# BioElectronics
# bio-impedance measurement and modeling

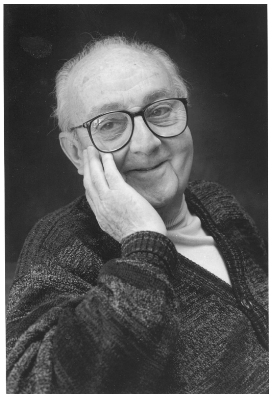
F. Kölbl

*Maître de Conférences*

*florian.kolbl@enseirb-matmeca.fr*

---

## Why modeling?



### Scientific aphorism

... all models are approximations. Essentially,
all models are wrong, but some are useful. However, the
approximate nature of the model must always be borne in mind...
George Box, *Empirial Model-Building and Response Surfaces*, 1987

In a largely pluri-disciplinary, context a model is an abstraction that we can discuss, whatever our field of expertise. It is an opportunity for engineers to meet biology

let's discuss bioelectronics with it!

# Today's agenda

## Lecture

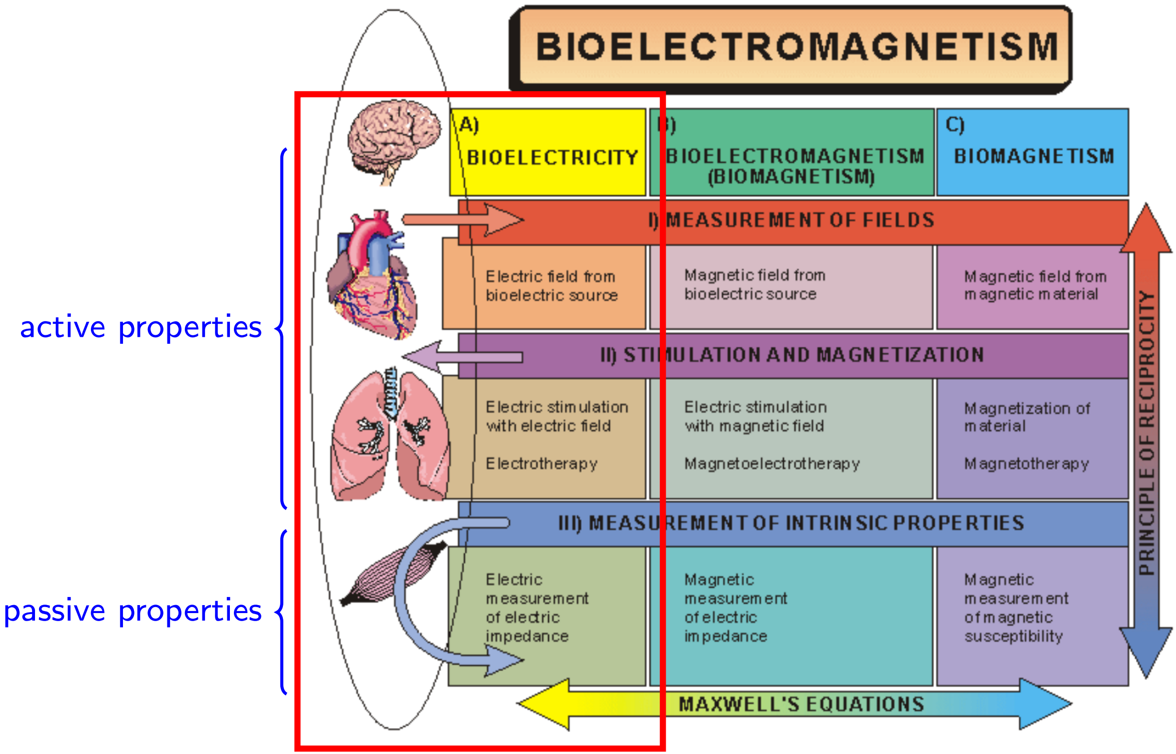
- What are the basic physics of (passive) bioelectricity?
- How to measure and model bio-impedance?

## Lab

- Electrodes and tissue impedance measurement,
- Bioelectrical measurement and modeling,
- Bioelectronics and potatoes!

---

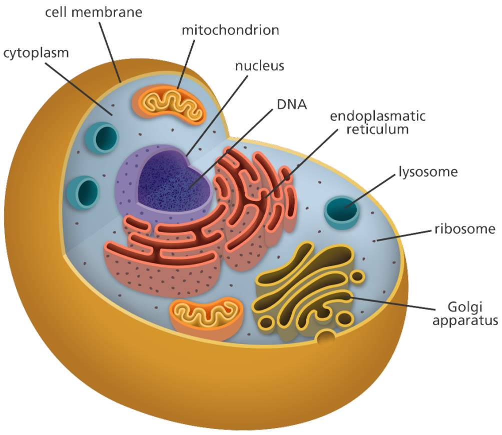
# Bioelectric interfaces



Scope of my researches

Malmivuo, J., Plonsey, R. (1995). Bioelectromagnetism: principles and applications of bioelectric and biomagnetic fields. Oxford University Press, USA.

# The cell



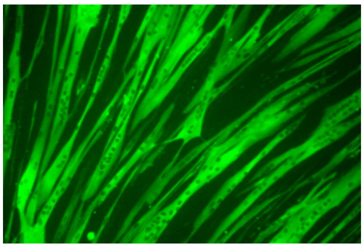
## Living cell

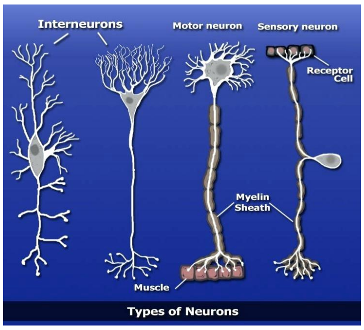
micrometric machine block of a living organism, with:

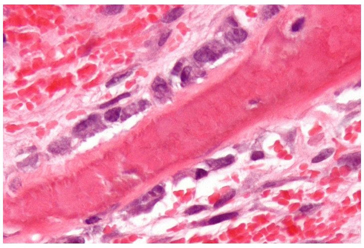
- chemical, molecular and protidic capabilities,
- procedure storage capabilities,
- potential electrical activity, at least electrical properties.

---

# Variety of cells







**muscle cells:**

- mechanically active,
- electro sensitive,

**neurons:**

- electrically active,
- electro sensitive,

**bone cells:**

- not excitable,
- have passive properties

All cells have common passive electrical and dielectrical properties, tissue-impendance is a singular characteristic.

# outline

1. Tissue passive properties
   - Conduction in ionic media
   - Unveiling the membrane
2. Bio-impedance mesurement
   - Connecting to the tissues: electrodes
   - Properties measurement: how-to
   - Example application

---

# Electrical Conduction in biological tissues

Electrical conduction has a different nature considering the medium

| Electrical Circuits | Tissue |
|---|---|
| *charge carrier:* electron | *charge carrier:* ions |

elec. charge:

$$-1 \cdot e$$

elec. charges:

$$Na^+, K^+ : +1 \cdot e$$
$$Cl^-, HCO_3^- : -1 \cdot e$$
$$Ca^{2+}, Mg^{2+} : +2 \cdot e ...$$

current:

$$i = \frac{dQ}{dt}$$

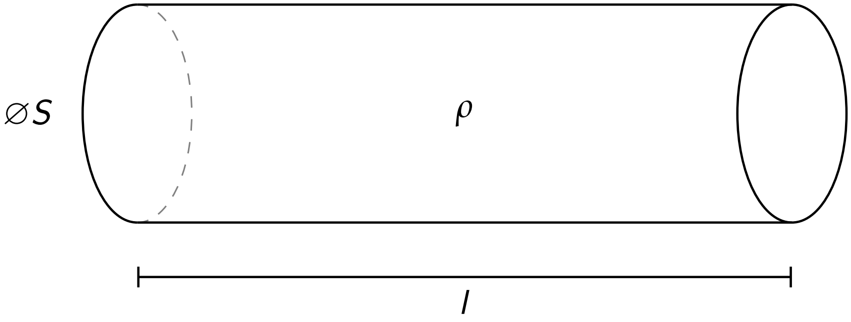
current:

$$i = \sum_{ions} I_{ion}$$

each ion can move due to *migration, diffusion, convection*

# Resistance, conductance

In a homogeneous material:



electrical resistance given by:

$$R = \rho \frac{l}{S} = \frac{1}{\sigma} \cdot \frac{l}{S}$$

with $\rho$ the resistivity in $\Omega \cdot m$ or $\sigma$ the conductivity in $S \cdot m^{-1}$,

to keep in mind:

| material | conductivity ($S \cdot m^{-1}$) |
|---|---|
| coper | $6 \cdot 10^{7}$ |
| germanium | 2.17 |
| deionized water | $5.5 \cdot 10^{-6}$ |

---

# Resistivity, conductivity

In a ionic solution:

the conductivity is given by:

$$\sigma = \sum_{k \ ions} \Lambda_k c_k$$

with $c$ the chemical concentration in $mol \cdot L^{-1}$ and $\Lambda$ the molar conductivity in $S \cdot m^2 \cdot mol^{-1}$

and in strong electrolytes, at very low concentration, as in living organisms, $\Lambda \approx \Lambda_0$ independant from the concentration.

to keep in mind:

| Cation | $\Lambda_0$ in $S \cdot cm^2 \cdot mol^{-1}$ | Anion | $\Lambda_0$ in $S \cdot cm^2 \cdot mol^{-1}$ |
|---|---|---|---|
| $H^+ / H_3O^+$ | 350 | $OH^-$ | 198 |
| $Na^+$ | 50 | $Cl^-$ | 76 |
| $K^+$ | 74 | $HCO_3^-$ | 45 |
| $Ca^{2+}$ | 119 | $CO_3^-$ | 72 |

# Resistivity, conductivity an example

**Example: Conductivity of the 0.9% Saline solution**

$9g$ of NaCl per Liter of water
the atomic mass of NaCls is $58.5g \cdot mol^{-1}$

$$NaCl = Na^+ + Cl^-$$

recall $\Lambda_{0,Na^+} = 50\ S \cdot cm^2 \cdot mol^{-1}$ and $\Lambda_{0,Cl^-} = 76\ S \cdot cm^2 \cdot mol^{-1}$

$$\left[Na^+\right] = \left[Cl^-\right] = \frac{m_{NaCl}}{M_{NaCl}} = \frac{9}{58.5} = 0.154\ mol \cdot L^{-1}$$

$$\sigma = \Lambda_{0,Na^+}\left[Na^+\right] + \Lambda_{0,Cl^-}\left[Cl^-\right] = \frac{0.154\,(50+76)}{1000} \approx 19\ mS \cdot cm^{-1}$$

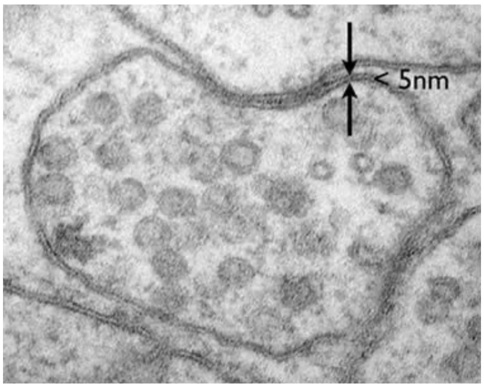
(divided by 1000 to convert the $L^{-1}$in $cm^{-3}$)

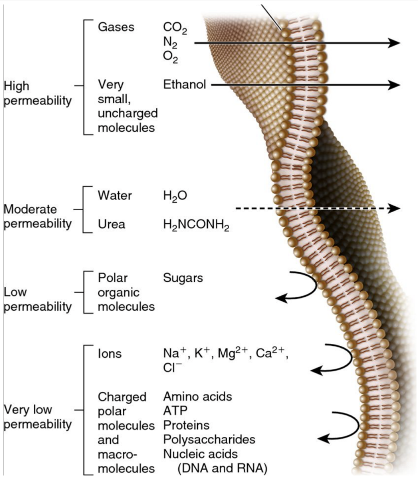
---

# Cell membranes

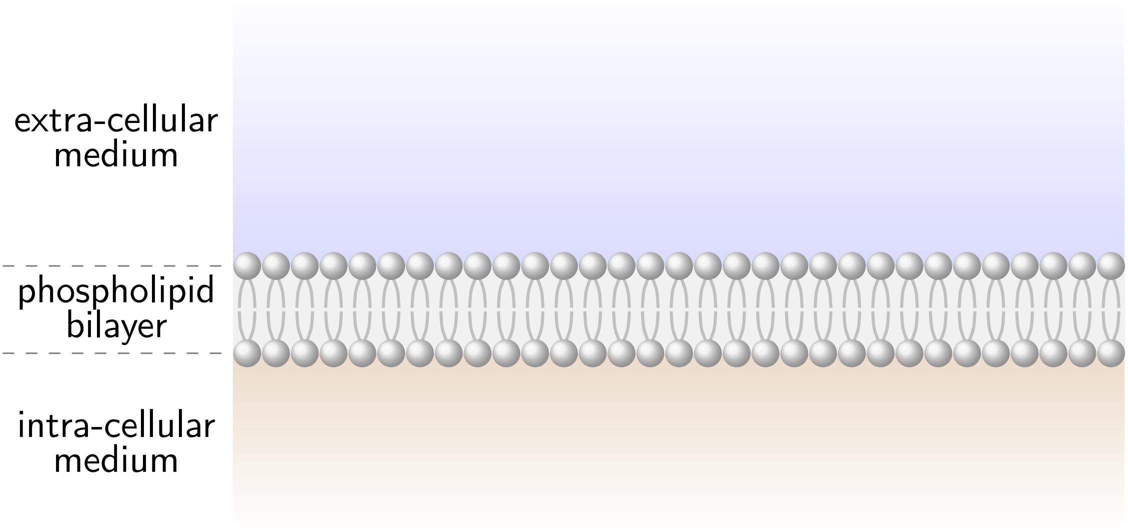
Physical separation between the intra- and extra-cellular medium

- about $5nm$ thick
- phospolipid-bilayer: one layer is composed of one hydrophobic and one hydrophilic lipid that self assemble in membrane





## Membrane, the electrical point of view



extra-cellular medium

phospholipid bilayer

intra-cellular medium

*Lipidic (insulating) membrane, sperating two conductive electrolytes that ionic moving charges cannot cross*

⇒ Equivalent to a capacitance

---

## Computation of the membrane capacitance

### Data

for a 5 *nm* thick membrane,
$\varepsilon_0 = 8.85418782 \cdot 10^{-12}\ m^{-3} \cdot kg^{-1} \cdot s^4 \cdot A^2$
the relative membrane permittivity is $\varepsilon_r = 5$

$$C = \varepsilon_0 \varepsilon_r \frac{S}{e} = \widetilde{c}_M \cdot S$$

where $\widetilde{c}_M$ is the specific membrane capacity $(F \cdot m^{-2})$

$$\widetilde{c}_M = \frac{\varepsilon_0 \varepsilon_r}{e} = \frac{5 \times 8.85418782 \cdot 10^{-12}}{5 \cdot 10^{-9}} \approx 8.85\ mF \cdot m^{-2} = 0.885\ \mu F \cdot cm^{-2}$$

$\widetilde{c}_M = 1\ \mu F \cdot cm^{-2}$ is a common value in the litterature

# Suming up passive properties

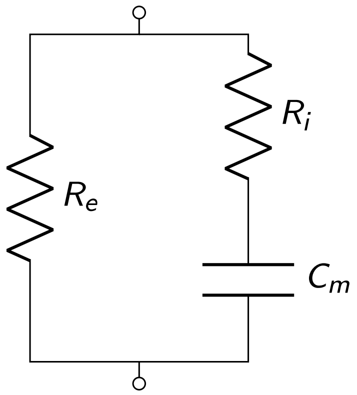
## Intra/extra-celllular medium

- two resistive media
- small ionic concentration changes enable to consider it as constant resistivity, (especially in extra-cellular space)

## All cellular membranes

capacitive

first approximation tissue impedance model:



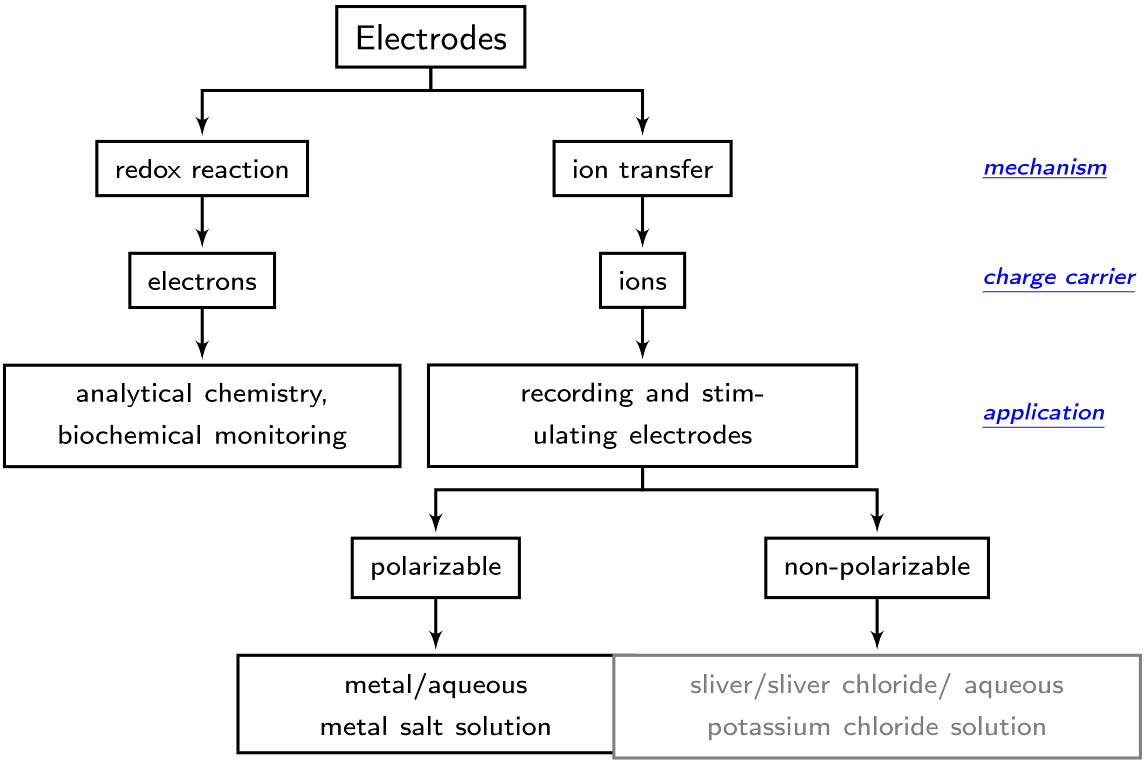
warning: tissue only, no electrode

---

# outline

1. Tissue passive properties
   - Conduction in ionic media
   - Unveiling the membrane
2. Bio-impedance mesurement
   - Connecting to the tissues: electrodes
   - Properties measurement: how-to
   - Example application

## Electrode classification



Electrodes

redox reaction

ion transfer

*mechanism*

electrons

ions

*charge carrier*

analytical chemistry, biochemical monitoring

recording and stimulating electrodes

*application*

polarizable

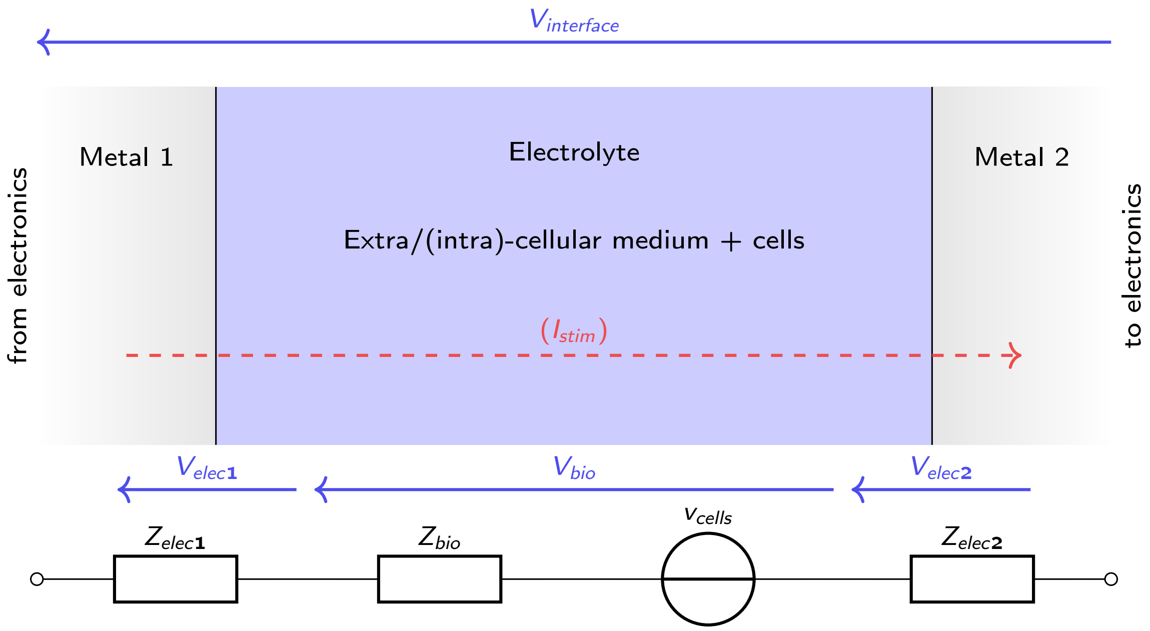
non-polarizable

metal/aqueous metal salt solution

sliver/sliver chloride/ aqueous potassium chloride solution

---

## First schematic view



Not a direct electrical acces to the tissue

One or more materials directly in contact with the tissue

# Which material? (1/2)

| | | toxicity | reactivity | |
|---|---|---|---|---|
| **conductors** | Gold | non-toxic | non-reactive | |
| | Silver | toxic | | |
| | Copper | toxic | | |
| | Iron | toxic | | |
| | Stainless Stell | non-toxic | | |
| | Platinum | toxic | | |
| | Tantalum | | reactive | |
| | Titanium | | | biocompatible |
| | Tungsten | | non-reactive | |
| | Gold–nickel–chromium | non-toxic | | |
| | Gold–palladium–rhodium | non-toxic | | |
| | Nickel–chromium (Nichrome) | non-toxic | reactive | |
| | Nickel–chromium–molybdenum | non-toxic | | |
| | Nickel–titanium (Nitinol) | | | biocompatible |
| | Platinum–iridium | non-toxic | | |
| | Platinum–nickel | non-toxic | | |
| | Platinum–rhodium | non-toxic | | |
| | Platinum–tungsten | non-toxic | | |
| | Platinized platinum (Pt black) | non-toxic | | |

...

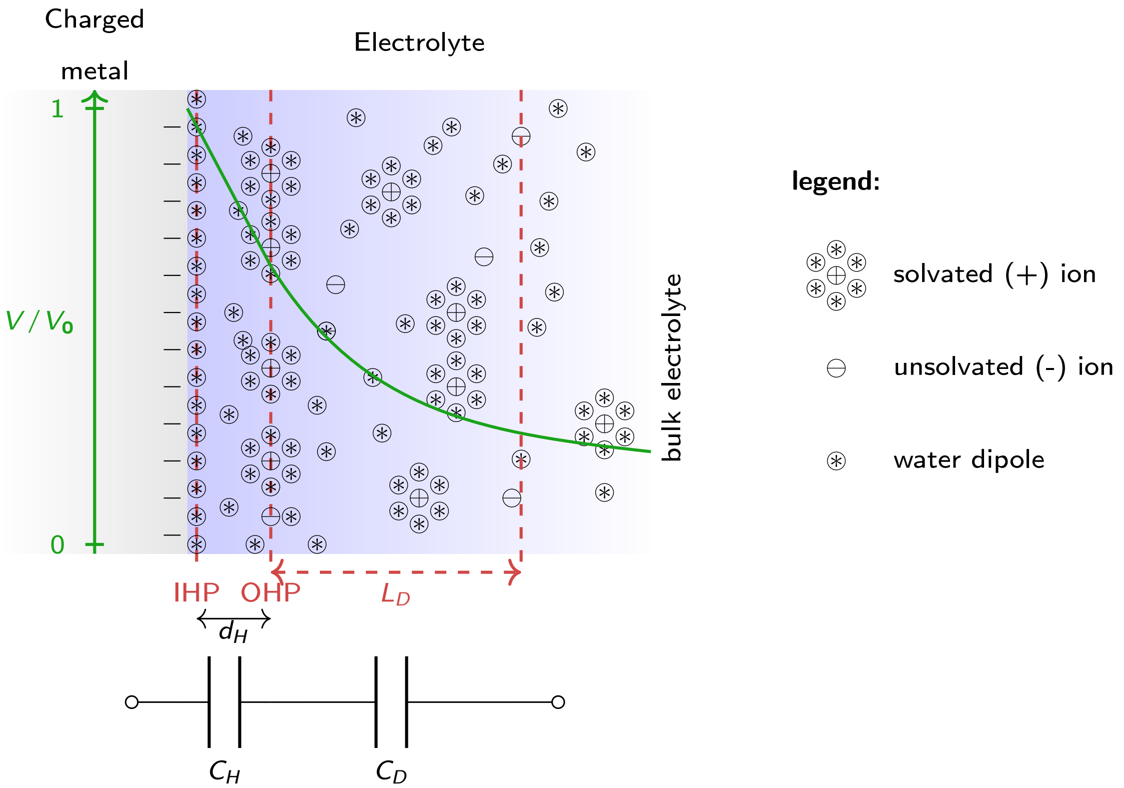
# Which material? (2/2)

| | | toxicity | reactivity | |
|---|---|---|---|---|
| | ... | | | |
| **Semi-conductors** | Silicon | | non-reactive | biocompatible |
| | Germaniom | toxic | | |
| **Insulators** | Alumina ceramic | | non-reactive | biocompatible |
| | Araldite (epoxy plastic resin) | | reactive | |
| | Polyethylene | | non-reactive | |
| | Polyimide | | | biocompatible |
| | Polypropylene | | non-reactive | |
| | Silicon dioxide (Pyrex) | | reactive | |
| | Teflon TFE (high purity) | | non-reactive | |
| | Teflon TFE (shrinkable) | | reactive | |
| | Titanium dioxide | | reactive | |

adapted from Merrill, D. R., Bikson, M., Jefferys, J. G. (2005). Electrical stimulation of excitable tissue: design of efficacious and safe protocols. Journal of neuroscience methods, 141(2), 171-198.

commonly used materials in electronics and micro-electronics (gold, stainless steel, silicon, polyimide) can be used!
**warning:** no copper

# The double layer (1/2)



---

# The double layer (2/2)

**Helmholtz Capacitance**

$$C_H = \varepsilon_0 \varepsilon_r \frac{A}{d_H}$$

- $d_H$ is a constant
- A the effective electrode Surface Area

about $230\mu F \cdot cm^{-2}$
value depends on surface roughness

**Gouy-Chapman Capacitance**

$$C_D = \frac{\varepsilon_0 \varepsilon_r}{L_D} \cosh\left(\frac{q_i \Phi_0}{2RT}\right)$$

- $q_i$ is the ion charge
- $L_D = \sqrt{\frac{\varepsilon_0 \varepsilon_r}{2RTc_i q_i}}$, with $c_i$ the ion concentration
- with $\Phi_0$ the junction voltage

about $50\mu F \cdot cm^{-2}$
possibly (voltage) non-linear

overall specific capacitance value about $40\mu F cm^{-2}$

# Electrochemical potential

At the junction between a metal and a conductive electrolyte: electrical voltage (Electrochemical half-cell potential) depending on the metal

| Material | Reaction | Potential |
|---|---|---|
| Aluminium | $Al^{3+} + 3e^-$ | $-1.67V$ |
| Iron | $Fe^{2+} + 2e^-$ | $-0.441V$ |
| Silver | $Ag^{+} + e^-$ | $+1.7996V$ |
| Platinum | $Pt^{2+} + 2e^-$ | $+1.2V$ |
| Gold | $Au^{3+} + 3e^-$ | $+1.52V$ |
|  | $Au^{+} + e^-$ | $+1.83V$ |
| $H_2$ | $2H^{+} + 2e^-$ | $0.000V$ (*Reference*) |

at $T = 298K$

Note that if symetrical materials → overal voltage $= 0V$

---

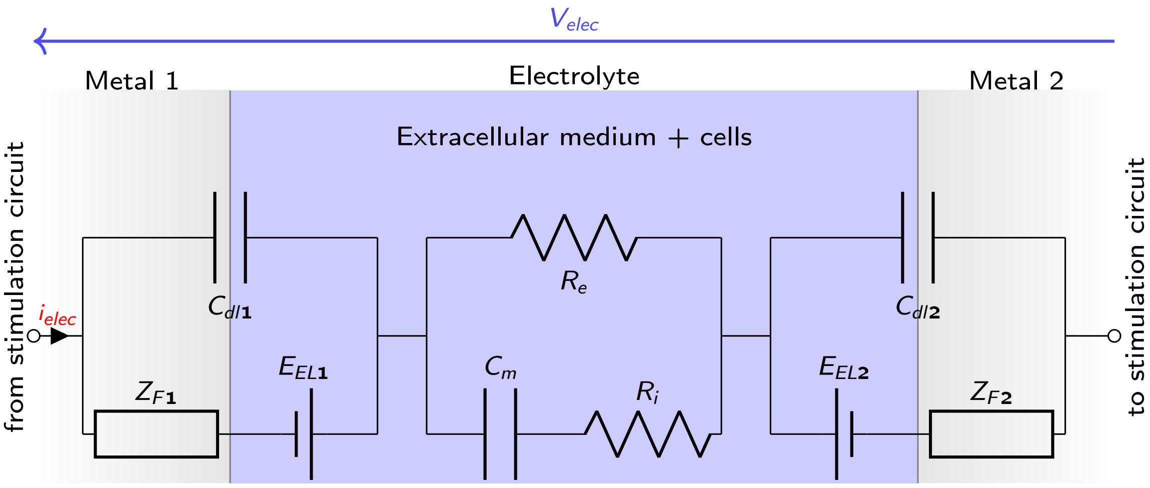
# The Faradaic impedance

charges may be shared by redox reactions:
**transfer** of electrons between the two phases (metal, electrolyte)

- Reactions depends on the material,
- higly (voltage) non-linear,
- complexe modeling (*resistive but not that much, nor capacitive*...),
- in electrochemistry, considered as a **Constant Phase Element**.

let us call it $Z_F$, we will speak about it later

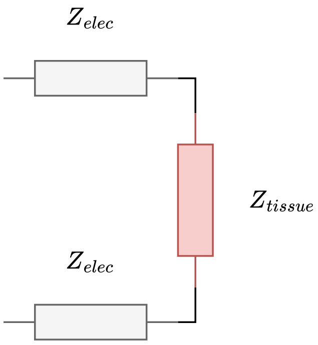
# First approximation physical model



---

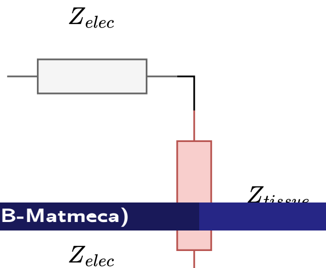
# Impedance Measurement: 2-points configuration:

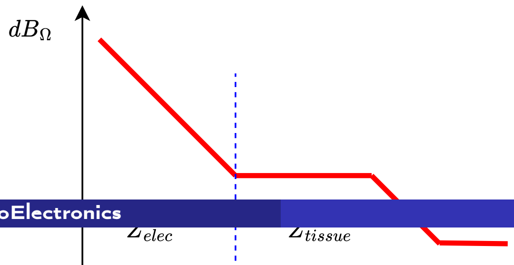
For bio-potential recording and impedance sensing
Electrical Impedance Spectroscopy



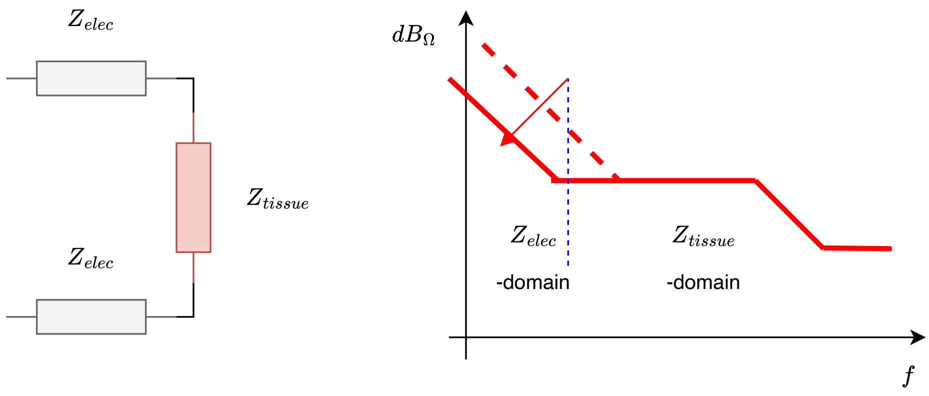
$Z_{elec}$ mostly capacitive
capacitance proportional to surface

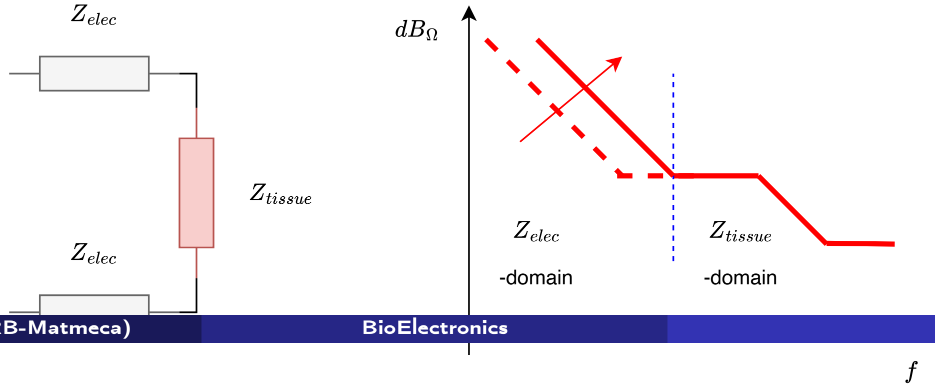
$Z_{tissue}$ Resistive - Capacitive





## 2-points: electrode size

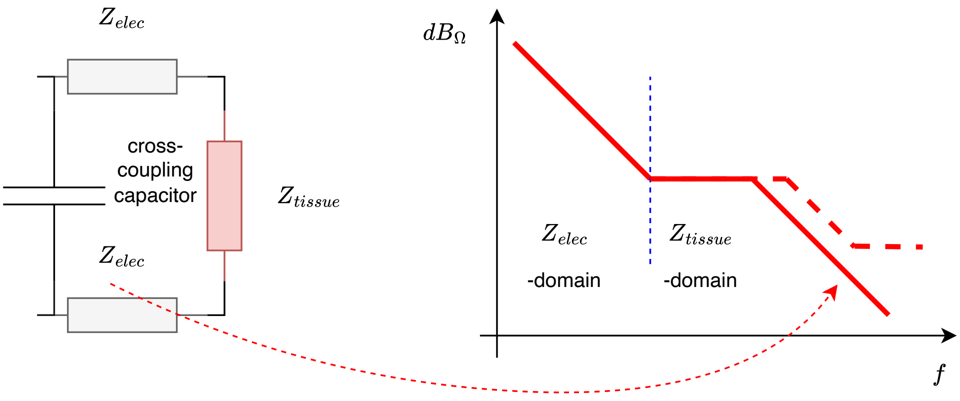


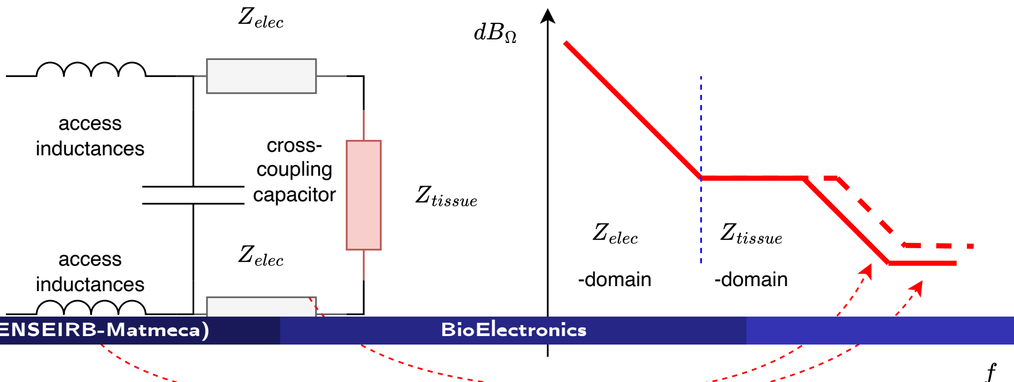


---

## 2-points: parasitics

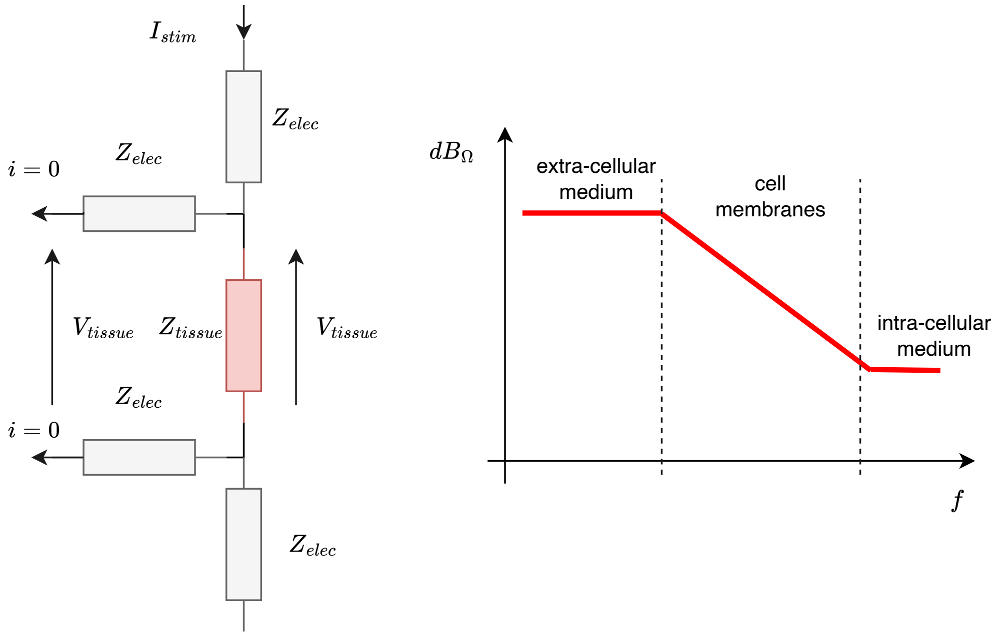
- Larg
- Low
- Sma
- Hig

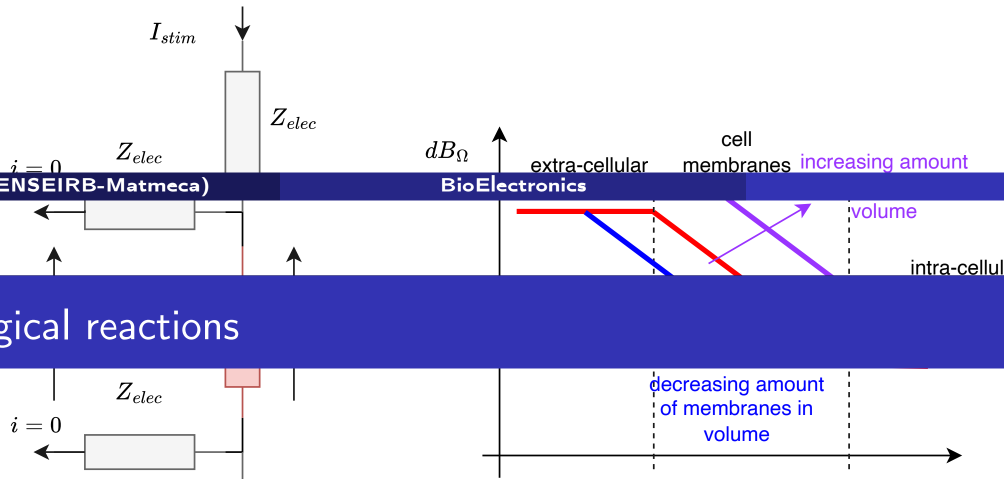




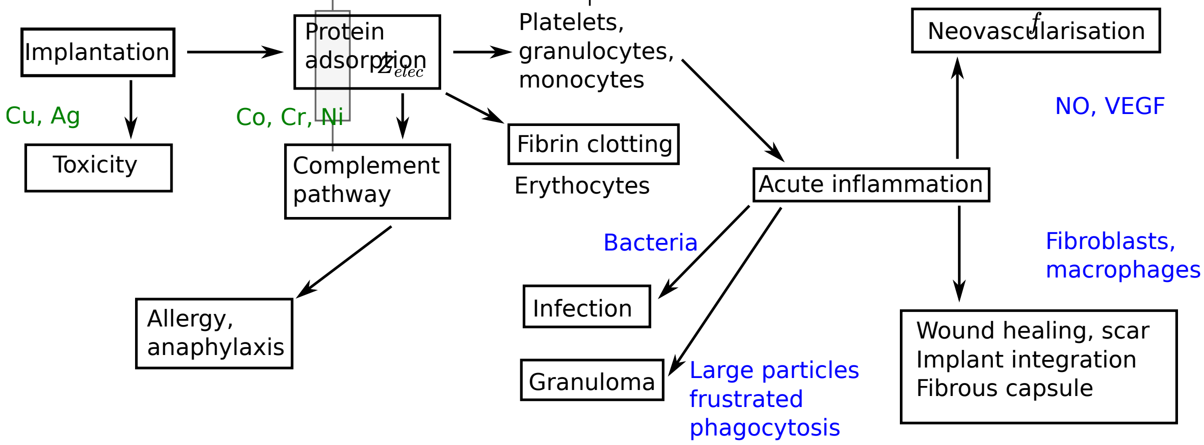
# 4-points configuration:

For bio-potential impedance sensing only





# Physiological reactions



Implantation → Protein adsorption → Platelets, granulocytes, monocytes

Implantation → Toxicity (Cu, Ag)

Protein adsorption → Complement pathway (Co, Cr, Ni) → Allergy, anaphylaxis

Protein adsorption → Fibrin clotting, Erythocytes

Platelets, granulocytes, monocytes → Acute inflammation

Acute inflammation → Neovascularisation (NO, VEGF)

Acute inflammation → Infection (Bacteria)

Acute inflammation → Granuloma (Large particles frustrated phagocytosis)

Acute inflammation → Wound healing, scar Implant integration Fibrous capsule (Fibroblasts, macrophages)

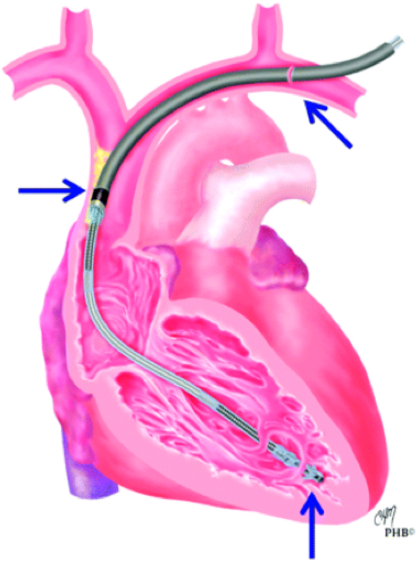
*Proteic layer* (seconds) → *Cell migration* (minutes) → *Growth* (hours) → *Differentiation* (days) → *Matrix secretion* (weeks)

Brette, R., Destexhe, A. (2012). Handbook of neural activity measurement. Cambridge University Press.

# Fibrosis on pacemakers

Problems after implantation directly on electrodes

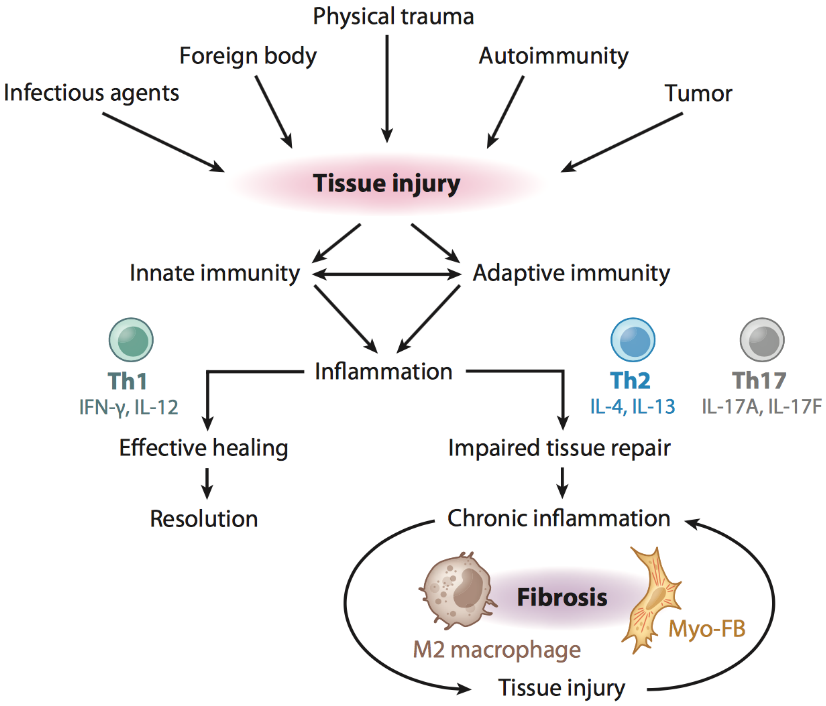
pacemaker implantation at time $t = 0$



explantation after $t = 5$ years

---

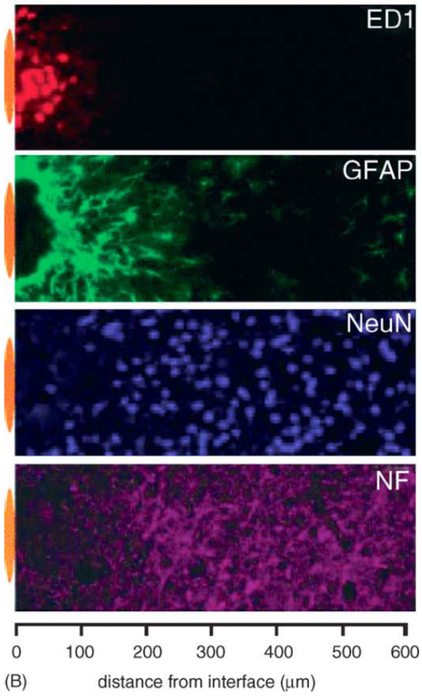
# Mechanism of fibrosis

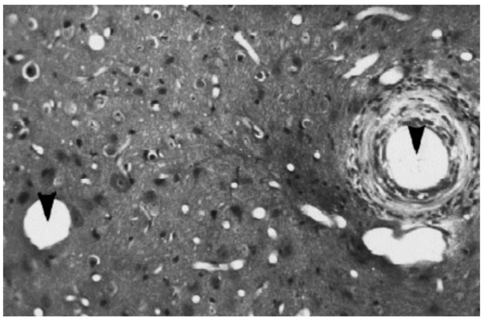


Physical trauma
Foreign body
Autoimmunity
Infectious agents
Tumor
**Tissue injury**
Innate immunity
Adaptive immunity
**Th1**
IFN-γ, IL-12
Inflammation
**Th2**
IL-4, IL-13
**Th17**
IL-17A, IL-17F
Effective healing
Impaired tissue repair
Resolution
Chronic inflammation
**Fibrosis**
M2 macrophage
Myo-FB
Tissue injury

WICK, Georg, GRUNDTMAN, Cecilia, MAYERL, Christina, et al. The immunology of fibrosis. Annual review of immunology, 2013, vol. 31, p. 107-135.

# A change in the medium



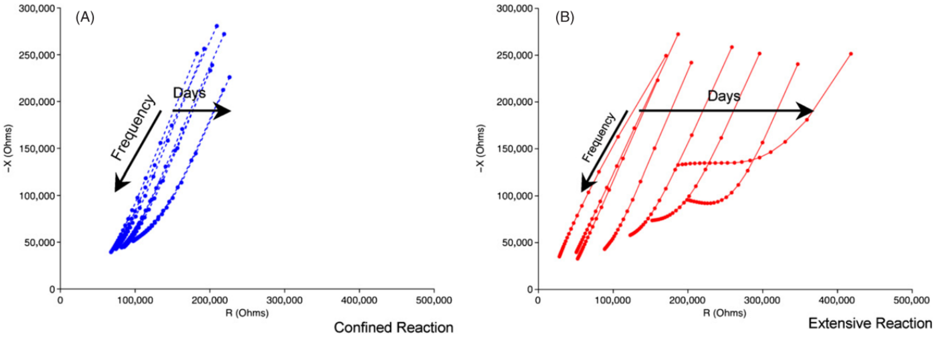


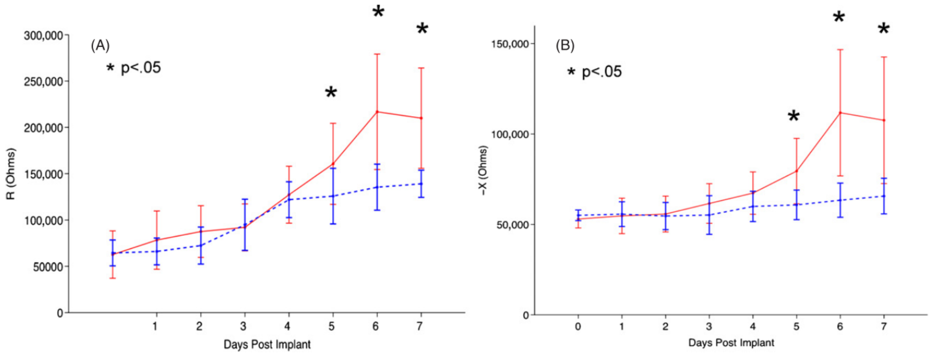
Warning: the reaction is highly local and unpredictivble

Polikov, V. S., Tresco, P. A., Reichert, W. M. (2005). Response of brain tissue to chronically implanted neural electrodes. Journal of neuroscience methods, 148(1), 1-18.

---

# Electrical consequences



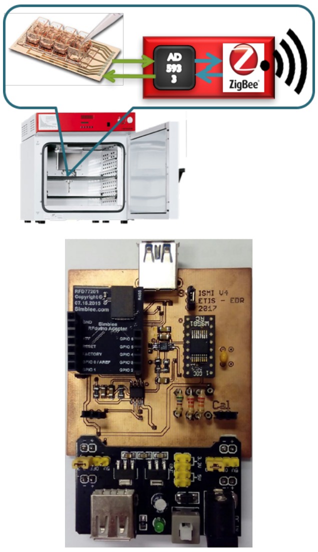


Williams, J. C., Hippensteel, J. A., Dilgen, J., Shain, W., Kipke, D. R. (2007). Complex impedance spectroscopy for monitoring tissue responses to inserted neural implants. Journal of neural engineering, 4(4), 410.

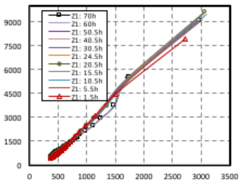
However: no clear correlation between impedance change and physiological reaction

# Example of investigation (ETIS work)

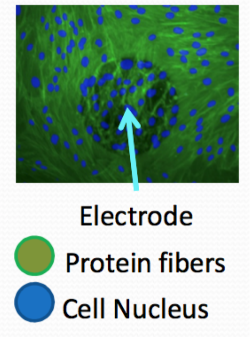
Investigation to correlate physiology (*biology*) and impedance (*electronics*)



design of an *in vitro* measurement bench on gold-microelectrodes



impedance control

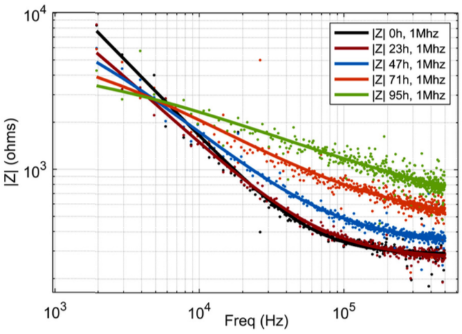


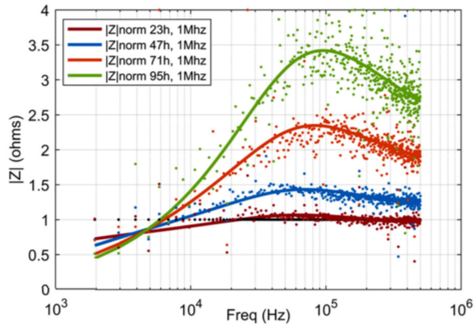
tissu evolution evaluation

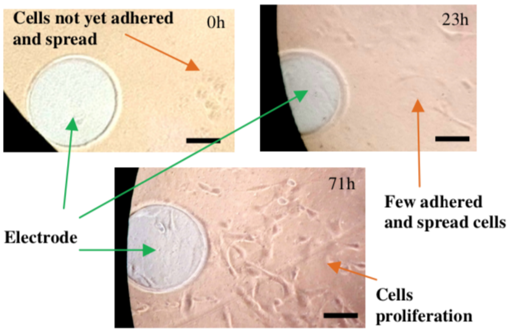
**Work of Edwin De Roux - ETIS - 2018**

---

# Cell proliferation monitoring





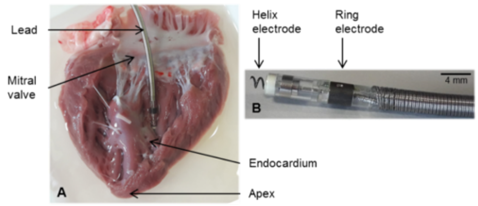


**Correlation between proliferation, apoptosys and impedance**

biomarker for large populations monitoring

# Tissue evolution monitoring

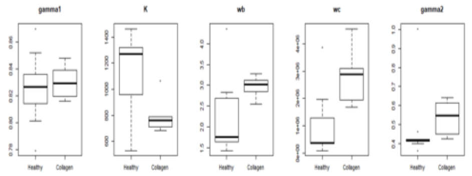
Ex vivo experiments



work of A. Degache, N. Lewis (IMS), O. Bernus (IHU Lyric), F. Kolbl (ETIS)

impedance model :

$$Z\left(\jmath\omega\right) = R\frac{1+\left(\frac{\jmath f}{f_\alpha}\right)^\alpha}{\left(\frac{\jmath f}{f_\alpha}\right)^\alpha}\frac{\left(\frac{\jmath f}{f_\beta}\right)^\beta}{1+\left(\frac{\jmath f}{f_\beta}\right)^\beta}$$



first demonstration of the possibility to use electrode as a sensor to discriminate tissues