Multifunctional microprobe arrays for the brain

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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).
In-vivo cerebral recordings in humans

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 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.
The NeuroProbes project

- **The problem:**
  - To electrically record three-dimensional neuron ensembles in vivo over long implantation periods, also in monkeys and humans;
  - To integrate such recordings with chemical sensing and drug delivery;
  - To perform electrical stimulation;
  - To provide telemetry where needed.

- **The solution:**
  - A new 3D technology that permits a combination of diverse functionalities;
  - Embedded, distributed electronics;
  - Extra thin backbone, conducive to floating operation.
**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 and stimulation
- Modular technology
- Microfluidics for inactivation studies
- Individual depth control for accurate placement
- Attachment and insertion technologies
- Conformation to convoluted surfaces such as sulci of highly folded cortices
- Integrated biosensor probes
- Telemetry
Key differentiators

- **Modular approach.** Probes are assembled in a Lego® fashion that permits to combine probes with different functionalities, shapes and sizes on a common backbone.

- **Chronic use.** A combination of diverse strategies (not limited to biocompatible coatings) for the management of foreign body reaction was investigated in NeuroProbes.

- **Electronic depth control.** Instead of relying on trial and error, our probes are designed to allow the individual control of electrode position with respect to single neurons.
Technology timeline

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Boundary conditions

- Recording in rats and monkeys
- Focus on the recording of single action potentials
- Possibility for chronic use (floating operation)
- Dual character of the project (technology & science): devices had to be available to users very early into the project
- Relatively short duration of the project: limited set of variations, parallel paths, additional concepts
- Flexibility to integrate diverse functions into the same platform
Modular integration

Original Michigan approach

Utah approach

NeuroProbes approach

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Platform concept

- Key point: electric and fluidic interconnect between off-plane probe and in-plane platform
- Focus: reliable electric interconnect, robust fabrication process
Drug delivery

• Of particular interest in inactivation studies
• A number of significant challenges: very small volumes, potentially large dead volumes, difficulty to control dosage, need for a miniaturized pumping scheme, rechargeability

PMP-NC²  NeuroMedicator  Fluidic microprobes
Chemical sensing

- Intrinsic difficulty to integrate with in vivo probes
- Constrained to two compounds of interest: choline and glutamate
According to J.C. Lilly, in “Correlations between neurophysiological 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.”
Need for depth control

- All multielectrode probes rely on trial and error for positioning. There is no way to optimize electrode positioning of multiple electrodes in the same shaft.
- Need to adjust electrode position with respect to cells.
- Need for fine adjustments in the course of an experiment.
- Need to reconfigure experiments.
Depth control approaches


Depth control in NeuroProbes

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Mechanical actuation – factors against it (at least in our case)

- Mechanical displacement moves all electrodes in tandem
- Needs a point of support (not available in floating operation)
- Not good if tissue reaction is to be minimized
Concept evolution

3D integration technology

Multi-function integration

Electrical depth control

Conformation to complex surfaces

- Large number of working electrodes
- Extra control and heavier computational power needed
Basic architecture

CMOS wafer shaped by post-processing

Interconnect matrix:

- electrode size, shape and column pitch determined by post-processing mask

8 electrodes at same time per shaft (but electrodes can also be connected in parallel)
• 37 dB Harrison amplifier for each output line (0.1Hz – 8.5kHz bandwidth)
• 200kHz 8:1 MUX (25 ksamples/s/channel)
• Class AB output buffer (526kHz BW, 1.4V/µs SR)

• 5mW overall power consumption
• 3.7µVrms total input referred noise (1Hz – 10kHz bandwidth): lower than electrode noise
Implementation

- 8mm long comb wire bonded to PCB
- Reference pin
- Ground pin
- 14-pin header to interface box
- Connector for direct electrode access
- CMOS front end
- MEMS motherboard
Control software

Control for data acquisition
Data visualization
Electrode selection

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Control software – electrode selection
Control software – SNR visualisation

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Target identification

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Experimental approach

EDC probe

motor cortex

sensory cortex
Experimental approach

- Passive probe
- EDC probe
- Sensory cortex
- Motor cortex
Experimental approach

EDC probe

passive probe

sensory cortex

motor cortex

EDC probe

sensory cortex
Acute recordings, 2D probes

Passive probe motor cortex

EDC probe sensory cortex

LFP

Passive probe motor cortex

EDC probe thalamus

MUA

Passive probe motor cortex

EDC probe thalamus
Cross correlograms of up-state onsets at different channels

Cortex-cortex from the same shaft

Cortex-cortex between shafts

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Cross correlograms of up-state onsets at different channels

Thalamus-thalamus from the same shaft

40ms shift
Thalamus leads!

Cortex-thalamus between shafts

0ms delay
Work in progress

- Analysis of the electrophysiological data (e.g. cross correlation peak maps)

- Histological reconstruction

- Correlation of electrophysiology data with the anatomy
Some conclusions

- Quite a bit of work for a 4½ year project
- Short duration inevitably led to technology compromises
- Significant achievements in system integration and development of electronic depth control
- Many ideas for follow up
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