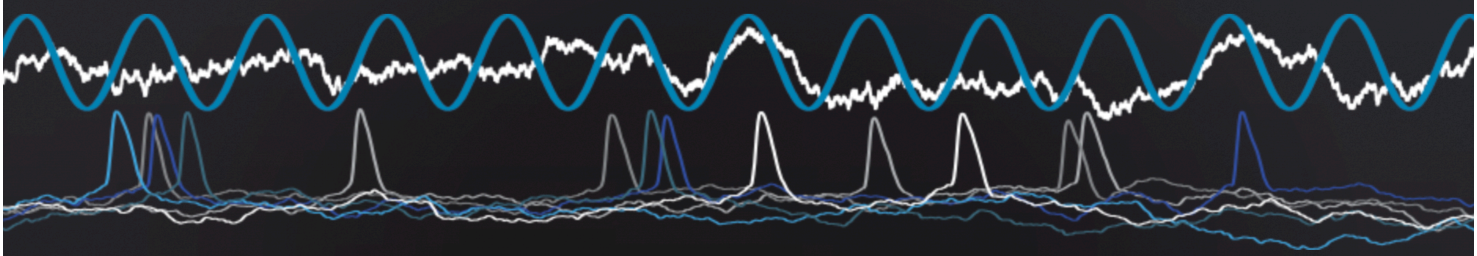
ELECTROPHYSIOLOGICAL SIGNALS



GENERATION AND CHARACTERISATION

Michele GIUGLIANO

Neuroelectronics

References for today's class content

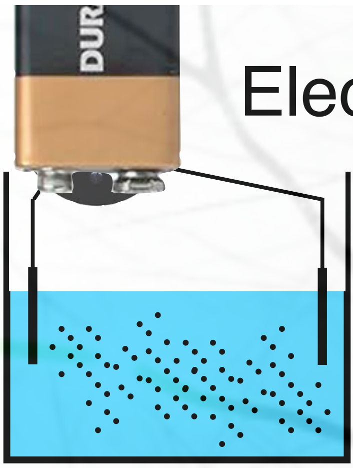
supporting <u>your</u> <u>own</u> <u>study</u> and <u>understanding</u>

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^{-})

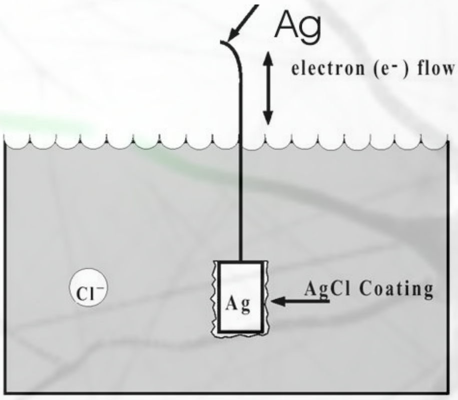
Dissociation of salts by ***solvation*** (e.g. NaCl <—> Na^{+} + Cl^{-}) into electrically charged particles. Globally, ***electroneutrality*** holds!

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 ≠ electrons, distinct “currency” for charge exchanges



$Ag + Cl^- \rightarrow$

charge is conserved

$AgCl + e^- \rightarrow Ag + Cl^-$

this is a model!

$$\Delta V = R\,I$$

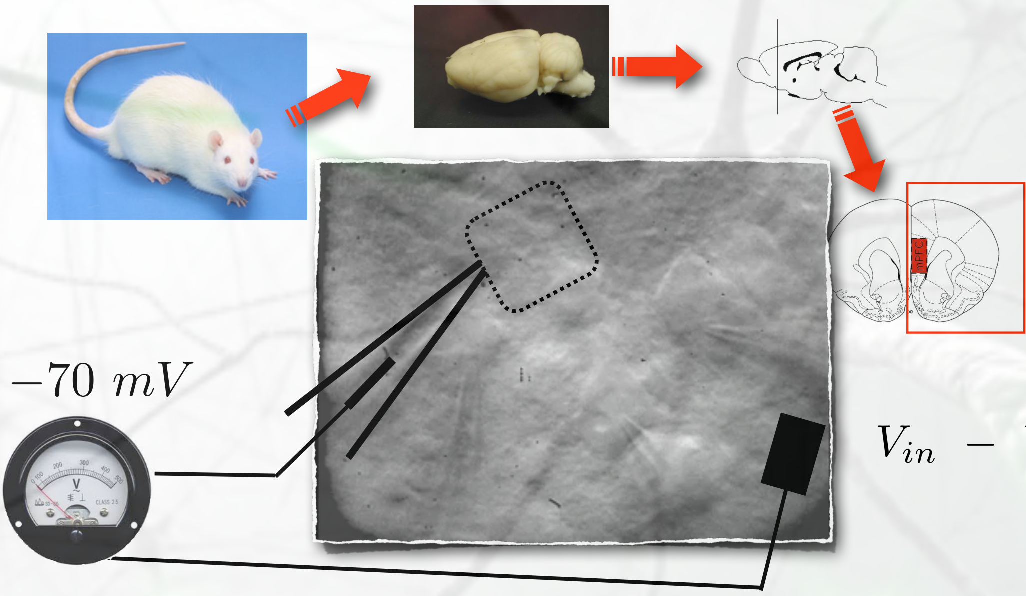
~ <u>measurement of</u> electrical potentials in solution
~ <u>“injection”</u> of external (ionic) currents

(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!)

$-70\ mV$

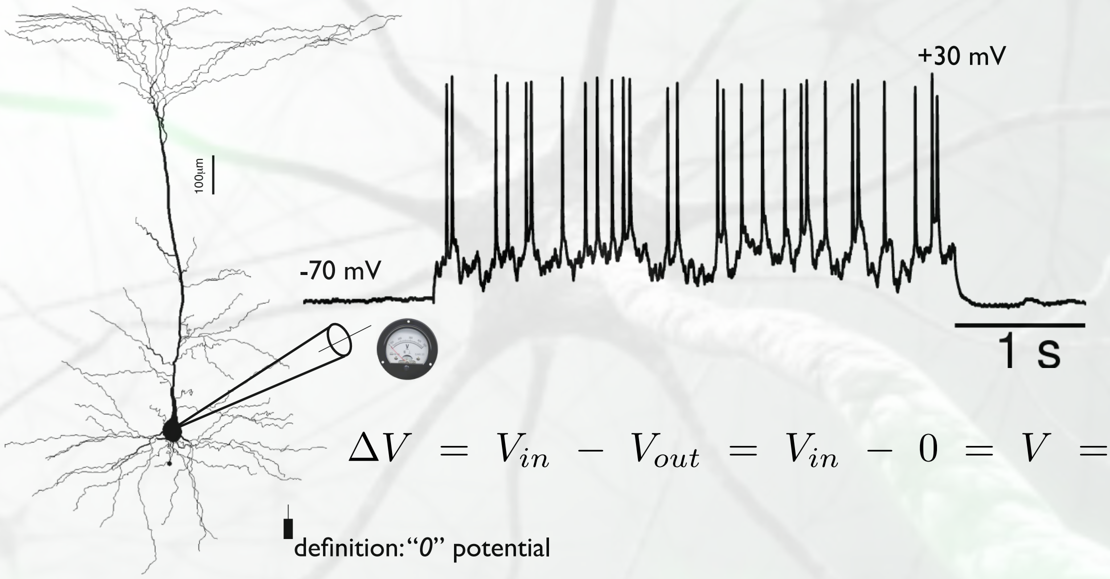


$$V_{in} - V_{out} = V_{in} - 0 = \\ = V = V_m$$

Understanding, from "first (biophysical) principles"

- the existence of a *difference* of electrical potential - across the plasmatic membrane of a *living* cell… $V_{in} - V_{out}$
  - electrical (electrostatic) potential??
    measured in 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

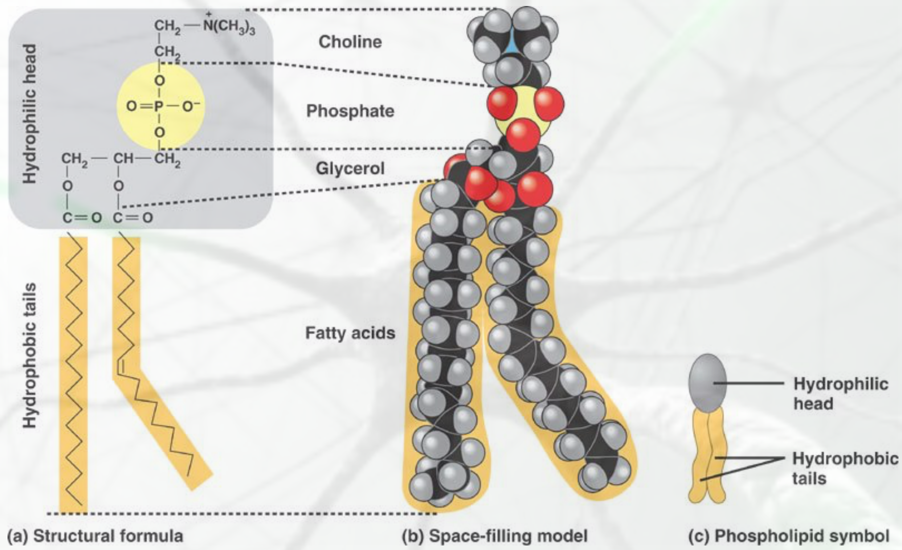


$$\Delta V = V_{in} - V_{out} = V_{in} - 0 = V = V_m$$

Origin of Bioelectricity

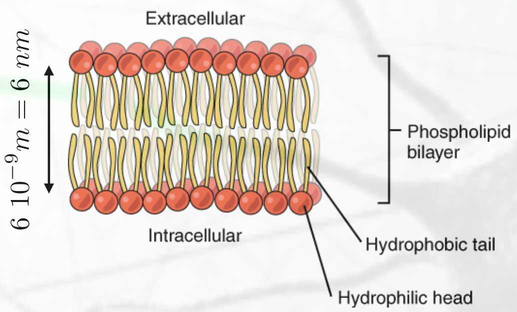
- we deal with **electrochemical systems** (in water): anions, cations
- we **measure** electrostatic potentials by **electrodes** (e.g. **AgCl** based)
- we **observe** -70mV at “rest” and swings up to +30mV in <1 ms
- we measure it across a thin membrane. What is a (cell) membrane?
- starting from **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?

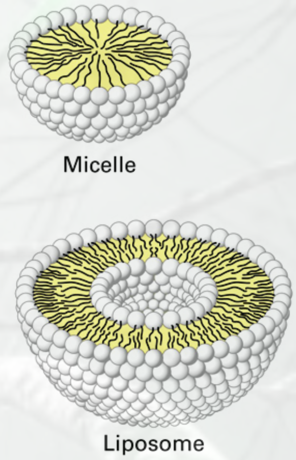
The plasmatic membrane of biological cells is (mostly) made of…



self-assembly of polymers (phospholipids)

The plasmatic membrane of biological cells is (mostly) made of…

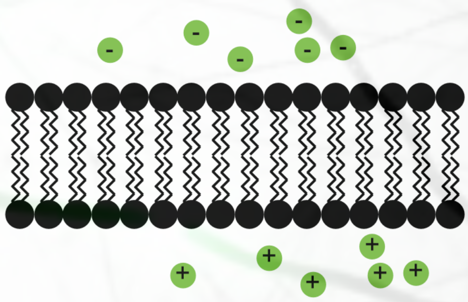




- ***hydrophilic*** heads (phosphate groups, charged)
- ***hydrophobic*** tails (fatty acids)

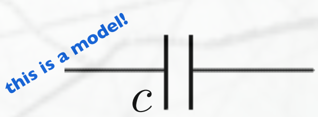
- self-organise in water, into segregated compartments (emergence of life!!)

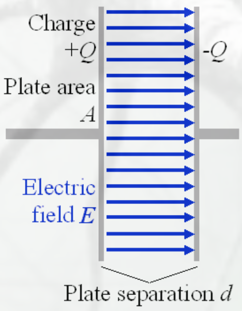
Plasmatic membrane: a physical *equivalent*?



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?





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

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

REMEMBER

Exercise

What is the membrane capacitance (per area unit) ?
What charge distribution "delta" leads to 70mV?

Unique membrane properties and enhanced signal processing in human neocortical neurons

Guy Eyal[1], Matthijs B Verhoog[2], Guilherme Testa-Silva[2], Yair Deitcher[3], Johannes C Lodder[2], Ruth Benavides-Piccione[4,5], Juan Morales[6], Javier DeFelipe[4,5], Christiaan PJ de Kock[2], Huibert D Mansvelder[2], Idan Segev[1,3*]

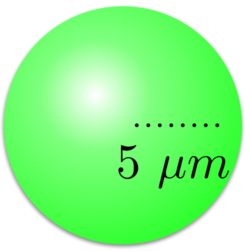
$$C \; = \; \frac{\epsilon A}{d} \qquad\qquad c \; = \; 1 \; \mu F/cm^2$$

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

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

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

Therefore, there is a difference of charge across the membrane!

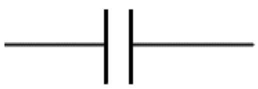


$523 \; 10^8 ions$ *50 billions*

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

$1.6 \; 10^{-19} C/ion$ $\quad 2.56 \; 10^{-11} C/\mu m^2$

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



$70mV$

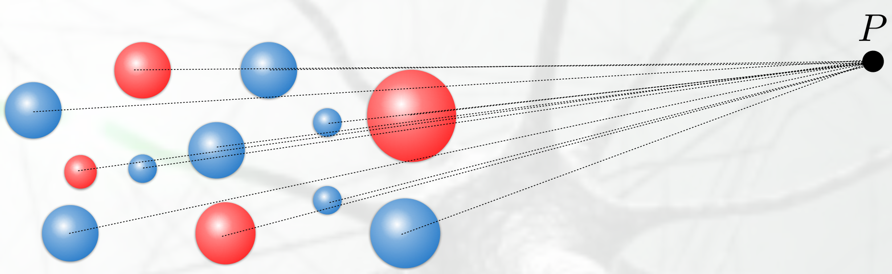
$$\frac{10^{-15}}{1.6 \; 10^{-19}} \; ions/\mu m^2 \approx 6 \; 10^3$$

$\boxed{\text{~1000 ions of difference, across the membrane}}$

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



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

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!

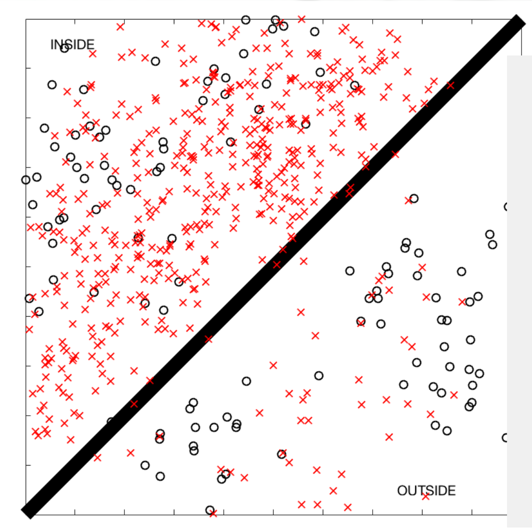
Exercise: (discrete) distribution of charge
anchored/fix/glued in free space
(restrained from self-organising)

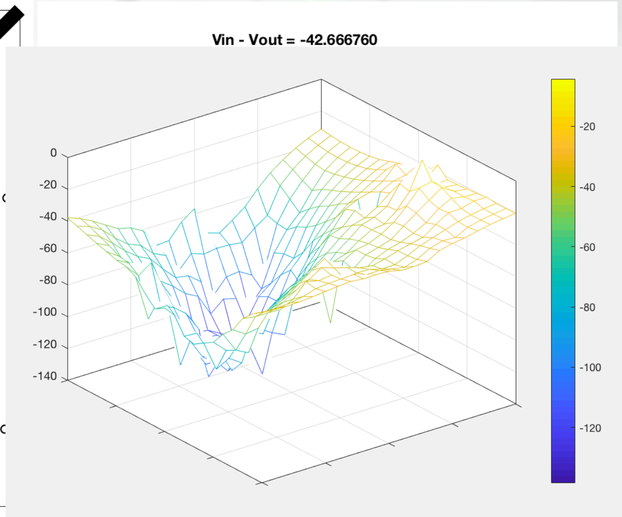
Given the potential (measured),
which is the corresponding distribution of charge??
?????

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

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

$$\Delta V = V_{in} - V_{out} \overset{?????}{} -70\ mV$$

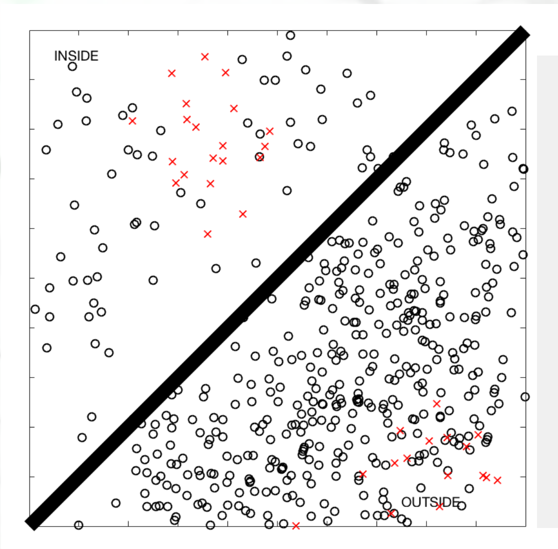


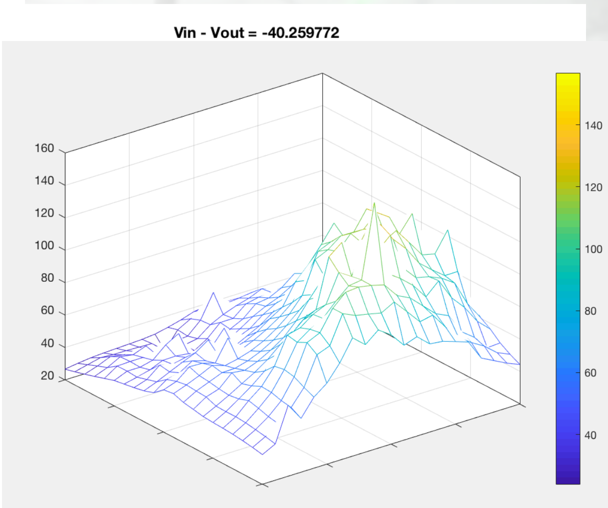


o: positively charged ions
x: negatively charged ions

Negative ions inside..

$$\Delta V = V_{in} - V_{out} \overset{?????}{} -70\ mV$$





o: positively charged ions
x: negatively charged ions

Unequal distribution of positive ions..

Important points

- ion**s** 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…

The existence of a (resting) membrane potential: **facts**

• global electro-neutrality holds => **isopotential** inside & outside the cell

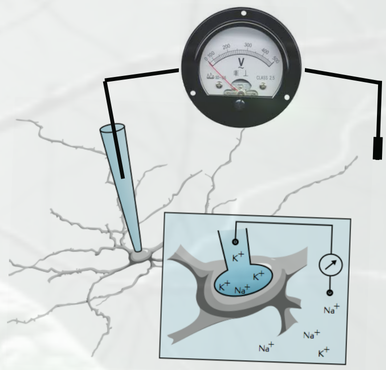
• ions species (Na^+, K^+, Cl^-,…) are distributed differently inside & outside

• 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 ~ -70 mV

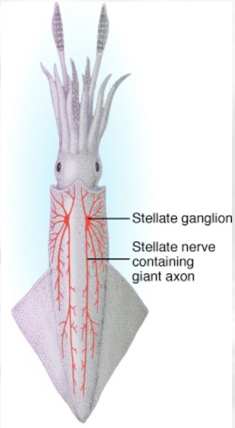
• in excitable cells, V may change abruptly in time
(e.g., neurons, myocytes, pancreatic β-cells)



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

REMEMBER

Why is there an electric potential across the cell membrane?

SPOILER

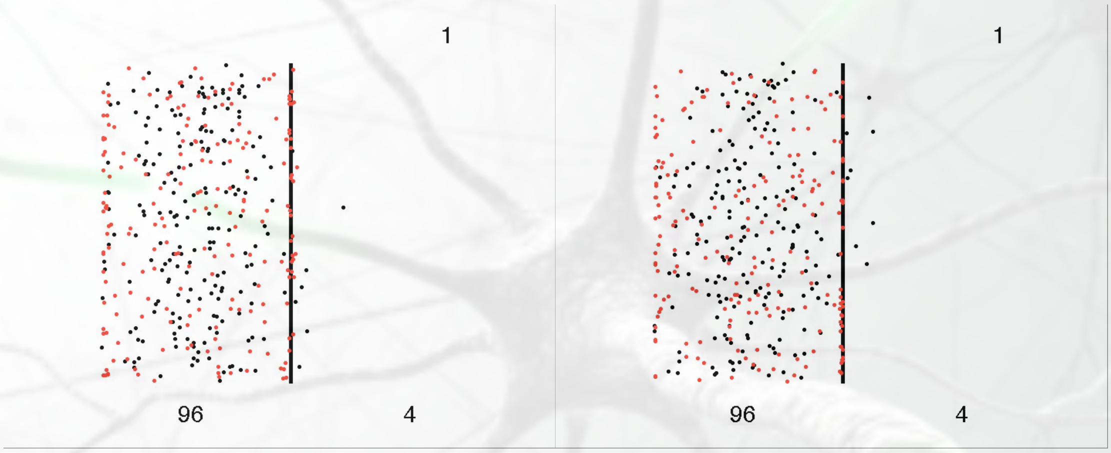
Because of a **heterogeneous distribution** of charges, across the membrane,…

…due to its semi-permeability!

REMEMBER

multiple ion-species, **NOT at the equilibrium**
distinct concentrations

Semi-permeability… really? YES



permeable (non-selective) membrane

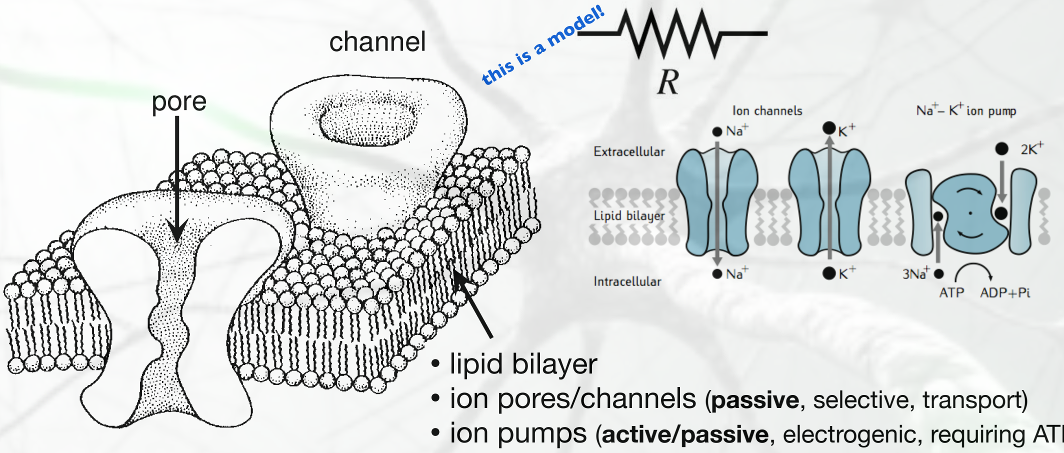
semi-permeable (selective, *black*-only) membrane

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

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?

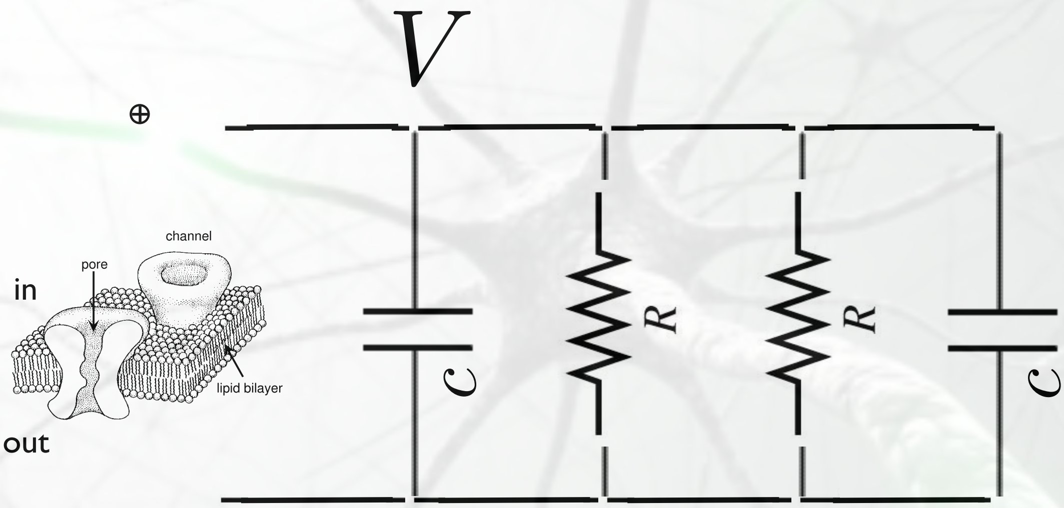
The plasmatic cell membrane is *selectively* permeable to specific ions



- lipid bilayer
- ion pores/channels (**passive**, selective, transport)
- ion pumps (**active/passive**, electrogenic, requiring ATP)

REMEMBER

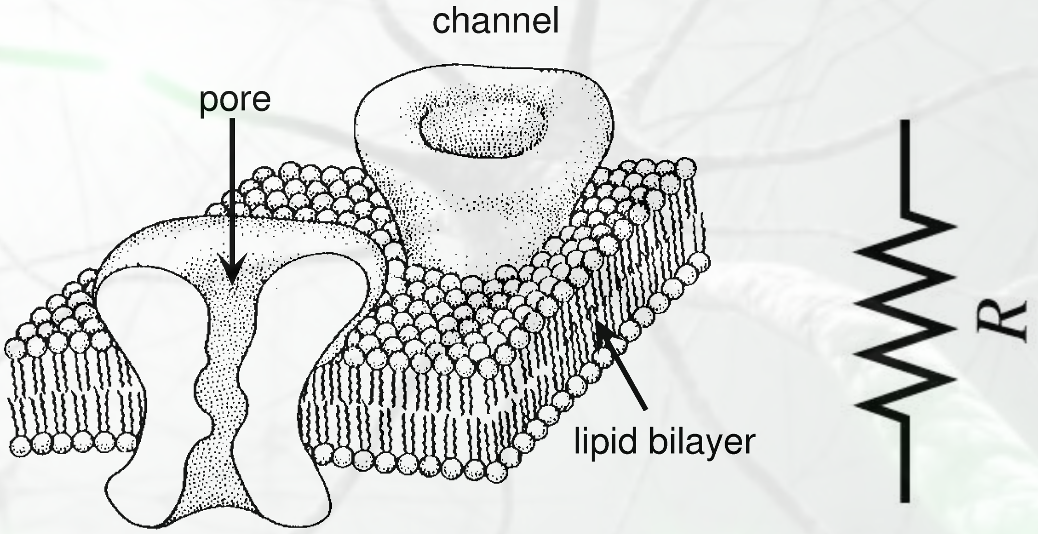
Towards a physical equivalent (electrical) circuit of the plasmatic cell membrane



REMEMBER

Is the “resistor” a good model for an ion channel…?

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



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

- 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

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

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)

REMEMBER

The phenomenon of (electro-)diffusion

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

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

Concept of (Taylor's) *expansion* into a *series of polynomials*

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

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

Walther Nernst
(1864-1941)

$$\longrightarrow J = 0 \qquad \longrightarrow J = 0$$

semi-permeable

x_{in} x_{out} x

$$J = J_{diff} + J_{drift}$$

$$\boxed{-J_{diff} = J_{drift}}$$

$$u\ c\ R\ T\ \frac{d}{dx} ln[c(x)] = -u\ c\ z\ F\ \frac{dV}{dx}$$

$$\int_{x_{in}}^{x_{out}} R\ T\ \frac{d}{dx} ln[c(x)]\ dx = \int_{x_{in}}^{x_{out}} -\ z\ F\ \frac{dV}{dx} dx$$

$$\frac{R\ T}{z\ F}\ (ln(c_{out}) - ln(c_{in})) = -(V(x_{out}) - V(x_{in}))$$

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

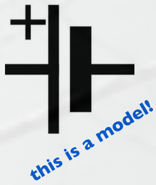
$$\frac{R\ T}{z\ F} = \frac{K\ T}{z\ q}$$

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

Walther Nernst
(1864-1941)

Nernst equation

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



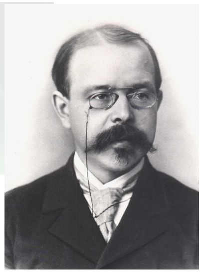
<u>Nernst equilibrium potential</u> for that ion
or also known as "reversal potential" (more on it later)

It does NOT depend on the ion's mobility!

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

Exercise

what is the Nernst's potential for individual ionic species, at room temperature (~20C = 300K)?



Walther Nernst
(1864-1941)

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

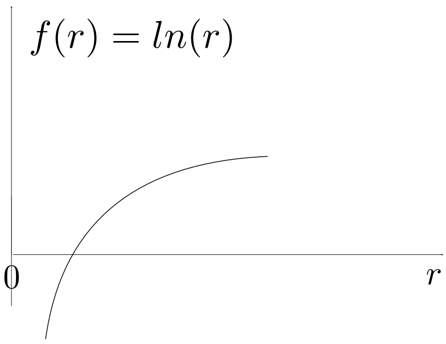
from Sterratt et al., 2011

K^+

Na^+

Cl^-

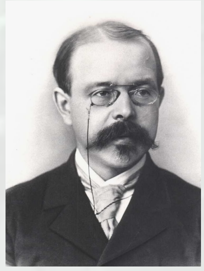
Ca^{2+}



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

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



Walther Nernst
(1864-1941)

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

$$K^+ \qquad 26mV\ ln(\frac{20}{400}) = -77.88\ mV$$
$$Na^+ \qquad 26mV\ ln(\frac{440}{50}) = +56.54\ mV$$
$$Cl^- \qquad -26mV\ ln(\frac{560}{40}) = -68.6\ mV$$
$$Ca^{2+} \qquad 13mV\ ln(\frac{10}{0.0001}) = +149.6\ mV$$

How to get -70mV ??

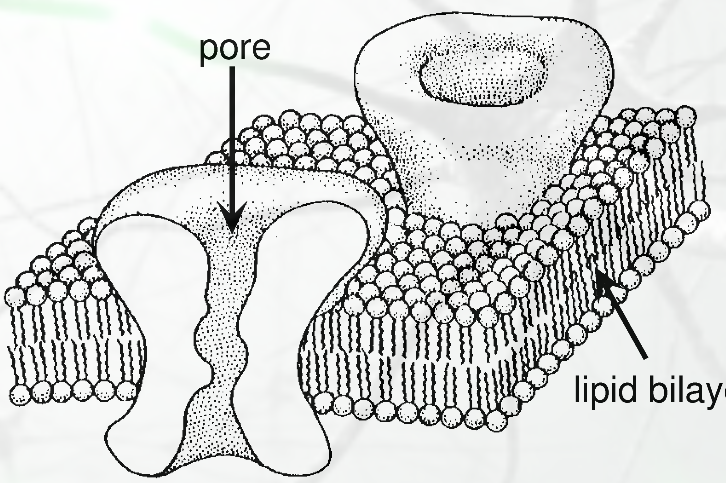
It must be from a *combination* of those potentials.

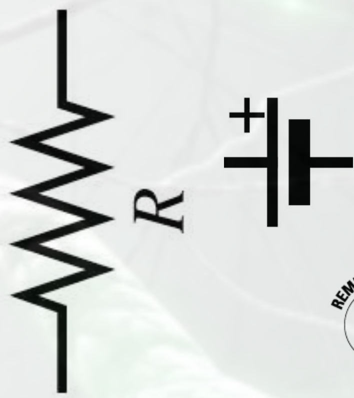
But.. how to combine them together??

Is the "resistor" a good model for an ion channel…?

NOT ONLY A RESISTOR

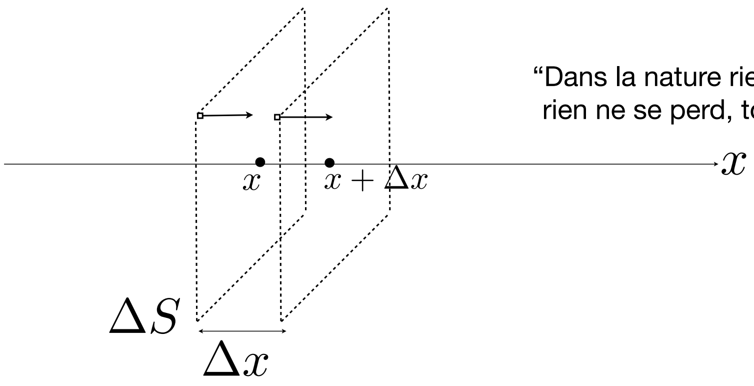
We first need to understand how ions flow across a permeable membrane !!!





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

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

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

$$\Big\downarrow \begin{matrix} \Delta x \to 0 \\ \Delta t \to 0 \end{matrix}$$

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

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

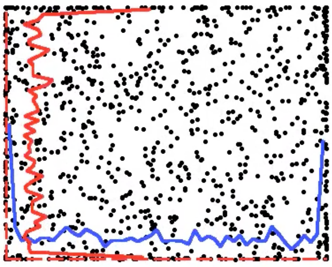
Non-charged particles in aqueous solution

Diffusion equation

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

at the steady-state...

$$c(x,t) = c(x) \qquad \boxed{0 = -D\frac{\partial^2 c}{\partial x^2}}$$



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

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

$$c(x) = k_1$$

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)
$9.6\ 10^4$ 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

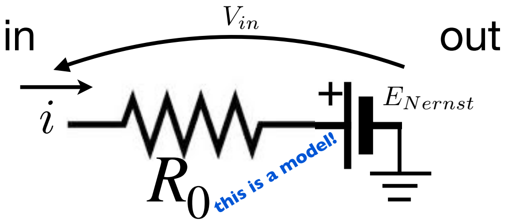
non-Ohmic approx

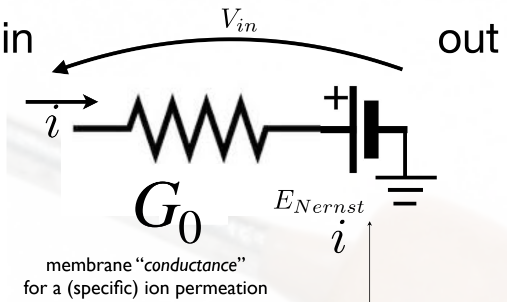
i current density

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

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

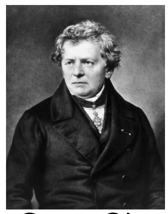
Ohmic approximation



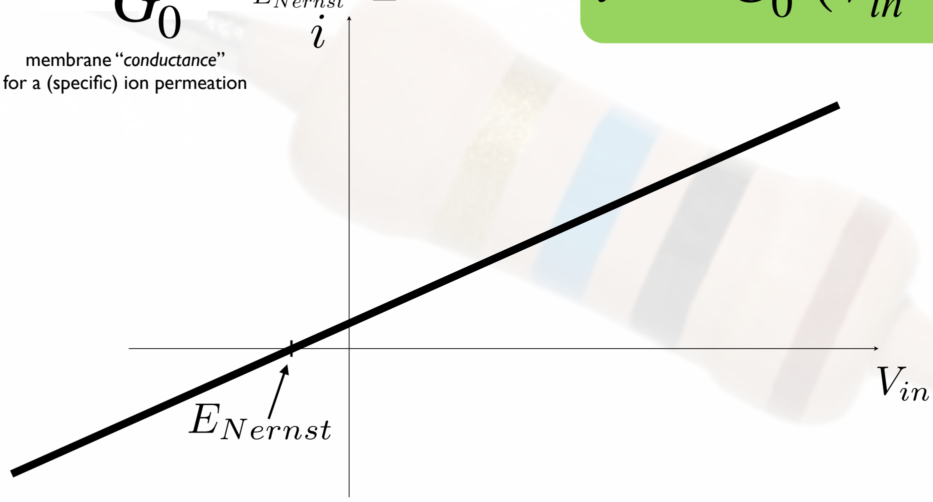


$$i\ R_0 \approx (V_{in} - 0) - E_{Nernst}$$

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



Georg Ohm (1789-1854)



$$G_0 = 1/R_0$$

This value is the *Nernst equilibrium potential* for that ionic species, or also known as "**reversal potential**"!

Alternatives to the Ohmic-approximation??

Goldman equation!

David E. Goldman (1910–1998)

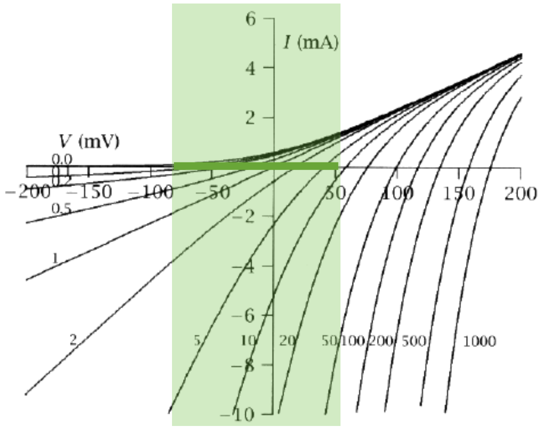


Figure 2.5 Current-voltage relations given by equation 2.7.17 (GHK current equation) for various values of $[C]_{out}/[C]_{in}$ (indicated by small numbers near each curve).

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

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

- It accounts for strong (**non-linear**) **rectification** (*in*ward or *out*ward, 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: derivation!

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

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

$$D = u\, R\, T$$

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

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

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

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

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

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

Goldman equation: derivation!

$$D = u\, R\, T$$

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

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

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

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

- hp: **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 Vin to Vout)

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

Goldman equation: derivation!

$$D = u\, R\, T$$

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

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

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

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

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

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

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

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

Goldman equation: derivation!

$$D = u\,R\,T$$

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

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

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

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

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

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

Goldman equation: derivation!

$$D = u\,R\,T$$

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

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

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

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

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

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

Goldman equation: Taylor series expansion?

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

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

$$J(V_{in}) = P\,a\,V_0\,\frac{c_{out} - c_{in}e^{a\,V_{in}}}{1 - e^{a\,V_{in}}}$$

$$V_0 = \frac{RT}{zF}\ln\frac{c_{out}}{c_{in}}$$

$$J(V) \approx J(V_0) + \frac{d}{dV}J(V)|_{V_0}\,(V - V_0)$$

Note:

$$c_{out} - c_{in}e^{\ln c_{out}/c_{in}} = 0$$

$$J(V_0) = P\,a\,V_0\,\frac{c_{out} - c_{in}e^{a\,V_0}}{1 - e^{a\,V_0}} = 0$$

$$\frac{d}{dV}J(V)|_{V_0} = P\,a\,\frac{c_{in}c_{out}}{c_{in} - c_{out}}\ln\frac{c_{out}}{c_{in}} = \frac{uzF}{x_{out} - x_{in}}\,\boxed{\frac{c_{in}c_{out}}{c_{in} - c_{out}}\ln\frac{c_{out}}{c_{in}}}$$

always < 0

What kind of fluxes can occur in solution?

Diffusive and Drift fluxes

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

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.

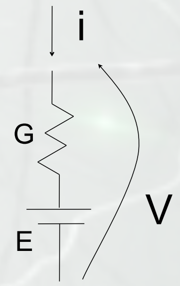
The membrane potential

multiple ion-species, NOT at the equilibrium

<u>Many</u> ionic species (e.g. K^+, Na^+, Cl^-, Ca^{++}, Mg^{++},...)

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

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



$$i_h = G_h(V - E_h) \qquad G_h = 1/R_h \qquad h = 1,2,3,...$$

Which is the **<u>total</u>** ionic current density across the membrane?

$$i_{tot} = i_1 + i_2 + i_3 + ...$$

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

$$= (G_1 + G_2 + G_3 + ... + G_N)\ V - (G_1E_1 + G_2E_2 + G_3E_3 + ... + G_NE_N)$$

The membrane potential

multiple ion-species, NOT at the equilibrium

<u>At "rest" (steady-state)</u>, the **<u>total</u> current density vanishes...**
This is NOT (thermodynamical) equilibrium for each specie (i.e. death)

$$i_{tot} \ = \ 0$$

$$= (G_1 + G_2 + G_3 + ... + G_N)\ V_{rest} - (G_1E_1 + G_2E_2 + G_3E_3 + ... + G_NE_N)$$

$$V_{rest} = \frac{(G_1E_1 + G_2E_2 + G_3E_3 + ...)}{(G_1 + G_2 + G_3 + ...)}$$

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

Goldman Hodgkin Katz equation

$$J_1 = P_1\, a\, V_{in} \frac{c_{out\ 1} - c_{in\ 1}\, e^{a\ V_{in}}}{1 - e^{a\ V_{in}}}$$

$$J_2 = P_2\, a\, V_{in} \frac{c_{out\ 2} - c_{in\ 2}\, e^{a\ V_{in}}}{1 - e^{a\ V_{in}}}$$

$$\vdots$$

$$J_k = P_k\, a\, V_{in} \frac{c_{out\ k} - c_{in\ k}\, e^{a\ V_{in}}}{1 - e^{a\ V_{in}}}$$

$$\vdots$$

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

hp: z is exactly the same for all ionic species
(a does not depend on k)

$$J_{tot} = a \frac{V_{in}}{1 - e^{a\ V_{in}}} \left(\sum_k P_k c_{out\ k} - e^{a\ V_{in}} \sum_k P_k c_{in\ k} \right)$$

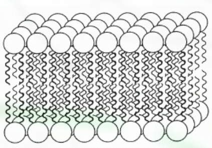
$$J_{tot} = 0 \longrightarrow \sum_k P_k c_{out\ k} = e^{a\ V_{in}} \sum_k P_k c_{in\ k}$$

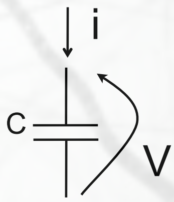
"Weighted sum"

$$\boxed{V_{rest} = \frac{RT}{zF} \ln \left(\frac{\sum_k P_k c_{out\ k}}{\sum_k P_k c_{in\ k}} \right)}$$

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

Equivalent electrical **circuit models**



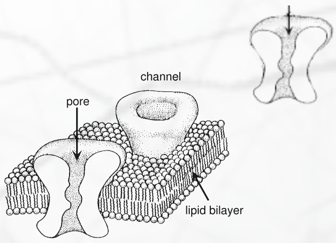


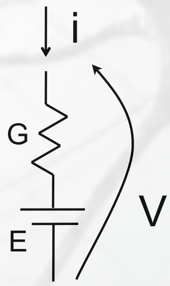
$$C = \frac{\Delta Q}{\Delta V}$$

$$i = \frac{\Delta Q}{\Delta t}$$

$$i = C\, \frac{dV}{dt}$$

$$c = 1\ \mu F/cm^2$$





$$i = G\ (V_{in} - E)$$

$$E = \frac{RT}{zF}\, ln \left(\frac{c_{out}}{c_{in}} \right)$$

REMEMBER

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 <u>**how**</u> **ionic permeability changes in time.**