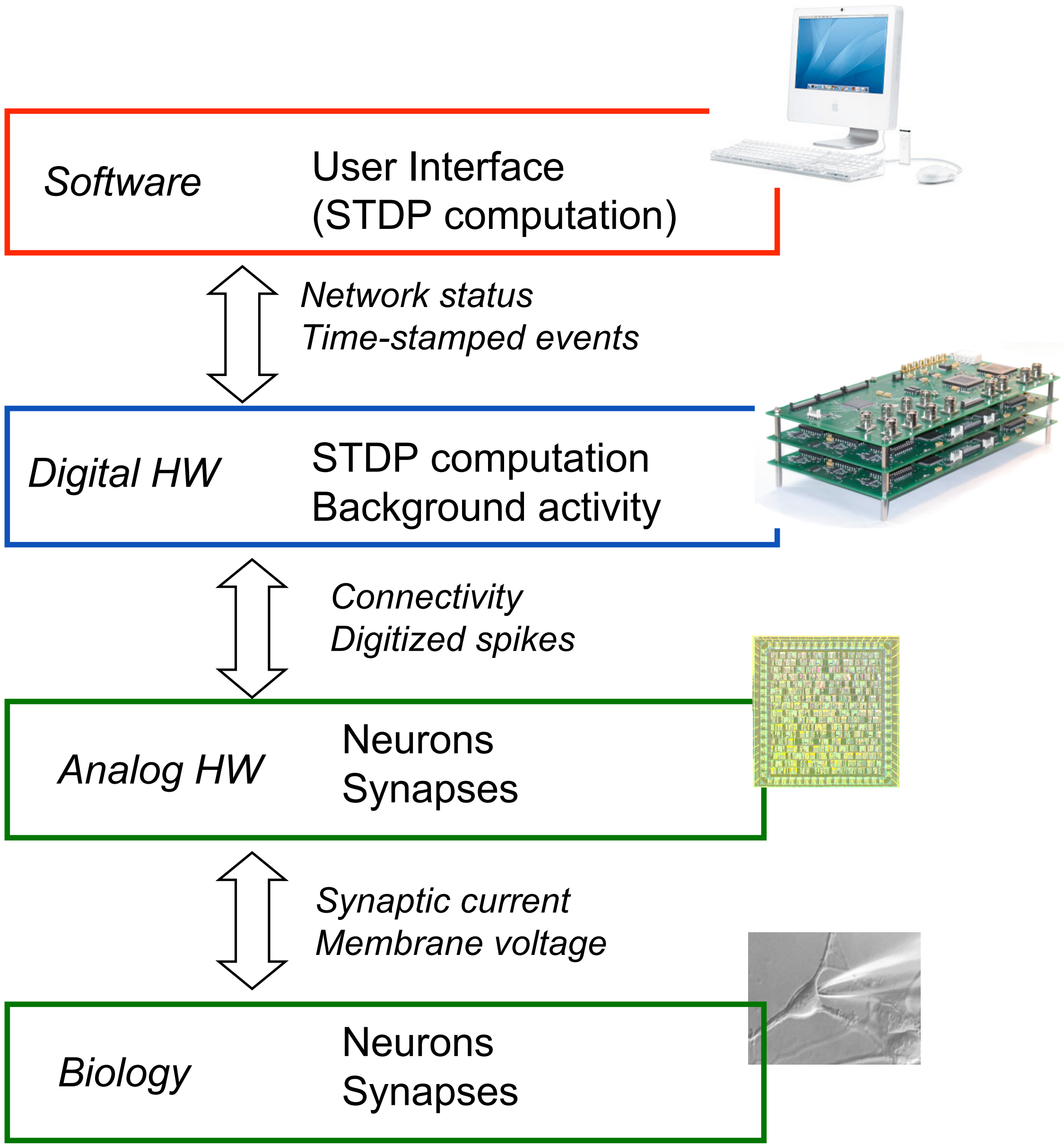
The influence of synaptic noise changes the transfer function of thalamocortical cells recorded in vitro. **a)** Voltage during injection of g_{input} (quiescent), inh.+exc. noise inputs (static), stochastically fluctuating noise inputs (noise); **b)** probabilities of input g to evoke ≥1 spike, fitted by a sigmoïd; **c)** decreasing the variance of noise increased the sigmoïd slope.

J.Wolfart et al., 'Synaptic background activity controls spike transfer from thalamus to cortex , Nature Neuroscience, 2005, 8-12, 1760-1766.

The future: Hybrid networks at the « small network » level

Artificial = Software AND Hardware

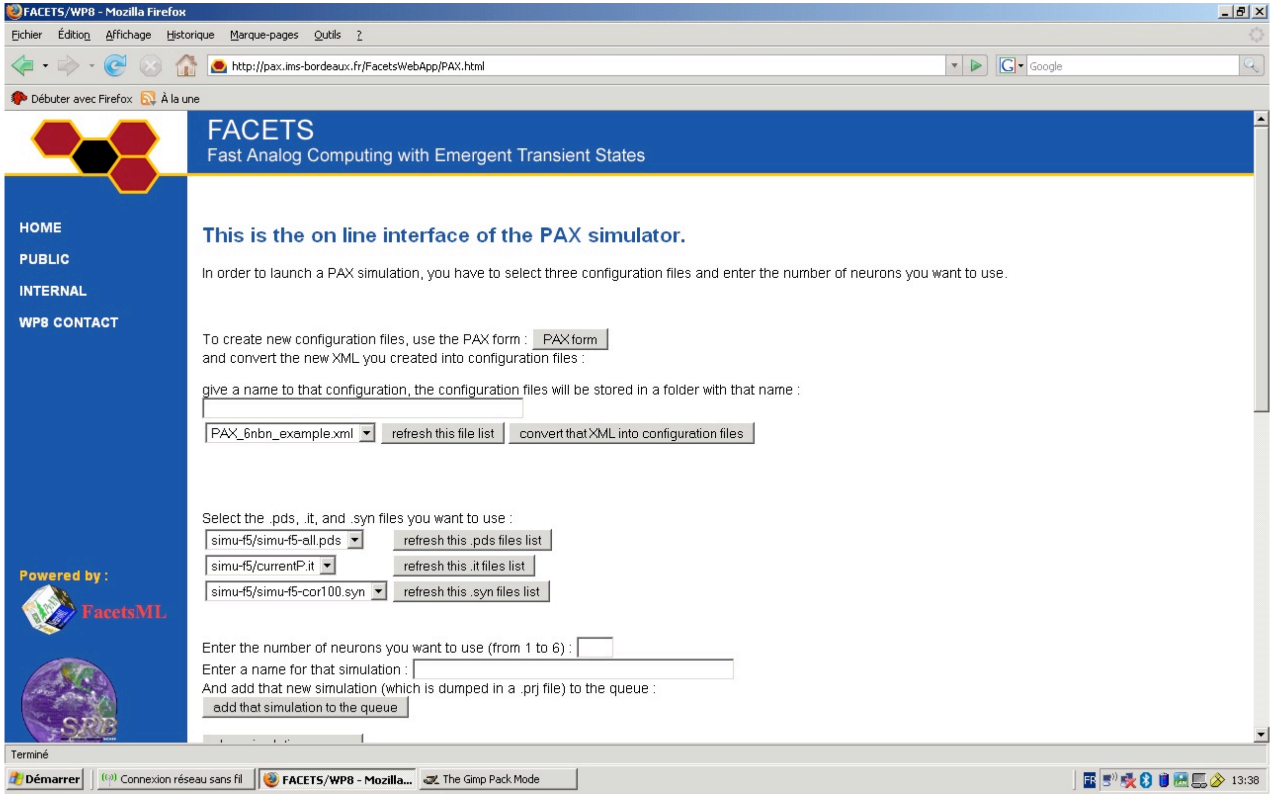
FACETS experimental set-up
(« single-cell » stream):
A tool to explore STDP
in spiking NN



Facets EU FET project -
http://facets.kip.uni-heidelberg.de

The future: Hybrid networks at the « small network » level

Artificial neurons = analog hardware
Connectivity = digital hardware
Network model = PyNN



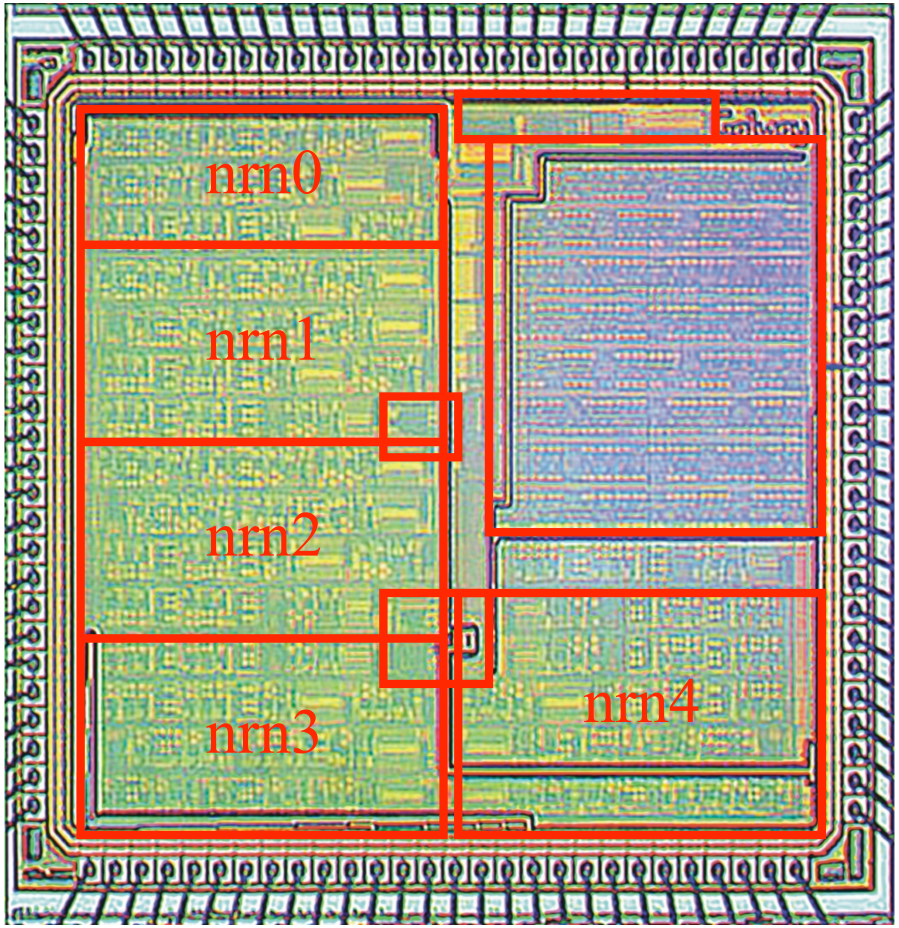
PyNN:
Python package for SNN specifications (http://neuralensemble.org/trac/PyNN)

(Python is a dynamic object-oriented programming language)

Facets EU FET project - http://facets.kip.uni-heidelberg.de/

The future: Hybrid networks at the « small network » level

Analog Hardware: HH configurable neurons



Example: *Galway* chip

Analog:
42 ionic and synaptic conductances /chip
(max 5 membranes)
Memory:
204 analog dynamic memory cells
Digital:
Topology and parameters control

BiCMOS technology
10,5 mm²
50k elements
105 pads

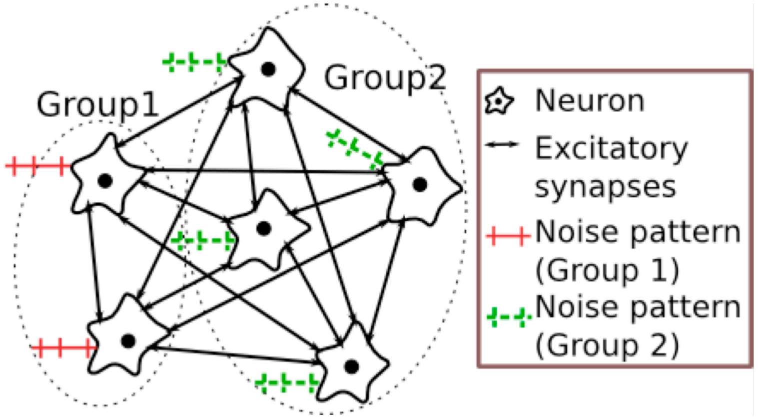
The future: Hybrid networks at the « small network » level

Plasticity model: STDP (from Badoual et al. , 2006)

$$\frac{dw_{ji}}{dt} = -\varepsilon_j \varepsilon_i \left[\left(w_{ji} - w_{LTP} \right) \sum_k P\left[t - \tilde{t}_j(t) \right] \varepsilon\left(t - t_{i,k} \right) + \left(w_{ji} - w_{LTD} \right) \sum_l Q\left[t - \tilde{t}_i(t) \right] \varepsilon\left(t - t_{j,l} \right) \right]$$

Potentiation, Depression, Soft bound, Eligibility factors

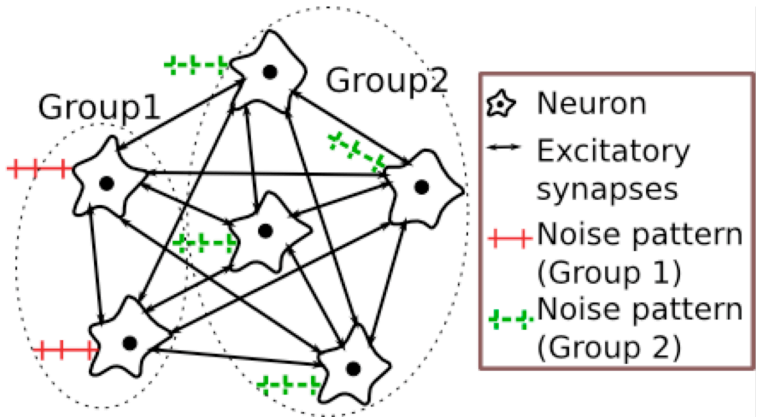
Experiment (HW 3-conductances neurons):



The future: Hybrid networks at the « small network » level

A network of cortical neurons receives « background activity » stimulation.
-> Investigate the weights convergence depending on the stimuli correlation

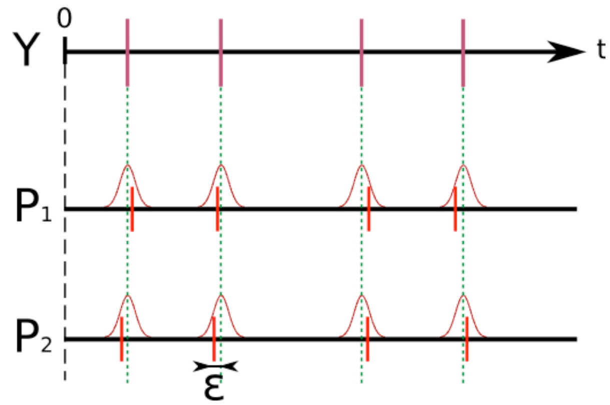
6 HW neurons (3-conductances).
All synapses follow a STDP rule.



Noise patterns:

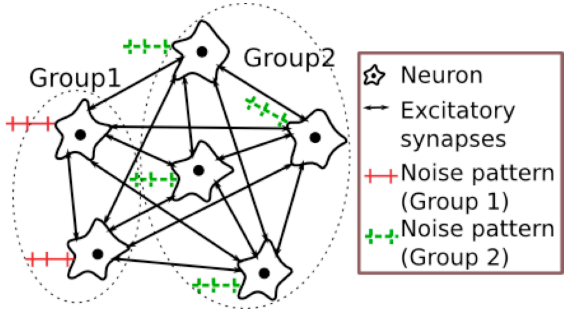
Reference pattern (Poisson, freq. F)

Stimulation patterns (correlation ε)



The future: Hybrid networks at the « small network » level

Experiment (HW 3-conductances neurons):



Representation of the weights convergence: *param1 vs param2*

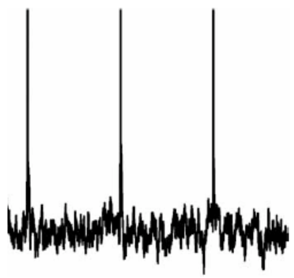
Unpublished data

For each group of plots, left is the normalized weights distribution histogram, right is the *param1* vs *param2* plot. *Top-left*: bimodal convergence, (*x*, *f(x))* tends to (0.5, 0.5). *Top-right*: minimized convergence, (*x*, *f(x))* tends to (1, 0). *Bottom-left*: confined convergence, (*x*, *f(x))* tends to (0, 0). *Bottom-right*: maximized convergence, (*x*, *f(x))* tends to (0,1).

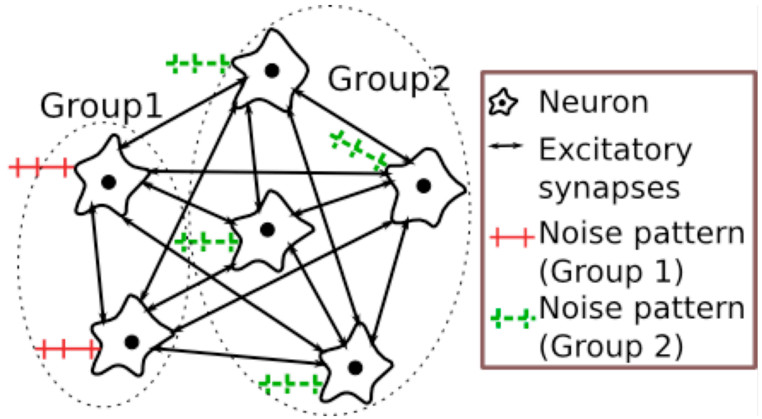
The future: Hybrid networks at the « small network » level

Hypothesis (Bal et al.):
Thalamocortical feedback exerts its function by using a separate channel of modulatory information: the variance of background synaptic input (originating from cortex).

Investigation to come using closed-loop experiments:
Effects of distributed synaptic background activity on the thalamocortical feedback



Thalamocortical cell



The story ….

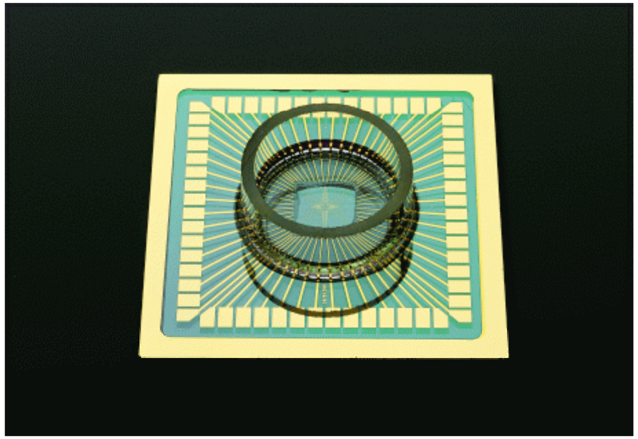
- ✓ Neuro-electronics interfaces
- ✓ The closed-loop approach
- ✓ Single-cell level interactions
- ✓ Network scale level interactions
- ✓ Multi-modal systems

Hybrid systems at the network level

MEA (multi-electrode arrays): microfabricated grid of electrodes,
parallel pre-processing units (1 /channel)

☺ : Spatial resolution

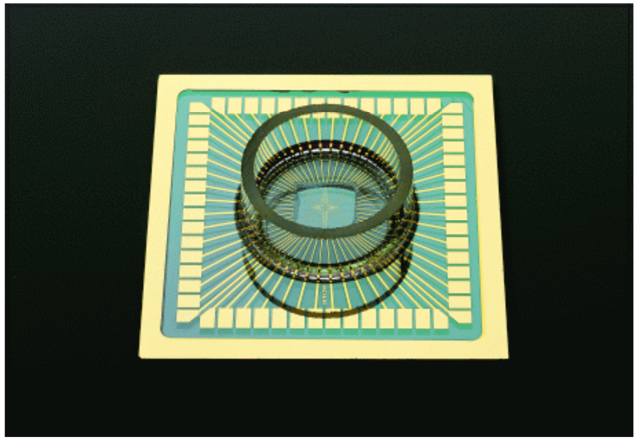
😐: Extra-cellular electrodes records the electric field induced by ionic currents



Minimize the pitch
(electrodes+pre-processing)

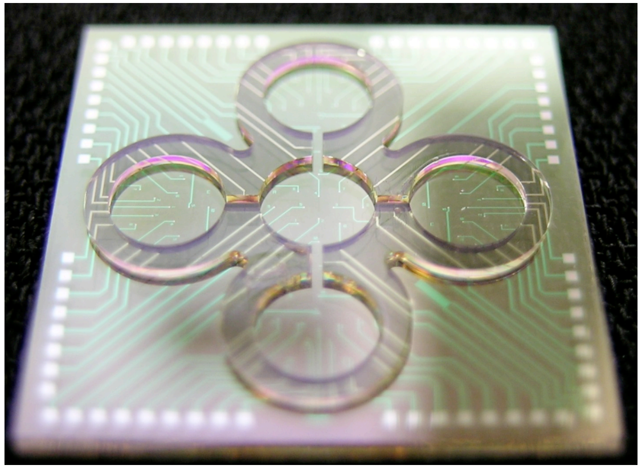
Hybrid systems at the network level

Standard MEA



MultiChannelsSystems
MEA 64 - up to 1k channels

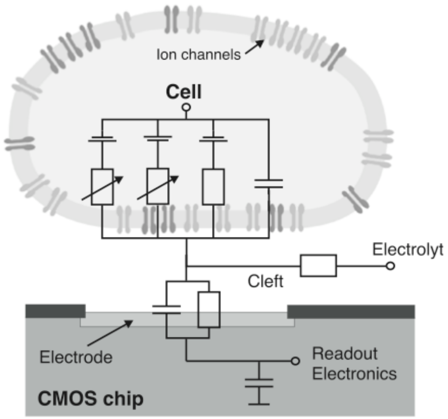
Clustered MEA

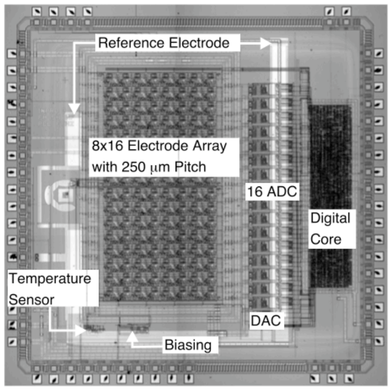


L. Berdondini,
M. Kudelka
IMT Neuchatel

3D active MEAs

Active arrays





PEL, ETH Zurich

Unpublished data

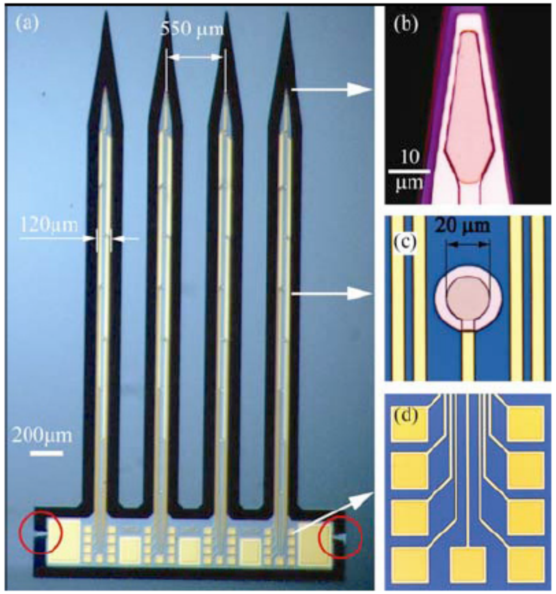
ESIEE, Cergy-Pontoise

In vivo: modular BMI

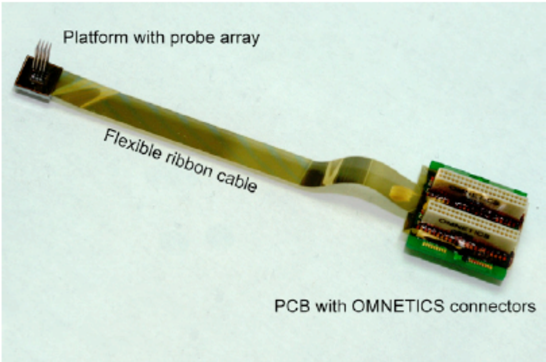
Neuroprobes EU project:

« develop a system platform based on multi-electrode arrays that will allow an extremely wide series of innovative diagnostic and therapeutic measures for the treatment and for the scientific understanding of cerebral systems and associated diseases »

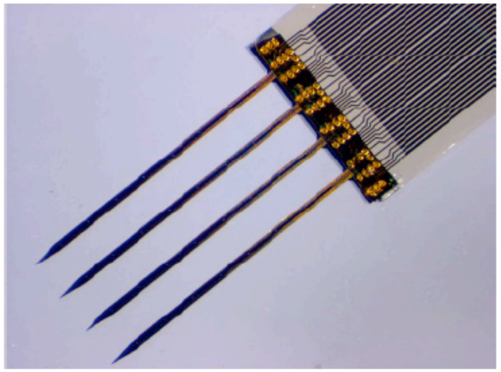
« Probes are assembled in a Lego fashion that permits to combine probes with different functionalities, shapes and sizes on a common backbone. Amplifiers are reported on the probes PCB»



Probe comb details



Complete system assembly



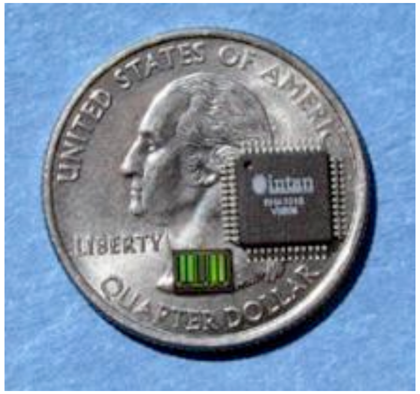
Single-comb assembly

Coordinators: IMEC (BE), IMTEK Freiburg, Univ. Leuven (Be)

http://naranja.umh.es/~np/

Hybrid systems at the network level

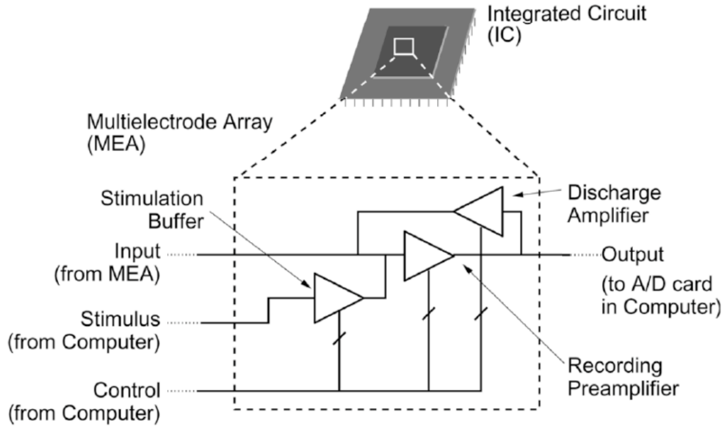
Low-level processing: on chip amplifiers, filters, spike detection …



Integrated, low-power amplifier array from Intan Technologies. This single-chip device contains 16 fully-differential amplifiers with programmable bandwidths suitable for many bioinstrumentation monitoring and recording applications.

Intan Tech. is a spin-off of R. Harrison (Univ. Utah)

Simultaneous multichannel stimulation and recording: arbitrary configuration of electrodes, preamplifiers, artifact blanking

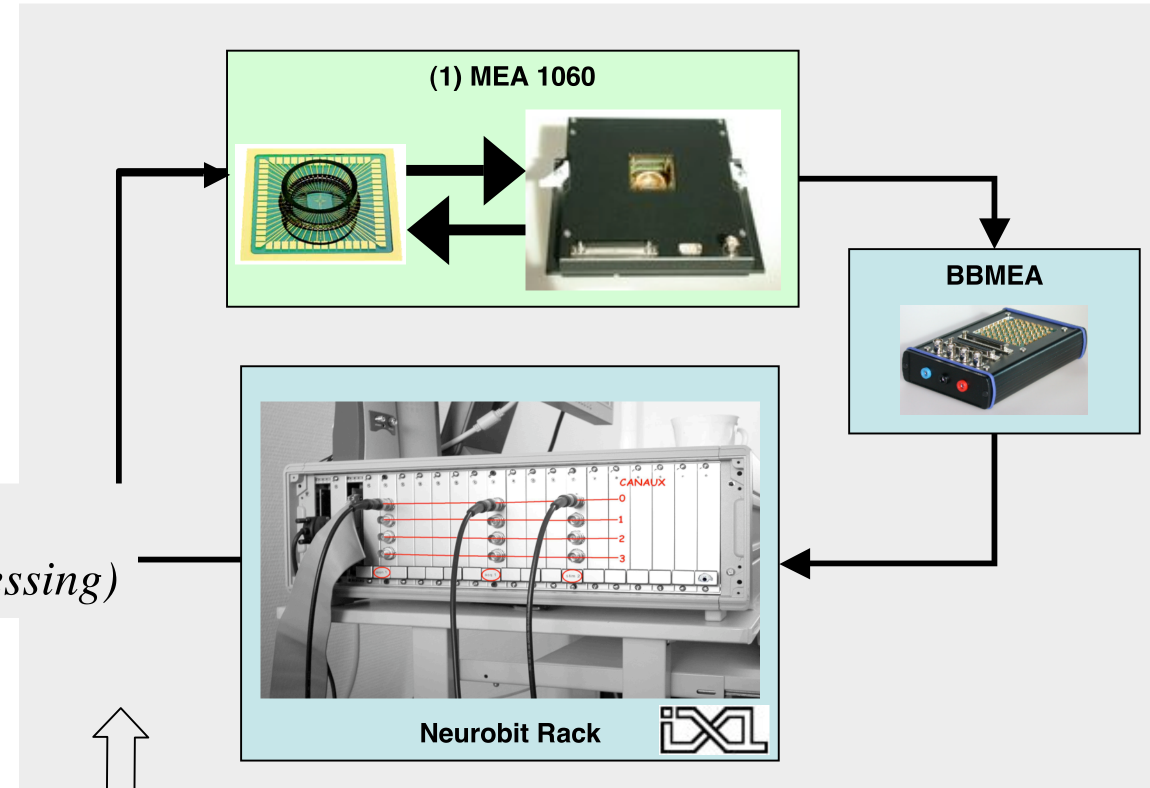


Blum et al, 2007

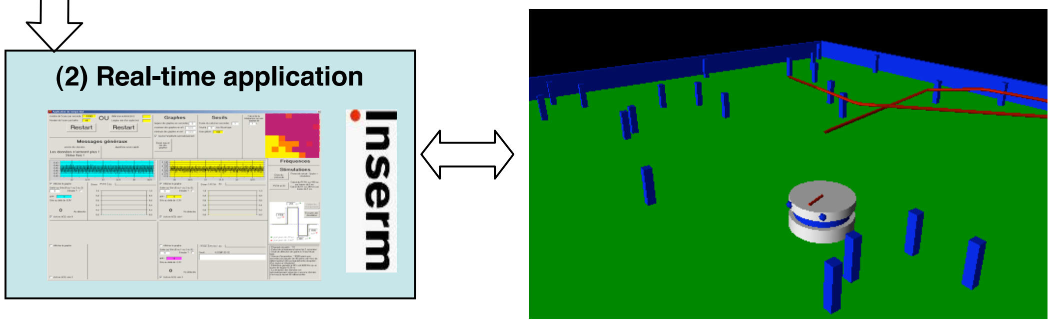
Hybrid systems at the network level: example

A closed-loop set-up to study the dynamics and learning of embodied living systems in a simple sensory-motor loop

Hardware (pre-processing)



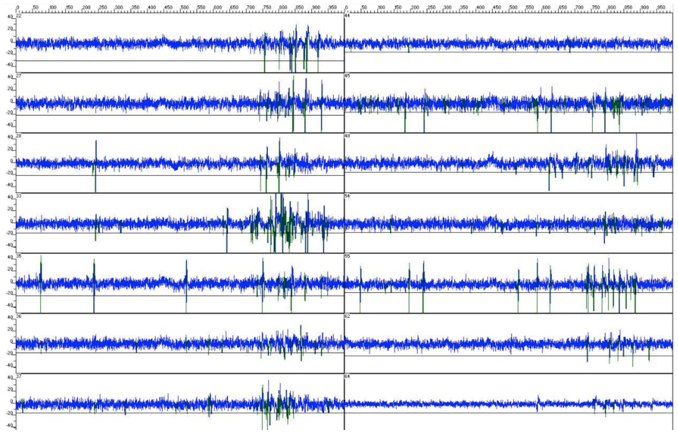
Software (on-line and off-line processing)



Neurobit /IDEA EU projects - M. Koudelka, IMT Neuchatel
(see also Martinoia - U. Genova; Potter - Georgia Tech)

Hybrid systems at the network level: example

Recordings



+

MEA sites

A. Garenne - INSERM/CNRS Bx (submitted)

+

On-line Burst Phasing Protocol (BPP)

Unpublished data

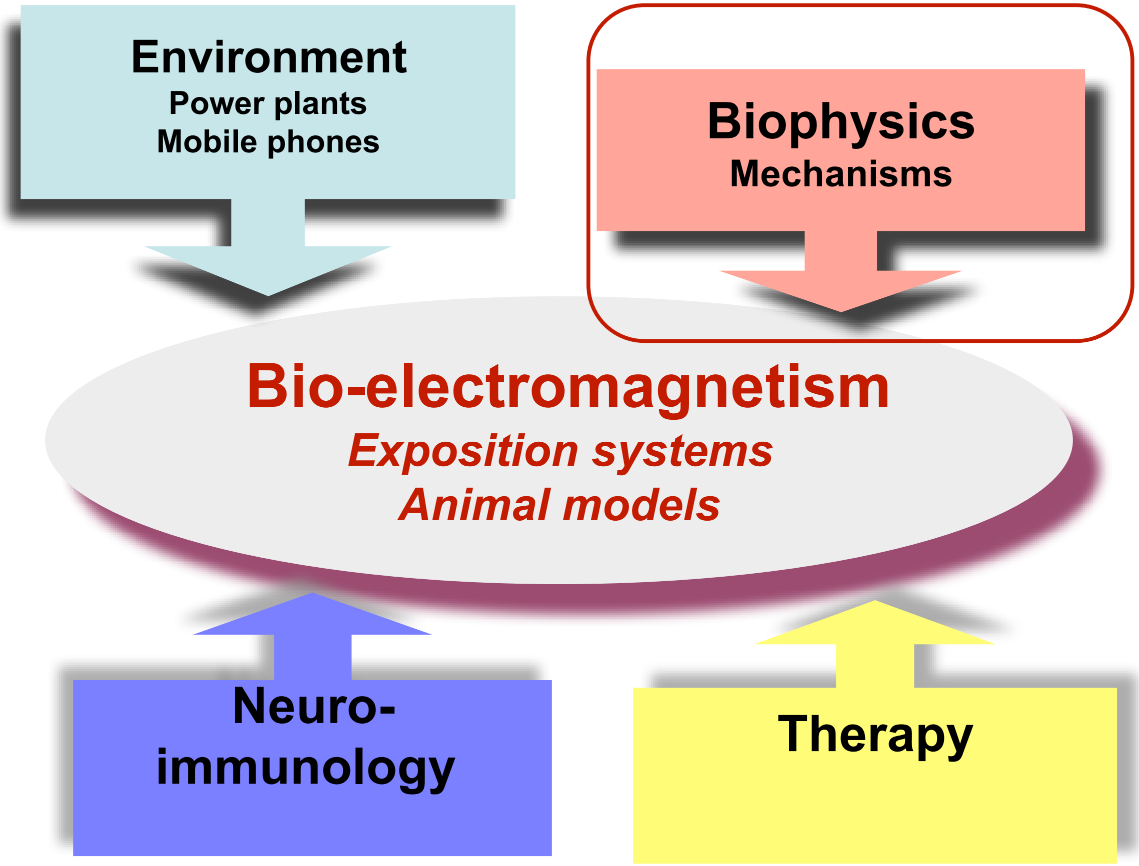
=

Culture adaptation

Unpublished data

Hybrid systems at the network level: example 2

Bio-Electro-magnetism (Bio-EM)



Project CNRS/ Fondation Santé et RF
B. Veyret (IMS Bordeaux)
A. Del'Angelo (Univ. Roma)

Hybrid systems at the network level: example 2

Bio-EM interaction mechanisms: investigate and model effects of low-power microwaves on culture networks of cortical cells.

Unpublished data

Integration constraints:

- Configurability

- Isolated and EM robust HW modules

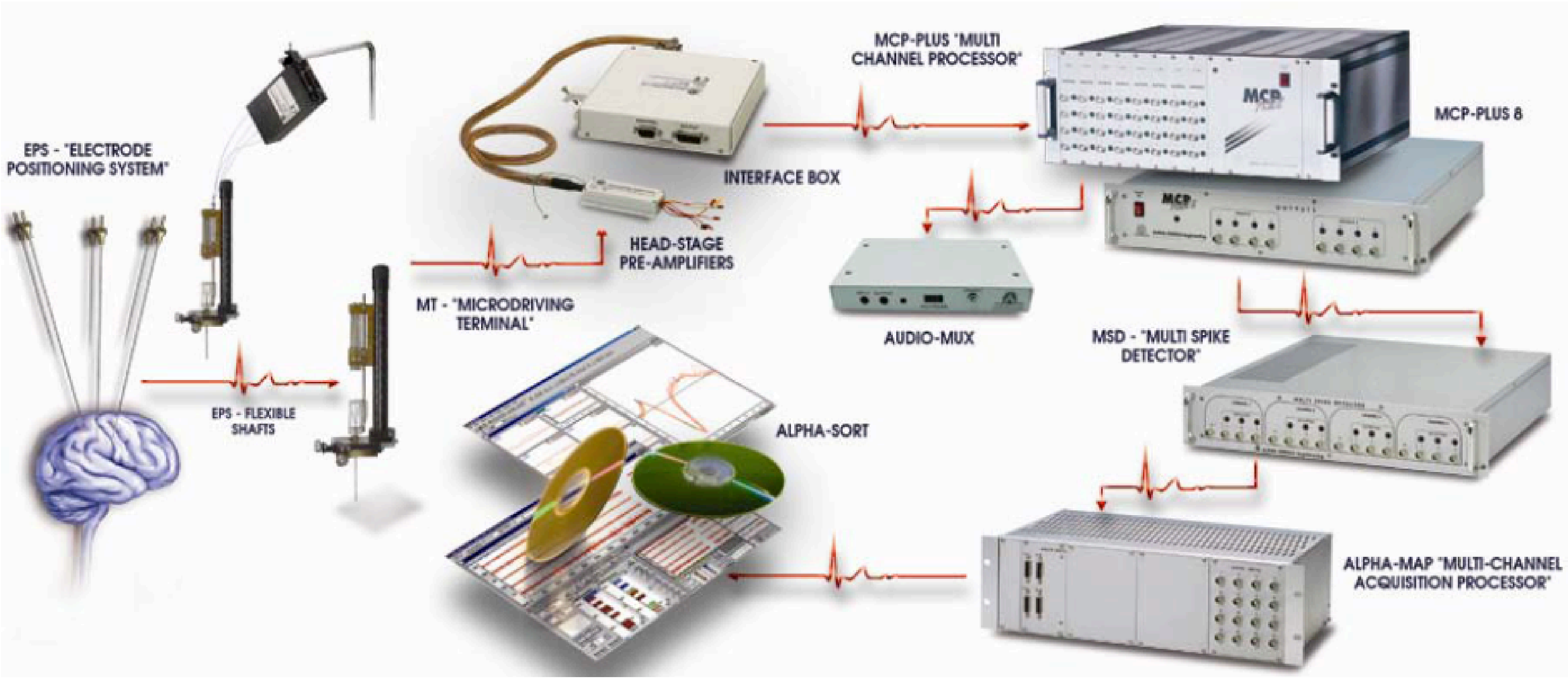
Project CNRS/ Fondation Santé et RF

B. Veyret (IMS Bordeaux)

A. Del'Angelo (Univ. Roma)

Hybrid systems at the network level: the DBS case

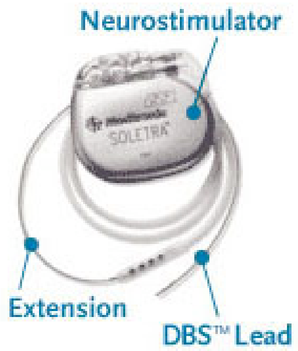
Principle: send electrical impulses to specific parts of the brain



http://www.alphaomega-eng.com

Hybrid systems at the network level: the DBS case

DBS Principle: send electrical impulses to specific parts of the brain



http://www.medtronic.com

DBS to control Parkinson symptoms:

Neurosurgery:
HFS (130Hz), parameters controlled by the surgeon

Neuroscience:
STN (sub-thalamic nucleus) activity-dependent stimulation
LPF (local field potential): filtered activity of a population through a low-impedance electrode

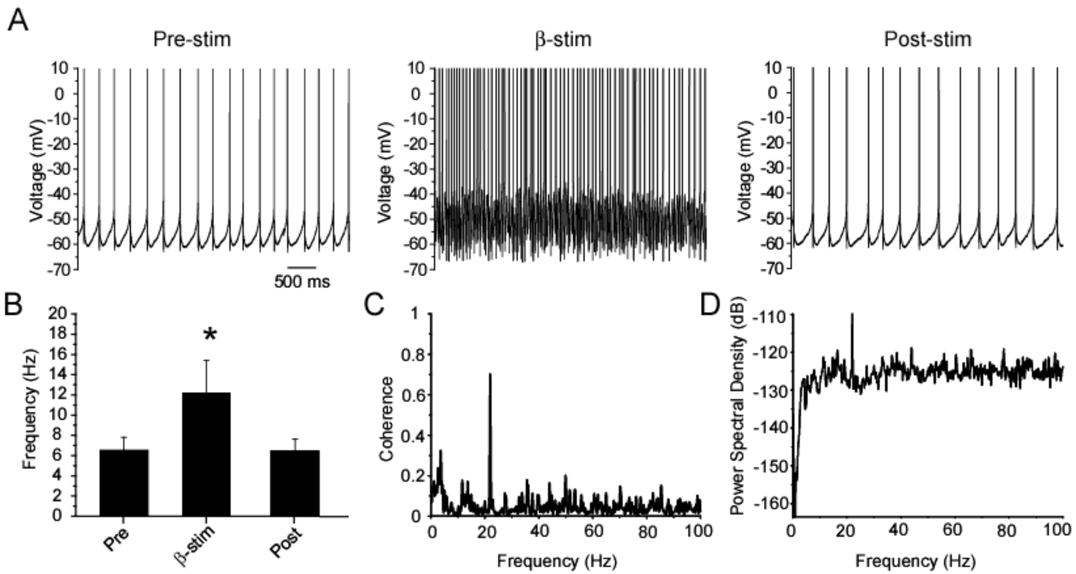
Adaptive stimulation -> Closed-loop BMI

Hybrid systems at the network level: the DBS case

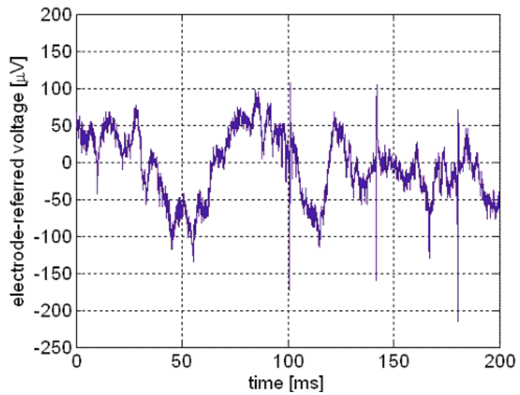
In vitro/in vivo hybrid networks for exploring oscillations in the STN network

Hypothesis:
"oscillations of STN neurons in beta band frequency contribute to the emergence of parkinsonian motor symptoms"

Method:
Cancel on-line the beta-band oscillations using dedicated analog electronics



In vitro experiments: LFP stimulation drive STN neurons activity in the beta band frequency in vitro

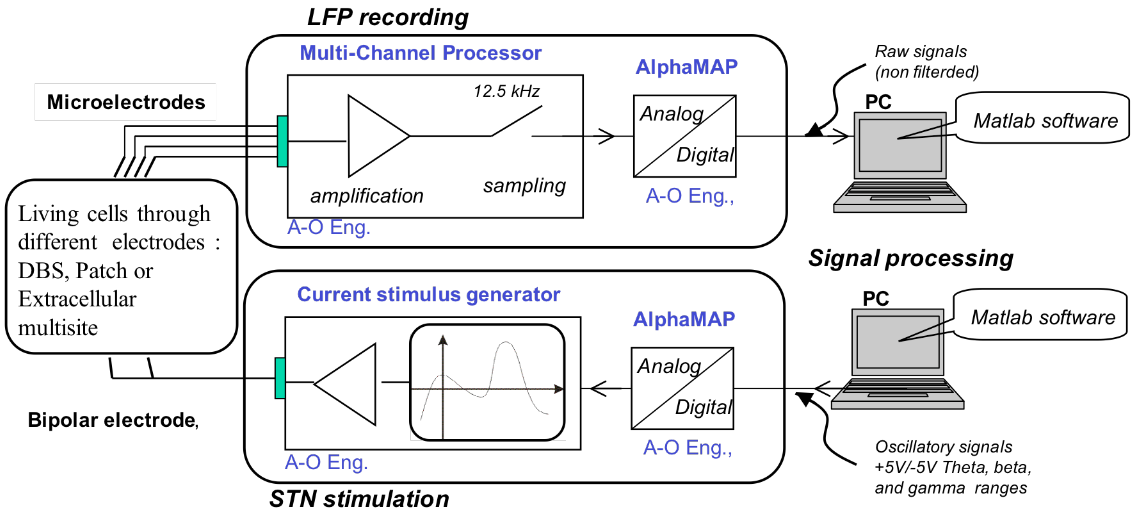


To come: In vivo experiments

A. Benazzouz, T. Boraud
CNRS/CHU Bordeaux

Hybrid systems at the network level: the DBS case

Actual set-up:
(in vitro, in vivo)



Under construction set-up :

Unpublished data

See also Foffani,
Milano/Philadelphia

The story ….

- ✓ Neuro-electronics interfaces
- ✓ The closed-loop approach
- ✓ Single-cell level interactions
- ✓ Network scale level interactions
- ✓ Multi-modal systems

Multi-modal hybrid systems: non-electrical sensors

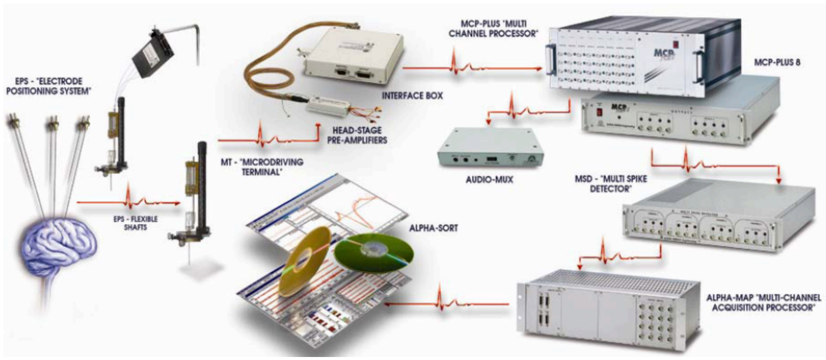
Closed loop configuration:

Control: electrical signals
Sensors (symptoms) ?

- Electrodes

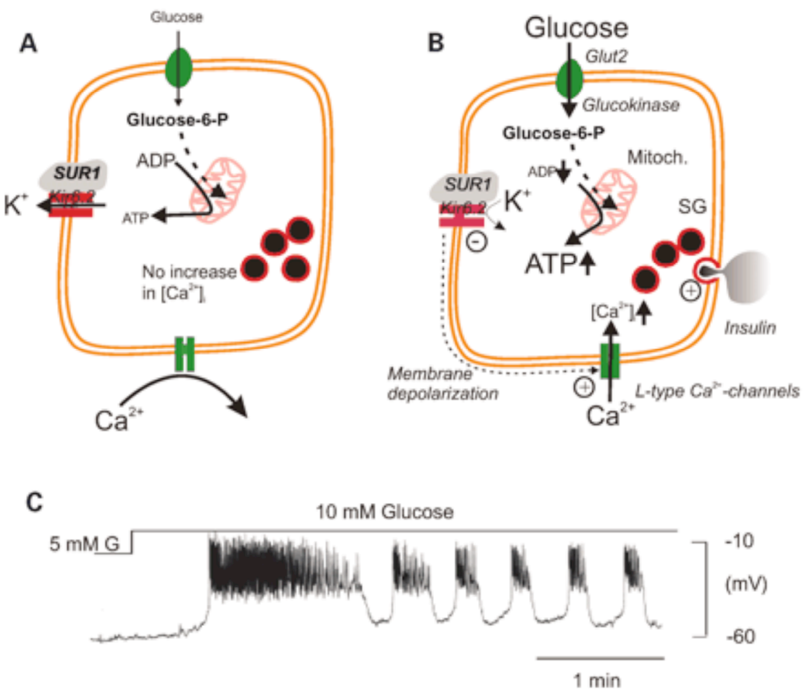
or

- Electro-mechanical sensor (rigidity,tremor)
- Neuro-imaging

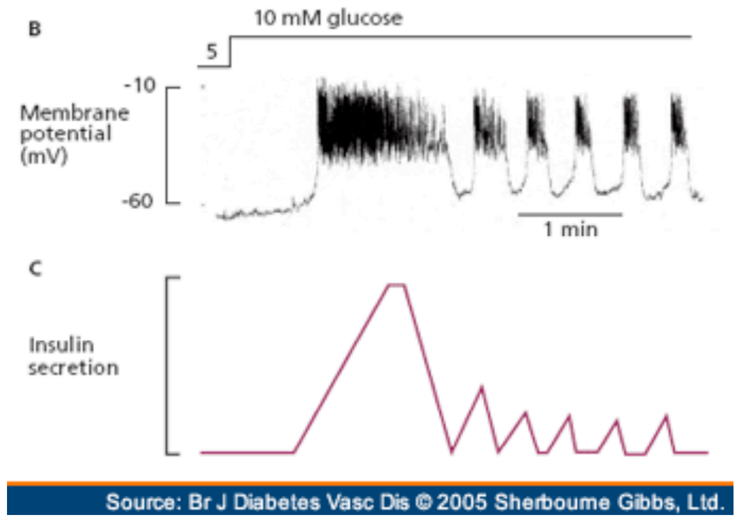


Multi-modal hybrid systems: non-electrical control

DELIVRER project:
investigate the dynamics of pancreatic cells to decode glucose-induced information, and the effect of insulin control



A. [Glucose] < 7mM :
⇒ hyperpolarized membrane
B. [Glucose] ≥ 7mM :
⇒ depolarized membrane
C. Membrane electrical activity



Glucose-induced electrical activity recorded from a beta-cell when the glucose concentration is increased (B). The bursts periods of electrical activity result in biphasic pulsatile insulin secretion illustrated schematically in (C).

DELIVRER project
J. Lang, B. Catargi - IECB /CHU Bx

Multi-modal hybrid systems: non-electrical control

DELIVRER project:
investigate the dynamics of pancreatic cells to decode glucose-induced information, and the effect of insulin control

Unpublished data

Feedback control?

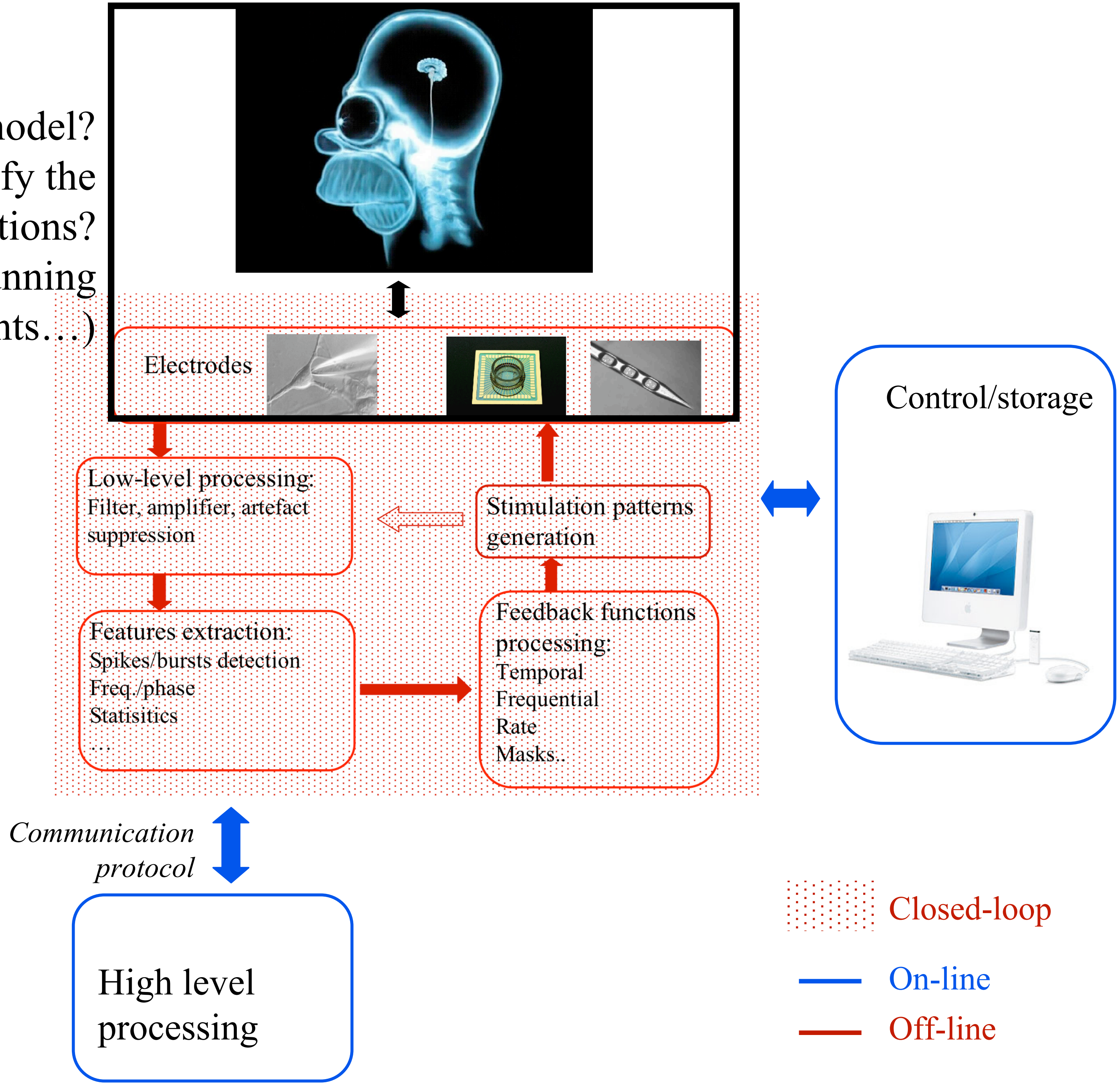
DELIVRER project
J. Lang, B. Catargi - IECB /CHU Bx

The story ….

- ✓ Neuro-electronics interfaces
- ✓ The closed-loop approach
- ✓ Single-cell level interactions
- ✓ Network scale level interactions
- ✓ Multi-modal systems
- ✓ but…

…. the bioware issue

What is the model?
How can we specify the control functions?
(without running experiments…)



An (electrode+bioware) model

Intracellular electrodes model + charge compensation

Method:
Model the response of an intracellular electrode to an injected current:
-> calculate equivalent non-linear circuit for electrode+cell (including current substraction during dynamic clamp experimente).

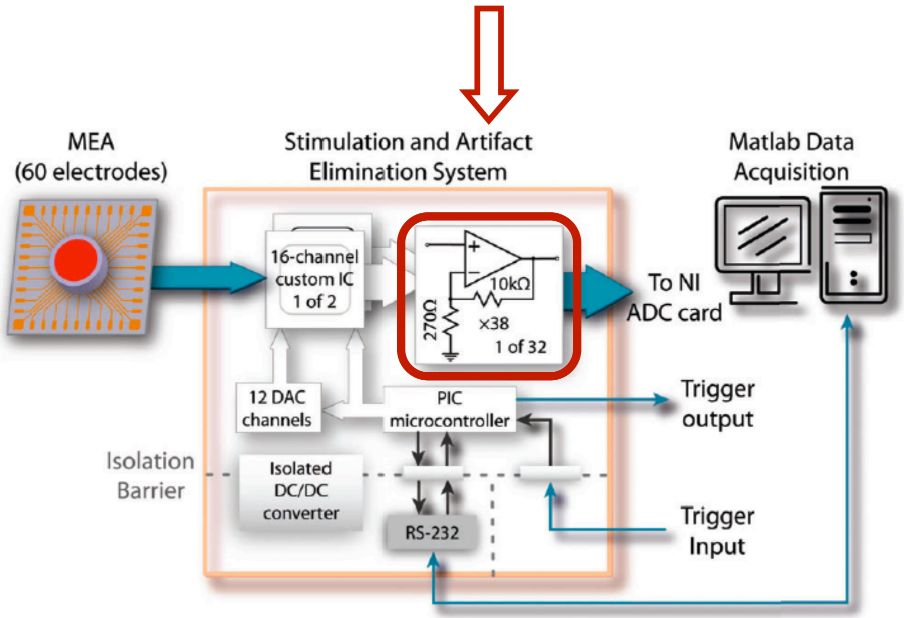
Results:
Fit natural states with dynamic clamp

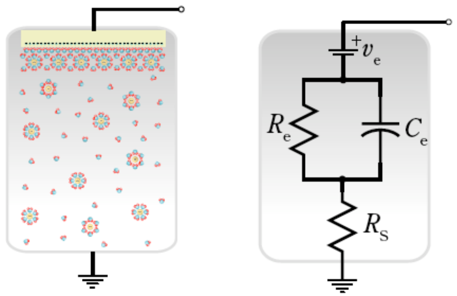
R. Brette, Z. Piwkowska, M. Rudolph, T. Bal, A. Destexhe,
A non-parametric electrode model for intracellular recording, Neurocomputing, 2007, 70:1597-1601.

An (electrode + bioware) adaptive compensation

Problem:
Record short-term response of tissues after stimulation is impossible due to the presence of stimulation artifact.

Solution:
Insert a feedback circuitry with a stable point at the discharged electrode condition





(Electrode+solution) model

E. Brown, J. Ross, R. Blum, S. DeWeerth, Stimulation and recording of neural tissues, Closing the loop on the artifact, ISCAS 2008.

What if….

The DBS problem for Parkinson disease:
For an adaptive control…
….if a LFP-dependent control is not efficient….
Is there a robust STN model ?
A behavioral model?
Handling diversity?

Conclusions (tentative)

- ✓ Hybrid systems help exploring the dynamics of biological systems
- ✓ Combine computation modes (it already combines living and artificial)
- ✓ Signal processing can be basics (filter, amplifiers…) or more complex
- ✓ Signal processing can be bio-inspired (spiking neural networks)
- ✓ The loop can be closed at different levels
- ✓ Models for each closed-loop module (including bioware)
- ✓Multi-modal processing can lead to multi-level processing
- ✓ Multi-level processing implies common tools and protocols
- ✓ Specifications (cross-disciplinary collaborations) are crucial.

. COMBINE INVESTIGATIONS AT DIFFERENT LEVELS

. COMBINE SENSORY / CONTROL modalities

⇒ so many configurations….

The story ….

« hybrid (bio-artificial) systems at the cellular level: when neuroengineers get involved »

… goes on.

Thanks to …

Jean Tomas
Sylvain Saighi
Noelle Lewis
Yannick Bornat
Alain Destexhe
Michelle Rudolph
Thierry Bal
Gwendal Le Masson
Timothée Lévi
Adel Daouzli
Bilel Belhadj
Laure Buhry
Fabrice Morin
Olivia Malot
Bernard Veyret
….
et les autres…

ims

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CNRS CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

Inserm

and happy Bastille Day …