OFET-based devices for electrophysiological applications

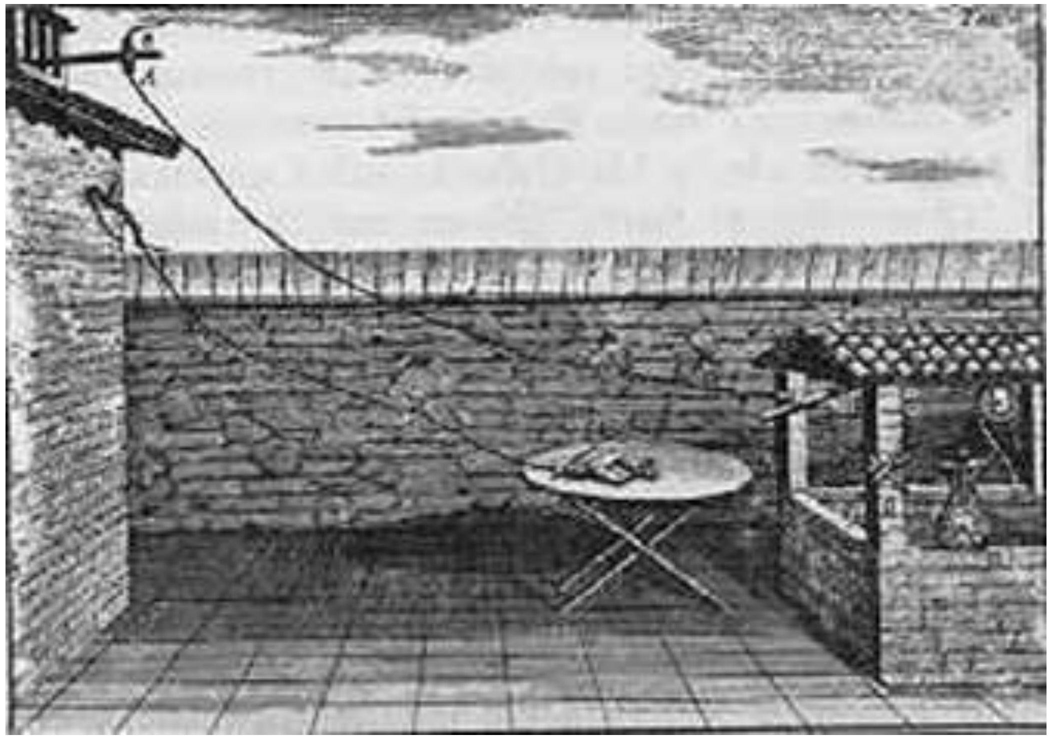
Andrea Spanu Ph.D.
andrea.spanu@diee.unica.it

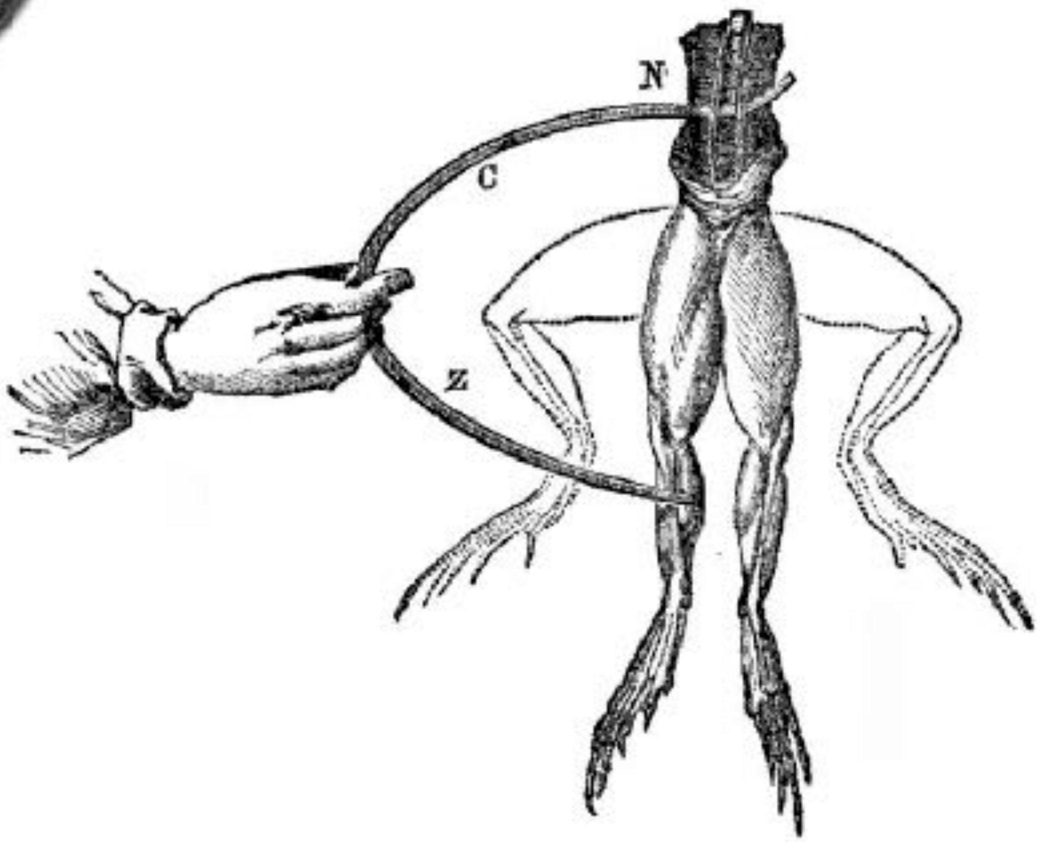
Outline

- Bio-electricity: From the fried frog to The Walking Dead
- The action potential: From Hodgkin & Huxley to the Cyborg Monkey
- Organic Electronics: a brief overview
- The Organic Charge Modulated FET (OCMFET)
- The Micro OCMFET Array (MOA): merging organic electronics and electrophysiology

Origin of bioelectricity

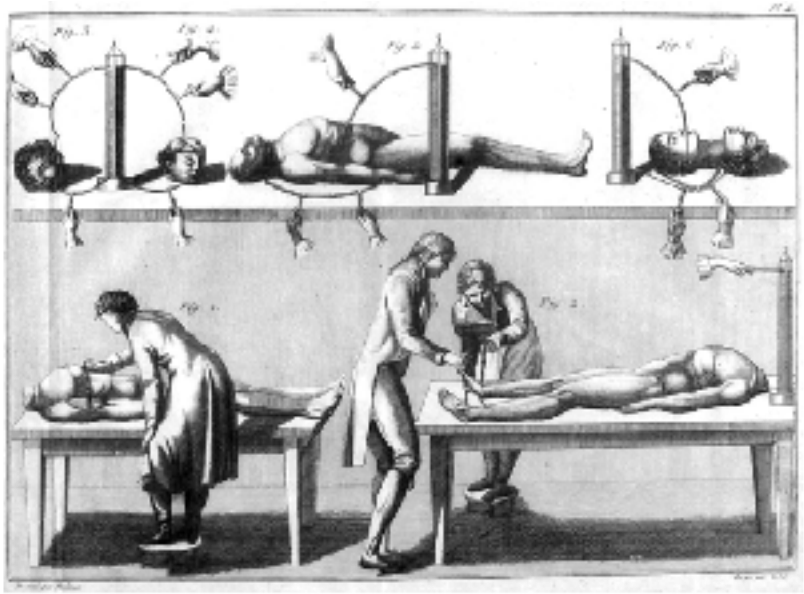
Luigi Galvani
(1737-1798)

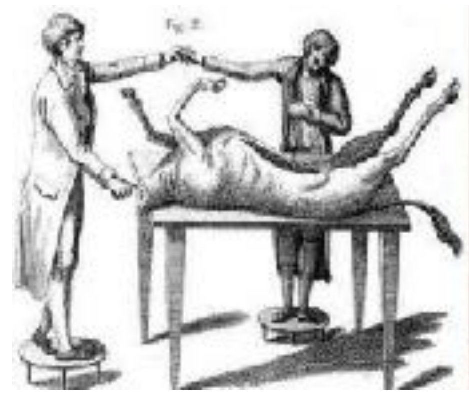


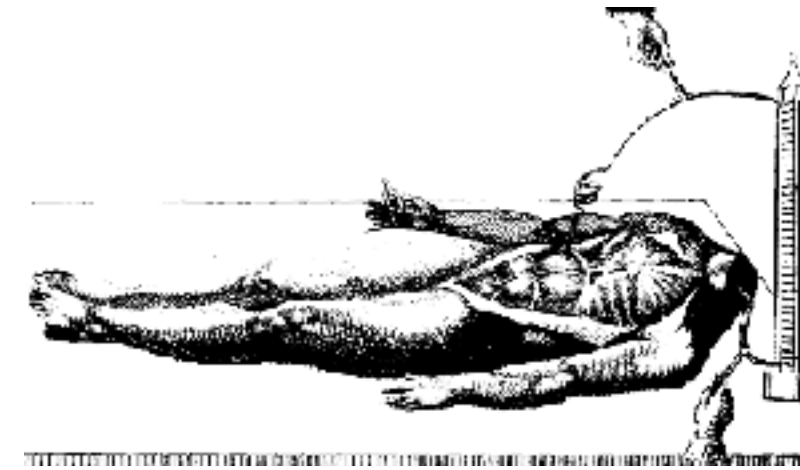


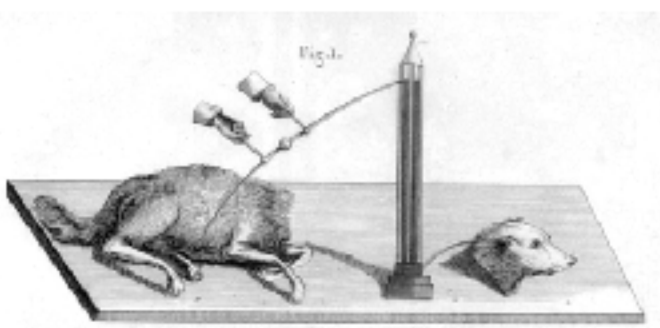
De Viribus Electricitatis In Motu Musculari Comentarius Cum Joannis Aldini Dissertatione Et Notis ; Accesserunt Epistolae ad animalis electricitatis theoriam pertinentes - 1792

Origin of bioelectricity





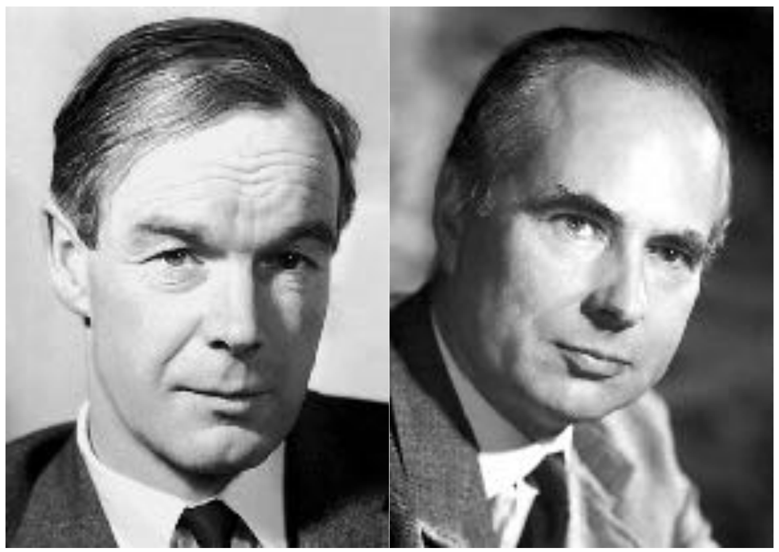


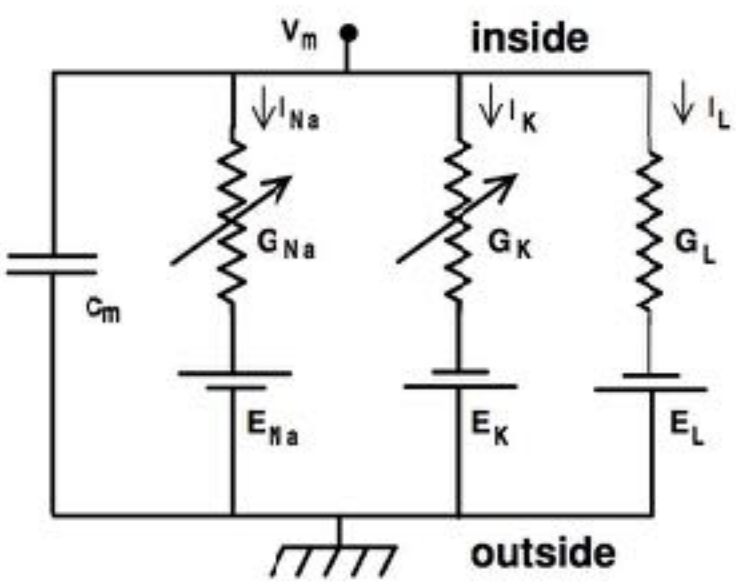


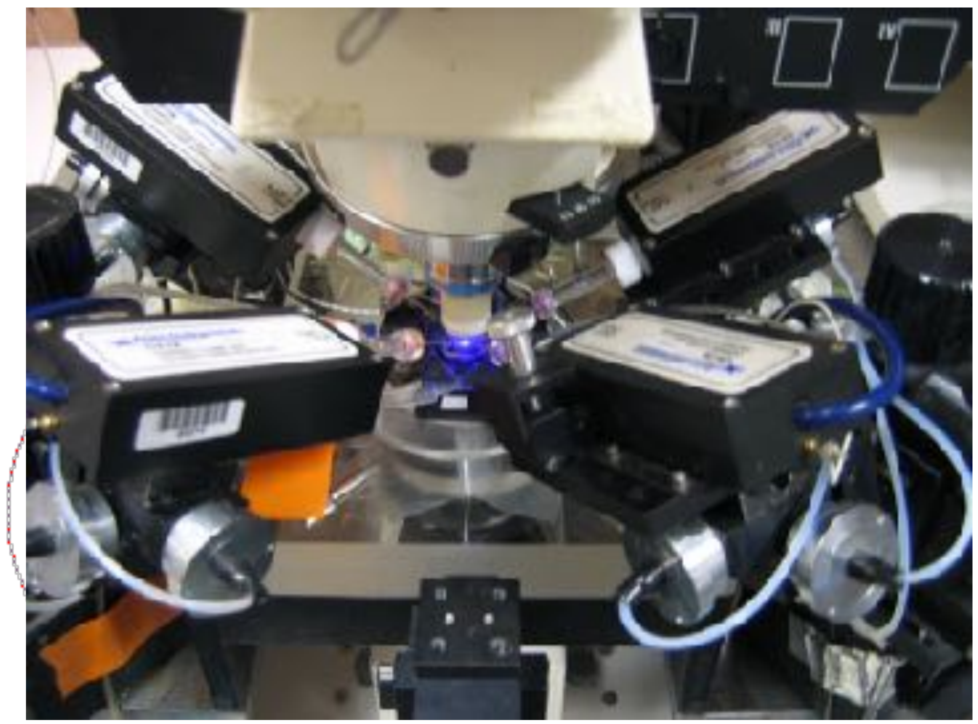
Early 1800: the voltaic pile era

Aldini G (1803) An account of the late improvements in galvanism, with a series of curious and interesting experiments performed before the commissioners of the French National Institute, and repeated lately in the anatomical theaters of London, by John Aldini

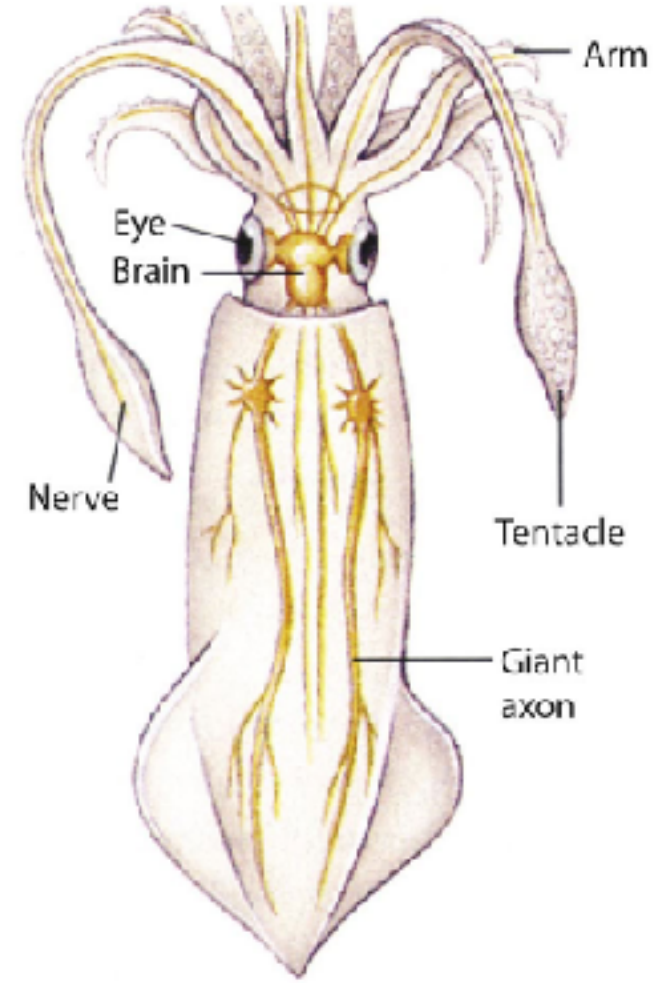
Intracellular electrophysiology

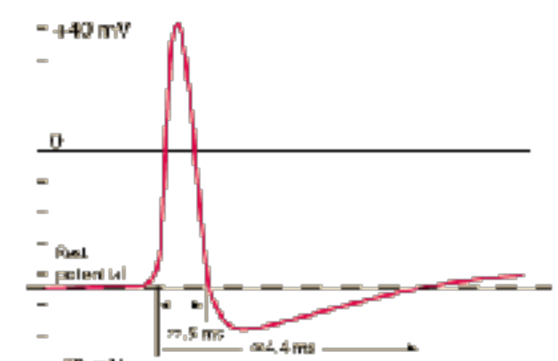






Patch clamp:
a single cell
approach

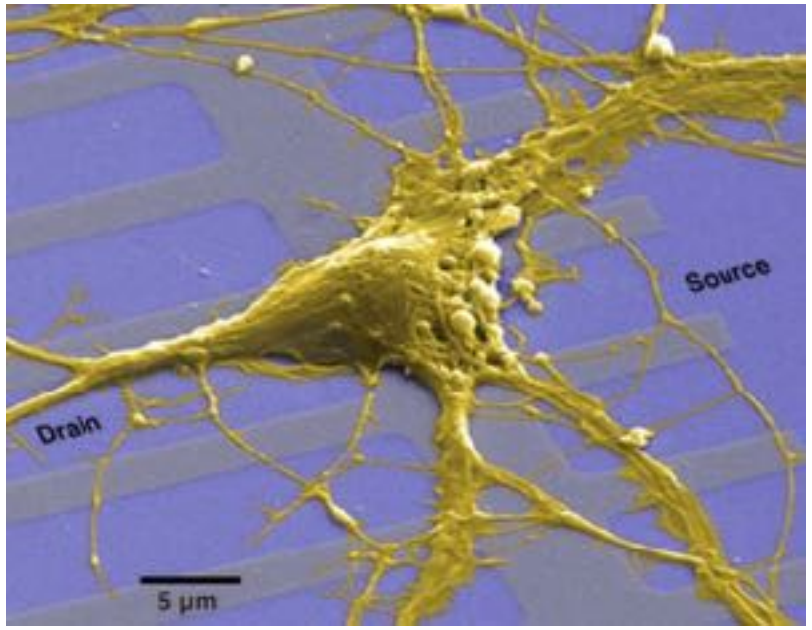




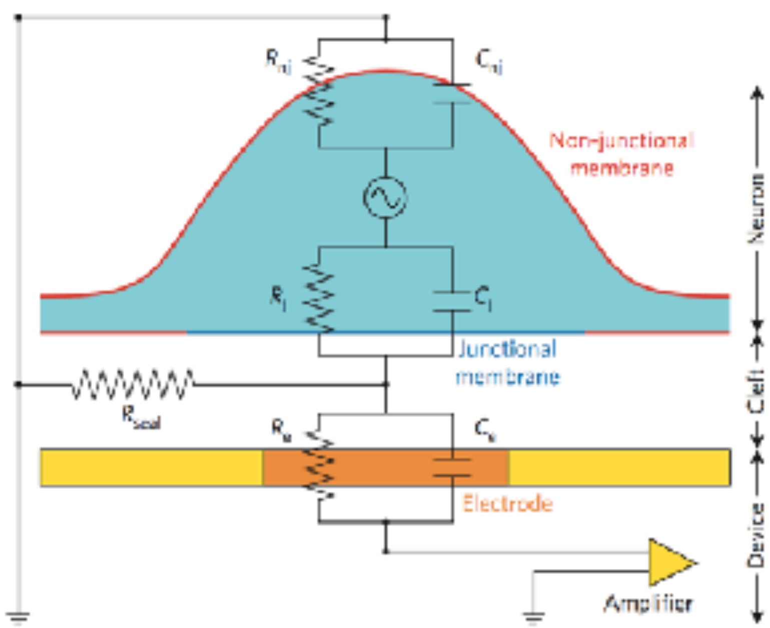
A. L. Hodgkin and A. F. Huxley, “A Quantitative Description of Membrane Current and Its application to Conduction and Excitation in Nerve”, J
Physiol., pp. 500–544, 1952.

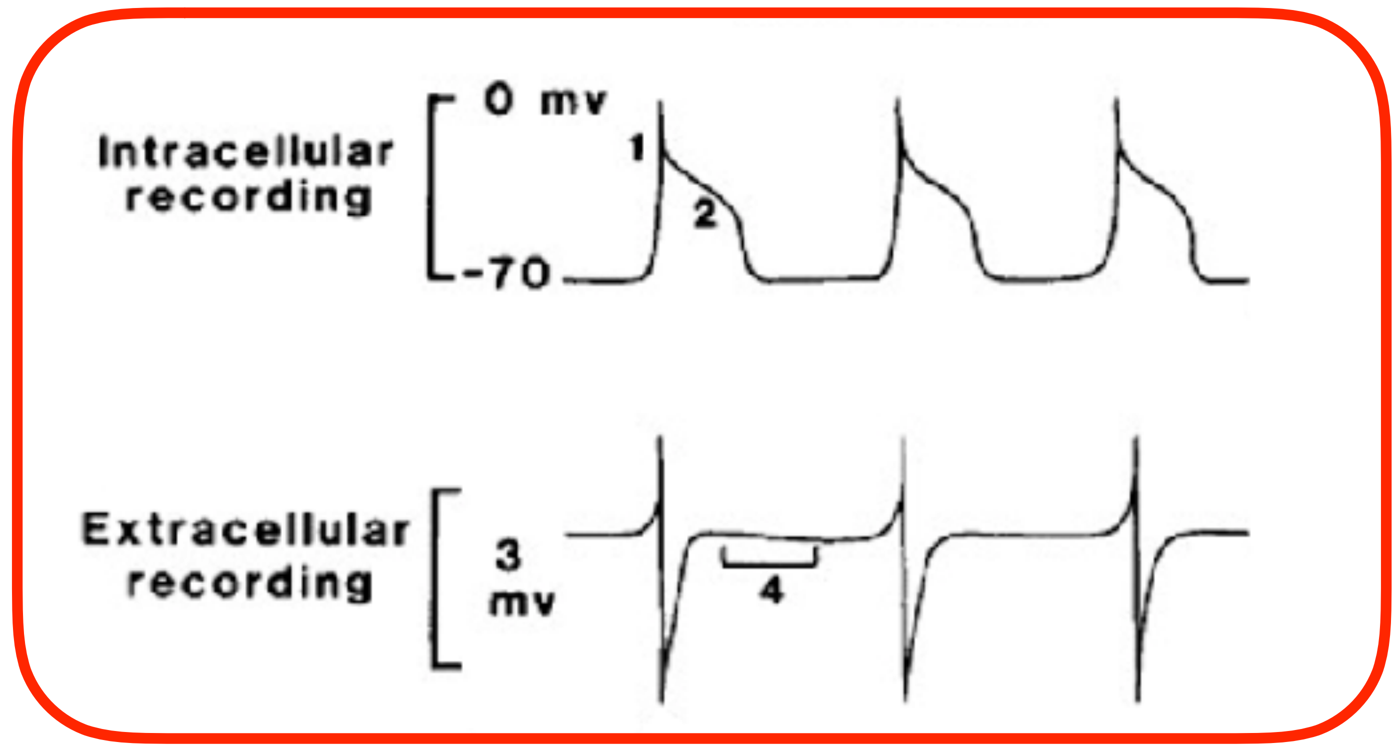
Extracellular electrophysiology

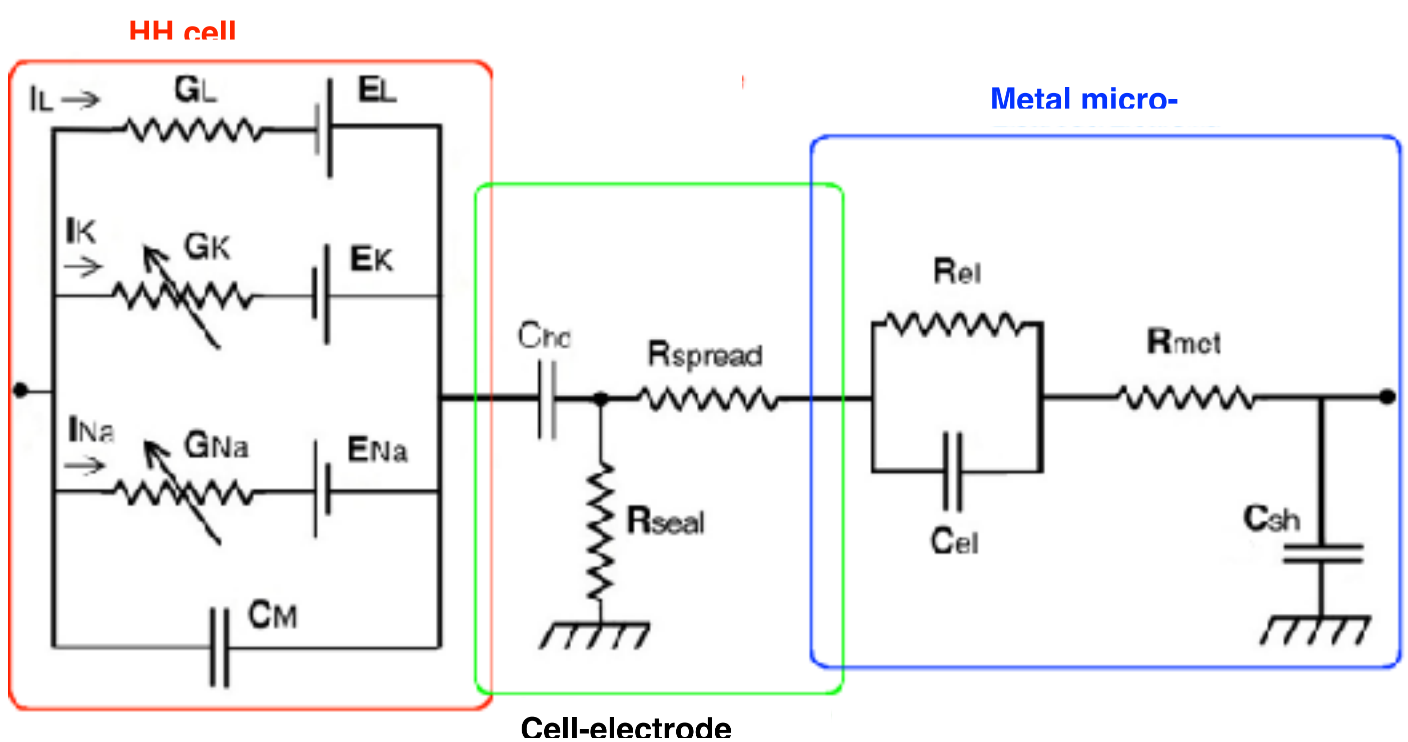
- Micro Electrodes Array
  - Simple electrical model
  - Both in-vivo and in-vitro applications
  - Bi-directional interfaces
- Field Effect devices
  - Both in-vivo and in-vitro applications
  - Bi-directional interfaces
  - Capacitive electrical coupling
  - High density devices



Micro Electodes Array - MEA

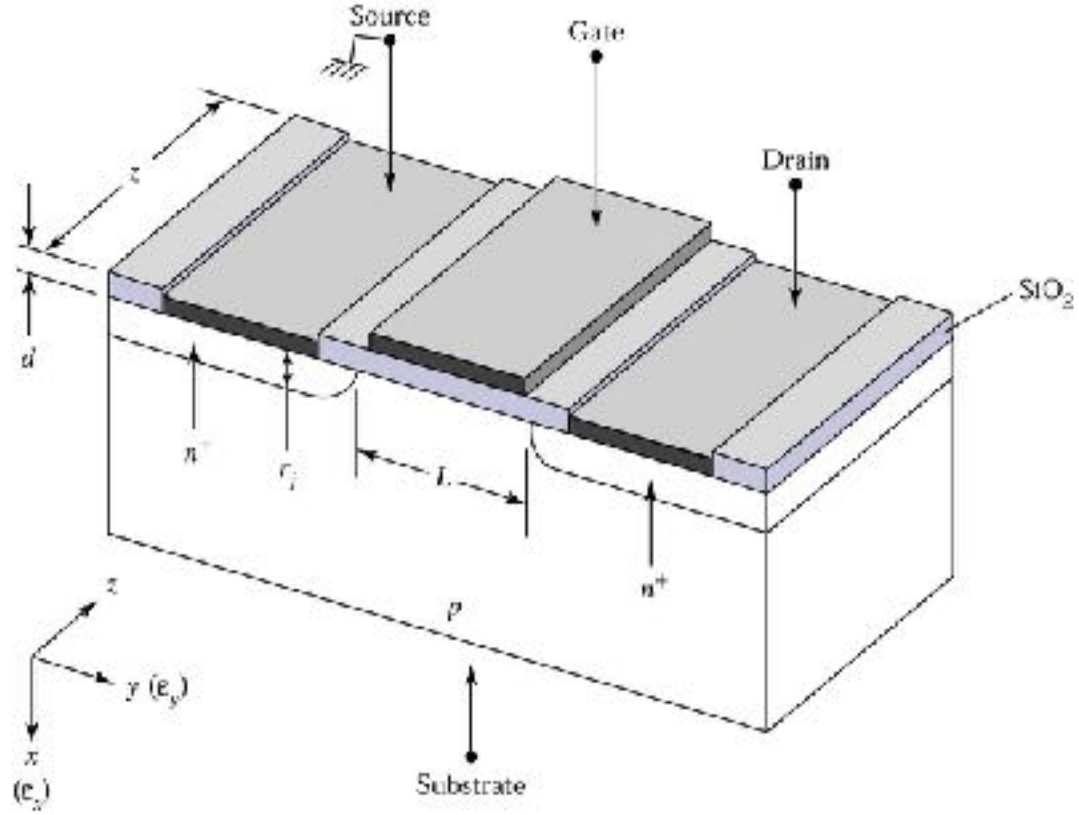






- **C**$_{\mathbf{hd}}$ = double layer capacitance
- High **R**$_{\mathbf{seal}}$ & Low **R**$_{\mathbf{spread}}$: good coupling!
- **C**$_{\mathbf{sh}}$ = (undesired) shunt capacitance

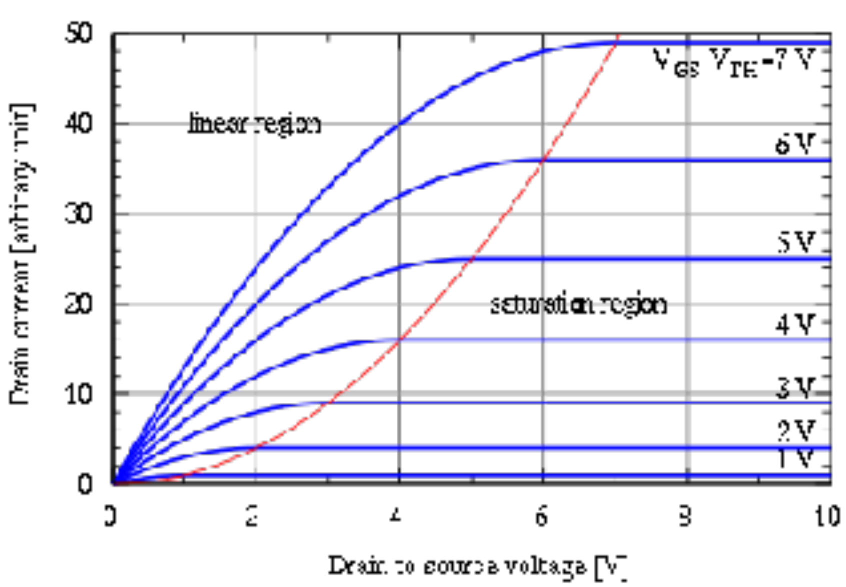
Field effect devices: the MOSFET

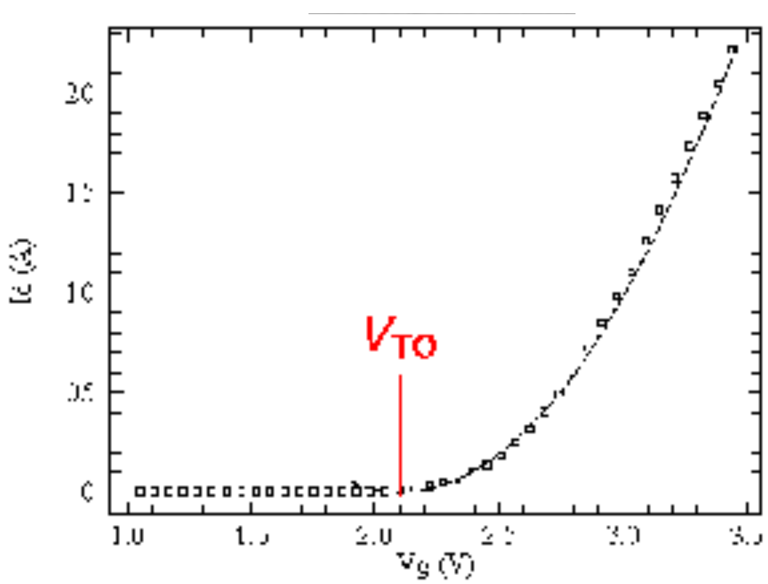


$$I_{DS} = \mu C_{ox} \frac{W}{L}\left[\left(V_{GS} - V_{TH}\right)V_{DS} - \frac{V_{DS}^2}{2}\right]$$

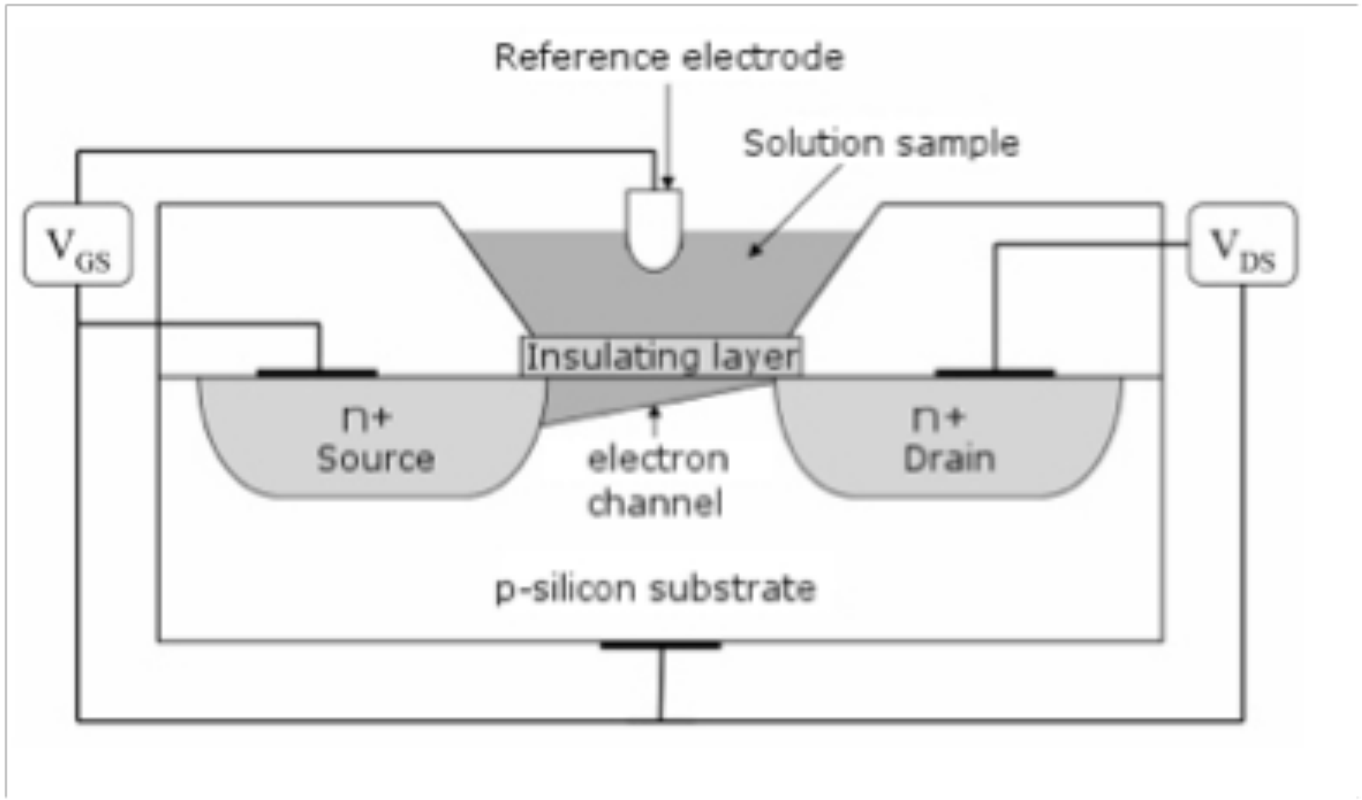
$$V_{TH} = V_{FB} - \frac{Q_B}{C_{ox}} + 2\phi_F$$

$$V_{FB} = \frac{\phi_M}{q} - \frac{\phi_{Si}}{q} - \frac{Q_0}{C_{ox}}$$





Field effect devices: the ISFET



$$I_{DS} = \mu C_{ox} \frac{W}{L}\left[\left(V_{GS} - V_{TH}\right)V_{DS} - \frac{V_{DS}^2}{2}\right]$$

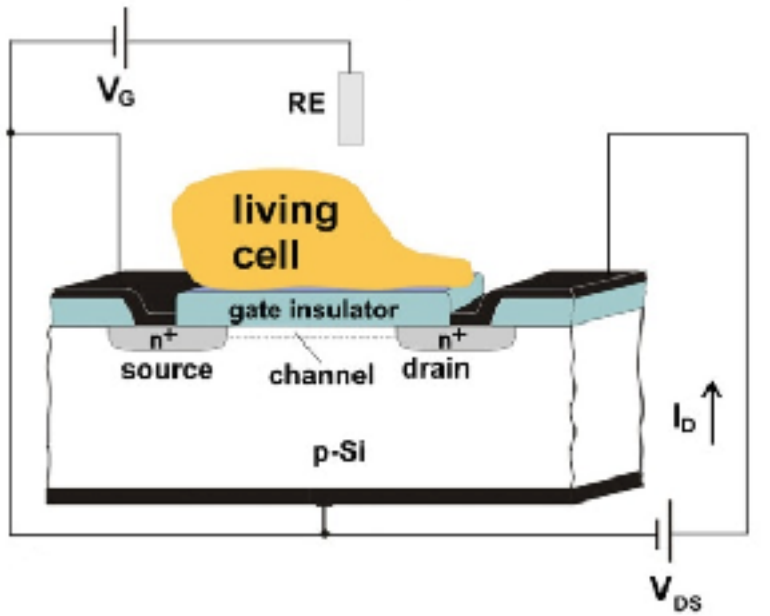
$$V_{TH} = V_{FB} - \frac{Q_B}{C_{ox}} + 2\phi_F$$

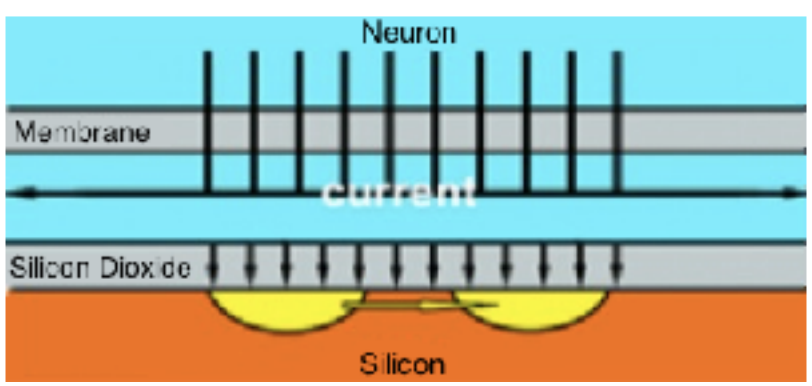
$$V_{FB} = \frac{\phi_M}{q} - \frac{\phi_{Si}}{q} - \frac{Q_0}{C_{ox}}$$

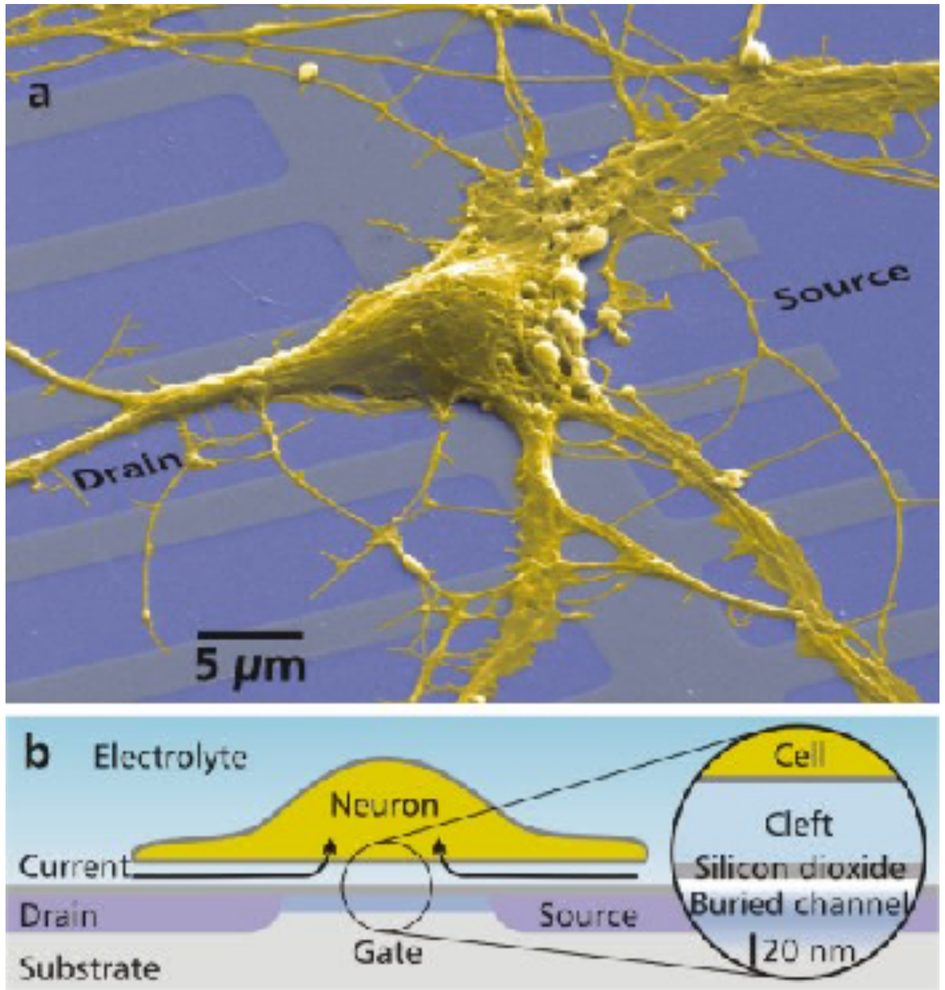
$$V_{FB_{ISFET}} = V_{FB_{MOSFET}} + E_{ref} + \varphi_{ij} + \chi_e + \varphi_{eo} - \phi_M$$

Field effect devices: the ISFET

‘90s: first example of a neuronal cell cultured onto the gate oxide of an ISFET



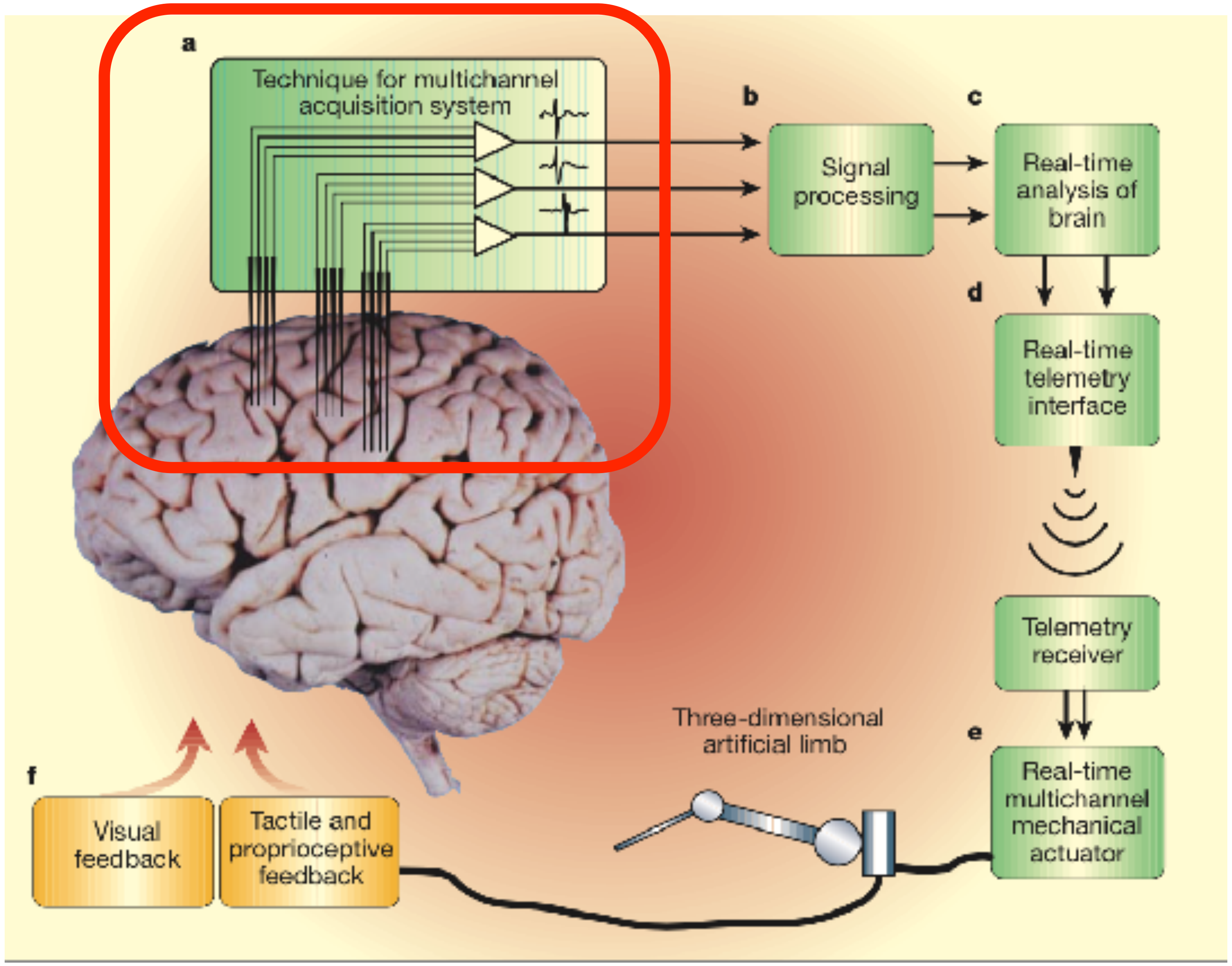




Fromherz, Peter; Offenhausser, A. V. T. W. J. A Neuron-Silicon Junction: A Retzius Cell of the Leech on an Insulated-Gate Field-Effect Transistor. Science (80-.). 252, (1991).

MEAs and FEDs Applications: Brain Machine Interfaces - BMIs

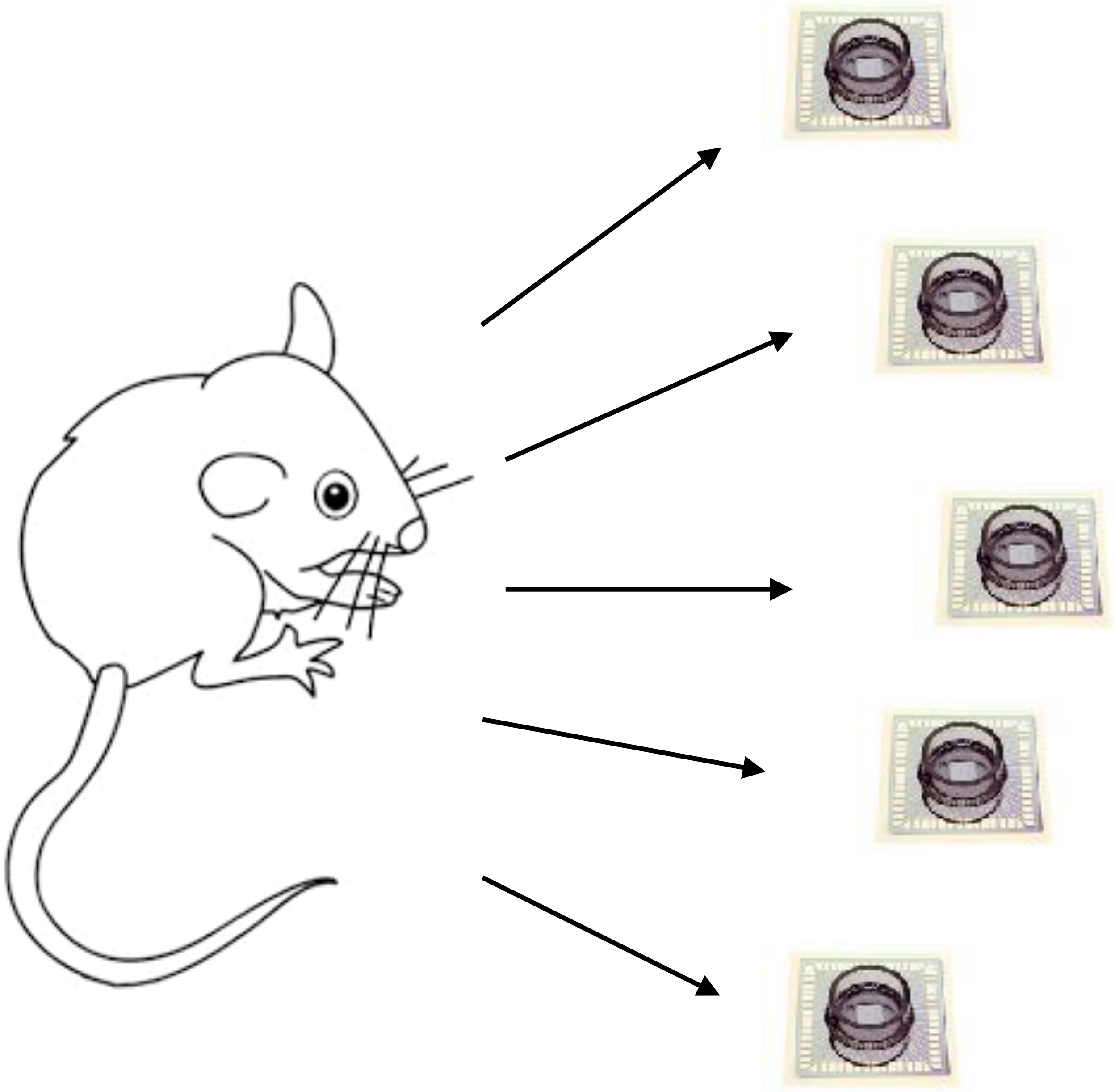
- Direct interface with the Central Nervous System (CNS)
- Very complex discipline
- material science, software engineering, electronic engineering, robotics…



M. Velliste, S. Perel, M. C. Spalding, A. S. Whitford, and A. B. Schwartz, "Cortical control of a prosthetic arm for self-feeding.," Nature, vol. 453, no. 7198, pp. 1098–101, Jun. 2008.

MEAs and FEDs Applications: in vitro Pharmacology testing

- Good correlation between in vivo and in vitro approaches
- Useful for preliminary drug testing
- Faster and cheaper than in vivo approach
- High reproducibility
- Ethical issue: reduced number of test animals



MEAs and FEDs: why not?

Very nice devices indeed…but:

Micro Electrode Arrays

- reference electrode needed
- limit on the number of recording sites
- high costs of fabrication

Field Effect Devices

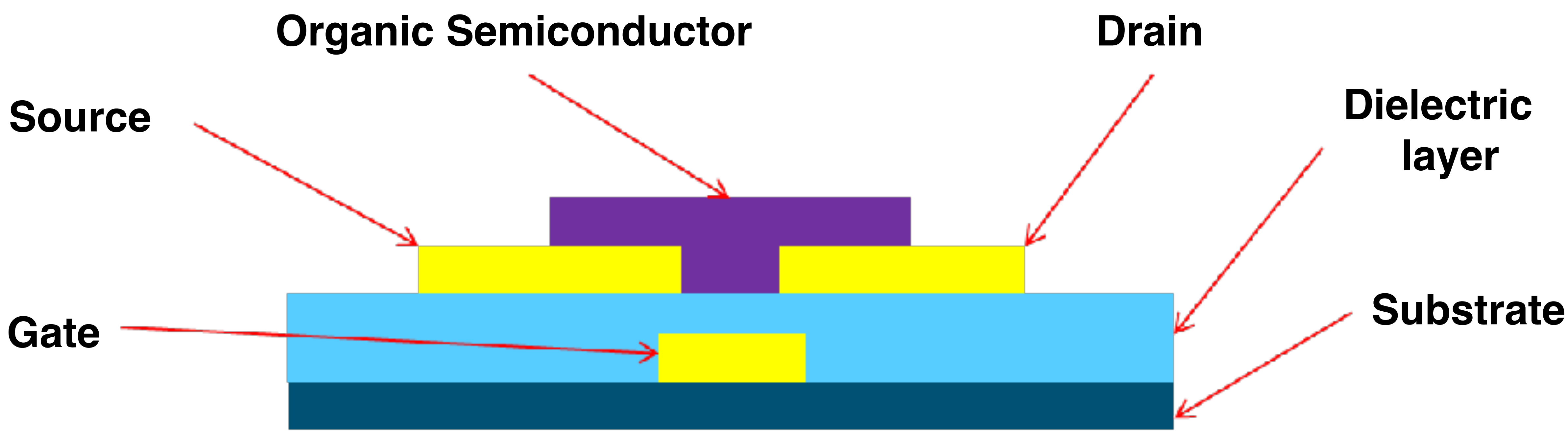
- gate oxide directly exposed to the culture medium (not good at all)
- high costs of fabrication
- rigid and not transparent devices
- reference electrode needed (not easy to handle in CMOS technology)

Organic electronics: a brief overview

Organic electronics may bring interesting novelty to a large number of applications, especially to the sensing and biosensing field thanks to:

- suitable for large area, low cost, fabrication techniques
- intrinsic biocompatibility of plastic materials
- interesting mechanical and optical properties (flexibility, transparency…)

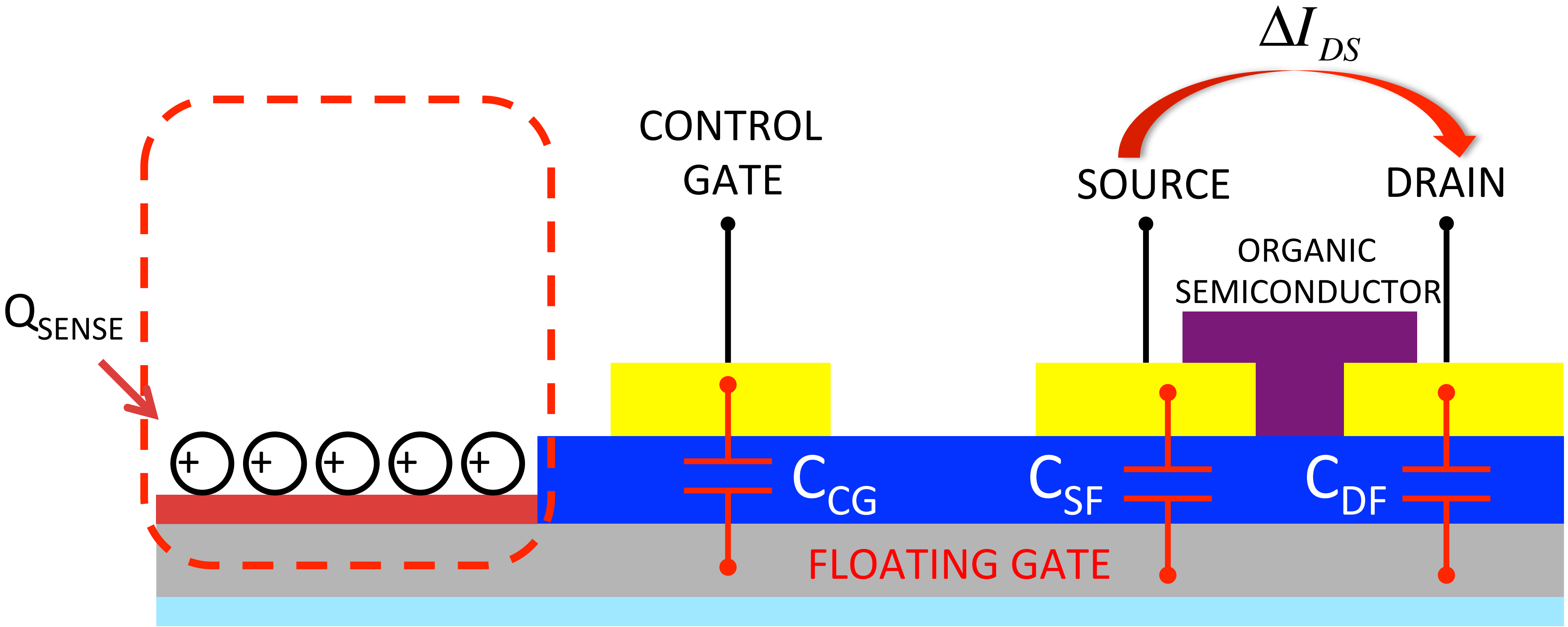
Organic electronics: Organic Thin Film Transistor



- All the materials are deposited as thin films
- OTFTs work in accumulation (not in inversion nor in depletion mode
- Ohmic contact between source/drain and the organic semiconductor

The Organic Charge Modulated FET
OCMFET

OCMFET: transduction principle



$$V_{FG} = \alpha V_{CG} + \beta V_{DS} + \gamma Q_{TOT}$$

$$V_{THE} = V_{TH} + (1-\alpha)V_{CG} - \beta V_{DS} - \gamma Q_{TOT}$$

$$\Delta V_{TH} = -\frac{Q_0 + Q_{SENSE}}{C_{TOT}}$$

$$\alpha = \frac{C_{CG}}{C_{TOT}} \qquad \beta = \frac{C_{DF}}{C_{TOT}}$$

$$\gamma = \frac{1}{C_{TOT}}$$

$$C_{TOT} = C_{CG} + C_{DF} + C_{SF}$$

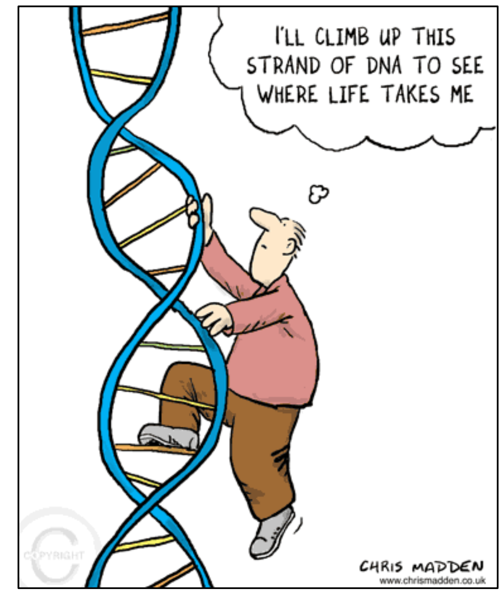
Charge Amplifier

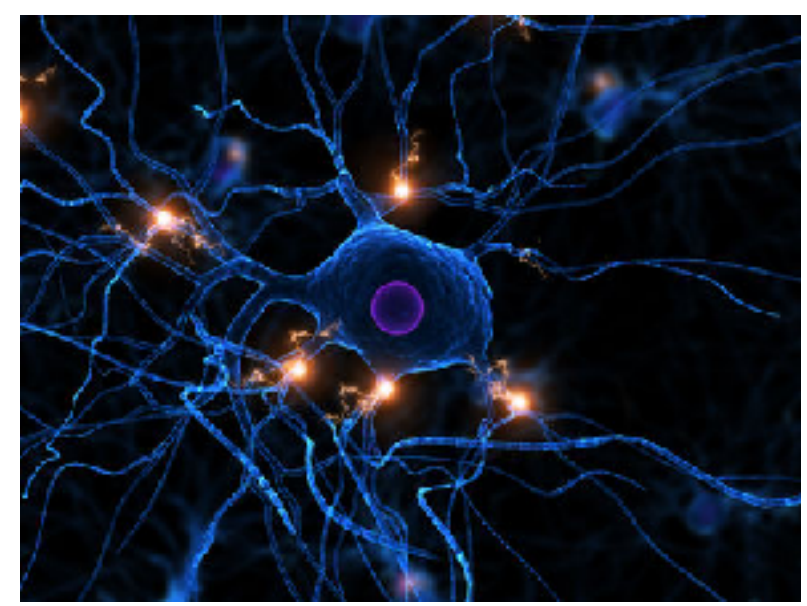
OCMFET: applications

The OCMFET has been already employed for:

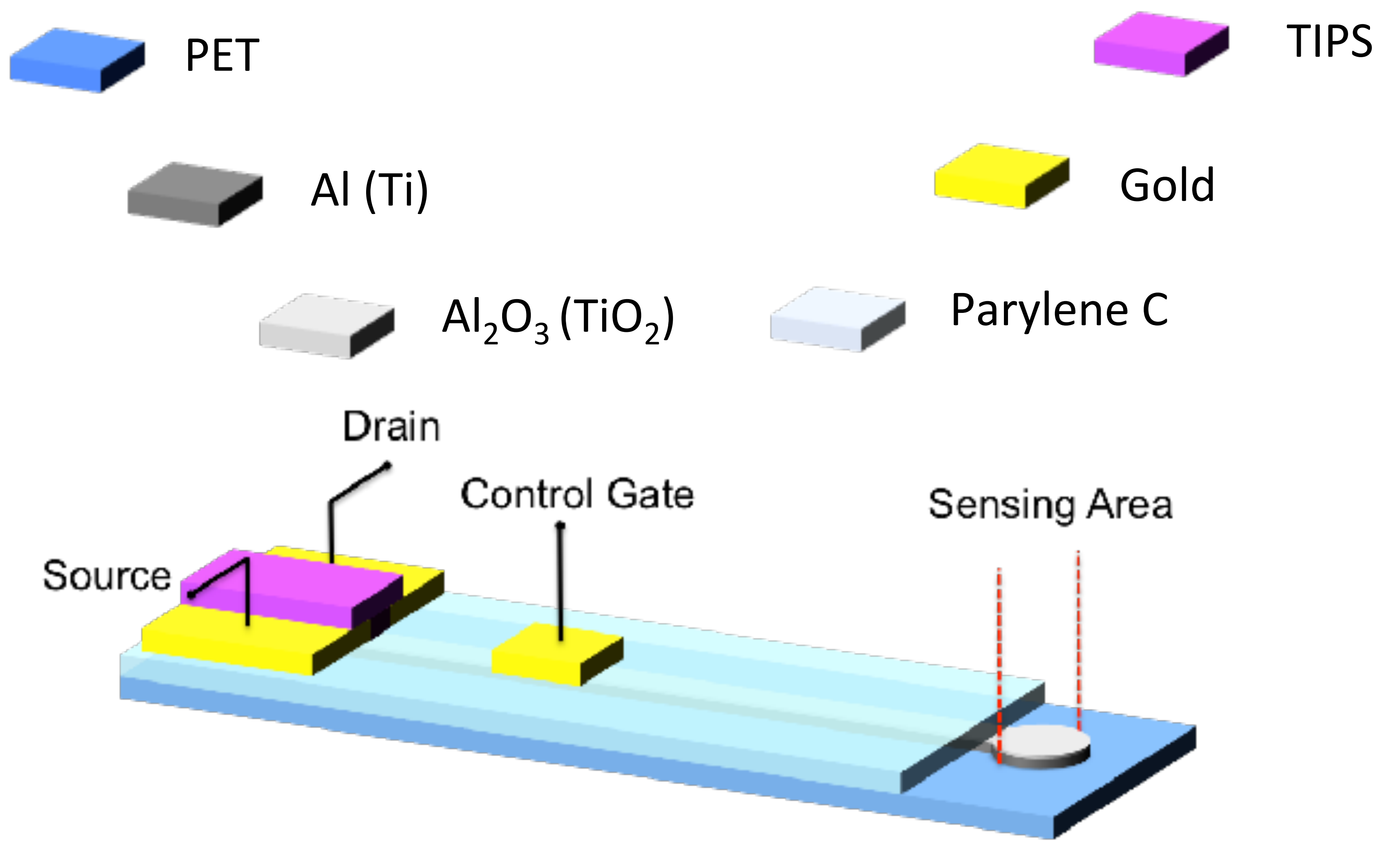
- pH sensing
- DNA hybridization sensing
- strain sensing
- temperature sensing
- pressure sensing
- cellular metabolic activity sensing
- cellular electrical activity sensing
- …

Whatever causes a charge variation onto the sensing area is likely to be sensed!





OCMFET: materials and methods



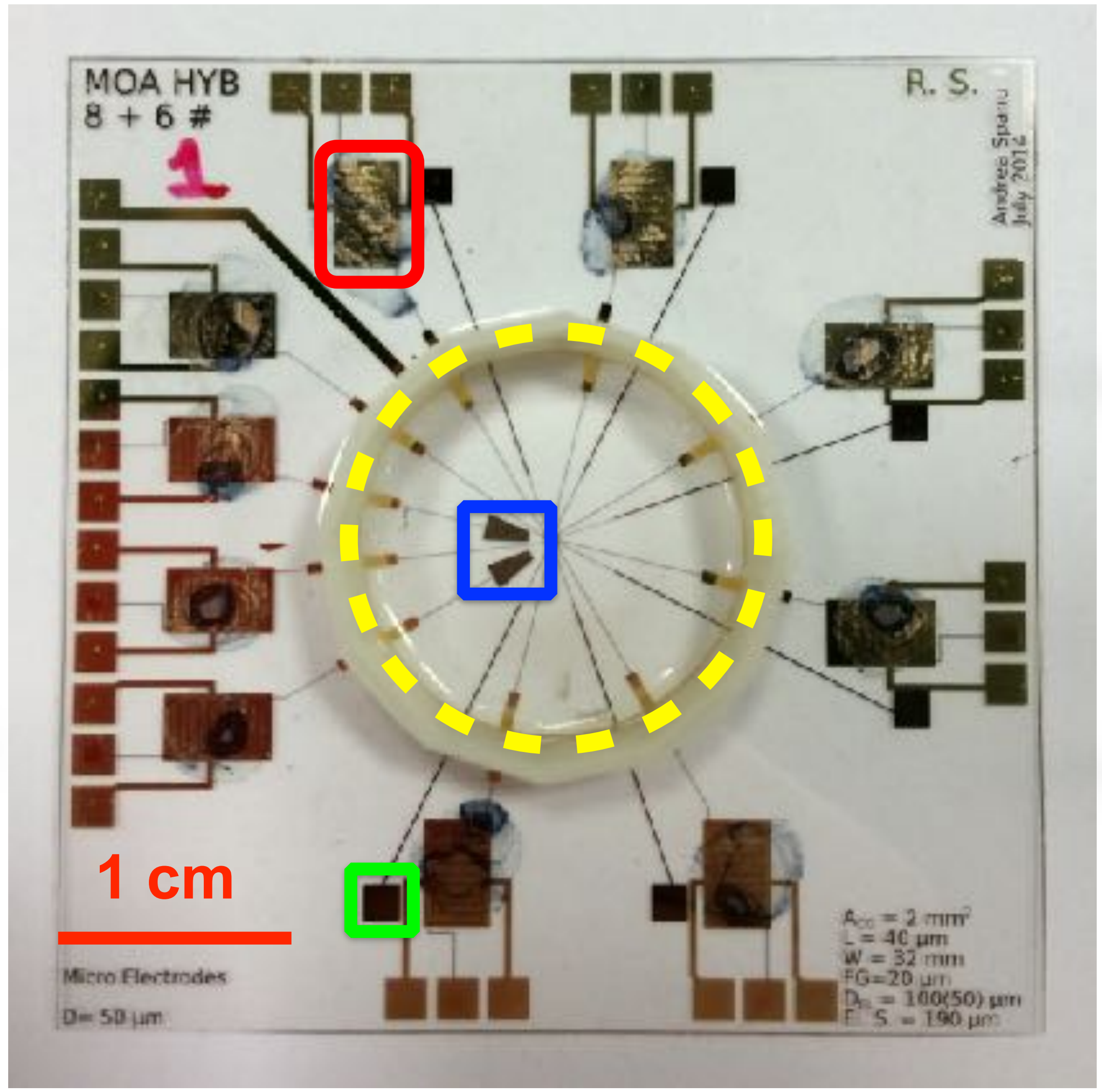
- Thermal evaporation (metals)
- Chemical vapor deposition (Parylene C)
- Low temperature ozonation (oxide growth)
- Drop casting (organic semiconductor)
- Plasma oxygen (Par C etching)

Micro OCMFET Array
Device development

MOA: structure

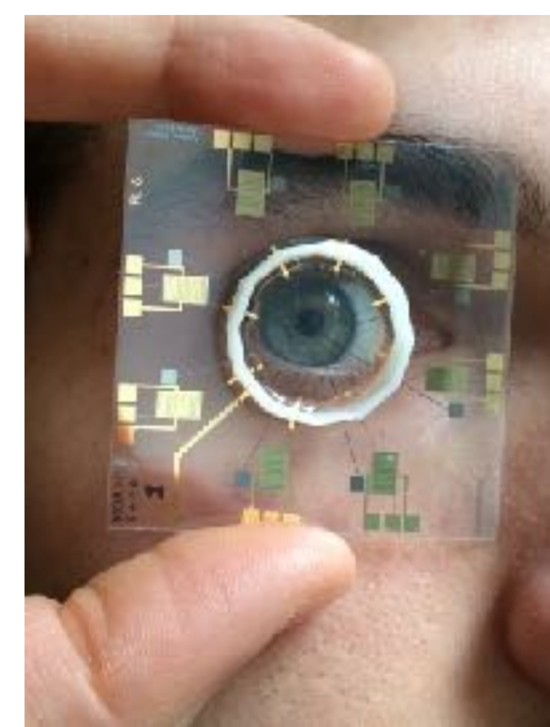
OCMFET

Delimiting ring
Sensing area



Passive
Microelectrodes

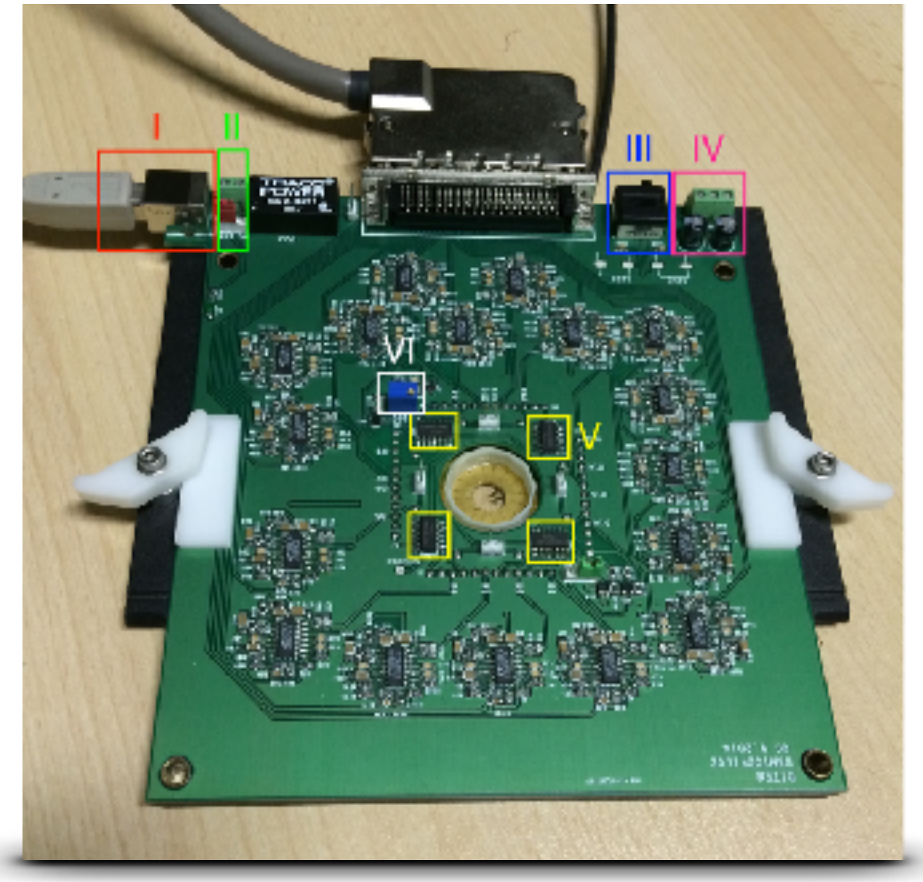
Additional
channels

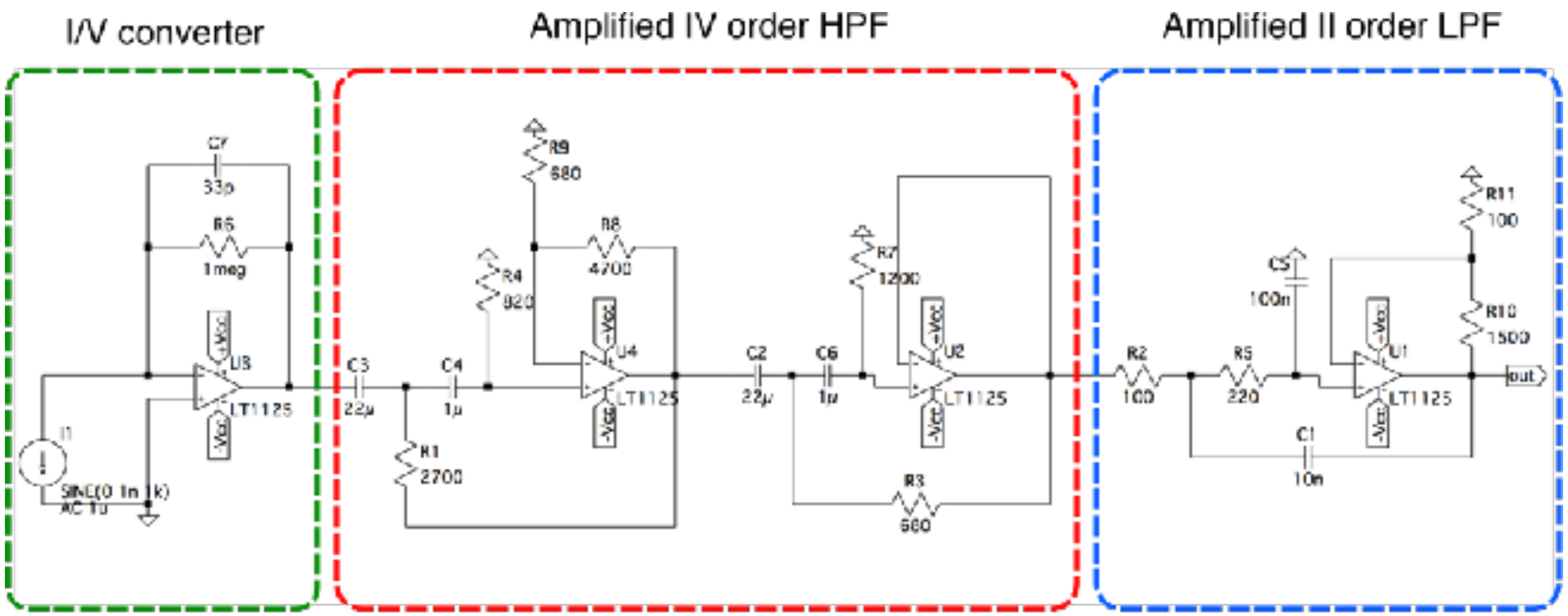


- Up to 16 OCMFET onto the same substrate
- Interdigitated source and drain contacts
- Sensing areas: 30X30 µm - 60X60 µm
- Passive microelectrodes integration
- Predisposition to pH/temperature/strain (…) measurements

MOA: Readout electronics

- 16 identical channels for electrical activity
- Bandwidth: 100 Hz - 4,3 kHz
- Fully compatible with Multi Channel Systems ground plates
- Portability: USB power supply
- Independent source biasing
- 2 additional channels dedicated to slow signals detection (pH, temperature, cell mechanical activity…)
- Electrodes for electrical stimulation

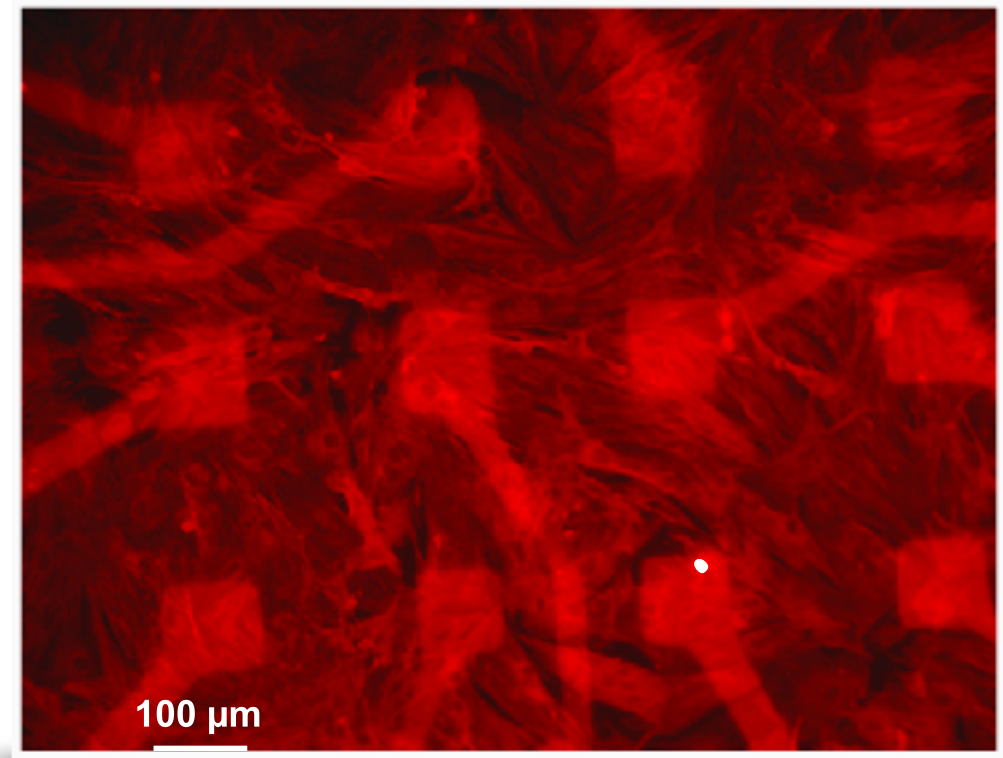




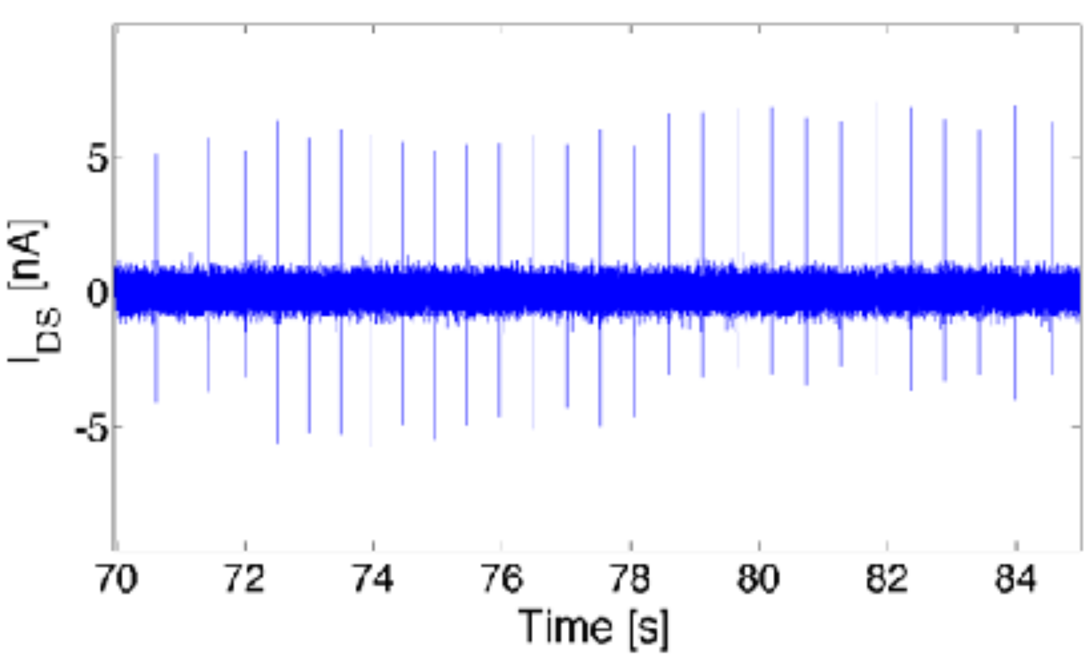
Simple readout circuit!

Preliminary validation: rat cardiac myocytes

- Rat cardiomyocytes primary cultures
- Measurements performed @ 37 °C
- $V_{GS}=V_{DS}= -1$ V
- All the experiments have been carried out inside a Faraday cage
- Activity of the same culture measured with different methods (Multi Channel Systems MEA1060 Amplifier)
- <u>No need of a reference electrode</u>

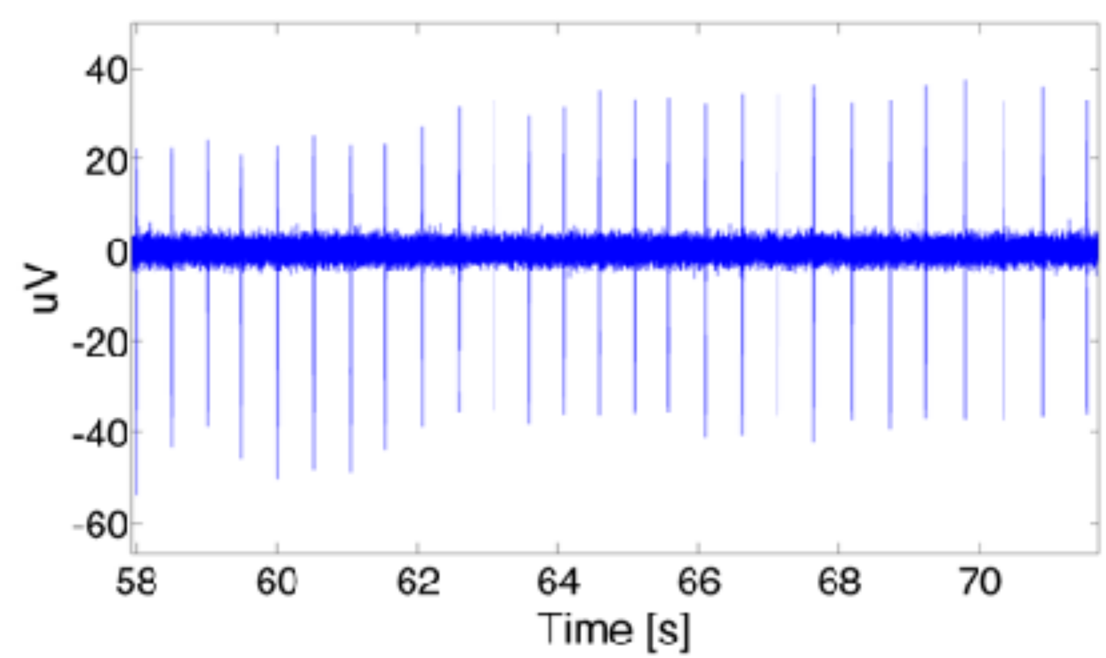


OCMFET Recording



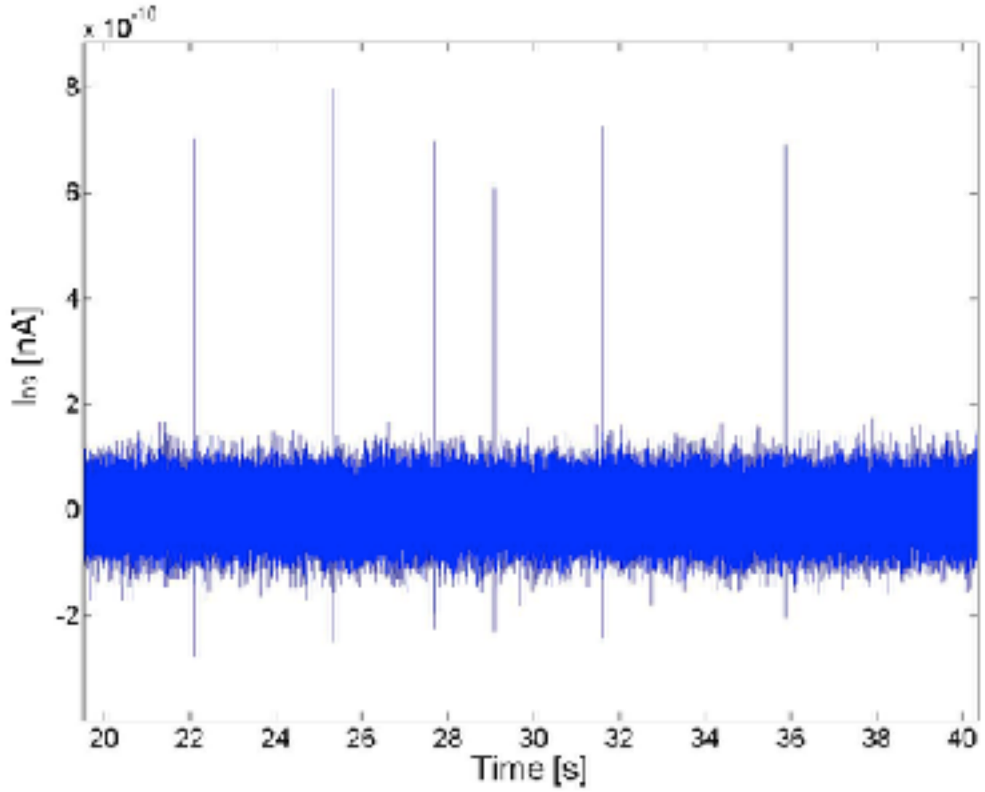
Same frequency…

Microelectrode Recording



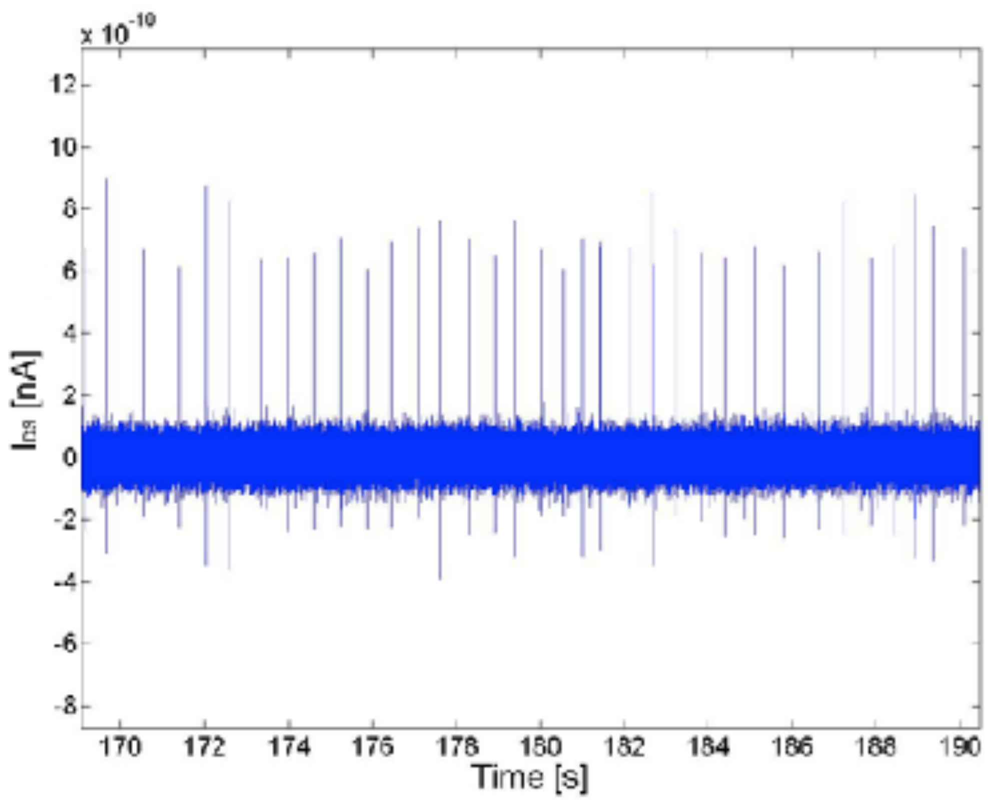
A. Spanu et al. An organic transistor-based system for reference-less electrophysiological monitoring of excitable cells. *Sci. Rep.* **5**, 8807 (2015) doi:10.1038/srep08807.

Chemical modulation of cardiomyocytes activity



Basal activity @ 37° C

Spike frequency: 0.3 Hz

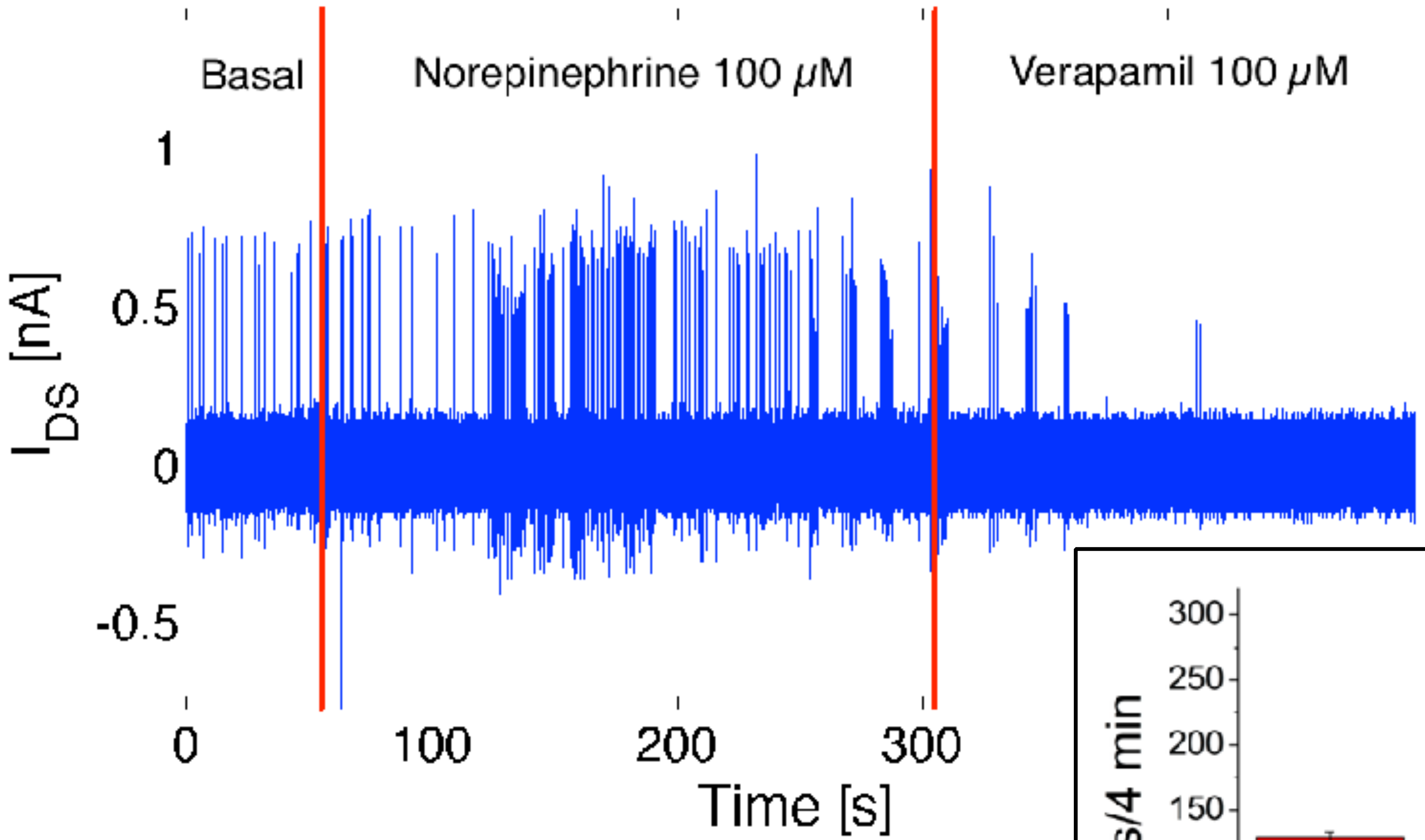


Norepinephrine (100 μM)
A neurotransmitter that acts as a cardio-stimulant

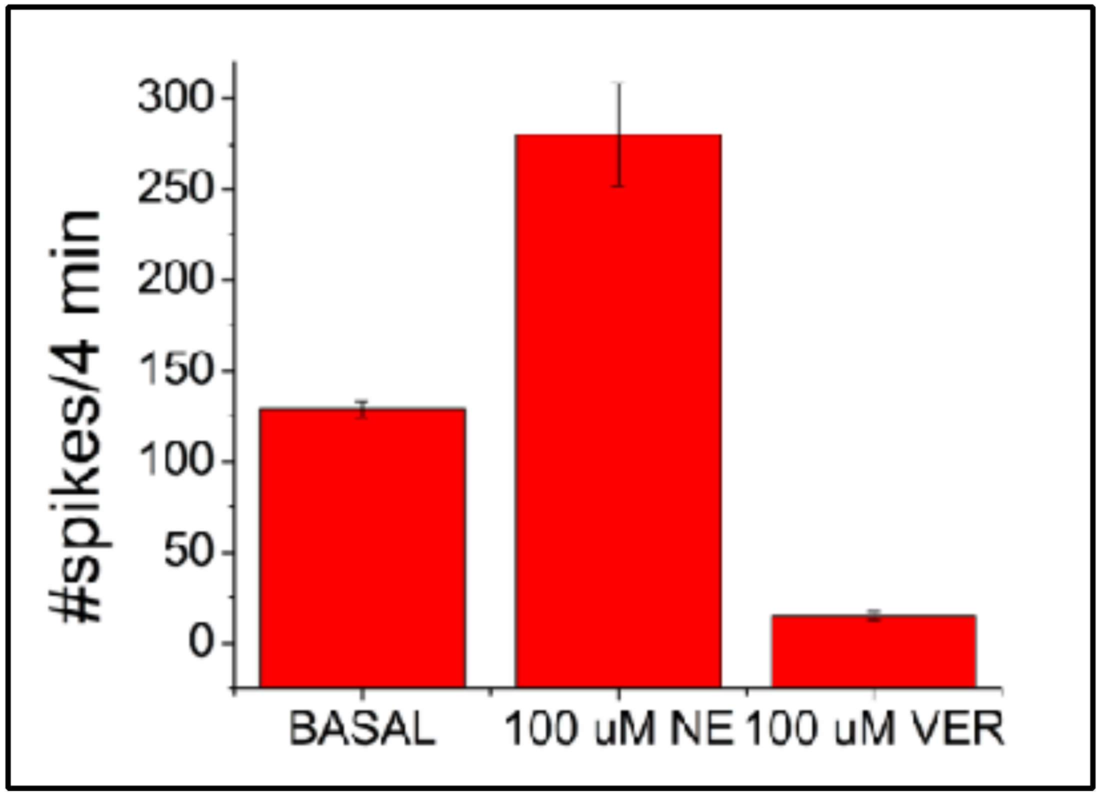
Spike frequency: 1.6 Hz

A. Spanu et al. An organic transistor-based system for reference-less electrophysiological monitoring of excitable cells. *Sci. Rep.* **5**, 8807 (2015) doi:10.1038/srep08807.

Chemical modulation of cardiomyocytes activity

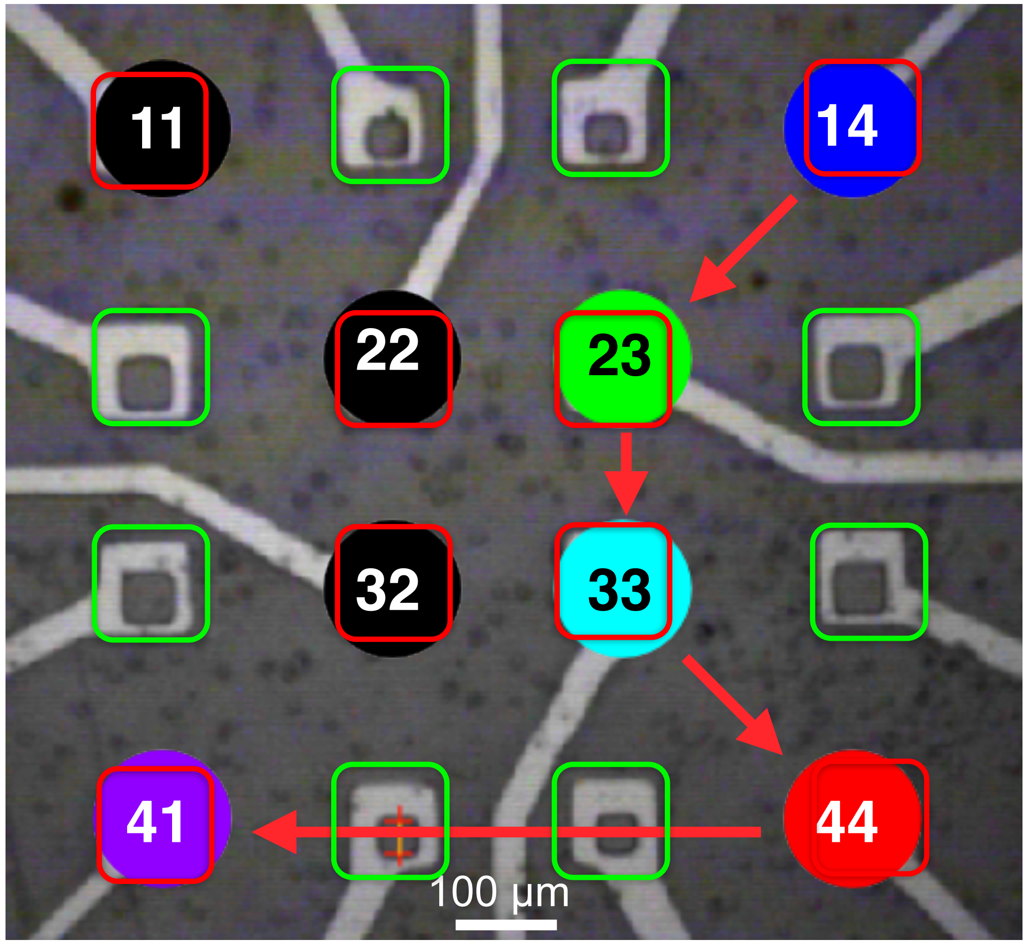


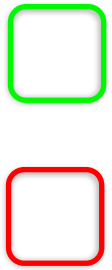
Statistics on 5 working OCMFETs on the same substrate

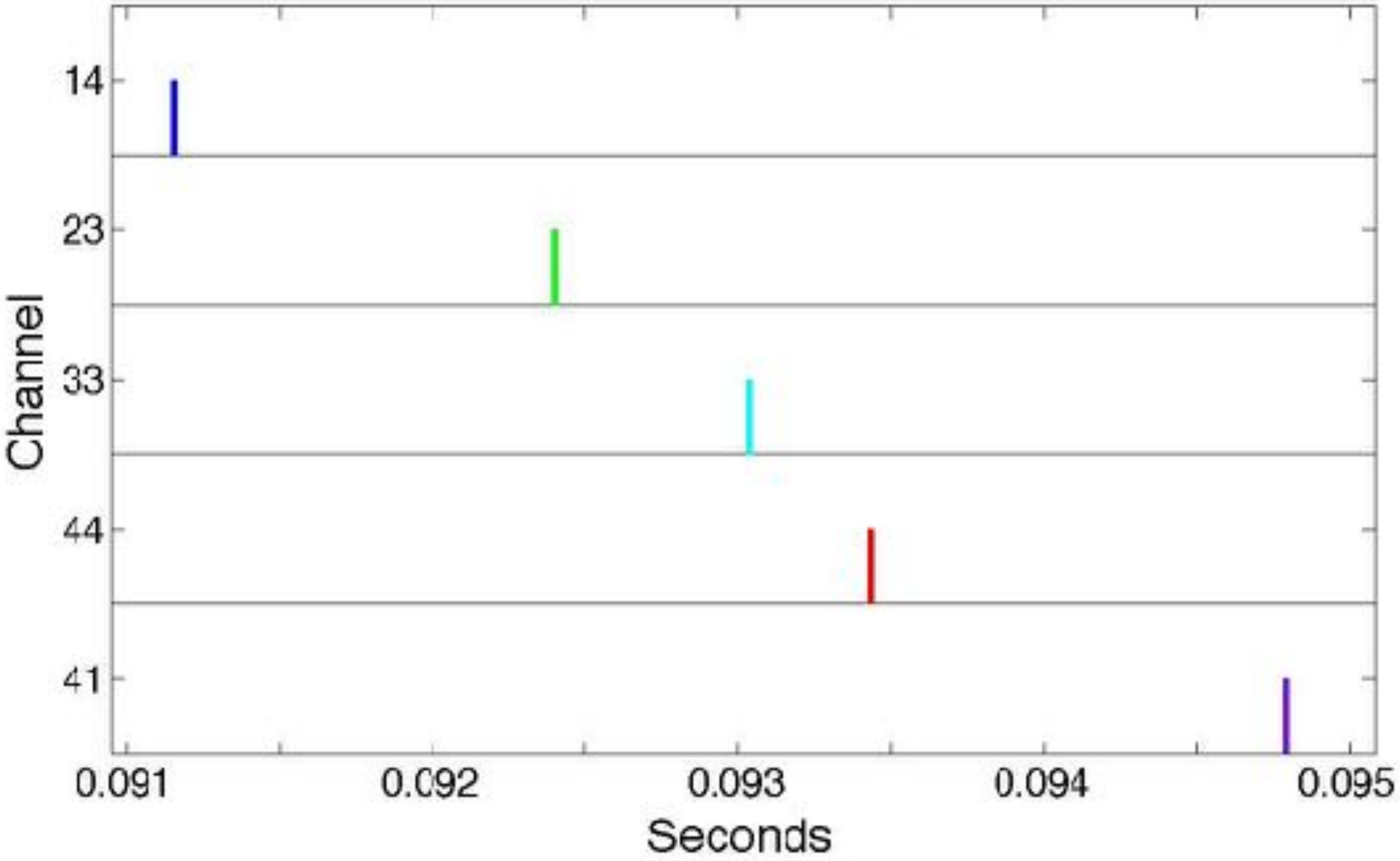


A. Spanu et al. An organic transistor-based system for reference-less electrophysiological monitoring of excitable cells. *Sci*. *Rep*. **5**, 8807 (2015) doi:10.1038/srep08807.

Multisite recordings



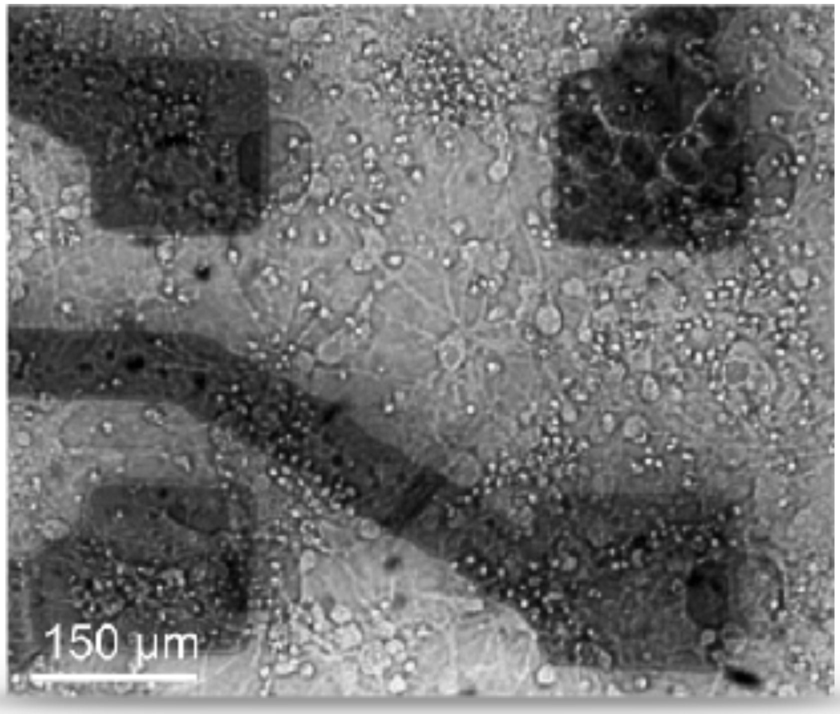


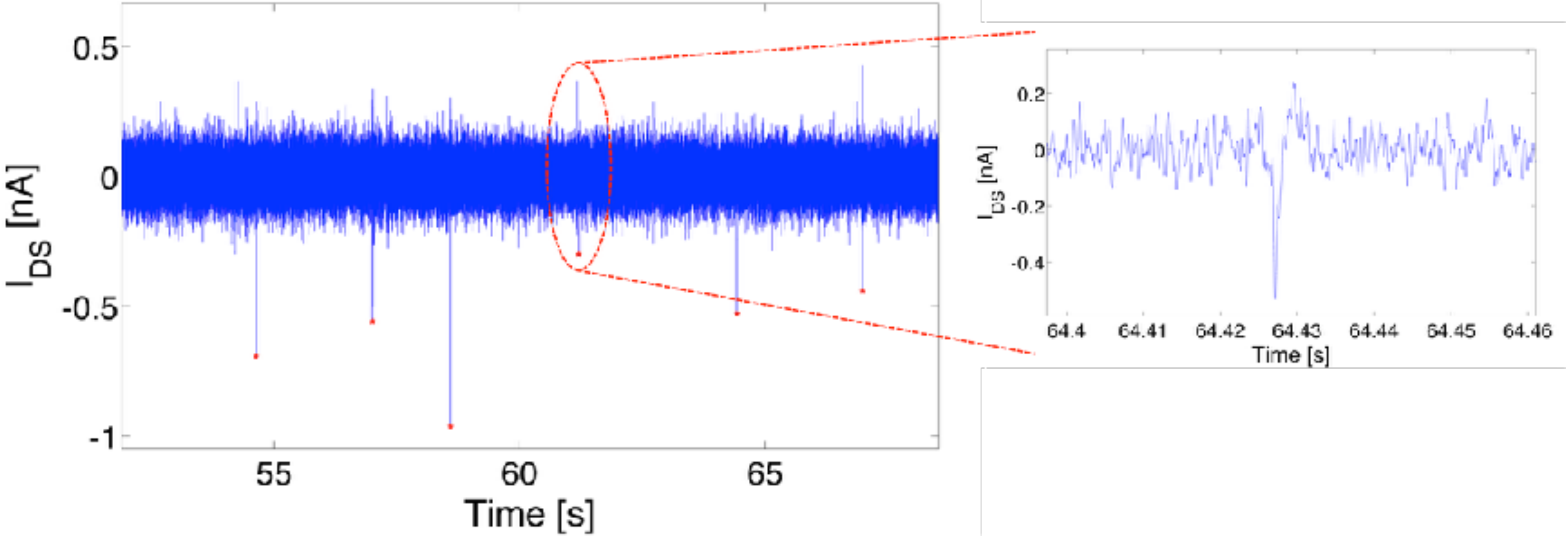


Propagation velocity = 0.4 m/s

Striatal neurons: preliminary recordings

Striatal primary neurons from post-natal (P2) rat maintained 21 days in vitro (21 DIV). Basal activity recordings





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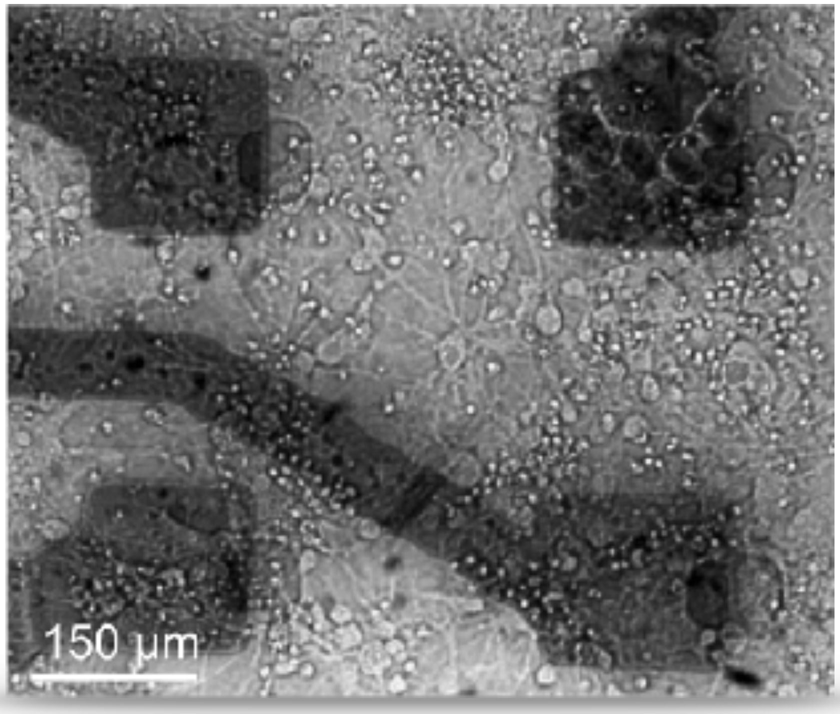
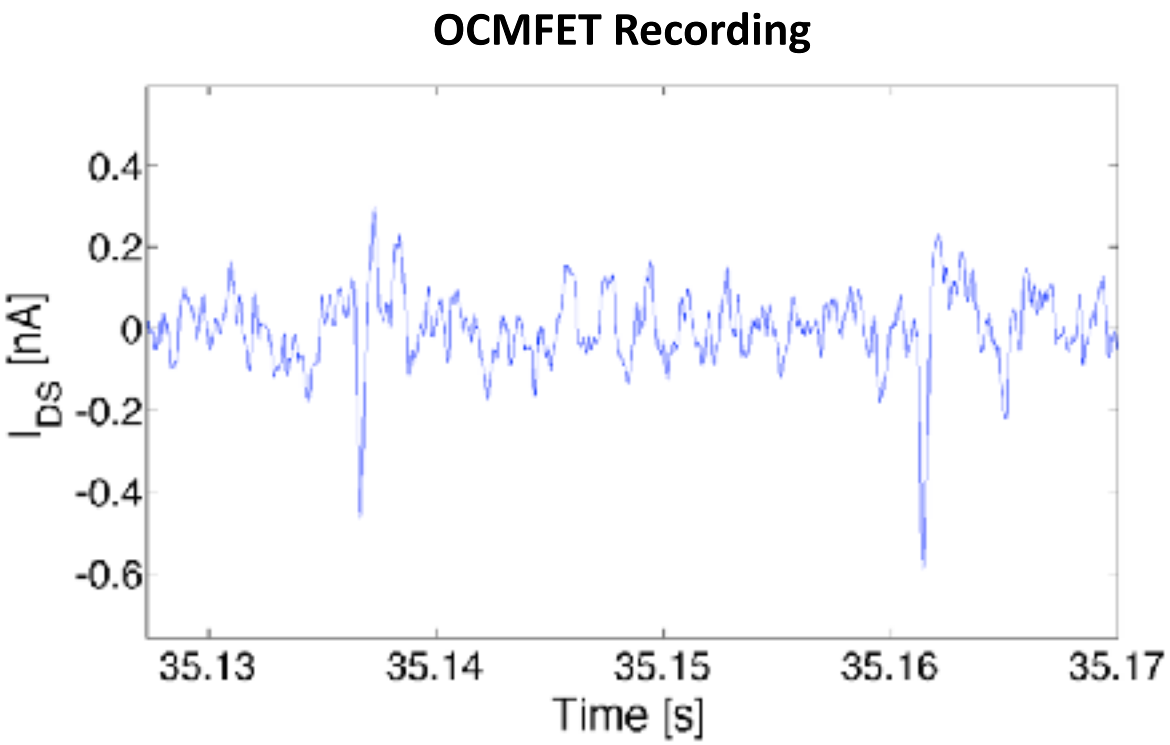
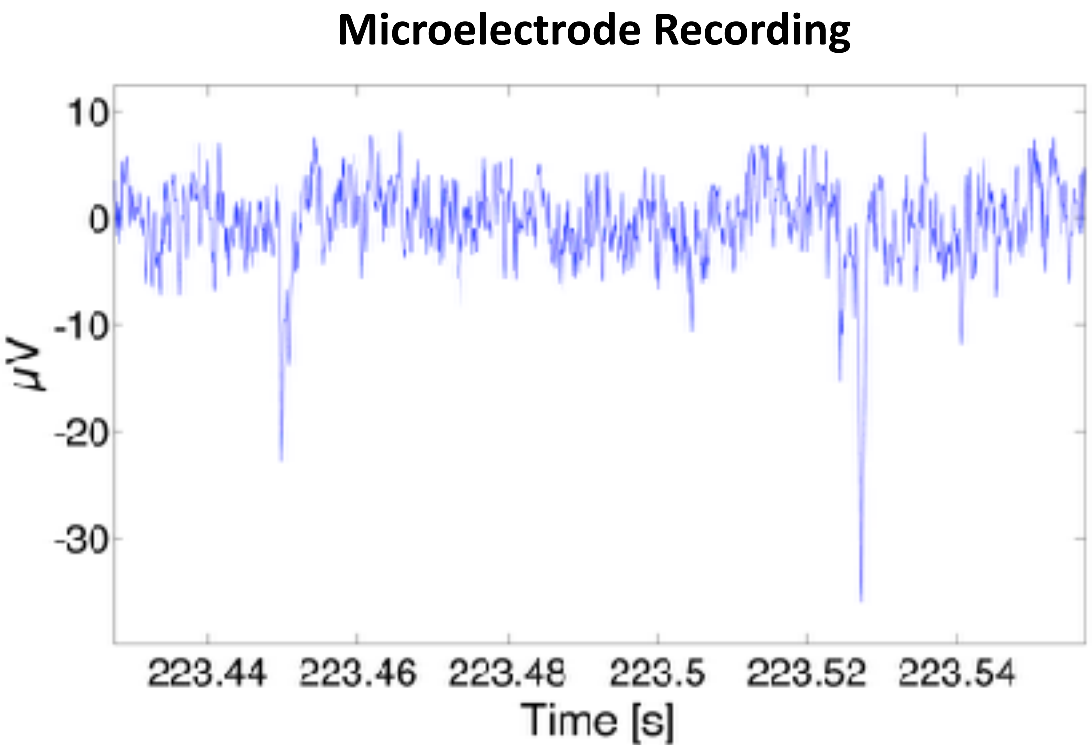
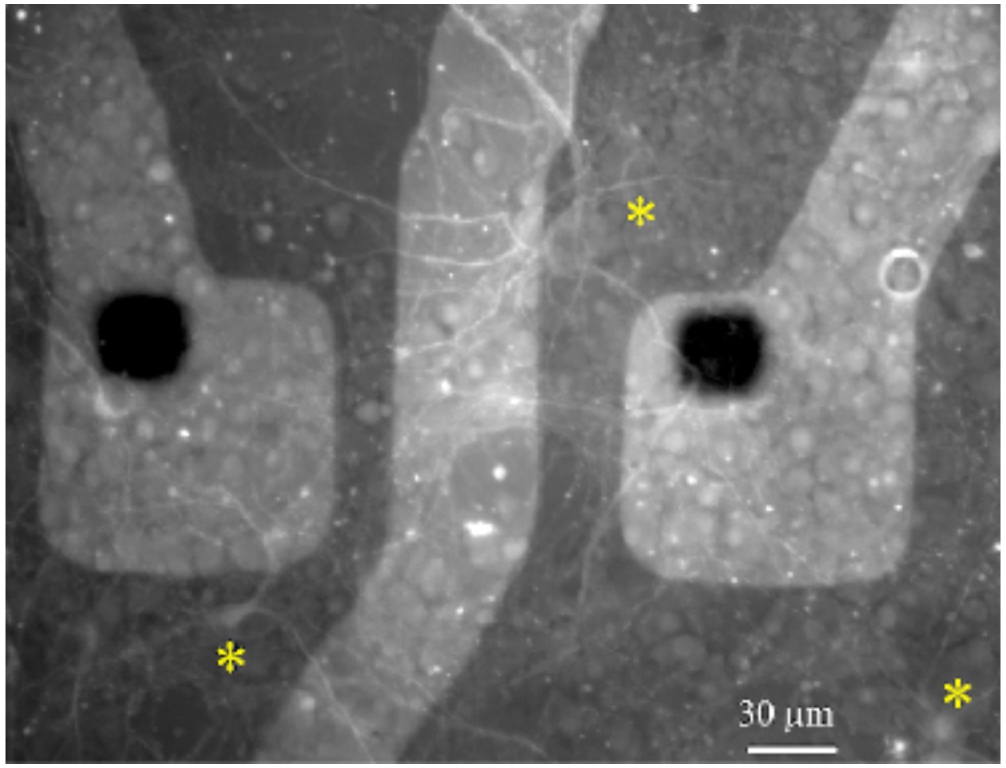




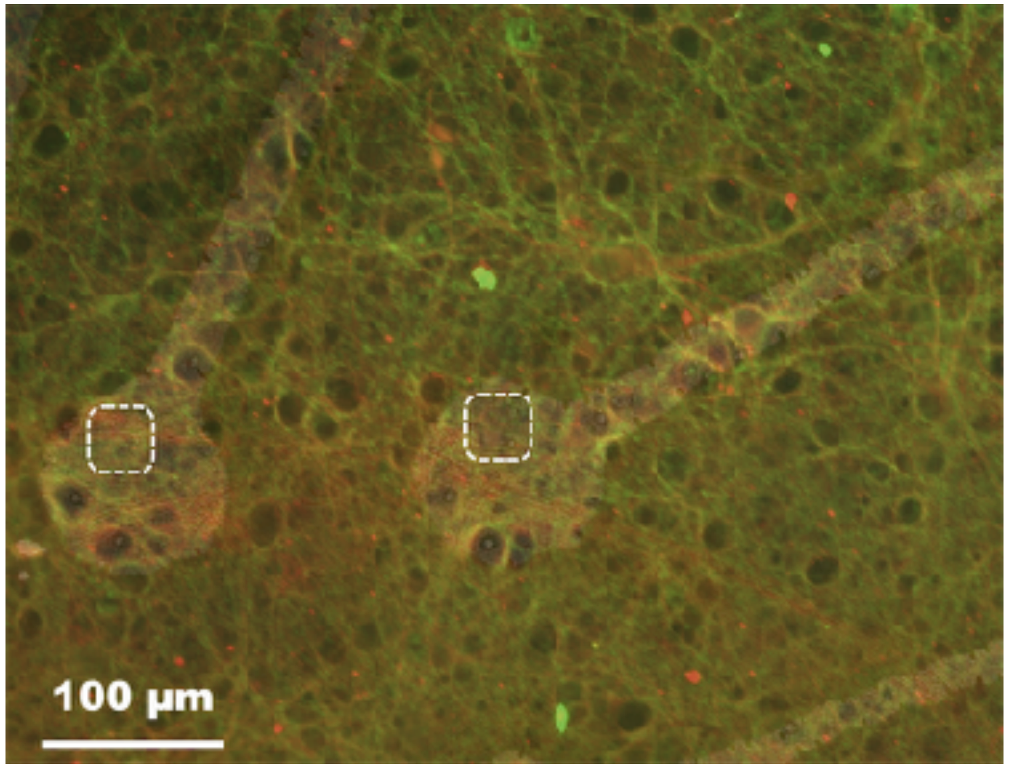


Hippocampal neurons

- Hippocampal primary neurons from post-natal (P2) rat maintained 21 days in vitro (21 DIV)
- Cell viability monitored by means of DIC microscopy, immunofluorescence, and recordings with the embedded passive microelectrodes



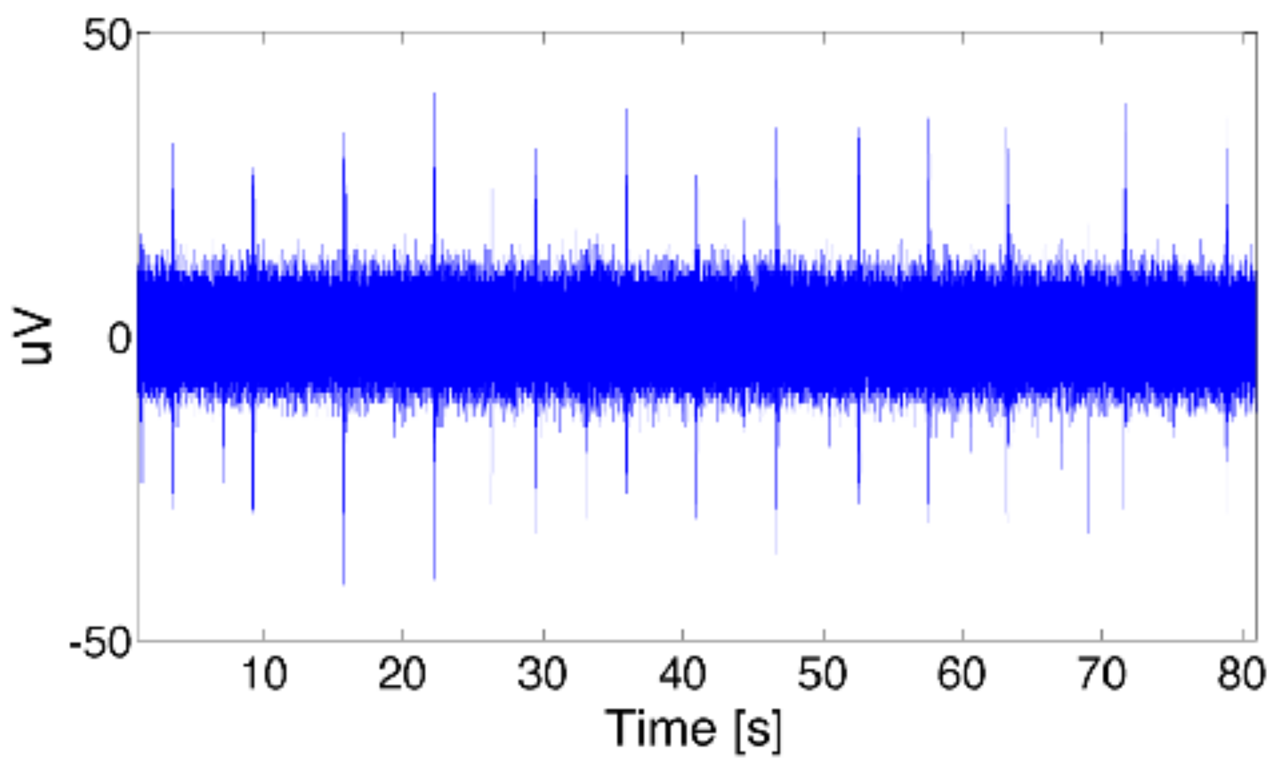
Rat hippocampal neurons cultured onto a MOA and fixed after a recording section



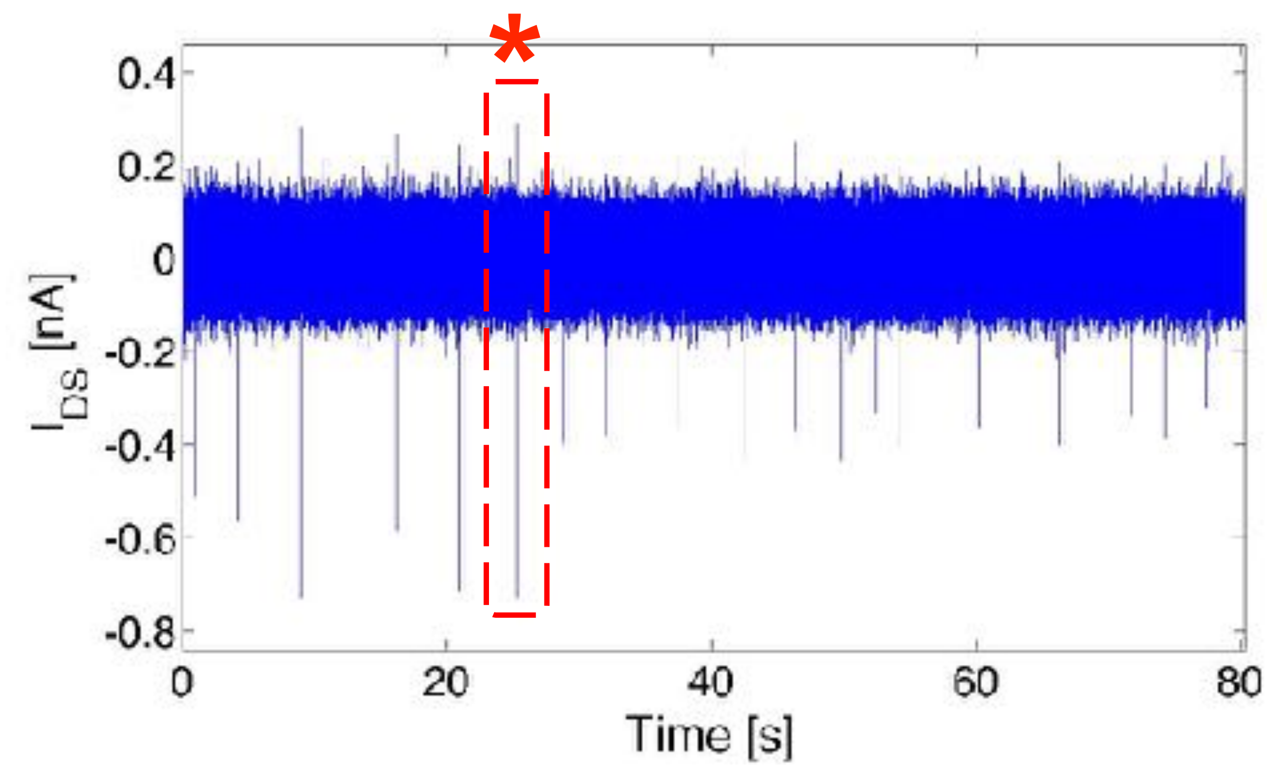
Fluorescence image of rat hippocampal neurons cultured onto a MOA device

Hippocampal neurons

Microelectrode Recording - Frequency = 0.2 Hz



MOA Recording - Frequency = 0.2 Hz

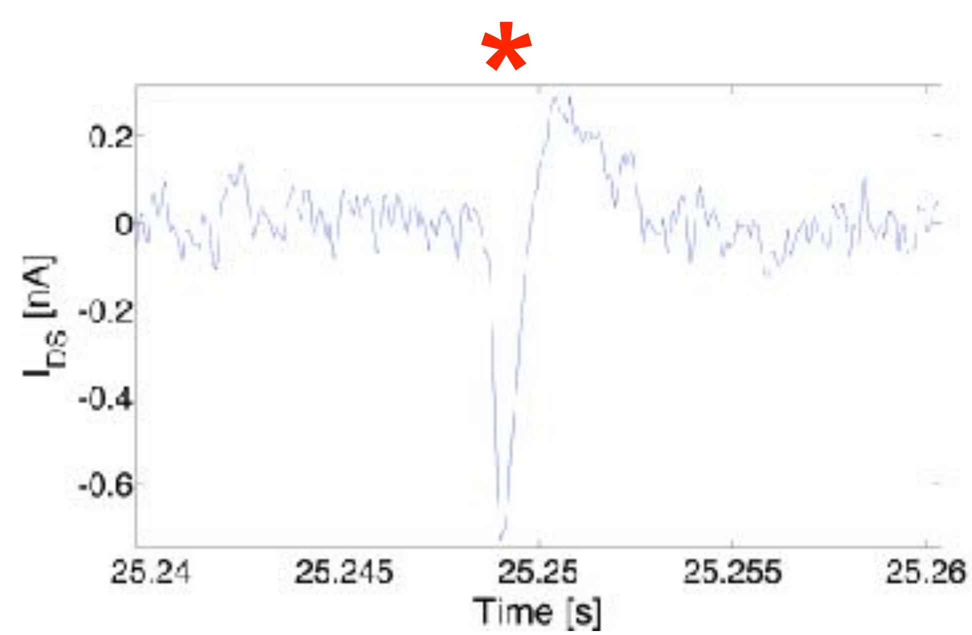


<u>Maximum SNR for OCMFET measurements:</u>

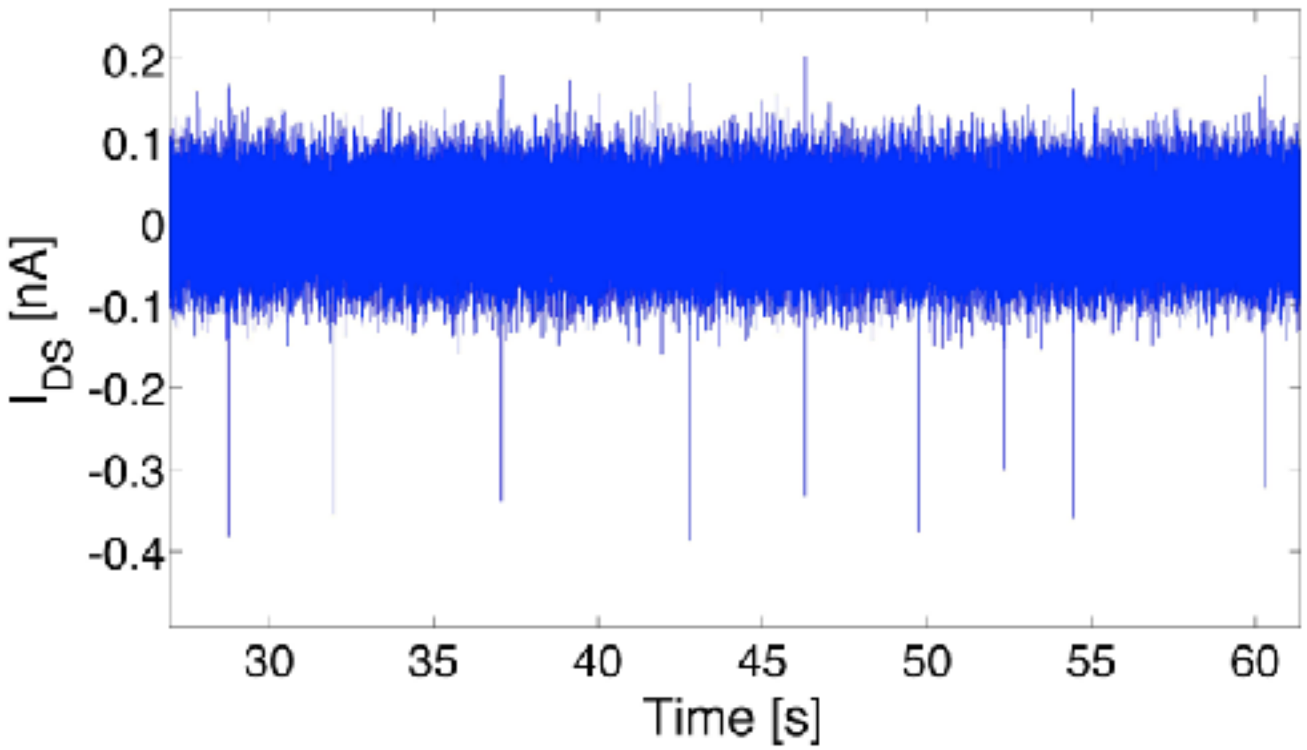
$$SNR = \frac{\bar{A}_{PP}}{6 * std_{noise}} = 2{,}7$$

<u>Maximum SNR for microelectrode measurements:</u>

$$SNR = \frac{\bar{A}_{PP}}{6 * std_{noise}} = 1{,}9$$

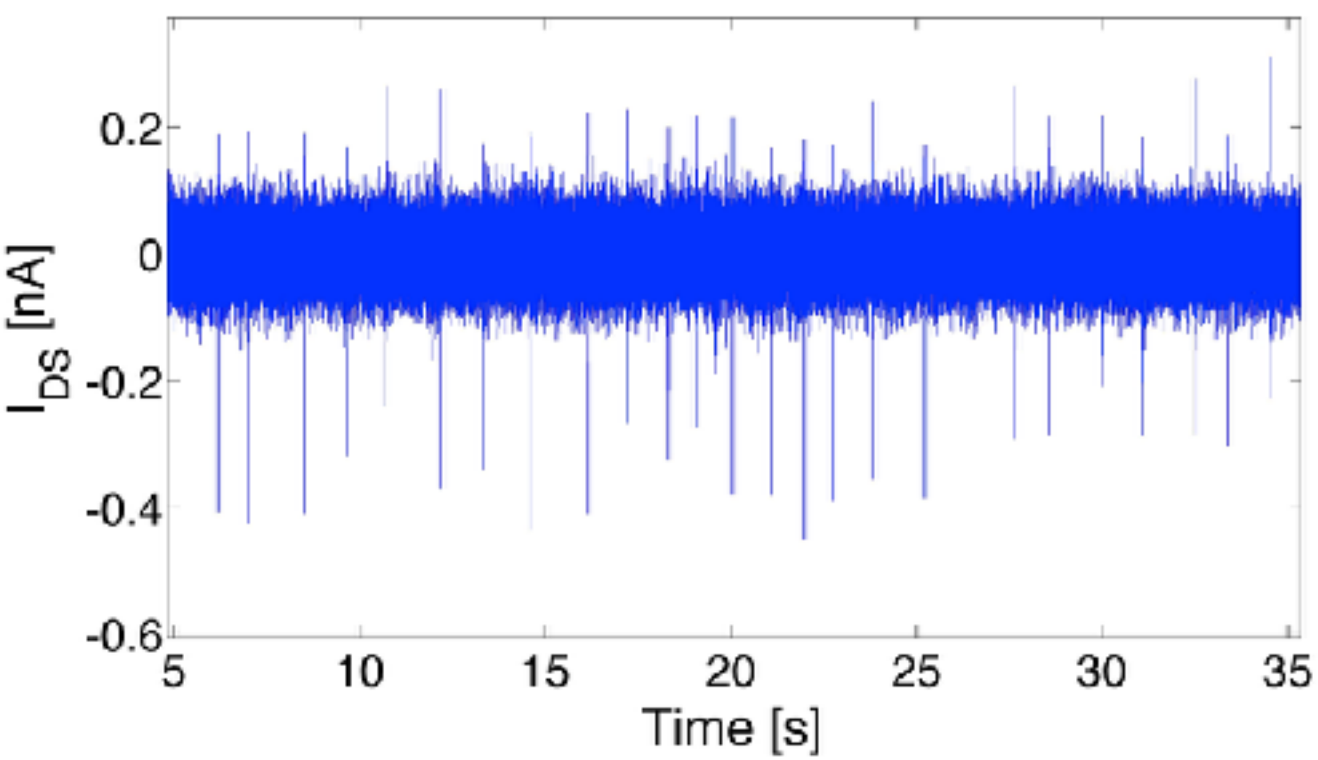


Hippocampal neurons - chemical modulation



Basal activity @ 37° C

Spike frequency: 0.3 Hz

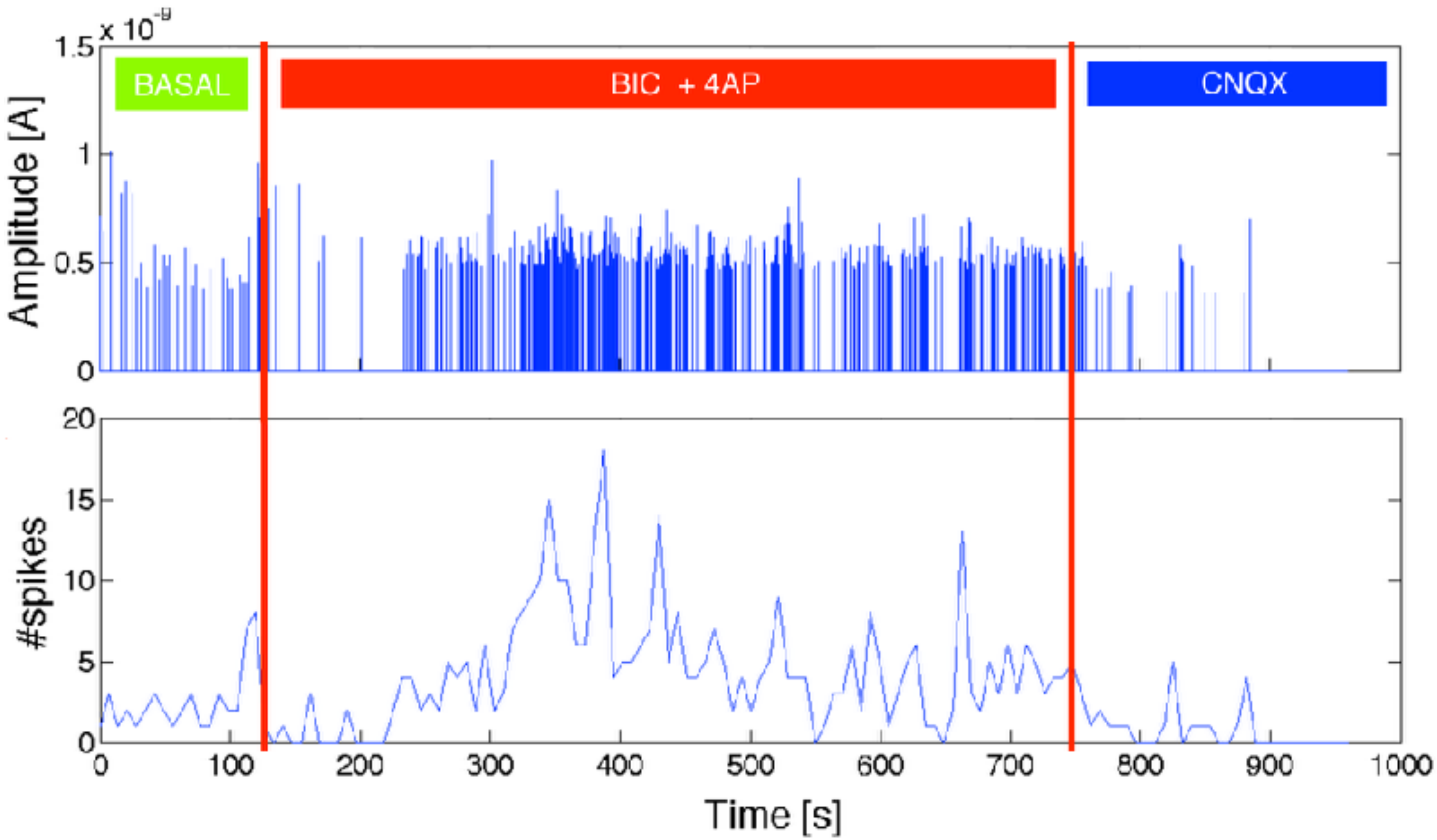


50 µM 4Amino Pyridine (4AP):
Reduction of the threshold of excitability

Spike frequency: 0.9 Hz

25 µM Bucuculline (BIC):
Blockade of the inhibitory action of $GABA_A$ receptors

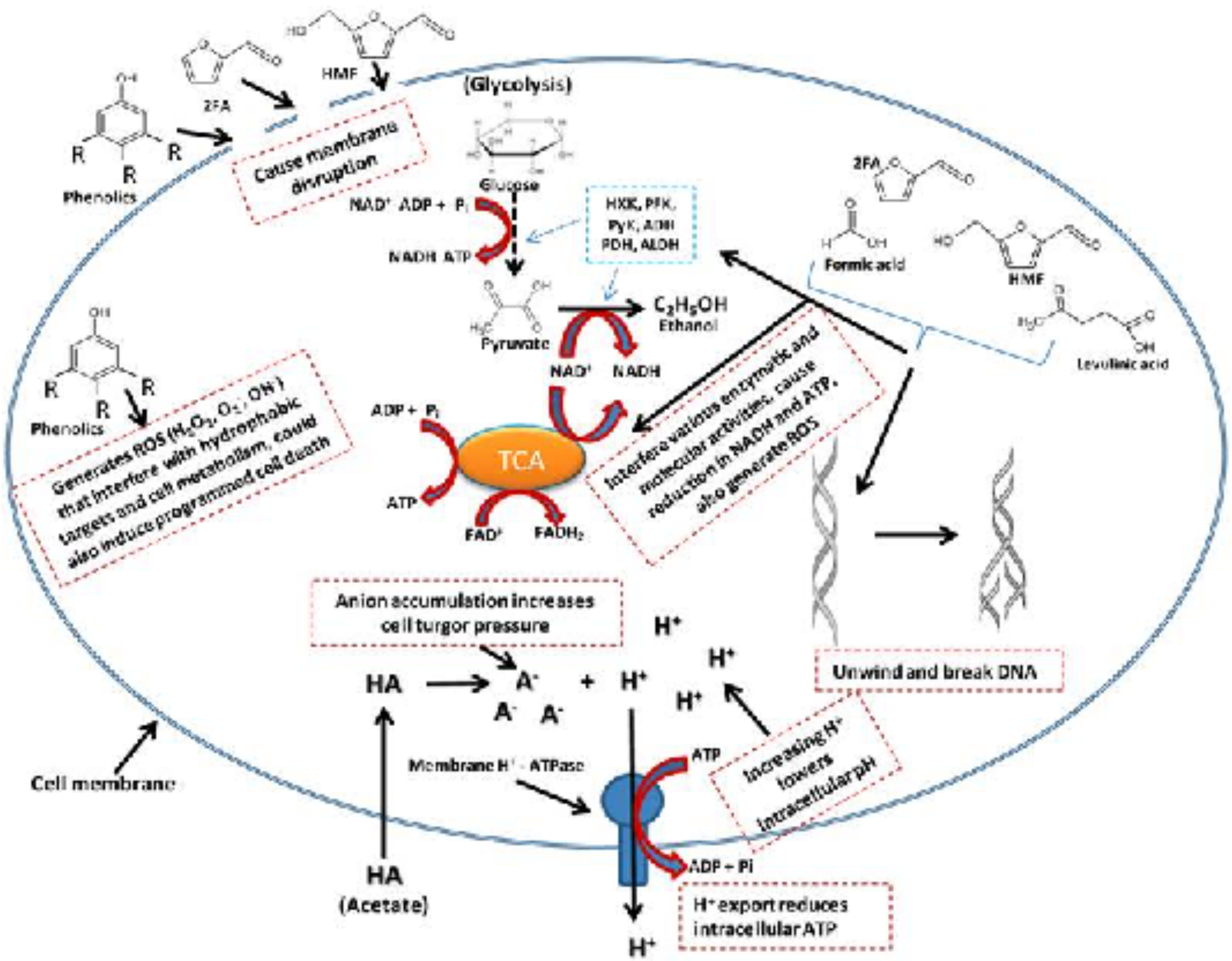
Hippocampal neurons - chemical modulation



Complete experiment: acceleration of the firing rate (drug cocktail) followed by the complete activity cessation (addition of CNQX)

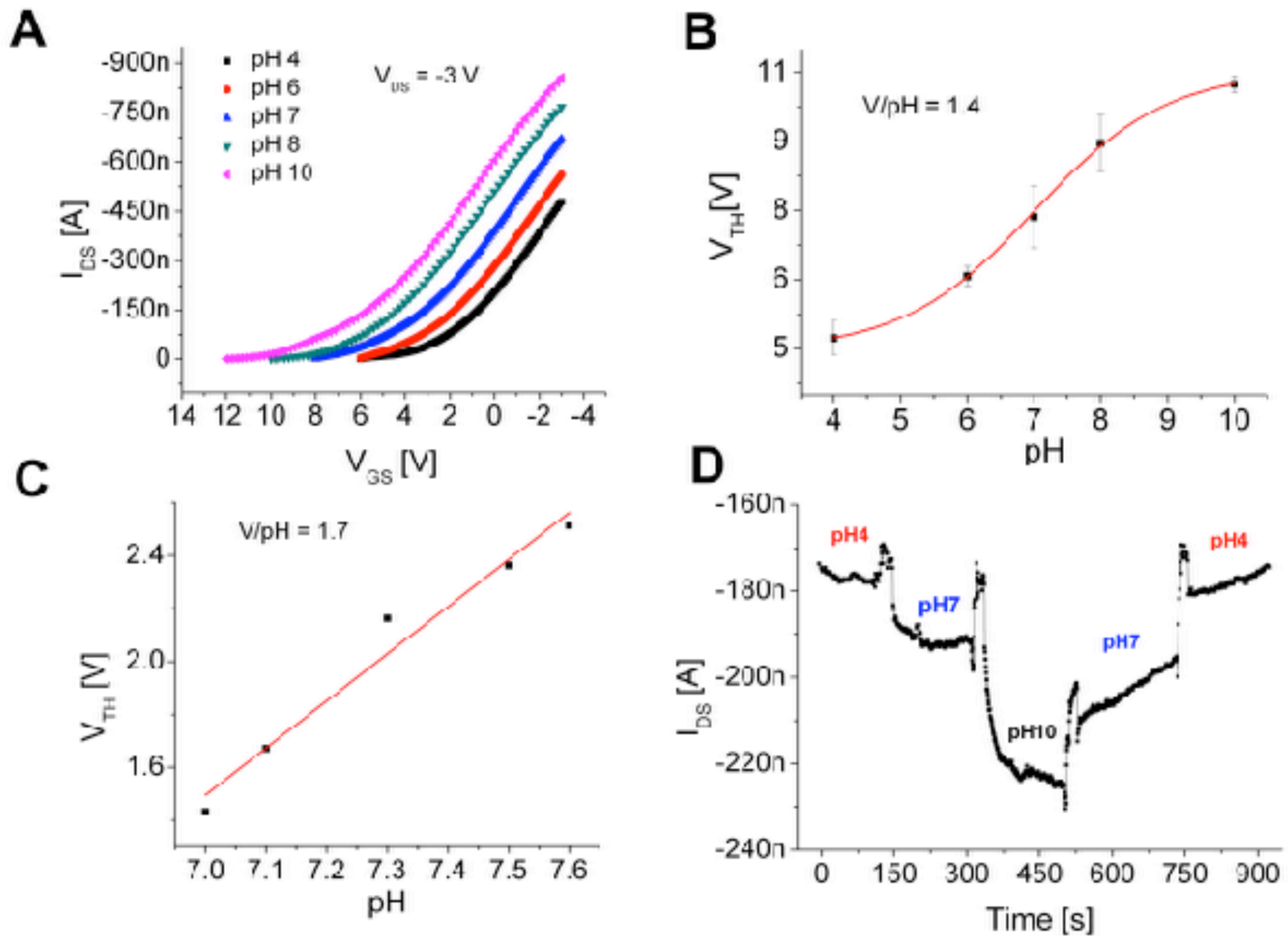
Metabolic activity recording

Monitoring pH during in vitro and in vivo electrophysiological applications is very important since living cells are sensitive to pH changes of the surrounding medium. Furthermore, local pH variation are associated to cells metabolic activity.



Martinoia, S. et al. Development of ISFET array-based microsystems for bioelectrochemical measurements of cell populations. *Biosens. Bioelectron.*, 1043–1050 (2001).

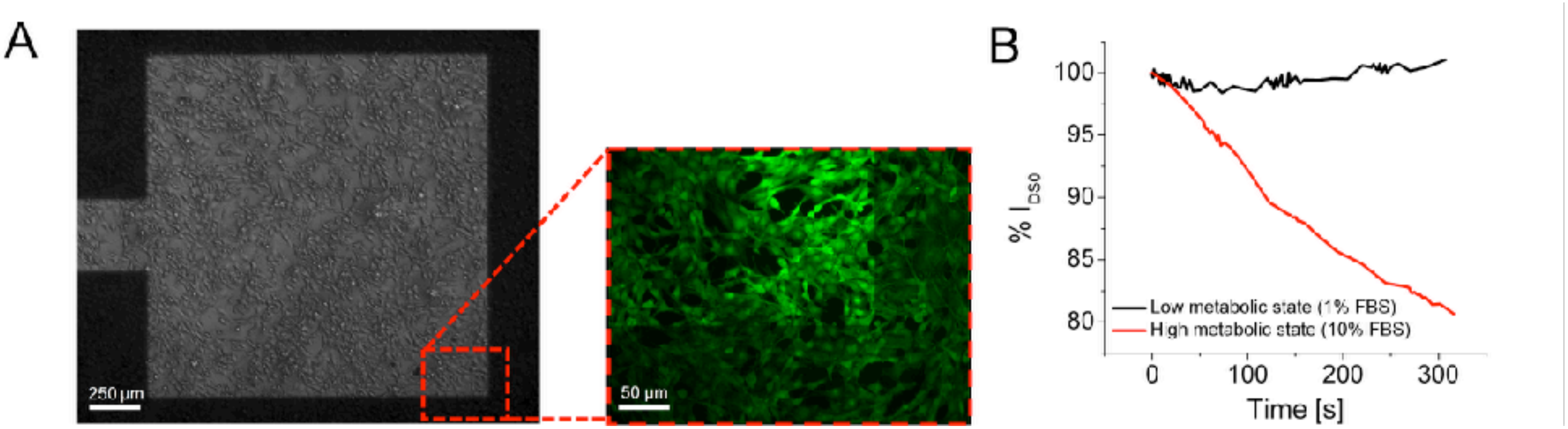
Metabolic activity recordings: pH sensing



- Supernernstian sensitivity (the Nernst limit is 59 mV/pH at room temperature) of more than 1 V/pH
- Reference-less device
- Suitable for metabolic activity recordings

Metabolic activity recordings: preliminary validation

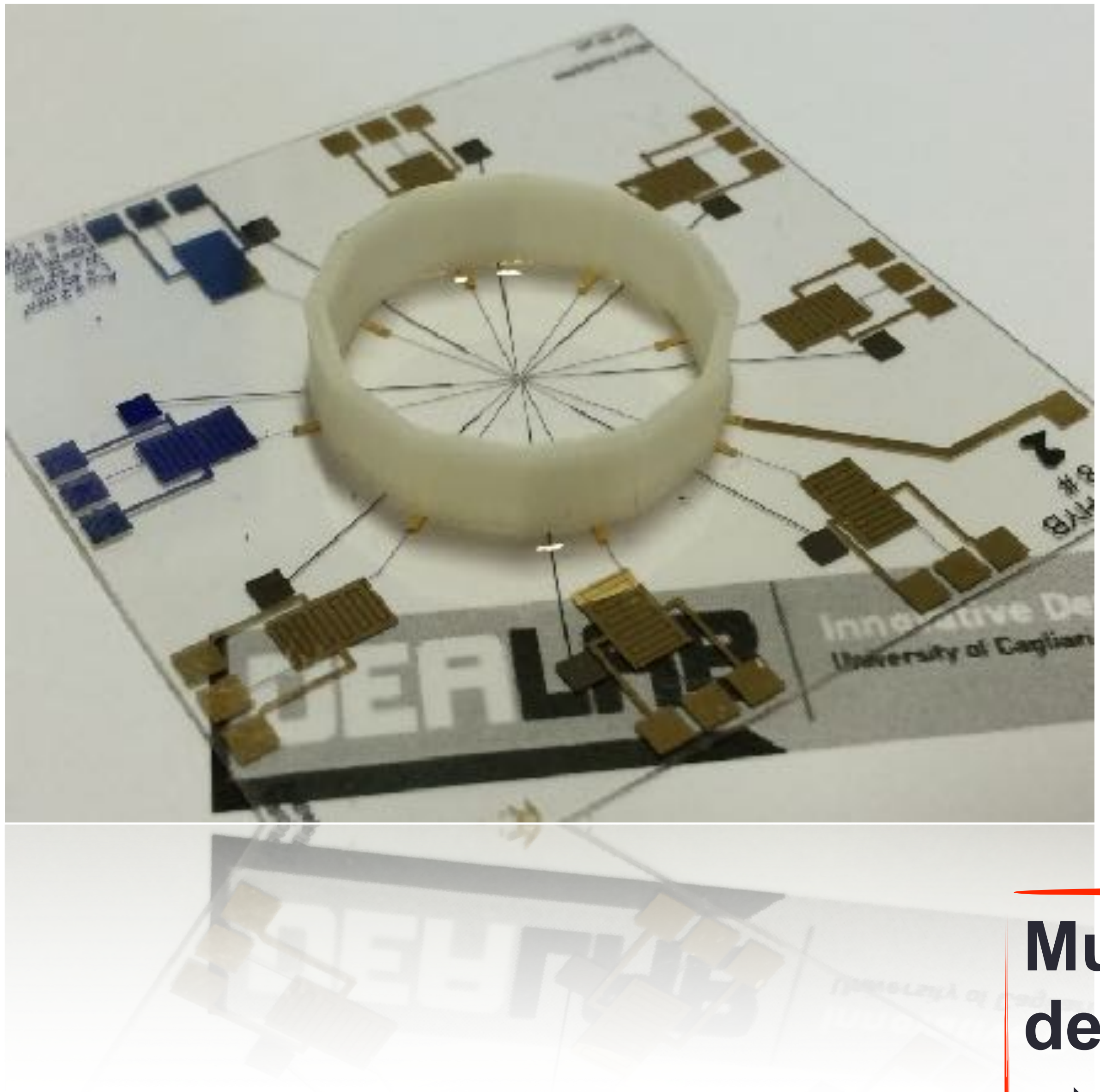
Fibroblast culture (no electrical activity)



The OCMFET has been able to discriminate between two different metabolic state:

- Low metabolic state (cells metabolism slowed-down): slow acidification rate
- High metabolic state (cell metabolism accelerated): fast acidification rate

What's next?



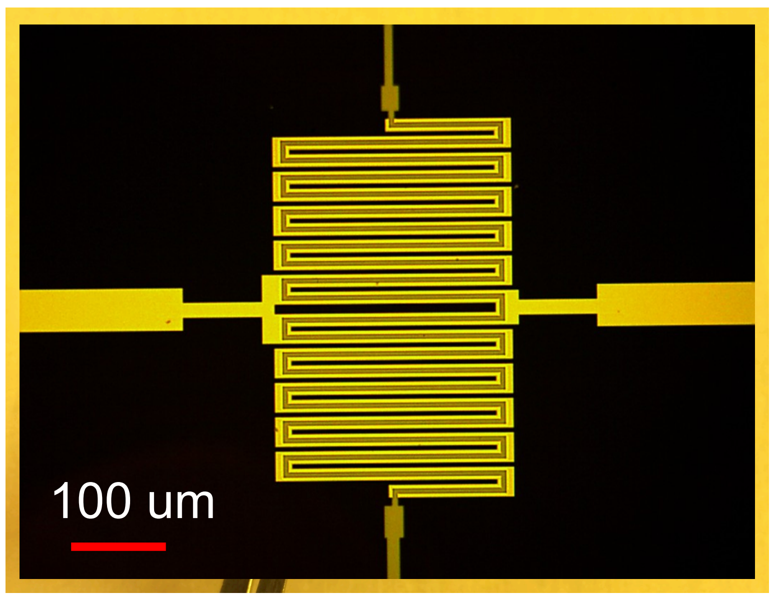
High density device

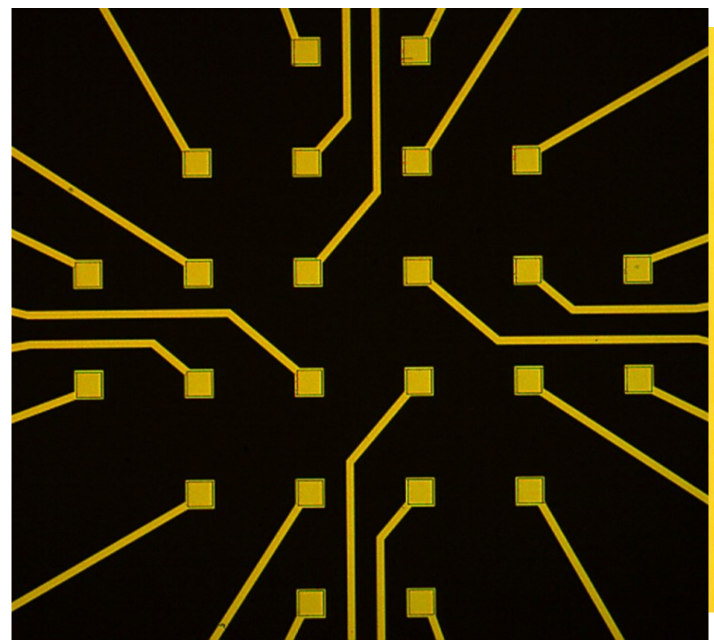
***In vivo* applications**

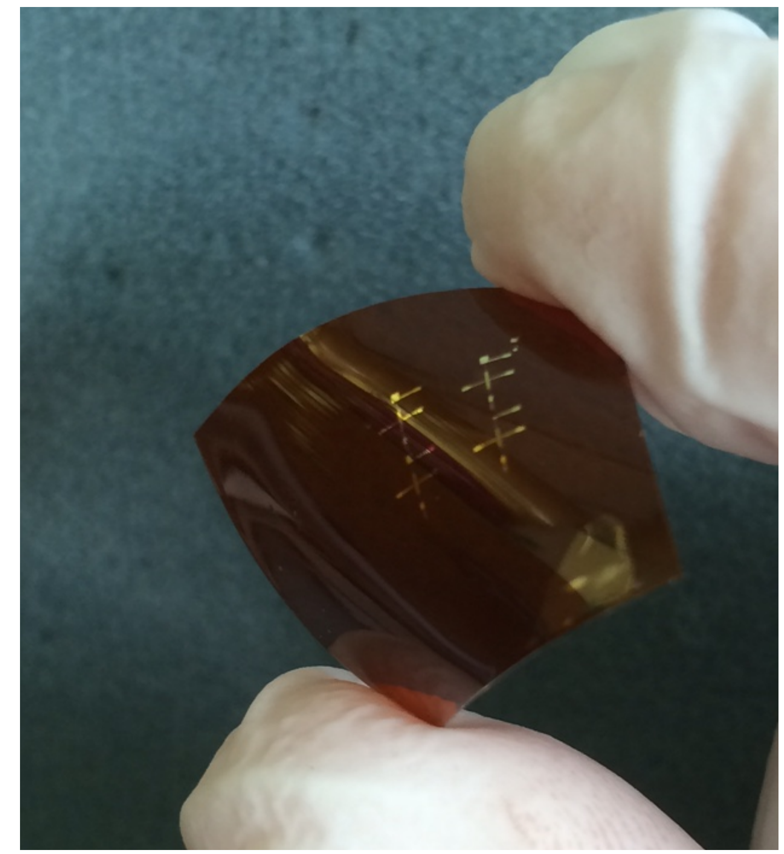
Multimodal low-cost devices

- pH sensing
- temperature sensing
- force sensing
- whatevercausesachargevariation sensing!

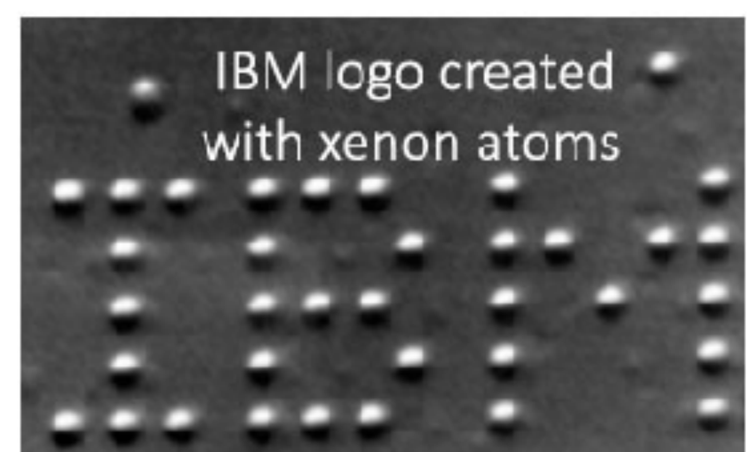
High Density devices for in vitro electrophysiology





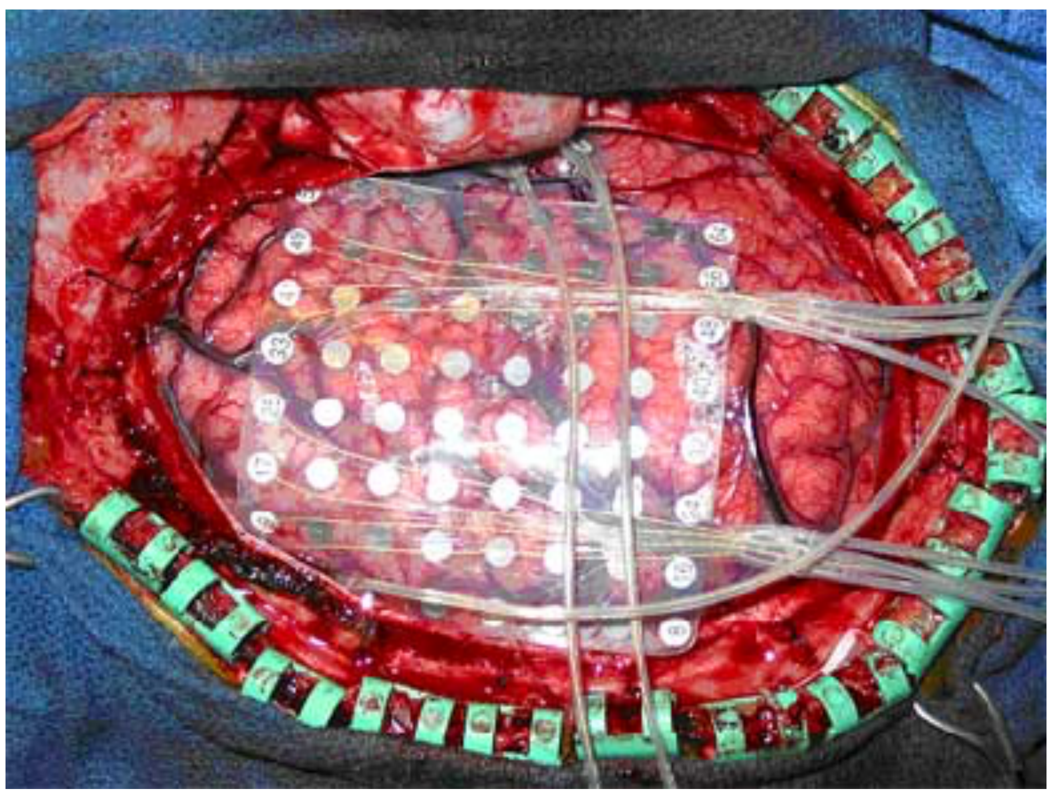


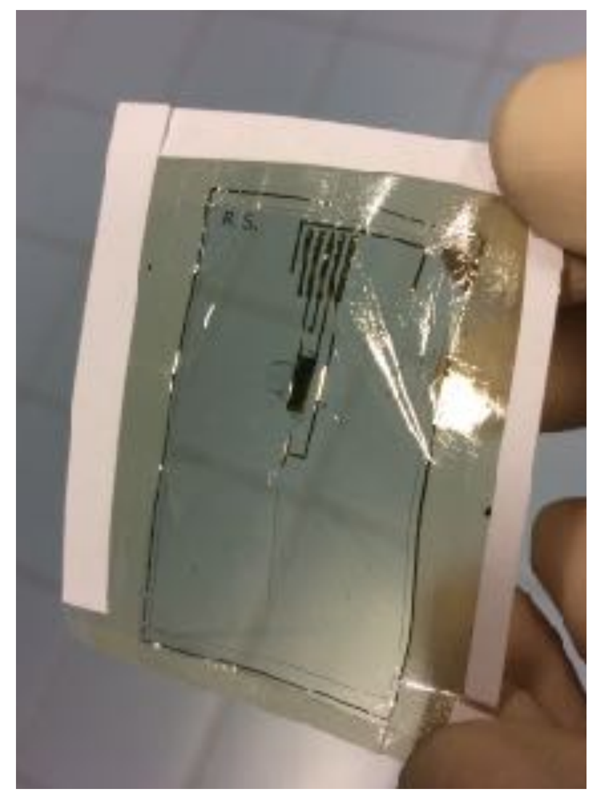
In collaboration with
University of Genova and
IBM Almaden Research Center
San Jose, California

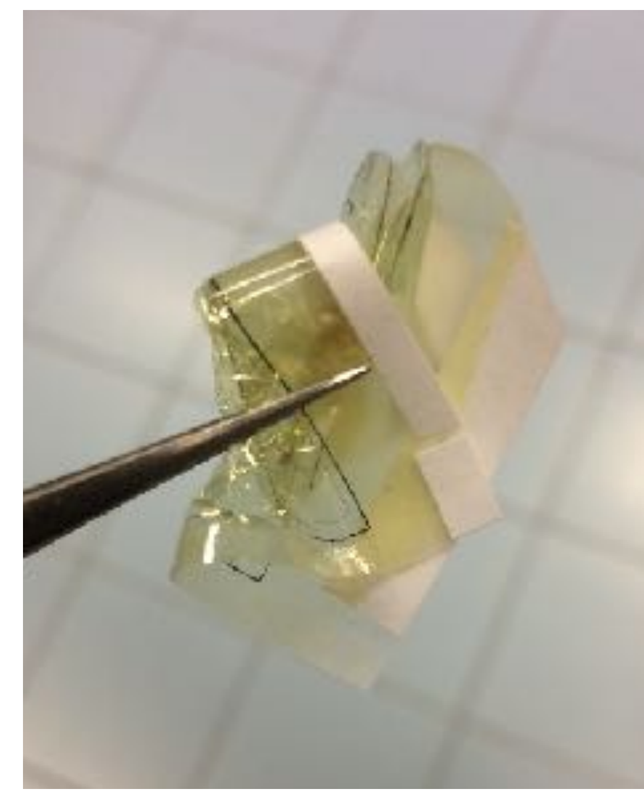


From *in vitro* to *in vivo* testing

- OCMFET on sub-micron substrates for conformal electrocorticography and sub-cortical (acute or chronic) implants for BMIs or pharmacology trials







In collaboration with the **Department of Biomedical Sciences** @ UNICA

But also…

- OCMFET devices for the simultaneous acquisition of **electrical** and **metabolic cellular signals** for *in vitro* electrophysiology
- Ultraflexible electronics for both the **acquisition ad the stimulation of neural activity *in vivo***
- Multimodal devices (temperature and pressure) for **electronic skin applications**
- All printed sensors for biomedical applications
- …