BioElectronics
bio-impedance measurement and modeling

F. Kölbl

Bioelectronic group - IMS

florian.kolbl@ims-bordeaux.fr

Today's agenda

Lecture

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

Today's agenda

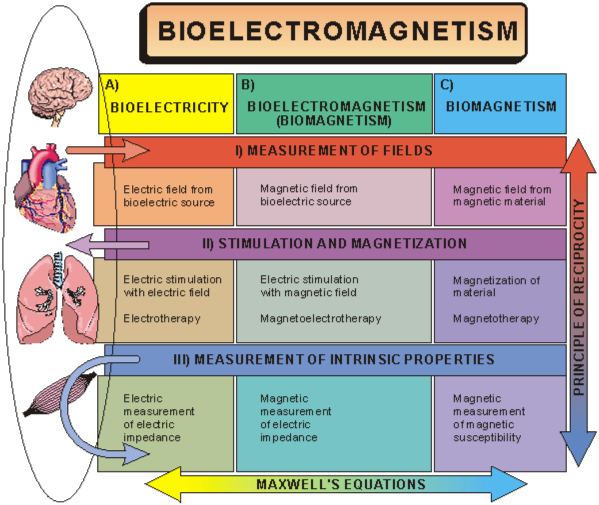
Lecture

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

Lab

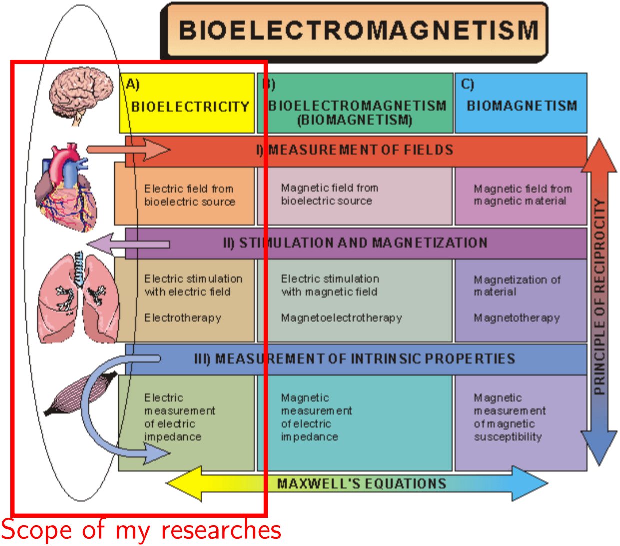
- Electrodes and tissue impedance measurement,
- Bioelectrical measurement and modeling,
- Bioelectronics and potatoes!

Bioelectric interfaces



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

Bioelectric interfaces

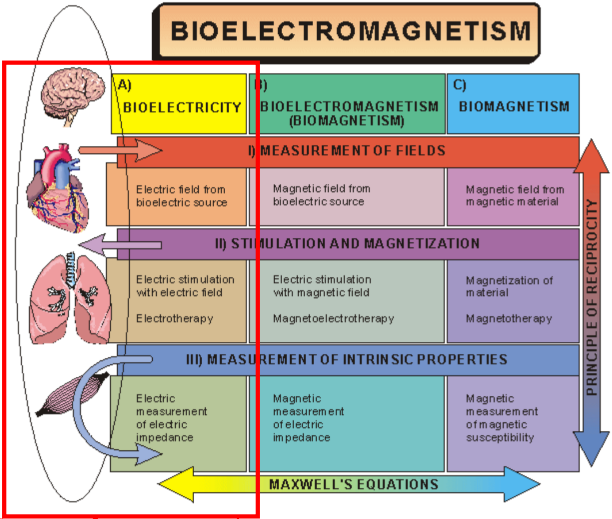


Malmivuo, J., Plonsey, R. (1995). Bioelectromagnetism: principles and applications of bioelectric and biomagnetic fields. Oxford University Press, USA.

Bioelectric interfaces

active properties

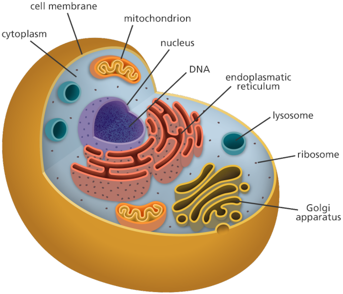
passive properties



Scope of my researches

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

The cell

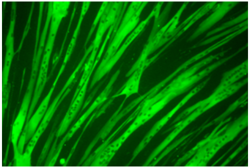


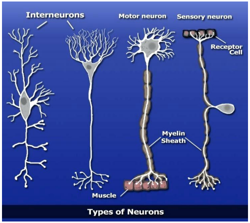
Living cell

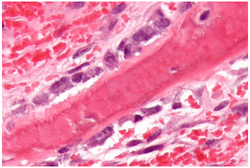
micrometric machine block of a living organism, with:

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

Variety of cells





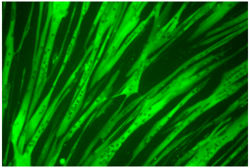


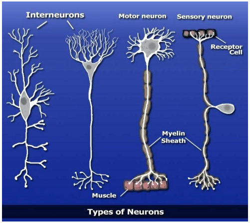
muscle cells:
- mechanically active,
- electro sensitive,

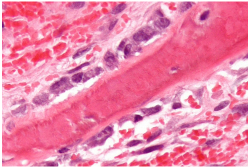
neurons:
- electrically active,
- electro sensitive,

bone cells:
- not excitable,
- have passive properties

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.

Cell morphology and cancer progression

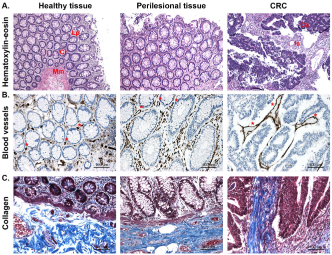


Figure 1. Tissue selection. Pair-wised healthy colon, perilesional area and CRC were evaluated by means of hematoxylin-eosin staining (**A**), CD34+ blood vessels (**B**) and collagen (blue staining) by means of Masson Trichrome stain (**C**). Cr; cryptae. Lp; lamina propria. Mm; muscularis mucosae. Ca; carcinoma. Is; intratumoral stroma. *blood vessels. Pictures are representative of pair-wised tissues from one of the six patients tested and listed in Supplementary Material 1.

Nebuloni et al (2016). Scientific reports, 6(1), DOI: 10.1038/srep22522.

Cell morphology and cancer progression

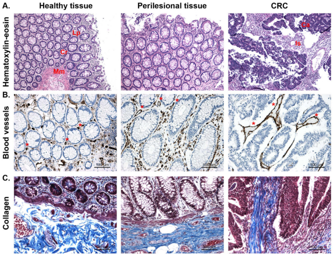


Figure 1. Tissue selection. Pair-wised healthy colon, perilesional area and CRC were evaluated by means of hematoxylin-eosin staining (**A**), CD34+ blood vessels (**B**) and collagen (blue staining) by means of Masson Trichrome stain (**C**). Cr; cryptae. Lp; lamina propria. Mm; muscularis mucosae. Ca; carcinoma. Is; intratumoral stroma. *blood vessels. Pictures are representative of pair-wised tissues from one of the six patients tested and listed in Supplementary Material 1.

Nebuloni et al (2016). Scientific reports, 6(1), DOI: 10.1038/srep22522.

Signiticant changes linked with passive properties

- Cell size and shape, density,
- Cell membrane properties, nuclueus size and shape,
- Extracellular matrix (ECM) composition

outline

1. Tissue passive properties
   - Conduction in ionic media
   - Unveiling the membrane
2. Connecting to the tissues: electrodes
3. Examples of applications in oncology

Electrical Conduction in biological tissues

Electrical conduction has a different nature considering the medium

Electrical Conduction in biological tissues

Electrical conduction has a different nature considering the medium

Electrical Circuits

charge carrier: electron

Electrical Conduction in biological tissues

Electrical conduction has a different nature considering the medium

Electrical Circuits

charge carrier: electron

Tissue

charge carrier: ions

Electrical Conduction in biological tissues

Electrical conduction has a different nature considering the medium

Electrical Circuits

charge carrier: electron

elec. charge:

$$-1 \cdot e$$

Tissue

charge carrier: ions

elec. charges:

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

Electrical Conduction in biological tissues

Electrical conduction has a different nature considering the medium

Electrical Circuits

charge carrier: electron

elec. charge:

$$-1 \cdot e$$

current:

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

Tissue

charge carrier: ions

elec. charges:

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

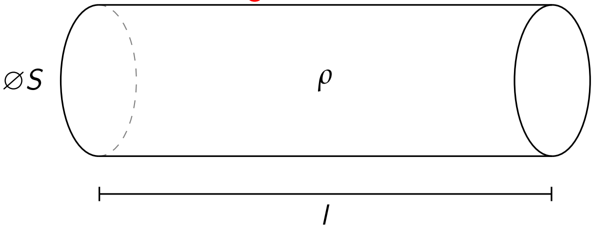
current:

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

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

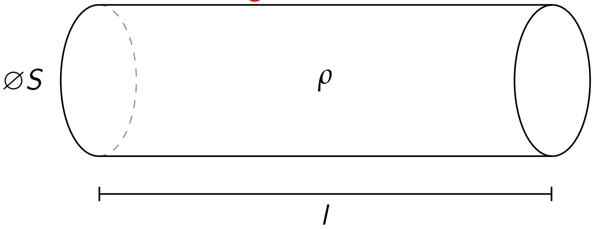
Resistance, conductance

In a homogeneous material:



Resistance, conductance

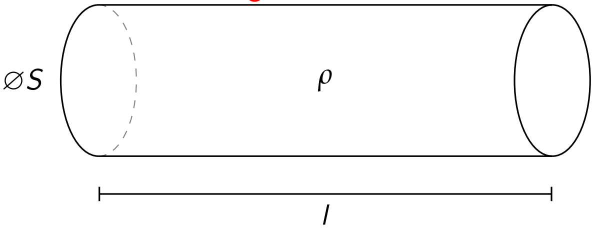
In a homogeneous material:



electrical resistance given by:

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

with ρ the resistivity in $\Omega \cdot m$ or σ the conductivity in $S \cdot m^{-1}$, In a homogeneous material:



electrical resistance given by:

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

with ρ the resistivity in $\Omega \cdot m$ or σ 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	$5.5 \cdot 10^{-6}$

In a ionic solution:

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 Λ the molar conductivity in $S \cdot m^2 \cdot mol^{-1}$

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 Λ 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.

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 Λ 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	Λ_0 in $S \cdot cm^2 \cdot mol^{-1}$	Anion	Λ_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 $58.5g \cdot mol^{-1}$

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 $\Lambda_{0,Cl^{-}} = 76\ S \cdot cm^{2} \cdot mol^{-1}$

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 $\Lambda_{0,Cl^{-}} = 76\ S \cdot cm^{2} \cdot mol^{-1}$

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

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 $58.5 g \cdot mol^{-1}$

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

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

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

$$\sigma = \Lambda_{0,Na^{+}} [Na^{+}] + \Lambda_{0,Cl^{-}} [Cl^{-}] = \frac{0.154\,(50 + 76)}{1000}$$

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

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 $58.5 g \cdot mol^{-1}$

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

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

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

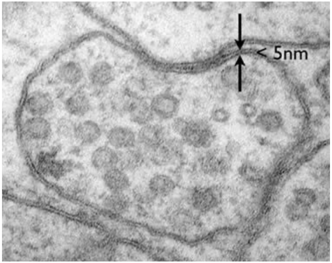
$$\sigma = \Lambda_{0,Na^{+}} [Na^{+}] + \Lambda_{0,Cl^{-}} [Cl^{-}] = \frac{0.154\,(50 + 76)}{1000} \approx 19\ mS \cdot cm^{-1}$$

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

Cell membranes

Physical separation between the intra- and extra-cellular medium

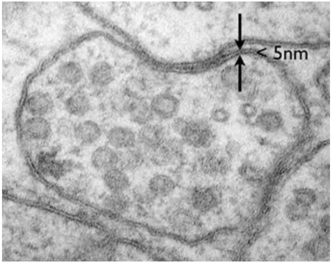
- about 5nm thick
- phospolipid-bilayer: one layer is composed of one hydrophobic and one hydrophilic lipid that self assemble in membrane

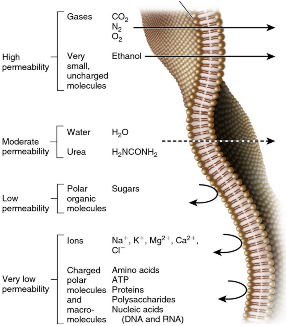


Cell membranes

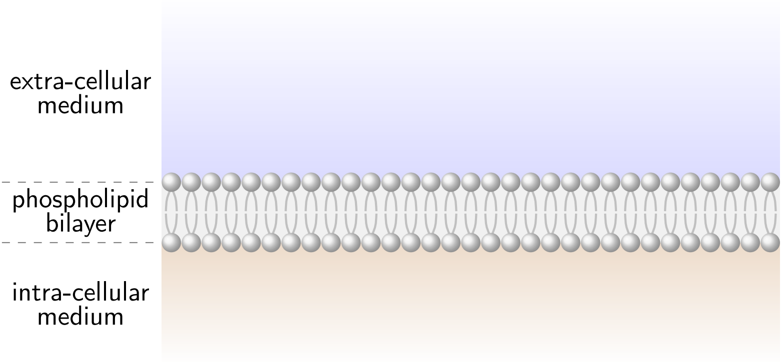
Physical separation between the intra- and extra-cellular medium

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



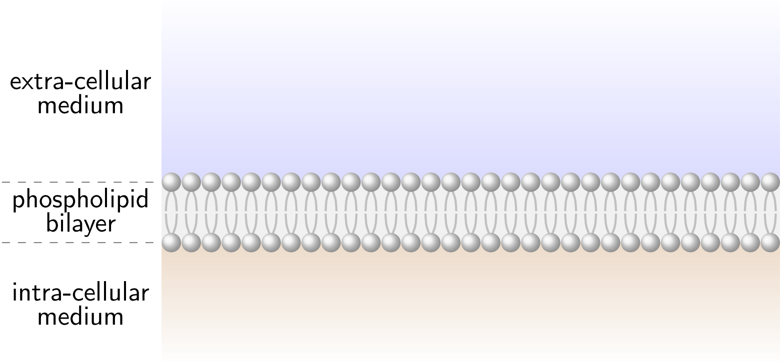


Membrane, the electrical point of view



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

Membrane, the electrical point of view



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

$\Rightarrow$ 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 $\varepsilon_r = 5$

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 $(F \cdot m^{-2})$

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 $(F \cdot m^{-2})$

$$\widetilde{c}_M = \frac{\varepsilon_0 \varepsilon_r}{e} = \frac{5 \times 8.85418782 \cdot 10^{-12}}{5 \cdot 10^{-9}}$$

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

Suming up passive properties

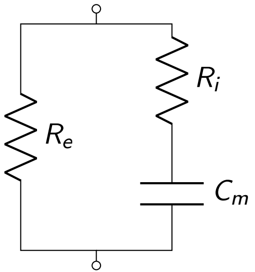
Intra/extra-celllular medium

- 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. Connecting to the tissues: electrodes
3. Examples of applications in oncology

Electrode classification

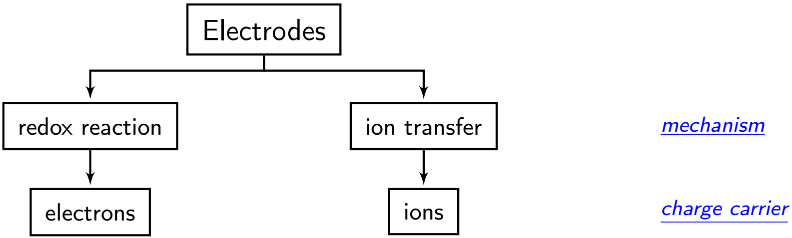
$\boxed{\text{Electrodes}}$

Electrode classification

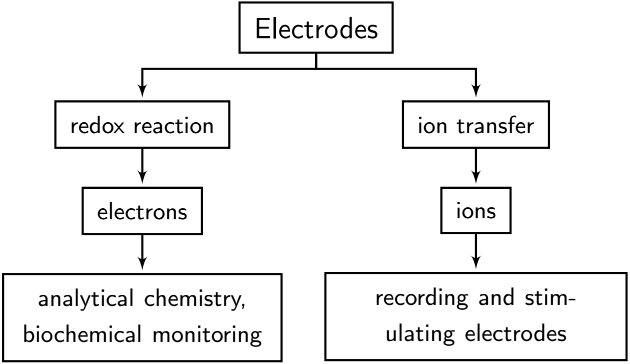
- Electrodes
  - redox reaction
  - ion transfer

mechanism

Electrode classification



Electrode classification

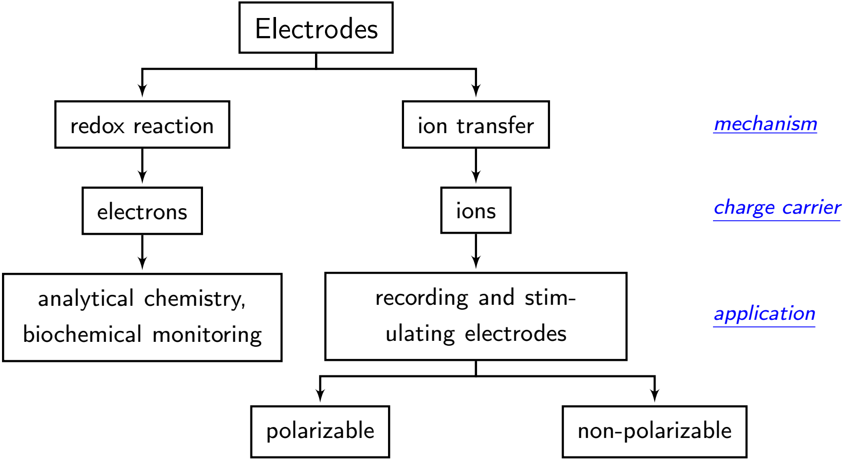


[*mechanism*]

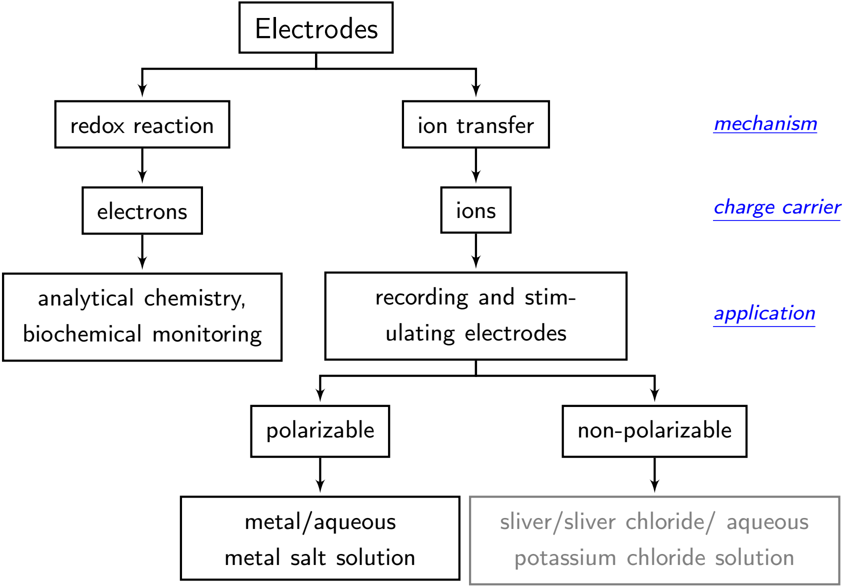
[*charge carrier*]

[*application*]

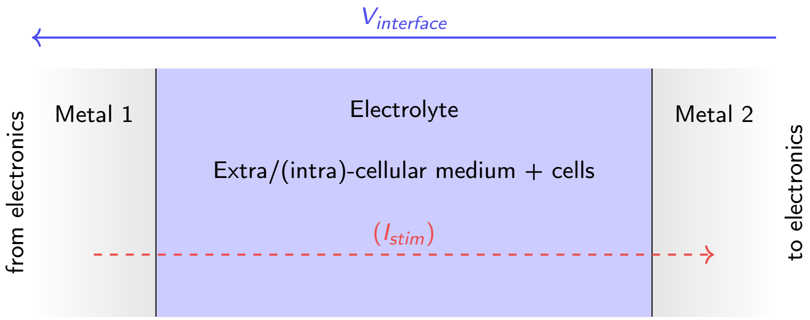
Electrode classification



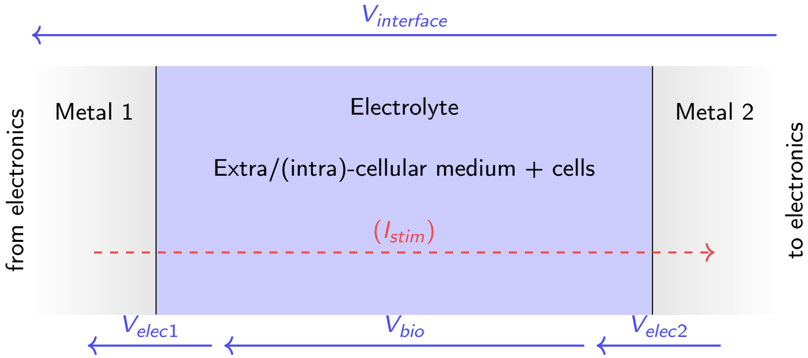
Electrode classification



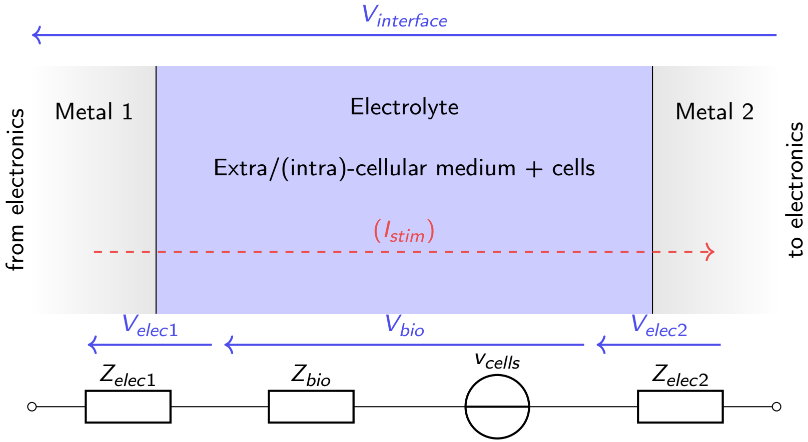
First schematic view



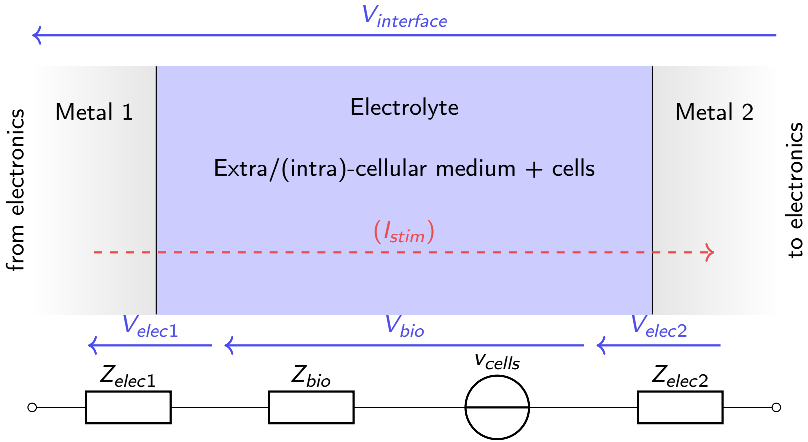
First schematic view



First schematic view

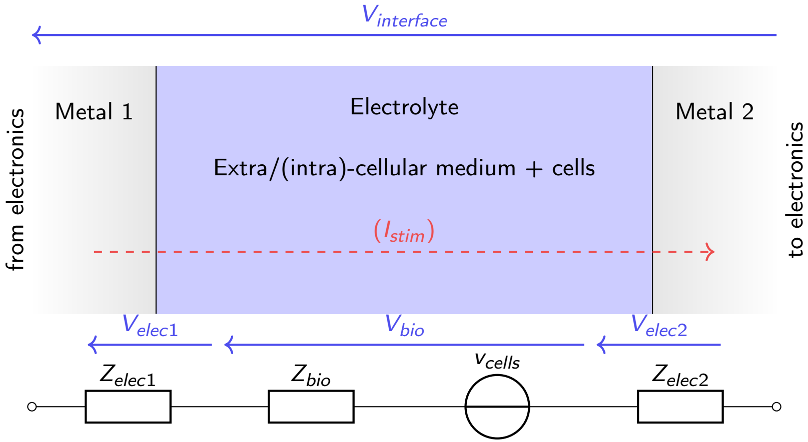


First schematic view



Not a direct electrical acces to the tissue

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		

...

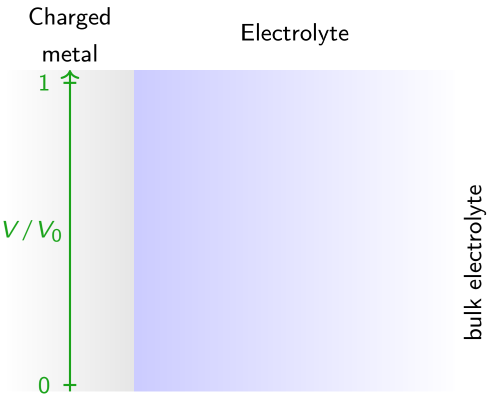
Which material? (2/2)

		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	

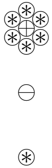
adapted from Merrill, D. R., Bikson, M., Jefferys, J. G. (2005). Electrical stimulation of excitable tissue: design of efficacious and safe protocols. Journal of neuroscience methods, 141(2), 171-198.

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

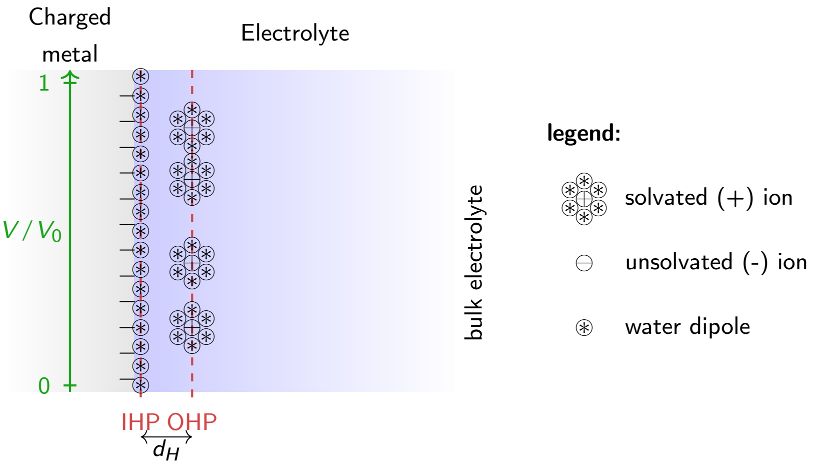
The double layer (1/2)



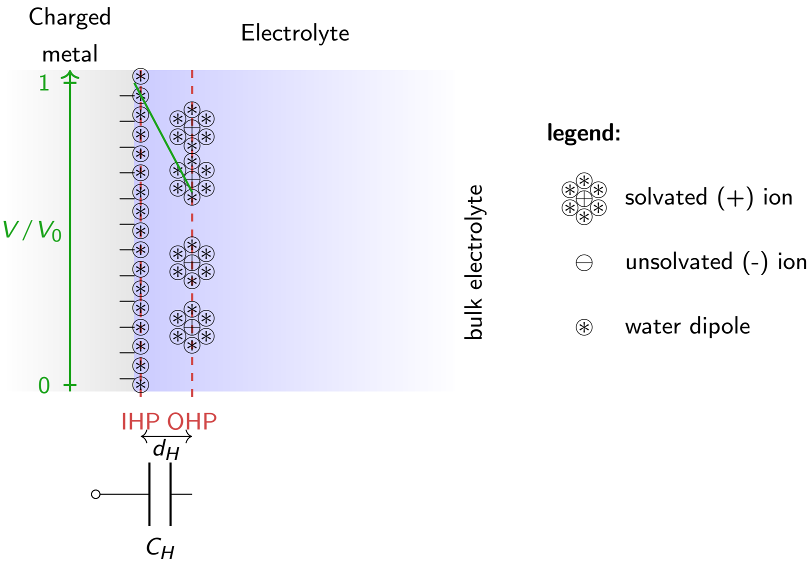
legend:



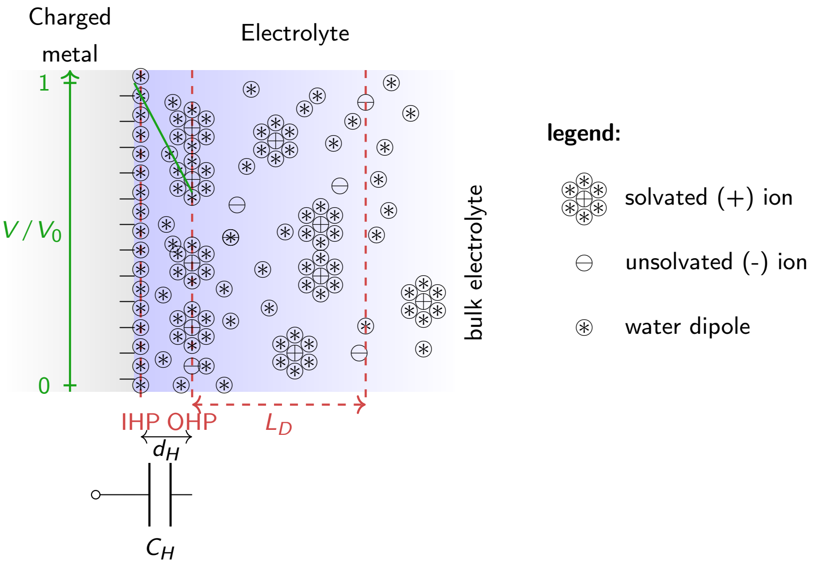
The double layer (1/2)



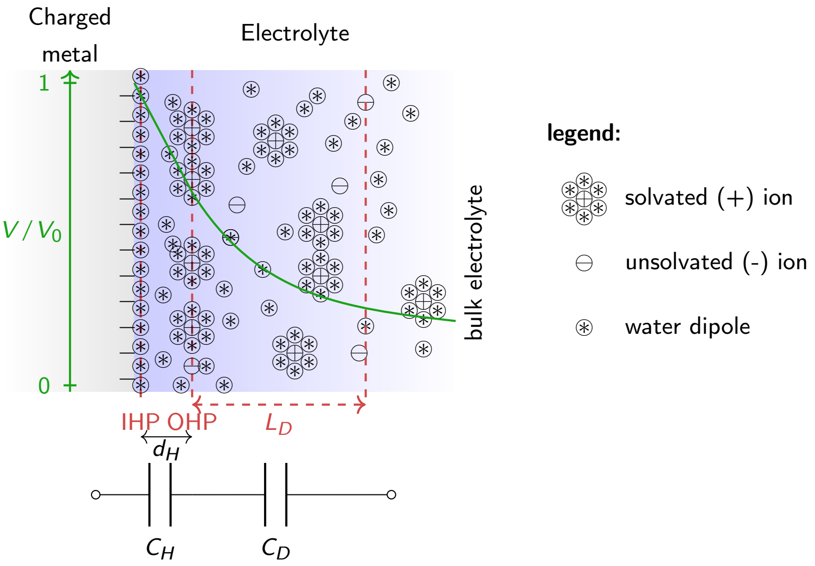
The double layer (1/2)



The double layer (1/2)



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

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 Φ_0 the junction voltage

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

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 Φ_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

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 $T = 298K$

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 $\rightarrow$ 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**.

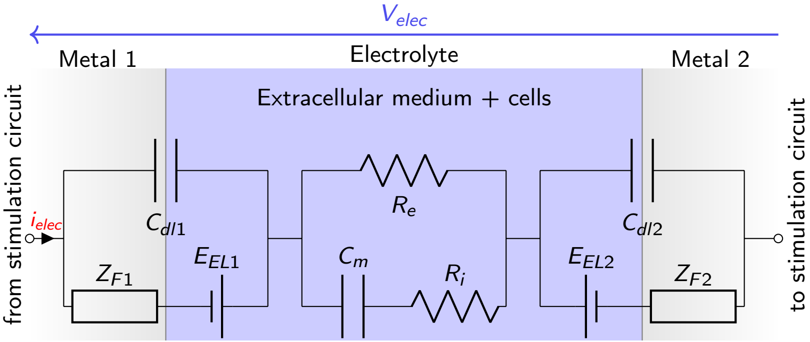
The Faradaic impedance

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**.

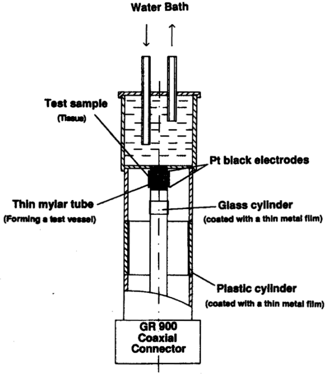
let us call it Z_F, we will speak about it later

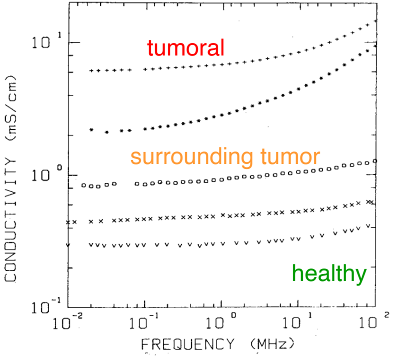
First approximation physical model



outline

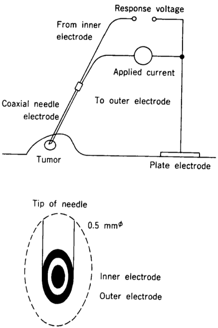
First in-vitro studies on brest carcinoma:

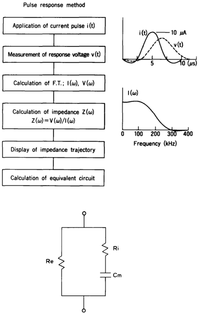


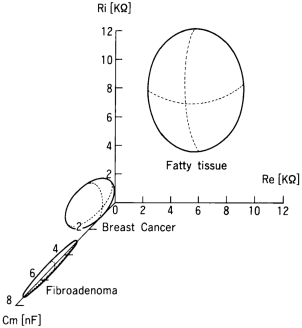


Surowiec et al. (1988). Dielectric properties of breast carcinoma and the surrounding tissues. IEEE Transactions on Biomedical Engineering, 35(4), 257-263.

To first needle devices for biopsy and cancer detection:



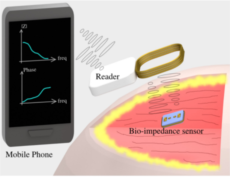


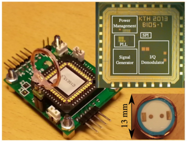


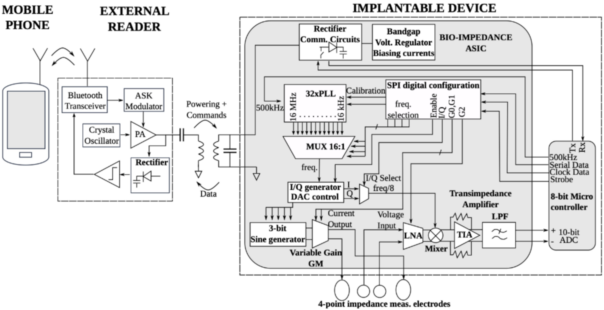
Morimoto et al. (1993). A study of the electrical bio-impedance of tumors. Journal of Investigative Surgery, 6(1), 25-32.

To more recent systems (1/2)

Example of embedded system to monitor bio-impedance

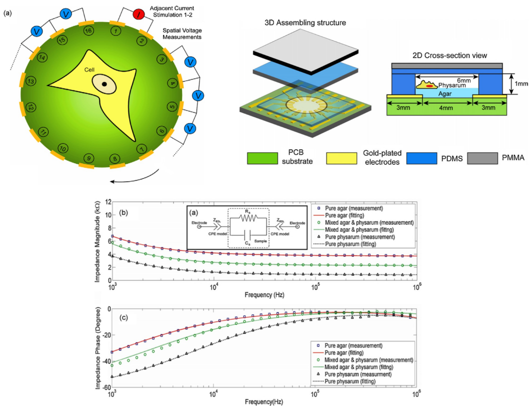


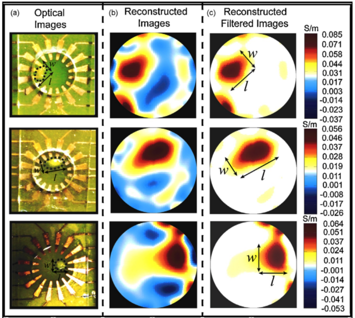




Rodriguez et al. (2015). A batteryless sensor ASIC for implantable bio-impedance applications. IEEE transactions on biomedical circuits and systems, 10(3), 533-544.

Example of imaging using impedance tomography





	Top Physarum Sample			Middle Physarum Sample			Bottom Physarum Sample		
	Optical	Electrical	Relative Difference	Optical	Electrical	Relative Difference	Optical	Electrical	Relative Difference
Width (w)	1.41mm	1.45mm	2.8%	1.61mm	1.64mm	1.8%	1.76mm	1.82mm	3.4%
Length (l)	2.47mm	2.54mm	2.8%	3.19mm	3.27mm	2.5%	1.76mm	1.82mm	3.4%

Sun et al. (2010). On-chip electrical impedance tomography for imaging biological cells. Biosensors and Bioelectronics, 25(5), 1109-1115.

And more to follow with the lab session