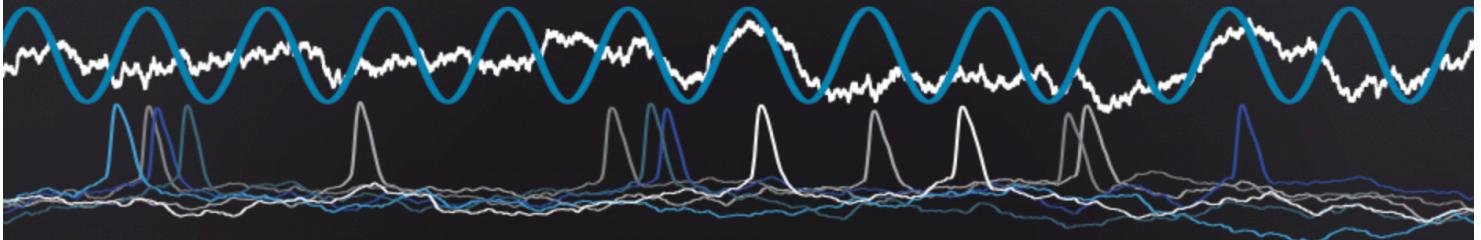


ELECTROPHYSIOLOGICAL SIGNALS



GENERATION AND CHARACTERISATION

Michele GIUGLIANO

Preliminaries in 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*”

Biophysics

definitions & refresher

- **density** or **concentration** of particles, in space
- Coulomb's **Force**, Electric **Field** and its **Potential**
- **mobility** of a particle in a fluid
- **flux** of particles through space

Some math concepts useful to us...



Richard P. Feynman,
The Character of Physical Law

“Mathematics is a language plus reasoning;
it is like a language plus logic.
Mathematics is a tool for reasoning.”

“If you want to learn about nature, to appreciate nature,
it is necessary to understand the language that she speaks in!”

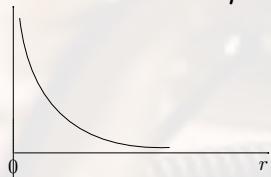


I mean it.

Graph of some notable functions



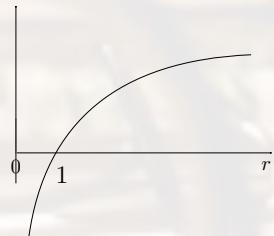
$$f(r) = \frac{1}{r}$$



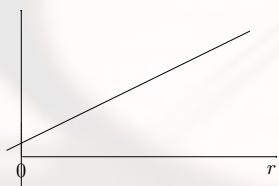
$$f(r) = (1 - e^{-\alpha r})$$



$$f(r) = \ln(r)$$



$$f(r) = m r + p$$



Concept of (first) derivative of a mathematical function



$$f(x) = \text{constant} \quad \frac{df(x)}{dx} =$$

$$f(x) = \frac{1}{x} \quad \frac{df(x)}{dx} =$$

$$f(x) = \ln(x) \quad \frac{df(x)}{dx} =$$

Derivative of a sum of functions ==>

$$\frac{d[f(x) + g(x)]}{dx} =$$

Derivative of a composite function ==>

$$\frac{dG(H(x))}{dx} = \quad \frac{d}{dx} \ln(c(x)) =$$

Concept of (first) derivative of a mathematical function



$$f(x) = \text{constant} \quad \frac{df(x)}{dx} = 0$$

$$f(x) = \frac{1}{x} \quad \frac{df(x)}{dx} = -\frac{1}{x^2}$$

$$f(x) = \ln(x) \quad \frac{df(x)}{dx} = \frac{1}{x}$$

Derivative of a sum of functions ==> sum of the derivatives!

$$\frac{d[f(x) + g(x)]}{dx} = \frac{df(x)}{dx} + \frac{dg(x)}{dx}$$

Derivative of a composite function ==> chain rule!

$$\frac{dG(H(x))}{dx} = \frac{dG(H)}{dH} \frac{dH(x)}{dx} \quad \frac{d}{dx} \ln(c(x)) = \frac{1}{c(x)} \frac{dc(x)}{dx}$$



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

$$f(x_0 + h) \approx$$



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

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



**First-order ordinary differential equation,
non-homogenous** (i.e. with constant “*external input term*”)

$$\frac{df(x)}{dx} = -af(x) + B \quad f(x) =$$



**First-order ordinary differential equation,
non-homogenous** (i.e. with constant “*external input term*”)

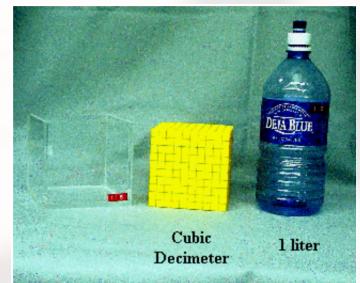
$$\frac{df(x)}{dx} = -af(x) + B \quad f(x) = ke^{-ax} + B/a$$



The Prefixes Used with SI Units

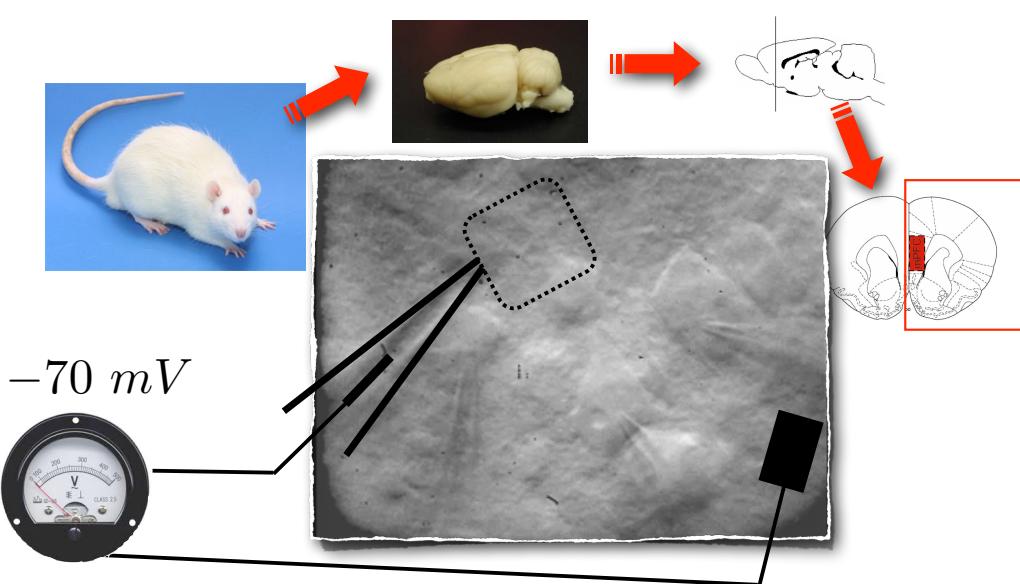
Prefix	Symbol	Meaning	Scientific Notation
exa-	E	1,000,000,000,000,000,000	10^{18}
peta-	P	1,000,000,000,000,000	10^{15}
tera-	T	1,000,000,000,000	10^{12}
giga-	G	1,000,000,000	10^9
mega-	M	1,000,000	10^6
kilo-	k	1,000	10^3
hecto-	h	100	10^2
deka-	da	10	10^1
—	—	1	10^0
deci-	d	0.1	10^{-1}
centi-	c	0.01	10^{-2}
milli-	m	0.001	10^{-3}
micro-	μ	0.000 001	10^{-6}
nano-	n	0.000 000 001	10^{-9}
pico-	p	0.000 000 000 001	10^{-12}
femto-	f	0.000 000 000 000 001	10^{-15}
atto-	a	0.000 000 000 000 000 001	10^{-18}

$$1 \text{ litre} = 1 \text{ dm}^3$$



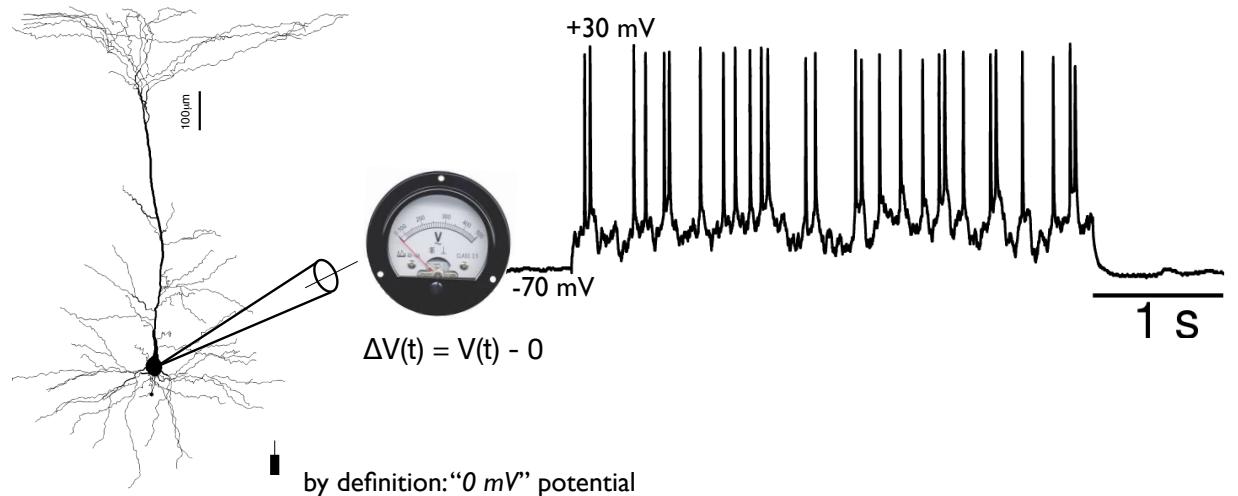
Why bother with biophysics of electrolytes, membranes, electrodes,...??

Understand why/how all cells have a membrane potential ("at rest")



Why are we bothering with biophysics of electrolytes, membranes, electrodes, etc???

Essential to understand the generation of ePhys signals **excitable electrical properties** of the cell membrane of neurons

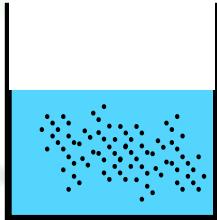


Biophysics definitions & refresher

- **density or concentration** of particles, in space
- Coulomb's **Force**, Electric **Field** and its **Potential**
- **mobility** of a particle in a fluid
- **flux** of particles through space

“density” and “concentration” are.. the same!

(e.g. aiming at describing a solute in an electrolyte)



density of molecules per unit of volume

$$\rho(x, y, z, t) = \frac{\text{number in a small Vol}}{\text{Vol}} = \frac{\text{num}}{\text{cm}^3}$$

concentration of molecules per liter

$$C(x, y, z, t) = \frac{\text{moles}}{\text{litre}} = \text{Molarity}$$

$$1 \text{ mole} = 6.022 \cdot 10^{23} \text{ molecules} = \frac{\text{Avogadro's number}}{\text{Molecular Weight}} \cdot \text{M.W. (grams)}$$

$$1 \text{ litre} = 1 \text{ dm}^3 = 1000 \text{ cm}^3$$



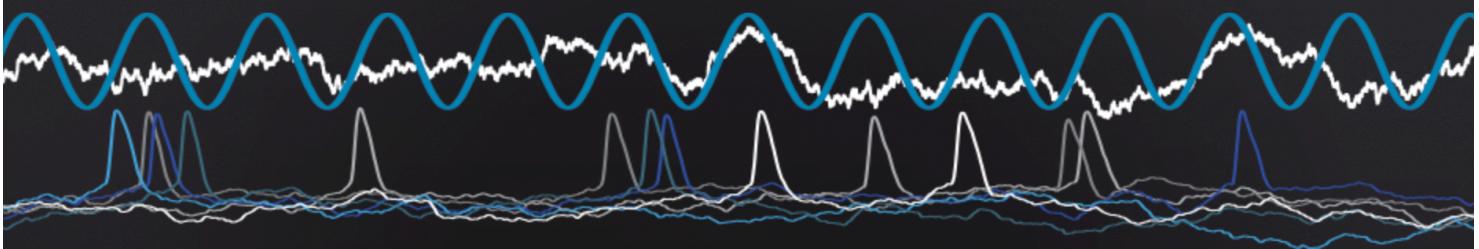
$$[Na^+] = 1 \text{ mM} = 10^{-3} \frac{\text{moles}}{\text{litre}} = \\ 10^{-3} \frac{6 \cdot 10^{23}}{1000 \text{ cm}^3} = 6 \cdot 10^{17} \frac{\text{ions}}{\text{cm}^3}$$



...as there are atoms in 12 grams of pure carbon-12 (^{12}C), the isotope of carbon.

$$\rho = N_A c$$

ELECTROPHYSIOLOGICAL SIGNALS



GENERATION AND CHARACTERISATION

Michele GIUGLIANO

Preliminaries in Neuroelectronics

ATTENDANCE TRACKING - **code ???**

(for statistical purposes only)

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

Neuroelectronics

- If not “dead” any biological cell display an **electrostatic potential (at “rest”)**: is it **positive**? is it **negative**? **How large** in neurons?
- Avogadro’s number: how many particles in a mole?



Exercise for you

- how many ions in a spherical cell, filled with a 150mM K-solution ?
- if all distribute near the membrane, which is the ions surface density?

$$Volume = \frac{4}{3}\pi r^3 = \frac{4}{3}\pi 125\mu m^3 \approx 523\mu m^3$$



$523 \cdot 10^8 \text{ ions}$ **50 billions**

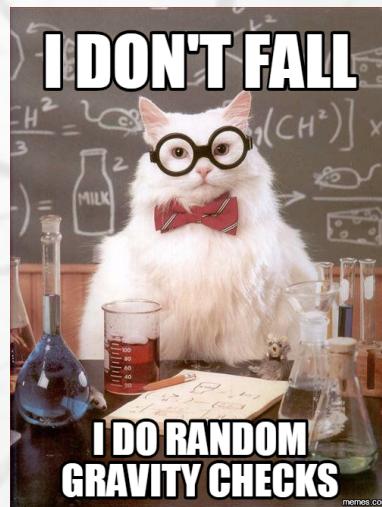
$$\text{Area} = 4\pi r^2 = 4 \pi 25\mu m^2 \approx 314\mu m^2$$
$$1.6 \cdot 10^8 \text{ ions}/\mu m^2 \quad (\text{shell})$$

$$[K^+] = 150 mM = 150 \cdot 6 \cdot 10^{17} \text{ ions}/cm^3$$
$$= 900 \cdot 10^{17} \text{ ions}/(10^{12} \mu m^3) \approx 10^8 \text{ ions}/\mu m^3$$

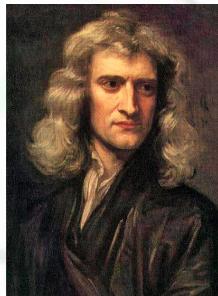
Biophysics definitions & refresher

- **density or concentration** of particles, in space
- Coulomb's **Force**, Electric **Field** and its **Potential**
- **mobility** of a particle in a fluid
- **flux** of particles through space

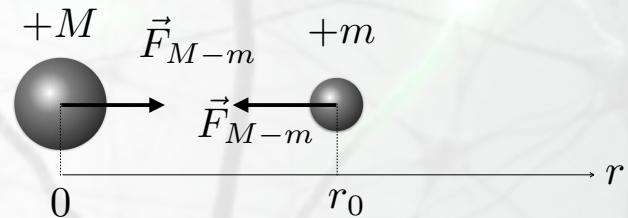
Coulomb's **Force**, Electric **Field** and **Potential**



...but let's first talk about *gravity*, first!



1642 – 1726

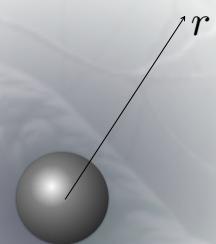


$$|\vec{F}_{m-M}| = G \frac{M m}{r_0^2} \quad N$$

Vector fields!

$$|\vec{E}_M| = G \frac{M}{r_0^2} \quad N/Kg$$

Vector fields!



$$\vec{F}_{m-M} = m \vec{E}_M \quad N$$

Vector fields!

Gravitation conserves mechanical energy
 work done - i.e. energy transferred - to move an object in the field
 depends on initial & final positions, not on the trajectory

(for “conservative” vector fields...)

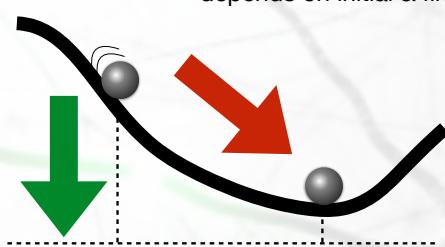
$$\vec{E} = -\vec{\nabla}V \quad \vec{E} = -\frac{d}{dr}V \quad V(r)$$

V is a scalar field and it is ...defined irrespectively of a (reference) constant!!

$$V_M(P) = -G \frac{M}{r}$$

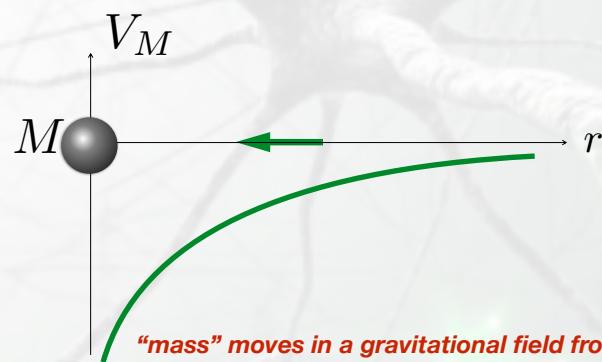
$$|\vec{E}_M| = -\frac{d}{dr}V_M \quad |\vec{E}_M| = G \frac{M}{r_0^2}$$

Gravitation conserves mechanical energy
 work done - i.e. energy transferred - to move an object in the field
 depends on initial & final positions, not on the trajectory



$$V_M(P) = -G \frac{M}{r}$$

$$|\vec{E}_M| = -\frac{d}{dr}V_M$$



Gravitational (field) potential = *amount of gravitational potential energy that a unitary point mass would have if located at that point in space;*
 = **work done** by the gravitational field in **carrying a unit mass** from ∞ to that point.

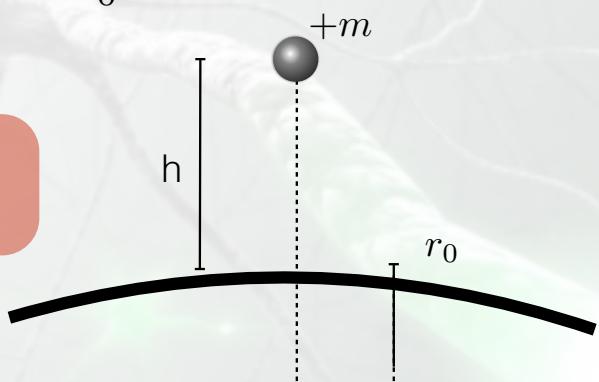
$$V_M(P) = -G \frac{M}{r}$$

V is a scalar field and it is ...defined irrespectively of a (reference) constant!!

$$V_M(r_0 + h) \approx -G \frac{M}{r_0} + G \frac{M}{r_0^2} h$$

$$m \ll M$$

$$\Delta V \approx g h$$



Biophysics

definitions & refresher

- **density or concentration** of particles, in space

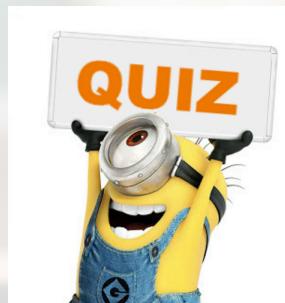
- Coulomb's **Force**, Electric **Field** and its **Potential**

- **mobility** of a particle in a fluid

- **flux** of particles through space

Fundamental Forces in Nature

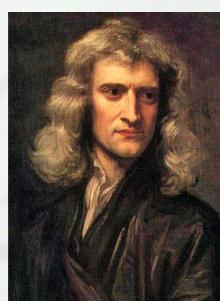
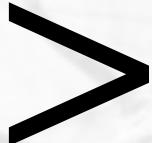
- Which is stronger? gravitation or electrostatics?
- Why both attenuates as $1/r^2$?



Coulomb's law & Electric Potentials electric (vector) *field*, and (scalar) electric *potential*



1736 – 1806



1642 – 1726

$\sim 1'000'000'000'000'000'000'000'000'000'000'000'000'000'000$

~39 orders of magnitude stronger
than gravitation force

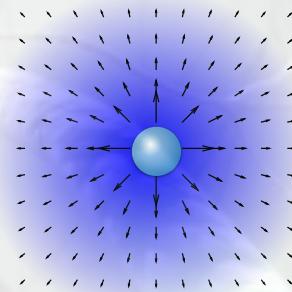
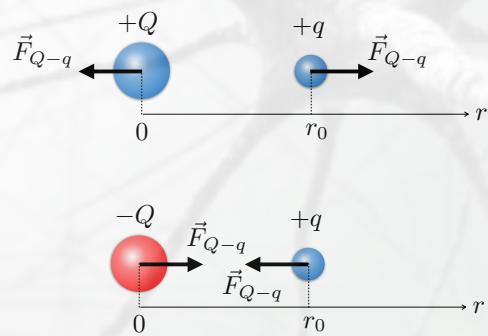
(between charged elementary particles)

Electrostatic Force & Electrostatic Field

$$|\vec{F}_{q-Q}| = \frac{1}{4\pi\epsilon_r\epsilon_0} \frac{Q q}{r_0^2} \quad N$$

$$|\vec{E}_Q| = \frac{1}{4\pi\epsilon_r\epsilon_0} \frac{Q}{r_0^2} \quad N/C = Volt/m$$

$$\vec{F}_{q-Q} = q \vec{E}_Q \quad N$$



$$\epsilon_0 = 8.85 \dots 10^{-12} F/m$$

Electrical permittivity of free space (vacuum):

measure of the resistance of the medium to the formation of an electric field

$$\epsilon_R = 1$$

Relative permittivity of vacuum

$$\epsilon_R \approx 1$$

Relative permittivity of air

$$\epsilon_R = 80 \quad (\text{at } 20^\circ C)$$

Relative permittivity of water

$$\epsilon_R = 7$$

Relative permittivity of phospholipids

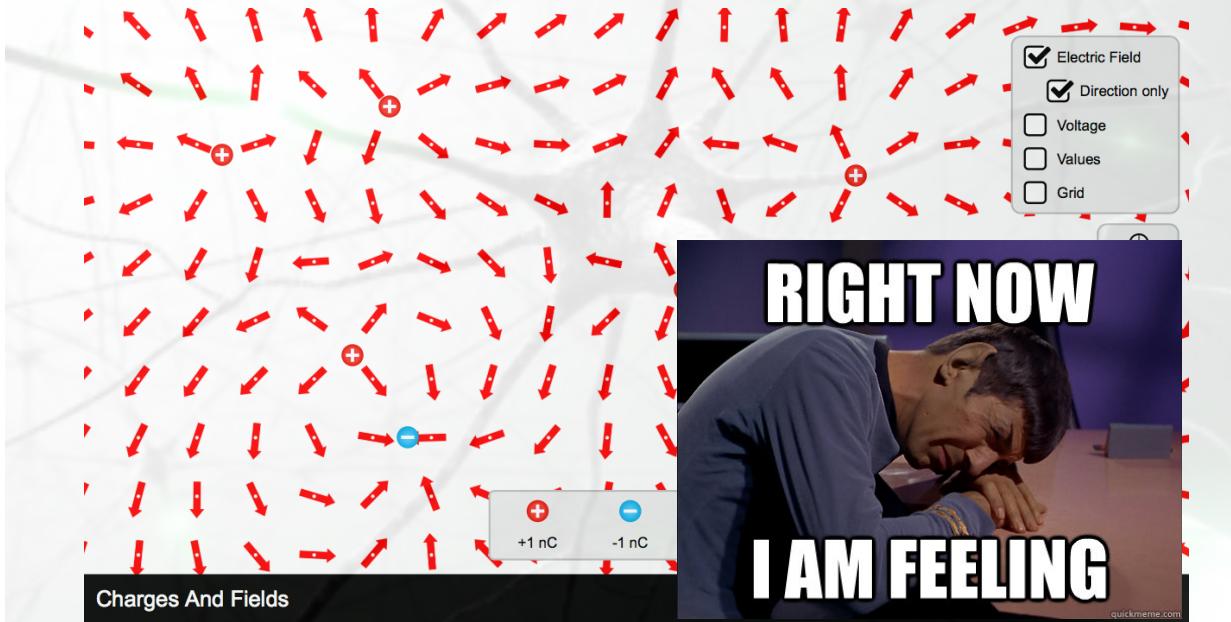
$$e = 1.602 \dots 10^{-19} C$$

Electrical charge is quantised:

always integer multiple of the charge of the proton (the electron)

Vector fields

$$\vec{E}(x, y, z, t) = \{E_x(x, y, z, t); E_y(x, y, z, t); E_z(x, y, z, t)\}$$



From vectors to scalar quantities?

(for “conservative” vector fields...)

$$\vec{E} = -\vec{\nabla}V \quad \vec{E} = -\frac{d}{dr}V$$

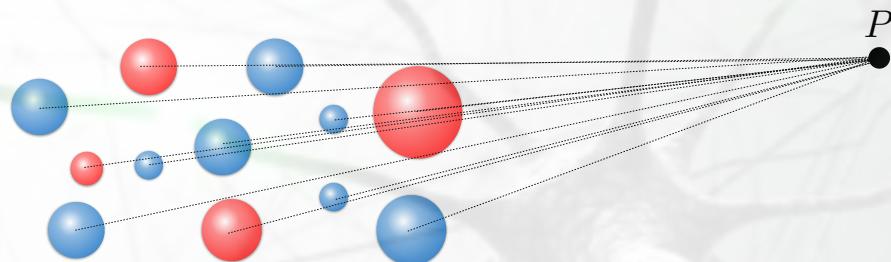
V is a scalar field and it is ...defined irrespectively of a (reference) constant!!

$$V_Q(P) = \frac{1}{4\pi\epsilon_r\epsilon_0} \frac{Q}{r}$$

Electric or electrostatic (field) potential = *amount of electric potential energy* that a unitary electric point-charge would have if located at that point in space;
= **work done** by an electric field in **carrying a unit positive** charge from ∞ to that point.



Superposition of the effects



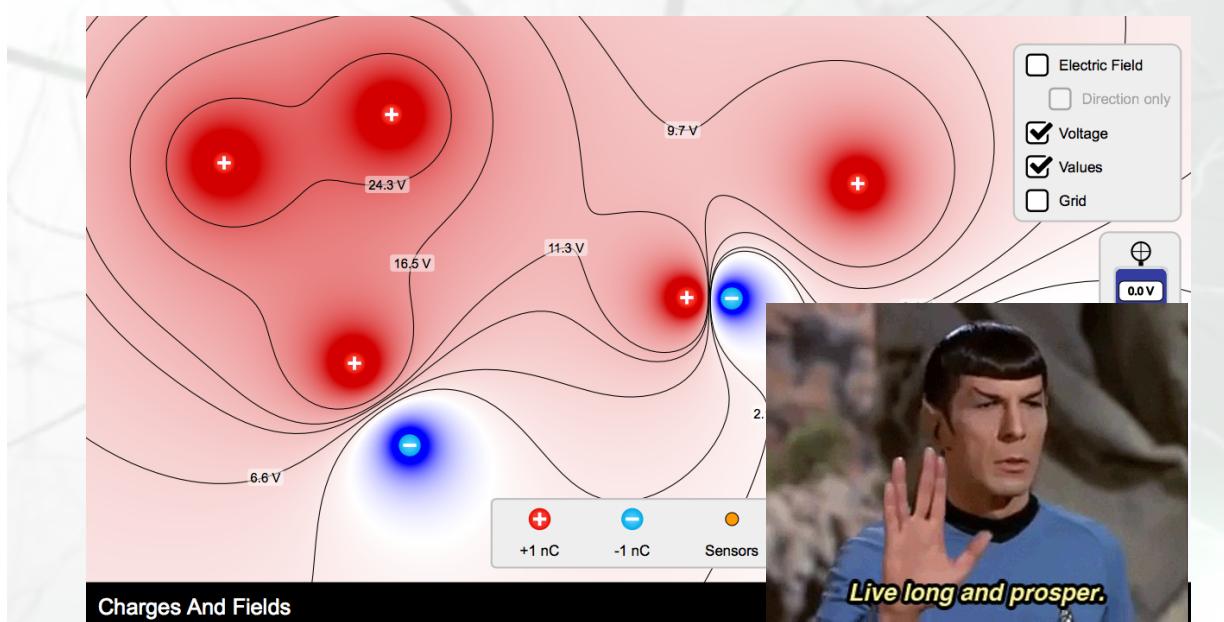
$$V_{total}(P) = \frac{1}{4\pi\epsilon_r\epsilon_0} \left(\frac{Q_1}{r_{P-Q_1}} + \frac{Q_2}{r_{P-Q_2}} + \dots + \frac{Q_M}{r_{P-Q_M}} \right)$$

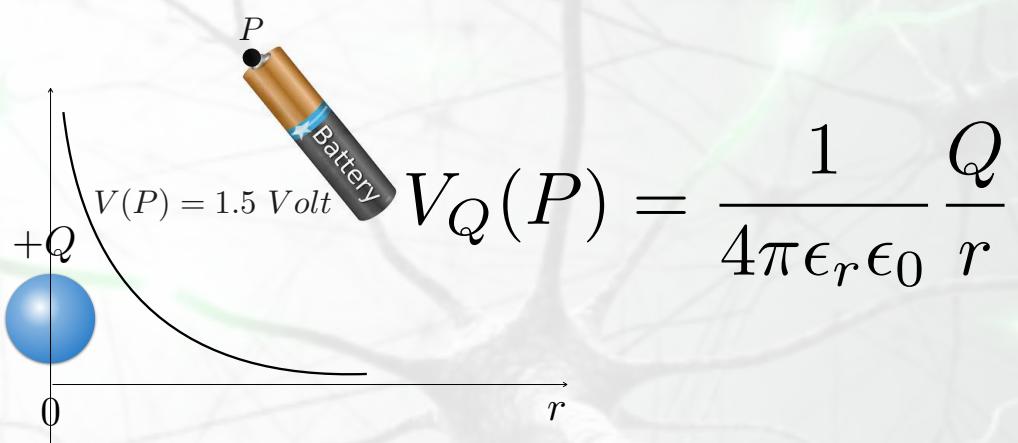


It is like the *weighted sum* of the inverse of the distances...

Scalar fields

$$V(x, y, z, t)$$





A **positive** charge (+q) moves from points with higher electrostatic potential to points with lower electrostatic potential (+Q).

A **negative** charge (-q) moves from points with lower electrostatic potential to points with higher electrostatic potential (+Q).

Electrostatic potential: -70mV inside with respect to outside

- After refreshing the definition of potential... what does it come to your mind?
- What could it explain “-70mV inside”?

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



Elementary Biophysics

- Def. of **density** and of **concentration** of particles
- Coulomb's **Force**, Electric **Field** and **Potential**
- Def. of **mobility** of a particle in a fluid
- Def. of **flux** of particles

Mobility u of an **particle** in an aqueous **solution**, under an **external force field**

• Stokes's Law

a continuous viscous medium (say a fluid) exerts a frictional force, **opposing and proportional to the velocity** of (very small) particles moving into it $v(t)$

⇒ Particles move with a velocity proportional (by u - **mobility**) to the external force field

$$F_{ext} + F_{friction} = m \frac{dv(t)}{dt} \quad \text{Newton's second law}$$

$$F_{friction} = -\lambda v(t) \quad \text{Stokes' law}$$

$$v(t) = k e^{-\frac{\lambda}{m}t} + \frac{F_{ext}}{\lambda} \quad \text{The usual, boring, first-order, ... o.d.e.!}$$

$$\frac{\lambda}{m} \gg 1$$

$$v(t) \approx \frac{F_{ext}}{\lambda} = u F_{ext}$$

“when it rains, drops do **NOT** accelerate until they get so fast to break your head!”

Mobility u of a **charged particle** in an aqueous solution, under an **external force field**

$$v(t) \approx \frac{F_{ext}}{\lambda} = u F_{ext} \quad v(t) \approx \frac{E_{ext}}{\lambda} = \hat{u} E_{ext} = \hat{u} \frac{F_{ext}}{|z| q}$$

our definition
(also called "absolute mobility")

alternative definition
(also called "electrical mobility")

$$[u] = \frac{m}{s N} \quad [\hat{u}] = \frac{m C}{s N} = \frac{m^2}{s V}$$

$$u = \frac{\hat{u}}{|z| q}$$

BEWARE OF THE UNITS, WHEN LOOKING AT MOBILITY VALUES

Mobility u : numerical values (in water, at 25 °C)

$$[\hat{u}] = \frac{m C}{s N} = \frac{m^2}{s V} \quad [u] = \frac{m}{s N}$$

K^+	$7.61 \times 10^{-8} \text{ m}^2/(\text{V}\cdot\text{s})$	$4.75 \times 10^{11} \text{ m}/(\text{N}\cdot\text{s})$
Na^+	$5.19 \times 10^{-8} \text{ m}^2/(\text{V}\cdot\text{s})$	$3.24 \times 10^{11} \text{ m}/(\text{N}\cdot\text{s})$
Cl^-	$7.9 \times 10^{-8} \text{ m}^2/(\text{V}\cdot\text{s})$	$4.93 \times 10^{11} \text{ m}/(\text{N}\cdot\text{s})$
Ca^{2+}	$6.16 \times 10^{-8} \text{ m}^2/(\text{V}\cdot\text{s})$	$3.84 \times 10^{11} \text{ m}/(\text{N}\cdot\text{s})$

Elementary Biophysics

- Def. of **density** and of **concentration** of particles
- Coulomb's **Force**, Electric **Field** and **Potential**
- Def. of **mobility** of a particle in a fluid
- Def. of **flux** of particles

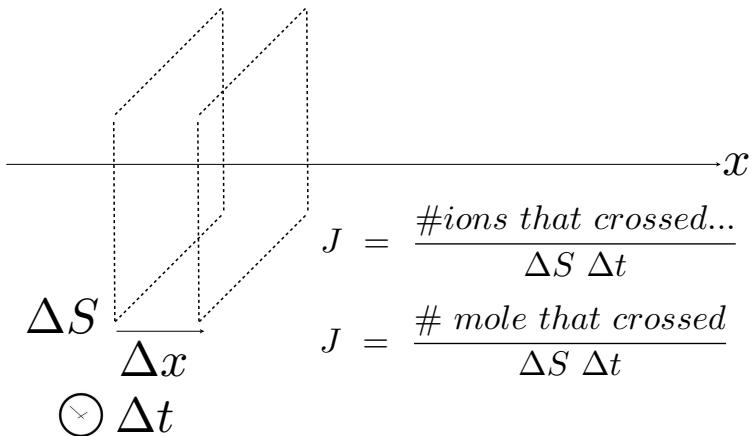
Flux of particles

- How would you define it or measure it?



“Flux” J of particles distributed/concentrated in solution moving in one-dimension with some **velocity v** (under external force field)

DEF: $J = \text{“number of particles or moles moving through a (unitary) surface, in a (unitary) time interval”}$ (e.g. through 10^{-4} m^2 and every 0.01 s)



$\rho(x, y, z, t)$	$1/\text{m}^3$
$c(x, y, z, t)$	mM
$1 \frac{\text{mol}}{\text{m}^3} = 1 \frac{\text{mmol}}{\text{l}} = 1 \text{ mM}$	

Teorell's formula
for the “molar flux”

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

$\text{mole } m^{-2} s^{-1}$
 $c \text{ in mM}$



From **Flux J** of charged particles to **ionic (electrical) current density i**

$$J = u \rho F_{ext} \quad \# \text{ particles } m^{-2} s^{-1}$$

$$\longrightarrow i \quad \frac{C}{s \text{ m}^2} = \frac{A}{\text{m}^2}$$

$$J = u c F_{ext} \quad \text{molar flux}$$

$\text{ionic current density}$

$$i = J \frac{\text{flux charge}}{Q}$$

$$i = q u \rho F_{ext}$$

this is
 $1.602 \cdot 10^{-19} \text{ Coulomb}$

$$i = N_A q u c F_{ext}$$

this is
 $F = 96485.33 \text{ Coulomb/mole}$
(known as Faraday's constant)



What kind of fluxes can occur in solution?

Diffusive fluxes

and

Drift fluxes

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

Charged particle (uniformly distributed) in aqueous solution?

They repel/attract each other!

- positively and negatively charged particles experience a **force**, proportional to the electric field E ... (*which might be self-generated*)
- for conservative fields (as E), a potential (V) can be defined apart from an arbitrary additive constant

$$F_{ext} = \frac{z}{N} \frac{q_+}{C} E = - z q_+ \frac{dV}{dx} \quad \begin{matrix} \text{when referred to} \\ \text{each particle} \end{matrix} \quad \rho(x, y, z, t)$$

$$F_{ext} = \frac{z}{N} \frac{N_A}{C} q_+ \frac{dV}{dx} \quad \begin{matrix} \text{when referred to} \\ \text{a mole of particles} \end{matrix} \quad c(x, y, z, t)$$

$$J = u c \left(z N_A q_+ \frac{dV}{dx} \right) = u c \left(-z F \frac{dV}{dx} \right) \quad \begin{matrix} \text{mole } m^{-2} s^{-1} \\ \text{c in mM} \end{matrix}$$

total of **96485.33 Coulomb**

*Resist the urge to consider $[F]$ as C/mol!
Here, F means only the total charge!*



Non-charged particle in aqueous solution? They diffuse!

Which force field?

- (non-zero) kinetic energy of water molecules at absolute temperature $T > 0^\circ \text{ K}$
- (kinetic) energy exchanged with water molecules, due random isotropic collisions

“Monte Carlo” simulation

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

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

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



in 2D

Non-charged particle in aqueous solution? They diffuse!

Which force field? The diffusion-force created by a concentration gradient



- (non-zero) kinetic energy of water molecules at absolute temperature $T > 0^\circ \text{ K}$
- (kinetic) energy exchanged with water molecules, due random isotropic collisions

$$F_{ext} = -K T \frac{d}{dx} \ln(c) \quad \begin{matrix} \text{when referred to} \\ \text{each particle} \end{matrix} \quad \rho(x, y, z, t)$$

$$N \quad J \text{ } K^{\circ -1} \quad K^{\circ} \quad m^{-1} \quad \begin{matrix} K: \text{Boltzmann} \\ \text{constant} \end{matrix}$$

$$F_{ext} = -N_A K T \frac{d}{dx} \ln(c) \quad \begin{matrix} \text{when referred to} \\ \text{a mole of particles} \end{matrix} \quad c(x, y, z, t)$$

$$N \quad J \text{ } K^{\circ -1} \quad K^{\circ} \quad m^{-1}$$

molar flux

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

8.3 Joule / kelvin = R

N_A is used for its value, without unit (like 1/mol).

diffusion flux

$$\text{mole } m^{-2} s^{-1}$$

c in mM

Resist the urge to consider [R] as Joule/(kelvin mol)!
Here, R is in J/(kelvin), the gas constant.

Diffusive flux

- Can we rewrite $\frac{d}{dx} \ln[c(x)]$, equivalently ?

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



Non-charged particle in aqueous solution? **They diffuse!**

Which force field? The diffusion-force created by a concentration gradient

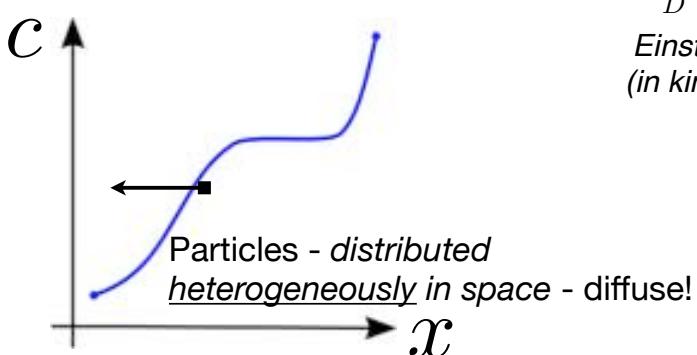
- (non-zero) kinetic energy of water molecules at absolute temperature $T > 0^\circ \text{ K}$
- (kinetic) energy exchanged with water molecules, due random isotropic collisions

$$\begin{array}{l} \text{molar flux} \\ J = u c \left(-R T \frac{1}{c} \frac{dc}{dx} \right) = -u R T \frac{dc}{dx} = -D \frac{dc}{dx} \\ \text{mole } m^{-2} s^{-1} \quad \text{in mM} \qquad \qquad \qquad \text{m } s^{-2} \text{ mol } m^{-3} \text{ m}^{-1} \end{array}$$

Fick's law of diffusion

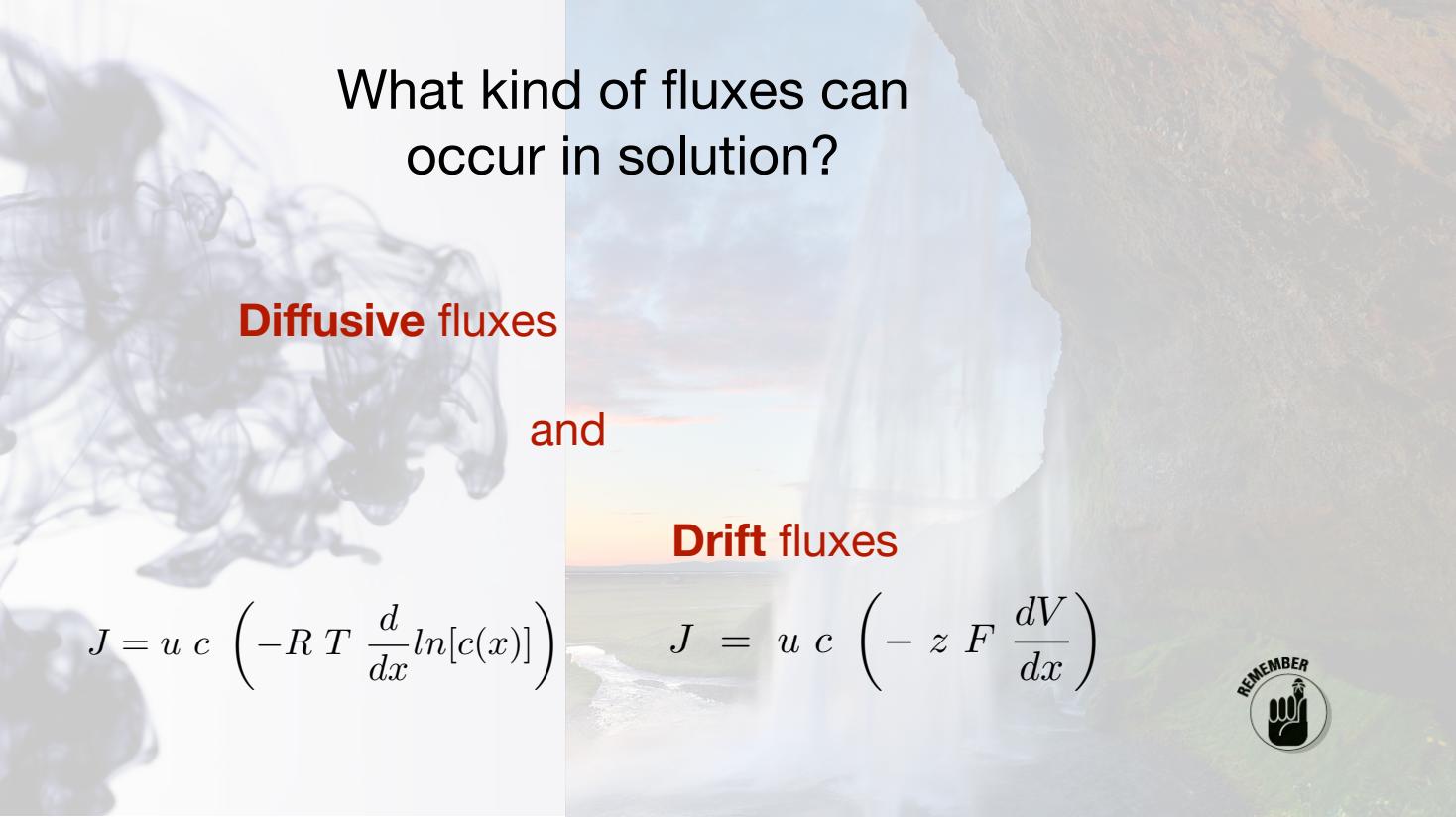
$$D = u K T$$

Einstein relation
(in kinetic theory)



$$[D] = m \text{ s}^{-2} \quad \text{as expected}$$

Once again, N_A is used here for its value, without any unit (like $1/\text{mol}$).



What kind of fluxes can occur in solution?

Diffusive fluxes

and

Drift fluxes

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

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



Flux of particles

- What happens if you have charged particles that are non-uniformly concentrated in solution?
- What happens if they are free to move?

