Solutions exercise 03

The formal solution is at the end, I also post here my hand written notes for those who were in the exercise session yesterday.
I solved exercise 3.3 here as well step by step for those who got confused. Let me know if you have questions!

Have a nice weekend!

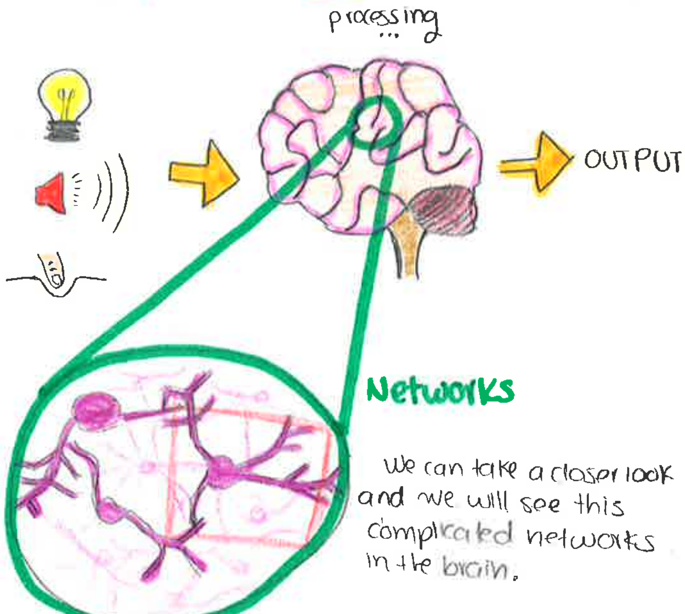
Karla

P.S. For those who submitted the exercise, the feedback is available now. Thanks

Introduction to Neuroinformatics

Karla Burelo

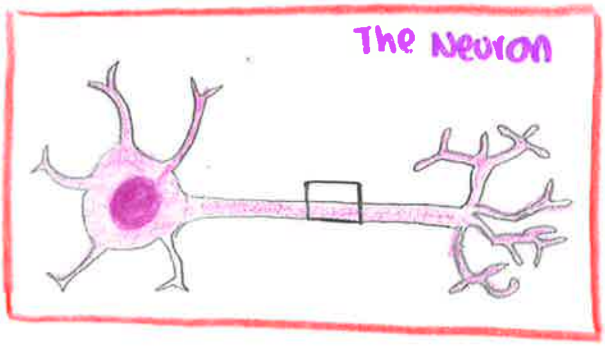
We started the exercise lecture by pointing out the most basic thing we know from the brain. We get an input from the environment this can be in different ways, for example pressure, temperatura, light...



We observe that our brain takes that input, does some sort of computation and produces an output. Now, we are interested on knowing how this happens. In this class we want to understand how the brain computes and take inspiration from it in order to apply it to our specific problems, but where do we start?

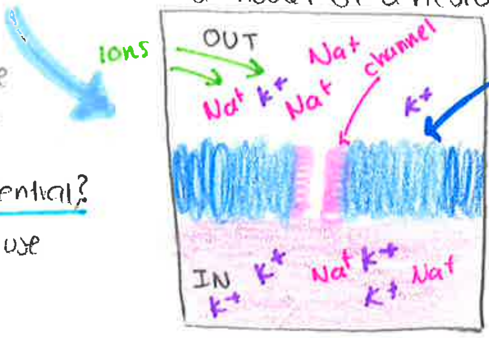
We can take a closer look and we will see this complicated networks in the brain.

Let's go even closer... let's observe a single neuron in this network.



Here is where we want to start, the basic component that we will look at first is the **neuron**. Yes, we might know already that a neuron integrates inputs from its vicinity and if a threshold is reached, the neuron spikes but why does this happen in the first place? Where do we start if we want to describe a model of a neuron?

Once again let's have an even closer look. In order to make a neuron spike, we have to 'disturb' the membrane potential, therefore we should start by understanding what is the membrane potential? how can we calculate it? and how to use it in future lectures?



Membrane

We know that the neuron has a membrane that separates the inside of the cell from the outside.

This membrane is permeable to some ions that are floting around.

Finally we know that for some reason potassium concentration is higher inside the cell... here is where we start...

Membrane Potential

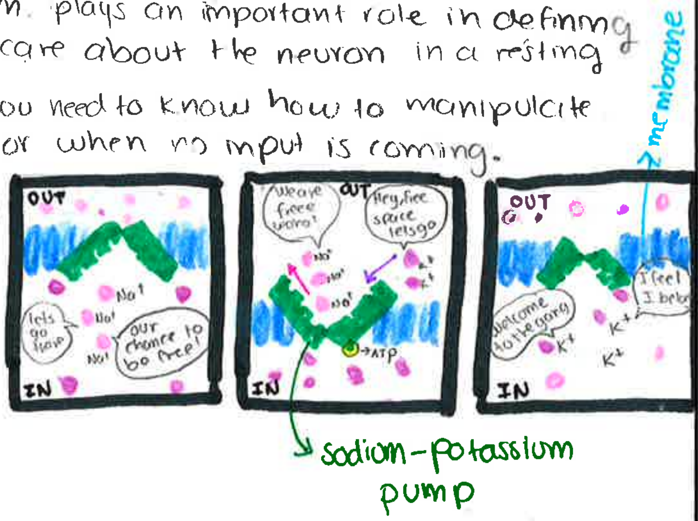
The difference in concentration of the potassium plays an important role in defining the resting membrane potential. Why do you care about the neuron in a resting phase? Well if you want to create a response, you need to know how to manipulate the neuron, so we first need to know its behavior when no input is coming.

Before we observe what happens to potassium why is the concentration of this ion higher inside in the first place?

this is how it looks in cartoon

Sodium-Potasium pump!

- will cause more positive charge outside the membrane
- needs energy to pump ions in and out.
- pumps 3 Na^+ out and 2 K^+ in



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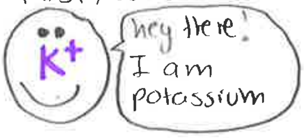
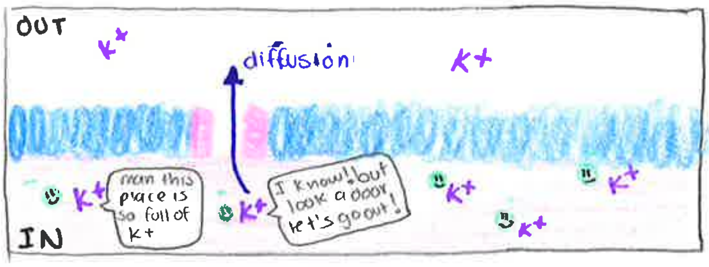
Ok now we know why potassium is more concentrated inside than outside, let's now see what is going to happen and what is the role of potassium in generating the electrical properties of a neuron.

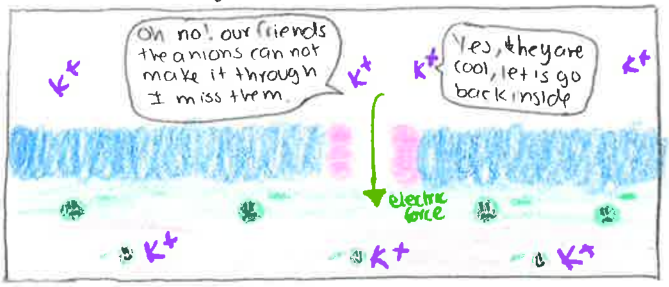
First, what we are going to see now is the effect of one single ion → potassium



but the following dynamics holds for all the other ions as well. You will see later why quantitativily Potassium has the biggest influence, for now keep in mind that the membrane is permeable & the permeability of K+ is greater than the one of other ions.



Lets see our friend K+, it is happily hanging around inside the cell (neuron). It is a bit crowded inside but K+ is ok with that until ... K+ realises there are some 'doors' channels that it can go through.



Now observe these guys ●, K+ is not hanging around alone, K+ likes to be with its other friend → anion ●, but, sad story, ● can not go through the channels that we describe here.
Therefore the flux of K+ to the outside will generate a difference in potential, imagine a layer of ● close to the membrane.

This potential difference generates an electric force that atracts K+ back inside.
At some 'point' the flux of K+ due to diffusion will equal the flux of K+ due to the electric force and we will reach a state of equilibrium → where the potential across the membrane does not change. When is that? How do we calculate this voltage?

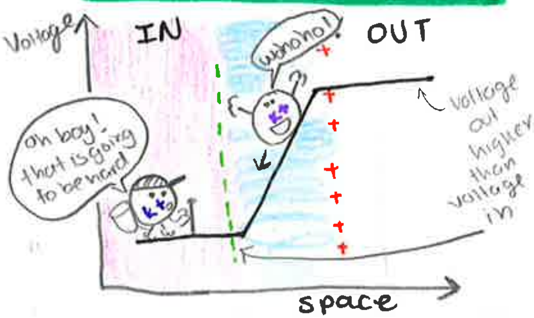
Nernst equation

Careful! We will look at the voltage generated by these two forces diffusion & electric force due to one ion → K+, I know we say K+ has the biggest influence on the voltage across the membrane → membrane potential but to know this, we will use other equation later.

Lets just quickly go through this equation. The nernst equation gives the voltage (reversal potential) that balances a given difference in chemical concentration across the cell membrane.

The expression is here

$$\boxed{V_{eq} = \frac{k_B T}{q} \cdot \ln \left(\frac{[K^+]_{out}}{[K^+]_{in}} \right)}$$



An easy way to know the origin of this equation:

We want to know the voltage at which our two mentioned forces are balanced: IN → = ← OUT

Beginning with the flux from outside to inside: we know that from the outside, the only thing we can look at is the concentration of K+ outside. Wait! but what about the electric force sending K+ inside? Yes you are right but look at it in this way... If by any chance K+ approaches the channel it will go through fast, easy, NO effort! On the other hand, from inside to outside K+ needs to gain enough energy to 'jump' to outside, that is why we write this term in the $F_{in\to out}$ equation. See the illustration on your left. Writing the expressions for $F_{in\to out}$ and $F_{out\to in}$ we get:

$$F_{in\to out} = \gamma [K^+]_{in} \cdot e^{\frac{qV_{eq}}{k_B T}} = F_{out\to in} = \gamma [K^+]_{OUT}$$

↑ because equilibrium

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Getting from $F_{in \to out} = \gamma' [K^+]_{in} \cdot e^{\frac{qV_{eq}}{k_B T}} = F_{out \to in} = \gamma' [K^+]_{out}$

to $V_{eq} = \frac{k_B T}{q} \cdot \ln\left(\frac{[K^+]_{out}}{[K^+]_{in}}\right)$ is here

① $\begin{cases} F_{in \to out} = \gamma' [K^+]_{in} \cdot e^{\frac{qV_{eq}}{k_B T}} \\ F_{out \to in} = \gamma' [K^+]_{out} \end{cases}$

② @ eq. $\to V_{eq}$

$F_{in \to out} = F_{out \to in} \therefore \cancel{\gamma'} [K^+]_{in} \cdot e^{\frac{qV_{eq}}{k_B T}} = \cancel{\gamma'} [K^+]_{out}$

③ $e^{\frac{qV_{eq}}{k_B T}} = \frac{[K^+]_{out}}{[K^+]_{in}}$

ln ln

④ $\frac{qV_{eq}}{k_B T} = \ln\left(\frac{[K^+]_{out}}{[K^+]_{in}}\right)$

⑤ $\boxed{V_{eq} = \frac{k_B T}{q} \ln\left(\frac{[K^+]_{out}}{[K^+]_{in}}\right)}$

This $\boxed{e^{\frac{qV_{eq}}{k_B T}}}$ term is telling us.

the probability that an ion will have the sufficient thermal energy $> qV$ to cross to the other side, once having the probability, we multiply by the concentration $[K^+]_{in}$

I went a bit further in the exercise lecture trying to explain the origin of $e^{\frac{qV_{eq}}{k_B T}}$, I will put it in the next **box** just for those curious, This is just if you want to know more but it is NOT necessary for the exam, you can ignore it. The result will be the same, at the end I will explain or write how to get to the Nernst eq. given in the exercise, which is a bit different but other than that feel free to ignore the following:

We mentioned that the chance of K^+ to go from inside to outside is no longer only a function of the concentration but given the voltage difference, a molecule of K^+ has to have the enough energy to cross that barrier and once that happen then concentration of K^+ inside will give us the rest. Ok but what is the minimum energy that K^+ needs?

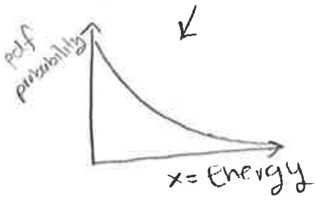
Well we know that the energy across the membrane is $E = zqV$ (energy; z: charge of ions; q: charge of an electron; V: voltage difference)

then the energy has to be $> zqV$.

Fine but how do I even calculate the energy of K^+?
The average energy of a particle is proportional to the temperature, Boltzmann found that, so now we now $E = k_B T$ (energy; k_B: Boltzmann constant; T: temperature)

Ok so we have the equation to calculate the energy and the minimum energy we need to cross, what is the problem? That the previous expression is the average response, we need to know the distribution of these energies. When we talk about distributions we mean the probability of a variable (in this case energy) to have a certain value.

Is there any distribution for this problem? There is! The Boltzmann distribution looks like this



and we write it like:

Boltzmann distribution $= \frac{1}{k_B T} e^{-\frac{x}{k_B T}}$

This starts to look like the expression above $\boxed{e^{\frac{qV_{eq}}{k_B T}}}$ but we need one more step. We said $F_{in \to out}$ depends on $[K^+]_{in} \cdot$ probability of energy being greater than zqV. Boltzmann dist. gives us the probability of any E... we need $P(E \geq zqV)$

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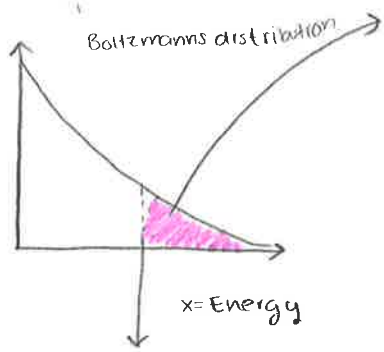
That means we need the 'tail' part of our distribution, we care about any energy greater than zqV



how to get this $\longrightarrow$ integral.

Do not panic! I promiss it is easy!

$$P(E > zqV) = \int_{zqV}^{\infty} \frac{1}{k_B T} e^{-\frac{x}{k_B T}} dx$$

evaluate the result from zqV to infinite

$x = zqV$

$$\boxed{\text{boltzmanns dist} = \frac{1}{k_B T} e^{-\frac{x}{k_B T}}}$$

constant, goes out

$$P(E > zqV) = \frac{1}{k_B T} \boxed{\int_{zqV}^{\infty} e^{-\frac{x}{k_B T}} dx}$$

Recap

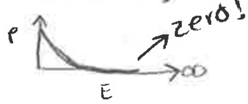
$$\boxed{\begin{aligned} \frac{d}{du} e^u &= e^u \\ \int e^u du &= e^u \end{aligned}}$$

$$k_B T \cdot e^{-\frac{x}{k_B T}} \Big|_{zqV}^{\infty}$$

$$P(E > zqV) = \frac{1}{\cancel{k_B T}} \cdot \left(-\cancel{k_B T} \cdot e^{-\frac{x}{k_B T}} \Big|_{zqV}^{\infty} \right)$$

$$P(E > zqV) = -e^{-\frac{x}{k_B T}} \Big|_{zqV}^{\infty} = \cancel{-e^{-\frac{\infty}{k_B T}}} \cancel{-}\left(\cancel{-} e^{-\frac{zqV}{k_B T}}\right)$$

what happens to probability when E goes to infinite?



$$P(E > zqV) = + e^{-\frac{zqV}{k_B T}}$$

Lets have our Fin→out expression here:

$$F_{in \to out} = [K^+]_{in} \cdot P(E > zqV)$$

$$F_{in \to out} = [K^+]_{in} \cdot e^{-\frac{zqV}{k_B T}}$$

we do the same as before

$$F_{in \to out} = F_{out \to in}$$

$$\frac{[K^+]_{OUT}}{[K^+]_{in}} = e^{-\frac{zqV}{k_B T}}$$

Almost there, if you were in class today you realize that minus sign is not in the final equation. The problem is I wrote V and what I should have written is $V_{in \to out}$, now remember we need the energy to be positive so if we do $V_{out \to in}$ instead we can 'eat' this minus sign and have the expression:

$$\frac{[K^+]_{OUT}}{[K^+]_{in}} = e^{\frac{zq V_{OUT \to in}}{k_B T}}$$

the rest you know...

☺

that's it!

Two diff. ways to write Nernst equation:

In class:

$$V_{equilibrium} = \frac{k_B T}{q} \cdot \ln\left(\frac{[K^+]_{out}}{[K^+]_{in}}\right)$$

In the exercise:

$$V_{equilibrium} = \frac{RT}{zF} \cdot \ln\left(\frac{[K^+]_{OUT}}{[K^+]_{in}}\right)$$

(also reversal potential, hence the E_{rev_K})

This is why:

$N_A = 6.023 \times 10^{23}$	avogadros number
$k_B = 1.38 \times 10^{-27}$	boltzmanns constant
$R = N_A k_B$	universal gas constant
$F = e^+ N_A$	Faradays constant

∴ Is the same!

Goldman - Hodgkin - Katz Equation

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Finally, another important equation to consider is the Goldman-Hodgkin-Katz equation, with this one we can know the membrane potential. Nernst eq will only give us the reversal potential due to one single ion and even though K^+ has the biggest influence, the membrane is also permeable to the other ions.

I mentioned that the permeability of K^+ is larger than the permeability of the other ions, in exercise 3.3 we have to calculate by how much. Here is my solution, I prefer to fill the numbers at the end:

$$V_{mem} = \frac{RT}{F} \ln \left(\frac{P_K \cdot [K^+]_{out} + P_{Na} \cdot [Na^+]_{out} + P_{Cl}[Cl^-]_{in}}{P_K \cdot [K^+]_{in} + P_{Na} \cdot [Na^+]_{in} + P_{Cl}[Cl^-]_{out}} \right)$$

neglect this

$$V_{mem} = \frac{RT}{F} \ln \left(\frac{P_K \cdot [K^+]_{out} + P_{Na} \cdot [Na^+]_{out}}{P_K \cdot [K^+]_{in} + P_{Na} \cdot [Na^+]} \right)$$

$$\frac{V_{mem} \cdot F}{RT} = \ln \left(\frac{P_K [K^+]_{out} + P_{Na} \cdot [Na^+]_{out}}{P_K [K^+]_{in} + P_{Na} \cdot [Na^+]_{in}} \right)$$

cancel ln by taking exponential on both sides...

$$e^{\frac{V_{mem} \cdot F}{RT}} = \frac{P_K [K^+]_{out} + P_{Na} \cdot [Na^+]_{out}}{P_K [K^+]_{in} + P_{Na} \cdot [Na^+]_{in}}$$

pass the denominator, multiplying the other side...

$$P_K [K^+]_{in} \cdot e^{\frac{V_{mem} \cdot F}{RT}} + P_{Na} \cdot [Na^+]_{in} \cdot e^{\frac{V_{mem} \cdot F}{RT}} = P_K [K^+]_{out} + P_{Na} [Na^+]_{out}$$

Bring P_K in one side of the eq...

$$P_K [K^+]_{in} \cdot e^{\frac{V_{mem} \cdot F}{RT}} - P_K [K^+]_{out} = P_{Na} [Na^+]_{out} - P_{Na} [Na^+]_{in} \cdot e^{\frac{V_{mem} \cdot F}{RT}}$$

$$P_K \left([K^+]_{in} \cdot e^{\frac{V_{mem} \cdot F}{RT}} - [K^+]_{out} \right) = P_{Na} \left([Na^+]_{out} - [Na^+]_{in} \cdot e^{\frac{V_{mem} \cdot F}{RT}} \right)$$

$$\boxed{\frac{P_K}{P_{Na}} = \frac{[Na^+]_{out} - [Na^+]_{in} \cdot e^{\frac{V_{mem} \cdot F}{RT}}}{[K^+]_{in} \cdot e^{\frac{V_{mem} \cdot F}{RT}} - [K^+]_{out}}}$$

$$e^{\frac{V_{mem} \cdot F}{RT}} = e^{\frac{-0.077 \cancel{V} \cdot 9.648510^4 \cancel{C}/\cancel{mol}}{8.314 \cancel{J}/(\cancel{mol} \cdot \cancel{K}) \cdot 293.15 \cancel{K}}}$$

$$V = \frac{J}{C}$$

293.15K → 20 °C

$$e^{\frac{V_{mem} \cdot F}{RT}} = 0.047$$

Now lets put some numbers:

$$\frac{P_K}{P_{Na}} = \frac{142\,mM - 10\,mM \cdot 0.047}{148\,mM \cdot 0.047 - 5\,mM} = \frac{141.53}{1.956} = 72.36$$

P_K is larger than P_{Na} by 72.36

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Solution 3.1: Diffusion

1. from A to B
2. negative
3. opposite

Solution 3.2: The Nernst Equation

1.

$$E_K = 58\text{mV} \cdot \log_{10}\left(\frac{[\text{K}^+]_{extracellular}}{[\text{K}^+]_{intracellular}}\right) = 58\text{mV} \cdot \log_{10}\left(\frac{5}{148}\right) = 58\text{mV} \cdot (-1.47) = -85.3\text{mV}$$

$$E_{Na} = 58\text{mV} \cdot \log_{10}\left(\frac{[\text{Na}^+]_{extracellular}}{[\text{Na}^+]_{intracellular}}\right) = 58\text{mV} \cdot \log_{10}\left(\frac{142}{10}\right) = 58\text{mV} \cdot 1.15 = 66.8\text{mV}$$

2.

$$E'_{Na} = 58\text{mV} \cdot \log_{10}\left(\frac{142+5}{10}\right) = 58\text{mV} \cdot 1.17 = 67.7\text{mV}$$

$$E'_K = 58\text{mV} \cdot \log_{10}\left(\frac{5+5}{148}\right) = 58\text{mV} \cdot (-1.17) = -67.9\text{mV}$$

$$\frac{E'_{Na} - E_{Na}}{E_{Na}} = +1.3\%$$

$$\frac{E'_K - E_K}{E_K} = -20.5\%$$

The extracellular change of $[\text{K}^+]$ has a more drastic effect. This condition is dangerous because the heart muscle contraction depends on the membrane potential, and this potential results from mechanisms very similar to the ones governing the neuron's potential.

Solution 3.3: The Goldman-Hodgkin-Katz Equation

Qualitatively:

Since $V_{membrane}$ is closer to E_K than to E_{Na}, we can conclude that the membrane must be more permeable to K^+, *i.e.*, P_K is bigger than P_{Na}.

Quantitatively:

$$V_{membrane} = \frac{RT}{F} \ln\left(\frac{P_K \cdot [\text{K}^+]_{out} + P_{Na} \cdot [\text{Na}^+]_{out}}{P_K \cdot [\text{K}^+]_{in} + P_{Na} \cdot [\text{Na}^+]_{in}}\right)$$

$$-77\text{mV} = 58\text{mV} \cdot \log_{10}\left(\frac{P_K \cdot 5 + P_{Na} \cdot 142}{P_K \cdot 148 + P_{Na} \cdot 10}\right)$$

$$10^{\frac{-77}{58}} = 0.0470 = \frac{P_K \cdot 5 + P_{Na} \cdot 142}{P_K \cdot 148 + P_{Na} \cdot 10}$$

$$P_K \cdot 148 \cdot 0.0470 + P_{Na} \cdot 10 \cdot 0.0470 = P_K \cdot 5 + P_{Na} \cdot 142$$

$$P_K \cdot (148 \cdot 0.0470 - 5) = P_{Na} \cdot (142 - 10 \cdot 0.0470)$$

$$\frac{P_K}{P_{Na}} = 72.2$$