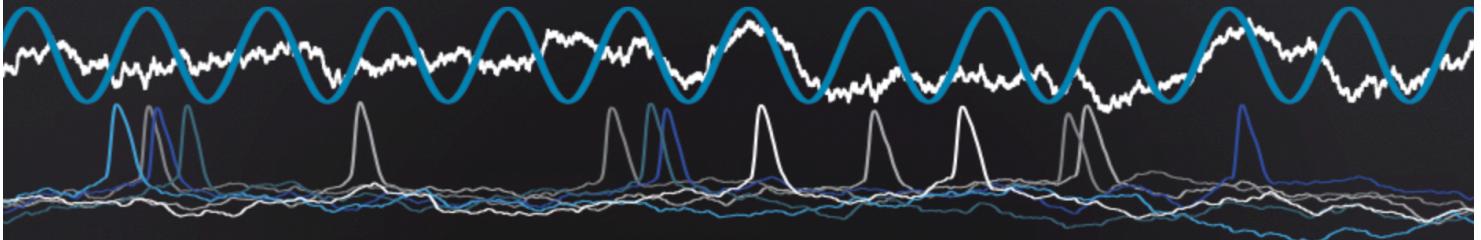


ELECTROPHYSIOLOGICAL SIGNALS



GENERATION AND CHARACTERISATION

Michele GIUGLIANO

Preliminaries in Neuroelectronics

ATTENDANCE TRACKING - **code LEYKT**
(for statistical purposes only)

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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*

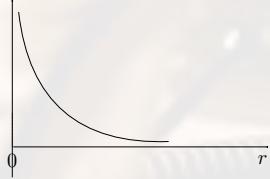
“Mathematics is a language plus reasoning;
it is like a language plus logic.
Mathematics is a tool for reasoning.”

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

Graph of some notable functions



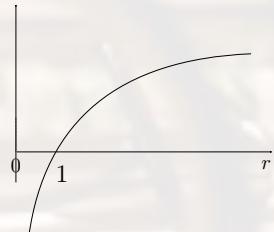
$$f(r) = \frac{1}{r}$$



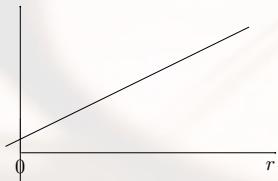
$$f(r) = (1 - e^{-\alpha r})$$



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



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



Concept of (first) derivative of a mathematical function



$$f(x) = \text{constant}$$

$$\frac{df(x)}{dx} =$$

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

$$\frac{df(x)}{dx} =$$

$$f(x) = \ln(x)$$

$$\frac{df(x)}{dx} =$$

Derivative of a sum of functions ==>

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

Derivative of a composite function ==>

$$\frac{dG(H(x))}{dx} =$$

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

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)

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

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”)

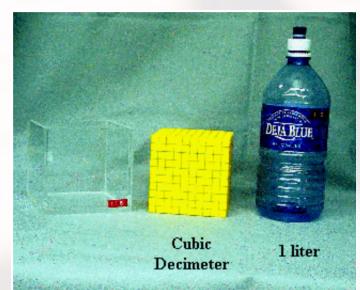
$$\frac{df(x)}{dx} = -af(x) + B \quad f(x) = ke^{-ax} + B/a$$



The Prefixes Used with SI Units

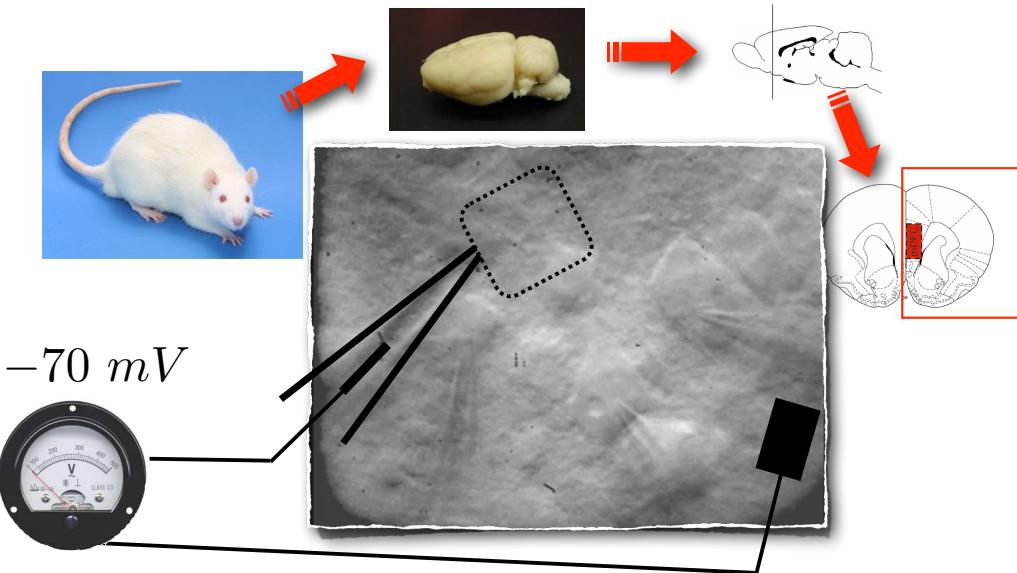
Prefix	Symbol	Meaning	Scientific Notation
exa-	E	1,000,000,000,000,000,000	10^{18}
peta-	P	1,000,000,000,000,000	10^{15}
tera-	T	1,000,000,000,000	10^{12}
giga-	G	1,000,000,000	10^9
mega-	M	1,000,000	10^6
kilo-	k	1,000	10^3
hecto-	h	100	10^2
deka-	da	10	10^1
—	—	1	10^0
deci-	d	0.1	10^{-1}
centi-	c	0.01	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}

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



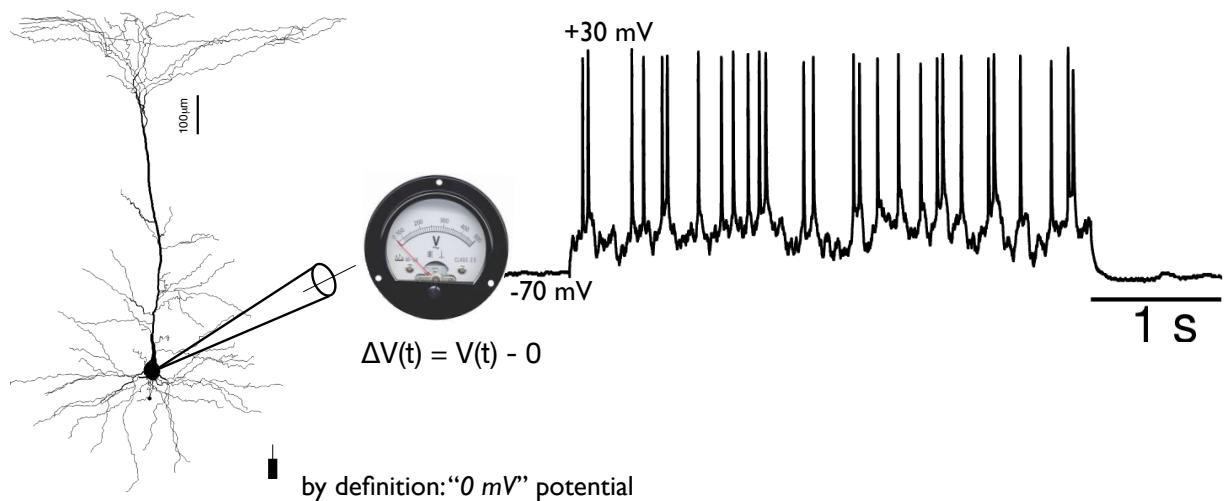
Why are we bothering with biophysics of electrolytes, membranes, electrodes, etc???

Understand why/how there is a membrane elec. potential ("at rest")
(in every cell, not just in nerve cells!)



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



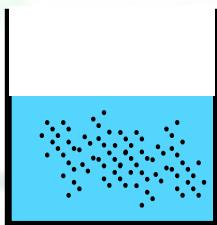
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- **flux** of particles through space

“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

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

$$\rho = N_A c$$

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

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



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

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



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**

$$Area = 4\pi r^2 = 4 \pi 25\mu m^2 \approx 314\mu m^2$$

$$1.6 \cdot 10^8 \text{ ions}/\mu m^2 \quad (\text{shell})$$

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

Biophysics definitions & refresher

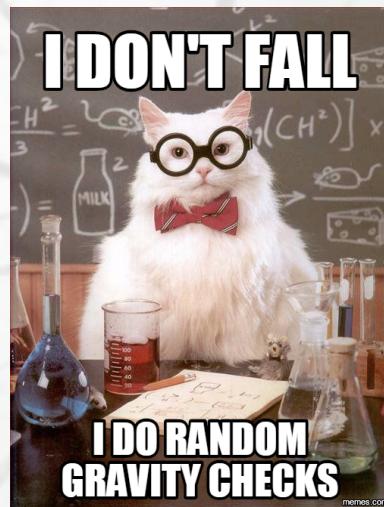
● **density or concentration** of particles, in space

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

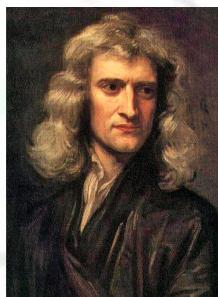
● **mobility** of a particle in a fluid

● **flux** of particles through space

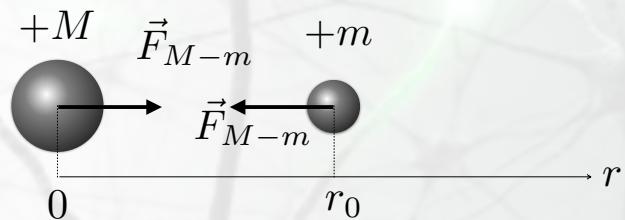
Coulomb's **Force**, Electric **Field** and **Potential**



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



1642 – 1726



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

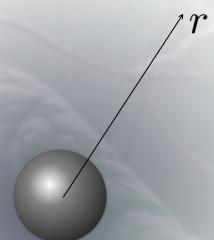
Vector fields!

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

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...)

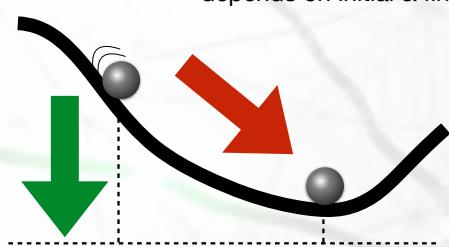
$$\vec{E} = -\vec{\nabla}V \quad \vec{E} = -\frac{d}{dr}V \quad V(r)$$

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

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

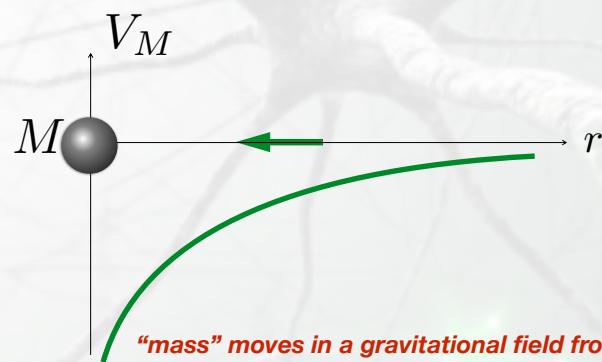
$$|\vec{E}_M| = -\frac{d}{dr}V_M \quad |\vec{E}_M| = G \frac{M}{r_0^2}$$

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.

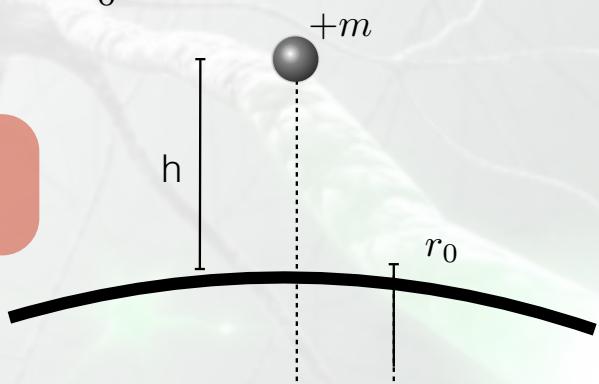
$$V_M(P) = -G \frac{M}{r}$$

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

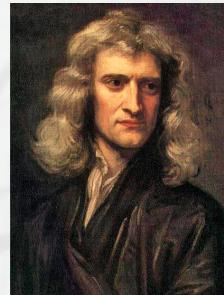
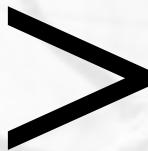
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Coulomb's law & Electric Potentials

electric (vector) field, and (scalar) electric potential



1736 – 1806



1642 – 1726

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

~ 39 orders of magnitude stronger
than gravitation force

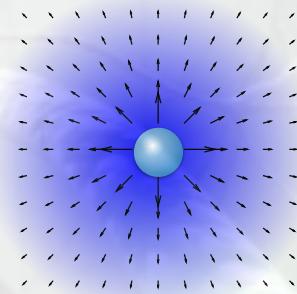
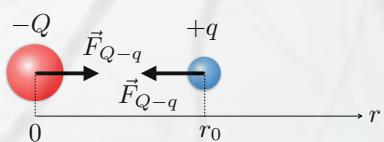
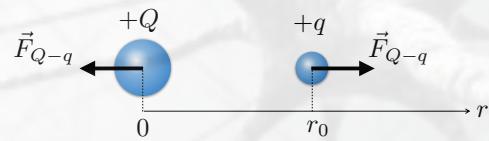
(between charged elementary particles)

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

$$\epsilon_R = 7$$

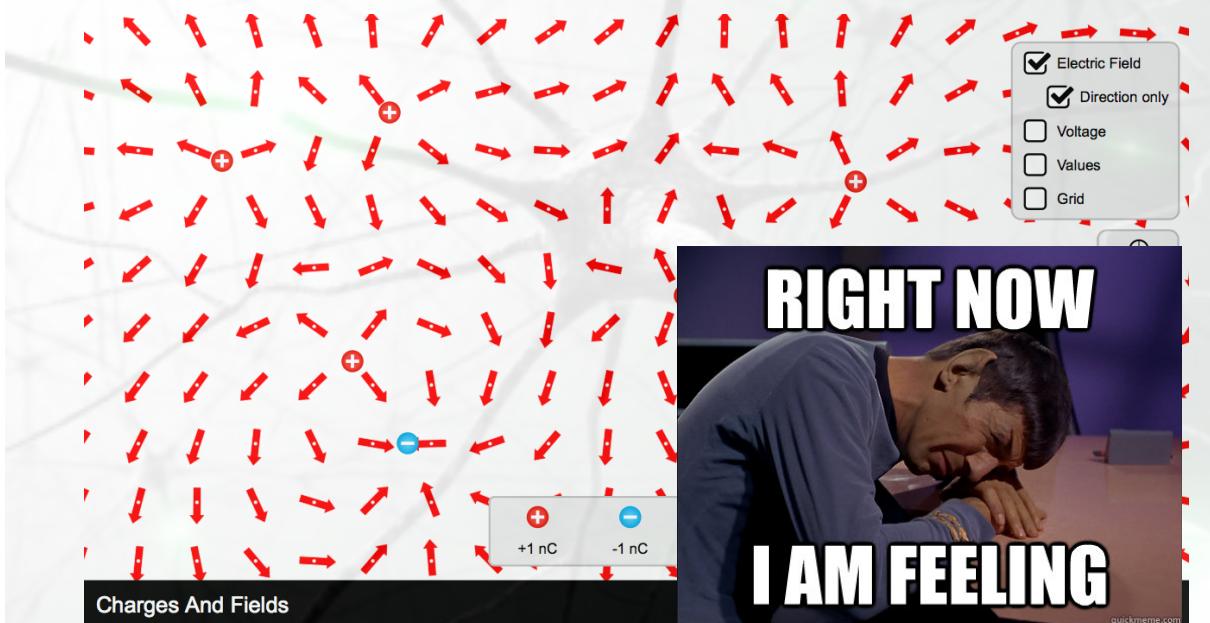
Relative permittivity of phospholipids

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

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...)

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

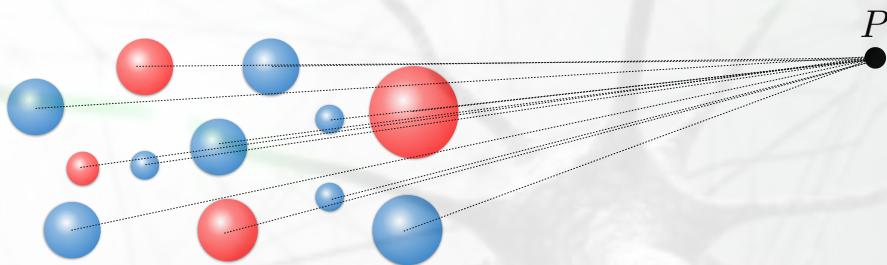
V is a scalar field and it is ...defined irrespectively of a (reference) constant!!

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

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



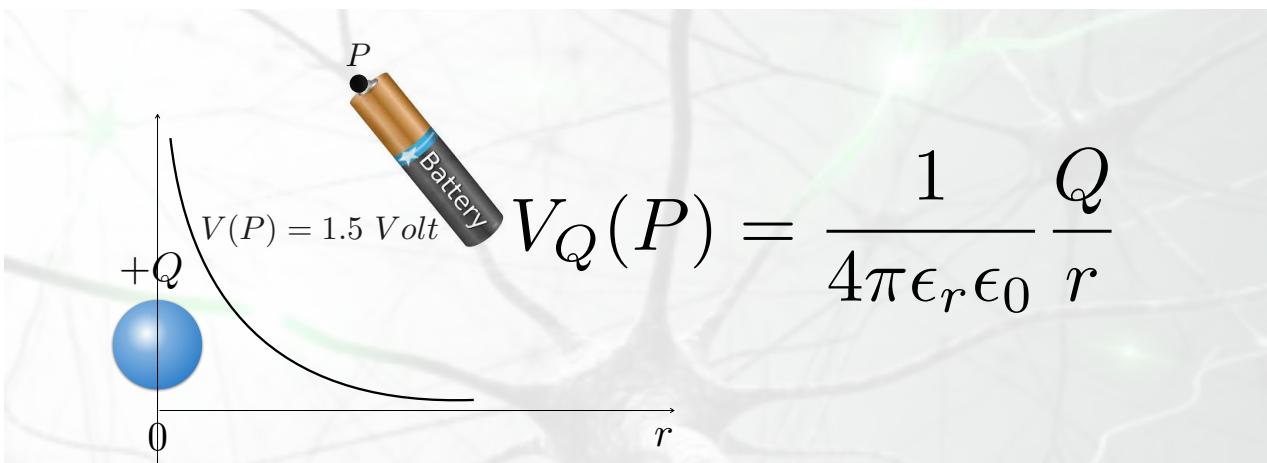
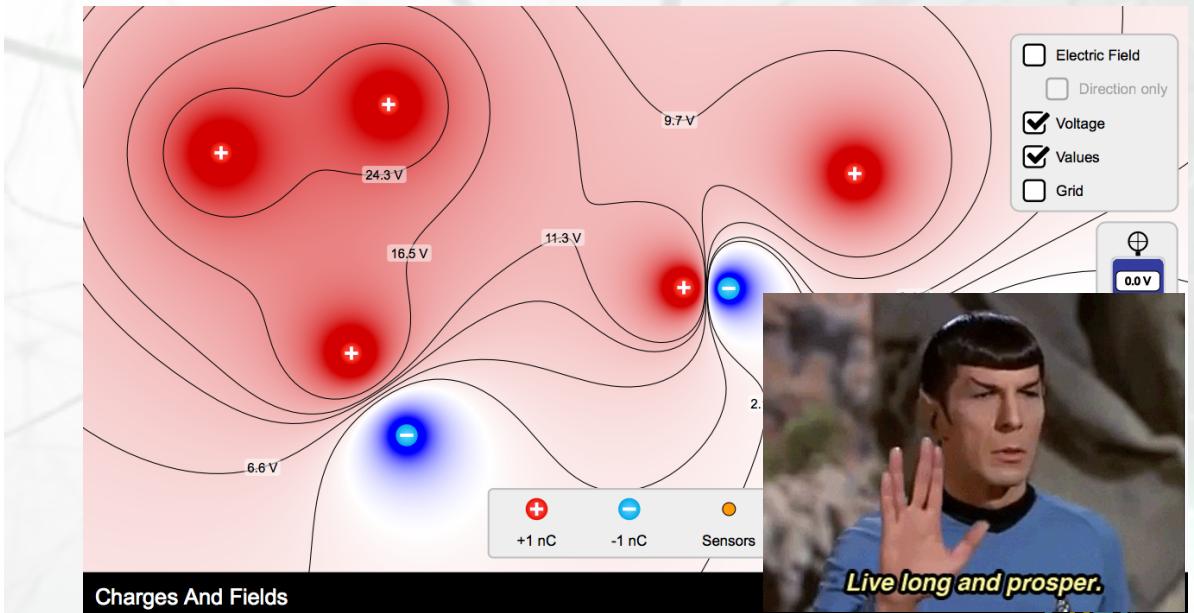
$$V_{total}(P) = \frac{1}{4\pi\epsilon_r\epsilon_0} \left(\frac{Q_1}{r_{P-Q_1}} + \frac{Q_2}{r_{P-Q_2}} + \dots + \frac{Q_M}{r_{P-Q_M}} \right)$$

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 ($+Q$).

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+}	$6.16 \times 10^{-8} \text{ m}^2/(\text{V}\cdot\text{s})$	$3.84 \times 10^{11} \text{ m}/(\text{N}\cdot\text{s})$

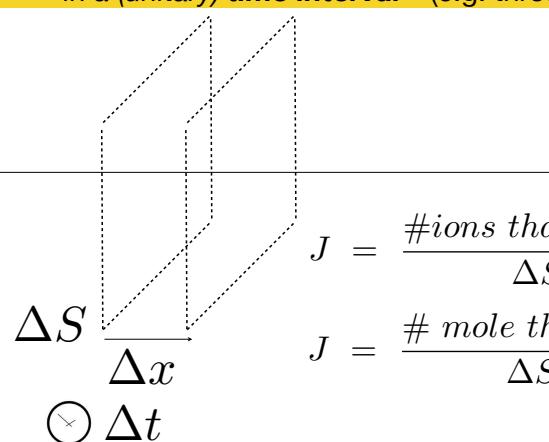
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- Def. of **flux** of particles

"Flux" J of particles distributed/concentrated in solution

moving in one-dimension with some **velocity v** (under external force field)

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



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

$$\begin{aligned}J &= \frac{\# \text{ions that crossed...}}{\Delta S \Delta t} = \frac{\rho \Delta S \Delta x}{\Delta S \Delta t} = \rho v & \# \text{ particles } m^{-2} s^{-1} \\ \Delta S \frac{\Delta x}{\Delta t} & J = \frac{\# \text{ mole that crossed}}{\Delta S \Delta t} = \frac{c \Delta S \Delta x}{\Delta S \Delta t} = c v & \begin{aligned} & \text{mole } m^{-2} s^{-1} \\ & c \text{ in mM}\end{aligned}\end{aligned}$$

Teorell's formula
for the "molar flux"

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

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



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

$$J = u \rho F_{ext} \quad \begin{matrix} \# \text{ particles } m^{-2} s^{-1} \\ \text{mole } m^{-2} s^{-1} \\ c \text{ in mM} \end{matrix} \quad \longrightarrow \quad i = \frac{C}{s m^2} = \frac{A}{m^2}$$

molar flux

$$i = J Q \quad \begin{matrix} \text{flux charge} \\ \text{ionic current density} \end{matrix}$$

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

this is
 1.602×10^{-19} Coulomb

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

this is
 $F = 96485.33$ 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

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

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

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

drift flux

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 $T > 0^\circ K$
- (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

$$F_{ext} = -K T \frac{d}{dx} \ln(c)$$

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

when referred to each particle $\rho(x, y, z, t)$

$K: \text{Boltzmann constant}$

$$F_{ext} = -N_A K T \frac{d}{dx} \ln(c)$$

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

when referred to a mole of particles $c(x, y, z, t)$

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

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

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

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

molar flux $J = u c \left(-R T \frac{1}{c} \frac{dc}{dx} \right) = -u R T \frac{dc}{dx} = -D \frac{dc}{dx}$

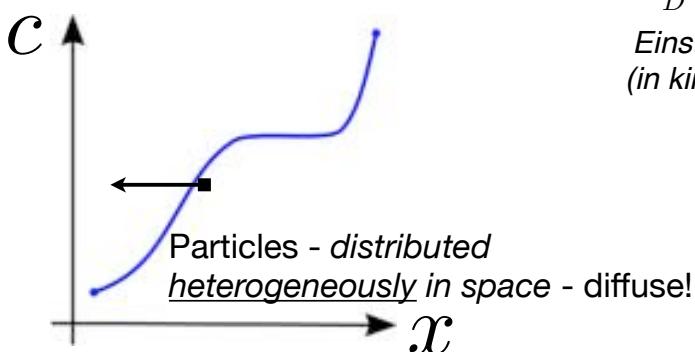
$\text{mole } m^{-2} s^{-1}$
 $c \text{ in mM}$

$m \text{ } s^{-2} \text{ mol } m^{-3} \text{ } m^{-1}$

Fick's law of diffusion

$$D = u K T$$

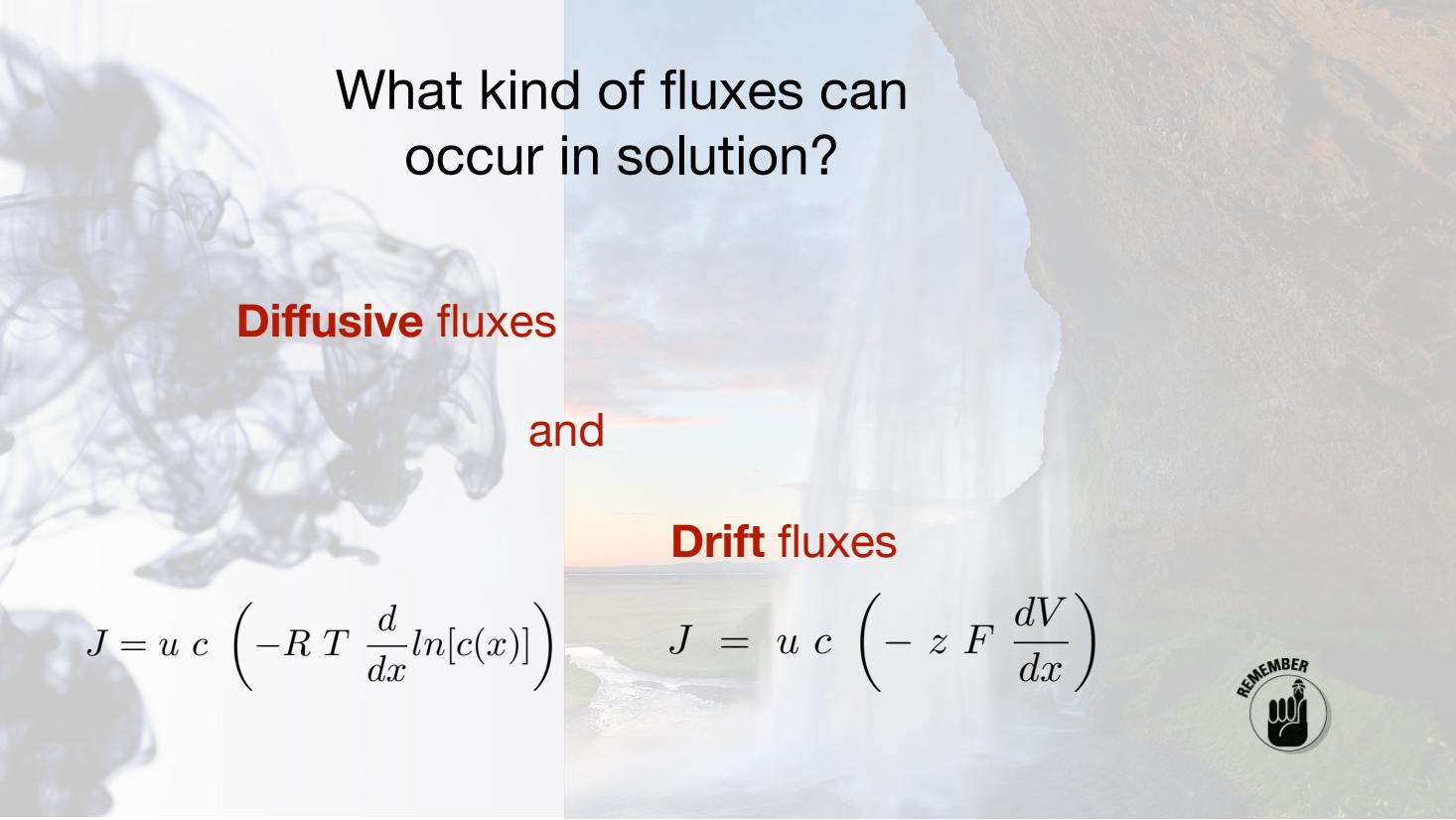
Einstein relation
(in kinetic theory)



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

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





What kind of fluxes can occur in solution?

Diffusive fluxes

and

Drift fluxes

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

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

