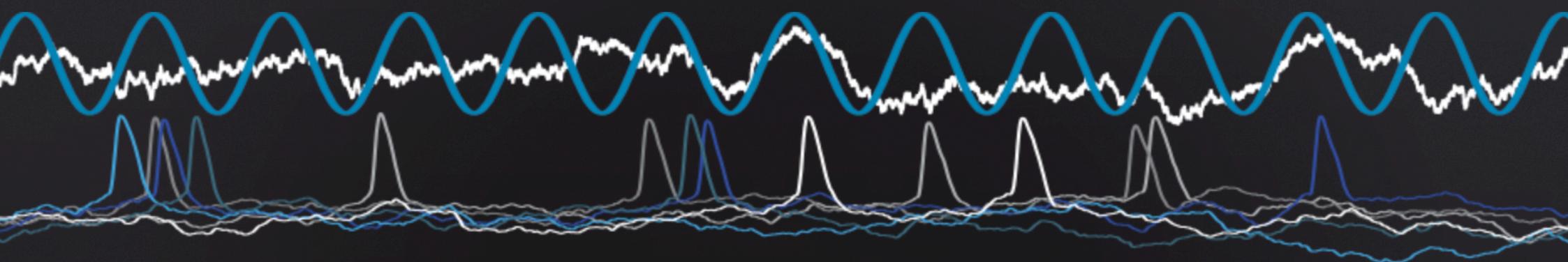


ELECTROPHYSIOLOGICAL SIGNALS



GENERATION AND CHARACTERISATION

Michele GIUGLIANO
Neuroelectronics

References for today's class content

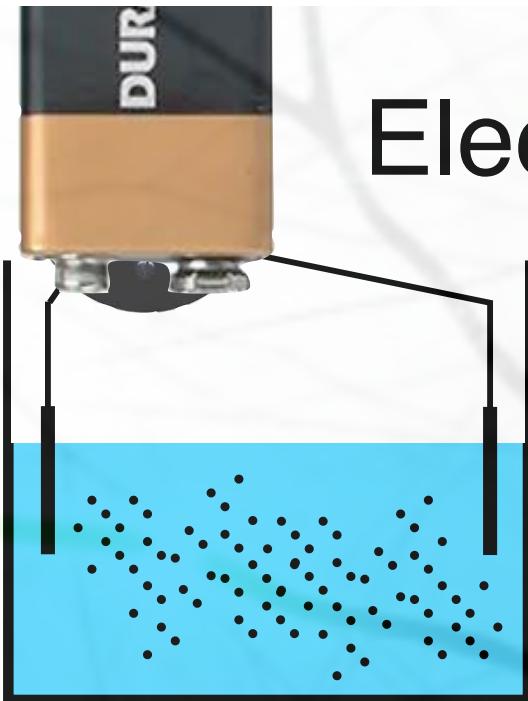
supporting your own study and understanding

Chapters from

- Weiss TF (1996) “*Cellular Biophysics*” vol. 1, MIT Press.
- Johnston & Wu, 1995 “Foundations of Cellular Neurophysiology”
- Sterratt et al. (2011) “*Principles of Computational Modelling...*”
- Abbott LF, Dayan P (2001) “*Theoretical Neuroscience*”

Origin of Bioelectricity

- we deal with **electrochemical systems** (in water): anions, cations
- we **measure** electrostatic potentials by **electrodes** (e.g. **AgCl** based)
- we **observe** -70mV at “rest” and swings up to +30mV in <1 ms
- starting from **the def.** of potential, we use **superposition of effects**
- anchored charges? ambiguous but intuition of **asymmetric concentrations**
- moving charges? **drift** & **diffuse**; there is a (cell) **membrane**
 - with **capacitive** properties as well as with ionic **permeability**
 - what is **permeability**? how **ions flow through** the membrane?



Electrochemical systems

aqueous solution (***solvent***)

+

molecules (e.g. ions) (***solute***)
(e.g., Na^+ , K^+ , Ca^{++} , Mg^{++} , Cl^-)

Dissociation of salts by ***solvation*** (e.g. $\text{NaCl} \longleftrightarrow \text{Na}^+ + \text{Cl}^-$)
into electrically charged particles. Globally, ***electroneutrality*** holds!

in **solutions**: *charge carriers* are *cations(+)* and *anions(-)*

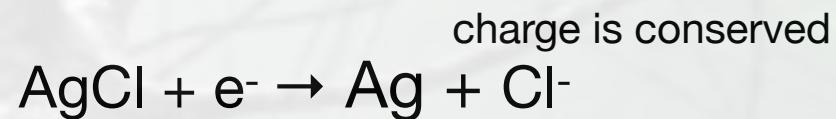
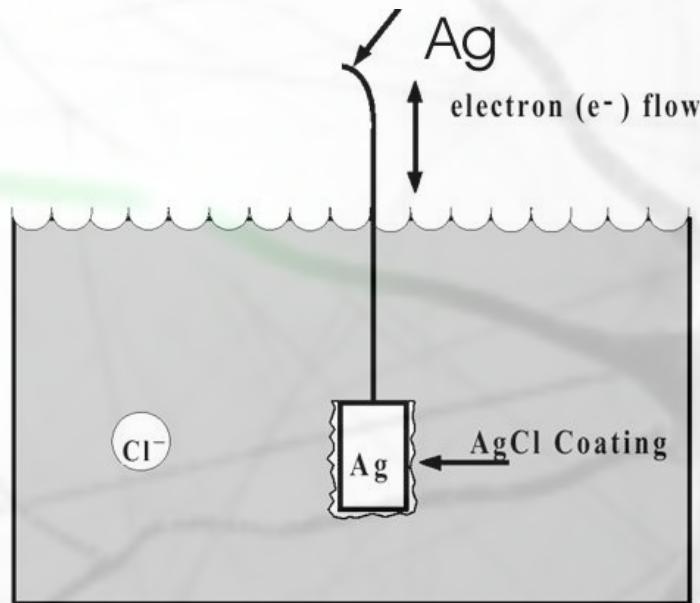
in **metals**: *charge carriers* are *electrons(-)*

(in semiconductors: *charge carriers* are *electrons(-)* and *holes(+)*)

electrodes: *anodic (+)* and *catodic electrodes (-)*

Silver-chloride junction

ions \neq electrons, distinct “currency” for charge exchanges



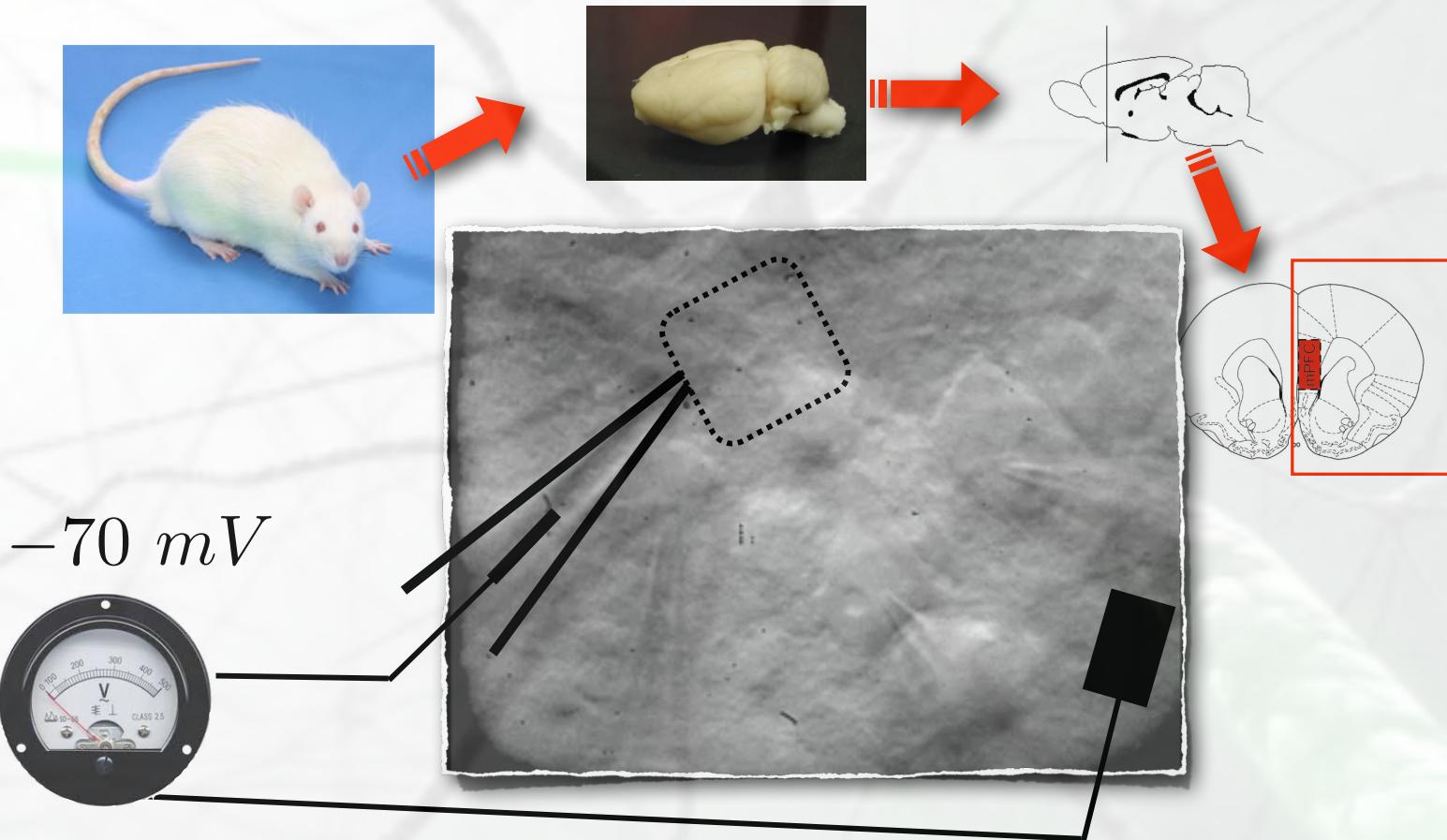
$$\Delta V = R I$$



- ~ measurement of electrical potentials in solution
- ~ “injection” of external (ionic) currents

(see sodium hypochlorite, NaClO)

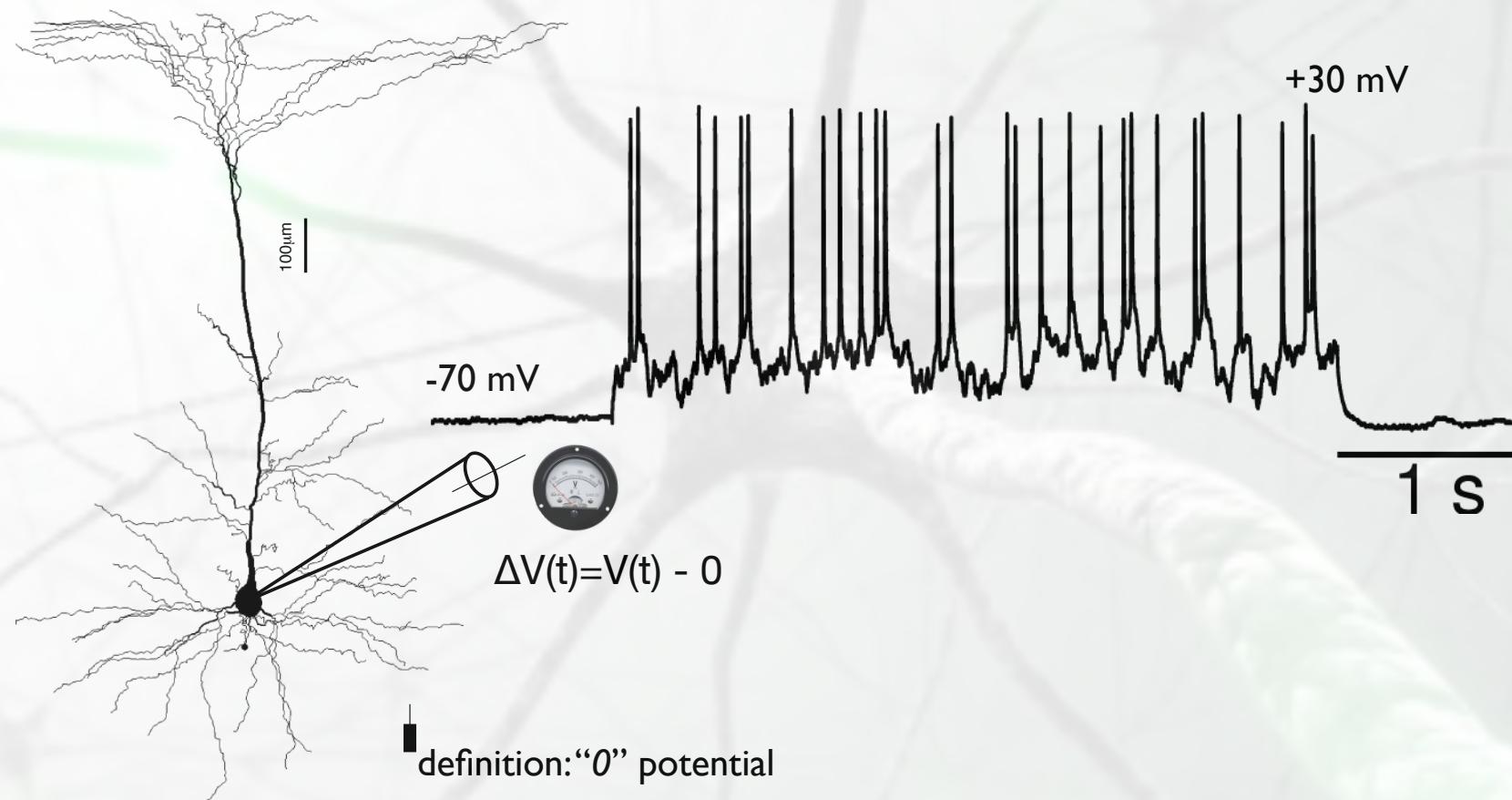
Our task for today: *understanding why*
there is a membrane electrical potential (“at rest”)
(in every cell, not just in nerve cells!)



Understanding, from “first (biophysical) principles”

- the existence of a *difference* of electrical potential - across the plasmatic membrane of a *living* cell...
 - electrical (electrostatic) potential measured in electrolytic solutions; involving electrolytes
 - the membrane? which physical (electrical) equivalent?
- ...in terms of its selective ionic permeability and of ionic flows.
- Towards a full (electrical) equivalent model of a cell membrane.

Such an understanding is **essential to explain** the ***excitable electrical properties*** of the cell membrane of neurons

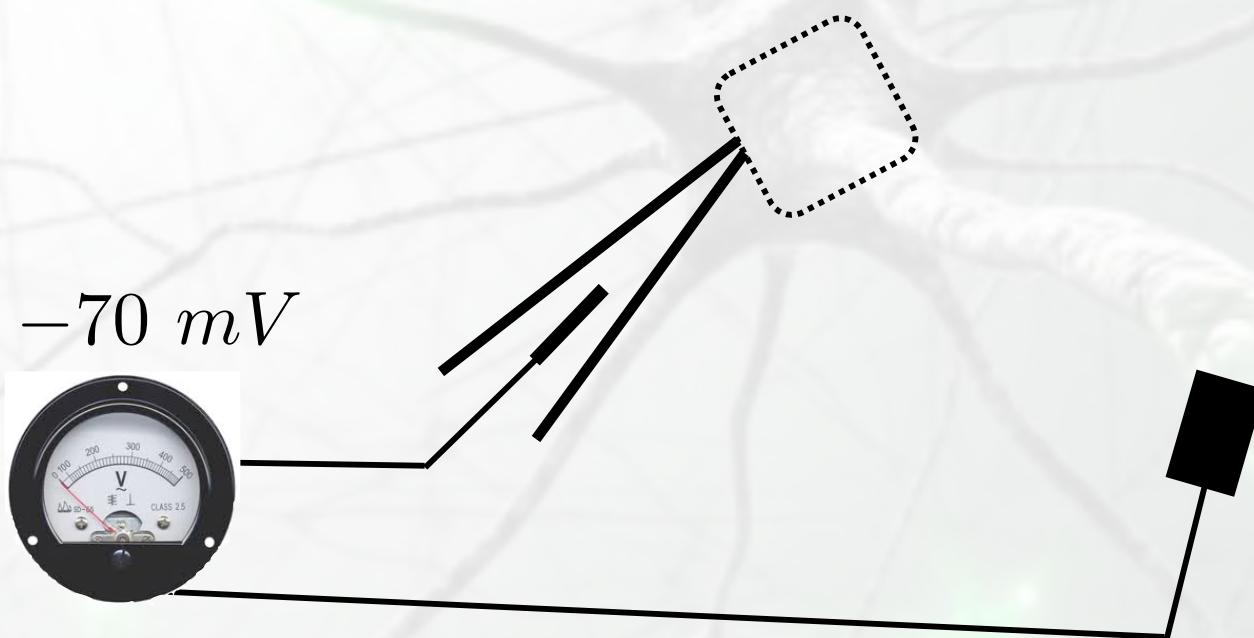


Important points

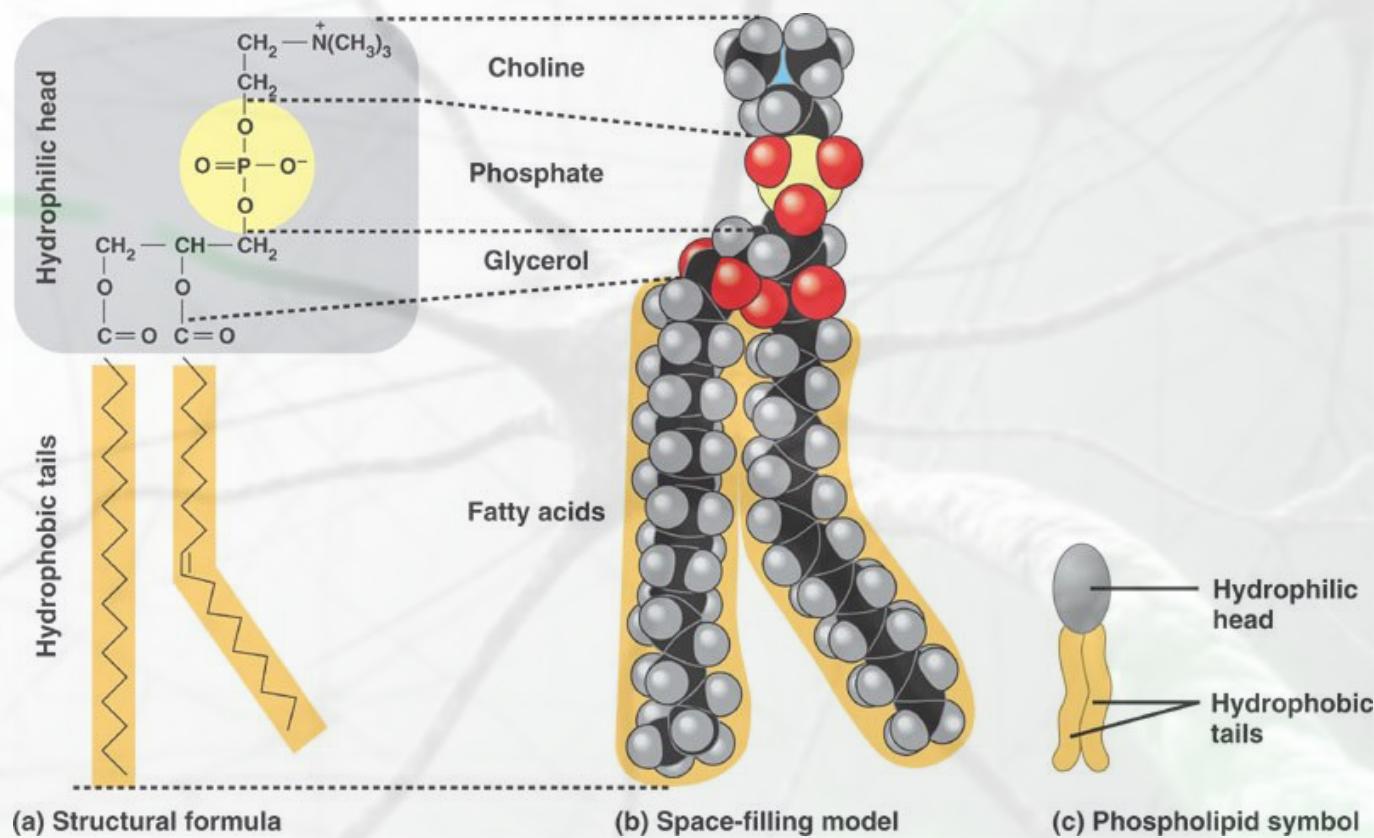
- thin (insulating) membrane across which we measure this potential...

Digression on biological membranes!

The existence of a (*resting*) electrical potential
across the *cell plasma membrane*

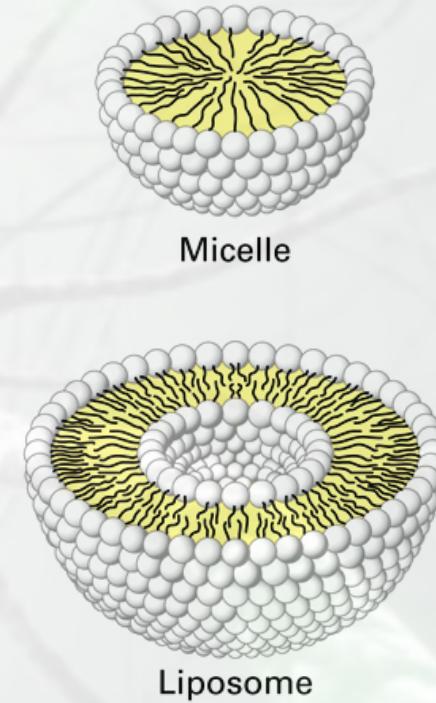
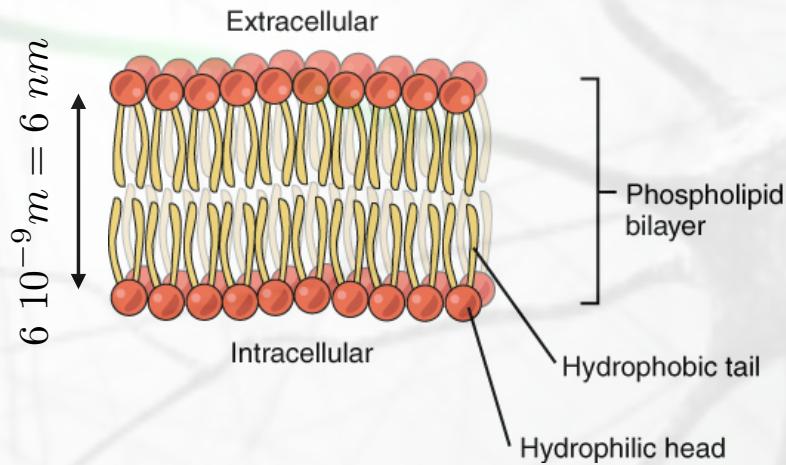


The plasmatic membrane of biological cells



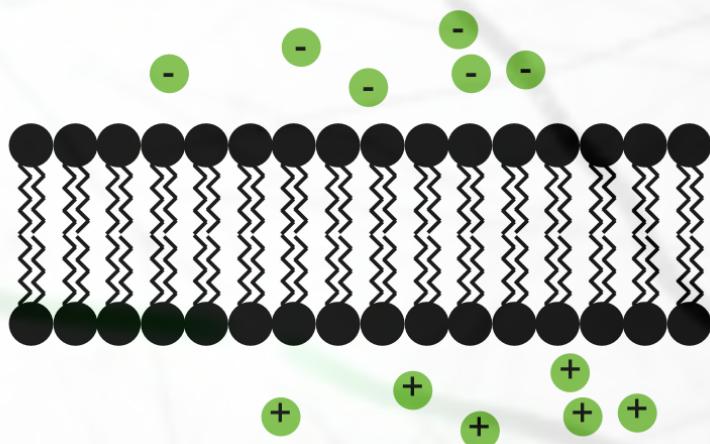
self-assembly of polymers (phospholipids)

The plasmatic membrane of biological cells



- **hydrophilic** heads (phosphate groups, charged)
- **hydrophobic** tails (fatty acids)
- self-organise in water, into segregated compartments (emergence of life!!)

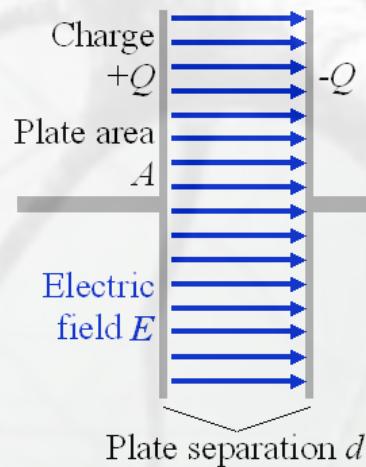
Plasmatic membrane: a physical equivalent?



Two volumes, where *charges* move freely
(as in an electrical **conductor**)

...separated by a *barrier* that cannot be crossed (as in an **insulator** or dielectric)

Does this ring any bell?



$$C = \frac{\Delta Q}{\Delta V}$$

$$C = \frac{\epsilon A}{d}$$



Exercise

what is the membrane capacitance (per area unit) ?
what charge distribution “delta” leads to 70mV?

$$C = \frac{\epsilon A}{d}$$
$$c = 1 \mu F/cm^2$$

$$C = \frac{7 \cdot 8.85 \cdot 10^{-12} \text{ } F/m \cdot A}{6 \cdot 10^{-9} m} = 0.010 \text{ } F/m^2 \cdot A = 1 \mu F/cm^2 \cdot A$$

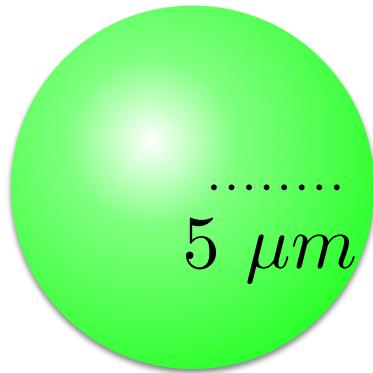
$$C = \frac{\Delta Q}{\Delta V}$$

$$e = 1.602...10^{-19} C$$

$$\Delta Q = 1 \mu F/cm^2 \cdot 70 mV = 7 \cdot 10^{-8} C/cm^2$$

Unique membrane properties and enhanced signal processing in human neocortical neurons

Guy Eyal¹, Matthijs B Verhoog², Guilherme Testa-Silva², Yair Deitcher³,
Johannes C Lodder², Ruth Benavides-Piccione^{4,5}, Juan Morales⁶,
Javier DeFelipe^{4,5}, Christiaan PJ de Kock², Huibert D Mansvelder², Idan Segev^{1,3*}



$523 \ 10^8 ions$

50 billions

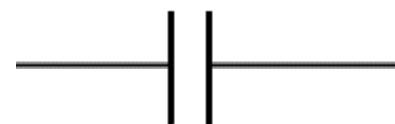
.....
 $5 \ \mu m$

$1.6 \ 10^{-19} C/ion$

$1.6 \ 10^8 ions/\mu m^2$ (*shell*)

$2.56 \ 10^{-11} C/\mu m^2$

$$7 \ 10^{-8} C/cm^2 = 7 \ 10^{-8} C/10^8 \mu m^2 \approx 10^{-15} C/\mu m^2$$



$70mV$

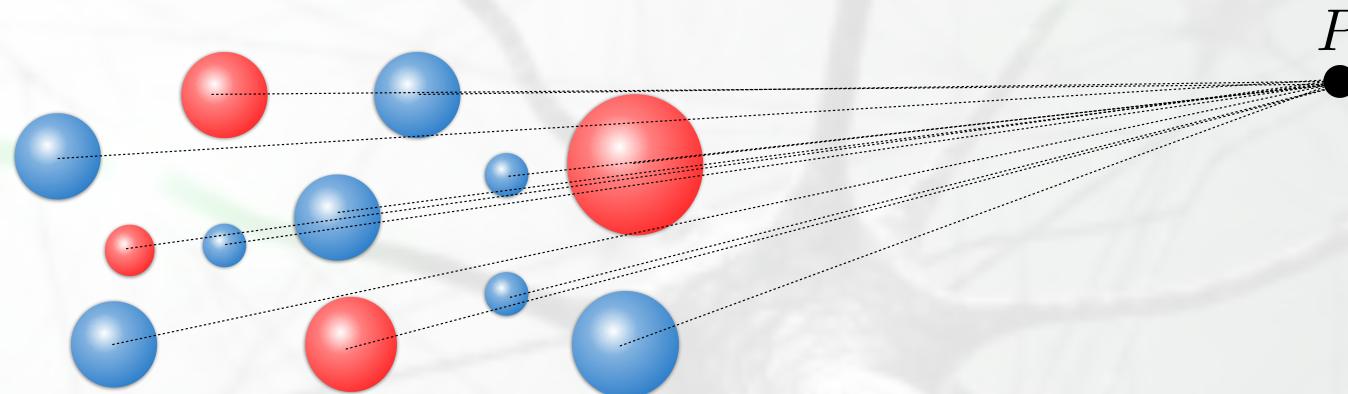
$$\frac{10^{-15}}{1.6 \ 10^{-19}} \ ions/\mu m^2 \approx 6 \ 10^3$$

**only 10'000 times less charge
or ~1000 ions less**

Origin of Bioelectricity

- we deal with **electrochemical systems** (in water): anions, cations
- we **measure** electrostatic potentials by **electrodes** (e.g. **AgCl** based)
- we **observe** -70mV at “rest” and swings up to +30mV in <1 ms
- starting from **the def.** of potential, we use **superposition of effects**
- anchored charges? ambiguous but intuition of **asymmetric concentrations**
- moving charges? **drift** & **diffuse**; there is a (cell) **membrane**
 - with **capacitive** properties as well as with ionic **permeability**
 - what is **permeability**? how **ions flow through** the membrane?

REMINDER: *superposition* of the effects



$$V_{total}(P) = \frac{1}{4\pi\epsilon_r\epsilon_0} \left(\frac{Q_1}{r_{P-Q_1}} + \frac{Q_2}{r_{P-Q_2}} + \dots + \frac{Q_M}{r_{P-Q_M}} \right)$$

It is like the *weighted sum* of the inverse of the distances...



Exercise: (discrete) distribution of charge
anchored/fix/glued in free space
(restrained from self-organising)

https://phet.colorado.edu/sims/html/charges-and-fields/latest/charges-and-fields_en.html

DEMO TIME!

Exercise: (discrete) distribution of charge
anchored/fix/glued in free space
(restrained from self-organising)

Given the potential (measured),
which is the corresponding distribution of charge??

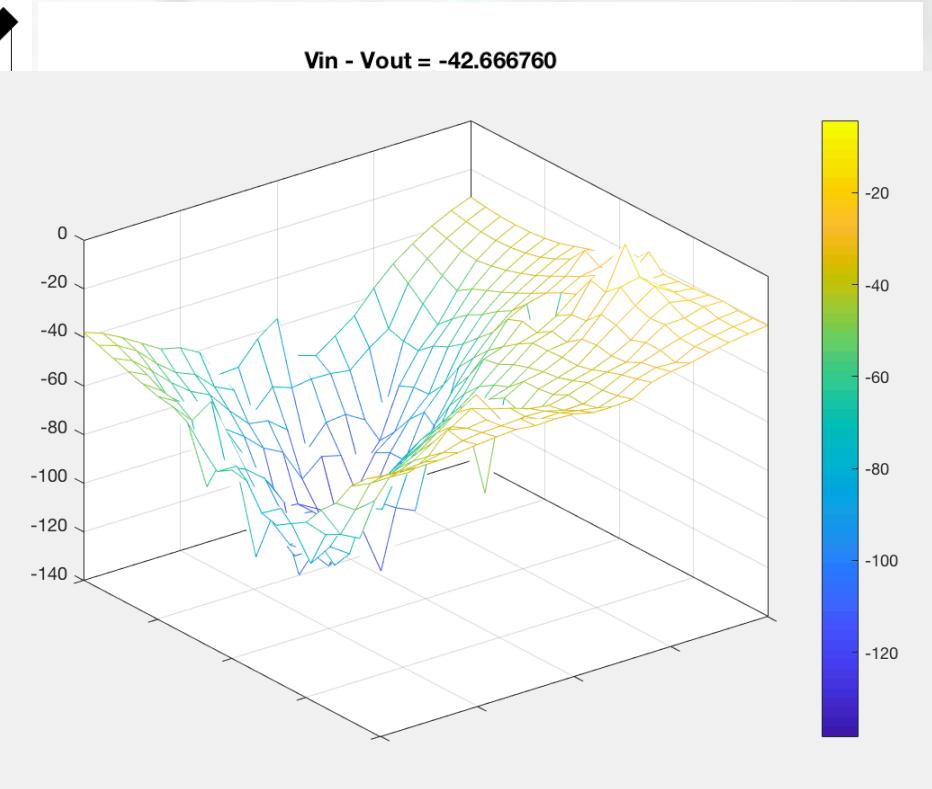
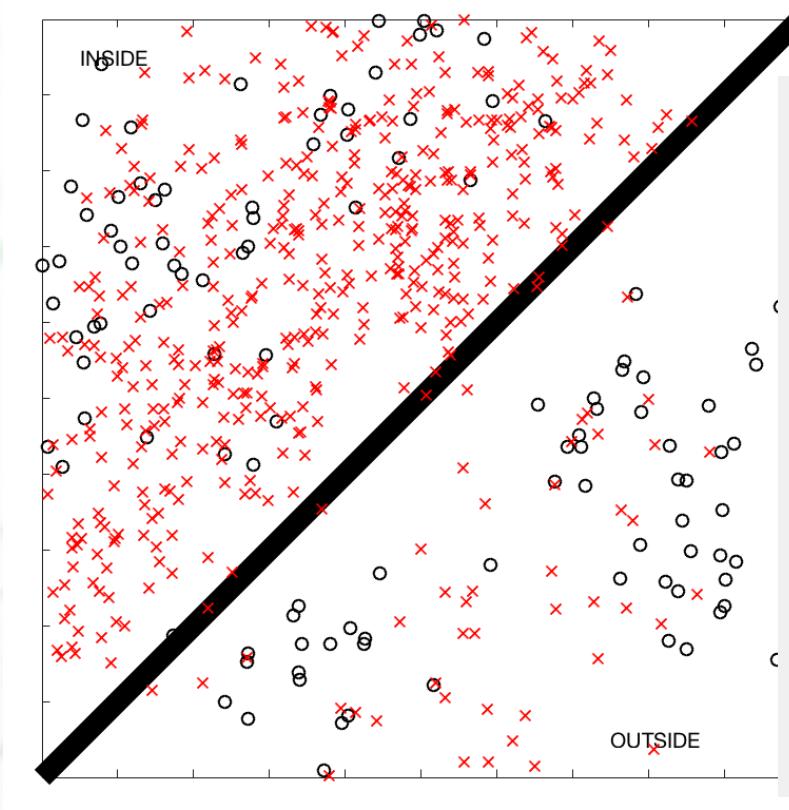
?????

$$\Delta V = V_{\text{in}} - V_{\text{out}} \quad -70 \text{ mV}$$

https://phet.colorado.edu/sims/html/charges-and-fields/latest/charges-and-fields_en.html

$$\Delta V = V_{in} - V_{out}$$

????? - 70 mV



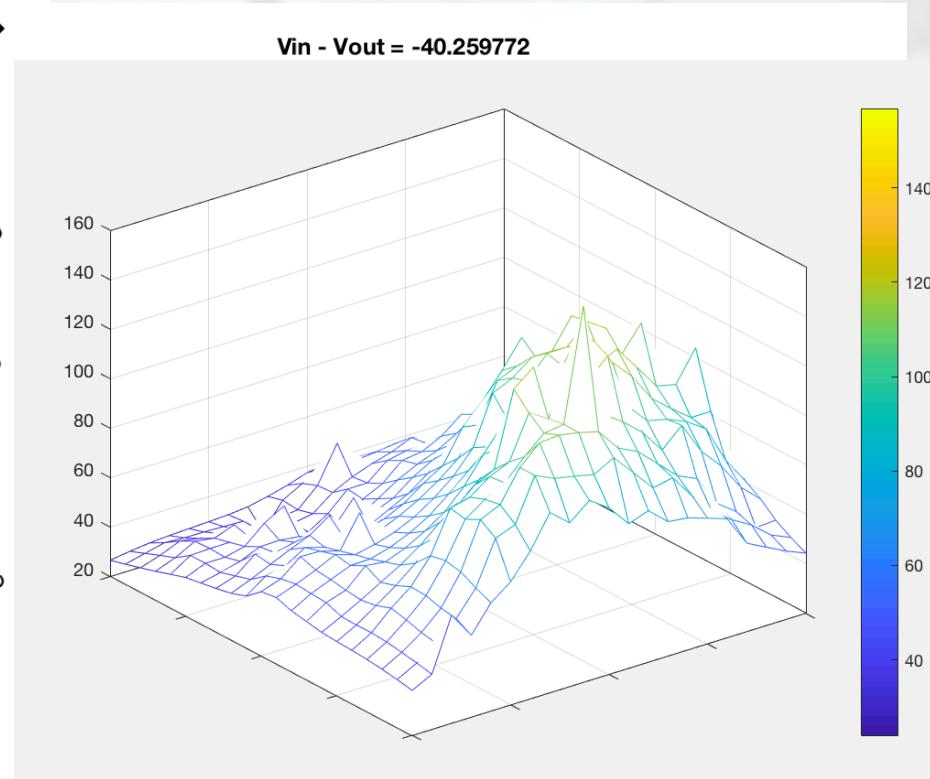
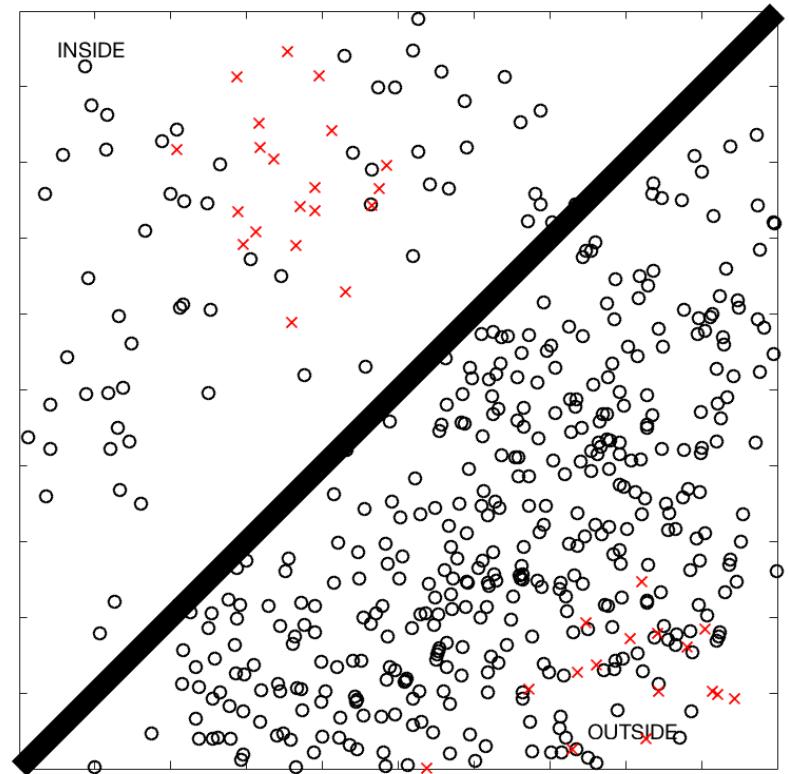
o: positively charged ions
x: negatively charged ions

Negative ions inside..



$$\Delta V = V_{in} - V_{out}$$

$$????? - 70 \text{ mV}$$



o: positively charged ions
x: negatively charged ions

Unequal distribution of positive ions..



Important points

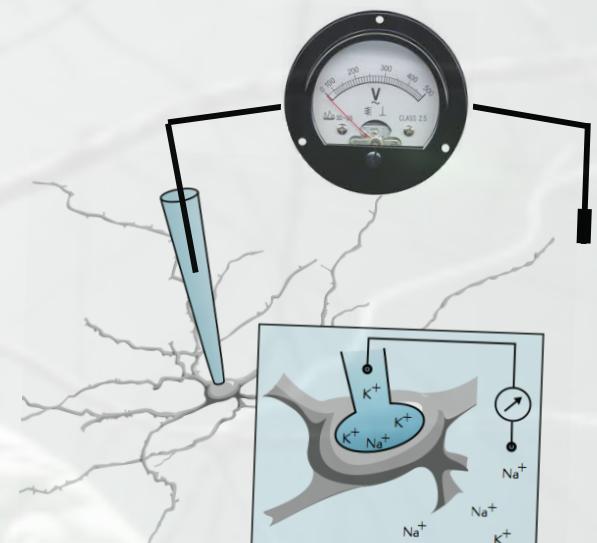
- **ions** are free to **move**... (to *diffuse* and to experience *drifting* forces, due to their own electric fields)
- thin (insulating) **membrane** across which we measure a potential...

Origin of Bioelectricity

- we deal with **electrochemical systems** (in water): anions, cations
- we **measure** electrostatic potentials by **electrodes** (e.g. **AgCl** based)
- we **observe** -70mV at “rest” and swings up to +30mV in <1 ms
- starting from **the def.** of potential, we use **superposition of effects**
- anchored charges? ambiguous but intuition of **asymmetric concentrations**
- moving charges? **drift** & **diffuse**; there is a (cell) **membrane**
 - with **capacitive** properties as well as with ionic **permeability**
 - what is **permeability**? how **ions flow through** the membrane?

The existence of a (resting) membrane potential: facts

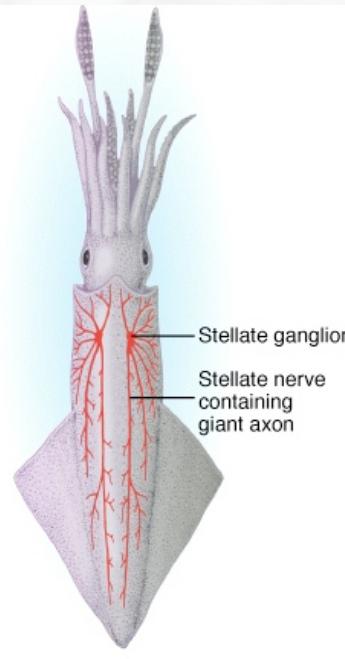
- global electro-neutrality holds => **isopotential** inside & outside the cell
- ions species (Na^+ , K^+ , Cl^- , ...) are **distributed differently** inside & outside
- the membrane bilayer is impermeable to water (and ions)
(i.e. double layer of phospholipids - hydrophobic!!);
- conventionally, we measure electric *potential* V , inside with reference to outside the membrane
- if a (generic) cell is not dead (NO thermodynamical equilibrium = identity with its surrounding), $V \sim -70 \text{ mV}$
- in excitable cells, V **may change abruptly** in time
(e.g., neurons, myocytes, pancreatic β -cells)



from Sterratt et al., 2011

Why ? How?

Ionic concentrations for the squid's giant-axon ("prep" used by Hodgkin & Huxley)



Ion	K^+	Na^+	Cl^-	Ca^{2+}
Concentration inside (mM)	400	50	40	10^{-4}
Concentration outside (mM)	20	440	560	10

from Sterratt et al., 2011



Why is there an electric potential across the cell membrane?



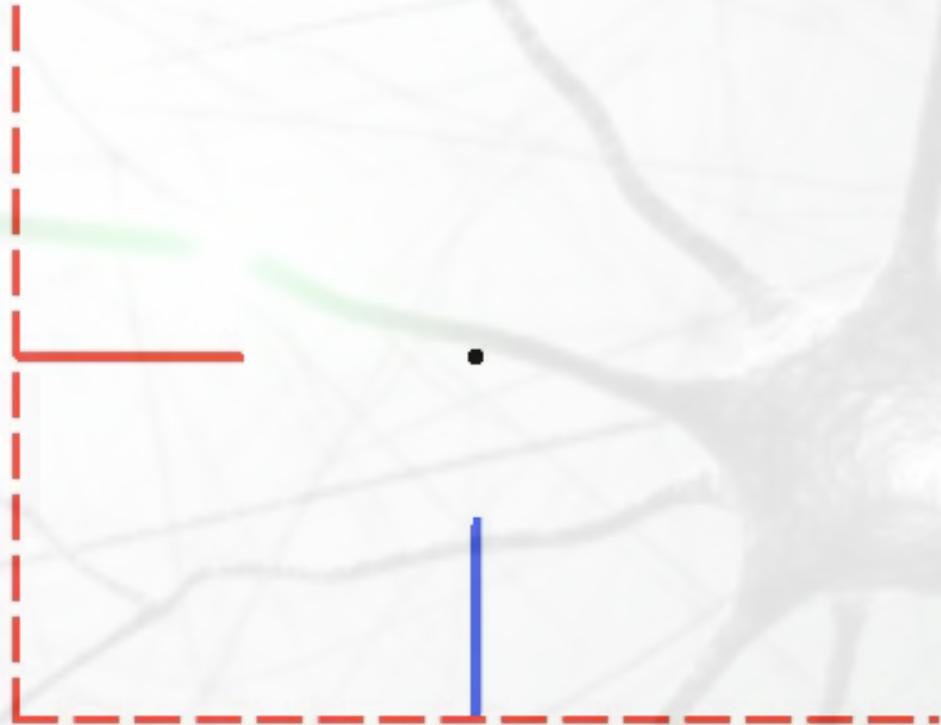
Because of a **heterogeneous distribution** of charges, across the membrane,...

...due to its semi-permeability!

multiple ion-species, NOT at the equilibrium
distinct concentrations



Already familiar with... *diffusion*?
(of non-charged particles)



Monte Carlo simulation = friction + random collisions...

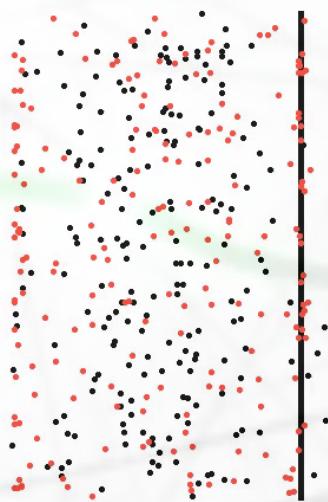
$$F_{ext} + F_{friction} = m \frac{dv(t)}{dt}$$

$$F_{friction} = -\lambda v(t)$$

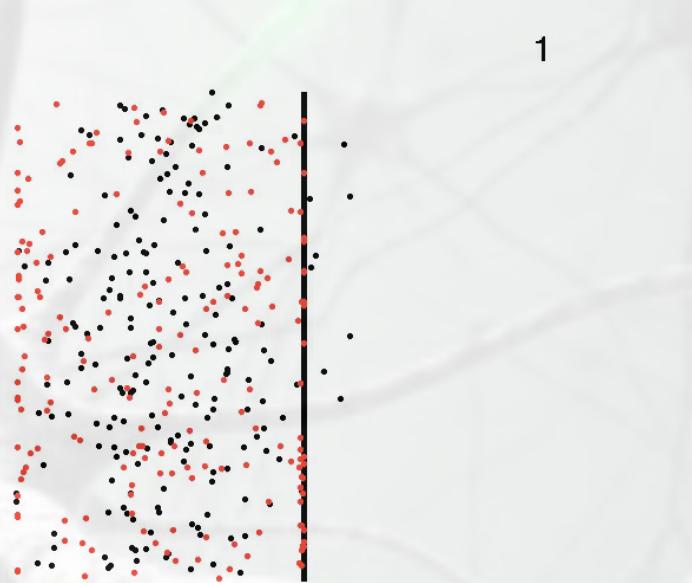
$$F_{ext} \approx \text{rand}()$$

free diffusion (in 2D) - not charged molecules

Semi-permeability... really? YES



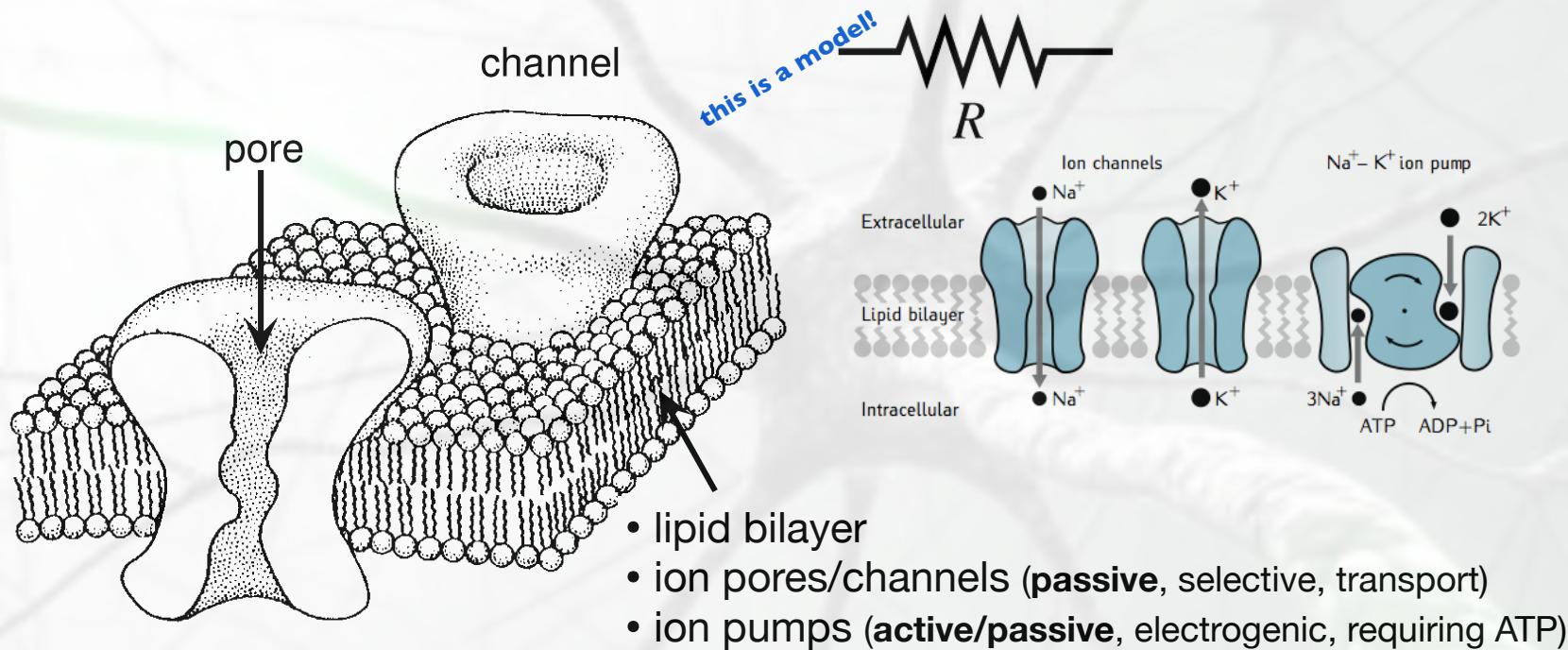
**permeable (non-selective)
membrane**



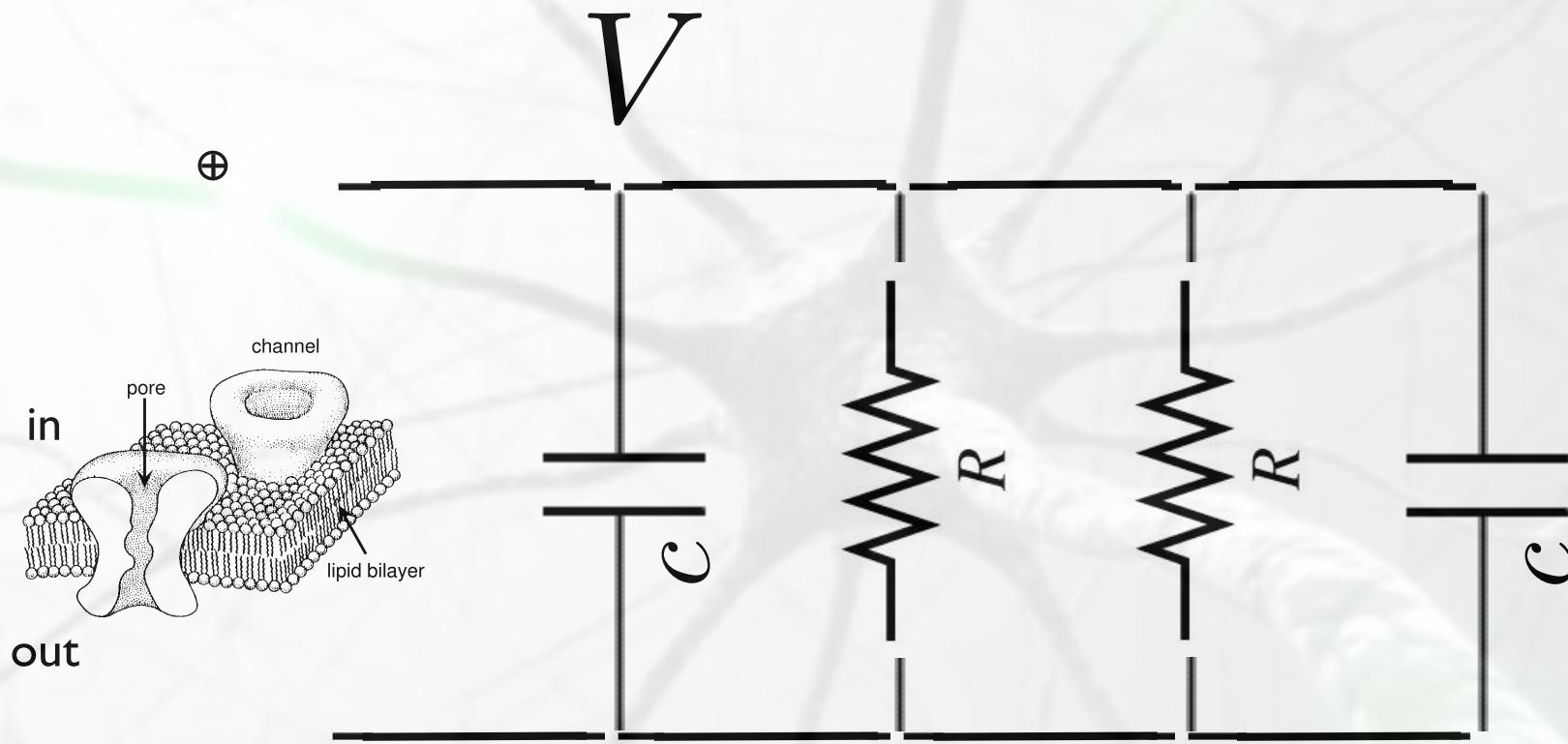
**semi-permeable (selective,
black-only) membrane**

Monte Carlo simulation = Coulomb's attractive forces + friction + random collisions...

The plasmatic cell membrane is *selectively* permeable to specific ions

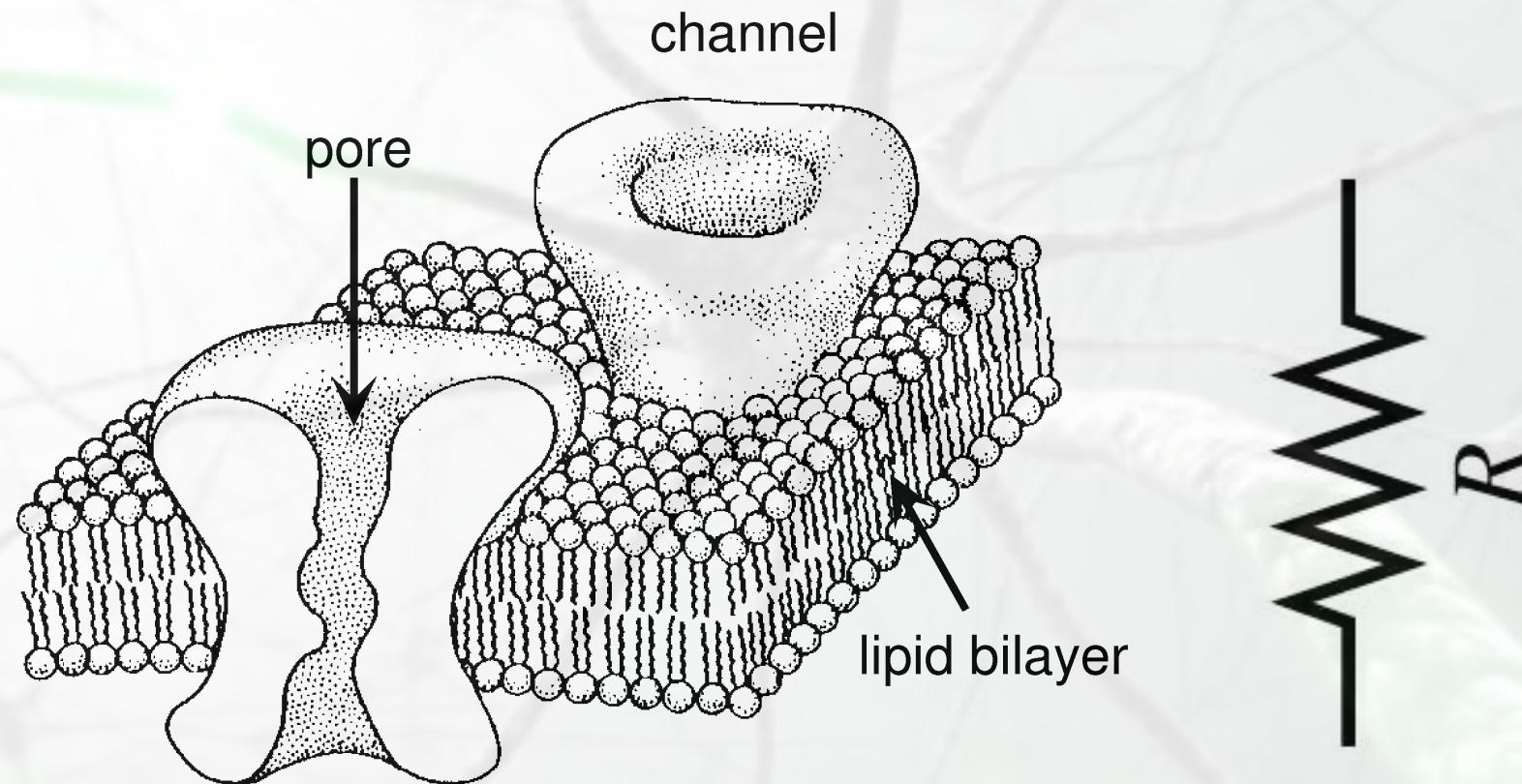


Towards a physical equivalent (electrical) circuit of the plasmatic cell membrane

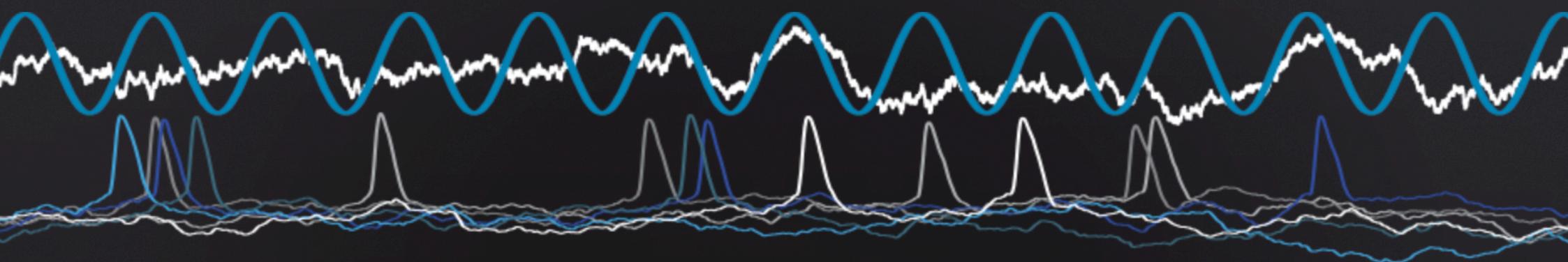


Is the “resistor” model for an ion channel... complete?

We first need to understand how ions flow across a permeable membrane !!!



ELECTROPHYSIOLOGICAL SIGNALS



GENERATION AND CHARACTERISATION

Michele GIUGLIANO
Neuroelectronics

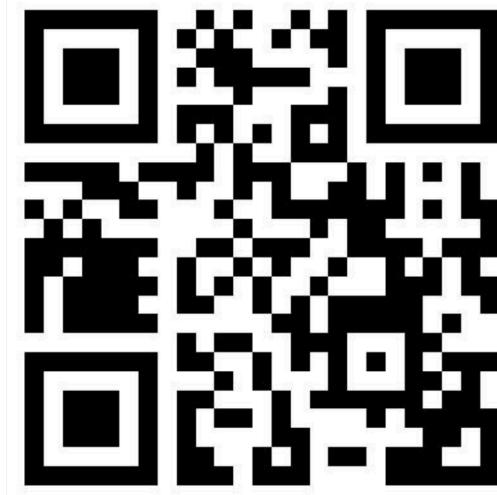
ATTENDANCE TRACKING - **code 7HB8C**

(for statistical purposes only)

Download for iPhone



Download for Android



<https://www.unimore.it/it/servizi/unimore-app>

Back to the key problem for today

- heterogenous charge concentrations (inside & outside) and -70mV

Tackle the self-consistence or self-organizing character of the resting potential.

Origin of Bioelectricity

- we deal with **electrochemical systems** (in water): anions, cations
- we **measure** electrostatic potentials by **electrodes** (e.g. **AgCl** based)
- we **observe** -70mV at “rest” and swings up to +30mV in <1 ms
- starting from **the def.** of potential, we use **superposition of effects**
- anchored charges? ambiguous but intuition of **asymmetric concentrations**
- moving charges? **drift** & **diffuse**; there is a (cell) **membrane**
 - with **capacitive** properties as well as with ionic **permeability**
 - what is **permeability**? how **ions flow through** the membrane?

Origin of Bioelectricity

- intuition for **ionic semi-permeability** (NOT identical permeabilities)
- single species, **equilibrium: Nernst** Potential
 - Na+, K+, Ca++, Cl-,?
- single species, non-equilibrium: **ion fluxes (ionic current densities)**
 - **Ohmic** approximation and non-Ohmic (**Goldmann eq.**)
- **multiple** species, **non**-equilibrium: **steady-state** hypothesis
 - **Goldman Hodgkin Huxley** equation(s) and **resting potential**

What kind of fluxes can occur in solution?

Diffusive and Drift fluxes

$$J = u \ c \left(-R \ T \ \frac{d}{dx} \ln[c(x)] \right)$$

$$J = u \ c \left(-z \ F \ \frac{dV}{dx} \right)$$

What does their knowledge predict?

The formation of a (Nernst) electrical potential in space,
given an unequal concentration of ions
(e.g. across a semi-permeable membrane)

The phenomenon of (electro-)diffusion



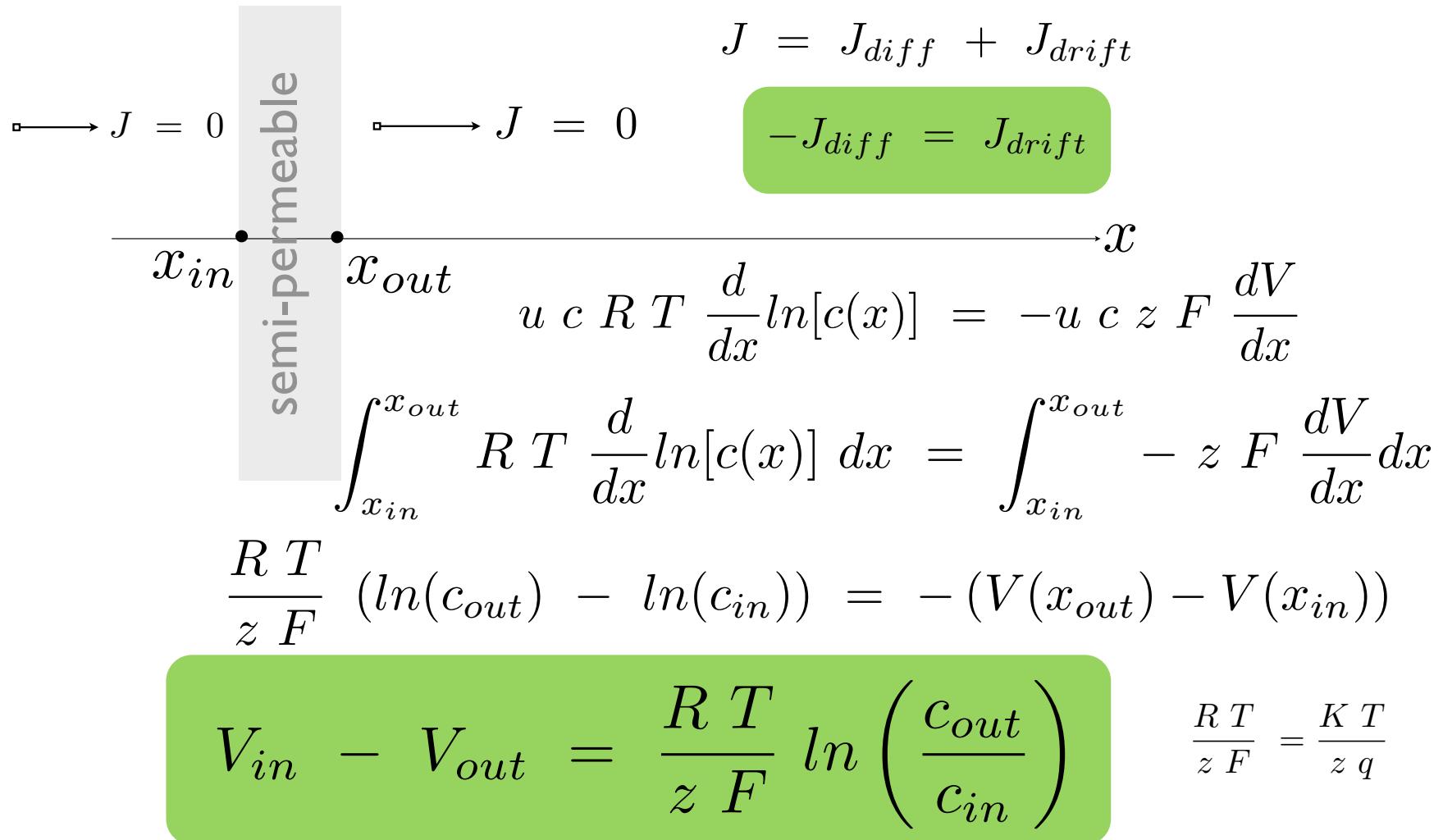


Concept of the *definite integral* (i.e. fundamental theorem)

$$\int_a^b \frac{1}{x} dx = \ln(x)|_a^b = \ln(b) - \ln(a) = \ln(b/a)$$

$$f(x_0 + h) \approx f(x_0) + \frac{df(x)}{dx}|_{x_0} h$$

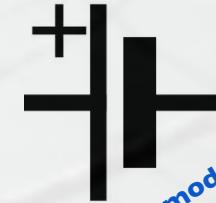
Two compartments and an existing concentration gradient
 [hp: **single** ion-specie, at **equilibrium (i.e. $J = 0$)**]



Two compartments and an existing concentration gradient
[hp: **single** ion-specie, at **equilibrium (i.e. $J = 0$)**]

Nernst equation

$$E_{Nernst} = V_{in} - V_{out} = \frac{R T}{z F} \ln \left(\frac{c_{out}}{c_{in}} \right)$$



this is a model!

Nernst equilibrium potential for that ion
or also known as “reversal potential” (more on it later)

It does NOT depend on the ion’s mobility!

$$\frac{R T}{z F} = \frac{K T}{z q} \quad \xleftarrow{T = 300^\circ, z = 1} \approx 26mV$$

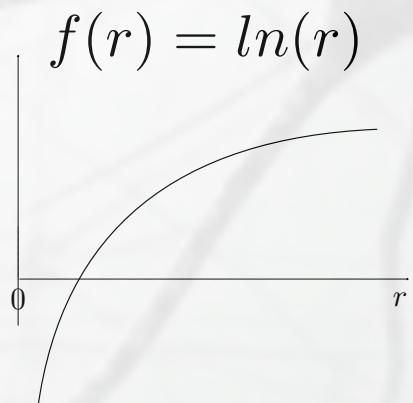


Exercise

what is the Nernst's potential for individual ionic species, at room temperature ($\sim 20^\circ\text{C} = 300\text{K}$)?

Ion	K^+	Na^+	Cl^-	Ca^{2+}
Concentration inside (mM)	400	50	40	10^{-4}
Concentration outside (mM)	20	440	560	10

from Sterratt et al., 2011



Ion	K ⁺	Na ⁺	Cl ⁻	Ca ²⁺
Concentration inside (mM)	400	50	40	10 ⁻⁴
Concentration outside (mM)	20	440	560	10

from Sterratt et al., 2011

$$E_{Nernst} = V_{in} - V_{out} = \frac{R T}{z F} \ln \left(\frac{c_{out}}{c_{in}} \right)$$

$$\begin{aligned} \frac{R T}{z F} &= \frac{K T}{z q} \\ T = 300^\circ, z = 1 & \\ \approx 26mV & \end{aligned}$$

$$K^+ \quad 26mV \ln\left(\frac{20}{400}\right) = -77.88 \text{ mV}$$

$$Na^+ \quad 26mV \ln\left(\frac{440}{50}\right) = +56.54 \text{ mV}$$

$$Cl^- \quad -26mV \ln\left(\frac{560}{40}\right) = -68.6 \text{ mV}$$

$$Ca^{2+} \quad 13mV \ln\left(\frac{10}{0.0001}\right) = +149.6 \text{ mV}$$



$$K^+ \quad 26mV \ln\left(\frac{20}{400}\right) = -77.88 \text{ mV}$$

$$Na^+ \quad 26mV \ln\left(\frac{440}{50}\right) = +56.54 \text{ mV}$$

$$Cl^- \quad -26mV \ln\left(\frac{560}{40}\right) = -68.6 \text{ mV}$$

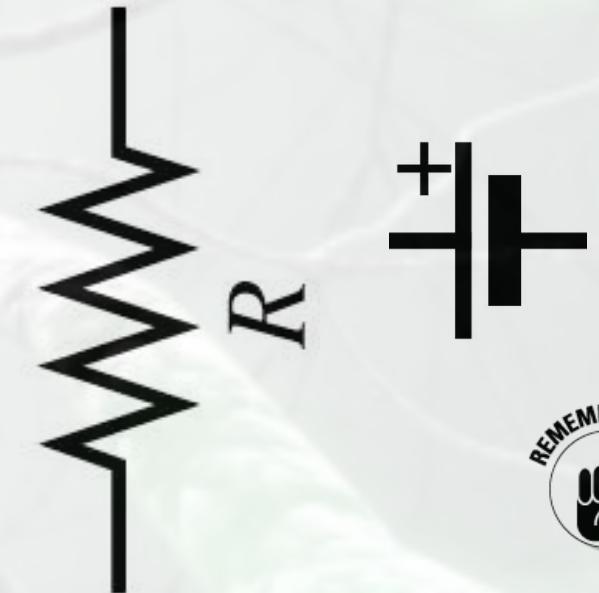
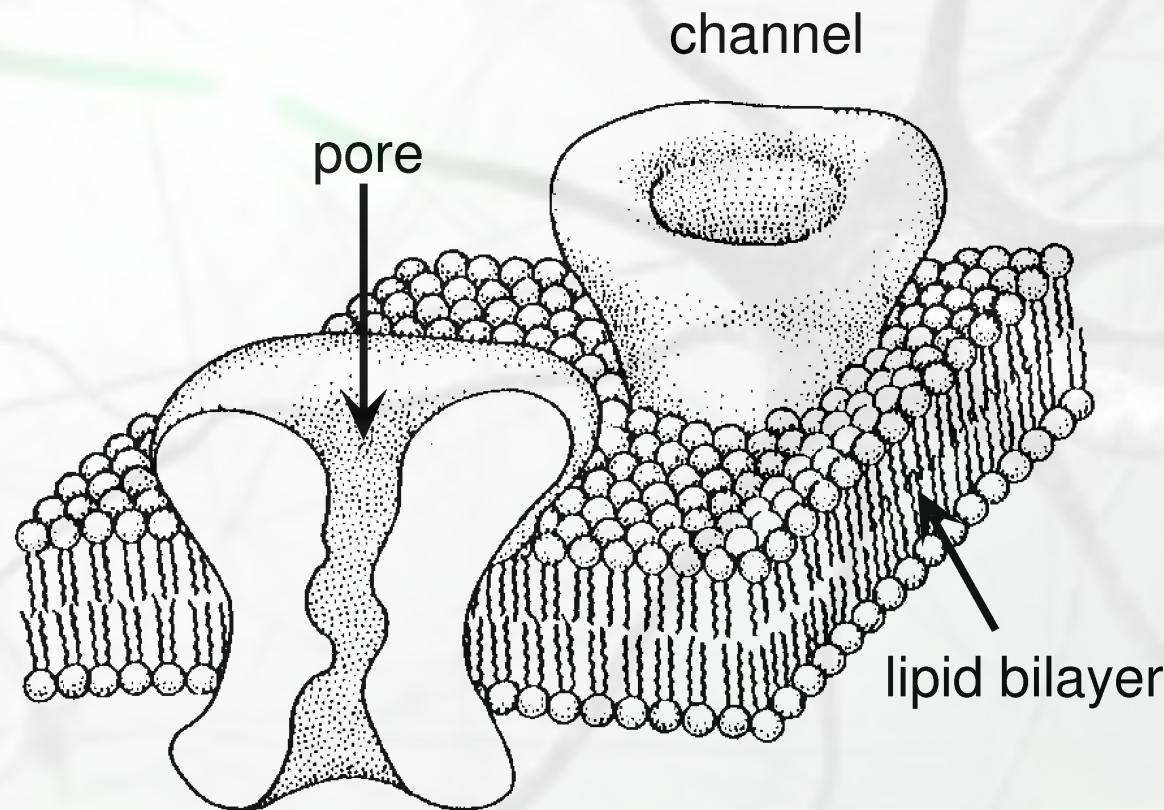
$$Ca^{2+} \quad 13mV \ln\left(\frac{10}{0.0001}\right) = +149.6 \text{ mV}$$

How to get -70mV ??

It must be from a *combination* of those equilibrium potentials.
But.. how to combine them together??

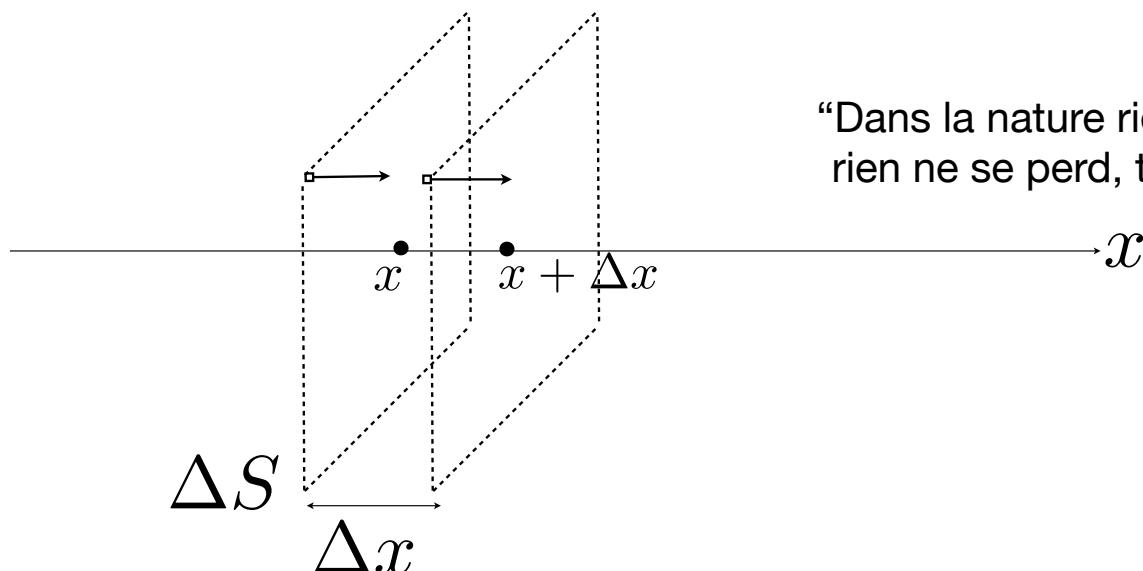
We first need to understand how ions flow across a permeable membrane !!!

Is the “resistor” model for an ion channel... complete?



Electro-diffusion equation

invoking conservation of mass for charged particles in aq. solution



“Dans la nature rien ne se crée,
rien ne se perd, tout change.”

⊗ Δt



A. Lavoisier

$$c(x, t + \Delta t) (\Delta S \Delta x) = c(x, t) (\Delta S \Delta x) + J(x, t) \Delta t \Delta S - J(x + \Delta x, t) \Delta t \Delta S$$

Electro-diffusion equation

invoking conservation of mass for charged particles in aq. solution

$$c(x, t + \Delta t) (\cancel{\Delta S} \Delta x) = c(x, t) (\cancel{\Delta S} \Delta x) + J(x, t) \Delta t \cancel{\Delta S} - J(x + \Delta x, t) \Delta t \cancel{\Delta S}$$

$$\frac{c(x, t + \Delta t) - c(x, t)}{\Delta t} = -\frac{J(x + \Delta x, t) - J(x, t)}{\Delta x}$$

$$\begin{array}{c} \downarrow \\ \Delta x \rightarrow 0 \\ \Delta t \rightarrow 0 \end{array}$$

$$\frac{\partial c(x, t)}{\partial t} = -\frac{\partial J(x, t)}{\partial x}$$

$$J = J_{diff} + J_{drift} \quad J = -D \frac{dc}{dx} - u c z F \frac{dV}{dx}$$

Electro - diffusion

Non-charged particles in aqueous solution

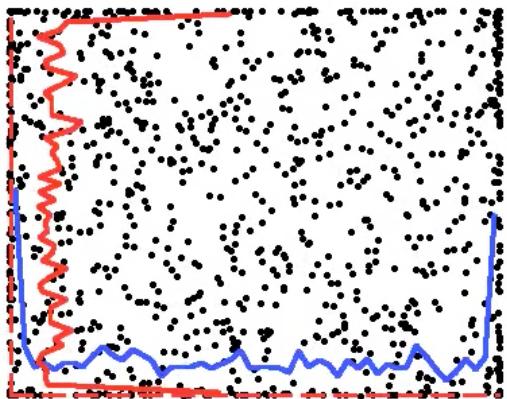
Diffusion equation

$$\frac{\partial c(x, t)}{\partial t} = - \frac{\partial J(x, t)}{\partial x} \rightarrow \frac{\partial c}{\partial t} = -D \frac{\partial^2 c}{\partial x^2}$$

at the steady-state...

$$c(x, t) = c(x)$$

$$0 = -D \frac{\partial^2 c}{\partial x^2}$$



$$c(x) = k_1 + k_2 x$$

$$J(L, t) = -D \frac{\partial c}{\partial x} |_{L=0} = 0$$

$$c(x) = k_1$$

from the Nernst equation...

$$V_{in} - V_{out} = 0$$

this is a model!

single ion-specie, semi-permeable mem., NOT @equilibrium

$$J = - u R T c \frac{d}{dx} \ln(c) - u z F c \frac{d}{dx} V$$

$$J = - u c z F \left[\frac{R T}{z F} \frac{d}{dx} \ln(c) + \frac{d}{dx} V \right]$$

F (Faraday constant)
9.6 10⁴ C mol⁻¹

$$\frac{J z F}{u c z^2 F^2} = - \left[\frac{R T}{z F} \frac{d}{dx} \ln(c) + \frac{d}{dx} V \right]$$

single ion-specie, semi-permeable mem., NOT @equilibrium

$$\int_{x_{in}}^{x_{out}} \frac{J z F}{u c z^2 F^2} dx = - \int_{x_{in}}^{x_{out}} \left[\frac{R T}{z F} \frac{d}{dx} \ln(c) + \frac{d}{dx} V \right] dx$$

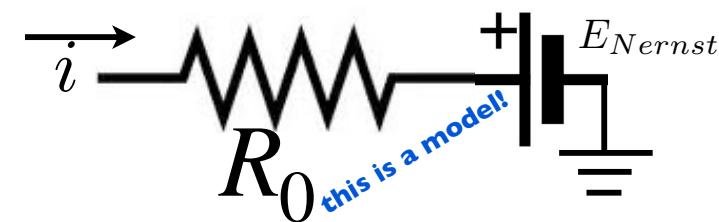
Ohmic approx
non-Ohmic approx

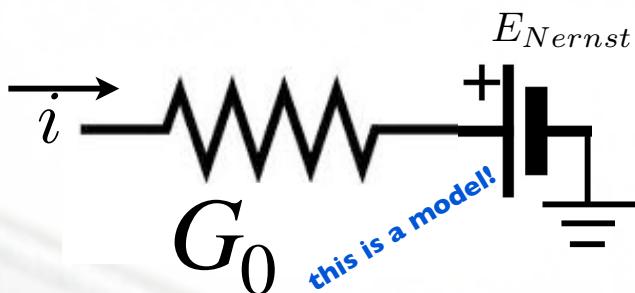
i current density

$$J(zF) \frac{1}{uz^2 F^2} \int_{x_{in}}^{x_{out}} \frac{1}{c} dx \approx -\frac{RT}{zF} \ln \frac{c_{out}}{c_{in}} + (V_{in} - V_{out})$$

$$i R_0 \approx (V_{in} - 0) - E_{Nernst}$$

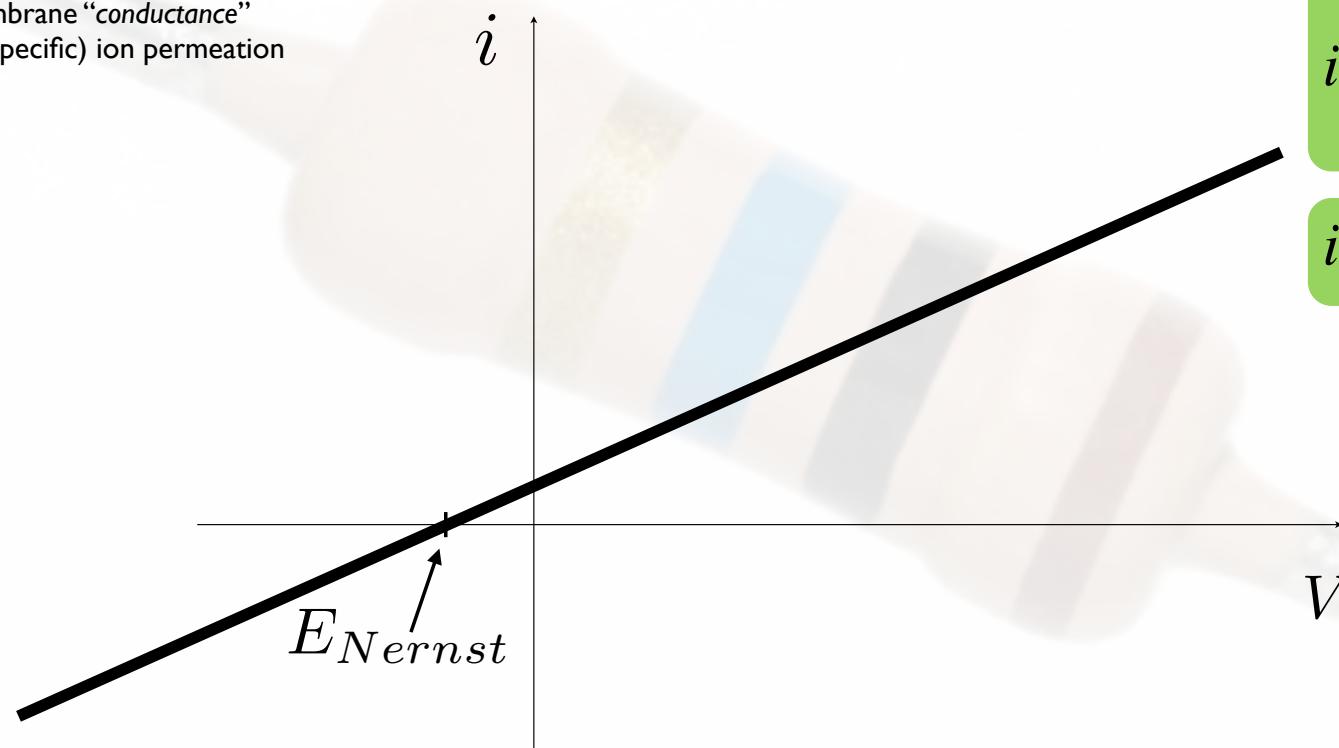
Ohmic approximation





membrane “conductance”
for a (specific) ion permeation

$$i R_0 \approx (V_{in} - 0) - E_{Nernst}$$



Nernst equilibrium potential for that ion
or also known as “reversal potential”

$$i \frac{1}{G_0} \approx (V_{in} - 0) - E_{Nernst}$$

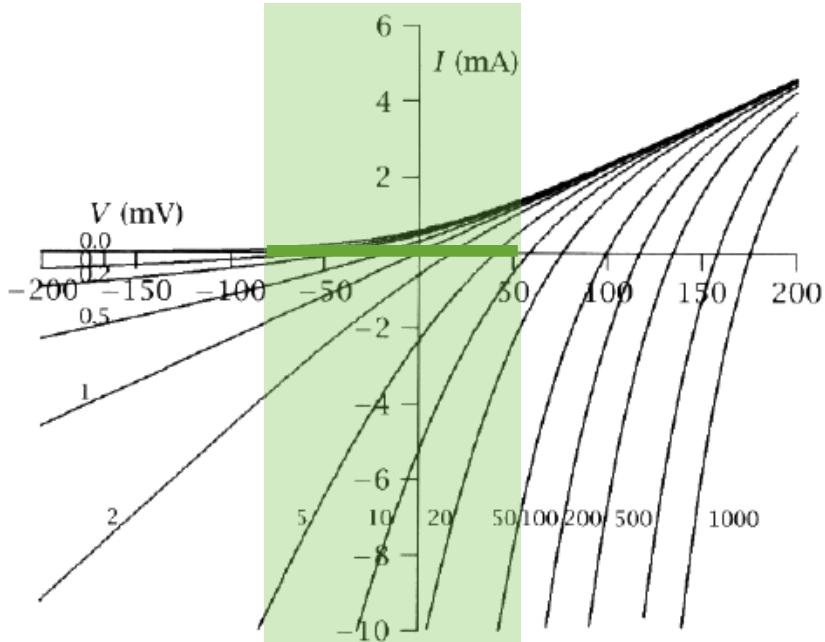
$$i \approx G_0 (V_{in} - E_{Nernst})$$

$$G_0 = 1/R_0$$



Alternatives to the Ohmic-approximation??

Goldman equation



$$J = P a V_{in} \frac{c_{out} - c_{in} e^{a V_{in}}}{1 - e^{a V_{in}}}$$

$$P = \frac{u R T}{x_{out} - x_{in}} \quad a = \frac{z F}{R T}$$

Figure 2.5 Current-voltage relations given by equation 2.7.17 (GHK current equation) for various values of $[C_{out}]/[C_{in}]$ (indicated by small numbers near each curve).

It accounts for strong (non-linear) rectification (*inward or outward*, depending on z , etc...)
 In the range of neuronal activity voltages and concentrations, often it can be approximated by a straight line (i.e. Ohmic approximation is its Taylor expansion!!)...
 e.g. For $[Ca^{++}]$ very unbalanced concentrations, the Ohmic approximation is poor!

single ion-specie, semi-permeable mem., NOT @equilibrium

Goldman equation

$$J = u c F_{ext}$$

$$J = -u R T c \frac{d}{dx} \ln(c) - u z F c \frac{d}{dx} V$$

$$D = u R T$$

$$a = \frac{z F}{R T}$$

$$h(x) = u R T c(x) e^{a V(x)}$$

$$\frac{d}{dx} h(x) = u R T \left(e^{a V(x)} \frac{d}{dx} c(x) + c(x) a e^{a V(x)} \frac{d}{dx} V(x) \right)$$

$$\frac{d}{dx} h(x) = u R T c(x) e^{a V(x)} \left(\frac{1}{c(x)} \frac{d}{dx} c(x) + a \frac{d}{dx} V(x) \right)$$

$$\frac{d}{dx} h(x) = -J e^{a V(x)}$$

single ion-specie, semi-permeable mem., NOT @equilibrium

Goldman equation

$$D = u R T$$

$$\frac{d}{dx} h(x) = -J e^a V(x)$$

$$a = \frac{z F}{R T}$$

$$\int_{x_{in}}^{x_{out}} \frac{d}{dx} h(x) dx = - \int_{x_{in}}^{x_{out}} J e^a V(x) dx$$

$$h(x_{out}) - h(x_{in}) = - \int_{x_{in}}^{x_{out}} J e^a V(x) dx$$

- hp: \mathbf{J} does **NOT** depend on x (inside the membrane).
- hp: the electric field within the membrane is **uniform**; thus $V(x)$ changes **linearly** (inside the membrane) - say $V(x) = m x + p$ (from V_{in} to V_{out})

single ion-specie, semi-permeable mem., NOT @equilibrium

Goldman equation

$$h(x_{out}) - h(x_{in}) = -J \int_{x_{in}}^{x_{out}} e^{a(mx+p)} dx$$

$$D = u R T$$

$$a = \frac{z F}{R T}$$

$$h(x_{out}) - h(x_{in}) = -J \frac{1}{a m} \left(e^{a(mx_{out}+p)} - e^{a(mx_{in}+p)} \right)$$

$$V(x) = \frac{x - x_{in}}{x_{out} - x_{in}} (V_{out} - V_{in}) + V_{in}$$

$$m = \frac{V_{out} - V_{in}}{x_{out} - x_{in}}$$

$$h(x_{out}) - h(x_{in}) = -J \frac{1}{a m} \left(e^{a V_{out}} - e^{a V_{in}} \right)$$

$$h(x_{out}) - h(x_{in}) = -J \frac{1}{a} \frac{x_{out} - x_{in}}{V_{out} - V_{in}} \left(e^{a V_{out}} - e^{a V_{in}} \right)$$

single ion-specie, semi-permeable mem., NOT @equilibrium

Goldman equation

$$h(x) = u R T c(x) e^{a V(x)}$$

$$\begin{aligned} D &= u R T \\ a &= \frac{z F}{R T} \end{aligned}$$

$$h(x_{out}) - h(x_{in}) = -J \frac{1}{a} \frac{x_{out} - x_{in}}{V_{out} - V_{in}} (e^{a V_{out}} - e^{a V_{in}})$$

$$u R T (c_{out} e^{a V_{out}} - c_{in} e^{a V_{in}}) = -J \frac{1}{a} \frac{x_{out} - x_{in}}{V_{out} - V_{in}} (e^{a V_{out}} - e^{a V_{in}})$$

$$J = u R T a \frac{V_{in} - V_{out}}{x_{out} - x_{in}} \frac{(c_{out} e^{a V_{out}} - c_{in} e^{a V_{in}})}{e^{a V_{out}} - e^{a V_{in}}}$$

single ion-specie, semi-permeable mem., NOT @equilibrium $D = u R T$

Goldman equation

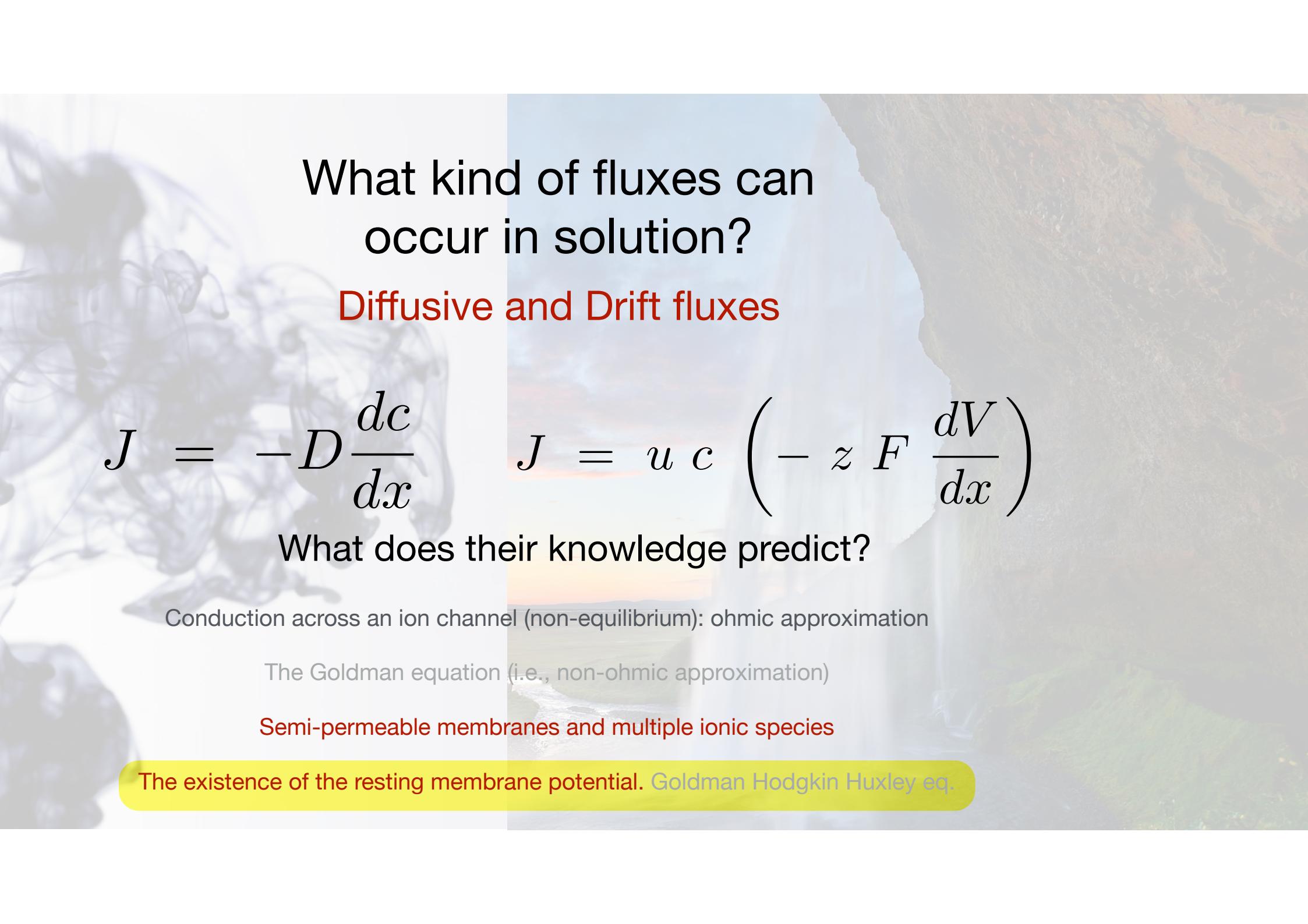
$$J = u R T a \frac{V_{in} - V_{out}}{x_{out} - x_{in}} \frac{(c_{out} e^{a V_{out}} - c_{in} e^{a V_{in}})}{e^{a V_{out}} - e^{a V_{in}}}$$

$$J = u R T a \frac{V_{in} - V_{out}}{x_{out} - x_{in}} \frac{(c_{out} - c_{in} e^{a (V_{in} - V_{out})})}{1 - e^{a (V_{in} - V_{out})}}$$

$$P = \frac{u R T}{x_{out} - x_{in}}$$

$$J = P a V_{in} \frac{c_{out} - c_{in} e^{a V_{in}}}{1 - e^{a V_{in}}}$$

$$a = \frac{z F}{R T}$$



What kind of fluxes can occur in solution?

Diffusive and Drift fluxes

$$J = -D \frac{dc}{dx}$$

$$J = u c \left(- z F \frac{dV}{dx} \right)$$

What does their knowledge predict?

Conduction across an ion channel (non-equilibrium): ohmic approximation

The Goldman equation (i.e., non-ohmic approximation)

Semi-permeable membranes and multiple ionic species

The existence of the resting membrane potential. Goldman Hodgkin Huxley eq.

The membrane potential **multiple ion-species, NOT at the equilibrium**

Many ionic species (e.g. K⁺, Na⁺, Cl⁻, Ca⁺⁺, Mg⁺⁺,...)

Biological membranes have **distinct conductances** (i.e. distinct G_h , h = Na, K, Cl...)

Ions have **distinct reversal potentials** (i.e. distinct E_h , h = Na, K, Cl...)

$$i_h = G_h(V - E_h)$$

$$G_h = 1/R_h$$

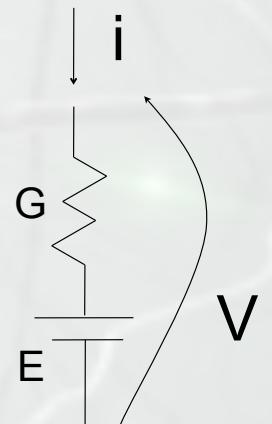
$$h = 1,2,3,\dots$$

Which is the **total** ionic current density across the membrane?

$$i_{tot} = i_1 + i_2 + i_3 + \dots$$

$$i_{tot} = G_1 (V - E_1) + G_2 (V - E_2) + G_3 (V - E_3) + \dots + G_N (V - E_N)$$

$$= (G_1 + G_2 + G_3 + \dots + G_N) V - (G_1 E_1 + G_2 E_2 + G_3 E_3 + \dots + G_N E_N)$$



The membrane potential **multiple ion-species, NOT at the equilibrium**

At “rest” (steady-state), the total current density vanishes...

This is NOT (thermodynamical) equilibrium for each specie (i.e. death)

$$\dot{i}_{tot} = 0$$

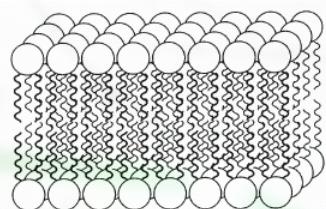
$$= (G_1 + G_2 + G_3 + \dots + G_N) V_{rest} - (G_1 E_1 + G_2 E_2 + G_3 E_3 + \dots + G_N E_N)$$

$$V_{rest} = \frac{(G_1 E_1 + G_2 E_2 + G_3 E_3 + \dots)}{(G_1 + G_2 + G_3 + \dots)}$$

It is **NOT** the algebraic sum of the individual Nernst potentials (one for each ion specie)! **Conductances** define the membrane potential!

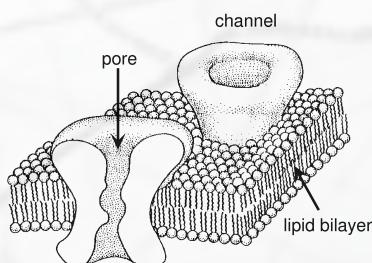


Equivalent electrical circuit models



A circuit diagram showing a capacitor symbol (two parallel lines) labeled 'c' connected in series with a voltage source 'V'. An arrow labeled 'i' indicates current flowing through the capacitor.

$$C = \frac{\Delta Q}{\Delta V} \quad i = \frac{\Delta Q}{\Delta t}$$
$$i = C \frac{dV}{dt}$$
$$c = 1 \mu F/cm^2$$



A circuit diagram showing a resistor symbol (a zigzag line) labeled 'G' connected in series with a voltage source 'V'. An arrow labeled 'i' indicates current flowing through the resistor. Above the circuit, there is a small inset diagram showing a protein channel with a wavy structure.

$$i = G (V_{in} - E)$$
$$E = \frac{RT}{zF} \ln \left(\frac{c_{out}}{c_{in}} \right)$$



Next stop: excitability

Concepts and Discoveries

1872-1905: Hermann proposed that propagation is an electrical self-stimulation of the axon **by inward currents** spreading passively from excited region to neighbouring unexcited regions;

1902-1912: Bernstein **proposed** that potentials might arise across a membrane that is selectively permeable and separates solutions of different ionic concentrations and that excitation involves an **increase in permeability**;

1938: Cole & Curtis, **experimentally did find** changes in ionic permeability

1949: Hodgkin & Katz, showed **inward currents**, by **selective permeability** to Na^+

1952: Hodgkin & Huxley, described **how ionic permeability changes in time.**