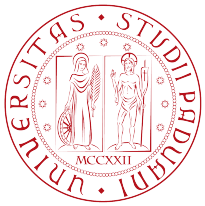

Description of a cell depolarization using the GHK equation

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MATLAB exercise for the Biological Physics exam

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Abstract: The Goldman–Hodgkin–Katz (GHK) flux equation describes the ionic flux across a cell membrane as a function of the transmembrane potential and of the concentrations of the ions inside and outside of the cell. The main ionic contributions in this process are due to sodium and potassium. If active sodium and potassium pumps, whose purpose is to regulate the correct concentration gradient between the two sides of the cellular membrane, are not present within the cell, the ion flux will depolarize the system. In this paper it will be analyzed the behaviour of a non-excitable cell membrane in absence of active pumps using the GHK equation.

Key words: *Goldman-Hodgkin-Katz equation, cell depolarization, computational biological physics*.

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1. Introduction

In order to describe the living cell and its lifecycle, several physical parameters are used: among them, the concentration of sodium and potassium ions and the resting potential are fundamental. How are these parameters related?

Given the concentration of a ion species inside the cell $[S]_{in}$ and the concentration of the same species outside the cell $[S]_{out}$, the Nerst potential is defined as the transmembrane potential that the cell needs to generate in order to counterbalance the effects of concentration gradients which lead the cell to equilibrium. The Nerst potential is described by the following equation, namely

$$V_{Nerst} = \frac{RT}{zF} \ln \frac{[S]_{out}}{[S]_{in}} \tag{1}$$

where R is the *universal gas constant*, T the *absolute temperature* in K at equilibrium, z is the *charge* of ion S, while F is the *Faraday's constant*[1].

In living cells, the resting membrane potential ΔV (i.e. the relatively static membrane potential of quiescent cells) is rarely governed by only one ion: if this were the case, the membrane potential could be predicted by the equilibrium potential for that ion, and could be easily calculated by using Equation (1). Instead, the membrane potential is generally established as a result of the relative contributions of several ions, such as Na^+, K^+. When more than one ion channel is present (and open) in the plasma membrane, the membrane potential ΔV can be calculated by using the Goldman-Hodgkin-Katz (GHK) flux[2] equation for the ion S, namely

$$I_S = P_S \frac{z_S^2 F^2 \Delta V}{RT} \cdot \frac{[S]_{in} \mathrm{e}^{\frac{z_S F \Delta V}{RT}} - [S]_{out}}{1 - \mathrm{e}^{\frac{z_S F \Delta V}{RT}}} \tag{2}$$

which will be described and derived in Section 2.1; it is important to notice that the condition $I_S = 0$ gives the canonical expression for the Nerst potential (1) of the ion S.

The relative contribution of any given ion is determined not only by its concentration gradient across the plasma membrane, but also by its relative membrane permeability P_S i.e. to the ease with which ions cross the membrane, and is directly proportional to the total number of open channels for a given ion in the membrane.

When two or more ions contribute to the membrane potential, it is likely that the membrane potential would not be at the equilibrium potential for any of the contributing ions: when an ion is not at its equilibrium, an electrochemical driving force acts on the ion, causing the net movement of the ion across the membrane down its electrochemical gradient. The driving force is quantified by the difference between the membrane potential and the ion equilibrium potential.

Transmembrane currents are related to the fact that the resting potential of a cell is typically different from the Nerst potential and therefore ion concentrations are not at equilibrium: this reason for which we can see the presence of a transmembrane currents. When the transmembrane currents aren't counterbalanced by active pumps, the total ion fluxes are not zero and the cell will depolarize, losing stability [1].

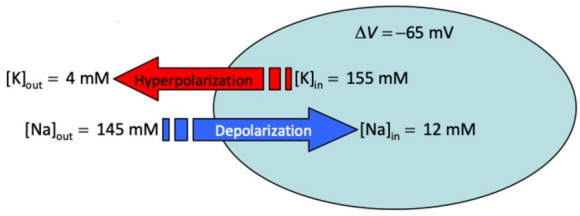

Figure 1: *Schematics of a cell depolarization due to the passive transport of ions between the two sides of the cellular membrane. Once the Na^+ channels open, the K^+ ions try to counterbalance the Na^+ flux but, being the amount of K^+ virtually unlimited outside the membrane, the cell depolarize to zero voltage resting potential after some time. In the Figure the initial values of the intra- and extracellular concentrations of the Na^+ and K^+ ions are reported, along with the cell resting potential value ΔV. Image taken from [3].*

In this paper we will consider Na^+ and K^+ ions as the major transmembrane current components of the living cell: the Na^+ flux will tend to depolarize the cell once Na^+ channels open. Despite

[1] Faraday's constant represents the magnitude of electric charge per mole of electrons and it is defined as $F := e \cdot N_A$, where N_A is the Avogadro number, while e is the elementary charge.

[2] In order to be more precise, I_S is the current density (flux) across the membrane carried by ion S.

the K^+ flux tries to counterbalance this effect, the amount of K^+ ions inside the cell is limited, while the amount of Na^+ ions outside the cell is virtually unlimited: at some point the internal concentration of potassium ions won't be able to hyperpolarize the cell anymore, letting sodium prevail on the K^+ flux. This implies that, in the absence of ion pumps that maintain the concentration gradient, after some time the cell will tend to depolarize to zero voltage resting potential and zero concentration ionic gradient.

In the presented work, supposing fixed extracellular concentrations (see Figure 1), we will simulate the voltage and the concentration changes occurring during cell polarization, starting form the resting potential condition $\Delta V = -65\,mV$.

In the end we will include the case in which a negative fixed charge is initially present in the cell in order to generate the potential difference across the membrane.

2. Methods

In this section we will justify the the theoretical model used in the simulations by deriving the GHK flux equation from the *Smoluchowki equation* and from the *Nerst - Planck equation*. In the end the simulation parameters will be included.

2.1. Theoretical model

The description of the passive transport of ions takes into account the fact that ions move under the influence of both a concentration gradient and a potential gradient across the membrane. For this reason the starting-off point for the discussion of the theoretical model used in this paper is the diffusion equation in the presence of an external field (or force), i.e. the *Smoluchowski equation*[3] [2]:

$$\frac{dC}{dt} = D\frac{d^2C}{dx^2} - BX\frac{dC}{dx} \tag{3}$$

where C is the concentration of the ion S, B the *mechanical mobility* of the particle (measured in $[m \cdot s^{-1} \cdot N^{-1}]$), X is the external force and D is the diffusion coefficient.

On the other hand, using the first Fick's law, we can describe the flux J of a diffusing molecular species as equal to the product of the concentration gradient and of a diffusion coefficient D :

$$J = -D\frac{dC}{dx} \tag{4}$$

Taking the space derivative on both sides of (4) and taking into account the second Fick's law, namely

$$\frac{dC}{dt} = D\frac{d^2C}{dx^2} \tag{5}$$

we can write the space derivative of (4) as:

$$\frac{dJ}{dx} \overset{(5)}{=} -\frac{dC}{dt} \tag{6}$$

Substituting the Smoluchowki equation (3) in the right member of (6) and performing a step of spatial integration we get:

$$J = -D\frac{dC}{dx} + BXC \tag{7}$$

Considering then a potential difference ΔV between the two sides of the membrane we can express the force X (being conservative) using its potential energy $U(x)$, such that $X = -d_xU(x)$. Therefore, remembering that $U(x) = zeV(x)$, we can write (7) as

$$J = -D\frac{dC}{dx} - zeBC\frac{dV}{dx} \tag{8}$$

where z is the ion valency[4] and e is the module of the elementary charge ($e = 1.602 \cdot 10^{-19}C$).

Equation (8) can be rewritten in terms of the current density I such that:

$$\begin{aligned} I &:= zeJ \cdot N_A = \\ &\overset{(8)}{=} -zeN_AD\frac{dC}{dx} - z^2e^2N_ABC\frac{dC}{dx} = \\ &= -zFD\left(\frac{dC}{dx} + \frac{zeBC}{D}\frac{dV}{dx}\right) \end{aligned}$$

Considering then the *Einstein relation* $D = k_BTB$, where $k_B := R/N_A$ is the *Boltzmann's constant* and T is the temperature in K, we find the *Nerst-Plank equation* for an ion species S diffusing in a membrane [3]:

$$I = -zFD\left(\frac{dC}{dx} + \frac{zFC}{RT}\frac{dV}{dx}\right) \tag{9}$$

[3] In this paper only the one-dimensional case will be treated.

[4] For the Na^+ and K^+ ions the ion valences are both equal to 1.

where D and C refer to the ion within the membrane.

In order to develop the GHK constant-field theory using the Nerst-Planck equation (9) it is important to assume that ions cross the membrane without interacting each other and that the electric field in the membrane is constant.

Multiplying both members of (9) by $\exp \frac{zFV}{RT}/D$ gives

$$I \cdot \frac{\mathrm{e}^{\frac{zFV}{RT}}}{D} = -zF\left(\frac{dC}{dx} + \frac{zFC}{RT}\frac{dV}{dx}\right)\mathrm{e}^{\frac{zFV}{RT}} = -\mathrm{z}F\frac{d}{dx}\left(C\mathrm{e}^{\frac{zFV}{RT}}\right)$$

If one assumes that the membrane is homogeneous with constant D and that the potential drops linearly in a constant electric field E from $x_1 = 0$ to $x_2 = d$, then $V = E \cdot x := (\Delta V/d)x$ integrating both sides of the previous equation between the two sides of the membrane gives

$$I = zF\frac{C\left(x_1\right)e^{\frac{2F\Delta V}{RT}} - C\left(x_2\right)}{\int_{x_1}^{x_2}\left(e^{\frac{2FV(x)}{RT}}/D\right)dx} \tag{10}$$

where we can impose that $V = \Delta V$ at x_2 and $V = 0$ at x_1 and so

$$I = \frac{z^2F^2D\Delta V}{RTd} \cdot \frac{C_{in}e^{\frac{zF\Delta V}{RT}} - C_{out}}{1 - e^{\frac{zF\Delta V}{RT}}} \tag{11}$$

In the previous equation $C_{in} = C(0)$ and $C_{out} = C(d)$ are the concentrations of the ion at membrane's boundaries. Defining then the *permeability* of the ions S as $P_S := D/d$ (with D computed *inside* the membrane) we can write

$$I_{\mathrm{S}} = P_{\mathrm{S}}\frac{z_{\mathrm{S}}^2F^2\Delta V}{RT} \cdot \frac{C_{in}\mathrm{e}^{\frac{z_{\mathrm{S}}F\Delta V}{RT}} - C_{out}}{1 - \mathrm{e}^{\frac{z_{\mathrm{S}}F\Delta V}{RT}}} \tag{12}$$

which is the GHK (current) equation for the ion S.

If we focus our attention on sodium and potassium ions[5], we can express the current equation for the equivalent circuit of a non-excitable cell in which only Na^+ and K^+ channels are present as

$$c\,\frac{dV}{dt} = I_{\mathrm{K}} + I_{\mathrm{Na}} \tag{13}$$

[5]From now on $S := \{\mathrm{Na}^+, \mathrm{K}^+\}$ only.

where c is the cell membrane specific capacitance per unit of area. From now on z_S will be set equal to 1 in order to simplify the notation (see note [4]).

Let's rewrite equation (13) using the GHK equation (16): what we get is that

$$c\frac{dV}{dt} = P_{\mathrm{K}}\frac{F^2\Delta V}{RT} \cdot \frac{[\mathrm{K}]_{in}\mathrm{e}^{\frac{F\Delta V}{RT}} - [\mathrm{K}]_{out}}{1 - \mathrm{e}^{\frac{F\Delta V}{RT}}} + + P_{\mathrm{Na}}\frac{F^2\Delta V}{RT} \cdot \frac{[\mathrm{Na}]_{in}\mathrm{e}^{\frac{F\Delta V}{RT}} - [\mathrm{Na}]_{out}}{1 - \mathrm{e}^{\frac{F\Delta V}{RT}}}$$

In order to describe the time evolution of the internal concentrations of the Na^+ and K^+ ions we need to write differential equations for $[\mathrm{K}]_{in}$ and $[\mathrm{Na}]_{in}$.

We can derived them by describing the current I_S of a monovalent ion species S as the movement of dN_S monovalent ions in the time dt across the cell membrane area A. Thus we can write $I_{\mathrm{s}} = (e/\mathrm{A})\,dN_S/dt$ or, in terms of mols, $M_{\mathrm{s}}I_{\mathrm{s}} = (e/\mathrm{A})\,N_{\mathrm{A}}dM_{\mathrm{s}}/dt = (F/A)dM_s/dt$.

Dividing both members by the cell volume v gives $I_{\mathrm{s}}/v = (F/A)d\left(M_{\mathrm{s}}/v\right)/dt = (F/\mathrm{A})d[\,\mathrm{S}]_{\mathrm{in}}/dt$ and thus, for an $S = \{\mathrm{Na}^+, \mathrm{K}^+\}$ ions we can write that:

$$\frac{d[S]_{in}}{dt} = P_S\frac{AF\Delta V}{vRT} \cdot \frac{[S]_{in}\mathrm{e}^{\frac{F\Delta V}{RT}} - [S]_{out}}{1 - \mathrm{e}^{\frac{F\Delta V}{RT}}}$$

such that

$$\frac{d[S]_{in}}{dt} := \frac{A}{v}j_S \tag{14}$$

where

$$j_S = P_S\frac{F\Delta V}{RT} \cdot \frac{[S]_{in}\mathrm{e}^{\frac{F\Delta V}{RT}} - [S]_{out}}{1 - \mathrm{e}^{\frac{F\Delta V}{RT}}} = \tag{15}$$

$$= P_S\frac{e\Delta V}{k_BT} \cdot \frac{[S]_{in}\mathrm{e}^{\frac{e\Delta V}{k_BT}} - [S]_{out}}{1 - \mathrm{e}^{\frac{e\Delta V}{k_BT}}} \tag{16}$$

is the ion flux of species S entering the cell and is related to the current density as follows [3]:

$$I_S = eN_Aj_S \tag{17}$$

Then, supposing that a negative fixed charge was initially present within the cell generating the

potential difference across the membrane and assuming a perfectly spherical cell[6], we can compute the cell's charge surface density as $\sigma := \mathcal{Q}_{tot}/A$, where

$$\mathcal{Q}_{tot} = Q_{ions} + Q \tag{18}$$

is the sum of the charge due to the presence of the sodium and potassium ions ($Q_{ions} = \left(C_{in}^{K} + C_{in}^{Na}\right) ev$) and of the internal fixed charge Q. Finally, knowing that [1]

$$\Delta V = \frac{\sigma}{c} \tag{19}$$

and substituting in the previous equation the definition of the cell's charge surface density we get that

$$\Delta V = \frac{\left(C_{in}^{K} + C_{in}^{Na}\right) ev + Q}{cA} \tag{20}$$

where C_{in}^{K} is the concentration of potassium ions inside the cell, C_{in}^{Na} the intramembrane concentration of sodium ions in the cell, v the cell's volume, A its area and Q is the fixed charge located inside the cell.

2.2. Simulation Parameters

In the simulation described in this paper a spherical cell of volume $V = 5000\,\mu m^3$ was considered, and its resting potential was set to a value ΔV equal to

$$\Delta V = -65\,mV$$

The initial values of the intramembrane ($_{in}$ subscript) and extramembrane ($_{out}$ subscript) concentrations of the Na^+ and K^+ ions are:

$$C_{in}^{Na} = 12\,\text{mM} \qquad C_{out}^{Na} = 145\,\text{mM}$$
$$C_{in}^{K} = 155\,\text{mM} \qquad C_{out}^{K} = 4\,\text{mM}$$

as represented in Figure 1. In the code reported in Section 5 the initial concentrations of the ions are considered as bi-dimensional arrays.

The permeability of the Na^+ and K^+ ions were respectively set to

$$P_{Na} = 0.2\,\mu m/s \qquad P_K = 10.0\,\mu m/s$$

while the cell membrane specific capacitance c was set equal to

$$c = 1.0 \cdot 10^{-2}\,F/m^2.$$

Using those parameters it was possible to compute, using the GHK flux equation (16), the initial fluxes of the the Na^+ and K^+ ions:

$$j_{Na} = 0.0791 \cdot 10^{-3} mol/m^3 s$$
$$j_K = -0.2304 \cdot 10^{-3} mol/m^3 s$$

The last parameter used in the simulation is the fixed charge Q initially present inside the cell during the second simulation: it was computed with the inverse formula of Equation (20), namely:

$$Q = Ac\Delta V - \left(C_{in}^{K} + C_{in}^{Na}\right) e\, v \approx -80.45\,nC$$

3. Results and discussion

The simulated system has been integrated with a first order time evolutor using a Forward Euler Method. The time step chosen for the simulation is $\Delta t = 10\,ns$ with a simulation time equal to $25\,ms$: it's easy to see from the following plots that after this time interval the system has reached equilibrium.

The simulations have been run using MatLab R2019b and are divided in two main parts using a `switch case` condition (see line 59 of Section 5). The results obtained from the two simulations will be discussed in the following sections.

3.1. First simulation: no fixed charge inside the cell

In the first simulation we computed the depolarization of the cell due to the Na^+ ion flux from outside the cell towards the inside of the cell and the counterbalance due to the K^+ flux going in the opposite direction. As consequence, the internal concentration of sodium ions inside the cell rises and the potassium one decreases, until the system reaches the equilibrium.

This process can be explained, as we can see from Figure 2, by the fact that at $t = 0$ there is positive current due to the Na^+ ions entering the cell and a negative one due to the K^+ ions.

From Figure 2 it can be deduced also that the total current $I_{Total} := I_{Na} + I_K$ is (beside the initial peak) almost zero both during the system's time evolution ($t \in [0; 15]\,ms$) and - as expected

[6] In the perfect spherical cell approximation we can suppose that all the internal charges in the cell are uniformly distributed on the internal surface of the cell membrane.

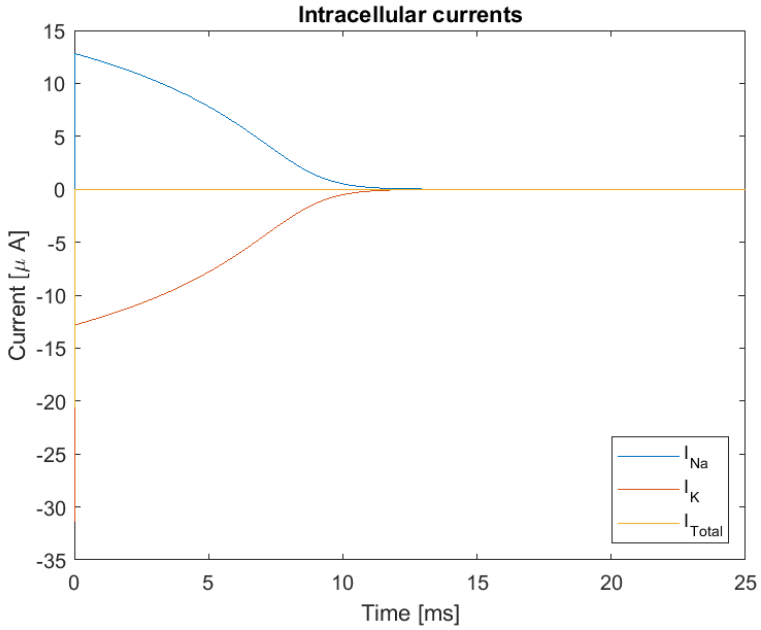

Figure 2: First simulation:*sodium and potassium currents as a function of time. The total current $I_{tot} = I_{Na} + I_K$ is also represented in this plot.*

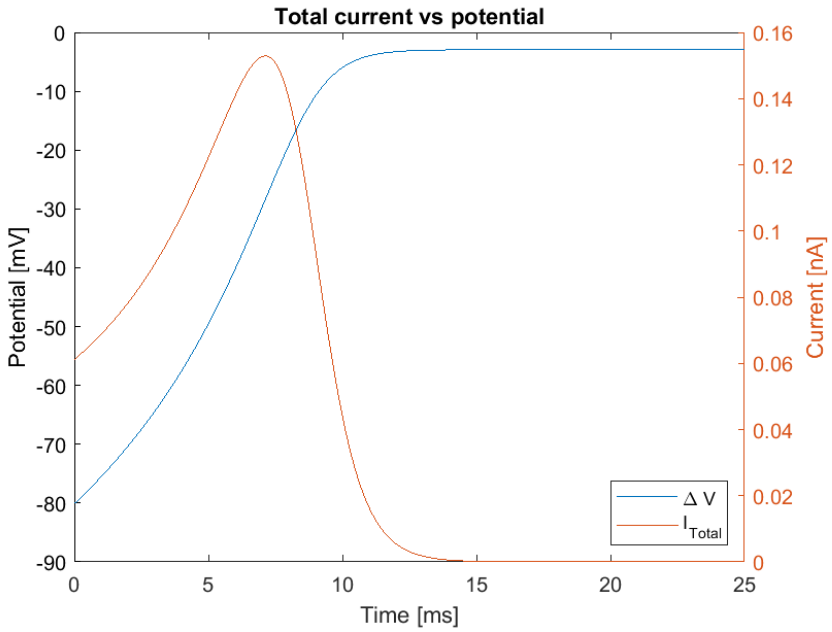

Figure 3: First simulation: *total current inside the cell and potential as functions of time. The values of t lower than $10\,\mu s$ were not included in the plot in order to exclude the initial current and potential peaks from the plot.*

- also when the system has reached its equilibrium ($t \in [15; 25]\,ms$). This is not completely true: even if I_{Total} is very low with respect to I_{Na} and I_K, it is never zero in the $[0; 15]\,ms$ temporal range, as we can see from Figure 3.

In fact, the plot of Figure 3 shows that the total current reaches its maximum at the potential flex ($t \approx 6\,ms$), while the current goes to zero when the potential reaches its equilibrium value $^*\Delta V = -2.9\,mV$. In the plot of Figure 3 the ini-

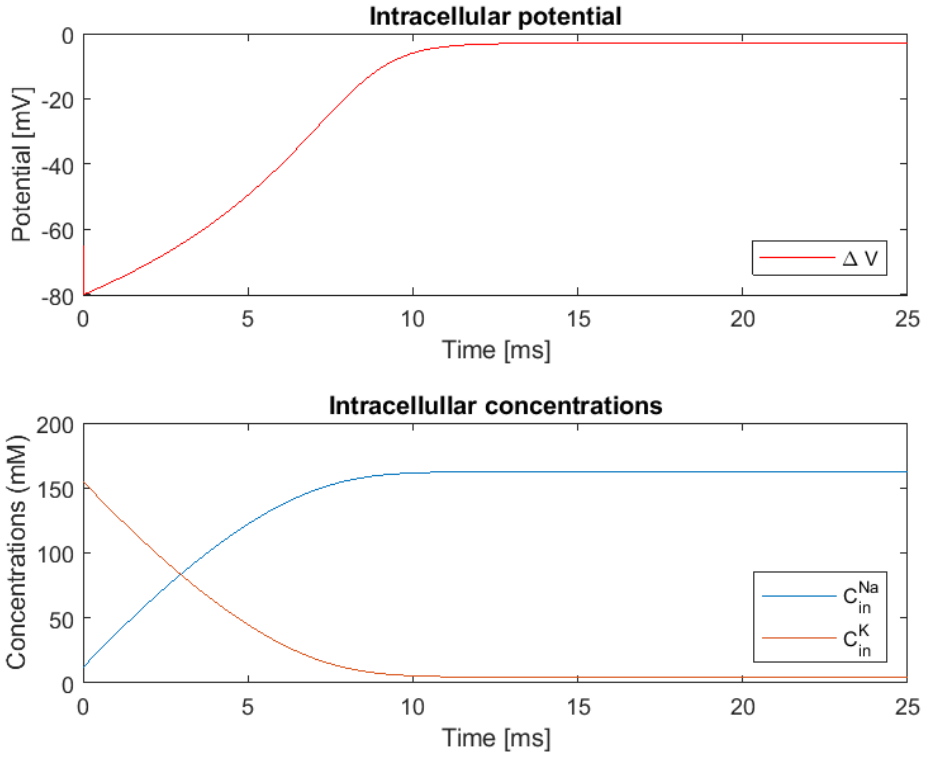

Figure 4: First simulation: *time evolution of the internal concentrations of sodium and potassium ions and of the cell potential, simulated until the system reaches equilibrium.*

tial peaks were excluded setting a time threshold of $10\,\mu s$ (lines 117-118 of the code in Section 5) in order to observe the total current behaviour more clearly during the time interval in which the system evolves.

The system was simulated by computing j_S using Equation (16) and by then discretizing equations (14) and (13), respectively:

$$\begin{cases} C_{in}^S(t+\Delta t) = C_{in}^S(t) + j_S(t)\dfrac{A}{v}\Delta t & (21) \\ \Delta V(t+\Delta t) = \Delta V(t) + e\dfrac{\sum_S j_S}{c}\Delta t & (22) \end{cases}$$

In order to speed up the `for` cycle of lines 66-73 (see Section 5) the ion fluxes, the ion currents, the ions' intramembrane concentrations and their permeability were considered as bi-dimensional arrays. Furthermore in lines 55-58 some constant simulation factors were computed before the simulation for the same reason. The equilibrium values[7] of the intra-extra cellular potential difference and of the internal concentrations reached by the system are:

$$\begin{aligned} {}^*\Delta V &= -2.9\,mV \\ {}^*C_{in}^{Na} &= 162.5\,\text{mM} \\ {}^*C_{in}^{K} &= 4.5\,\text{mM} \end{aligned}$$

and their evolution over time is represented in Figure 4.

It's interesting to point out that the *equilibrium values* of the internal concentrations of the potassium and sodium ions (${}^*C_{in}^S$) are really close to the values of the ions' (fixed) extramembrane concentrations C_{out}^S reported in section 2.2: the percentage change between C_{out}^{Na} and ${}^*C_{in}^{Na}$ is about 10.8%, while the percentage change between C_{out}^K and ${}^*C_{in}^K$ is about 11.1%.

The equilibrium values of the internal concentrations of the ions are not exactly equal to the external fixed ones because of the (small) non-zero potential difference ${}^*\Delta V$.

[7] The system's equilibrium values are denoted with *.

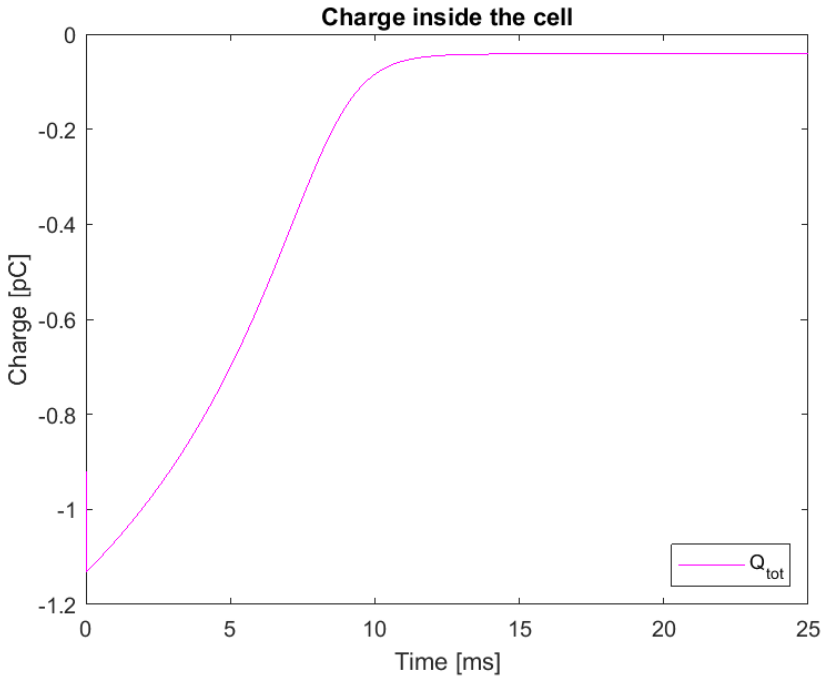

Figure 5: Second simulation: *time evolution of the total charge $\mathcal{Q}_{tot}$ inside the cell.*

The final values of the the Na^+ and K^+ fluxes are negligible after the cell has reached the equilibrium ($j_S \sim 10^{-12} mol/m^3 s$).

3.2. Second simulation: negative fixed charge inside the cell

In the second simulation we included the case in which a negative fixed charge was initially present within the cell to generate the potential difference across the membrane.

The aim of this complexification is to reproduce more realistically what happens in a living cell in the absence of active pumps.

The presence of negative charges inside the cell is usually due to large proteins which are not able to go across the plasma membrane and so the charge Q was assumed to be constant in time (because it remains inside the cell).

Because of the presence of the additional charge, the update rules presented in Section 3.1 need to be modified as follows by means of equation (20):

$$\begin{cases} C_{in}^S(t+\Delta t) = C_{in}^S(t) + j_S(t)\dfrac{A}{v}\Delta t & (23) \\ \Delta V(t+\Delta t) = \dfrac{\left(\sum_S C_{in}^S(t+\Delta t)\right) ev + Q}{cA} & (24) \end{cases}$$

In the second simulation it was possible to compute the temporal evolution of the total charge inside the cell, reported in the plot of Figure 5.

As expected, as time passes by and the system moves towards equilibrium, the charge of the cell tends to zero in order to reach neutrality: the value of the total charge inside the cell at $t = 0$ is equal to $\mathcal{Q}_{tot}(t = 0) = -0.92\, pF$, while the final equilibrium value of the internal charge reached by the cell is:

$$^*\mathcal{Q}_{tot} = -41.51\, fF$$

For what concerns the system's evolution we can state that the results of the second simulation are the same of the first one. In particular the equilibrium values computed are again

$$^*\Delta V = -2.9\, mV$$
$$^*C_{in}^{Na} = 162.5\,\text{mM}$$
$$^*C_{in}^{K} = 4.5\,\text{mM}$$

and the plot of Figure 6 reproduces the same results of the plot of Figure 2, while the evolution of the cell's ion internal concentrations over time (Figure 7) is equal to the one presented in Figure 4.

This confirms that the two approaches are both valid solutions to simulate the problem.

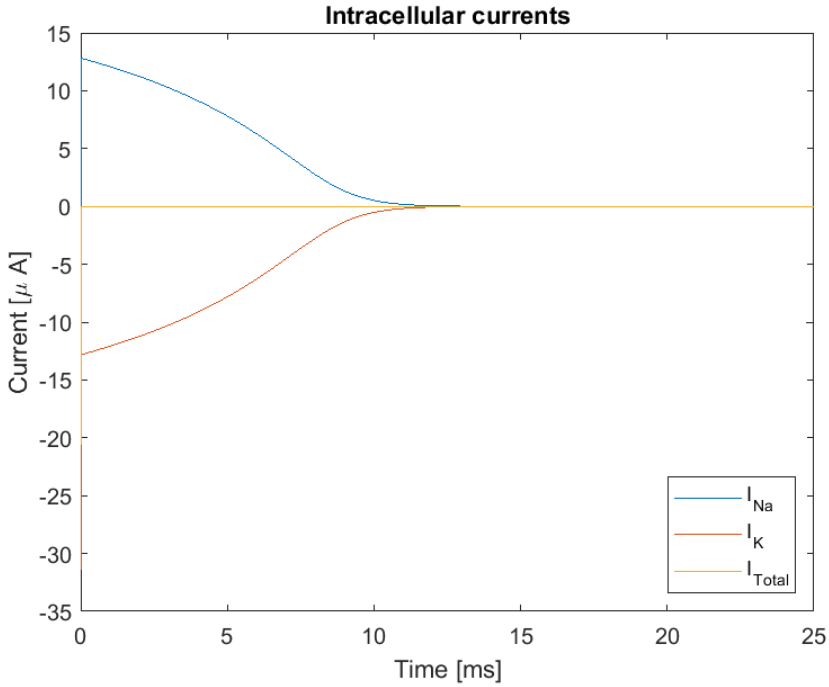

Figure 6: Second simulation: *total current inside the cell and potential as functions of time. The values of t lower than $10\,\mu s$ were not included in the plot in order to exclude the initial current and potential peaks from the plot.*

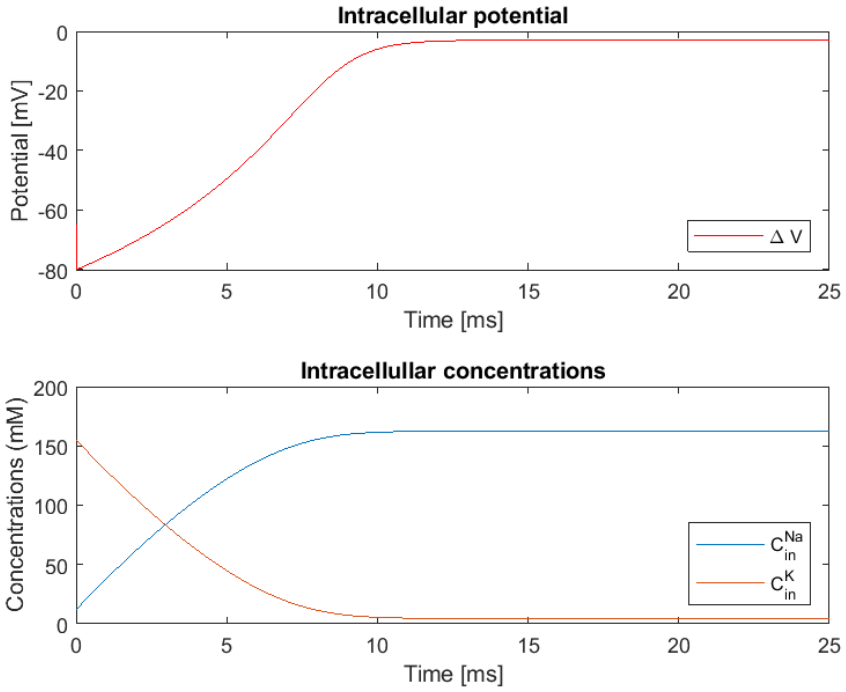

Figure 7: Second simulation: *time evolution of the internal concentrations of sodium and potassium ions and of the cell potential, simulated until the system reaches equilibrium.*

4. Conclusions

In this paper we described the depolarization of a living cell using the GHK equation. We considered Na^+ and K^+ ions as the major transmembrane current components of a living cell: the Na^+ flux tends to depolarize the cell once the Na^+ channels open, while the K^+ flux tries to counterbalance this effect. Being the amount of K^+ ions inside the cell is limited, while the amount of Na^+ ions outside the cell is virtually unlimited we were able to assume fixed external concentrations of the ions.

The aim of this work was to simulate that, supposing ion pumps (such as Na^+/K^+-ATPase pumps) inactive, a non-excitable finite cell reaches equilibrium depolarizing zero voltage resting potential and zero concentration ionic flux.

The initial values of the intra- and extramembrane concentrations of sodium and potassium and the resting potential were chosen in order to resemble realistic resting values of mammalian skeletal muscle cell.

We simulated the system's evolution towards equilibrium using two different approaches: both simulations found the same results and in particular the final equilibrium values of the resting potential and of the intracellular concentrations of the sodium and potassium ions are

$$^*\Delta V = -2.9\, mV$$
$$^*C_{in}^{Na} = 162.5\,\text{mM}$$
$$^*C_{in}^{K} = 4.5\,\text{mM}$$

In the end, during the second simulation, (in which we imposed a fixed negative charge to be initially present inside the cell in order to resemble the large proteins that we can typically find inside the cells), we were able to compute also the total charge inside the cell once the system reached the equilibrium

$$^*\mathcal{Q}_{tot} = -41.51\, fF$$

showing that the cell moves towards charge neutrality.

In the end, this work could be improved in the future by adding active ionic pumps in order to reproduce more realistically the mechanism of the cell depolarization.

References

[1] Jackson, M. (2006). *Molecular and cellular biophysics.* Cambridge University Press.

[2] Hille, B. (2001). *Ionic channels of excitable membranes*. New York, NY: Oxford University Press.

[3] Lecture notes from the *Biological physics course* by Mario Bortolozzi, University of Padua, a.y. 2019-2020.

5. Appendix

This sections contains the code developed in order to solve the exercise.

```
function GHK_Piccolo_Giovanni()

    close all;
    clc;

    %December 2020, Version 3.1, Giovanni Piccolo
    %description of a cell depolarization using GHK equations


    %Time step simulation parameters
    dt = 1e-8; %time steps [s]
    total_time = 0.025; %[s]
    N_steps = ceil(total_time/dt);

    %problem data
    V=5000e-18; %m^3
    R=(3*V/(4*pi))^(1/3); %m
    A=4*pi*R^2; %m^2

    C_in=[12 155]; %Intramembrane concentration of [Na+ K+] in mM
    C_out=[145 4]; %Extramembrane concentration of [Na+ K+] in mM
    P=[0.2e-3 10e-3]; %Permeability of [Na+, K+] in um/s
    capacitance=1e-2; %F/m^2

    %the valence numbers are [1 1] for [Na+ K+], not included in the
    %computation since they are superfluos

    Delta_V=-65e-3; %resting potential [V]
    q=1.6e-19; %fundamental charge [C]
    N_A = 6.022e23; %avogadro number

    k_B=1.380649e-23; %Boltzmann constant [J/K]
    T=25; %Celsius degrees, Standard Ambient Temperature
```

```
kT=k_B*(273.15+T);

%pre-allocate vectors
potential = zeros(N_steps,1);
current = zeros(N_steps,2);
C = zeros(N_steps,2); %concentrations
flux = zeros(1,2);

potential(1) = Delta_V;
C(1,:) = C_in;

%Calculations of initial fluxes using factors in order to reduce the computational time
exponential=exp(q*Delta_V/kT);
prefactor= P.*q*Delta_V/(kT);
initial_fluxes= prefactor.*((C_in.*exponential)-C_out)./(1-exponential);
disp('Initial fluxes of:')
disp('      Na+        K+');
disp(initial_fluxes);
disp('mmol/m^3s');

%Factors used to speed up the simulation cycle
alpha_simulation = P.*q/kT;
beta_simulation = q/kT;
gamma_simulation = A * dt / V;
delta_simulation =  q*N_A*A;

n=input('Enter "0" for the basic case; enter "-1" for the case with the negative charge:  ');
    switch n
    case 0

    %GHK simulation
    %tic
    for i = 2:N_steps

        flux = alpha_simulation.*potential(i-1).*(C(i-1,:).*exp(beta_simulation*potential(i-1))-C_out)./(1-exp(beta_simulation*potential(i-1)));
        C(i,:) = C(i-1,:) + flux * gamma_simulation ;
        current(i,:) = delta_simulation*flux ;
        potential(i) = potential(i-1) + q*N_A*dt*sum(flux)/capacitance;

    end
    %toc

    disp('Final fluxes of: ');
    disp('      Na+        K+');
    disp(flux);
    disp('mmol/m^3s');

    disp('Final concentrations in [mM] of: ');
    disp('      Na+        K+');
    disp(C(N_steps,:));

    disp('Equilibrium potential [V]: ');
    disp(potential(N_steps));

    opengl software; %legend bug without this line of code due to the AMD graphics driver.

    t=0:dt:dt*(N_steps-1); %X axe

    %double plot (t,V) and (t,C)
    y1 = potential*1e3;
    y2 = C;
    tiledlayout(2,1);

    % Top plot
    ax1 = nexttile;
    plot(ax1,t*1e3,y1,'r');
    title(ax1,'Intracellular potential');
    xlabel('Time [ms]');
    ylabel(ax1,'Potential [mV]');
    legend({'\Delta V'},'Location','southeast');
    %grid on;

    % Bottom plot
    ax2 = nexttile;
    plot(ax2,t*1e3,y2);
    title(ax2,'Intracellullar concentrations');
    xlabel('Time [ms]');
    ylabel(ax2,'Concentrations (mM)');
    legend({'C_{in}^{Na}','C_{in}^{K}'},'Location','southeast');
    %grid on;

    figure();
    total_current= sum(current,2);
    limiter = 0.00001; %[s]: to cut initial peaks
    plot(t ( t > limiter)*1e3 , potential( t > limiter)*1e3);
    hold on;
    title("Total current vs potential");
    xlabel("Time [ms]");
    ylabel("Potential [mV]");
    yyaxis right;
    ylabel("Current [nA]");
    plot(t( t > limiter)*1e3, total_current( t > limiter) * 1e9);
    legend({'\Delta V','I_{Total}'},'Location','southeast');
    hold off;
```

```
128
129         figure();
130         plot(t*1e3,[current,
    total_current] * 1e6);
131         title("Intracellular currents");
132         xlabel("Time [ms]");
133         ylabel("Current [\mu A]");
134         legend({'I_{Na}','I_{K}','I_{
    Total}'},'Location','southeast');
135         %grid on;
136
137     case -1
138
139         Q_pm = A*Delta_V*capacitance -
    sum(C_in)*N_A*q*V;
140         disp("Initial charge [pC]: ");
141         disp(A*Delta_V*capacitance*1e12)
142
143         %disp(Q_pm*1e9);
144
145         additional_charge_factor=Q_pm/(A*
    capacitance);
146
147         %GHK simulation
148         %tic
149         for i = 2:N_steps
150
151             flux = alpha_simulation.*
    potential(i-1).*(C(i-1,:).*exp(
    beta_simulation*potential(i-1))-C_out
    )./(1-exp(beta_simulation*potential(i
    -1)));
152             C(i,:) = C(i-1,:) + flux *
    gamma_simulation ;
153             current(i,:) =
    delta_simulation*flux ;
154             potential(i) = sum(C(i,:))*q*
    N_A*V/(A*capacitance)+
    additional_charge_factor;
155
156         end
157         %toc
158
159         disp('Final fluxes of: ');
160         disp('      Na+        K+');
161         disp(flux);
162         disp('mmol/m^3s');
163
164         disp('Final concentrations in [mM
    ] of: ');
165         disp('      Na+        K+');
166         disp(C(N_steps,:));
167
168         disp("Final Charge [pC]:");
169         disp((sum(C(N_steps,:))*q*N_A*V+
    Q_pm)*1e12 )
170
171         disp('Equilibrium potential [V]:
    ');
172         disp(potential(N_steps));
173
174         opengl software;
175
176         t=0:dt:dt*(N_steps-1); %X axe
177
178         %double plot (t,V) and (t,C)
179         y1 = potential*1e3;
180         y2 = C;
181         tiledlayout(2,1);
182
183         % Top plot
184         ax1 = nexttile;
185         plot(ax1,t*1e3,y1,'r');
186         title(ax1,'Intracellular
    potential');
187         xlabel('Time [ms]');
188         ylabel(ax1,'Potential [mV]');
189         legend({'\Delta V'},'Location','
    southeast');
190
191         % Bottom plot
192         ax2 = nexttile;
193         plot(ax2,t*1e3,y2);
194         title(ax2,'Intracellullar
    concentrations');
195         xlabel('Time [ms]');
196         ylabel(ax2,'Concentrations (mM)')
    ;
197         legend({'C_{in}^{Na}','C_{in}^{K}
    '},'Location','southeast');
198
199         figure();
200         plot(t*1e3,(sum(C,2)*q*N_A*V+Q_pm
    )*1e12,'m');
201         title("Charge inside the cell");
202         xlabel("Time [ms]");
203         ylabel("Charge [pC]");
204         legend({'Q_{tot}'},'Location','
    southeast');
205
206         figure();
207         total_current= sum(current,2); %I
     = I_K + I_Na
208         plot(t *1e3,[current,
    total_current] * 1e6);
209         title("Intracellular currents");
210         xlabel("Time [ms]");
211         ylabel("Current [\mu A]");
212         legend({'I_{Na}','I_{K}','I_{
    Total}'},'Location','southeast');
213         %grid on;
214
215     otherwise
216         disp('Input number not recognized
    . Terminating process...');
217         end %switch case end
218 end
```