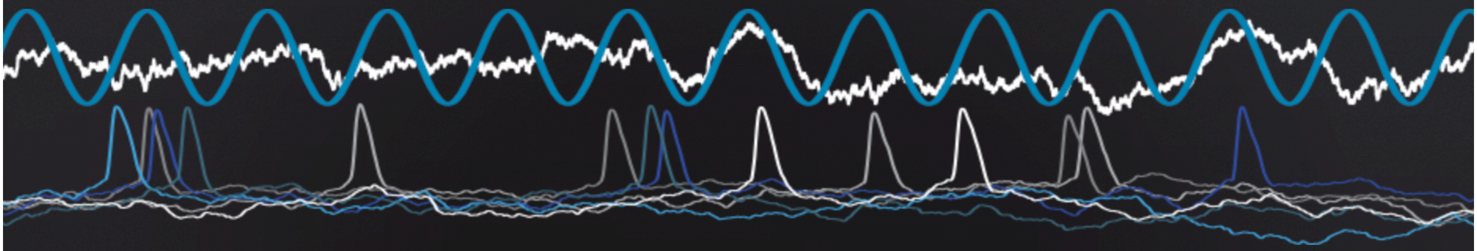
ELECTROPHYSIOLOGICAL SIGNALS



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*** <u>or</u> ***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

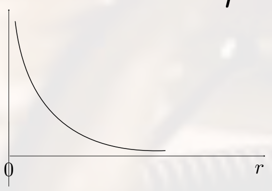
"Mathematics is a language plus reasoning;
it is like a language plus logic.
Mathematics is a tool for reasoning."

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

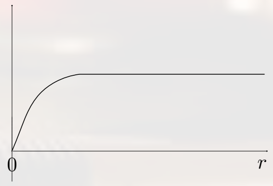
I mean it.

Graph of some notable functions

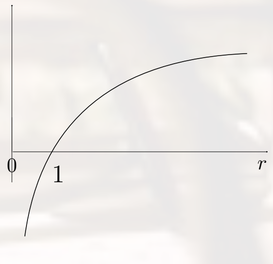
$$f(r) = \frac{1}{r}$$



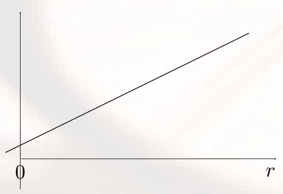
$$f(r) = (1 - e^{-\alpha r})$$



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



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



Concept of (first) *derivative* of a mathematical function

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

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

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

Derivative **of a** ***sum*** **of functions ==>**

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

Derivative of a ***composite*** **function ==>**

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

Concept of (first) *derivative* of a mathematical function

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

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

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

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!**

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

REMEMBER

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

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

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

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

REMEMBER

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*”)

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

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

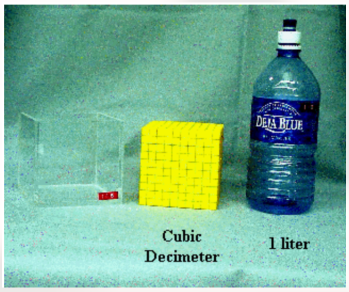
$$\frac{df(x)}{dx} = -af(x) + B \qquad f(x) = ke^{-ax} + B/a$$

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}

The Prefixes Used with SI Units

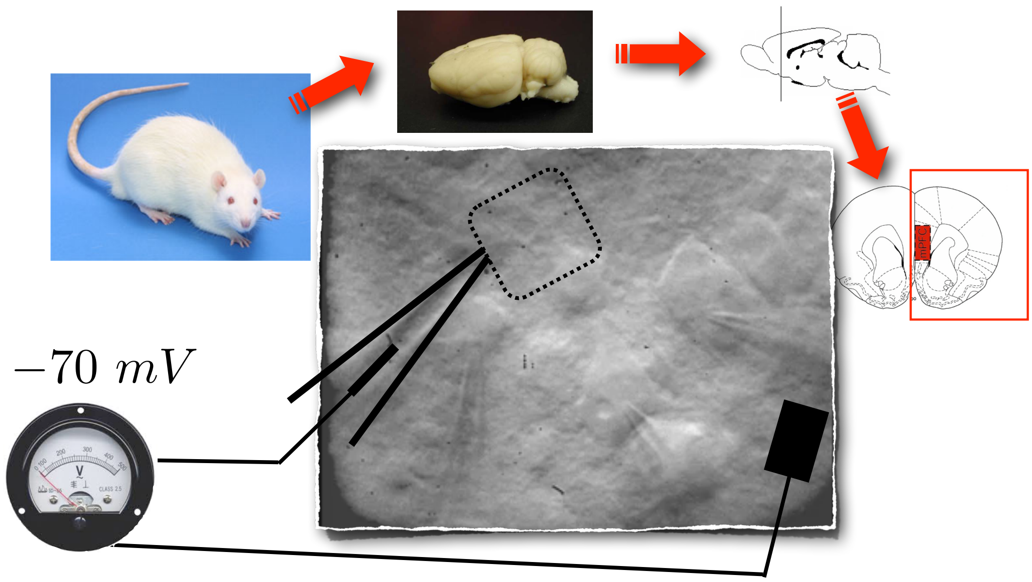
REMEMBER

$$1\ litre\ =\ 1\ dm^3$$



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

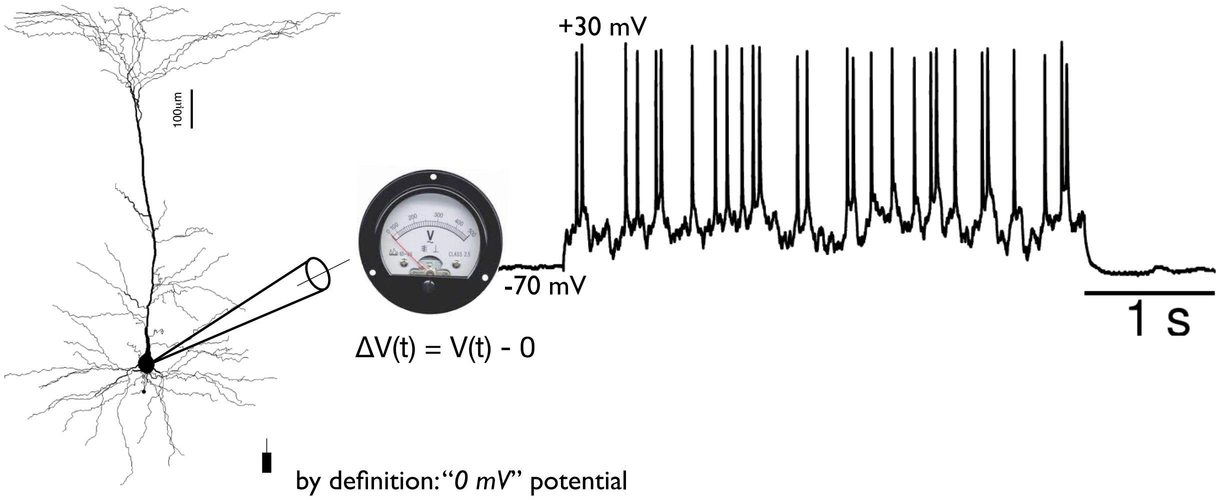
Understand why/how all cells have a membrane potential (“*at rest*”)



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



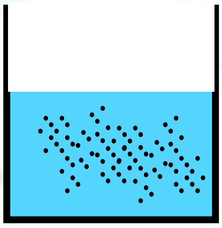
Biophysics

definitions & refresher

- ***density*** <u>or</u> ***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

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

concentration of molecules per liter

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

$$\rho = N_A\ c$$

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

$$1\ litre = 1\ dm^3 = 1000\ cm^3$$

$$[Na^+] = 1mM = 10^{-3}\frac{moles}{litre} =$$

$$10^{-3}\frac{6\ 10^{23}}{1000\ cm^3} = 6\ 10^{17}\frac{ions}{cm^3}$$

...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?

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

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

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

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

$$[K^+] = 150mM = 150\ 6\ 10^{17} ions/cm^3$$

$$= 900\ 10^{17}\ ions/(10^{12}\ \mu m^3) \approx 10^8 ions/\mu m^3$$

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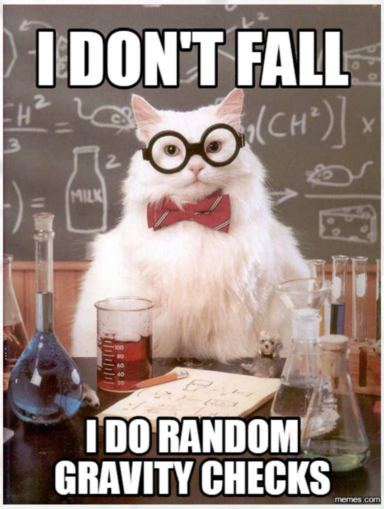
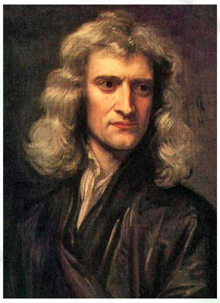
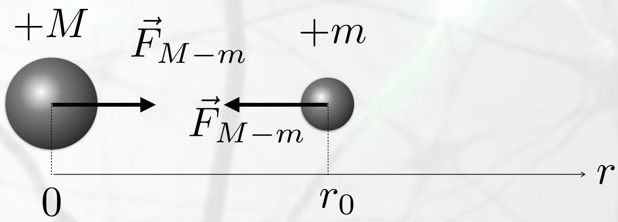
Coulomb's ***Force***, Electric ***Field*** and ***Potential***



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



1642 –1726

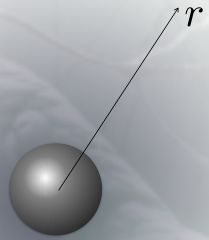


$$|\vec{F}_{m-M}| = G\,\frac{M\ m}{{r_0}^2} \qquad N$$

Vector fields!

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

Vector fields!



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

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" <u>vector</u> fields...)

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

V is a <u>scalar</u> field and it is ...*defined irrespectively of a (reference) constant!!*

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

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

Gravitation *conserves* mechanical energy

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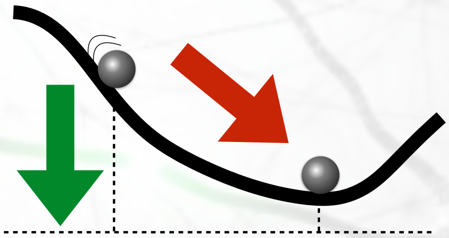

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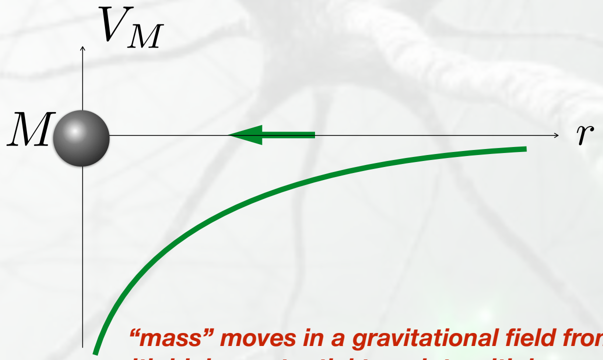


"mass" moves in a gravitational field from point with higher potential to points with lower potential

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.*

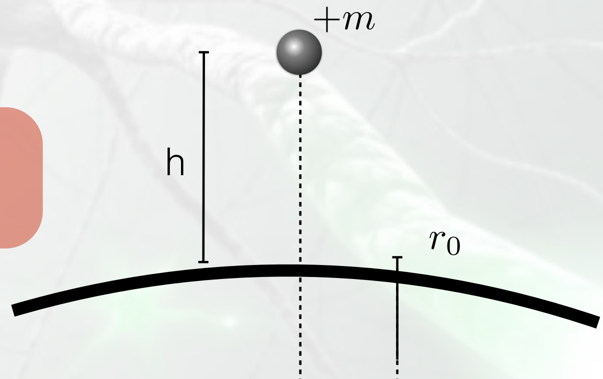
$$V_M(P) = -G\frac{M}{r}$$

V is a <u>scalar</u> field and it is ...*defined irrespectively of a (reference) constant!!*

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

$$m << M$$

$$\Delta V \approx g\ h$$



Biophysics
definitions & refresher

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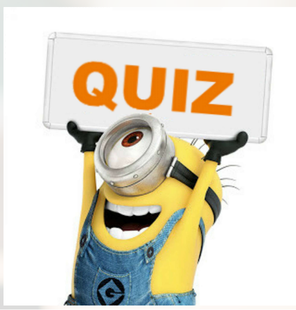
Fundamental Forces in Nature

- What is stronger gravitation of electrostatics?
- Why both attenuates as 1/r^2 ?

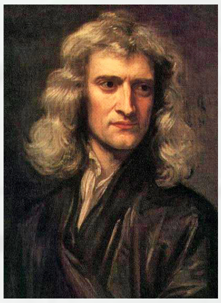


Coulomb's law & Electric Potentials

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

1736 –1806

$>$



1642 –1726

~1'000'000'000'000'000'000'000'000'000'000'000'000'000

~39 orders of magnitude stronger than gravitation force

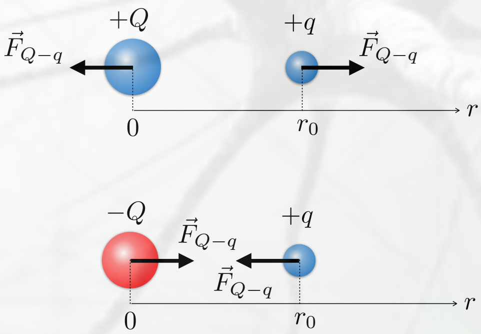
(between charged elementary particles)

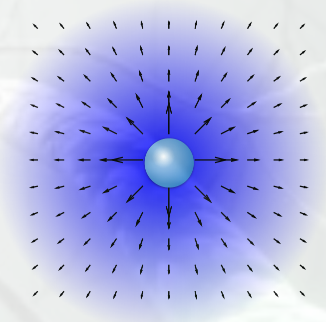
Electrostatic Force & Electrostatic Field

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

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

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





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

Electrical permittivity of free space (vacuum):
measure of the resistance of the medium to the formation of an electric field

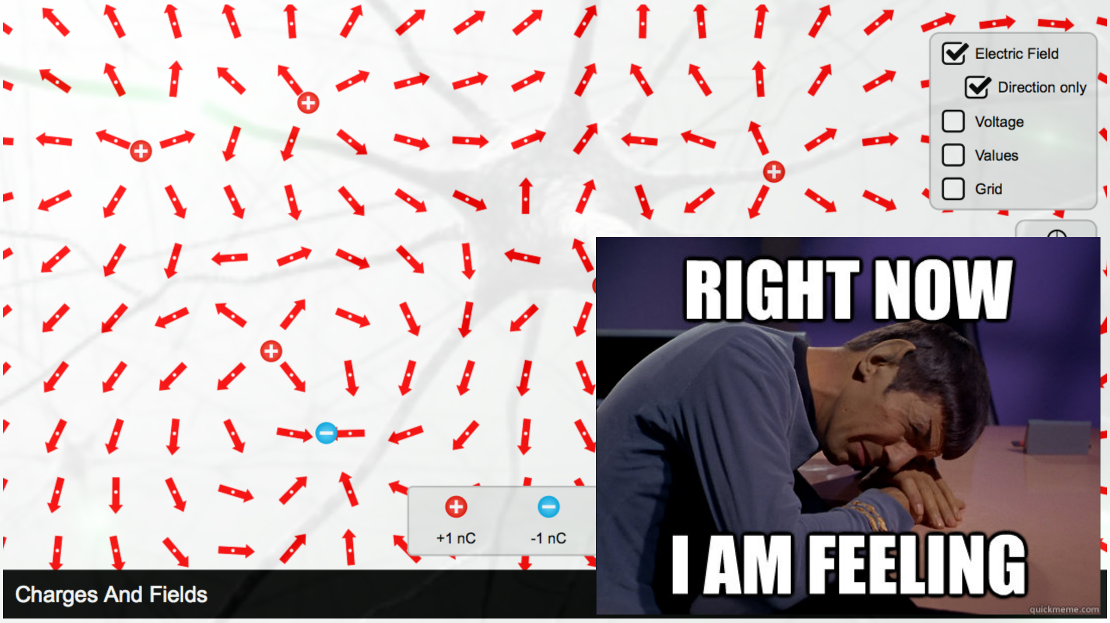
$\epsilon_R = 1$	**Relative permittivity of vacuum**
$\epsilon_R \approx 1$	**Relative permittivity of air**
$\epsilon_R = 80 \quad (at\ 20^o C)$	**Relative permittivity of water**
$\epsilon_R = 7$	**Relative permittivity of phospholipids**

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

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...)

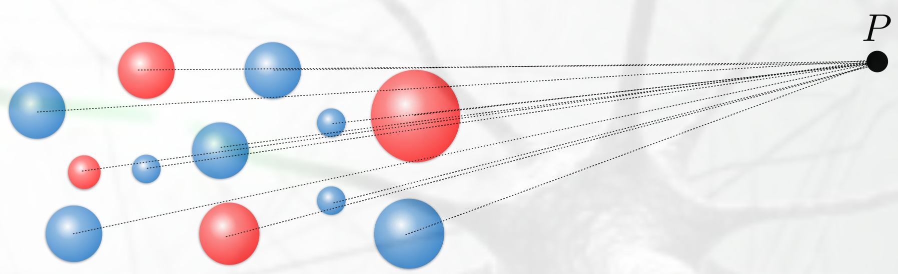
$$\vec{E} = -\vec{\nabla} V \qquad \vec{E} = -\frac{d}{dr} V$$

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

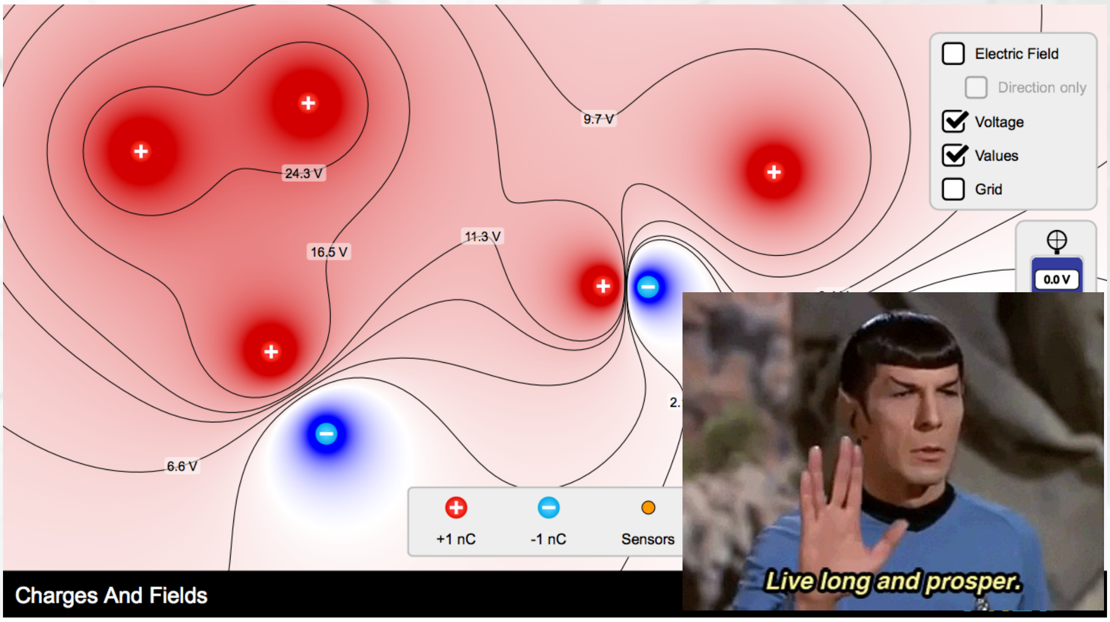


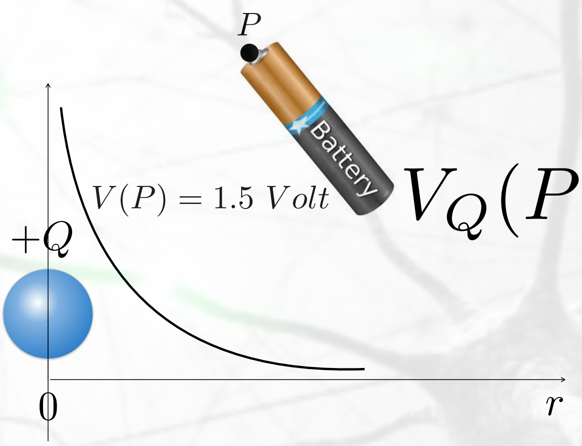
$$V_{total}(P) = \frac{1}{4\pi\epsilon_r\epsilon_0}\left(\frac{Q_1}{r_{P-Q_1}} + \frac{Q_2}{r_{P-Q_2}} + \ldots + \frac{Q_M}{r_{P-Q_M}}\right)$$

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

Scalar fields

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





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

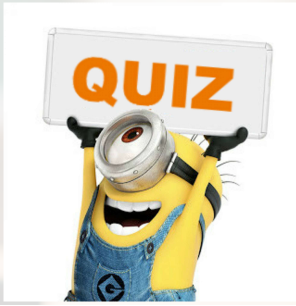
A **positive** charge (+q) moves from points with higher electrostatic potential to points with lower electrostatic potential (+Q).

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

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

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

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

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

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

"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**

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

our definition
(also called "absolute mobility")

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

alternative definition
(also called "electrical mobility")

$$[u] = \frac{m}{s\ N}$$

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

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

BEWARE OF THE UNITS, WHEN LOOKING AT MOBILITY VALUES

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

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

K^+	*7.61×10⁻⁸ m²/(V·s)*	*4.75×10¹¹ m/(N·s)*
Na^+	*5.19×10⁻⁸ m²/(V·s)*	*3.24×10¹¹ m/(N·s)*
Cl^-	*7.9×10⁻⁸ m²/(V·s)*	*4.93×10¹¹ m/(N·s)*
Ca^{2+}	*6.16×10⁻⁸ m²/(V·s)*	*3.84×10¹¹ m/(N·s)*

Elementary Biophysics

- Def. of ***density*** and of ***concentration*** of particles
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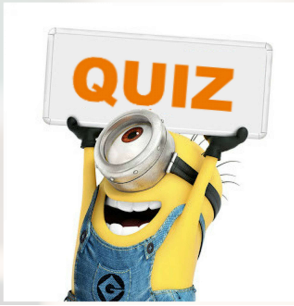
- Def. of ***flux*** of particles

Flux of particles

- How would you define it or measure it?



"Flux" J of particles distributed/concentrated in solution

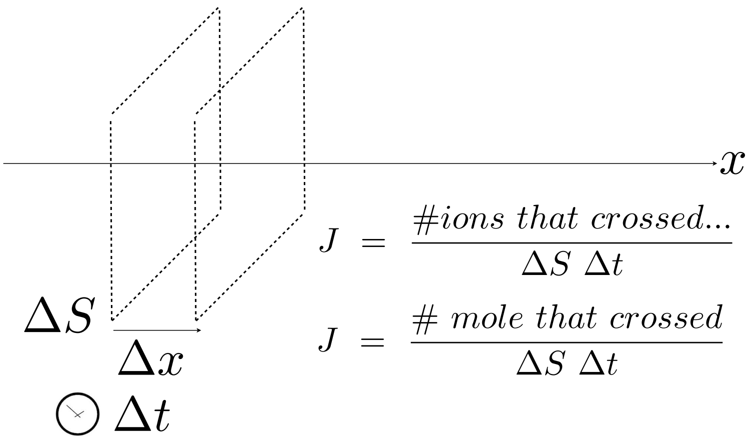
moving in one-dimension with some **velocity *v* (under external force field)**

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

$$\rho(x, y, z, t) \qquad 1/m^3$$

$$c(x, y, z, t) \qquad mM$$

$$1\ \frac{mol}{m^3} = 1\frac{mmol}{l} = 1\ mM$$



$$J = \frac{\#ions\ that\ crossed...}{\Delta S\ \Delta t} = \frac{\rho\ \Delta S\ \Delta x}{\Delta S\ \Delta t} = \rho\ v \qquad \#\ particles\ m^{-2}\ s^{-1}$$

$$J = \frac{\#\ mole\ that\ crossed}{\Delta S\ \Delta t} = \frac{c\ \Delta S\ \Delta x}{\Delta S\ \Delta t} = c\ v \qquad mole\ m^{-2}\ s^{-1} \quad c\ in\ mM$$

Teorell's formula
for the "<u>molar</u> flux"

$$\boxed{J = u\ c\ F_{ext}} \qquad mole\ m^{-2}\ s^{-1} \quad c\ in\ mM$$

REMEMBER

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

$$J \;=\; u\;\rho\;F_{ext} \qquad \#\,particles\;m^{-2}\;s^{-1}$$

$$J \;=\; u\;c\;F_{ext} \qquad mole\;m^{-2}\;s^{-1} \qquad c\;in\;mM$$

molar flux

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

ionic current density

flux charge

$$i \;=\; J\;\boxed{Q}$$

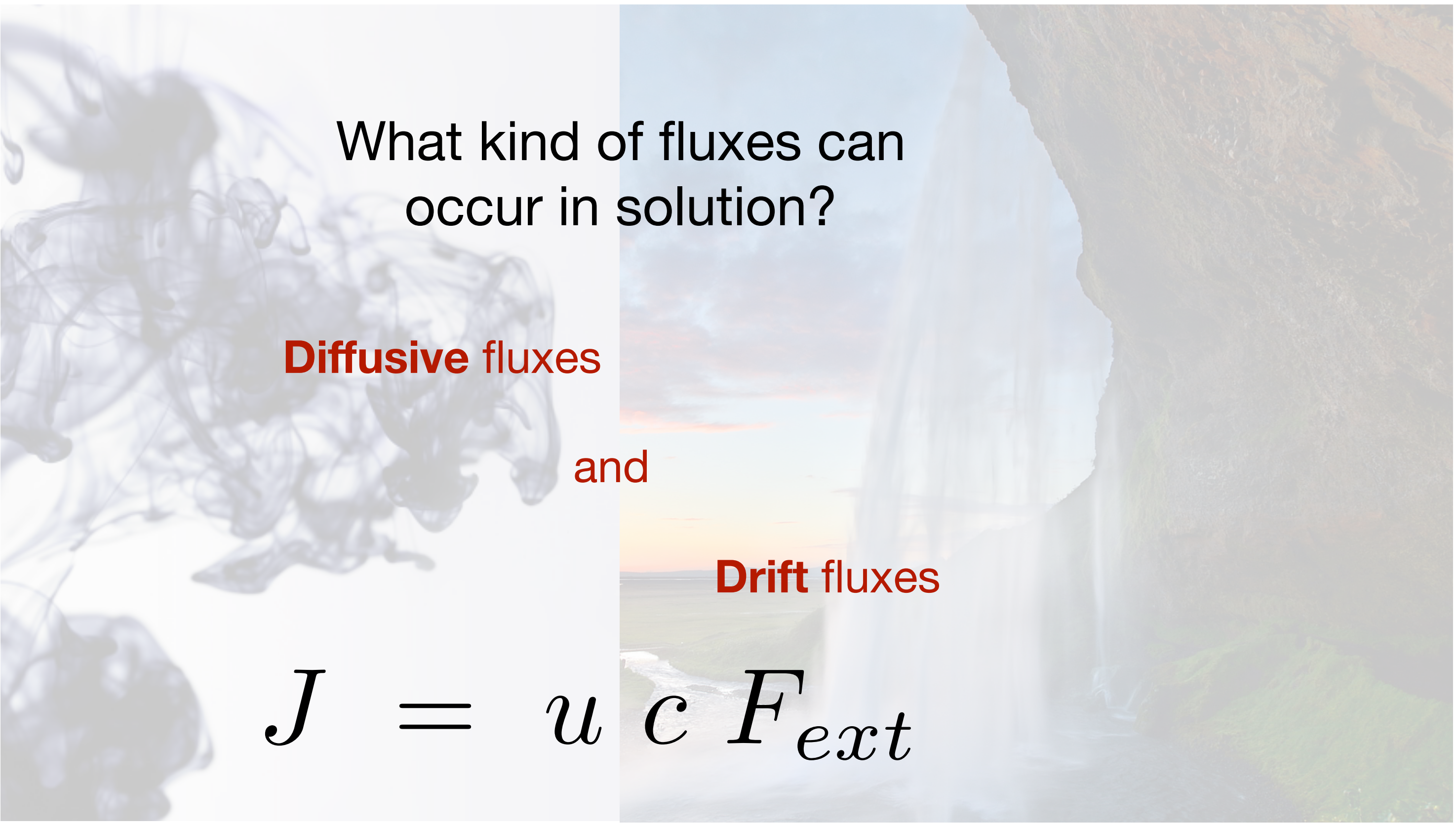
$$i \;=\; \boxed{q}\;u\;\rho\;F_{ext}$$

this is
***1.602 10–19* Coulomb**

$$i \;=\; \boxed{N_A\;q}\;u\;c\;F_{ext}$$

this is
F = *96485.33* Coulomb/mole
(known as Faraday's constant)

REMEMBER



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

$$\underset{N}{F_{ext}} = z \underset{C}{q_+} \underset{NC^{-1}}{E} = - z \, q_+ \frac{dV}{dx}$$

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

$$\underset{N}{F_{ext}} = z \underset{C}{N_A \, q_+} \underset{NC^{-1}}{\frac{dV}{dx}}$$

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

$$J = u \, c \left(z \; N_A \, q_+ \boxed{\frac{dV}{dx}} \right) = u \, c \left(-z \; F \, \frac{dV}{dx} \right)$$

drift flux

total of ***96485.33* Coulomb**

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

$c \; in \; mM$

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

REMEMBER

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

Which force field?

- (non-zero) kinetic energy of water molecules at absolute temperature T >0° K
- (kinetic) energy exchanged with water molecules, due random isotropic collisions

"Monte Carlo" simulation

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

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

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

REMEMBER

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° K
- (kinetic) energy exchanged with water molecules, due random isotropic collisions

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

$N \quad J\,K^{o\;-1} \quad K^o \quad m^{-1}$

K: Boltzmann constant

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

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

$N \quad J\,K^{o\;-1} \quad K^o \quad m^{-1}$

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

molar flux

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

diffusion flux

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

$c \; in \; mM$

8.3 Joule / kelvin = R

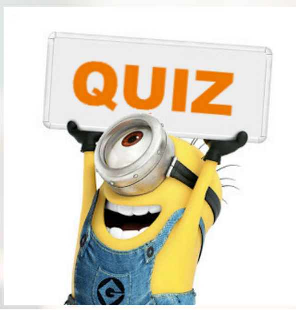
N_A is used for its value, without unit (like 1/mol).

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° K
- (kinetic) energy exchanged with water molecules, due random isotropic collisions

molar flux

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

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

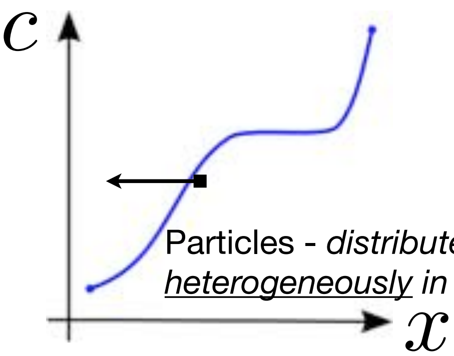
$c\ in\ mM$

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

Fick's law of diffusion

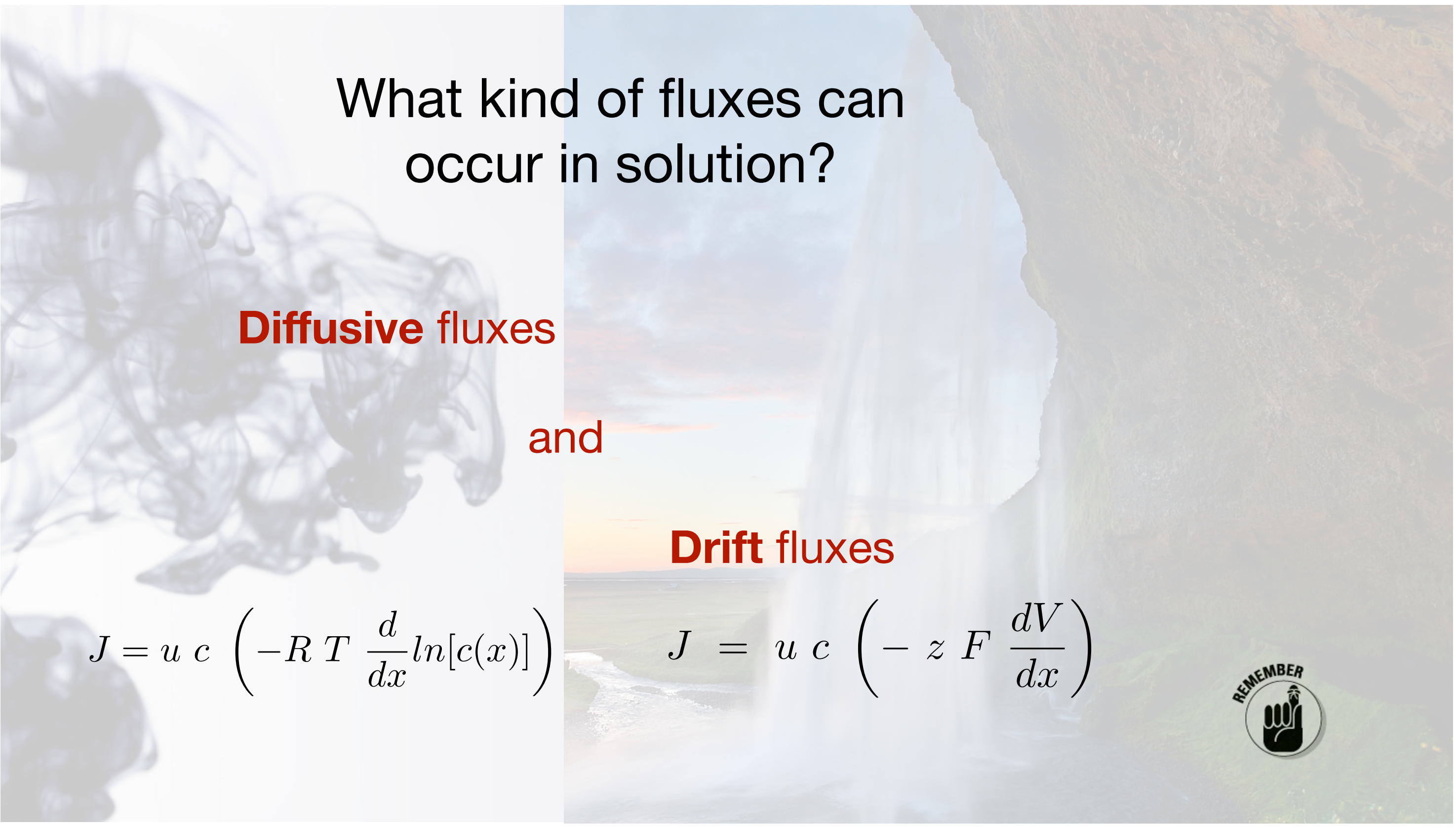
$$D = u\ K\ T$$

Einstein relation
(in kinetic theory)



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

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



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?