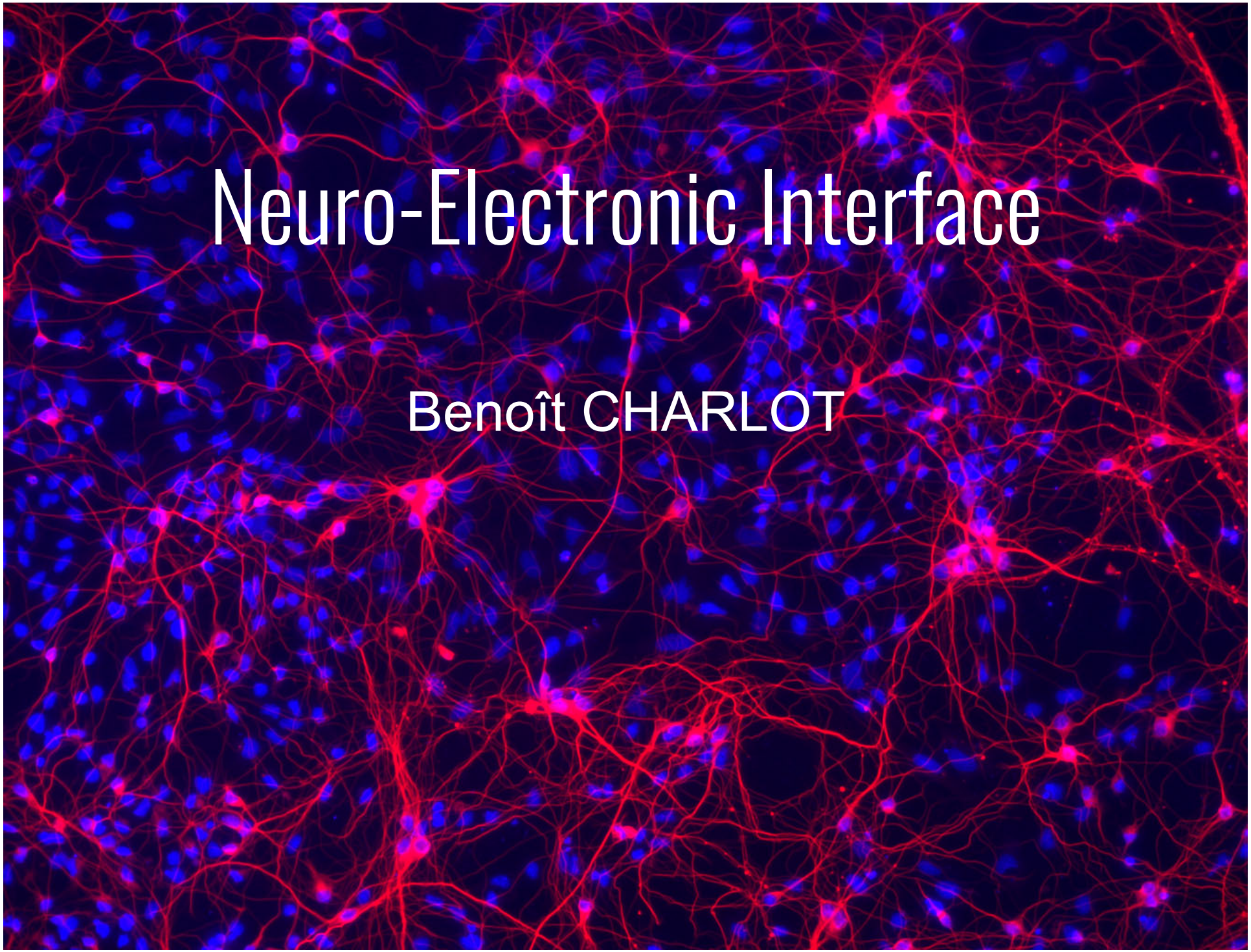


# Neuro-Electronic Interface

Benoît CHARLOT

# Outcome

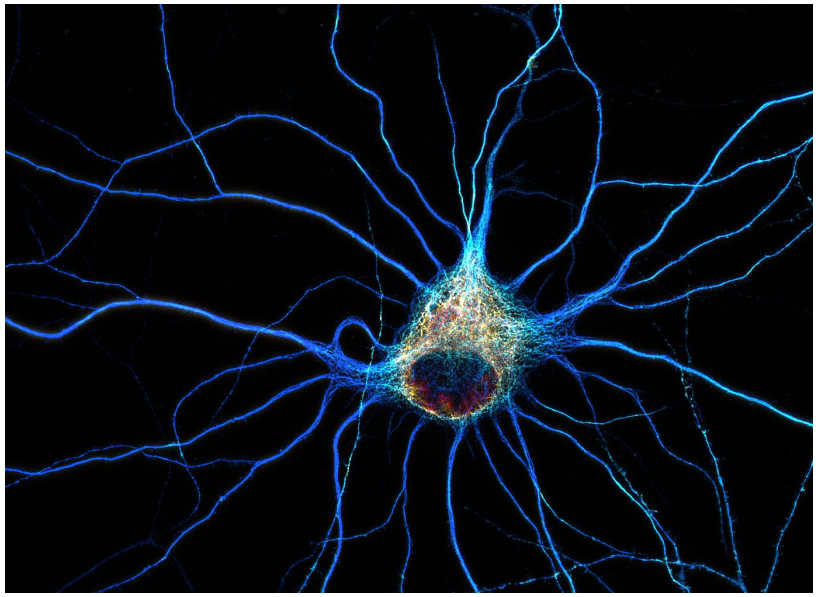
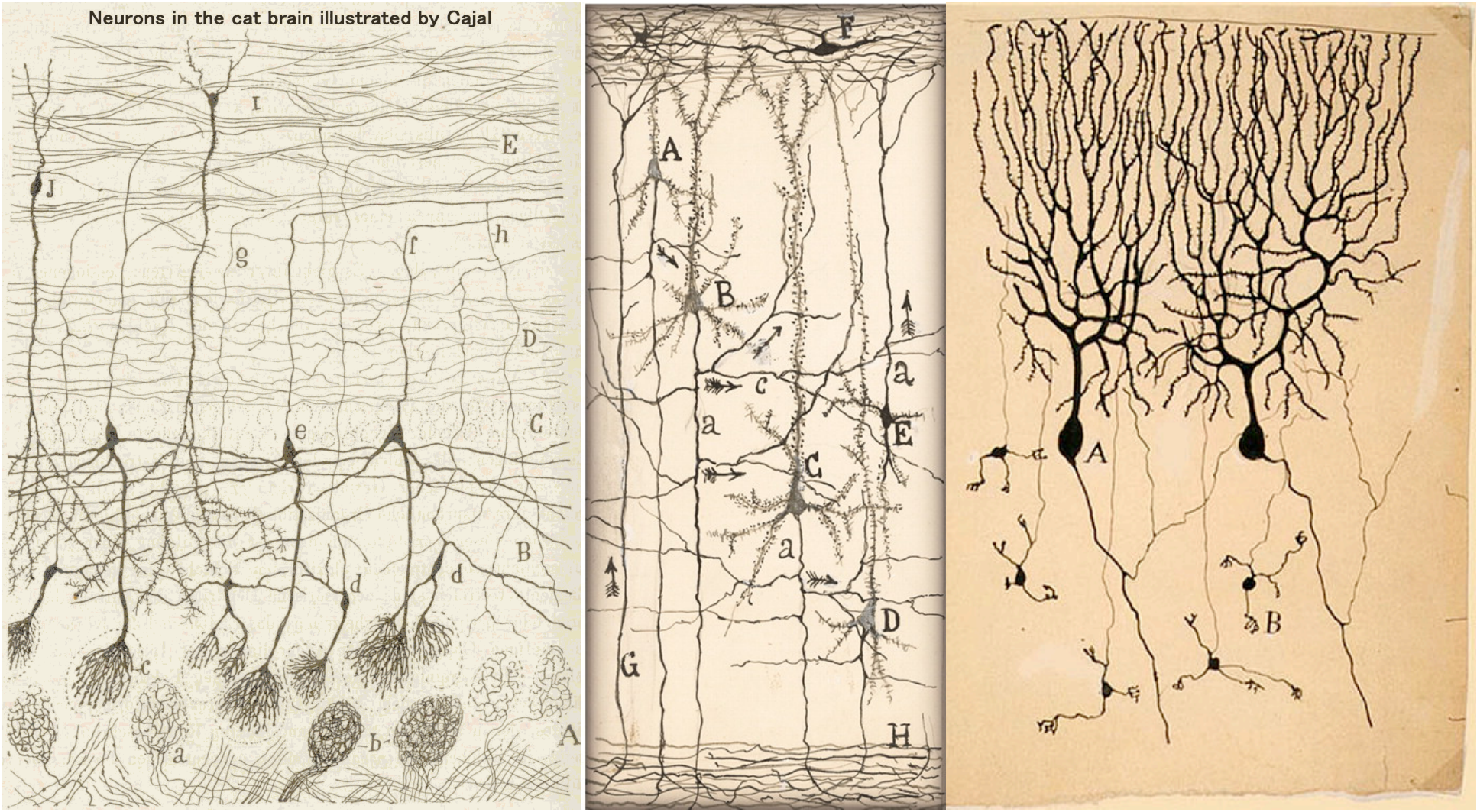


Image : Christophe Leterrier

1. Electrophysiology
    - Neurons, synapses, Nervous influx
    - Action potentials and Hodgkin Huxley model
    - Patch clamp
2. Neuron-Electrode interface
    - Neuron on electrode stucture
    - Modelling
    - Extracellular potentials analysis
3. Technology andApplication
    - Planar Micro Electrode Array
    - Implantables Electrodes

# Neurons




Santiago Ramón y Cajal (***Recuerdos de mi Vida***, Moya, Madrid, 1917)

# Santiago Ramón y Cajal

Neuro-scientist

# Neurons

One multipolar Neuron:

- **1** axon
- **Several** dendrites
- **1 000** synapses

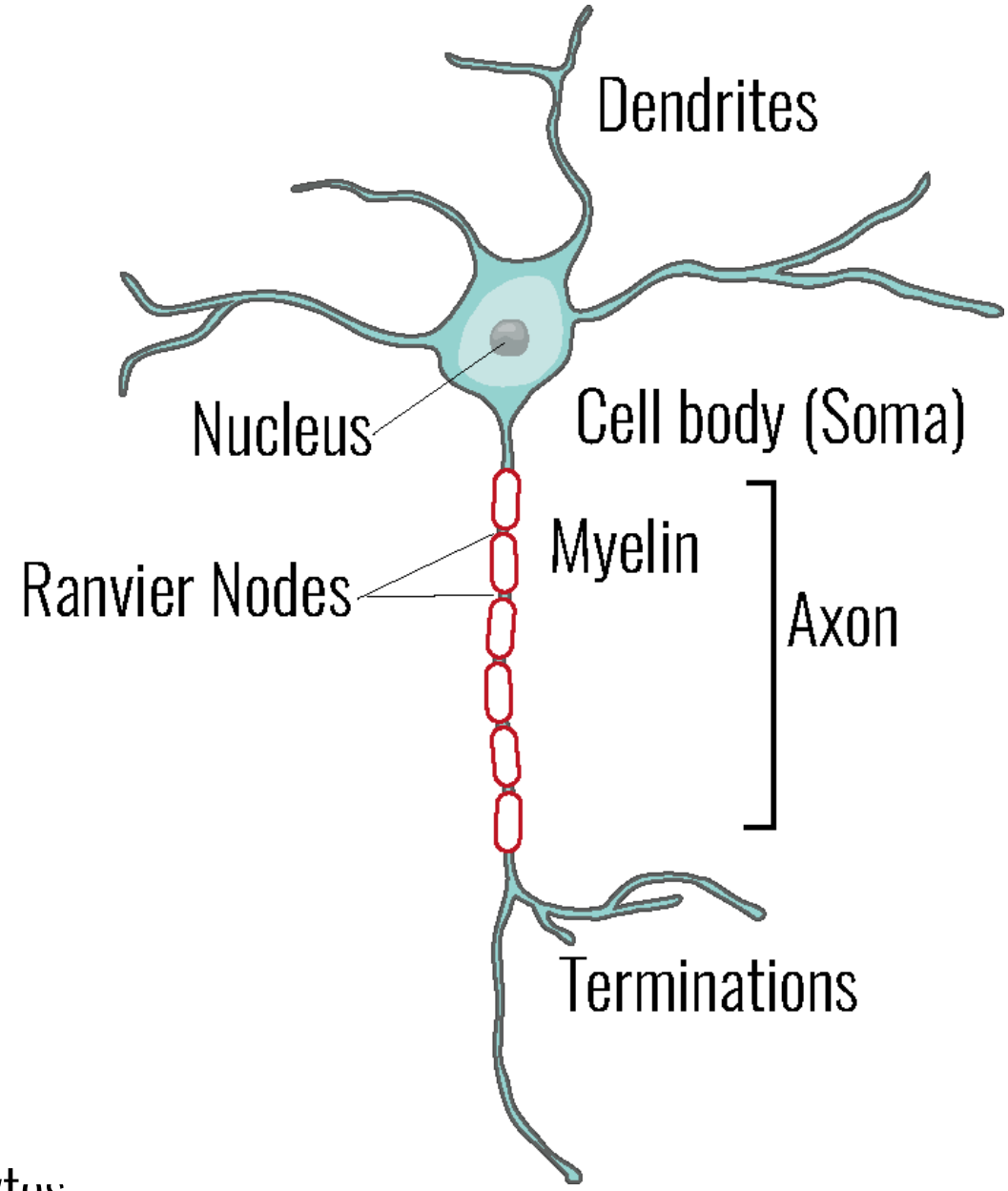
One human brain

- **100 Billions** neurons
- **10 000 billions** dsynapses

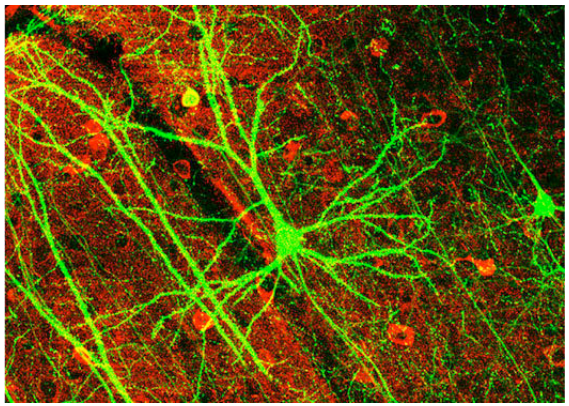
Types :

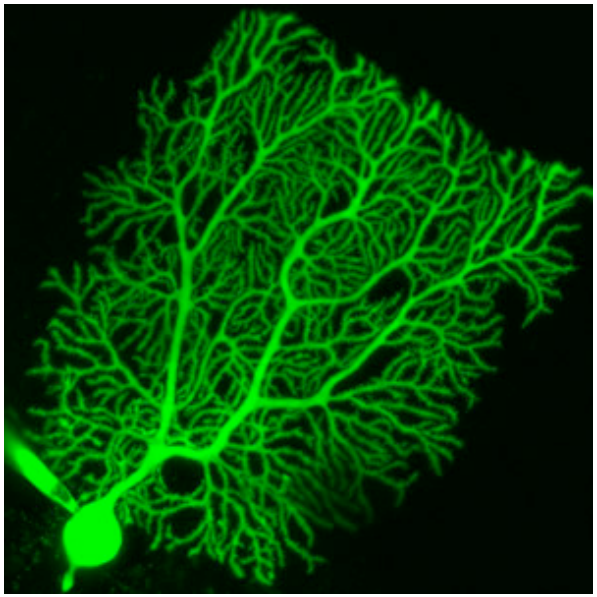
- Afferent (Sensitive periphery)
- Efferents (muscles and glands)
- Interneurons (Short and long)

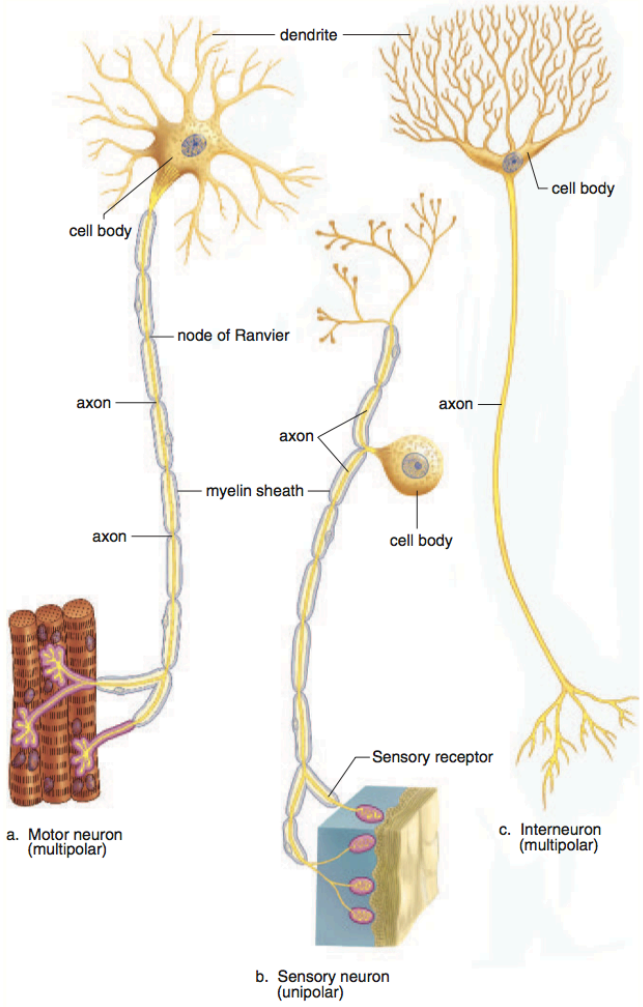
+glial cells, astrocytes, oligodendricytes

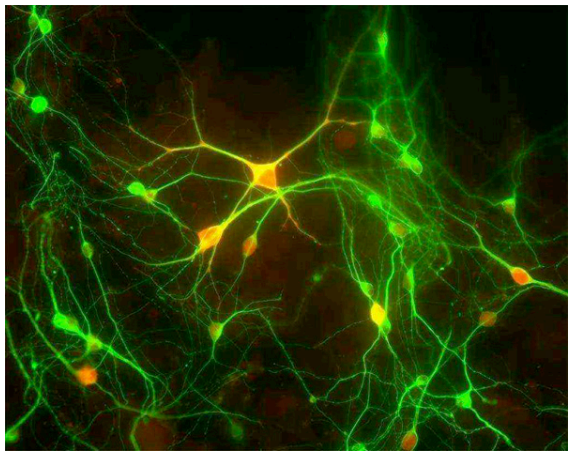


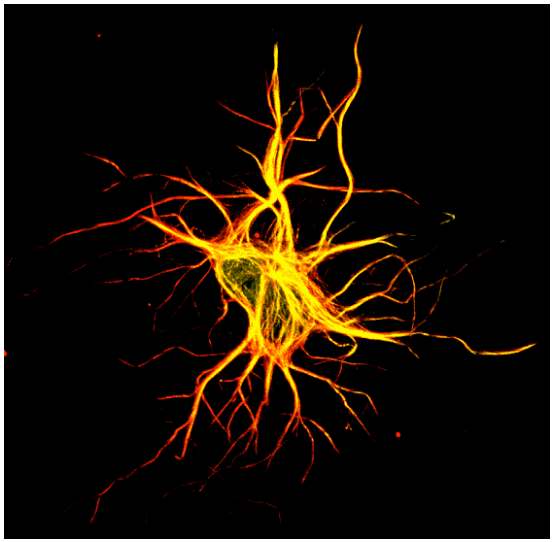
# Neurons






dendrite
cell body
cell body
node of Ranvier
axon
axon
axon
myelin sheath
axon
cell body
Sensory receptor
a. Motor neuron (multipolar)
b. Sensory neuron (unipolar)
c. Interneuron (multipolar)





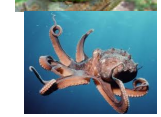
# Number of neurons by species









| | | |
|---|---|---|
| Caenorhabditis elegans | 302 | |
| Pond snail | 11,000 | |
| Aplysia | | 18,000 |
| Drosophila | 100,000 | |
| Lobster | | 100,000 |
| Ant | | 250,000 |
| Honey bee | 960,000 | |
| Cockroach | 1,000,000 | |
| Frog | | 16,000,000 |
| Octopus | | 300,000,000 |
| Human | | 100,000,000,000 |
| Elephant | | 200,000,000,000 |

# A brain in action

Crystal skull  50,000 neurons in the outer layers of the brain.

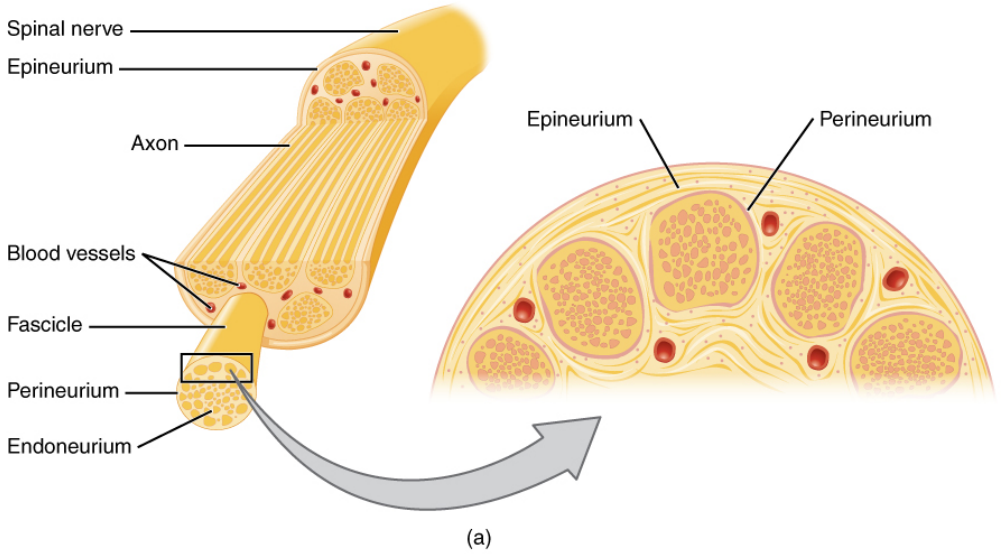
Kim T.H. et al. *Cell Rep.* 17, 3385-3394 (2016)

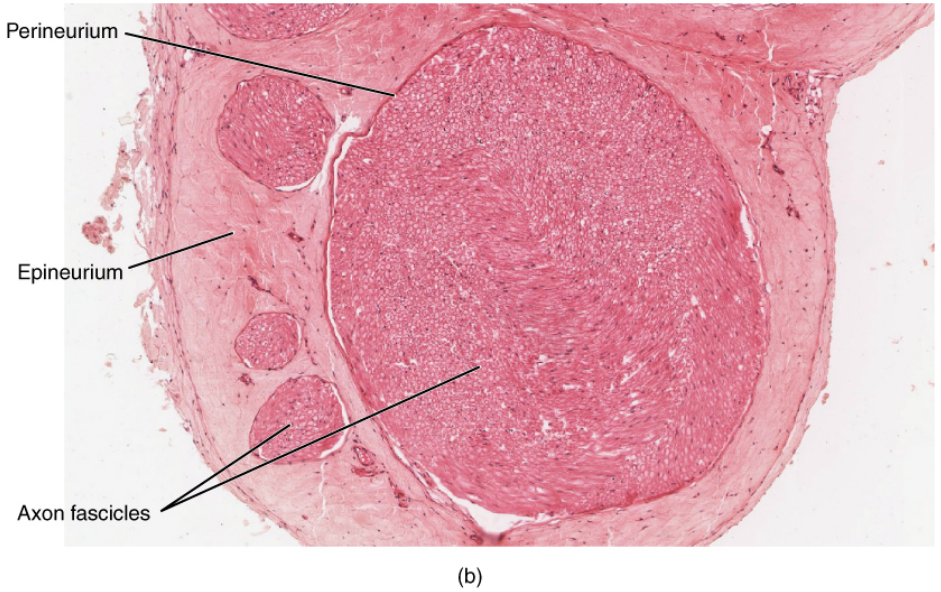
# Nerves

cable-like bundle of axons

**Afferent nerves** conduct signals from sensory neurons to the central nervous system, for example from the mechanoreceptors in skin.

**Efferent nerves** conduct signals from the central nervous system along motor neurons to their target muscles and glands.



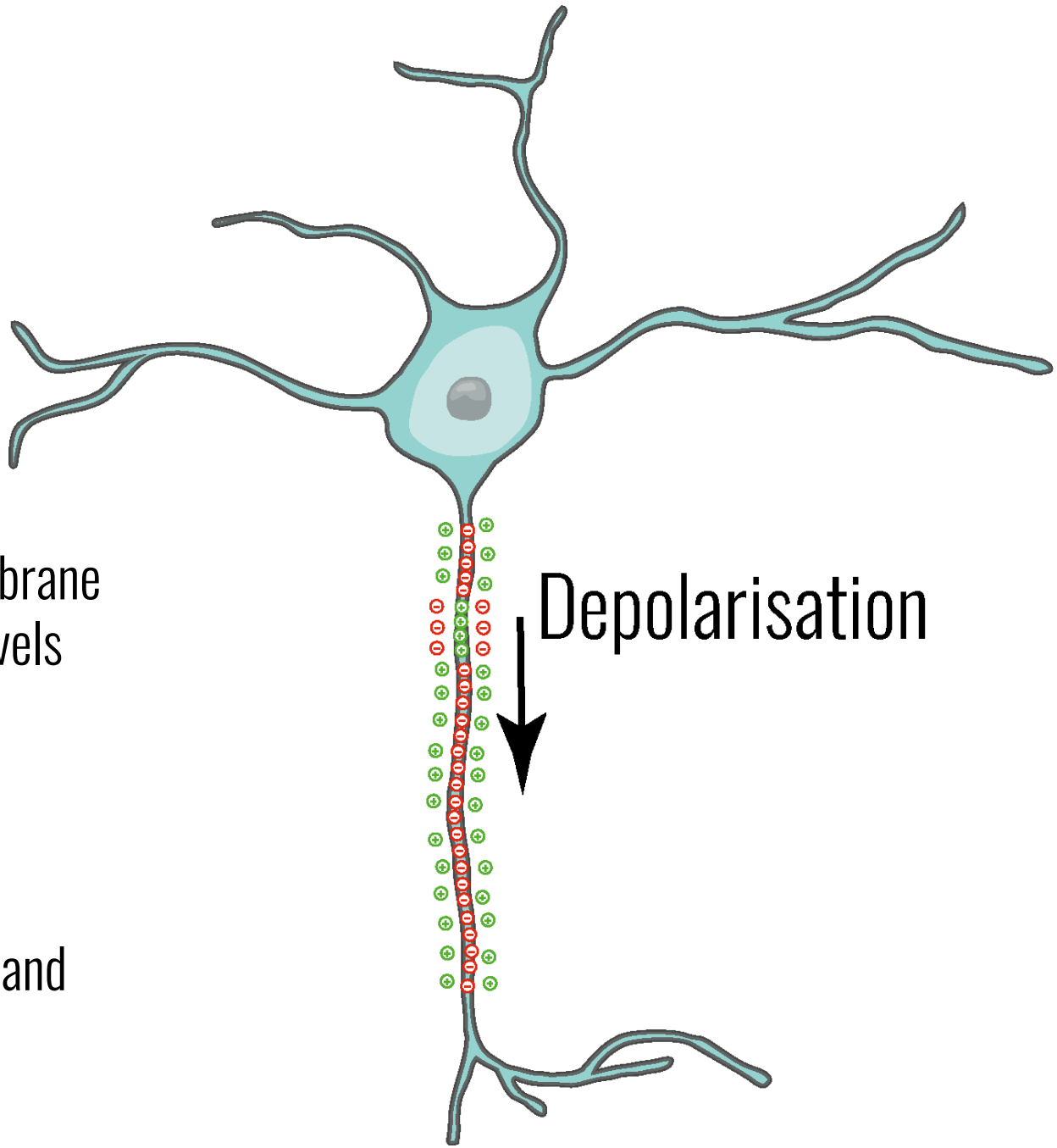
# Nervous influx

The Nervous influx is a set of Action Potentials (AP)

An AP is the propagation of a **depolarisation wave** of the membrane that initiate in the cell body and travels down the terminations

~digital signal

Information coding by the number oand frequency of Aps

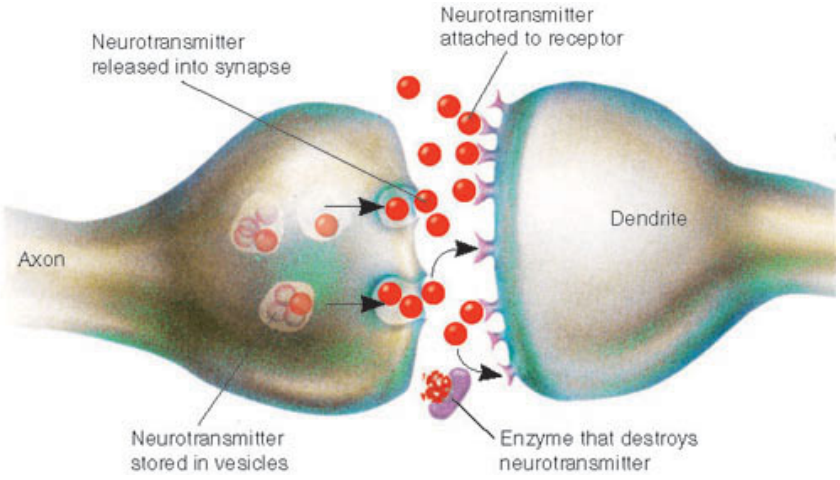


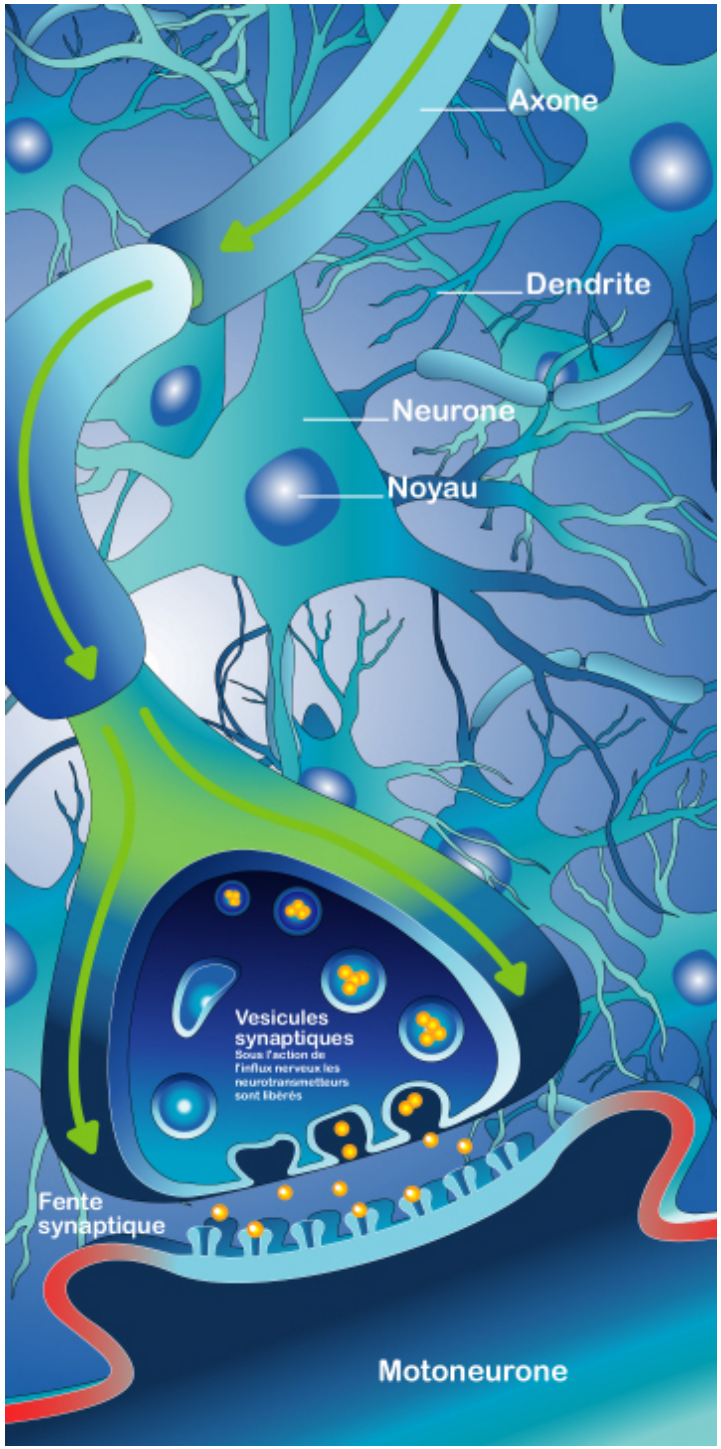
# Synapses

It is the zone of contact that spread between two neurons or between one neuron and another cell

Chemical synapse uses neurotransmitters
Electrical synapse

Synaptic cleft : between **10 and 40 nm**



# Synapses

Synapses transmit AP from one cell to another

Briefly :

The arrival of one AP in the synaptic cleft induces the progressive delivery of neurotransmitters

Diffusion of neurotransmitters in the cleft

Neurotransmitters are captured by receptors

Excitation or inhibition

# Synapses

The **synaptic potential** is
- Weak (0.1-10 mV)
- progressive  (~analogic)
- Passive propagation (diffusion driven)
- hyperpolarisation, or depolarisation

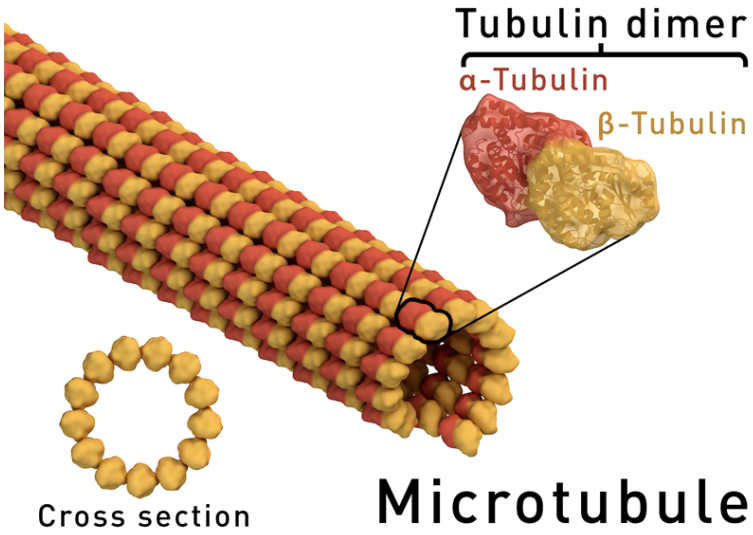
The **Action potential** is
- High (70-110 mV)
- « all or nothing» (~digital)
- Active propagation
- depolarisation

# Axonal transport

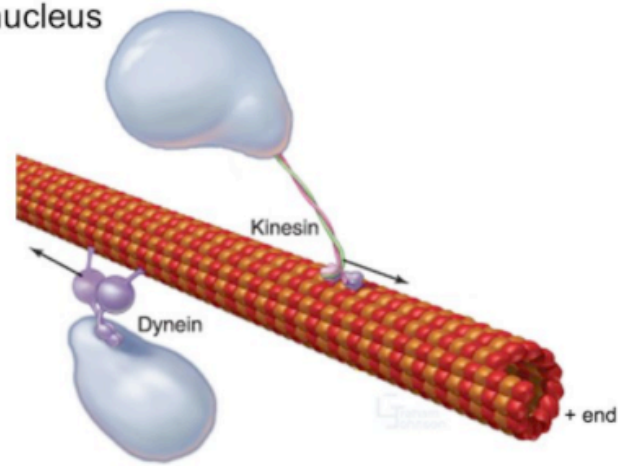
Neurotransmitters are synthetised in the cell body

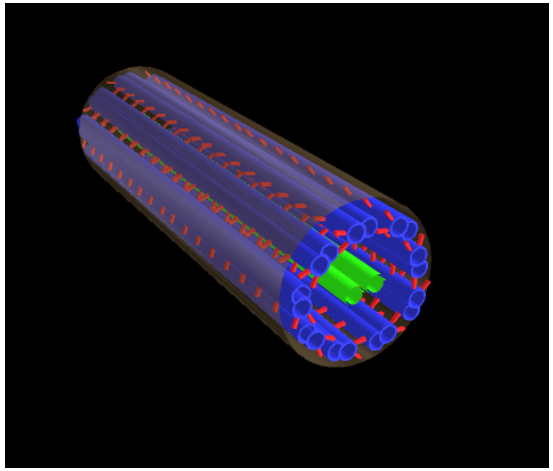
Some axons can extend up to 1 meter

How NT are sent from the cell body down to the synapses?

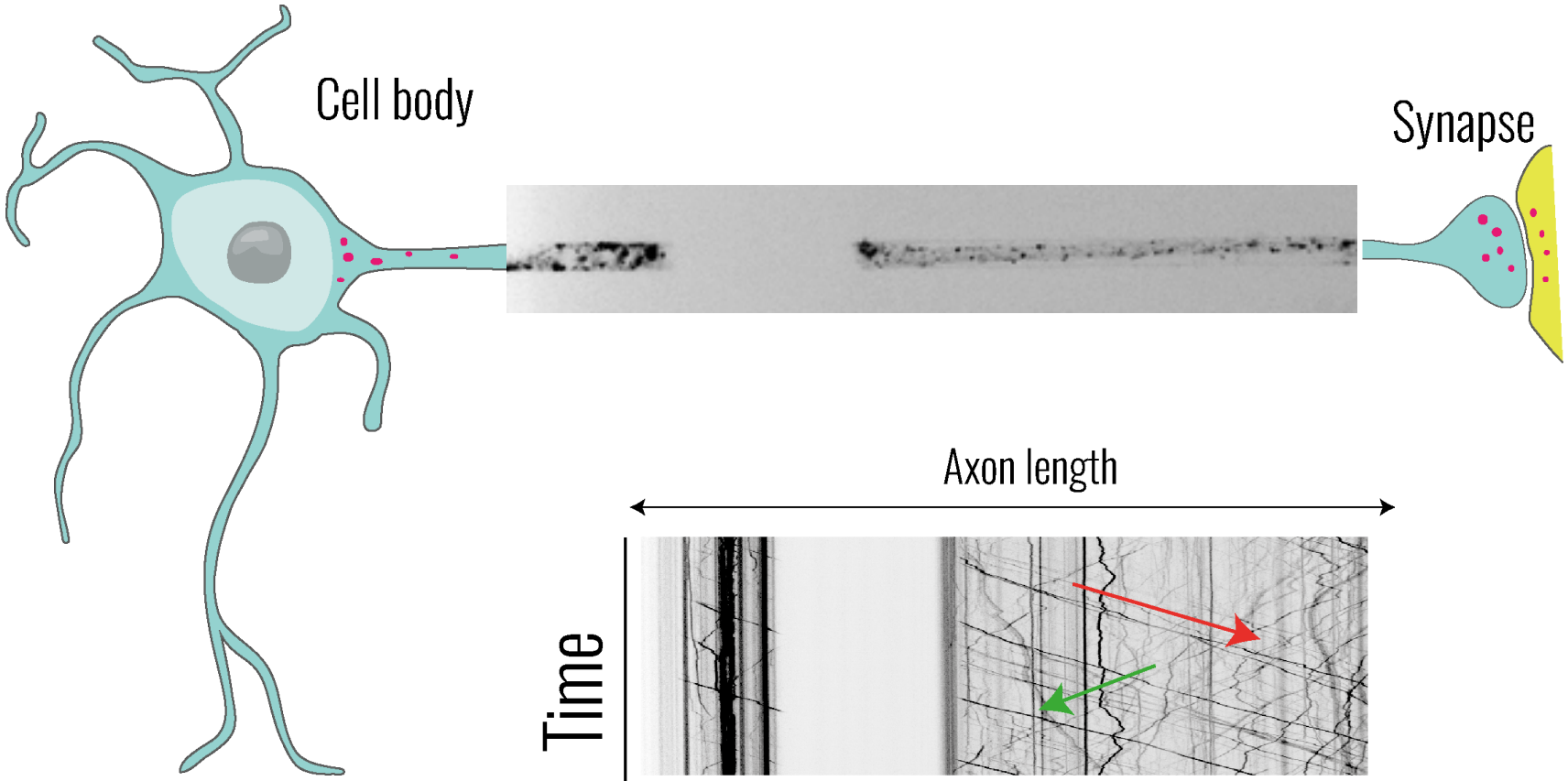



- Vesicular transport
  - Kinesin
    - Toward +
    - Away from nucleus
  - Dynein
    - Toward –
    - Toward Nuc
  - 0.1-1 um/s

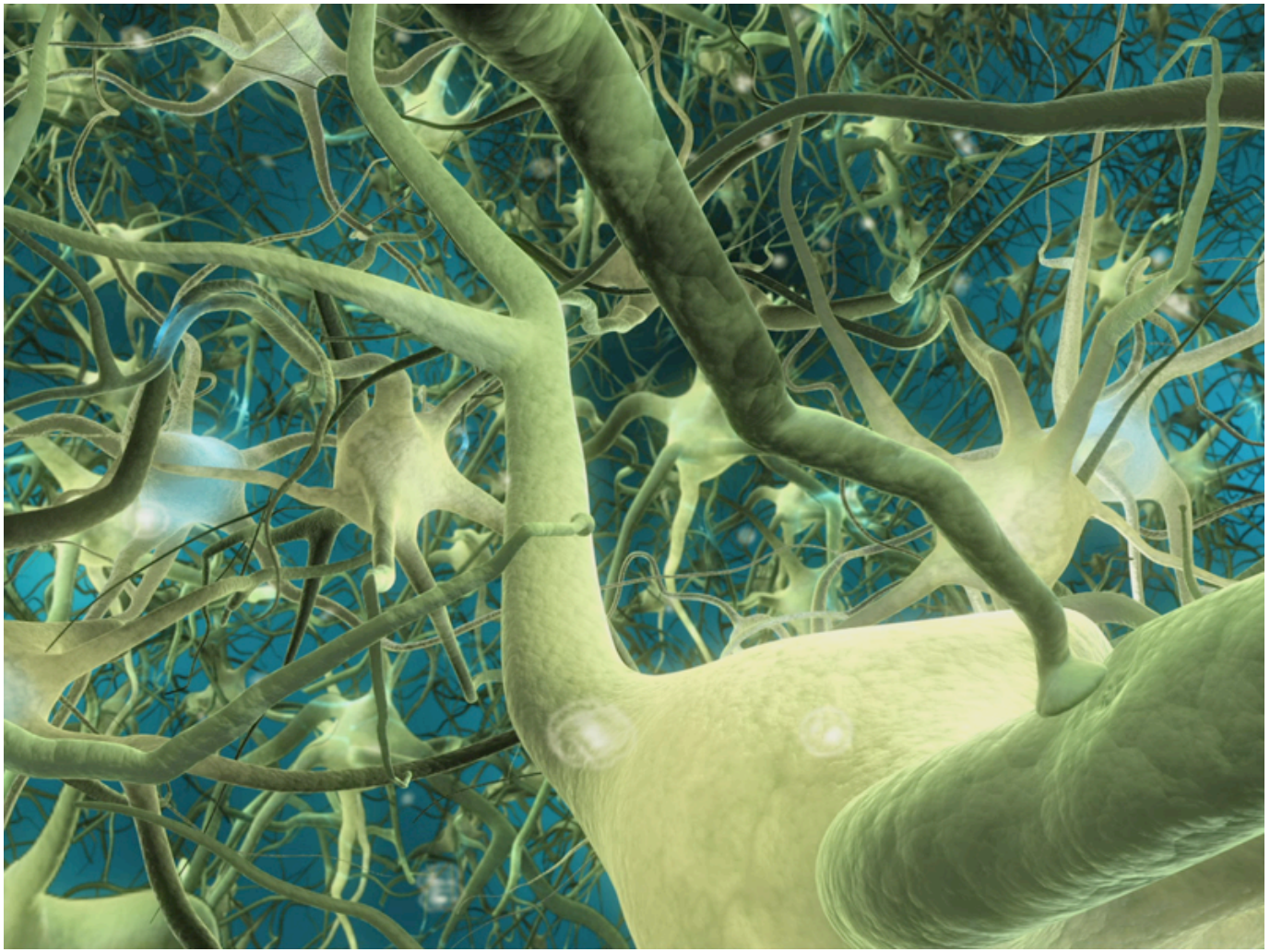


# Axonal transport

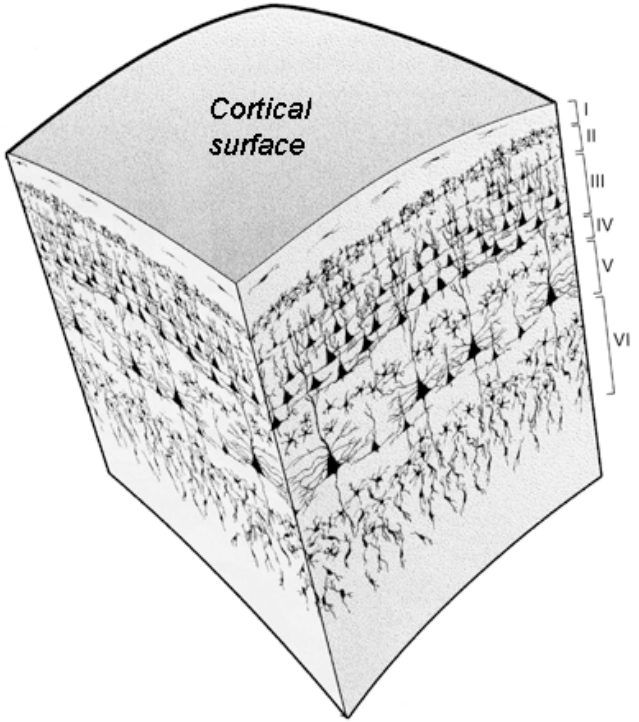


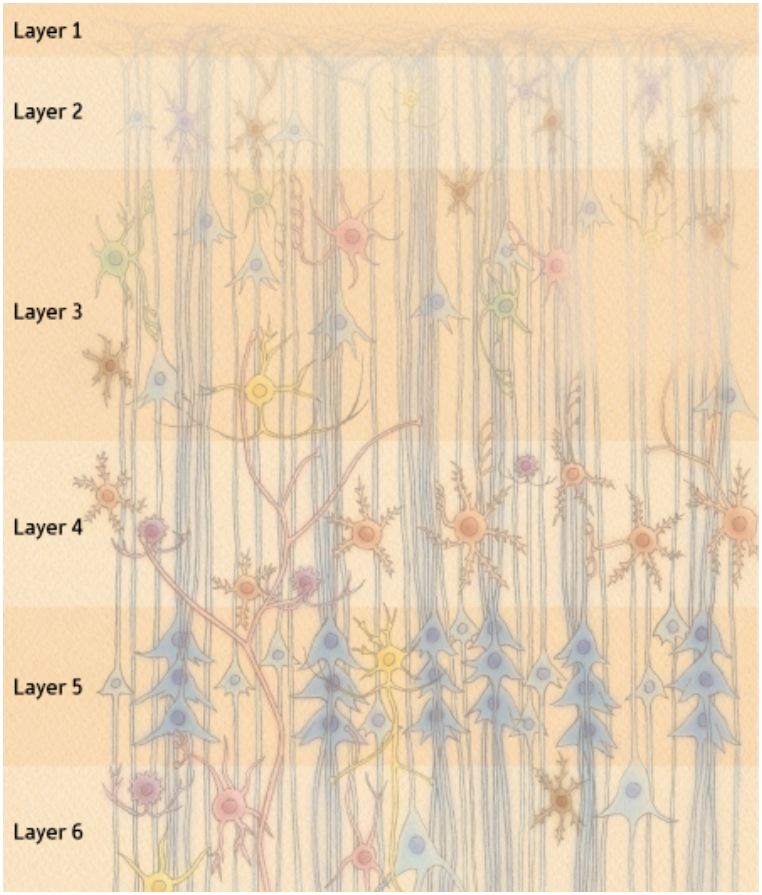
# Neuronal Network

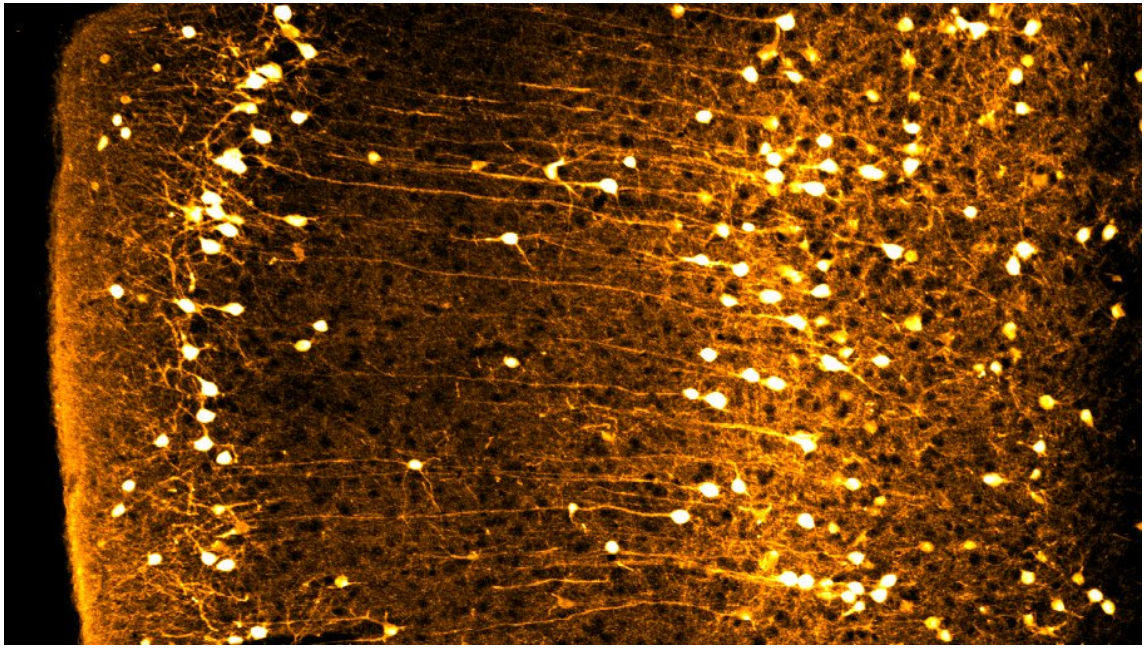


# Neuronal Network

Cortical layers

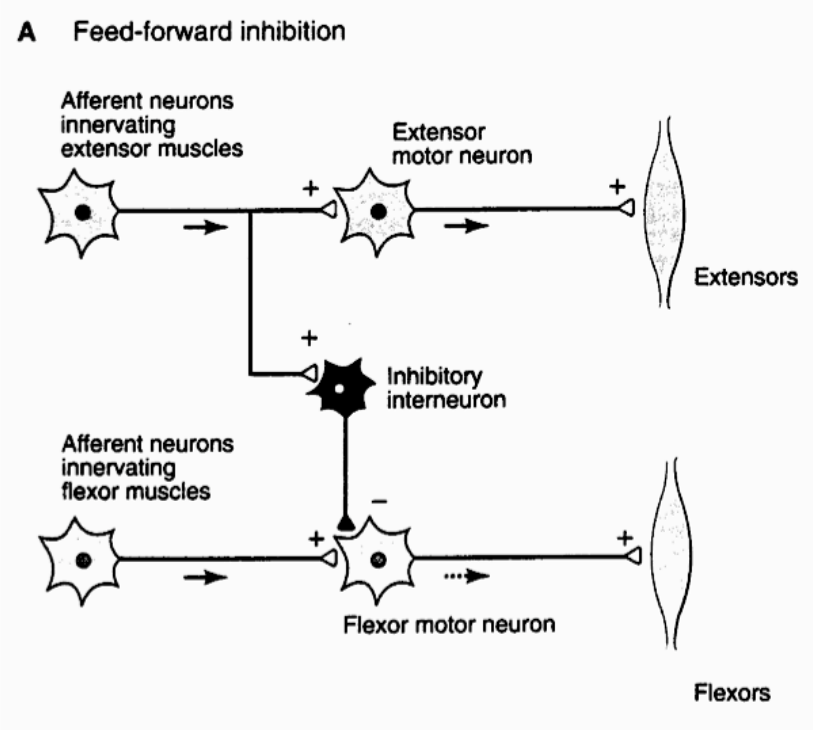


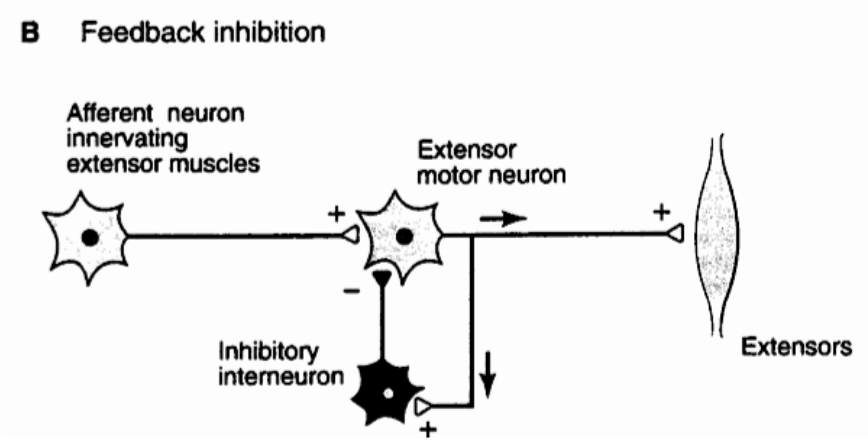



# Neuronal Network

Exemples

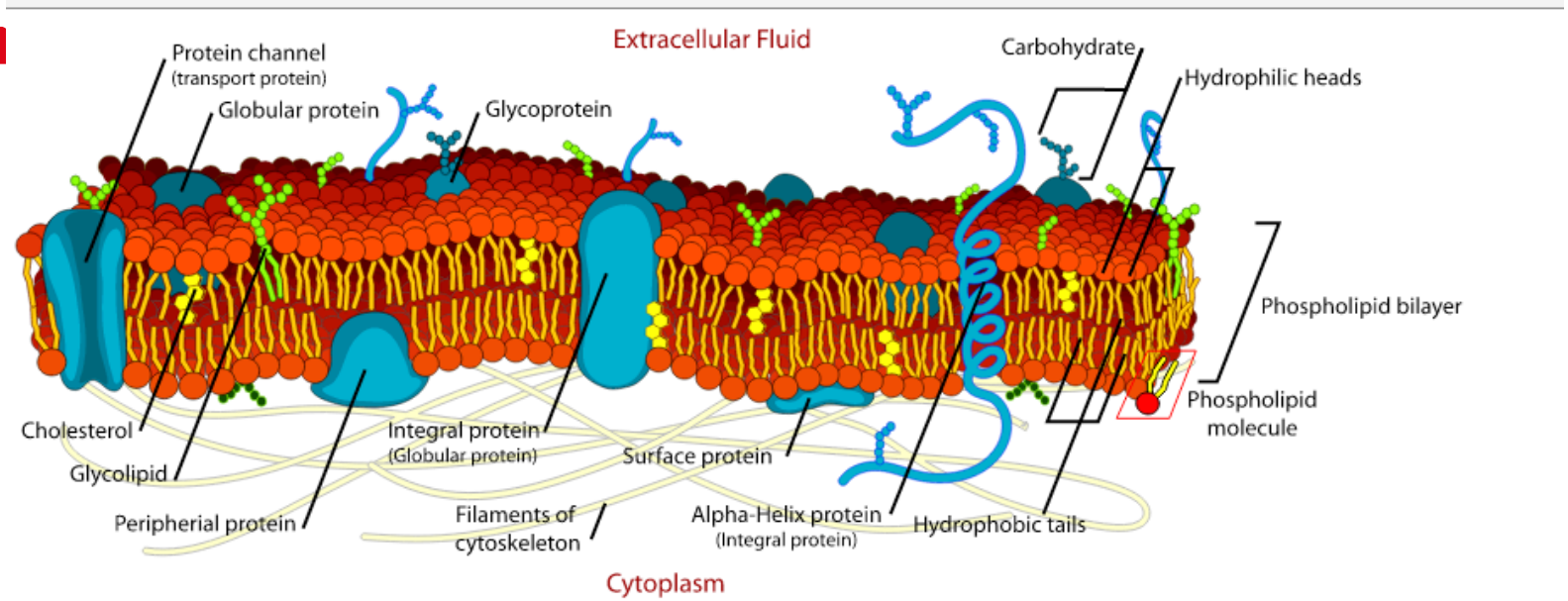


# Cell Membrane

Thickness **7nm**

Phospholipids
Lipid bilayer




By LadyofHats Mariana Ruiz - Own work. Image renamed from File:Cell membrane detailed diagram.svg, Public Domain, https://commons.wikimedia.org/w/index.php?curid=6027169

Cellular membrane divide intra and extracellular compartments

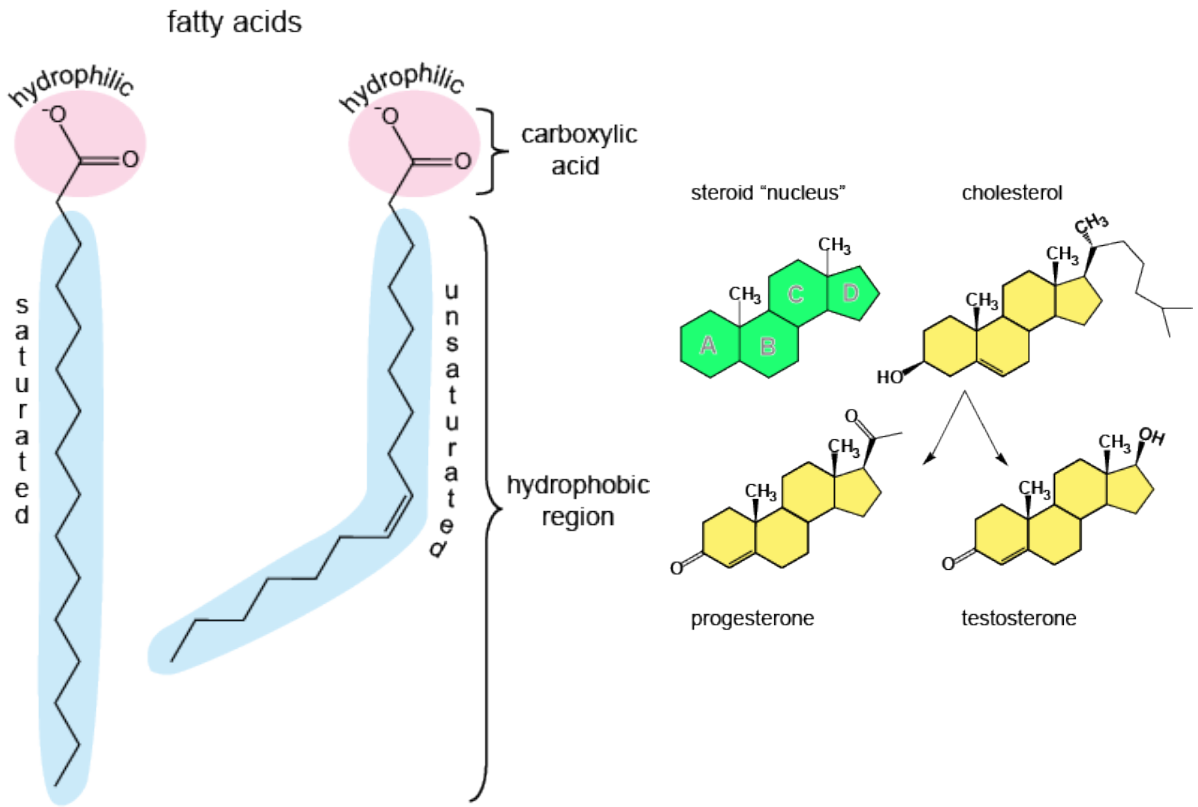
Ion concentrations in these compartments are different

This difference induce a voltage across the membrane

# Lipids

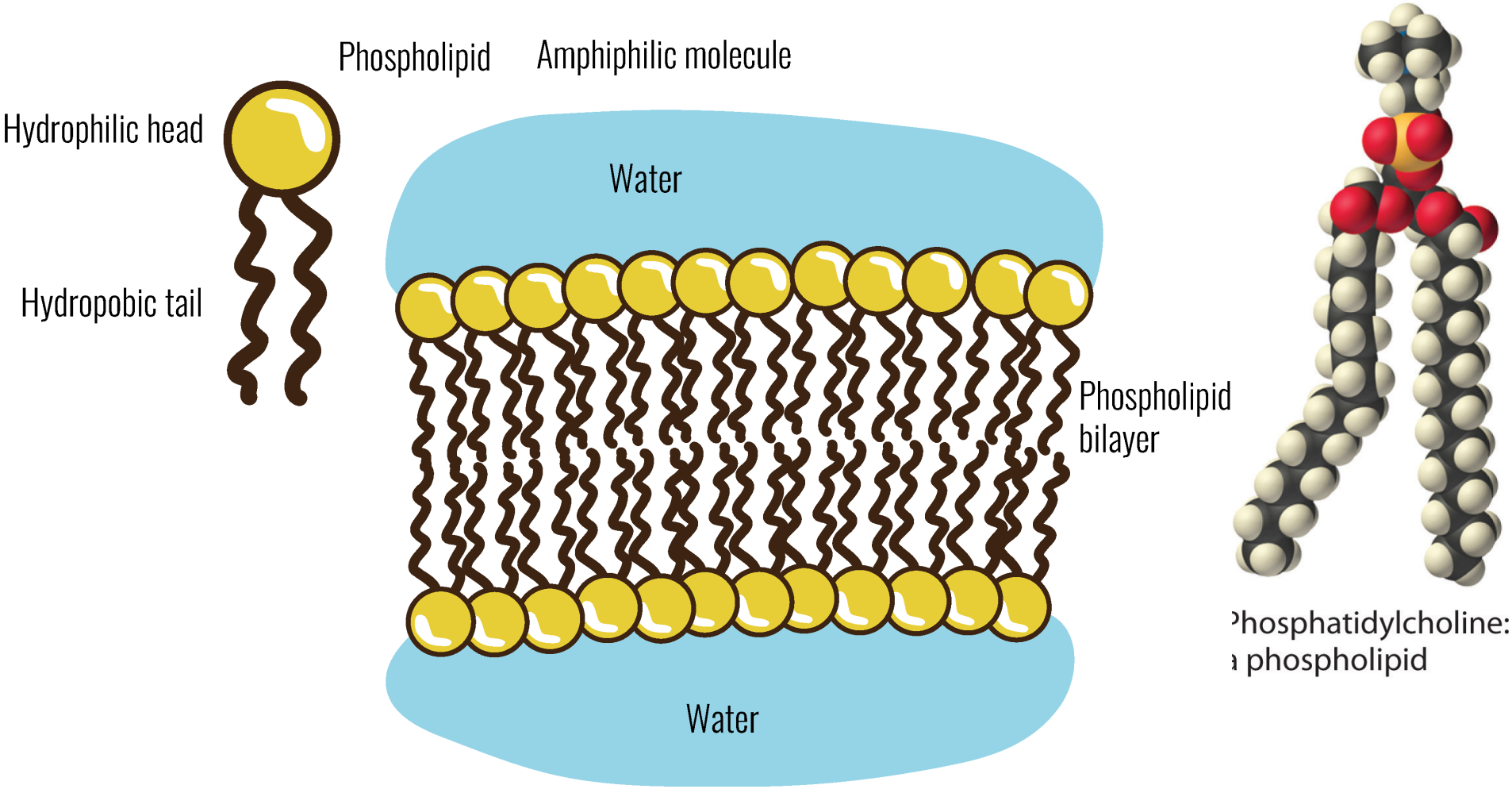
Acides gras (huiles, graisses, cires)

Stéroides




Non polaires

# Phospholipids

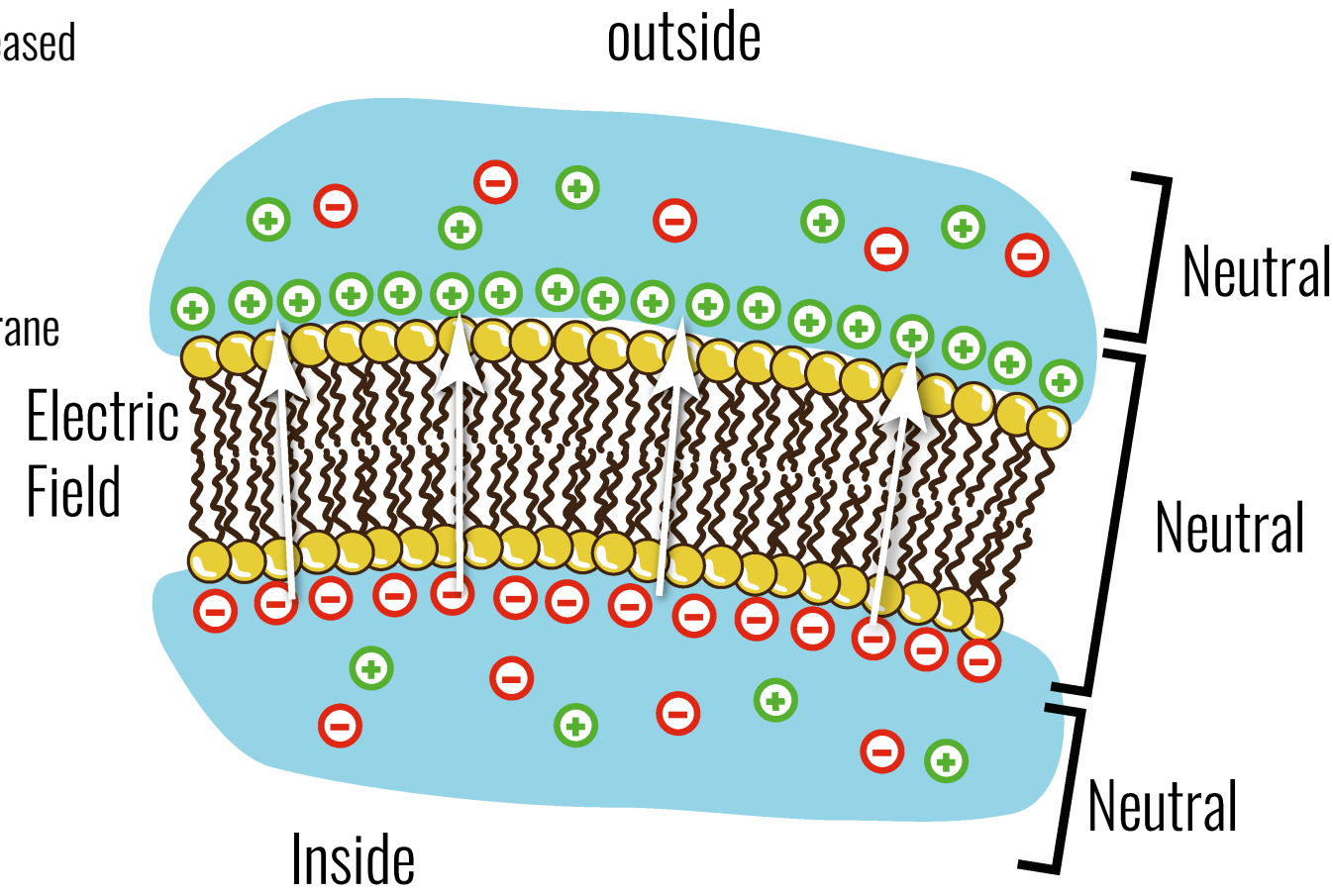


# Field in membrane

Membrane resting potential= **65mV**
Electric field : **10MV.m$^{-1}$**

If the membrane potential is decreased of 10mV (-65 to -55) an action potential is fired

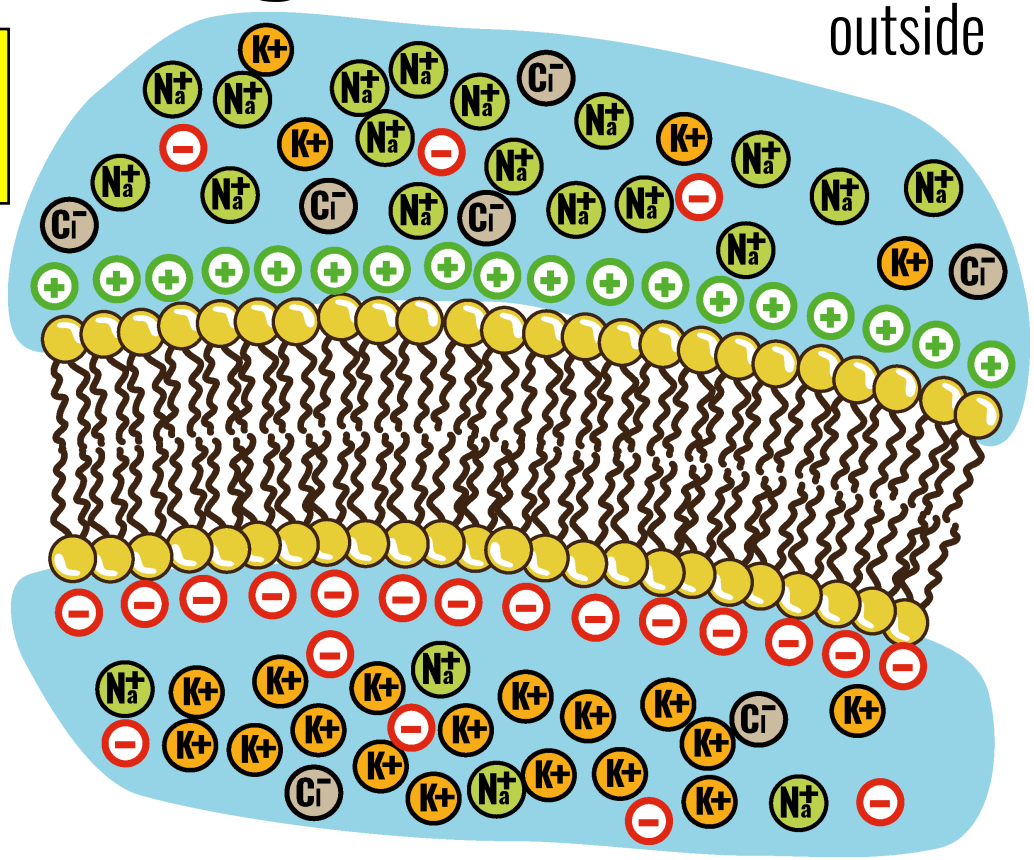
The membrane is an insulator
Ions can pass through with membrane proteins (with leaks)



# Ions and charges in neurons

Na+ 150mM
K+ 5mM

outside



Na+ 15mM
K+ 150mM

Inside

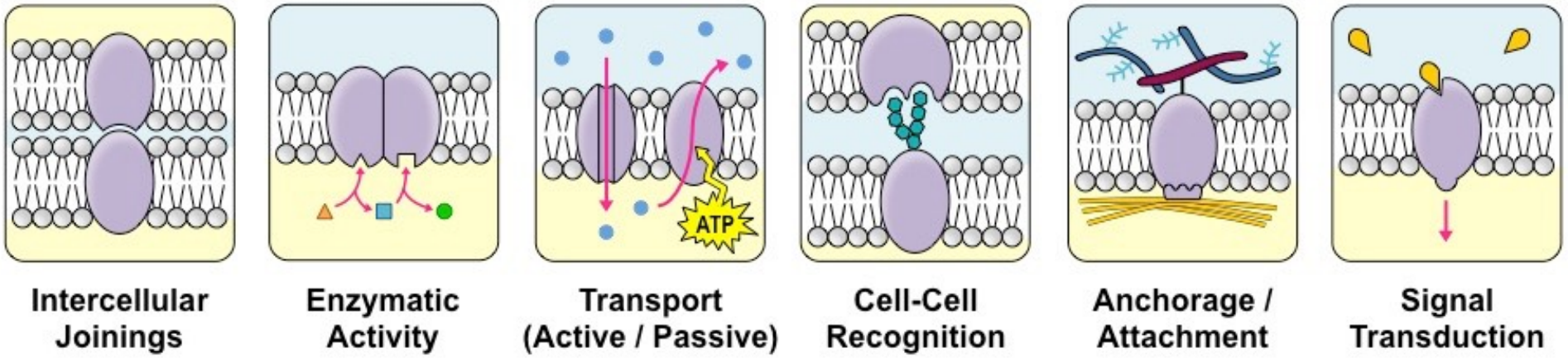
The electrochemical potential can be computed with **Nernst equation**

$$E_K = -\frac{RT}{ZF}\log\frac{[K]_{int}}{[K]_{ext}}$$

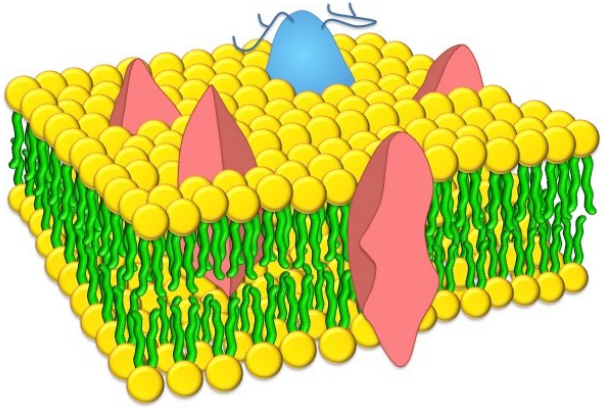
R : Perfect gazes constant
Zx: valence of ion ;
T : Absolute temperature
F : Faraday number

# Membrane Proteins

Molecules encaged in the membrane, several functions




These ones are interesting for Action Potential



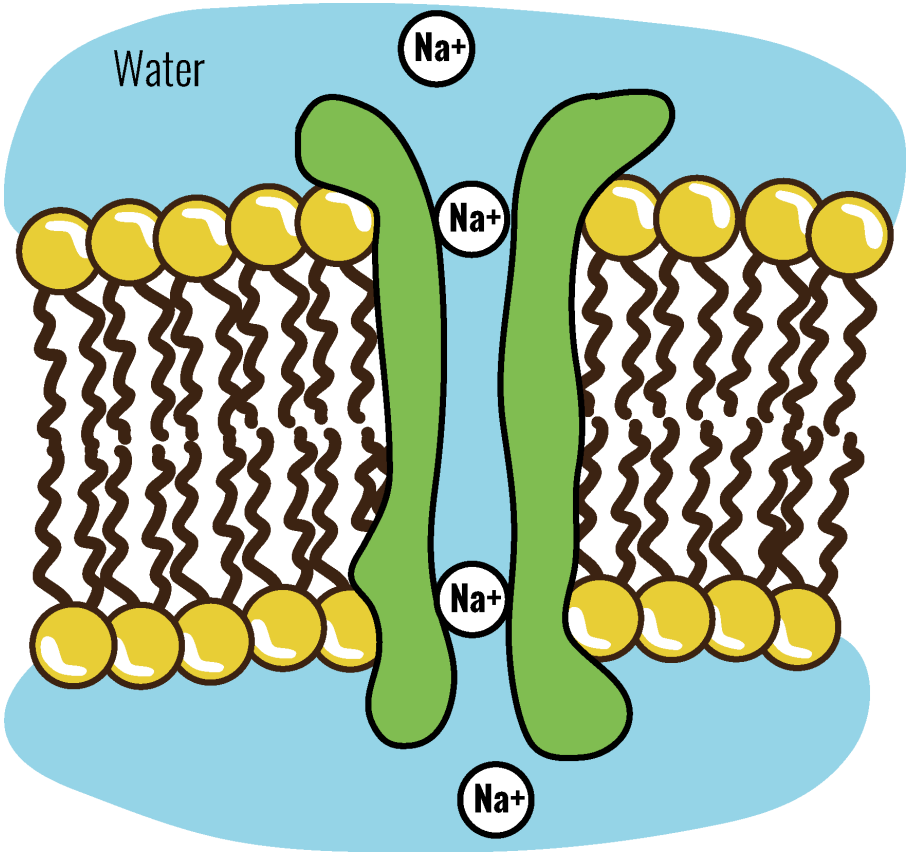
# Ion Channels

Ion Channels are membrane proteins gating the flow of ions across the cell membrane

Selective valves permeable to unique ion species

The rate of ion transport : $10^6$ ions/s

There are over 300 types of ion channels in a living cell



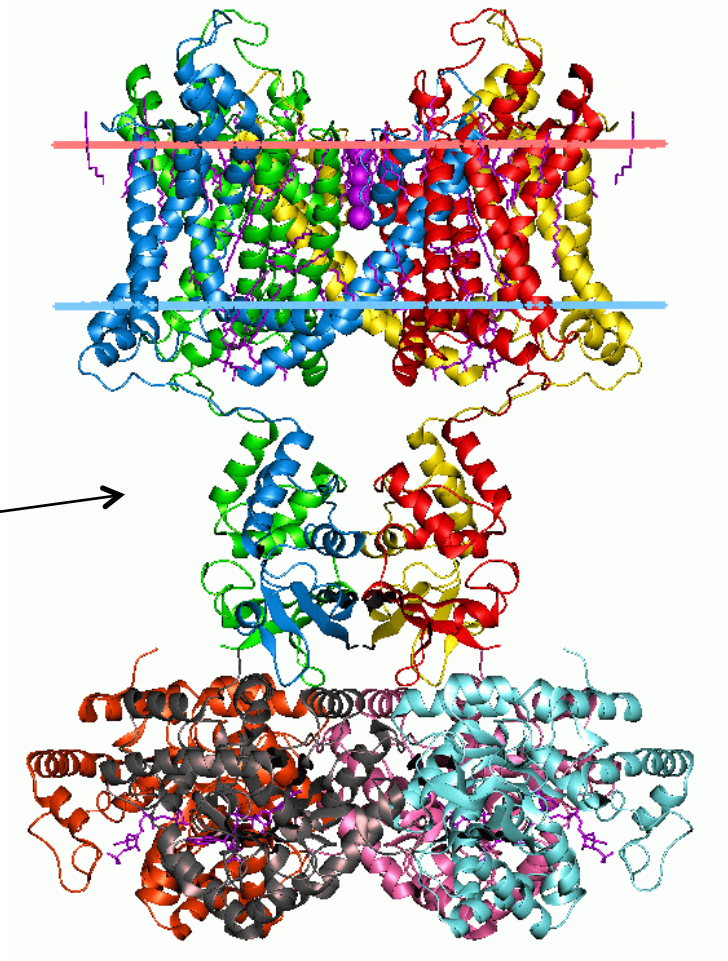
# Ion Channels

Ion channels are **passive** valves (driven by electrochemical gradient)
≠ membrane pumps

No use of metabolic energy

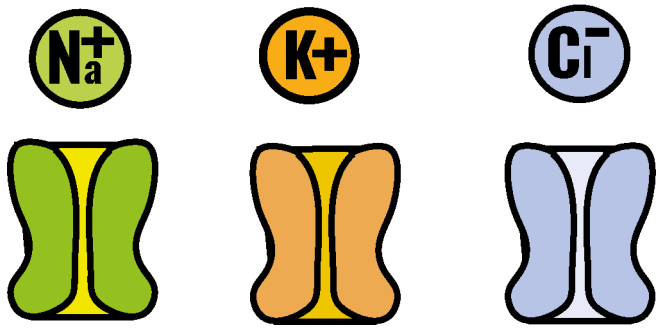
-Voltage dependants

**$Na^+$, Sodium**
**$Ca^{2+}$, Calcium**
**$K^+$, Potassium**
**$Cl^-$, Chloride**
**$H^+$, protons**



The opening and closing of the channels are triggered by changing ion concentration

# Ion Channels




**Passive** Ion Channels
Found on dendrites, cell body, and axon.

**Chemically-gated** Ion Channels
Found on dendrites & cell body

**Voltage-gated** Ion Channels
Found on axon hillock, unmyelinated axons and at nodes of Ranvier on myelinated axons.

The opening and closing of the channels are triggered by changing ion concentration

# Ion Channels

## Other type of Ion channels

-Ligand-gated ion channel : opens with the binding of neurotrasmitters : GABA, Glutamate, serotonin, ATP, nicotin...

-Inwardly rectifying potassium channels (Cl, K, Na, Ca, H)

-Calcium-activated potassium channel

-Light-gated ion channel : Channelrhodopsin

-Mechanosensitive channels (Piezo, TREK)

-Temperature-gated channels (TRPV)

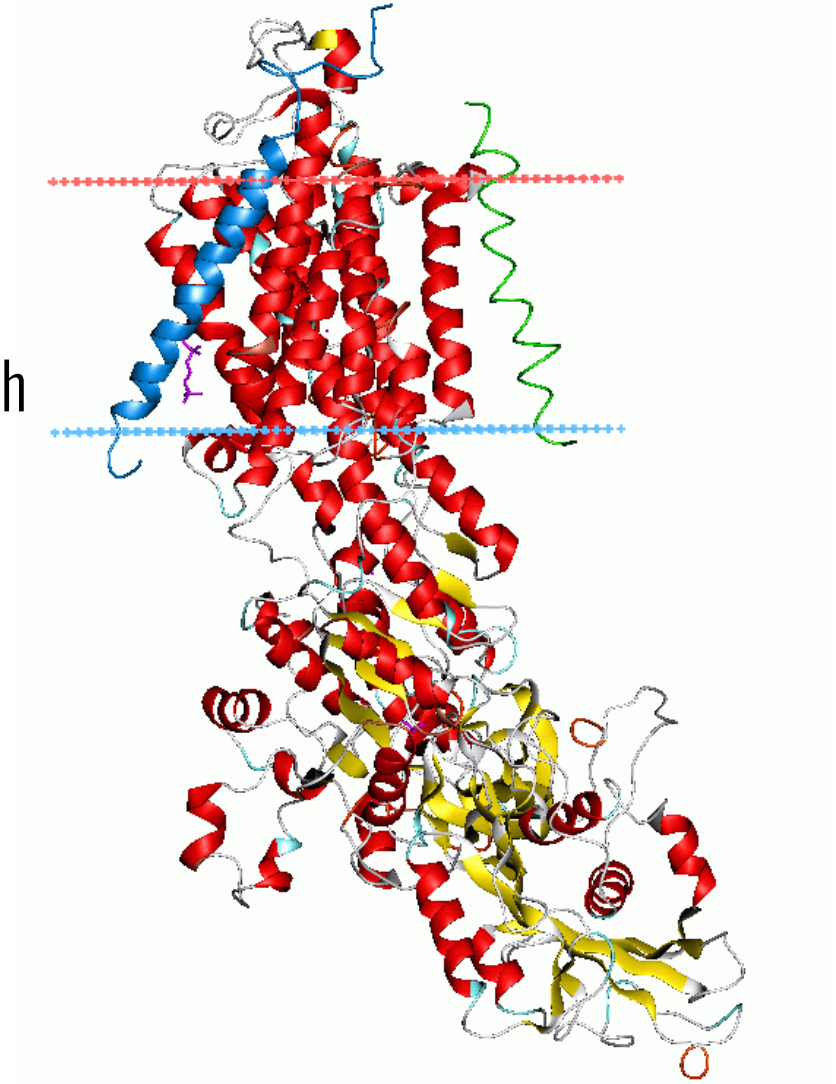
# Ion pumps

Na+/K+ -ATPase

Ion pumps are enzymes that pumps sodium out of cells while pumping potassium into cells, both against their concentration gradients.

Active process  (consumes ATP)

Responsible for the generation of the resting membrane potential

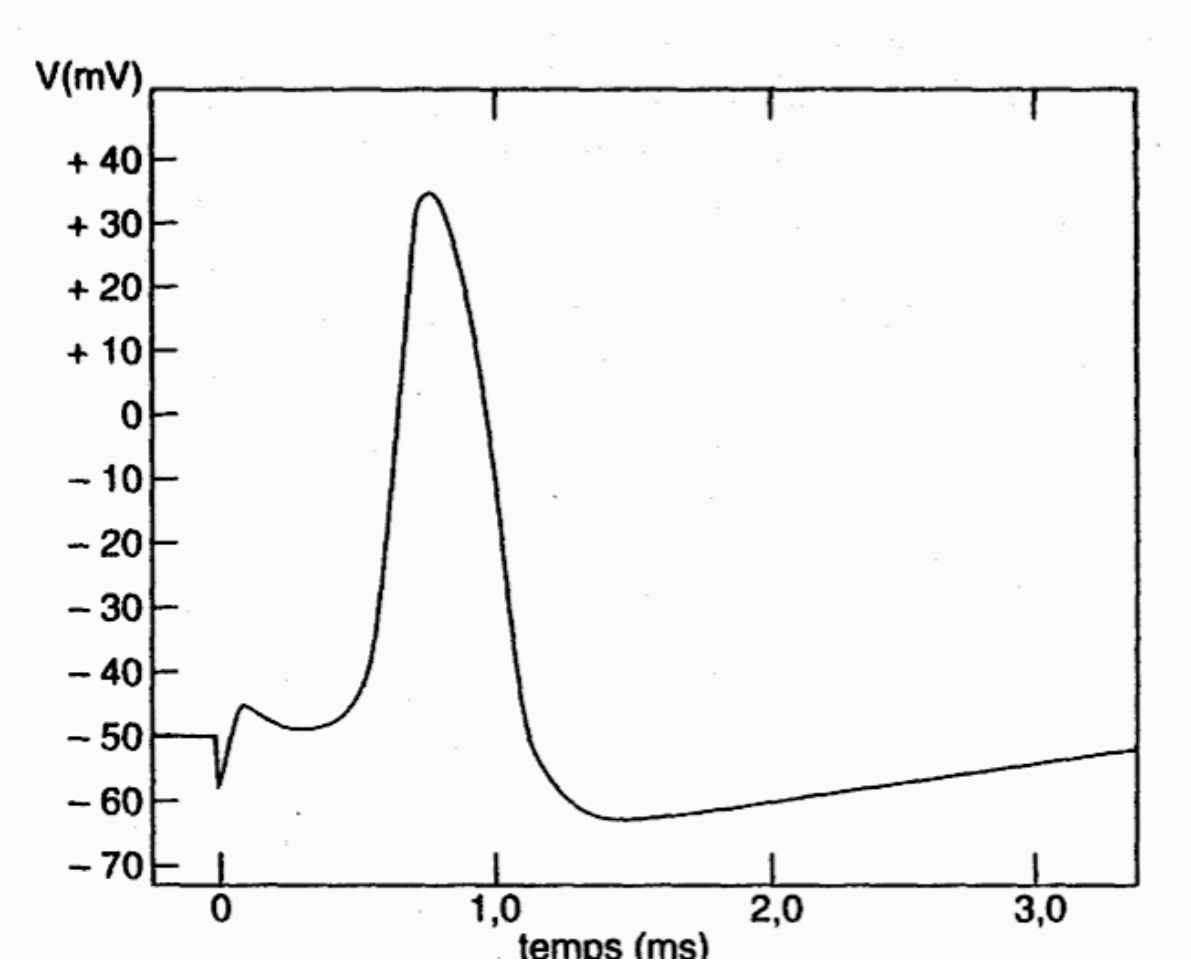


# Electrochemical gradients

outside

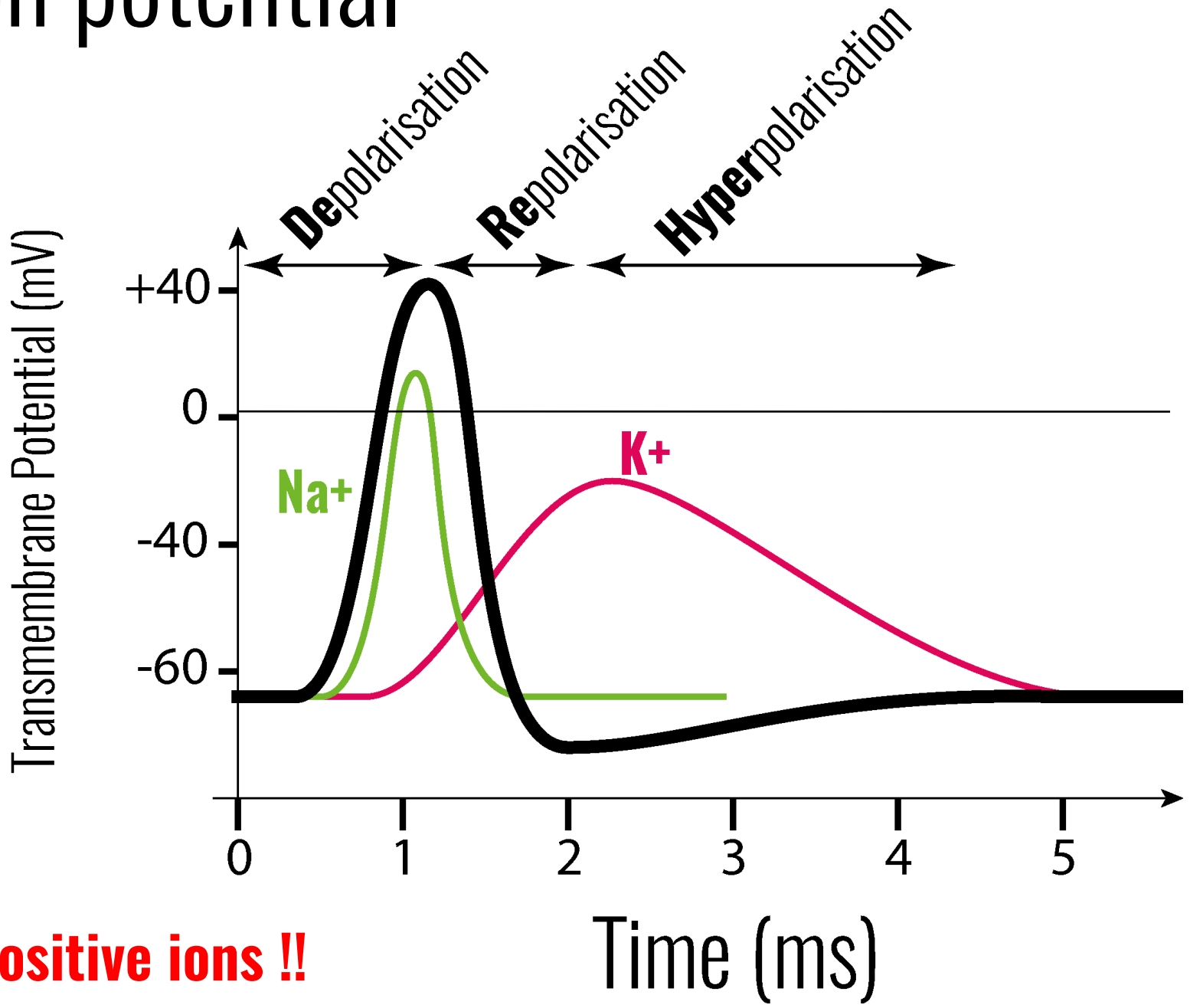
# Action potential

## What it looks like?




**Intracellular recording of a giant squid axon under current Stimulation**

# Action potential



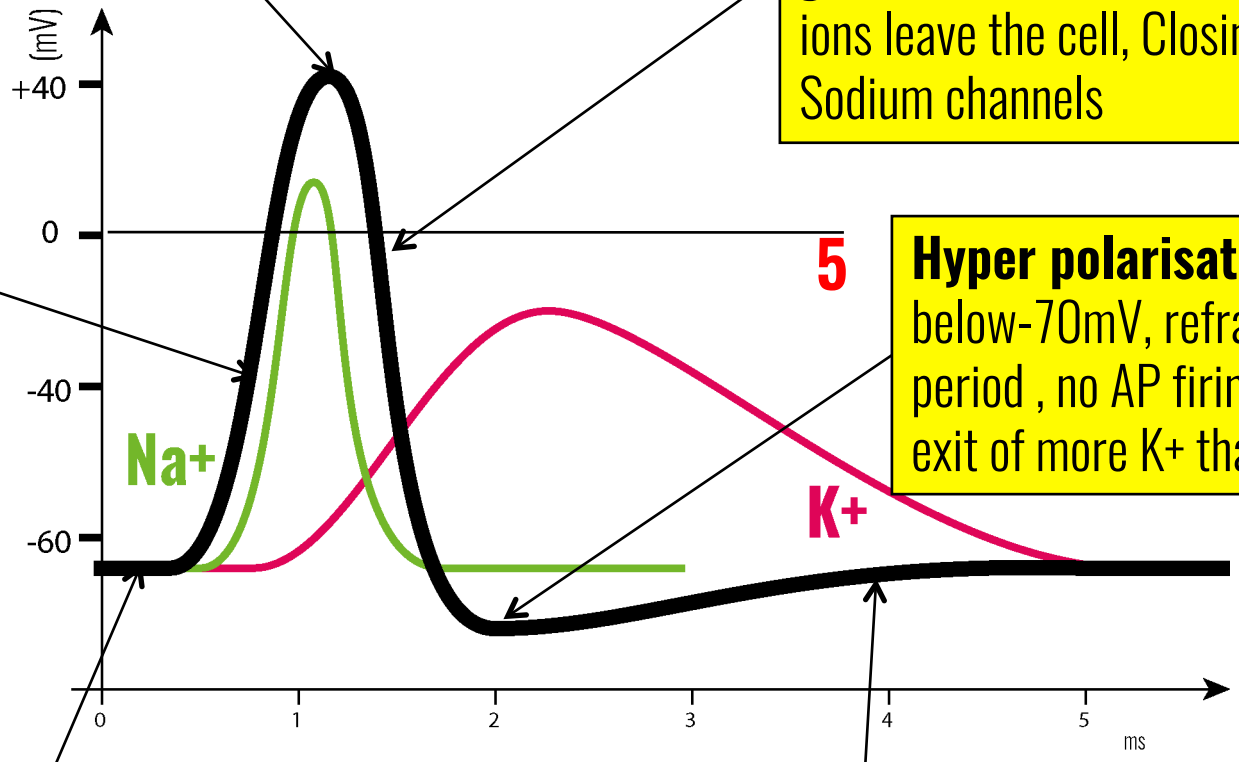

**Only positive ions !!**

# Action potential

**3** **Maximum** : All Na+ channels are open, maximum concentration, minimum gradient

**4** **Repolarisation** : return to -70mV opening of voltage gated rectification channels. K+ ions leave the cell, Closing of Sodium channels

**2** **Depolarisation** : rise up to +30mV opening of voltage gated sodium channels, Na+ ions enter the cell

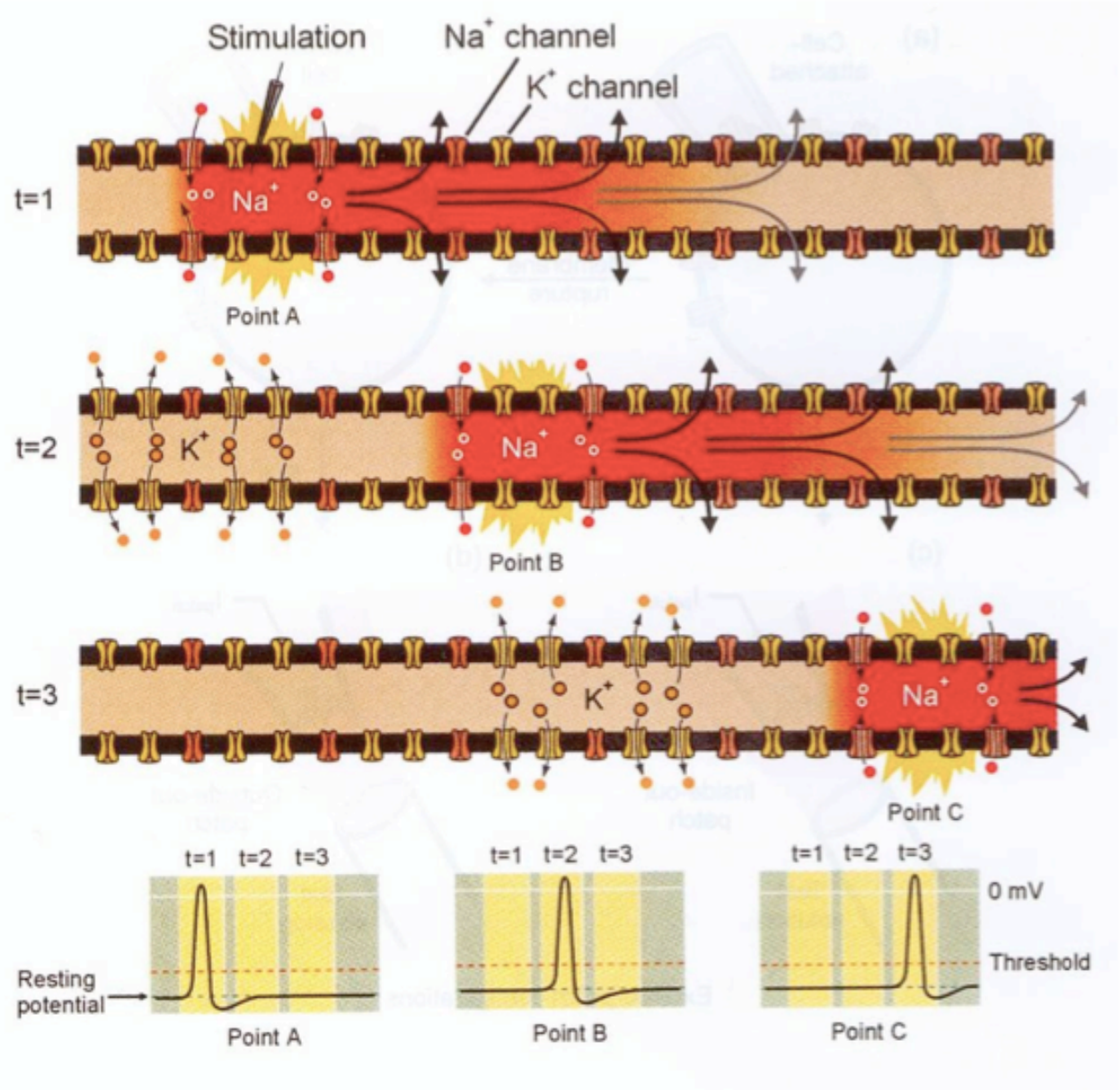



**5** **Hyper polarisation** : below-70mV, refractive period , no AP firing PA, exit of more K+ than Na+

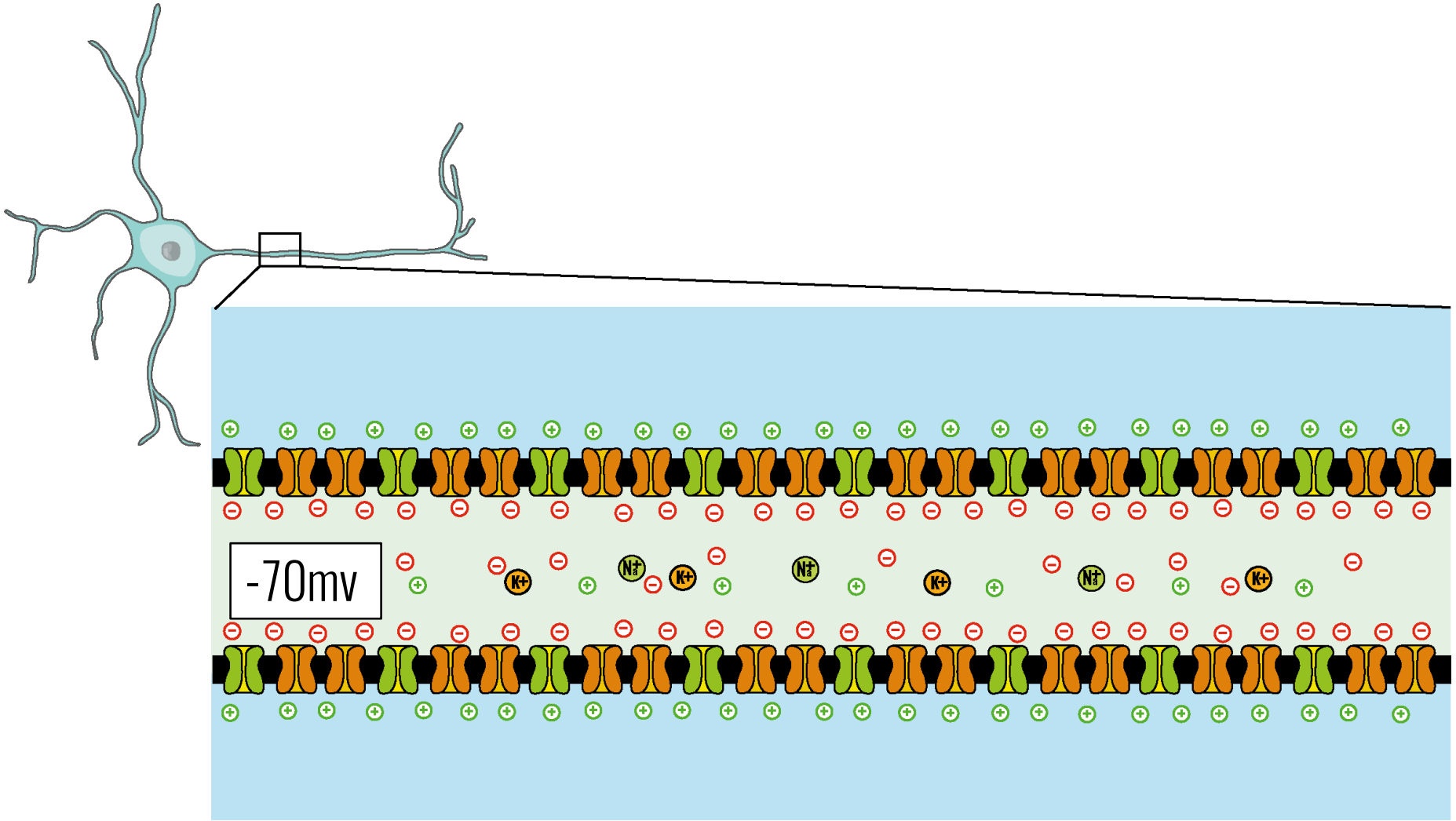
**1** **Rest** : transmemb. potential = -65mV

**6** **Restauration** of initial concentrations with Ionic pumps ATP dependant : K+ enters, Na+ exits

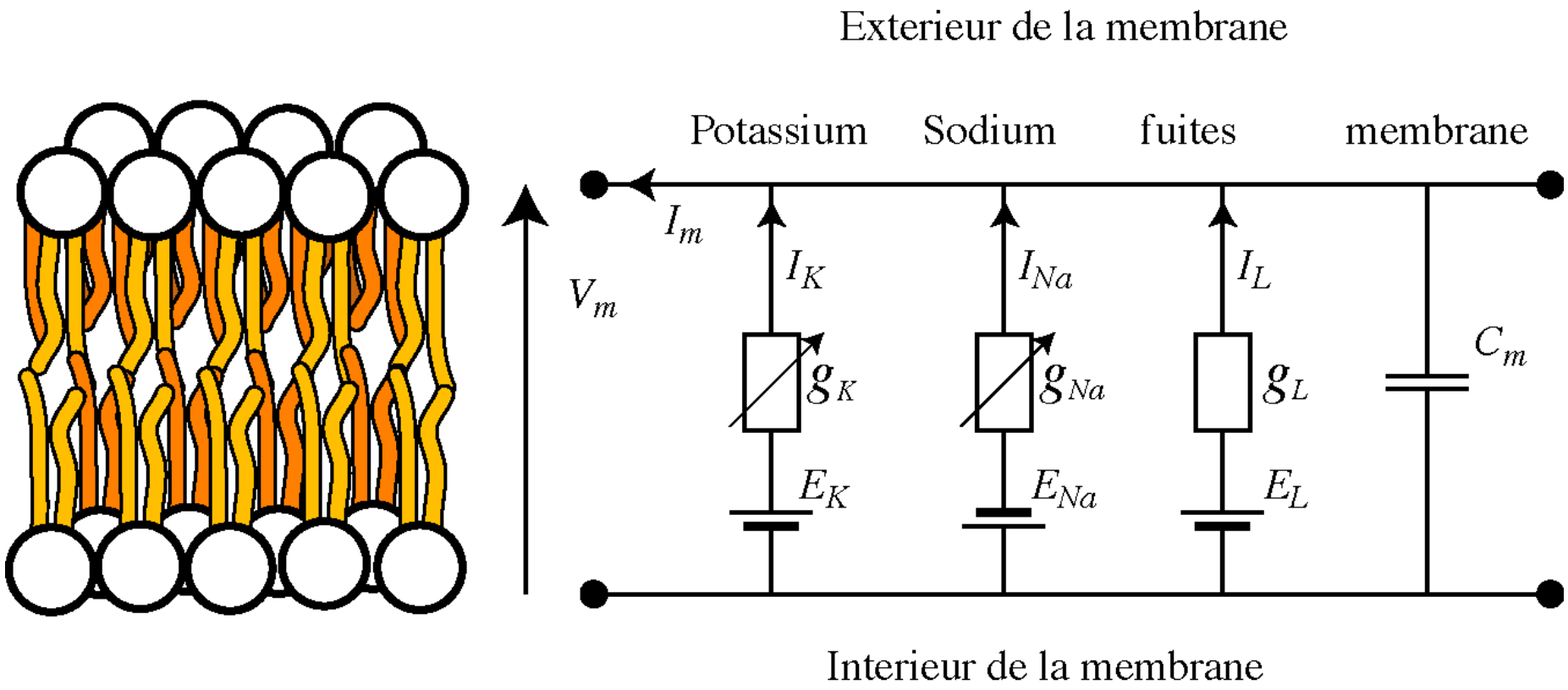
# Propagation



# Action potential propagation



# Hodgkin-Huxley Model




$$I_m = I_K + I_{Na} + I_L + C_m \frac{dV_m}{dt}$$

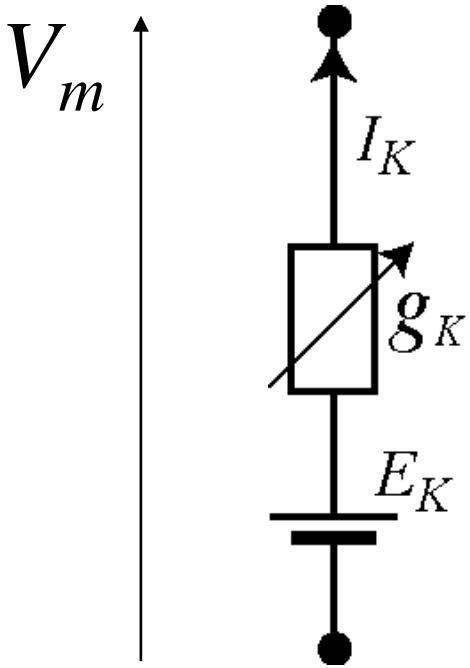
# Hodgkin-Huxley Model

## Courants ioniques

$V = RI$ Loi d'Ohm

$I = gV$ conductance

$$I_K = g_K(V_m - E_K)$$




Modèle pile / résistance variable

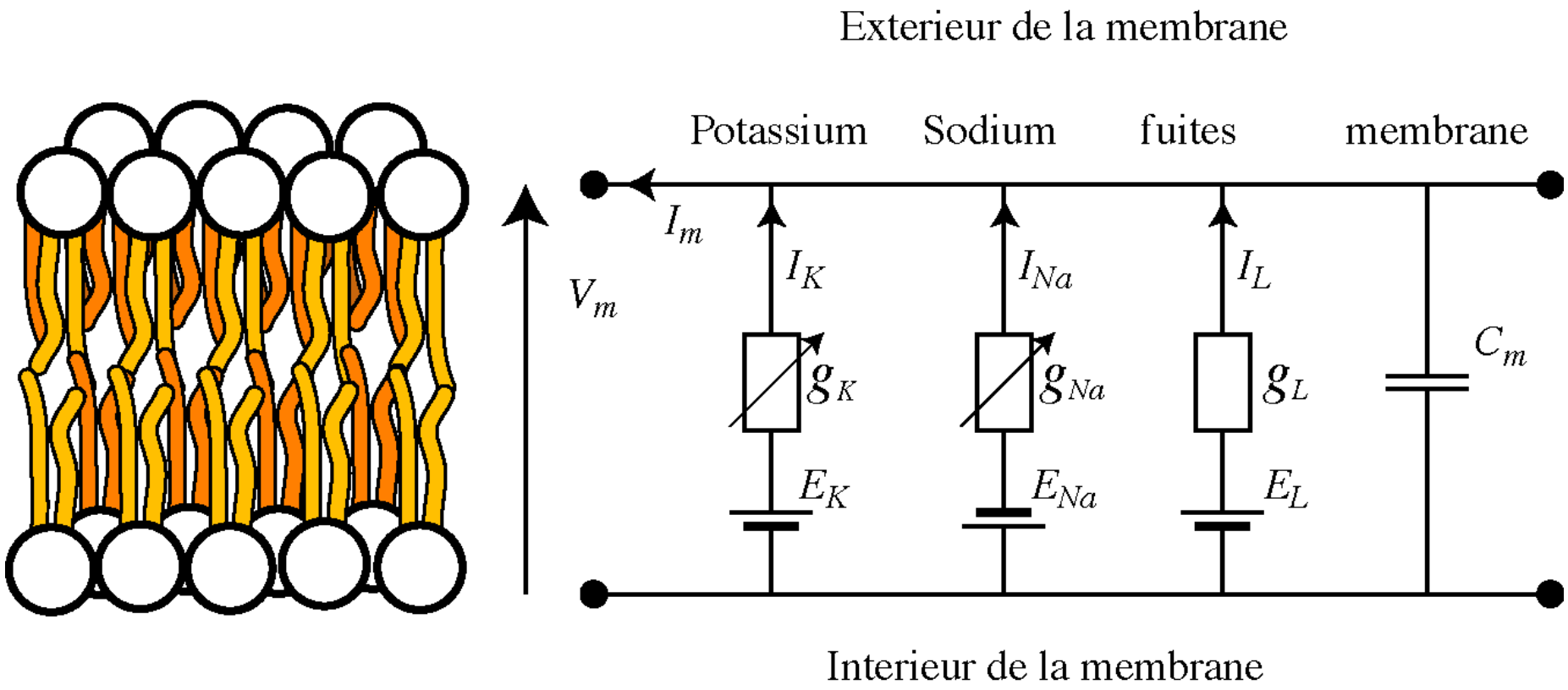
Le potentiel électrochimique peut se calculer avec l'équation de Nernst

$$E_K = -\frac{RT}{ZF}\log\frac{[K]_{int}}{[K]_{ext}}$$

R : constante des gaz parfaits
T : température absolue
Zx: valence de l'ion
F : nombre de Faraday

$E_{Na}$= + 64 mV  $E_K$= -90 mV

# Modèle Hodgkin-Huxley

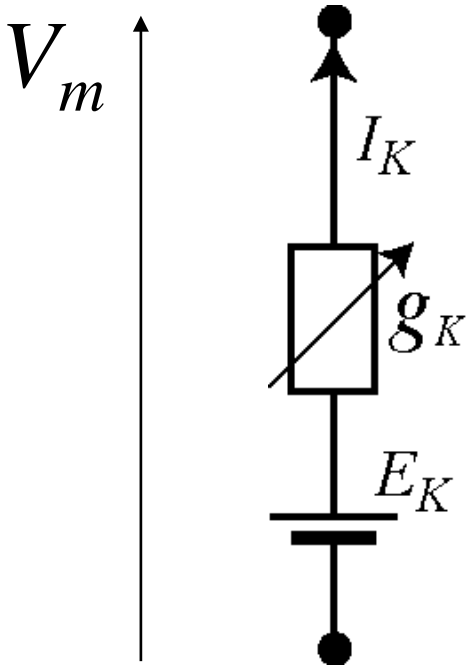



$g_L$ modélise le courant de fuite est constant

$g_{Na}$ et $g_k$ ne sont pas constant... $=f(V_M,t)$

# Modèle Hodgkin-Huxley

## Modelisation de la conductance des canaux ioniques




Le modèle considère les canaux comme un ensemble de portes ayant une certaine probabilité d'être ouvertes, cette probabilité dépendant de la tension $V_m$

$$g_K = \bar{g}_K n^4$$

$$g_{Na} = \bar{g}_{Na} m^3 h$$

m, n : porte d'activation
h : porte d'inactivation

$\bar{g}_K$ $\bar{g}_{na}$ Étant les conductance moyenne quand tous les canaux sont ouverts

n, m, h ???? Qu'est ce que c'est ?

# Modèle Hodgkin-Huxley

Conductance des canaux ioniques

$$g_K = \bar{g}_K n^4$$

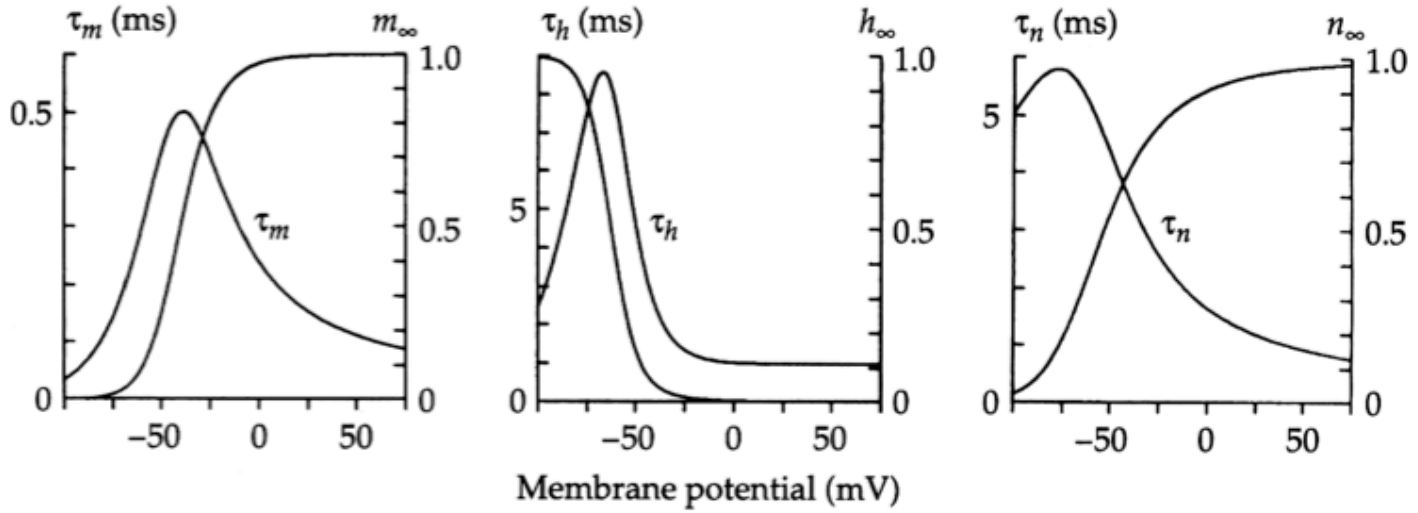
$$g_{Na} = \bar{g}_{Na} m^3 h$$

$$n, m, h = f(V_M, t)$$

$$\frac{dm}{dt} = \frac{m_\infty(V_m) - m}{\tau_m(V_m)}$$

$$\frac{dh}{dt} = \frac{h_\infty(V_m) - h}{\tau_h(V_m)}$$

$$\frac{dn}{dt} = \frac{n_\infty(V_m) - n}{\tau_n(V_m)}$$



# Modèle Hodgkin-Huxley

## Détermination des paramètres

$m_\infty = \bar{A}_m/(A_m+B_m)$ and $\tau_m = 1/(A_m+B_m)$

$$\frac{dm}{dt} = A_m(V)[1-m] - B_m(V)m \qquad A_m(V) = \frac{\alpha_m(V-V_{\alpha m})}{1-e^{-(V-V_{\alpha m})/K_{\alpha m}}} \qquad B_m(V) = \beta_m e^{-(V-V_{\beta m})/K_{\beta m}}$$

$$\frac{dh}{dt} = A_h(V)[1-h] - B_h(V)h \qquad A_h(V) = = \alpha_h e^{-(V-V_{\alpha h})/K_{\alpha h}} \qquad B_h(V) = \frac{\beta_h}{1-e^{-(V-V_{\beta h})/K_{\beta h}}}$$

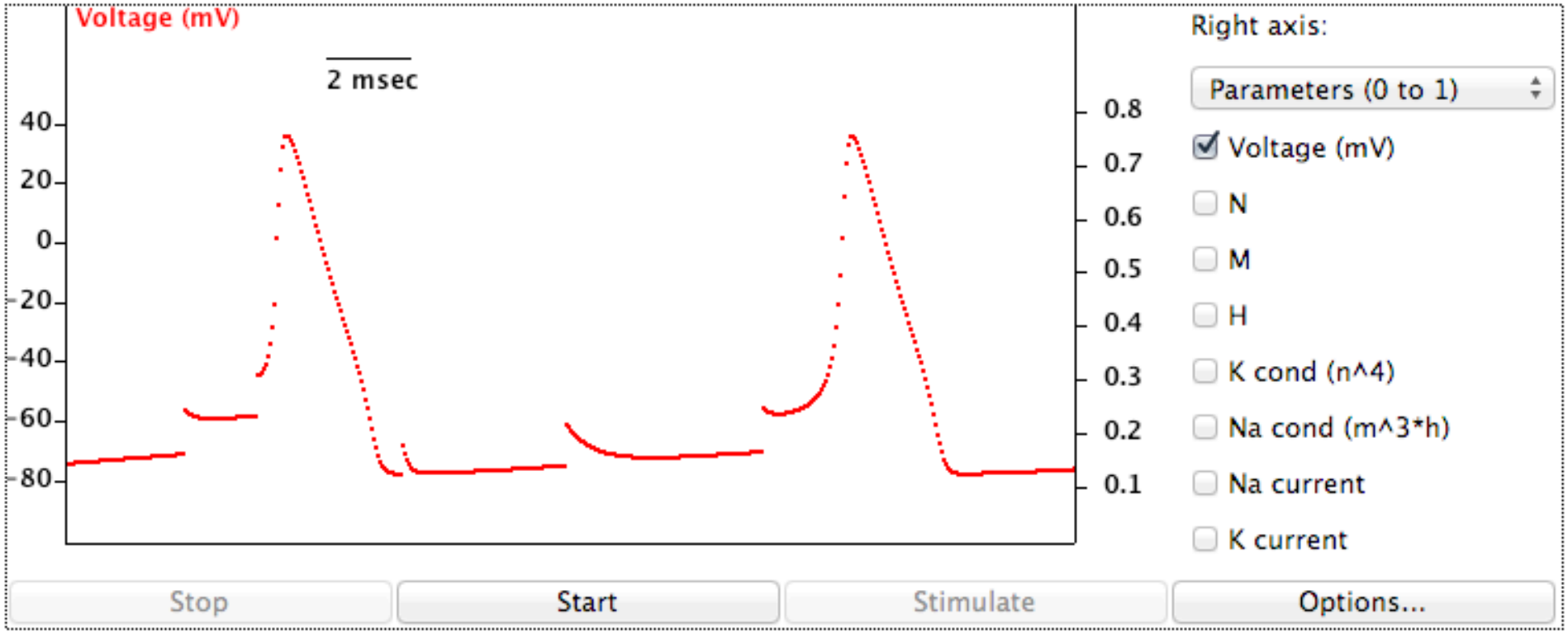
$$\frac{dn}{dt} = A_n(V)[1-n] - B_n(V)n \qquad A_n(V) = \frac{\alpha_n(V-V_{\alpha n})}{1-e^{-(V-V_{\alpha n})/K_{\alpha n}}} \qquad B_n(V) = \beta_n e^{-(V-V_{\beta n})/K_{\beta n}}$$

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| $\bar{G}_L$ | 0.3 | 0.75 | mS/cm$^2$ | $\alpha_h$ | 0.07 | 0.0081 | ms$^{-1}$ |
| $\bar{G}_K$ | 36 | 21.6 | mS/cm$^2$ | $\beta_h$ | 1 | 4.38 | ms$^{-1}$ |
| $\bar{G}_{Na}$ | 120 | 150 | mS/cm$^2$ | $V_{\alpha h}$ | -60 | -45 | mV |
| C | 1 | 4 | µFd/cm$^2$ | $V_{\beta h}$ | -30 | -45 | mV |
| $E_L$ | -87 | * | mV | $K_{\alpha h}$ | 20 | 14.7 | mV |
| $E_K$ | -95.3 | -72 | mV | $K_{\beta h}$ | 10 | 9 | mV |
| $E_{Na}$ | 36.7 | 55 | mV | | | | |
| $\alpha_m$ | 0.1 | 0.288 | ms$^{-1}$ | $\alpha_n$ | 0.01 | 0.0131 | ms$^{-1}$ |
| $\beta_m$ | 4 | 1.38 | ms$^{-1}$ | $\beta_n$ | 0.125 | 0.067 | ms$^{-1}$ |
| $V_{\alpha m}$ | -36 | -46 | mV | $V_{\alpha n}$ | -50 | -40 | mV |
| $V_{\beta m}$ | -60 | -46 | mV | $V_{\beta n}$ | -60 | -40 | mV |
| $K_{\alpha m}$ | 10 | 10 | mV | $K_{\alpha n}$ | 10 | 7 | mV |
| $K_{\beta m}$ | 18 | 18 | mV | $K_{\beta n}$ | 80 | 40 | mV |

En règle générale, ça se programme…

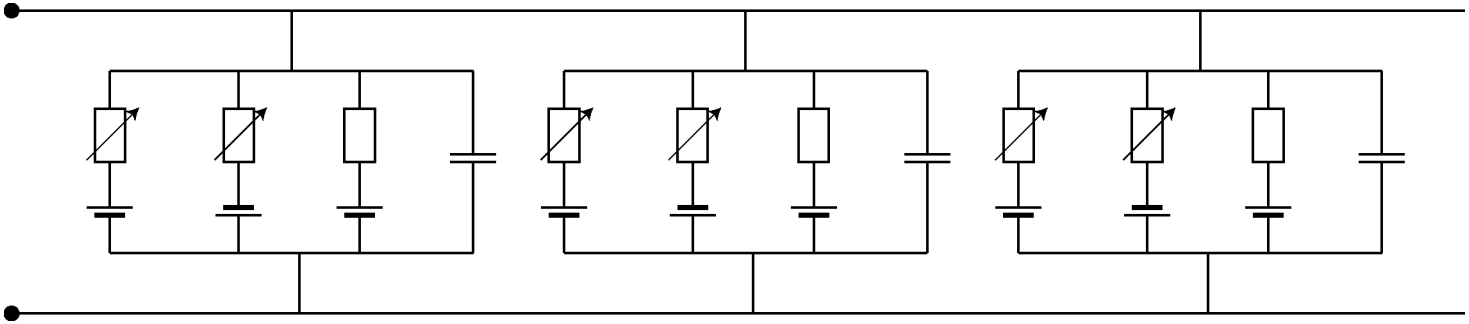
# Modèle Hodgkin-Huxley

## Simulation



# Hodgkin-Huxley 2:

## propagation axonale d'un potentiel d'action

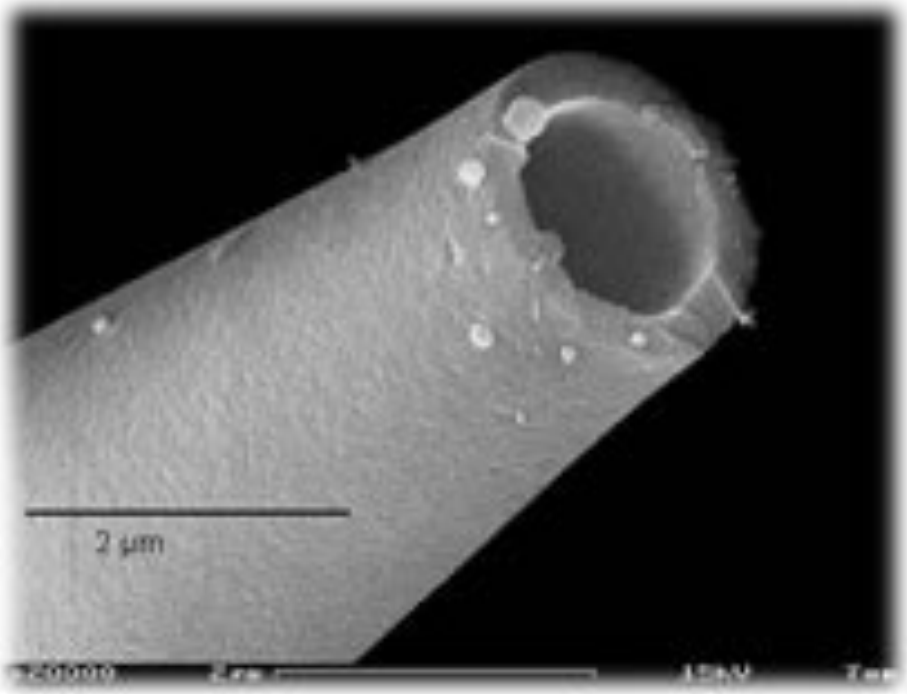


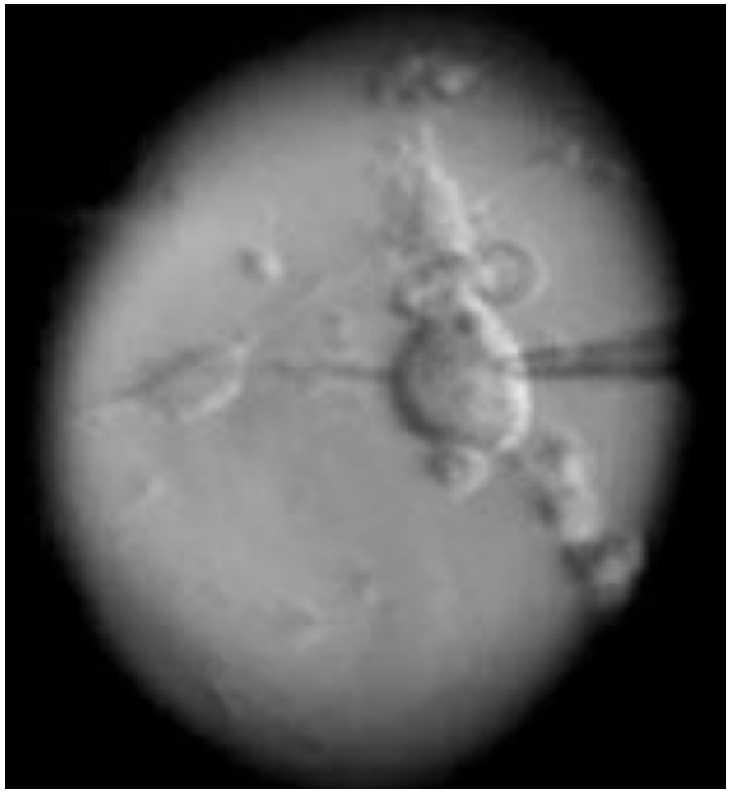
$$\frac{1}{R}\frac{\partial^2 V}{\partial x^2} = C_m \frac{\partial V}{\partial t} + \left[ g_{Na}^{max} m^3 h (V - V_{Na}) + g_K^{max} n^4 (V - V_K) + g_l^{max} (V - V_l) \right] 2\pi r L$$

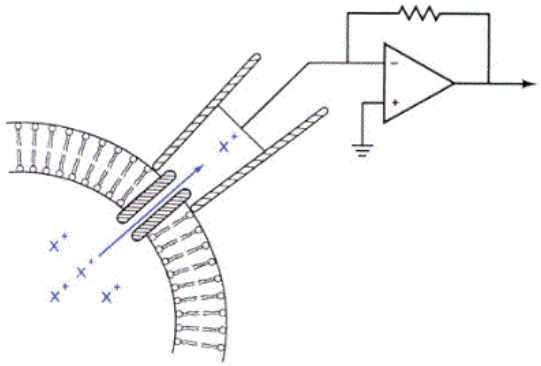
# Patch Clamp

Technique d'enregistrement des courants ioniques transitant à travers les membranes cellulaires

Perforation de la membrane par une micro pipette



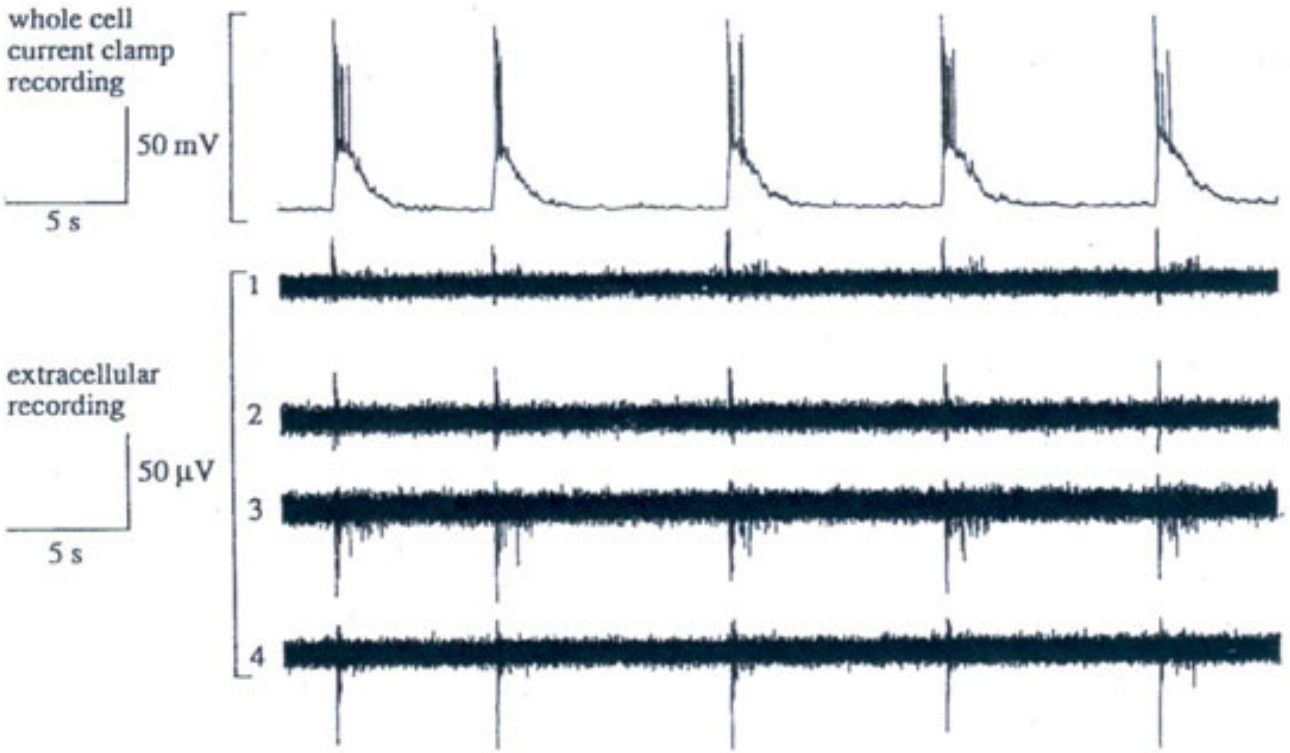





# Patch Clamp

Deux modes :

- Potentiel im
- Courant imp



# Interface Iono-Electronique

**Potentiel Intracellulaire** : dans la cellule, accessible par Patch clamp

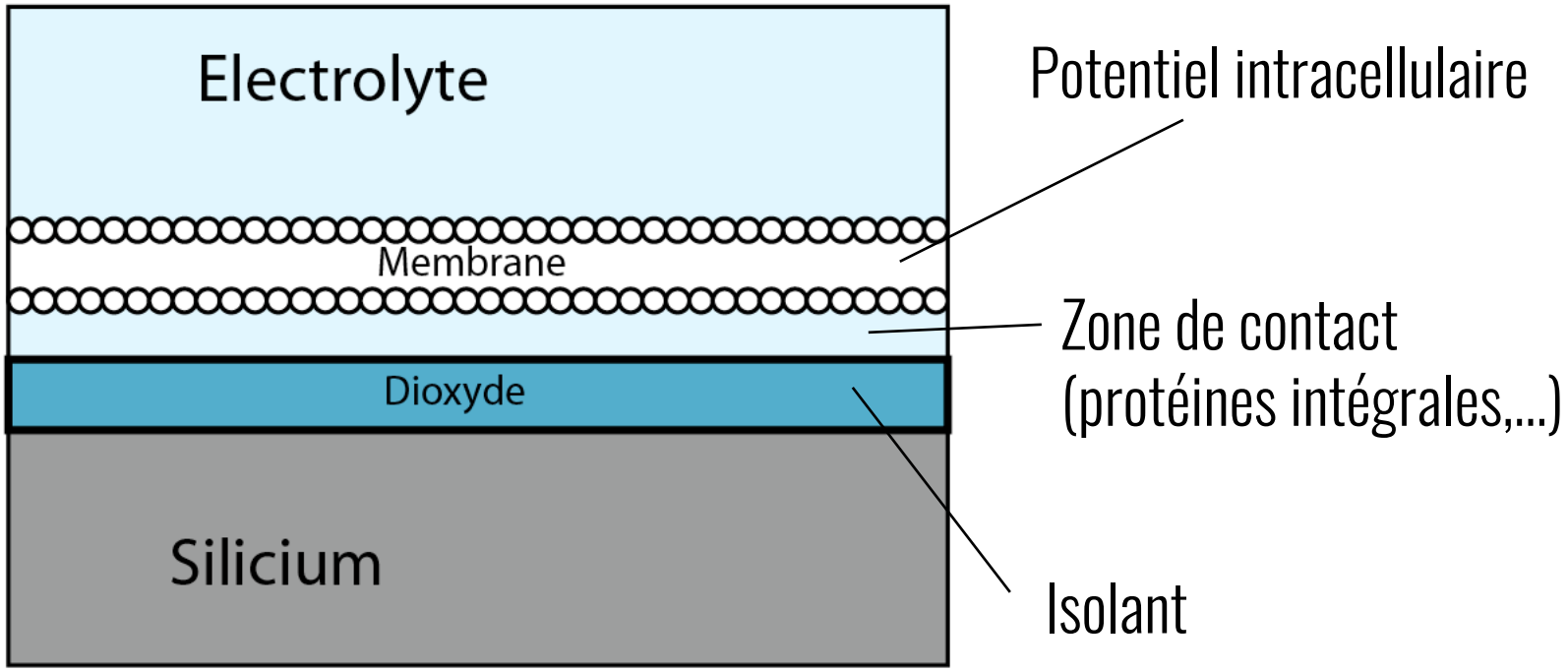
**Potentiel extracellulaire** : à l'extérieur de la cellule les courants ioniques modifient l'équilibre électrique.

Le ***Local Field Potential*** (LFP) est mesuré loin des cellules et caractérise l'activité d'une région

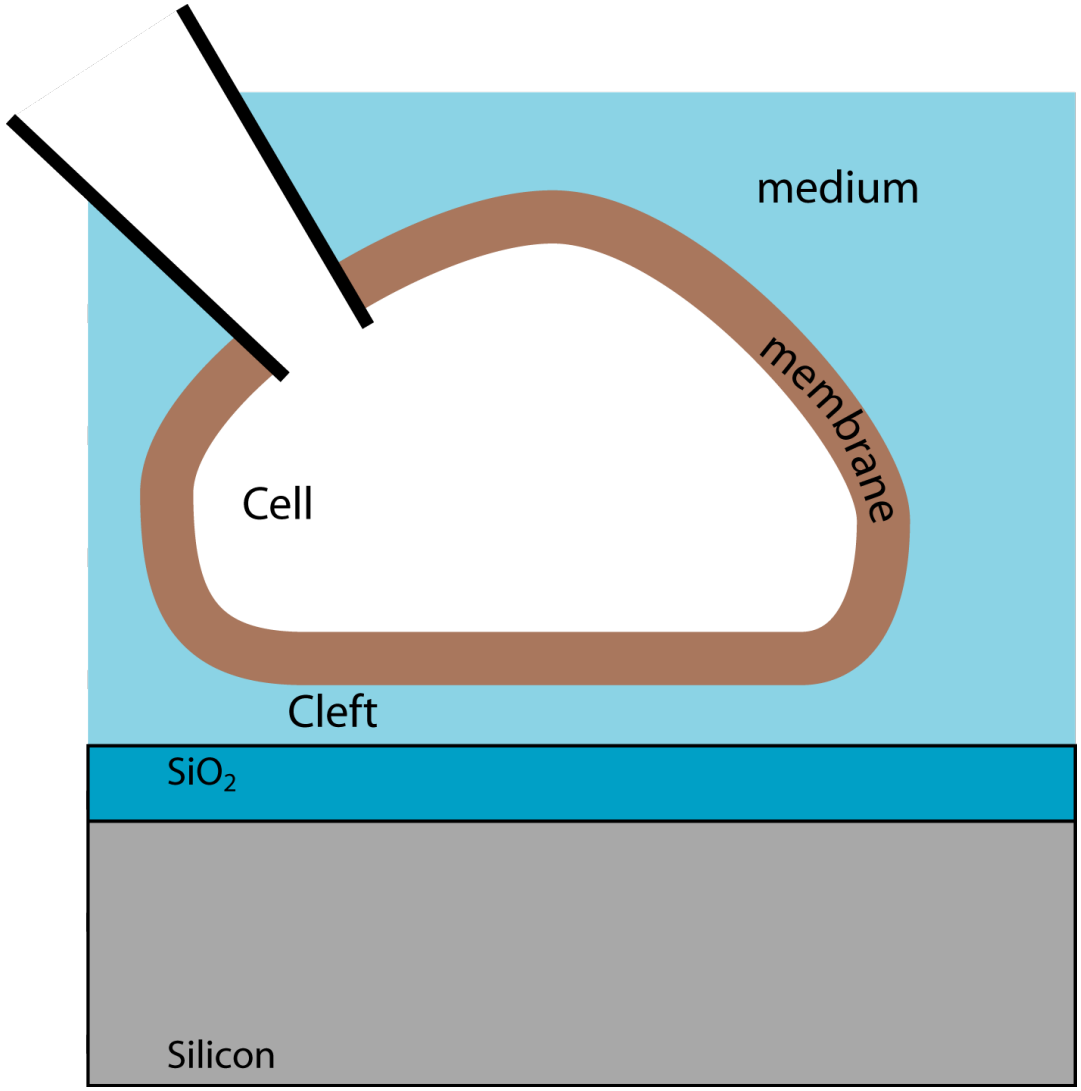
Si on veut accéder a l'activité d'une cellule unique il faut se placer à proximité.

# Interface Iono-Electronique

Approchons une cellule électriquement active a la surface d'une structure silicium/oxyde



# Interface Iono-Electronique

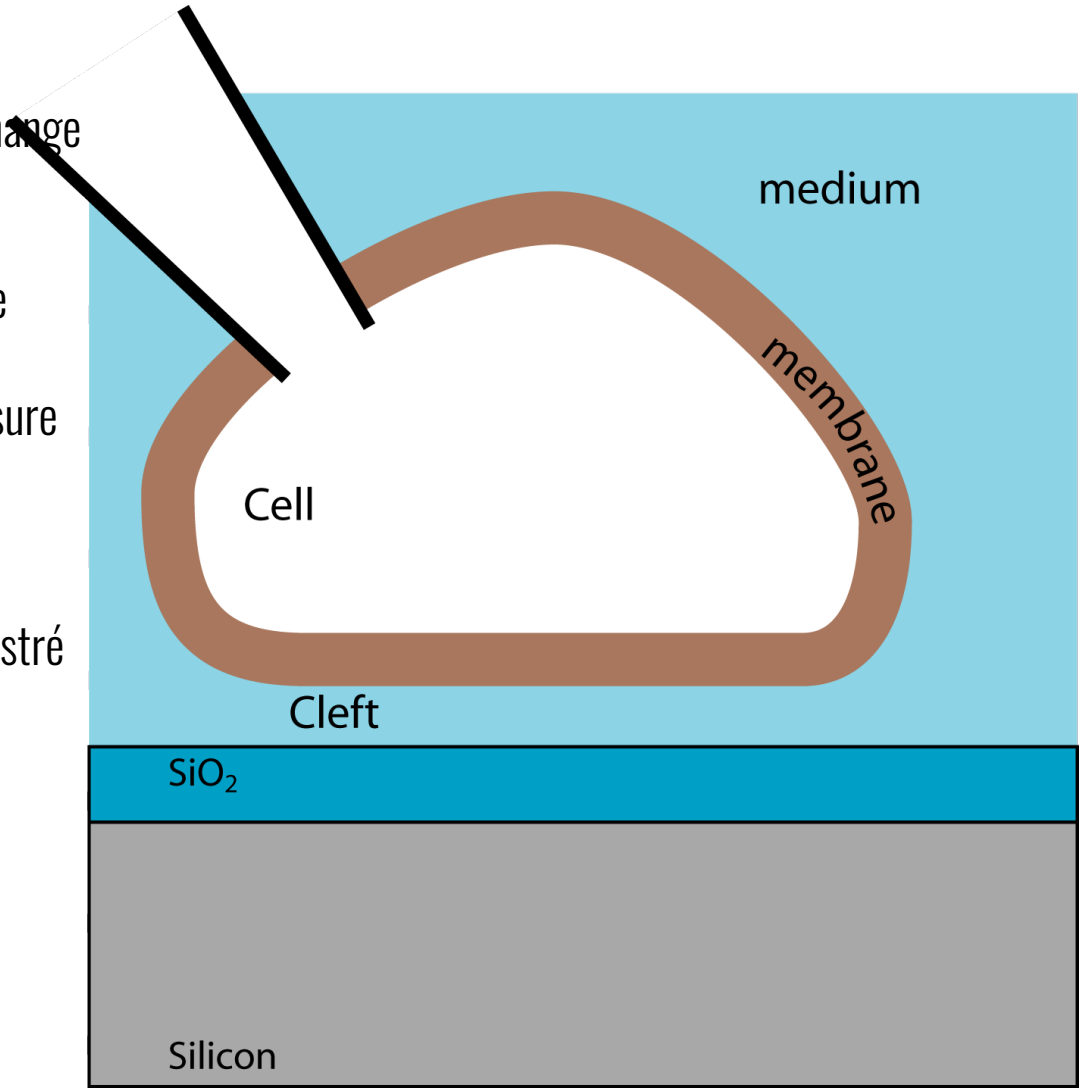


# Interface Iono-Electronique

- Un potentiel d'action est déclenché
- Le potentiel électrique trans-membranaire change
- Ouverture et fermeture des canaux ioniques (courants)
- Le champ électrique à l'extérieur de la cellule varie
- En fonction de la position de l'électrode : mesure des spikes d'un ou de plusieurs neurones.

Le type de signal enregistré à l'intérieur de la cellule est très différent de celui qui est enregistré depuis l'extérieur

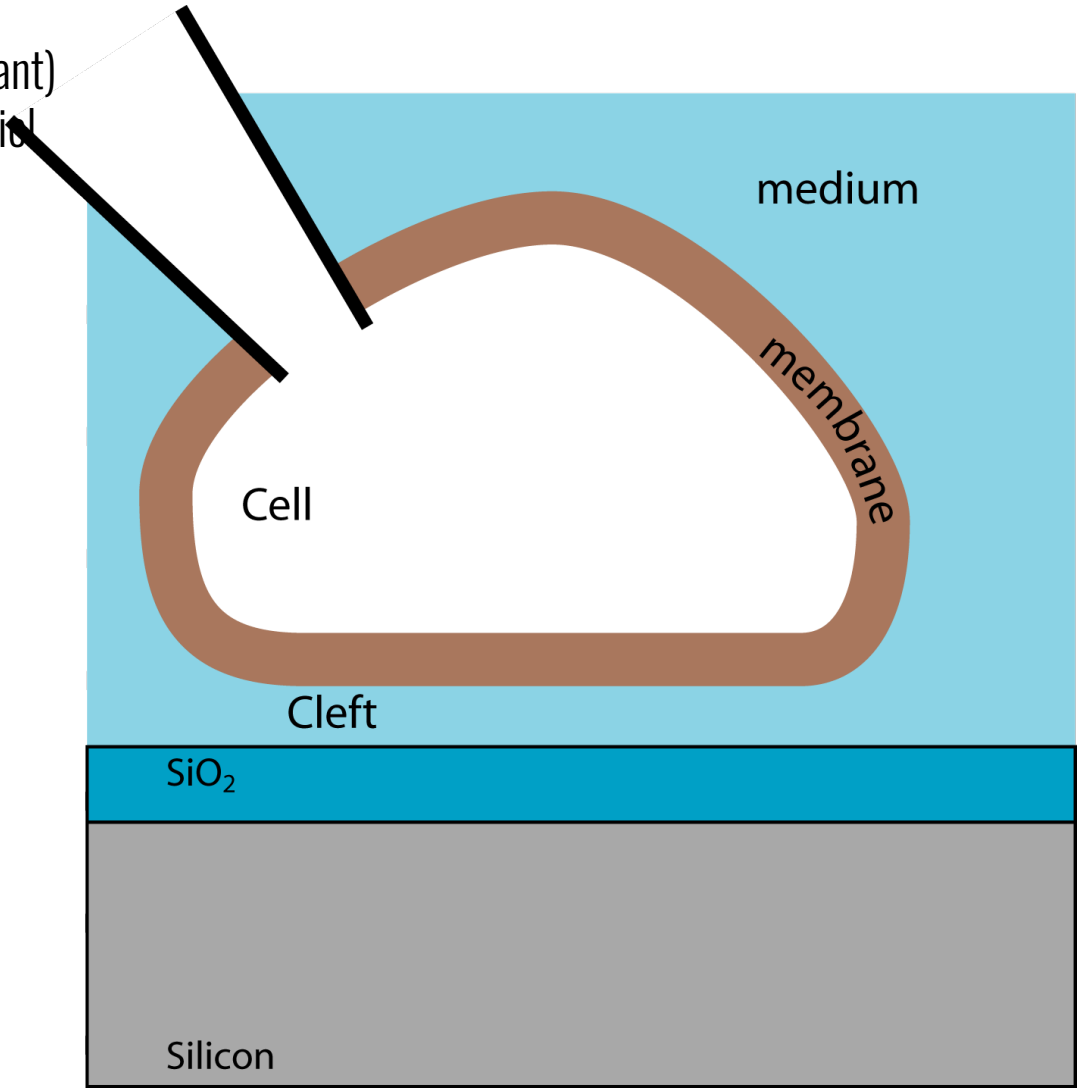
**Seuls les potentiels d'action sont enregistrés par les électrodes extracelluaires**



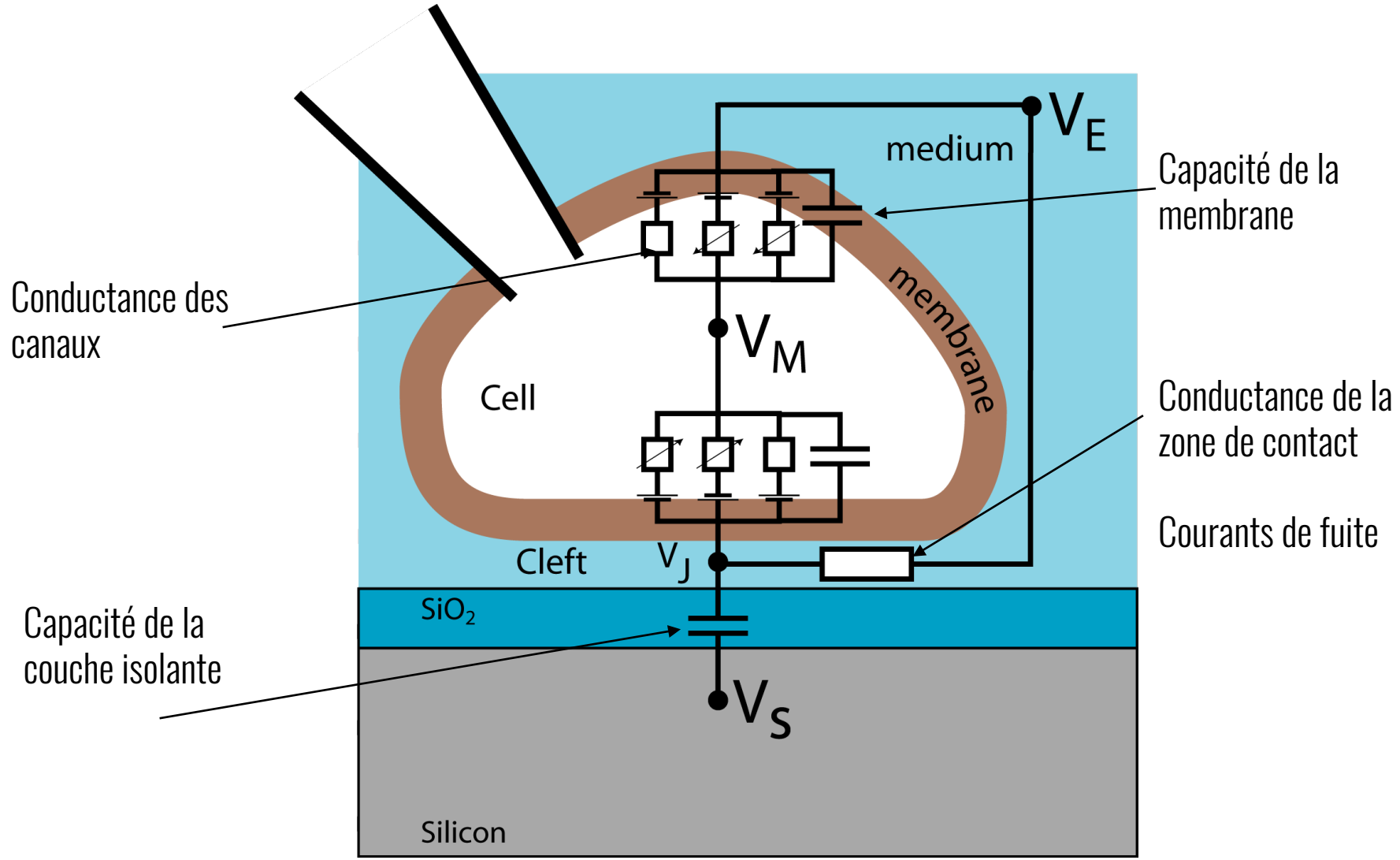
# Interface Iono-Electronique

Quel est la relation entre la tension (ou le courant) mesurée dans le silicium par rapport au potentiel intracellulaire?

Modélisation....



# Modélisation

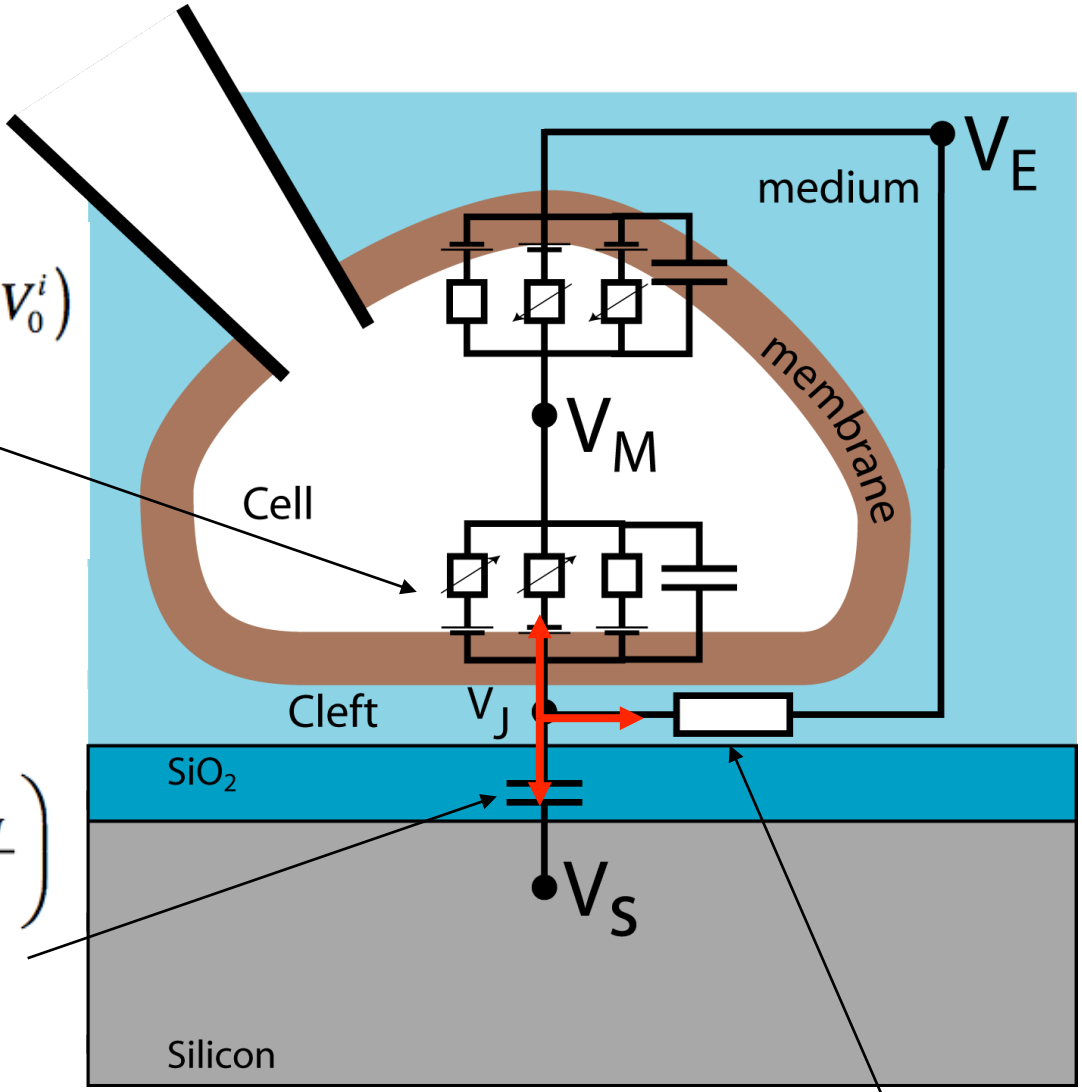


# Modélisation

$$I_M = \sum_i g_{JM}^i \left( V_M - V_J - V_0^i \right)$$

$$+C_M \left( \frac{dV_M}{dt} - \frac{dV_J}{dt} \right)$$

$$I_S = C_S \left( \frac{dV_S}{dt} - \frac{dV_J}{dt} \right)$$




$$I_{cleft} = g_J \left( V_J - V_E \right)$$

# Modélisation

Loi de Kirchoff : $I_{cleft}=I_M+I_S$

$$g_J\left(V_J - V_E\right) = C_S\left(\frac{dV_S}{dt} - \frac{dV_J}{dt}\right) + C_M\left(\frac{dV_M}{dt} - \frac{dV_J}{dt}\right) + \sum_i g_{JM}^i\left(V_M - V_J - V_0^i\right)$$

Partie capacitive

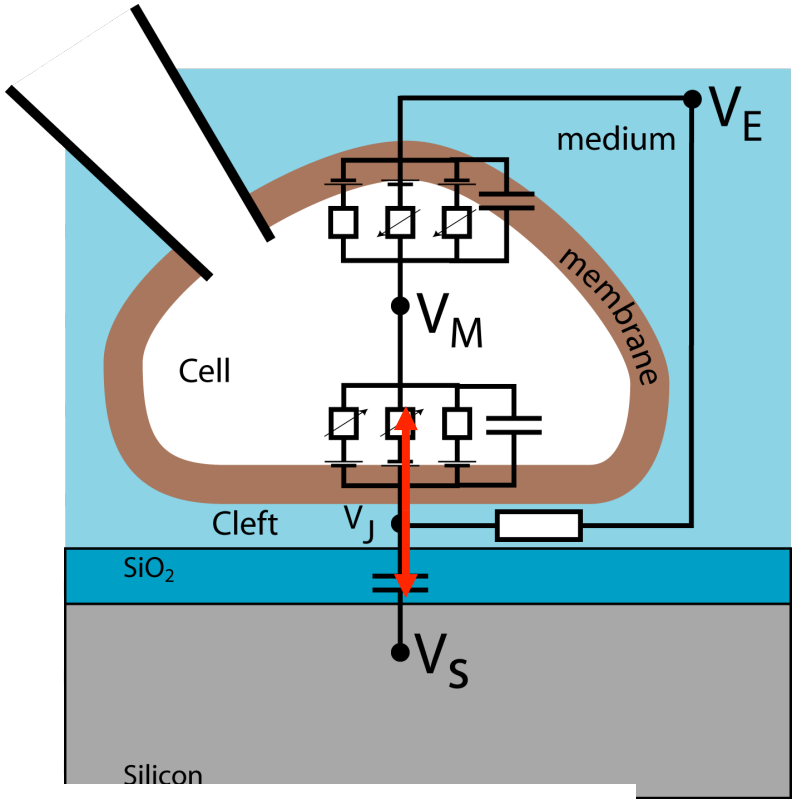
Partie conductive

# Modélisation

Dynamique intra cellulaire:
Neutralité électrique dans la cellule

Surface de la membrane en contact : $A_{JM}$

Surface de la membrane libre : $A_{FM}$




$$\beta_{FM} = \frac{A_{FM}}{A_{JM}}$$

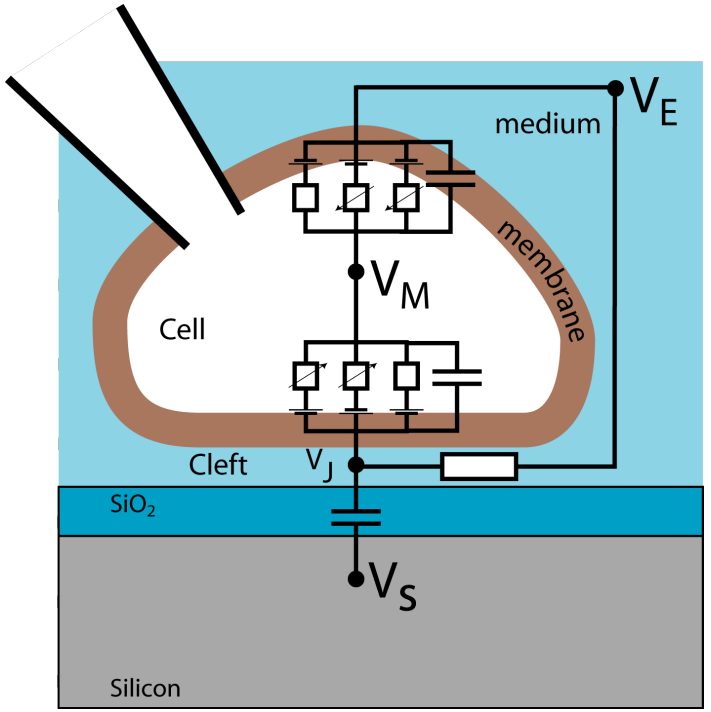
$$A_{JM}\left[\sum_i g_{JM}^i \left(V_M - V_J - V_0^i\right) + C_M\left(\frac{dV_M}{dt} - \frac{dV_J}{dt}\right)\right]$$

$$= -A_{FM}\left[\sum_i g_{FM}^i \left(V_M - V_J - V_0^i\right) + C_M\left(\frac{dV_M}{dt} - \frac{dV_E}{dt}\right)\right]$$

# Modélisation

On a donc un jeu d'équations décrivant le potentiel extracellulaire $V_J$ en fonction du Potentiel intra et de plusieurs facteurs :

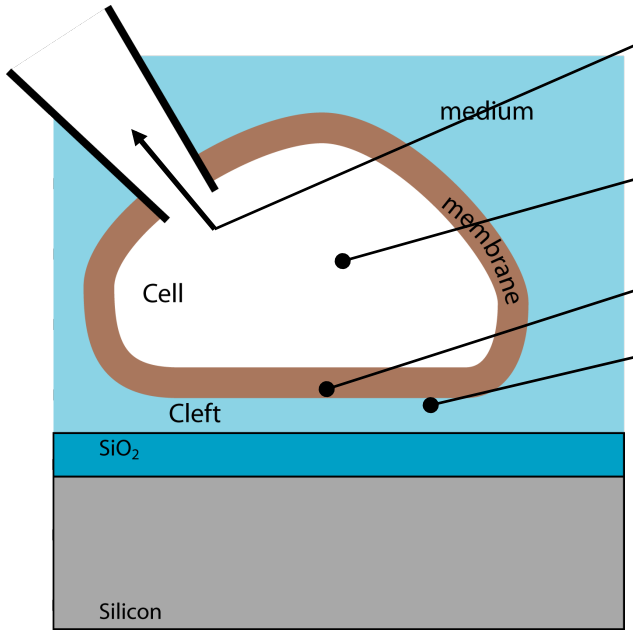
- Surface de contact (ratio)
- Conductance de membrane
- Densité des canaux ioniques
- Epaisseur et conductivité de la zone de contact



# Modélisation

Courant impose par patch

Hypothèse petits signaux




Courant impose par patch

Potentiel intracellulaire $V_M$

Potentiel de Jonction $V_J$

Courant de fuite $g_j$

$$g_J V_J = \sum_i g_{JM}^i \left(V_M - V_0^i\right) + C_M \frac{dV_M}{dt}$$

Le rapport entre les conductances $g_{JM}$ de membrane et la conduction de contact $g_J$ va donner deux types de réponses.

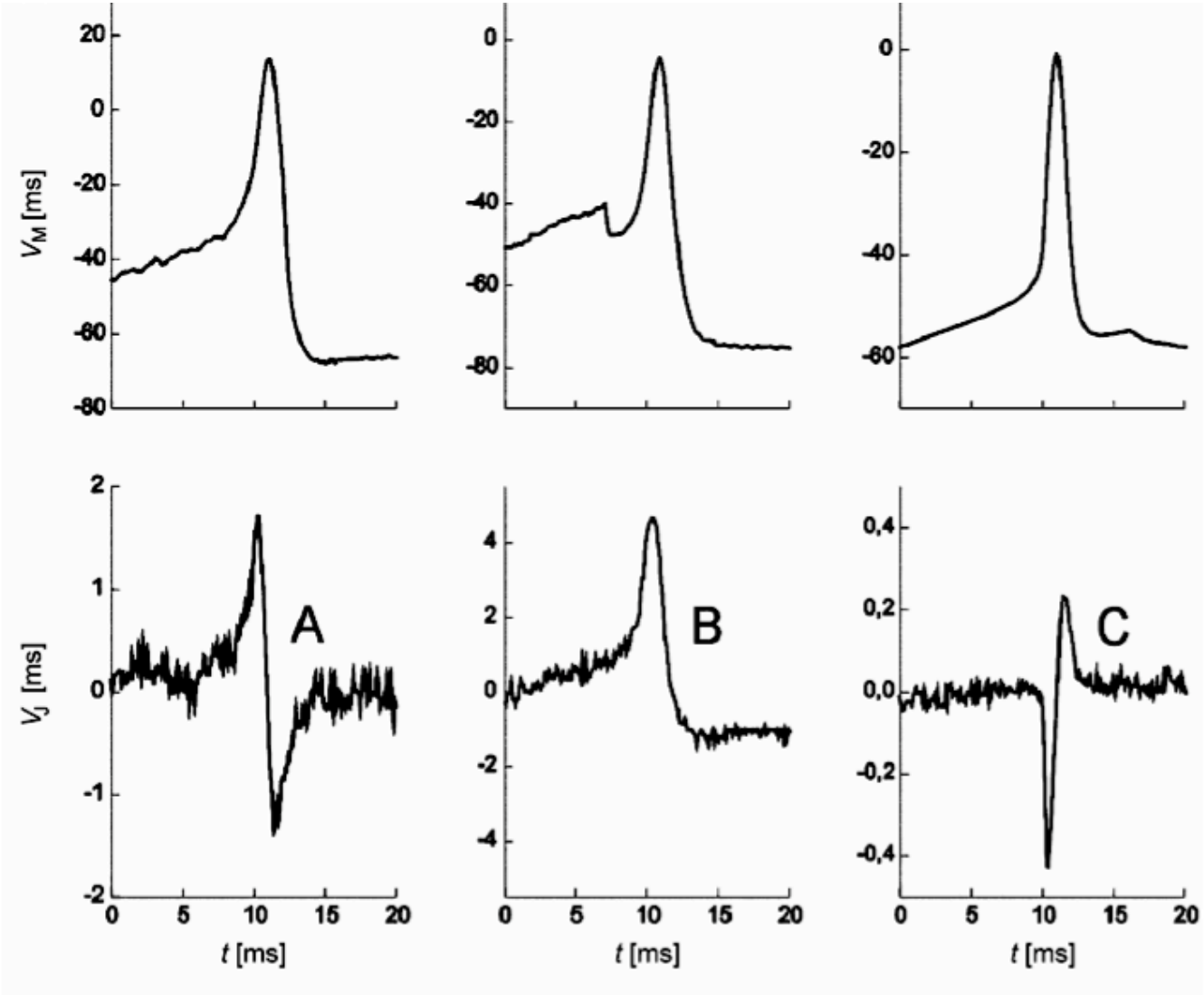
A Jonction capacitive

B Jonction Ohmique

# Mesure

Potentiel Intracellulaire $V_M$

Potentiel extracellulaire $V_J$




~ Dérivée de $V_M$

Jonction capacitive

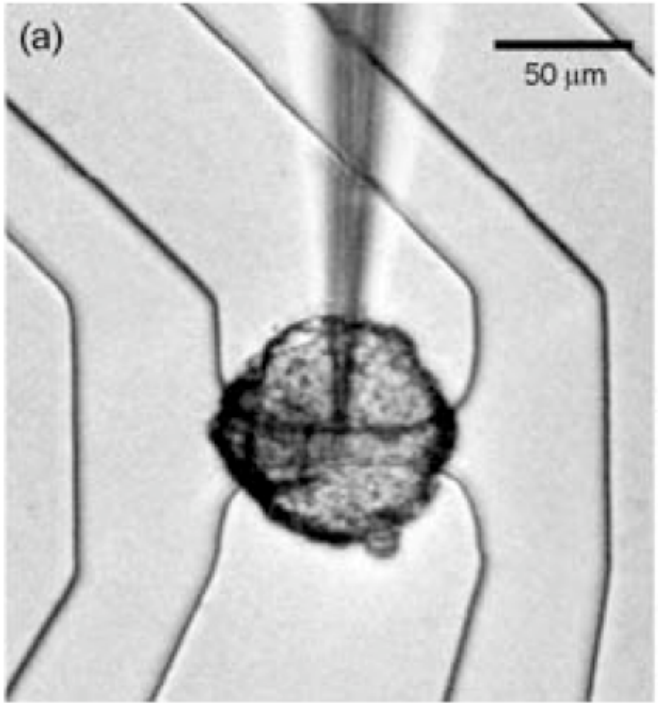
~ $V_M$

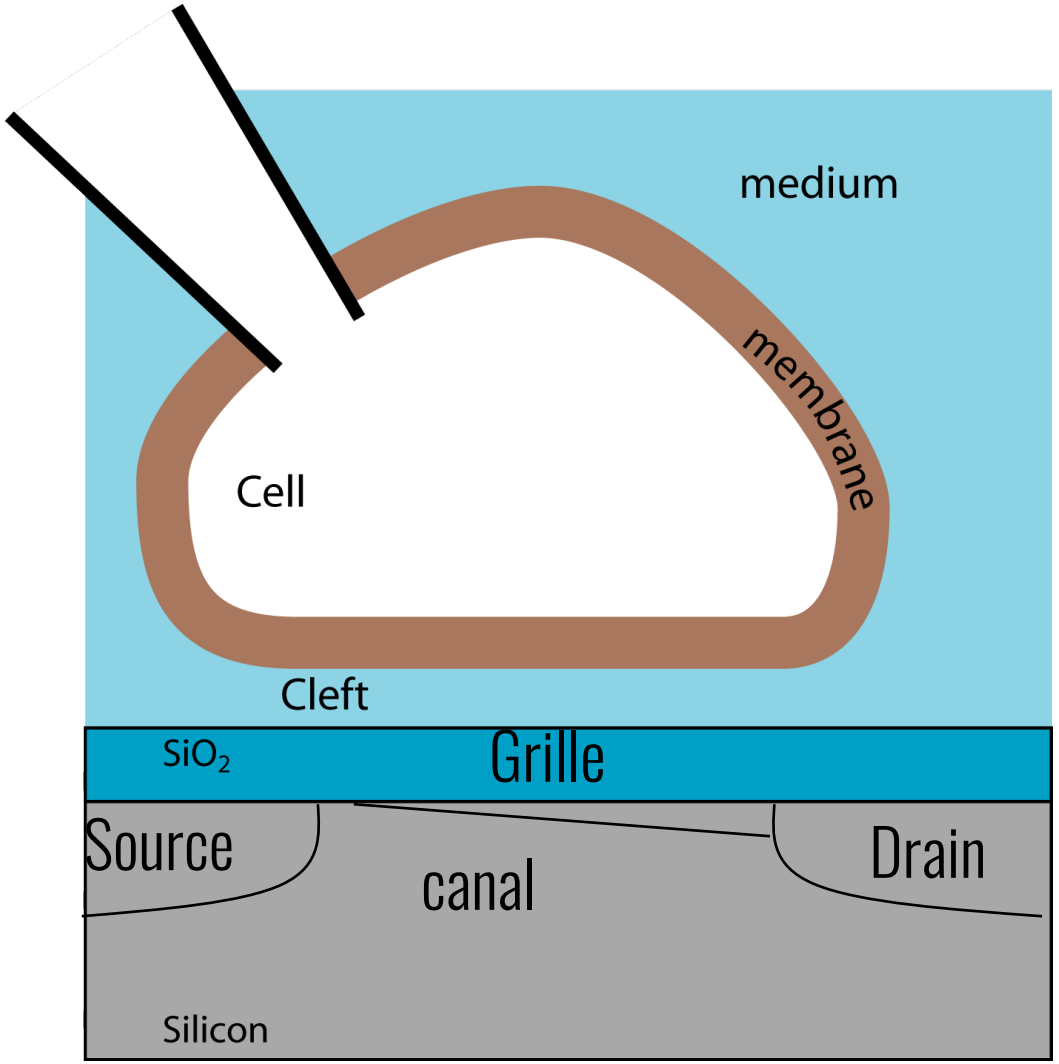
Jonction ohmique

# Transistor

Faibles tensions mesures
Avantage de la structure MOS
Transistor a effet de champ

EOSFET
(electrolyte / oxyde /semicon)



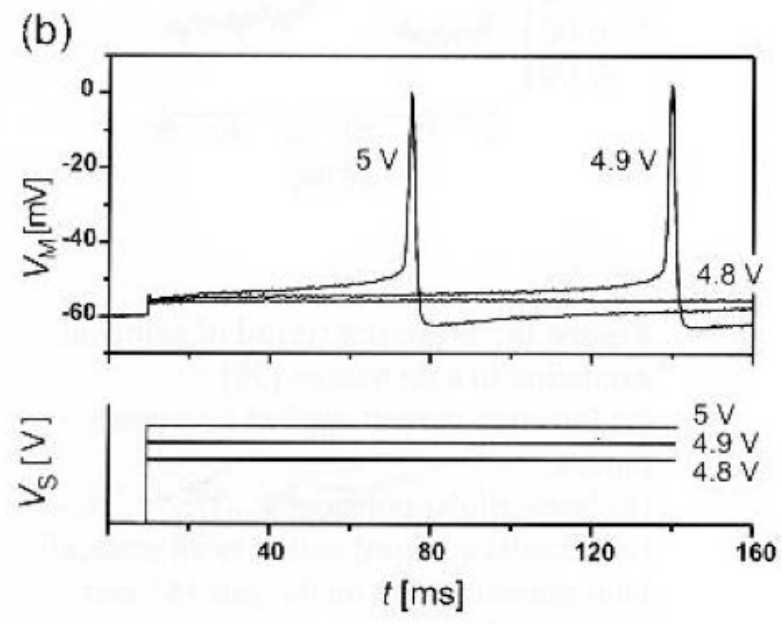



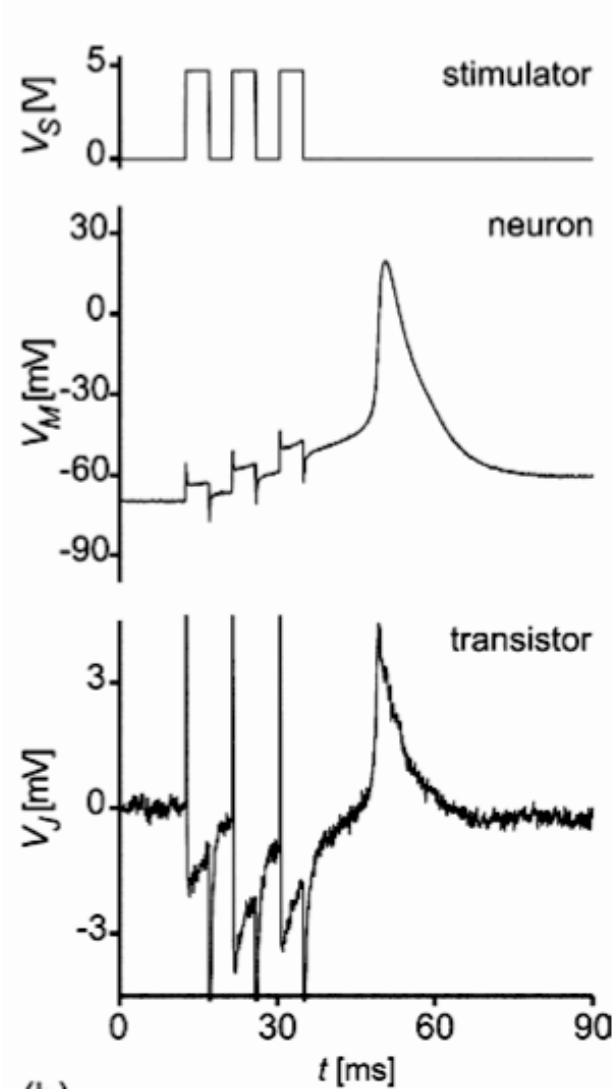
# Stimulation

En appliquant un échelon de tension sur l'électrode

- Courant au long de la zone de contact
- Potentiel extracellulaire
- Ouverture des canaux ioniques Voltage dépendant

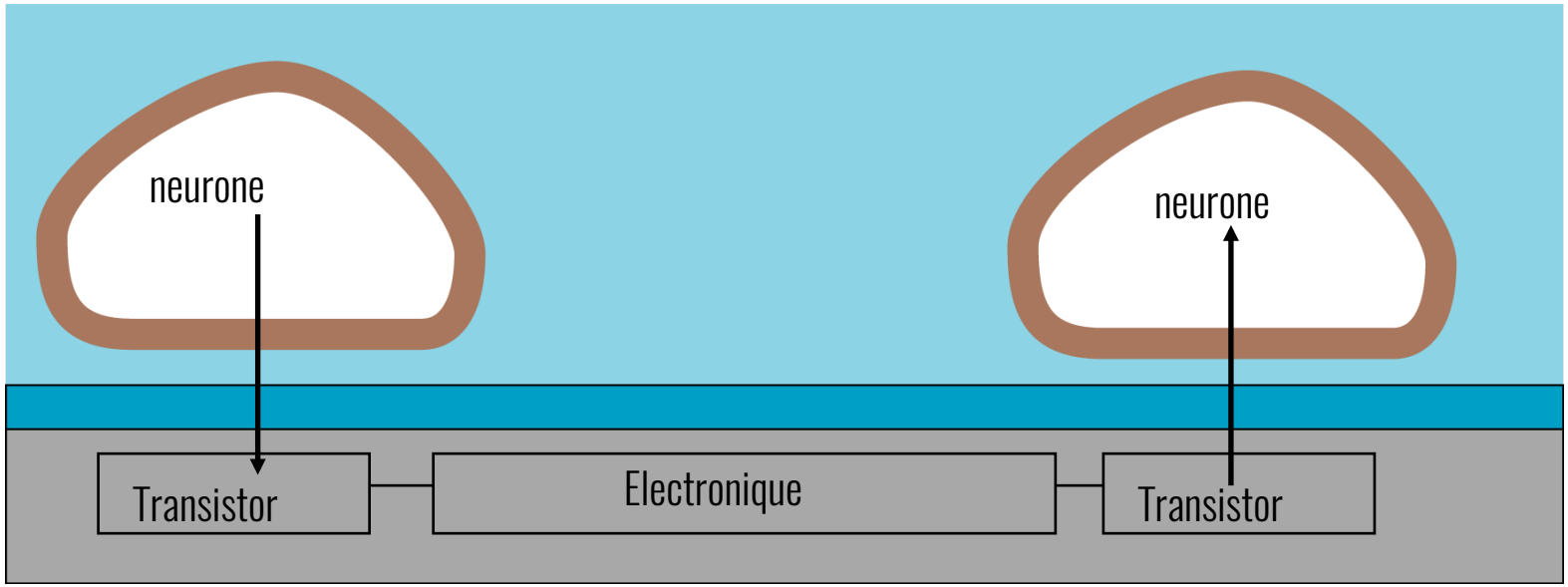
Dépends du type de configuration A, B C

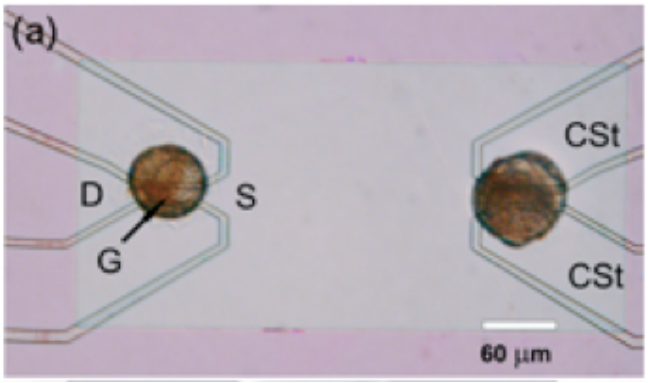


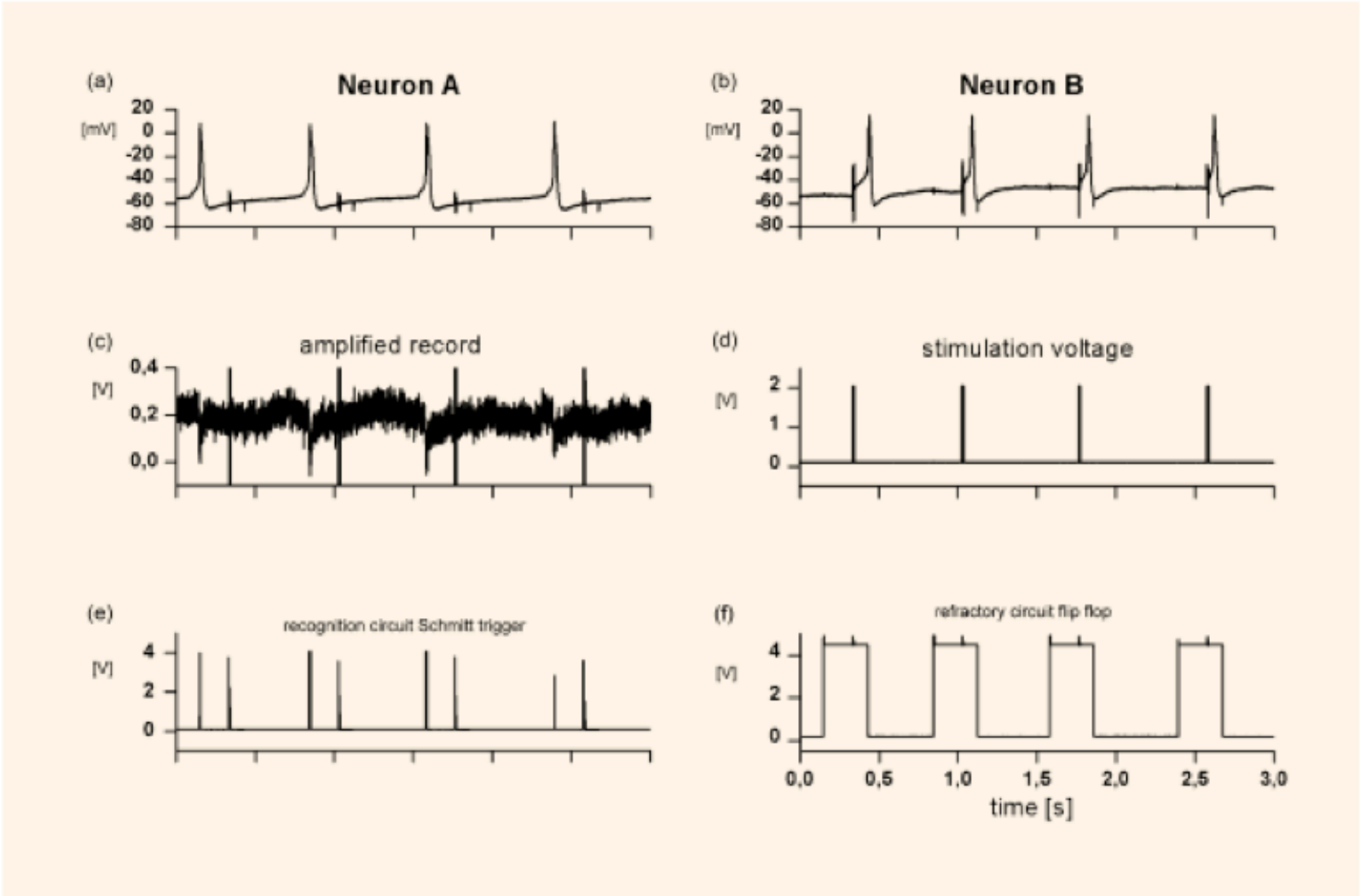
# Détection / Stimulation

Il est possible des lors de relier deux neurones
Détection des PA par le TEP
Stimulation de PA



# Détection / Stimulation

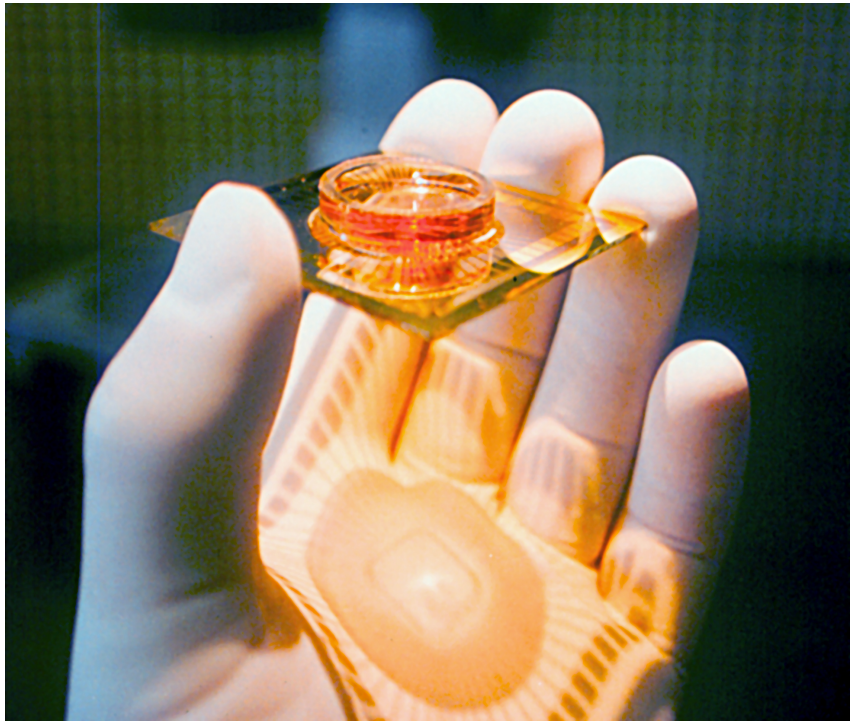


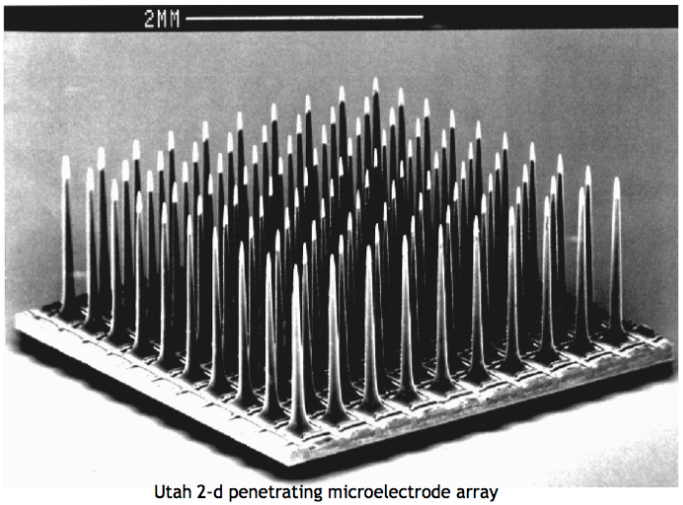
# Micro Electrode Arrays

Il existe différent types de réseaux d'électrodes  suivant leur utilisation :

**in vitro**
Matrices (8x8) a plat sur substrat transparent pour culture cellulaire (ou tranches) et visualisation de fluorescence. Electrodes de 10 a 30µm

**in vivo**
Pour implantation, souples ou rigides (tapis de fakir)



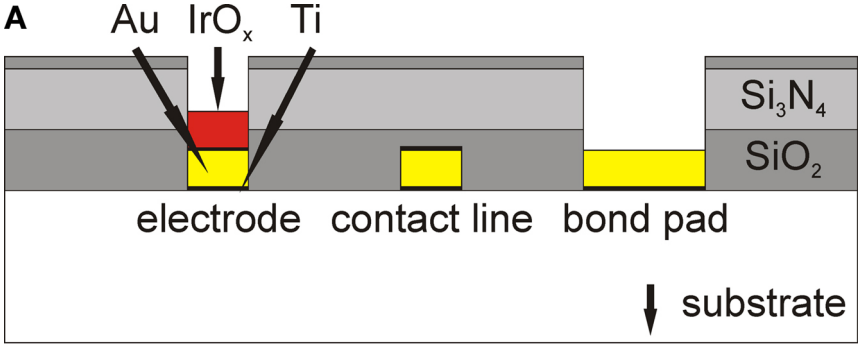


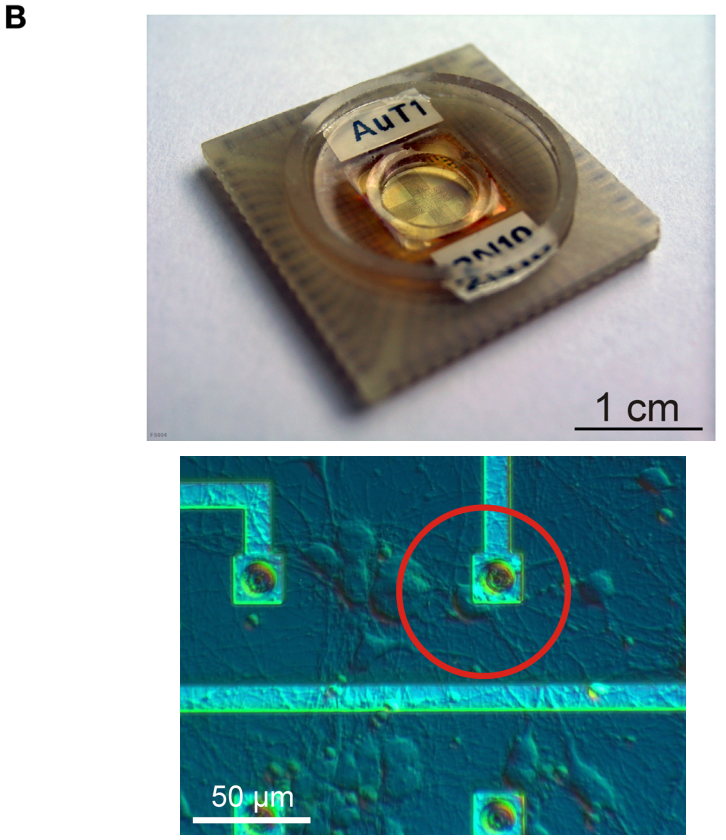
Utah 2-d penetrating microelectrode array

# Planar Micro Electrode Arrays

Réseau de microélectrodes pour observer l'activité électrophysiologique de cellules en culture

Substrat : Verre, silicium
Electrodes : Or, noir de platine, nitrure de titane (nanoporosité, impédance)
Interconnexions : ITO (Indium TiN Oxyde) : transparence
Isolation : $SiO_2$, $Si_3N_4$, Polyimide, Polyacrylamide, SU-8 (biocompatibilité)
Couche d'adhérence : Poly-Lysine, Laminin,

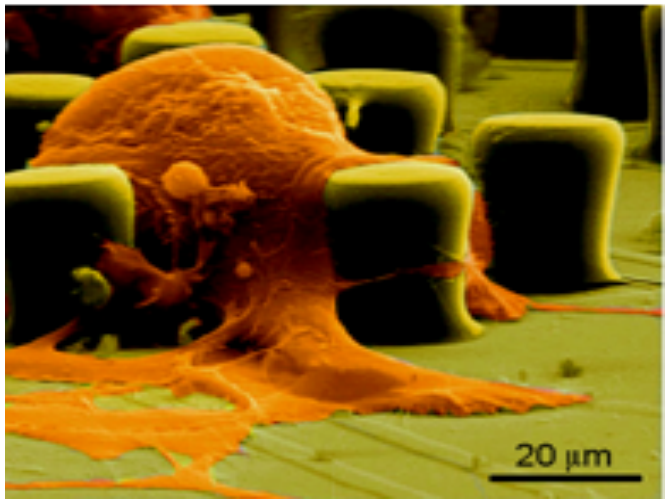


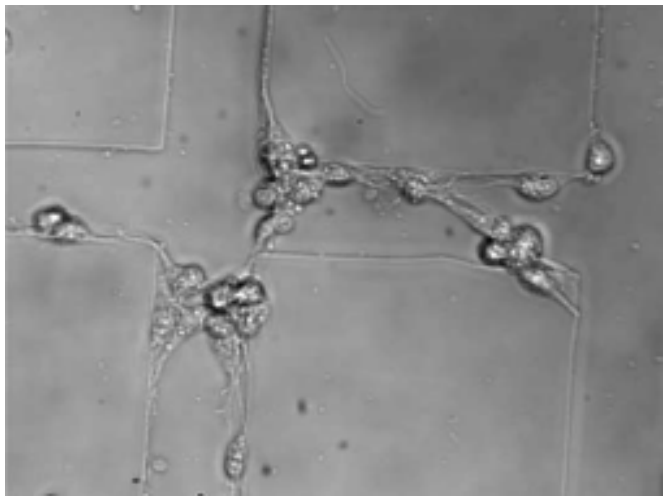
# Planar Micro Electrode Arrays

Immobilisation des cellules

Micro-fabricated pickets (green) with a neuron (orange) trapped in the middle.




Neurons cultured on cell adhesive molecules immobilized on micro-stamped surface.



# Micro Electrodes Implantables

BCI : Brain Computer Interface

*Commande par la pensée*

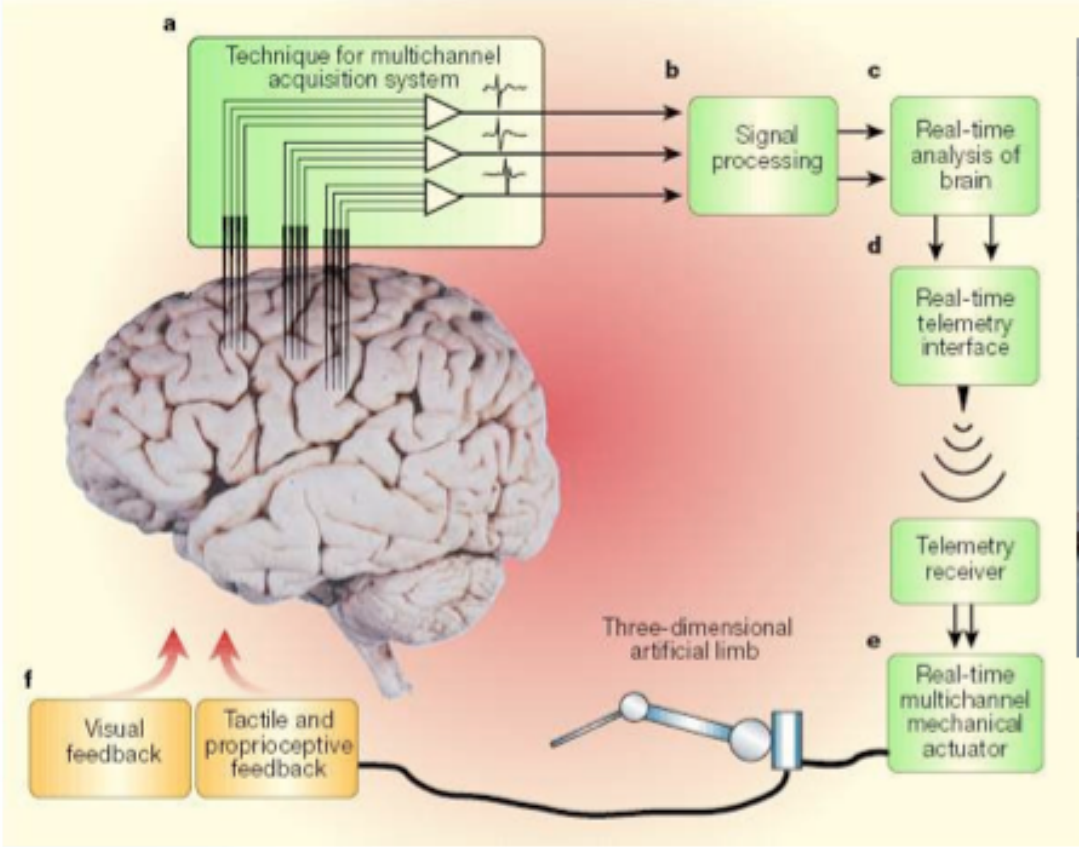
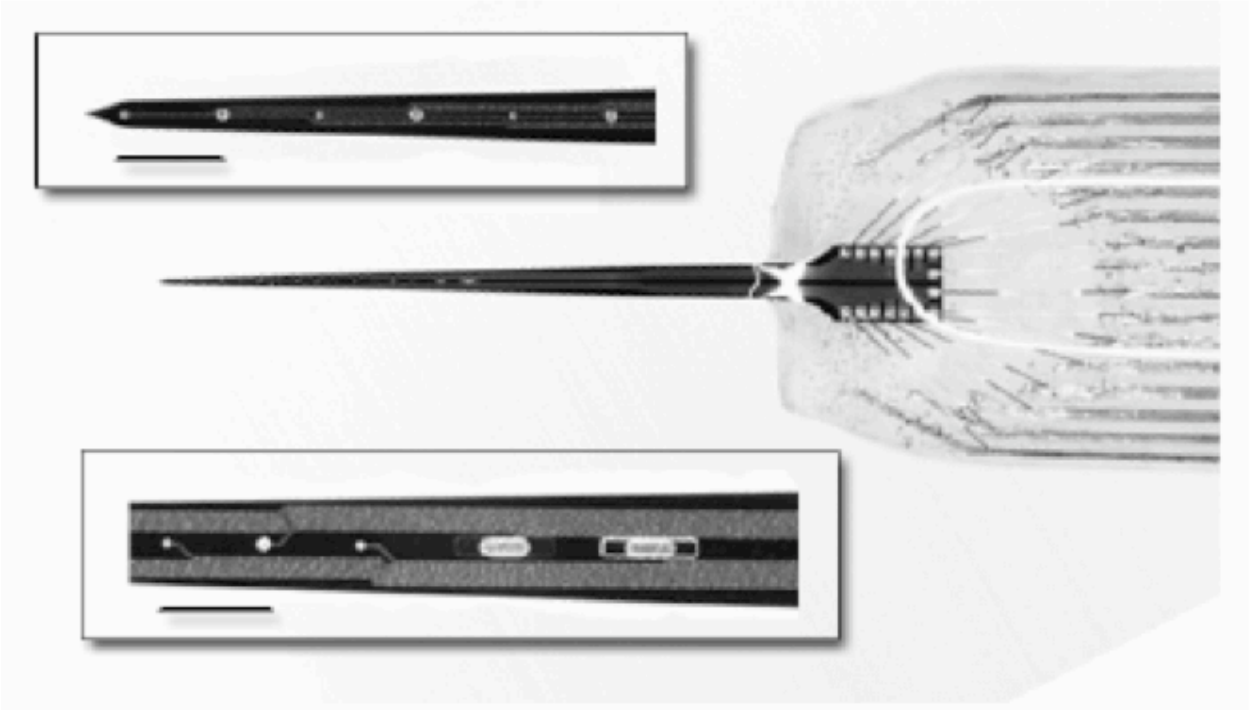


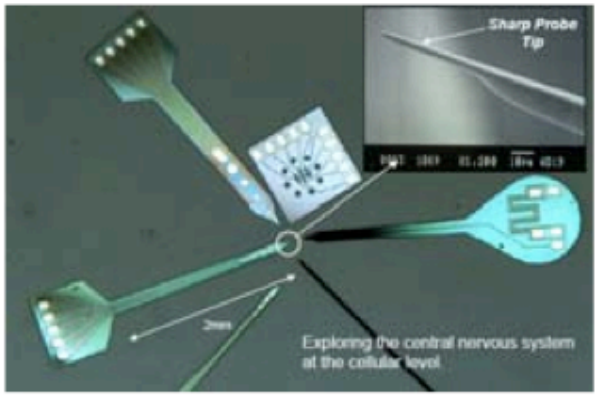

Schéma Pr Nicolélis

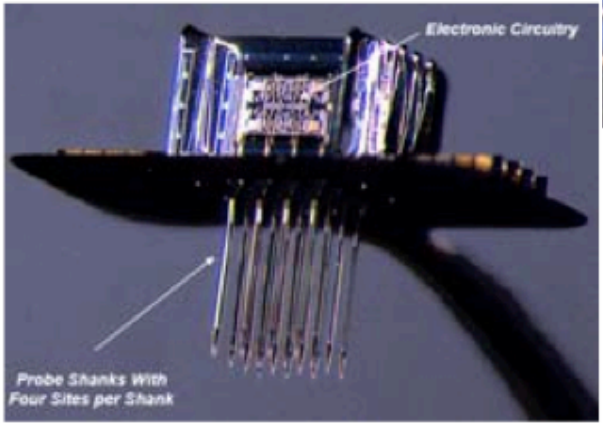
# Micro Electrodes Implantables

Aiguille unique, plusieurs électrodes

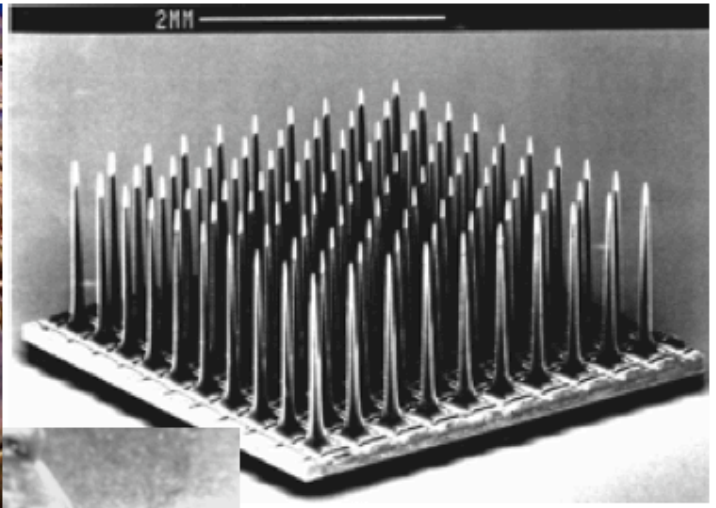


# Micro Electrodes Implantables

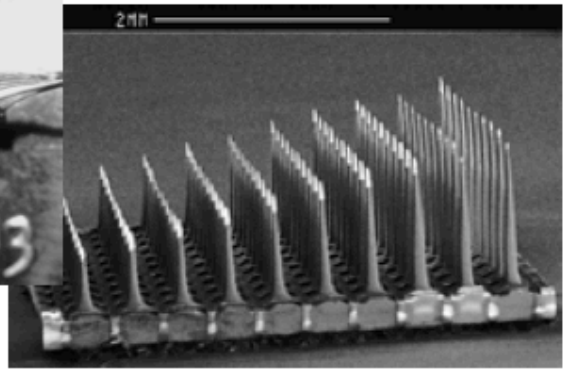



"Michigan Probe" (Ken Wise, UM). Marketed by NeuroNexus Technologies.

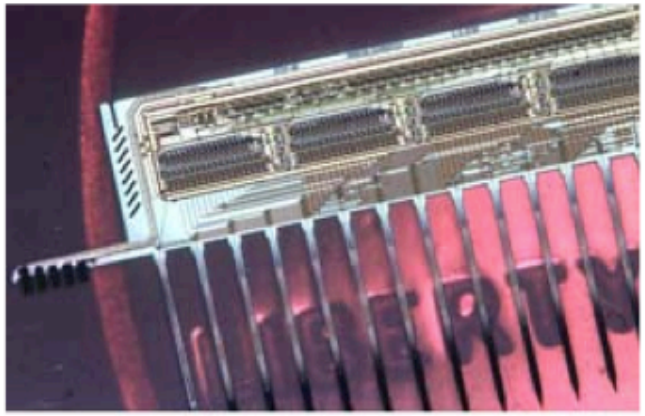


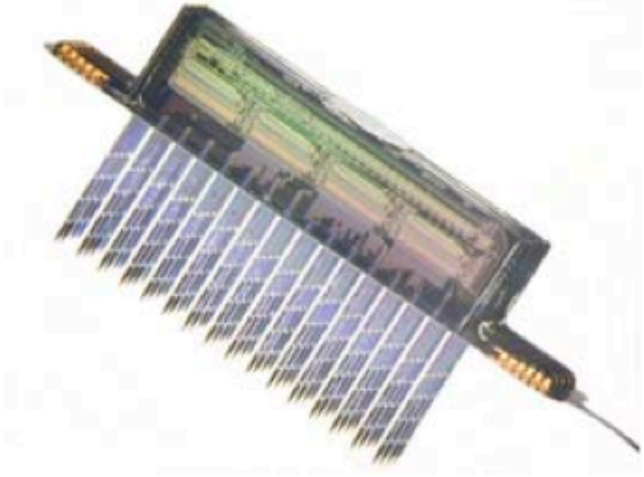




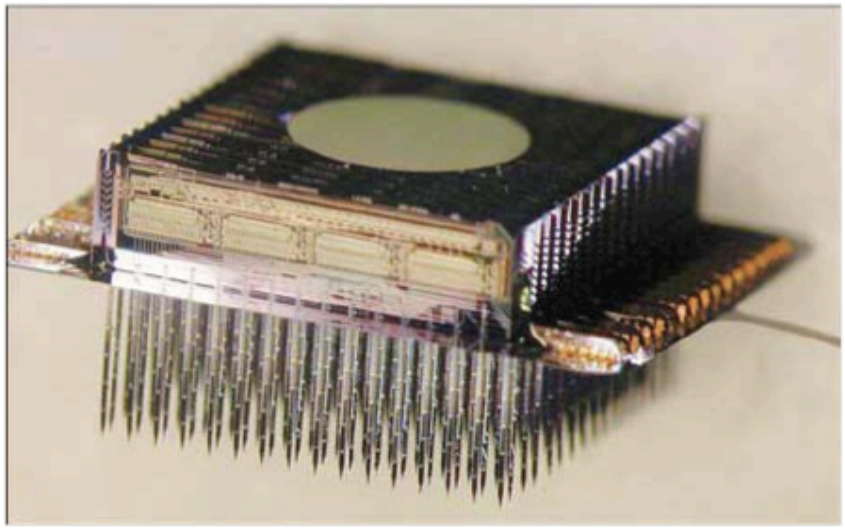

"Utah Array" (Greg Clark, et al., Univ Utah). Marketed by Cyberkinetics, Inc.

# Micro Electrodes Implantables

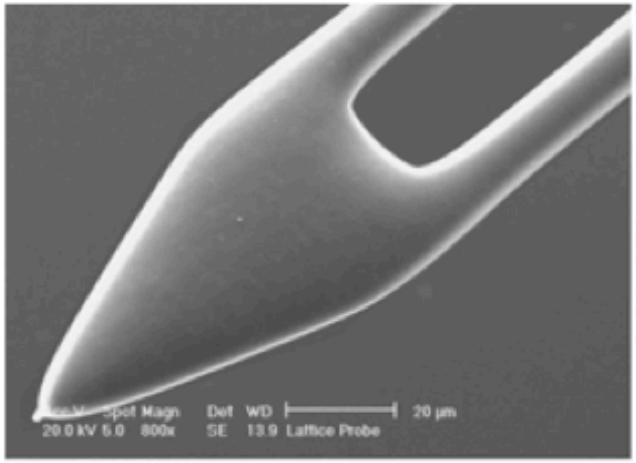


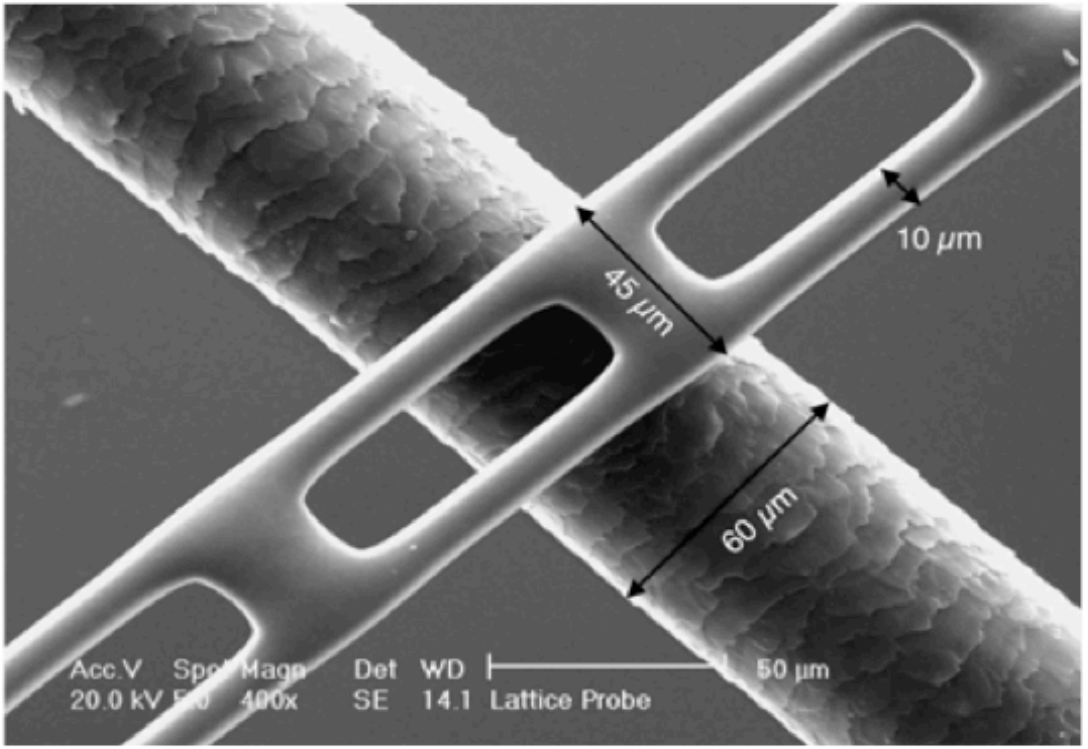


"Microelectrodes, Microelectronics, and Implantable Neural Microsystems," Kensall D. Wise, Amir M. Sodagar, Ying Yao, Mayurachat Ning Gulari, Gayatri E. Perlin, and Khalil Najafi, Proceedings of the IEEE | Vol. 96, No. 7, July 2008.

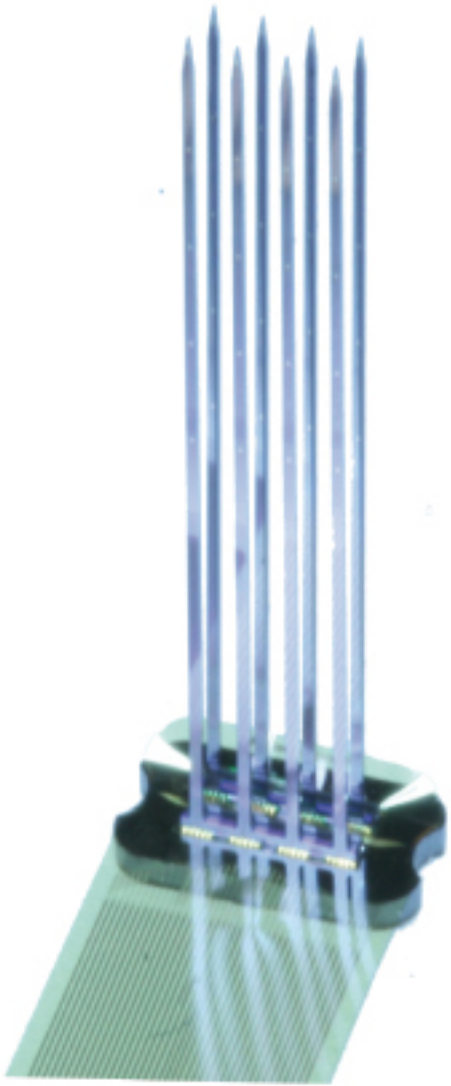


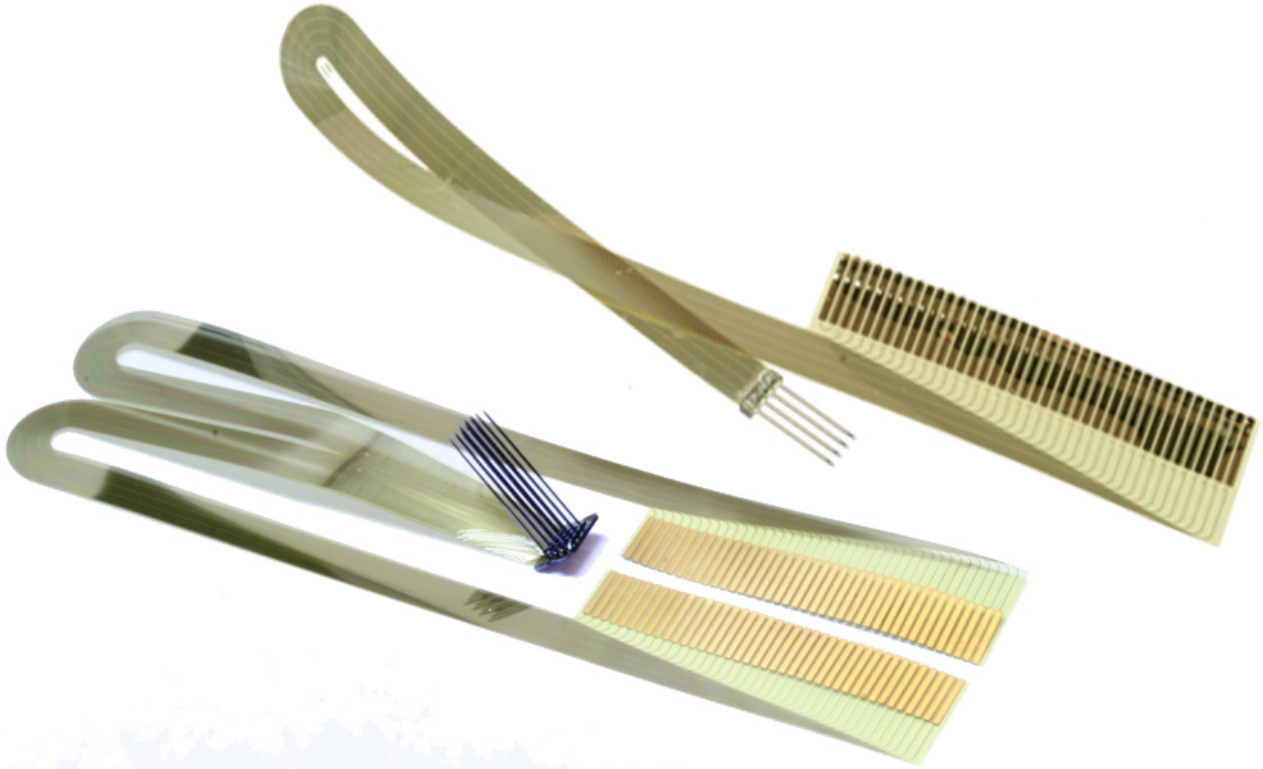
# Micro Electrodes Implantables



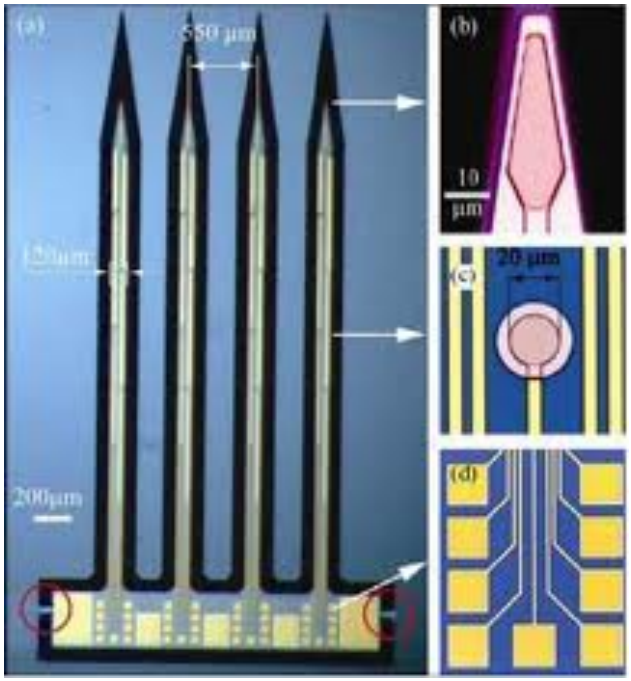



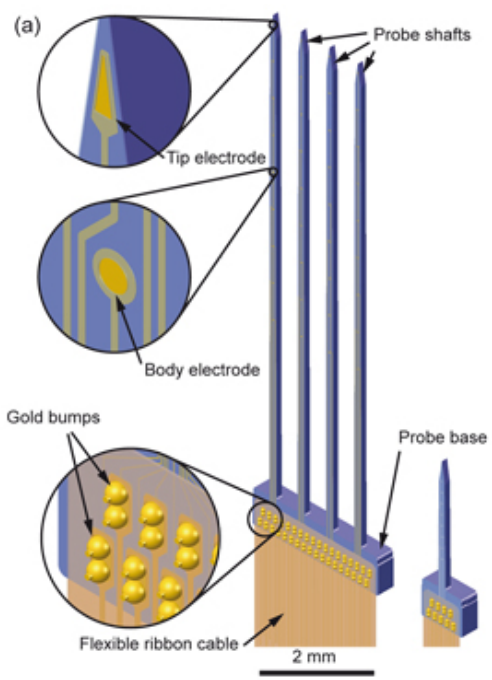
# Implantable brain micro electrodes

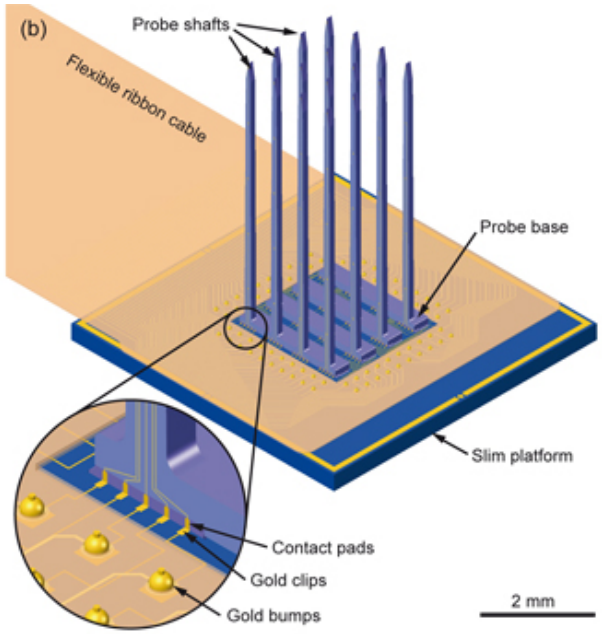




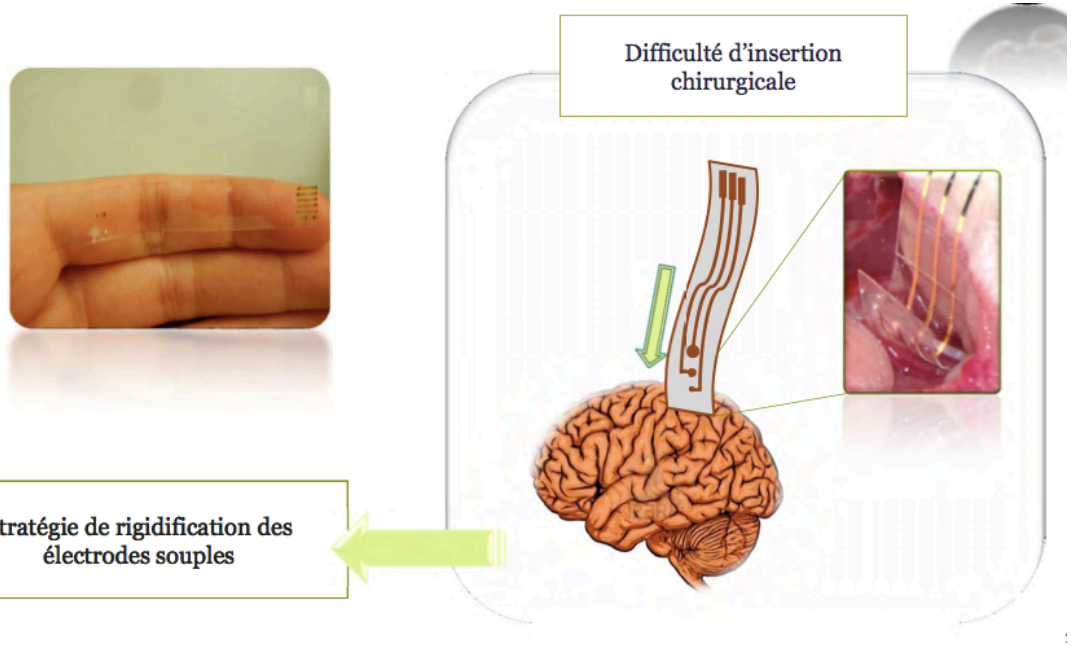
# Implantable brain micro electrodes



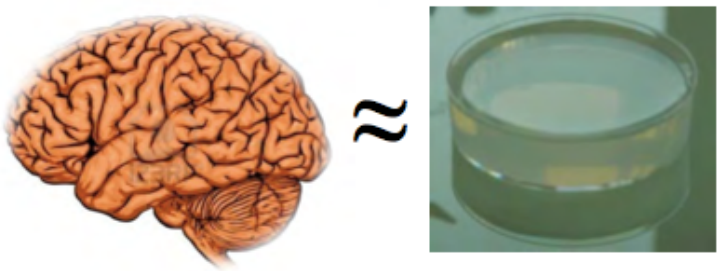



# Implantable brain micro electrodes

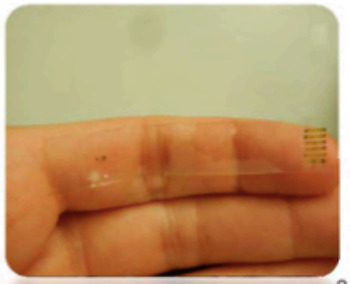



Cerveau ≈ gel agarose 0,6%

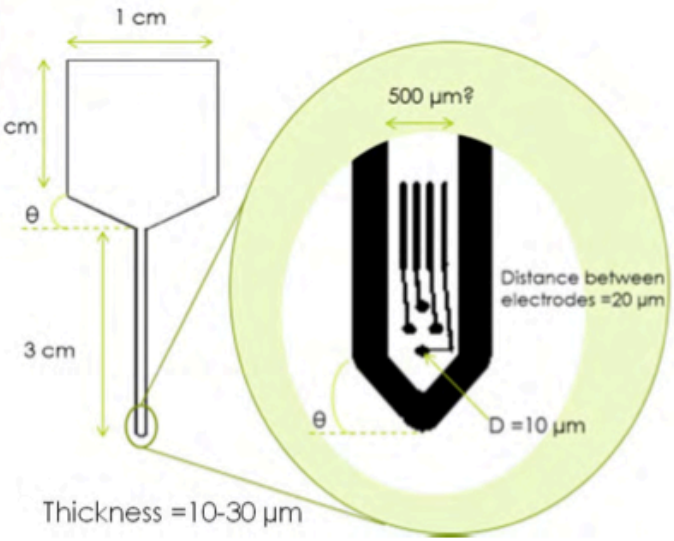


# Implantable brain micro electrodes

E.Descamps, LAAS Toulouse

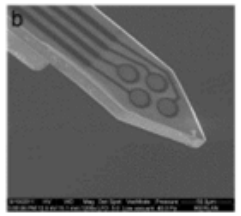


Design pour l'implantation




Connecteur

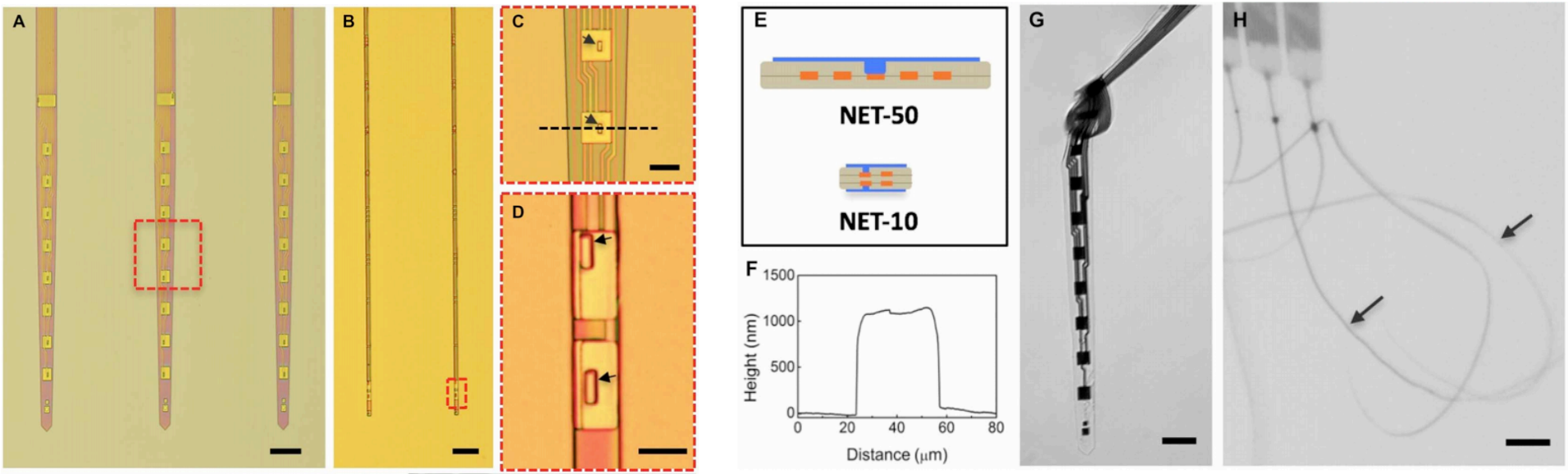
Dans la littérature




Altuna, Biosens and Bioelec (2012)

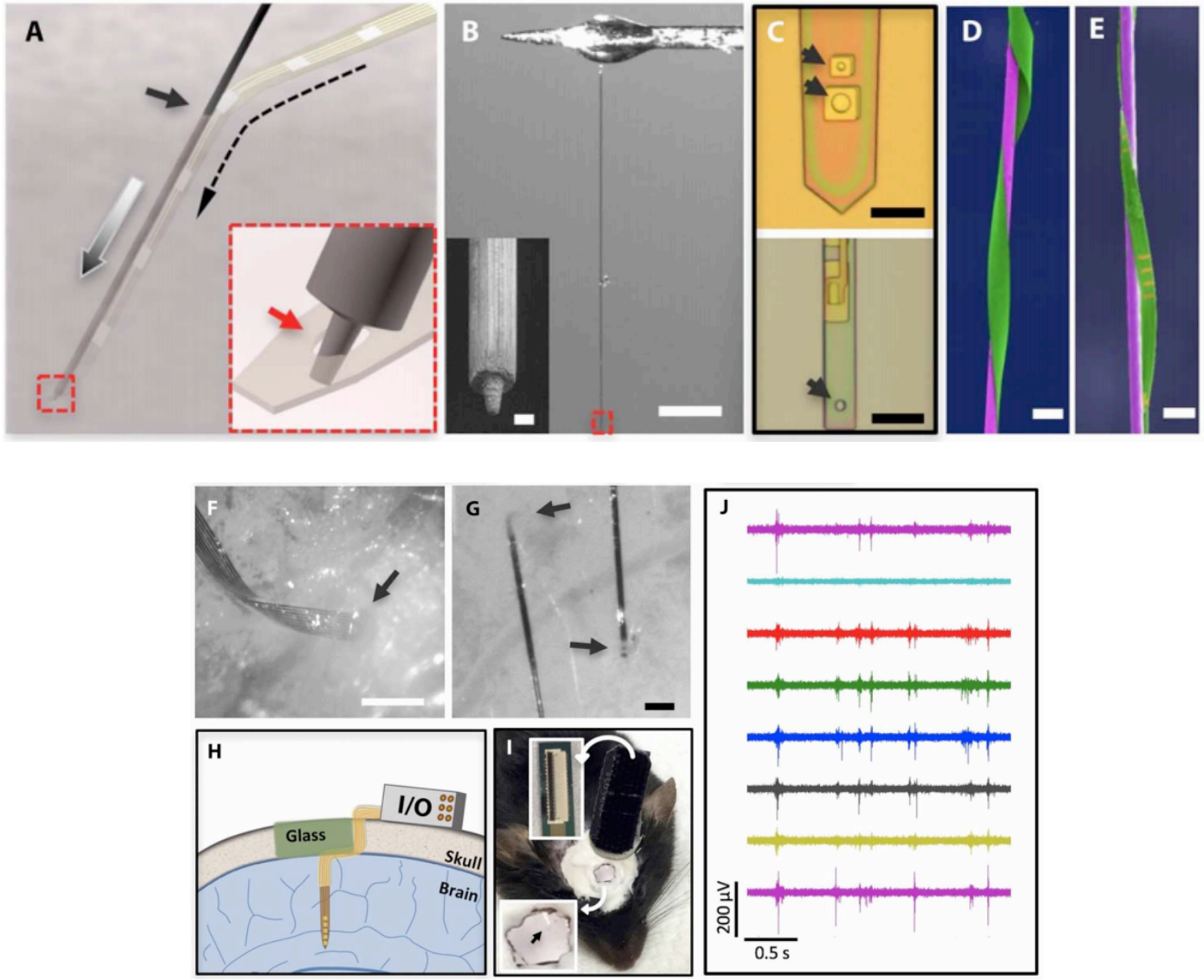
# Implantable brain micro electrodes

Ultra thin (1μm) microelectrode made with SU8 photoresist
Deformable and implantable with metal fiber guide.
subcellular dimensions
glial scar–free neural integration




L.Luan et al. Ultraflexible nanoelectronic probes form reliable, glial scar–free neural integration, Sci. Adv. 2017;3: e1601966

# Implantable brain micro electrodes



# Références

Nanoelectronics and Information technology.
Wiley-VCH 781-810

***Peter FROMHERZ***
Neuroelectronic interfacing: Semiconductor chips with ion schannels, nerve cells, and brain