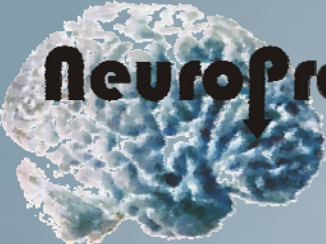


Microsystem technology in the brain: what can we offer and what can be expected?

Herc Neves, Ph.D.
Principal Scientist, Biomedical Microsystems
IMEC

Coordinator of  **NeuroProbes**

Personalised Health Systems – Brussels, 12-13 February 2007

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The fundamental question

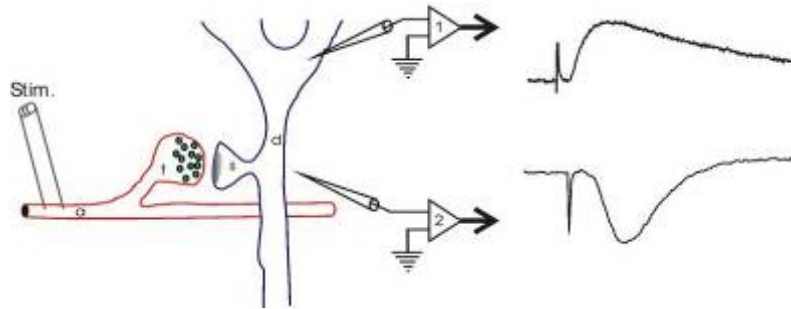
How do we correlate actions, perceptions and thoughts with the activities of individual neurons?

Our tools

- There is a long successful history of electrically interacting with biological tissue.
- Monitoring chemical activity – especially over long periods of time – is a much more demanding task.
- Optical monitoring of neural network activity is a complex endeavour, requiring techniques such as two-photon laser scanning microscopy.

Neural recording

- It is the only possibility for investigating the link between neural ensemble activity and subject behaviour.
- In-vivo studies aim to observe single-unit activity by measuring extracellular potentials.



- Extracellular recordings collect signals from all the nearby neurons (field potential). This usually has to be resolved into single units (action potentials).
- For this reason, electrodes have to be sufficiently close to neurons (typically less than 100 μm).
- Potential application: man-machine interface

Recording in neuroprosthesis

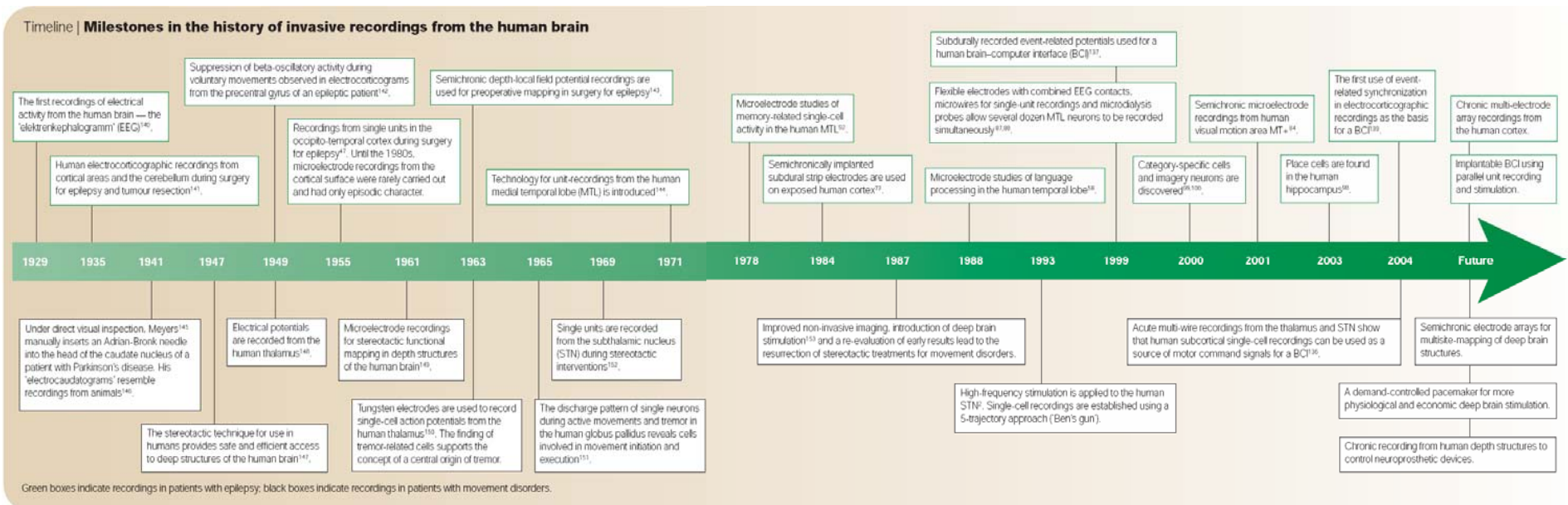
Although at first glance neuroprosthesis has to do exclusively with stimulation, recording is also of paramount importance in the characterisation and mapping of the areas of interest.

- Perhaps the most relevant neuroprosthetic device to date is the cochlear implant. Its success has to do with the tonotopic organisation of the cochlea, which was first investigated using extracellular recordings.
- What we know today about the mapping of the primary visual cortex is also owed to extracellular recordings.

Neural recording is also important in closed-loop prosthesis; for instance, the recording of signals in the motor cortex can be used for controlling robotic devices.

Clinical relevance

- Modern non-invasive techniques such as fMRI cannot provide information on physiological processes in the brain at the cellular level. Clinical use of brain recording is used mainly in two areas:
 - Management of movement disorders resulting from pathologies affecting deep brain structures (thalamus, basal ganglia);
 - Localisation of pathological activity foci for surgical excision in intractable epilepsy.



Source: Nature Reviews Neuroscience (© Nature Publishing Group)

Neural stimulation

INDUSTRIAL NEUROTECH

The neurostimulation market will reach US \$3.6 billion by 2008, says publisher Neurotech Reports. Here are the companies to watch and what they do.

1 MEDTRONIC INC. Minneapolis, Minn.

Deep brain stimulators, spinal cord stimulators, sacral nerve stimulators

- Market leader in neurostimulation
- Active deep brain stimulator recently approved for Parkinson's and other tremors
- Spinal cord stimulators treat chronic back pain
- Sacral nerve stimulators for urinary incontinence

2 COCHLEAR LTD. Lane Cove, Australia

Cochlear implants, neural prostheses

- Market leader in cochlear implants
- Its Neoprxis Pty. group is developing a standing/walking prosthesis for the paralyzed

3 SYNAPSE BIOMEDICAL LTD. Oberlin, Ohio

Diaphragm pacing system

- Phrenic nerve stimulator for pacing breathing eliminates need for mechanical ventilator in severely paralyzed

4 ADVANCED BIONICS INC. Sylmar, Calif.

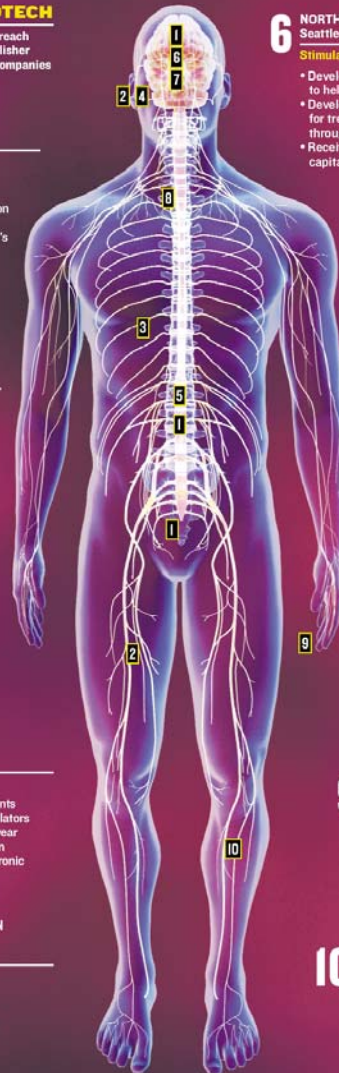
Cochlear implants

- Among top three in cochlear implants
- Hopes to sell injectable Bion stimulators for urinary incontinence within a year
- Coming: spinal cord and deep brain stimulators to compete with Medtronic

5 ADVANCED NEUROMODULATION SYSTEMS INC. Plano, Texas

Spinal cord stimulators

- No. 2 in neurostimulation
- Genesis spinal cord stimulator has cut into Medtronic's market
- Coming: deep brain stimulator



6 NORTHSTAR NEUROSCIENCE Seattle, Wash.

Stimulators for stroke rehabilitation

- Developing brain stimulator to help stroke patients recover movement
- Developed, then sold off a stimulator for treating back pain using through-the-skin electrodes
- Received \$37 million in venture capital in 2002

7 CYBERKINETICS INC. Foxborough, Mass.

Brain-computer interfaces, microelectrode arrays

- Start-up is developing BrainGate brain-computer interface to interpret signals from brain, so paralyzed patients can control neural prosthesis or external device
- Recently merged with Bionic Technologies, maker of an implantable microelectrode array

8 CYBERONICS INC. Houston, Texas

Vagus nerve stimulators

- Device implanted in chest wall activates vagus nerve leading to brain that is thought to pace physiological functions like respiration and heartbeat
- Stimulator has been shown to suppress epileptic seizures, and is being evaluated for treating depression and obesity

9 AFFERENT CORP. Providence, R.I.

Sensory stimulators

- Device for restoring sense of touch and balance lost because of stroke, diabetes, or other disorders

10 ROBOMEDICA INC. Culver City, Calif.

Step training

- System to teach people with neurological disorders and other impairments to walk

Source: IEEE Spectrum (©IEEE)

Social relevance

- Disease management leading to improved quality of life
- Opportunity to address rare diseases, the limbo of healthcare
- Fundamental research still much needed to understand mechanisms so far implicated in important disorders
 - Link between glutamate function and schizophrenia
 - Link between acetylcholine and cognitive decline in Alzheimer's disease

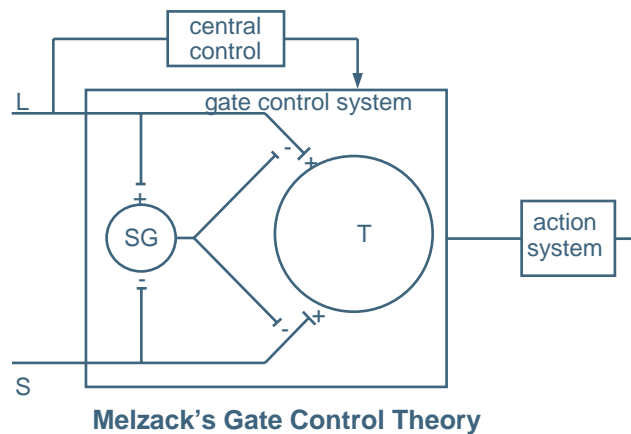
Pain management

“Physicians have the obligation to relieve pain and suffering and to promote the dignity and autonomy of dying patients in their care. This includes providing effective palliative treatment.....adequate pain control may decrease dramatically the demand for euthanasia and assisted suicide”.

Council on Ethical and Judicial Affairs, American Medical Association

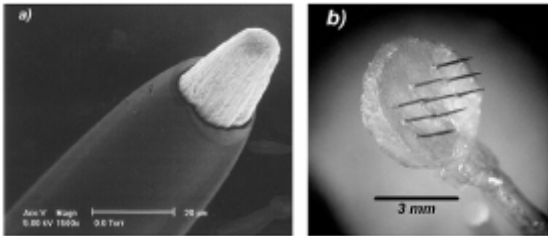


After René Descartes, 1664.

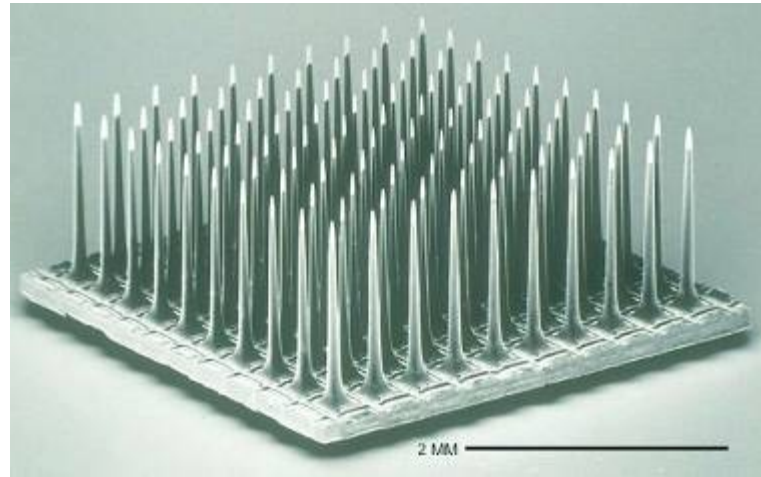


Medtronic's neurostimulator

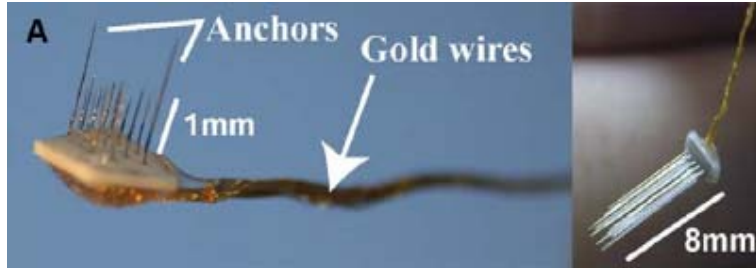
State of the art in cortical interfacing



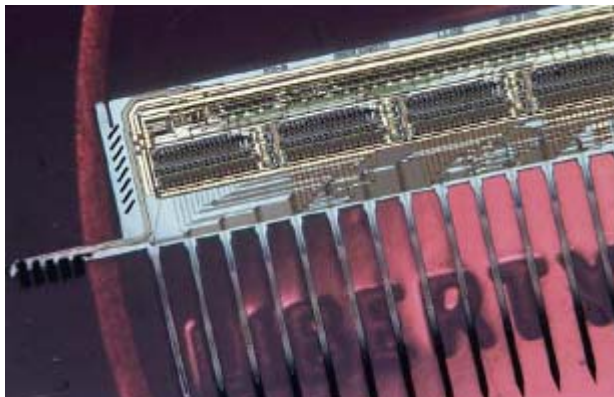
© Huntington Medical Institute



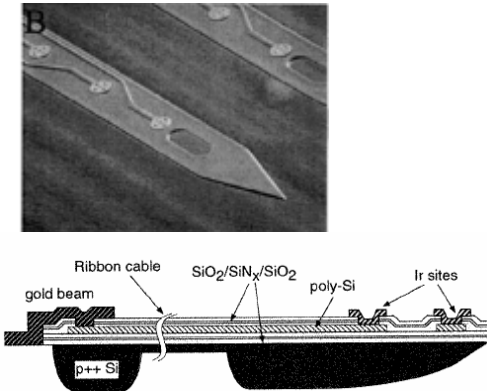
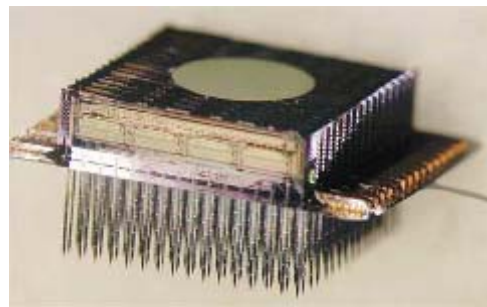
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Challenges of in-vivo extracellular recording

- According to J.C. Lilly, in “Correlations between neuro-physiological activity in the cortex and short-term behavior in monkey”, *Biochemical Bases of Behavior* (1940),

“... one of the large difficulties in correlating structure, behavior, and CNS activity is the spatial problem of getting enough electrodes, and small enough electrodes, in there with minimal injury. Still another difficulty is the temporal problem of getting enough samples from each electrode per unit of time, over a long enough time, to begin to see what goes on during conditioning or learning, especially when a monkey can learn with one exposure to a situation, as we see repeatedly. As for the problem of the investigator’s absorbing the data – if he has adequate recording techniques, he has a lot of time to work on a very short recorded part of a given monkey’s life.”

The problem from a microsystem perspective

- Microsystems largely confined to two dimensions – 3D integration
- Most solutions limited to hybrid system-in-package
- Full solution needed
- Diversity of environment needs customisable solutions
- Interactions with tissue largely seen as a “black & white problem”
 - Biocompatibility, biostability
 - Passive materials
 - True opportunity for nano
- Dynamic biological systems vs. static microsystems
- The dark art of electrode technology
 - Factors influencing electrode performance are thought to be well known
 - Actual interface with biological medium far more complex

The NeuroProbes Integrated Project



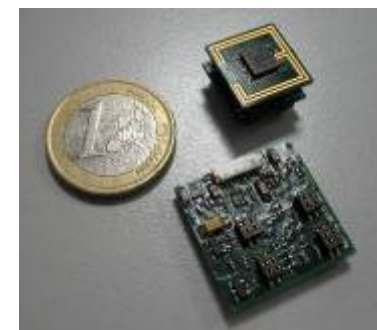
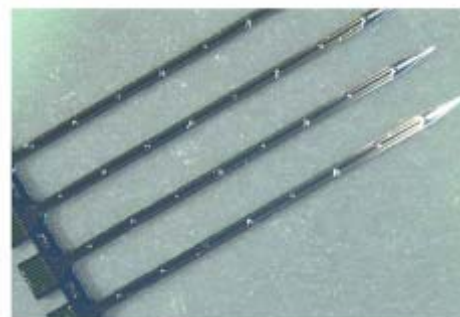
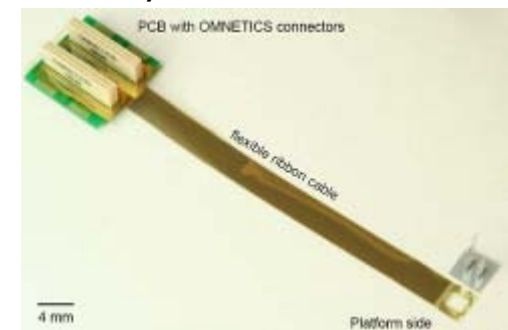
Objective

Development of arrays of multifunctional microprobes for high temporal and spatial resolution brain studies that include freely moving subjects, with recording **and** stimulation done both electrically and chemically.

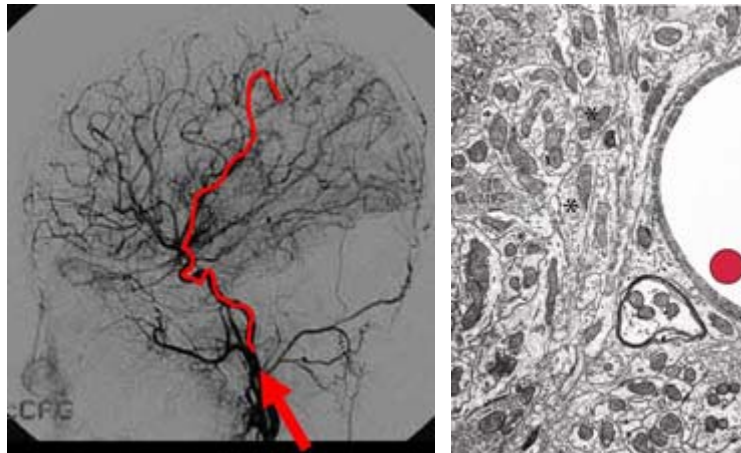
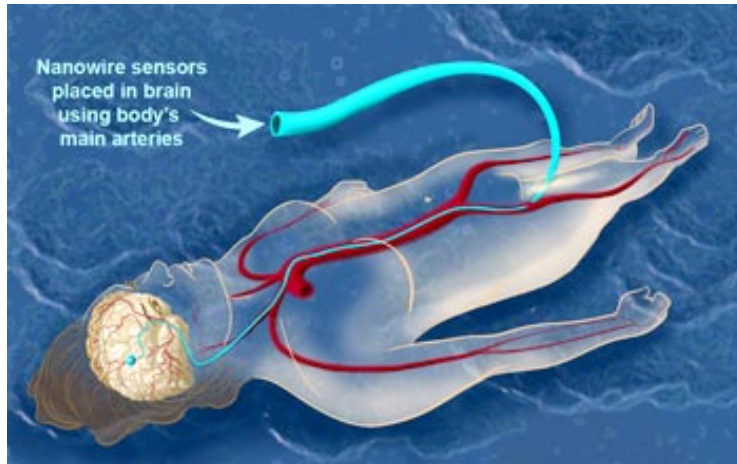


Features

- Dense 3-D microelectrode arrays for recording
- Modular technology
- Microfluidics for inactivation studies
- Individual and independent control of electrode position
- Attachment and insertion technologies
- Conformation to convoluted surfaces such as *sulci* of highly folded cortices
- Integrated biosensor probes
- Telemetry



Future of cerebral interfacing



© MIT

Challenges

- Invasiveness
- Tackling a 3D problem with a 2D solution
- Using static devices in a dynamic environment
- Chemical interfacing
- Electronics
- Energy

Possible solutions

- Departure from traditional designs (e.g. function splitting)
- Microsystem integration (incl. electronics)
- Materials investigation

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The graphic features a central point from which numerous thin white lines radiate outwards, curving downwards and to the left. These lines converge towards a small orange and yellow circular element at the center. Several larger, semi-transparent circular elements, each containing a similar orange and yellow core, are positioned along the left side of the image, appearing to be part of the radiating structure.