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9.40 - PSET 1

Problem 1: 1D DIFFUSION

Diffusion in 1D can be seen as a random walk. A random walk is the process by which randomly-moving objects wander away from where they started. The simplest random walk to understand is a 1-dimensional walk. Suppose that a particle is sitting at the center of a integer number line. Let's call this position, x = 0. Then, at each time point the particle takes a step of length 1 either to the left or to the right, with equal probability (1/2 in each direction). During the diffusion process, the particle keeps taking steps either left or right each time independently of what has happened at previous time points.

The file randomwalk.mat contains a matrix X that summarizes a random walk experiment for multiple particles.

The matrix X contains 500 rows and 1001 columns. In this matrix, each row represents the position of a given particle over time. These positions are in units of microns (1 micron = 10-6 m). Conversely, each column represents a time point in our experiment. Thus, the first column is the position of all particles at t = 0. We have tracked the particles positions in time increments of 1 millisecond. So, column 2 are the positions of all particles a t = 1 msec, column 3 at t = 2 msec and so on.

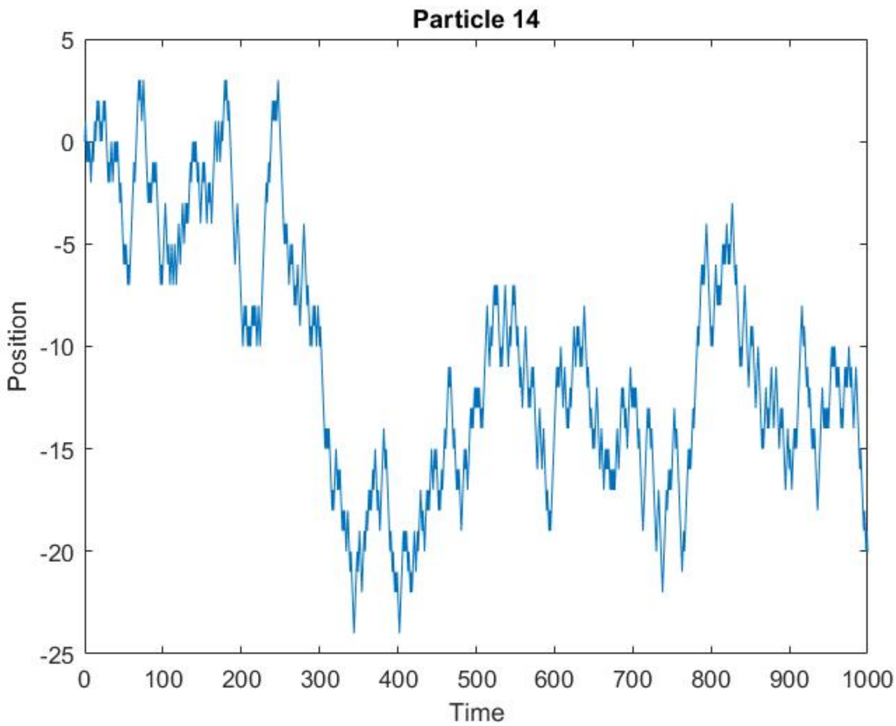
Q1.1 Look at matrix X and determine the initial position for all particles.

Ans. Initial position is X = 0 (Printing the 1st column ie column of python index 0 gives an vector of zeros)

Q1.2 What is the value of time time interval for the last column of matrix X?

Answer. 1000 milliseconds

Q1.3 Plot the trajectory of particle 14 as a function of time.



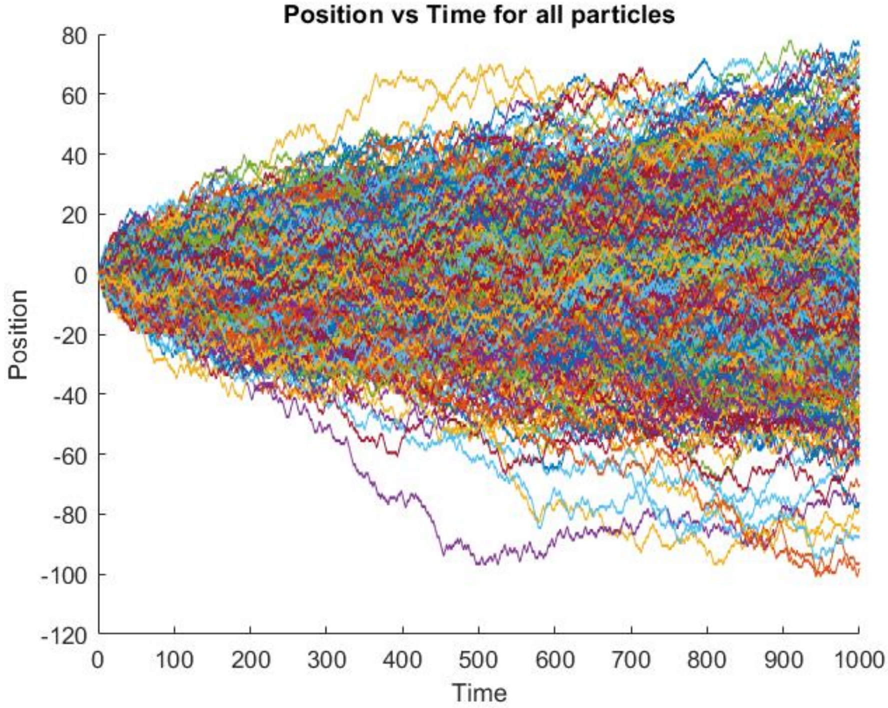
Time is in mS, Position in microns

Q1.4

In a single figure panel, plot the trajectory of all particles as a function of time.

a. What do you observe?

b. Why each particle follows a different trajectory?



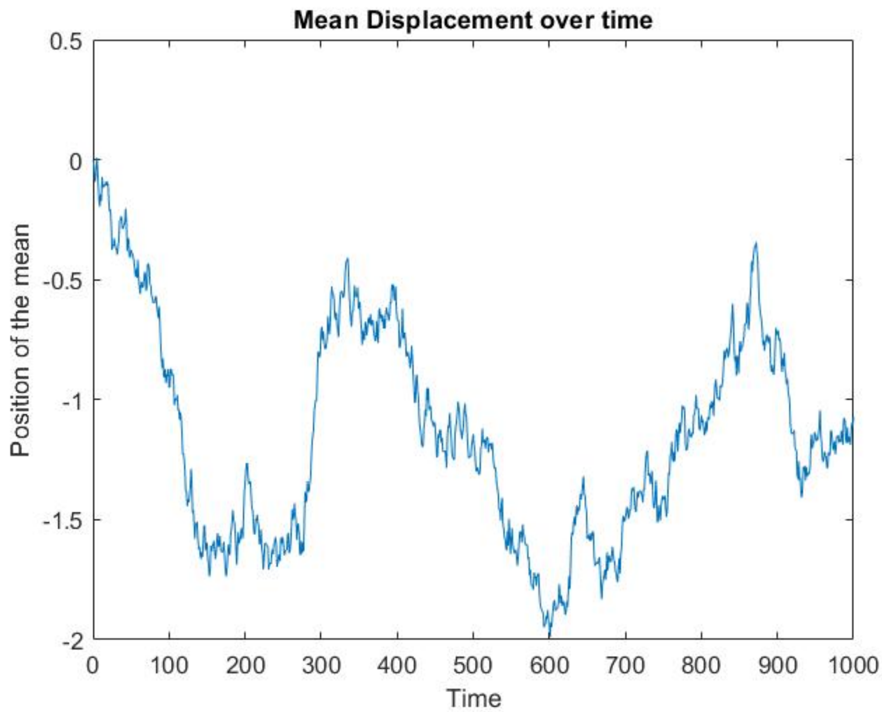
Answer questions here:

a. The graph is roughly symmetrical about the x axis ie. almost equal number of particles move to the left and to the right in each time step. It is also observed that the graph spreads wider as time increases which is proof that the particles are moving from t=a high conc. area (x=0) towards a low conc. area

b. Only a collision can change a particle's direction or the diffusion gradient at that point of time. **This answer is incomplete and I do not have a strong argument for why different**

Q1.5

Plot the average position of the particles as a function of time.



Answer: As almost equal number of particles move left and right at each time step, the mean particle position stays at a value around zero

Q1.6

Plot the mean square displacement of the particles as a function of time.

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a. Is there any trend in this plot?

b. Interpret the trend
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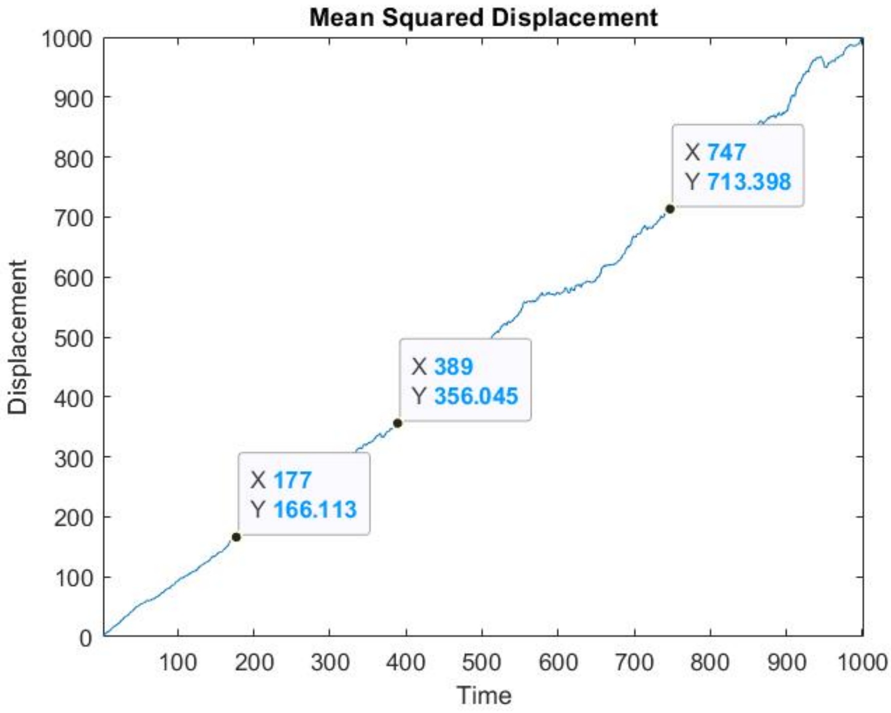
Y axis label should read Mean Squared Displacement and not Displacement



Interpretation: The mean squared displacement increases as time passes which shows that particles are moving to a low conc region and the majority number of particles are moving away from x =0

Q1.7

a. Use the plot in question 6 to estimate the diffusion coefficient of these particles.

b. Briefly explain the methodology implemented to estimate this quantity.

The mean squared displacement at any instant can be approximated to the time step at that instant (By observation we see that the graph for mean squared displacement is roughly $y = x$)

Therefore,

$$< x_i^2(t) >= t$$
$$\text{Since} < x_i^2(t) >= 2Dt$$
$$D = \frac{1}{2}$$

The unit of D is nm/second (Because $\frac{10^{-12} meters\ (micron \times micron)}{10^{-3} seconds\ (millisecond)} = 10^{-9} meters\ /\ seconds)$

Problem 2: Equivalent Circuit Model

The equivalent circuit model of a neuron that we built in class is essentially a simple RC circuit with the addition of battery to capture the non-zero membrane resting potential. The lipids on the cell membrane provides electrical insulation between the intracellular fluid and the extracellular fluid. This creates a capacitor, with capacitance proportional to the cell's surface area (A). The cell membrane is not a perfect insulator. Pores in the membrane allow ions to move across it. A cell's total membrane conductance (Gm) represents how easily ions flow across the membrane. Note that the total conductance is also proportional to the cell's area and recall that conductance is the reciprocal of resistance.

For simplicity let's assume that our modeled neuron is a perfect sphere of radius 0.06 mm and resting membrane potential Vrest = -70 mV. The membrane of this neuron has a specific membrane capacitance (cm) of 10 nF/mm2 and specific membrane conductance (gm) of 1 .

This modeled neuron obeys the following differential equation:

$$V(t) + \tau_m \frac{dV(t)}{dt} = V_{rest} + R_m I_e \tag{2.1}$$

where V(t) is the membrane potential at time t, Vrest is the resting membrane potential, Rm is the membrane resistance, Cm is the membrane capacitance, Ie is the current injected, and is the membrane time constant.

The objective of this exercise is to understand how this cell responds to injected current. To achieve this objective, we need to solve equation 2.1 to find V(t) for a given current waveform. We can do this either analytically or numerically. Luckily, the above differential equation has analytical solution for constant applied current:

$$\begin{aligned} V(t) = V_{rest} + R_m I_e \\ + (V_0 - V_{rest} - R_m I_e)\exp\left(-\frac{t-t_0}{\tau_m}\right) \end{aligned} \tag{2.2}$$

where t_0 is a reference time when the initial condition is set to V_0.

This equation constitutes the core a numerical integration method to solve first order linear ordinary differential equations known as the exponential Euler scheme. This scheme is further discussed in the accompanying document NumericalIntegration.pdf. By implementing this numerical scheme in Python, we will be able to simulate the response of our modeled neuron to square pulses of injected current and answer the following questions:

Q2.1 Draw the equivalent circuit model for this neuron, labeling intracellular space, extracellular space, membrane capacitance, and membrane resistance.

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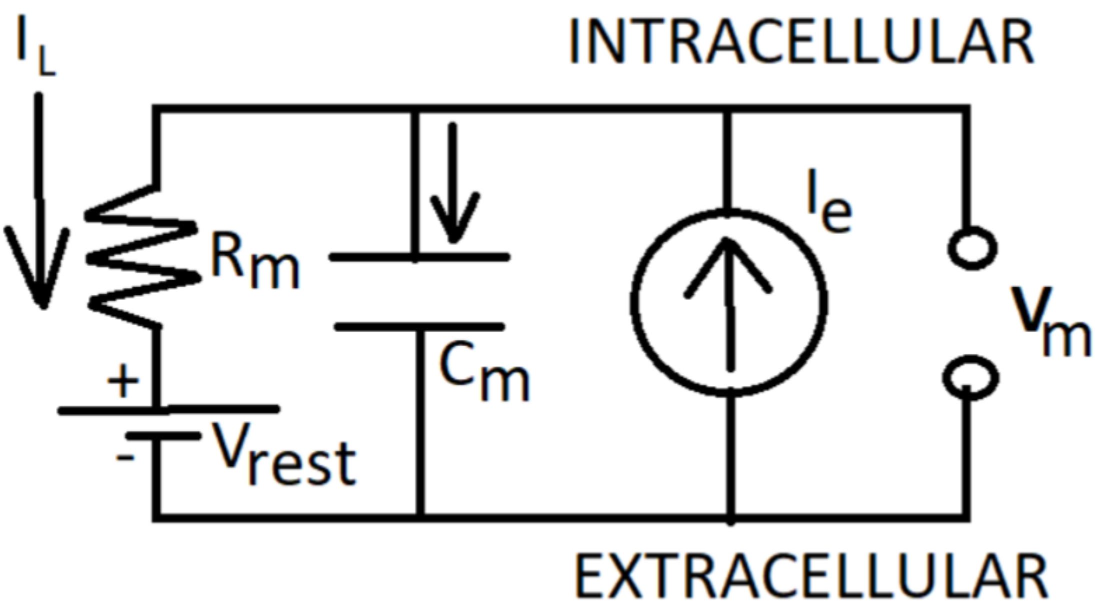


...

Q2.2 Calculate the total membrane conductance Gm and the total membrane resistance Rm for this modeled neuron.

Specific membrane conductance $g_m = 1\ \mu S/mm^2$

Radius of spherical neuron $r = 0.06\ mm$

Surface area of a sphere $A = 4\pi r^2 = 144\pi \times 10^{-4}\ mm^2$

Total membrane conductance $\boxed{G_m = g_m \times A = 144\pi \times 10^{-10}\ S}$

Total membrane resistance $\boxed{R_m = \frac{1}{G_m} = \frac{10^{10}}{144\pi}\ \Omega}$

Q2.3 Calculate the total membrane capacitance Cm for this modeled neuron.

Answer = $144\pi \times 10^{-3}$ nF

$$\text{Specific membrance capacitance} \quad c_m = 10\ nF/mm^2$$

$$\text{Total membrane capacitance} \ \boxed{C_m = c_m \times A = 144\pi \times 10^{-12}\ F}$$

Q2.4 What is the analytical value of the time constant for this modeled neuron?

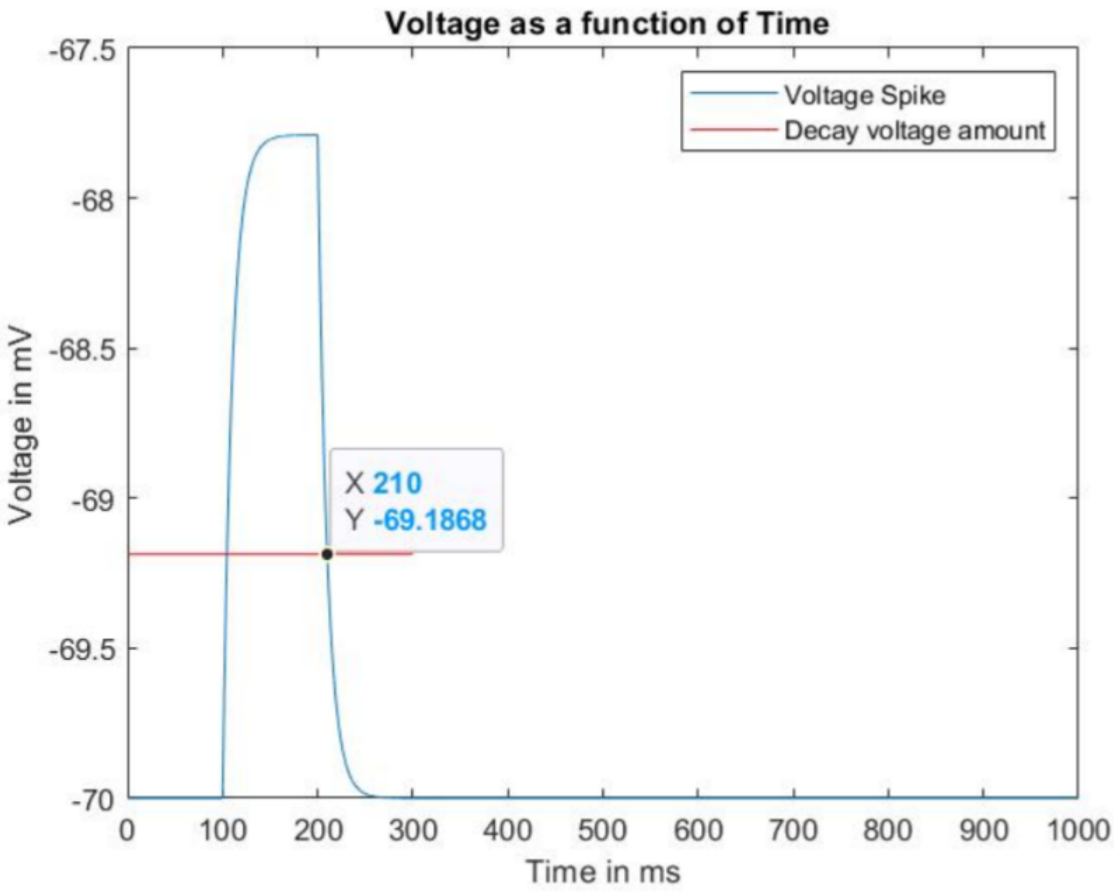
Answer = $10\ ms$

$$\text{Time constant} \ \boxed{\tau_m = R_m C_m = 10^{-2}\ seconds}$$

Q2.5 Implement the exponential Euler scheme with $V_0 = V_{rest}$, time step $dt = 0.01\,ms$.

Q2.6 Simulate the cell for 1 second using a time-step of 0.1 ms.

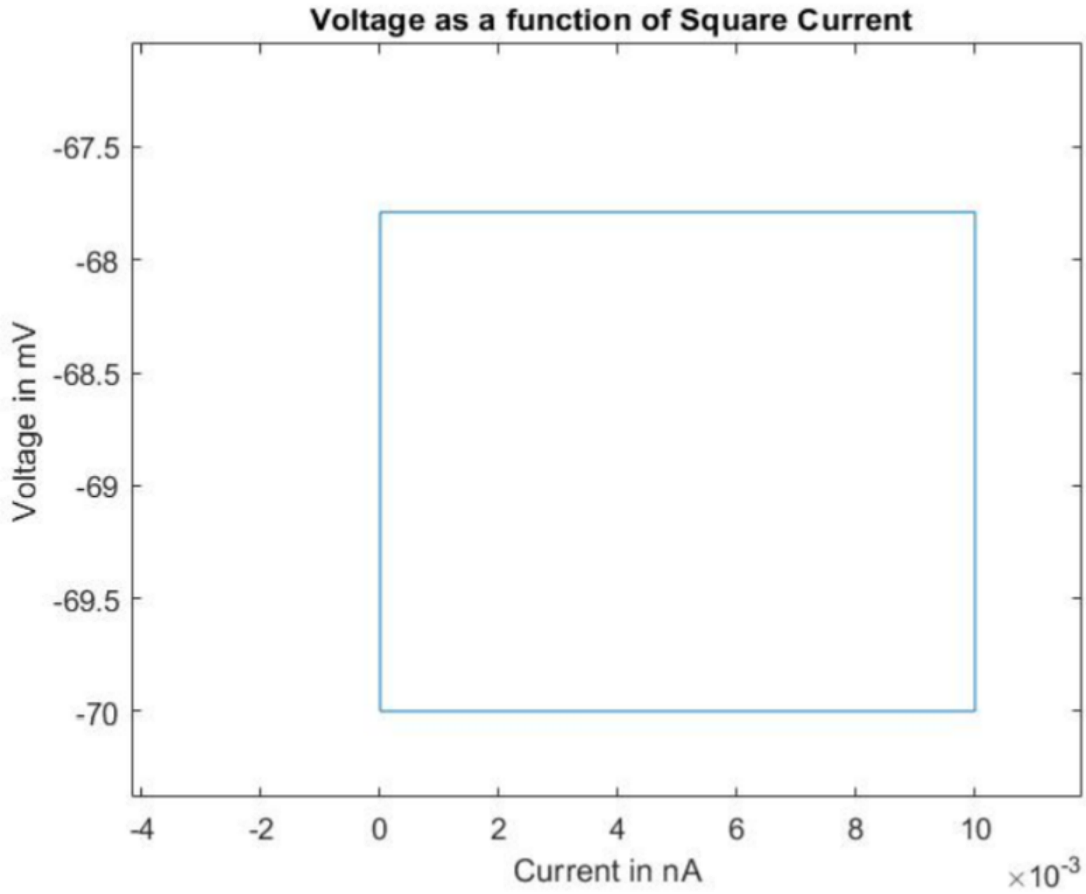
Plot the voltage as a function of time in one panel and the square current pulse in another.



This plot of voltage as a function of square current pulse has some error I believe. The arrays inputted were

x-axis array : element wise product of array with curent values with itself

y-axis array : array of voltage values corresponding to the indices of the current array



Q2.7 From the previous plot estimate the time constant of the cell (Recall that as the voltage changes from V_0 to steady state, only $1/e$ of the total voltage change is left at time $t = \tau_m$).

From plotting the decayed voltage amount (i.e $\frac{1}{e}$ times the total voltage change) in the "Voltage as a function of Time" graph in part 6, it is observed that the decayed voltage amount line intersects the the voltage graph at time $= 210\ ms$

The neuron spikes at time $= 200\ ms$

Therefore we can calculate the time constant from the graph as

$$\tau = \text{Time of intersection} - \text{Time of Spiking}$$

$$\boxed{\tau = 10\ ms}$$

Q2.8 How does the value obtained in question 7 compares to the value obtained in question 4?

Answer: It matches

Q2.9 Show analytically (manipulate the equations, no Python simulations) that equation 2.2 is indeed a solution to the RC differential equation 2.1.

The differential equation of the neuron is

$$\boxed{V(t) + \tau_m \frac{dV(t)}{dt} = V_{rest} + R_m T_e}$$

The equation can be rearranged and rewritten as

$$\boxed{\frac{dV(t)}{dt} = \frac{V_{rest} + R_m T_e - V(t)}{\tau_m}}$$

where, t is integrated from t_0 to t
V is integrated from V_0 to $V(t)$

On separating the variables and integrating within the limits, we get

$$\boxed{\log \frac{V_{rest} + R_m T_e - V(t)}{V_{rest} + R_m T_e - V_0} = -\left(\frac{t - t_0}{\tau_m}\right)}$$

This can be rearranged to get the equation in the question

$$\boxed{V(t) = V_{rest} + R_m I_e + (V_0 - V_{rest} - R_m I_e)\ exp\left(\frac{t - t_0}{-\tau_m}\right)}$$

□

Q2.10 Show analytically that equation 2.2 satisfies $V(t_0) = V_0$.

Answer:

At $t = t_0$, $V(t) = V_0$

On substituting these values of t and $V(t)$ in the final equation from part 9, we get,

$$\boxed{V_0 = V_{rest} + R_m I_e + (V_0 - V_{rest} - R_m I_e)\ \exp\left(\frac{t_0 - t_0}{-\tau_m}\right)}$$

It is observed that both the sides of the above equation cancel out.

Hence $V(t_0) = V_0$ satisfies the equation. □

Q2.11

Show analytically that for equation 2.2, as $t \to \infty$

$$V(t) \to V_{rest} + R_m I_e = V_\infty \tag{1}$$

also known as the steady state of the system.

Answer:

As $t \to \infty$, $\exp\left(\frac{t \ - t_0}{-\tau_m}\right) \to 0.$

Therefore

$$\boxed{V(t) \to V_{rest} + R_m I_e = V_\infty}$$

□

Q2.12

Suppose the cell is at V_{rest} at $t = 0$, when a current step of $I_e = 500pA$ is turned on. How long will it take for the cell to reach $-60mV$? What is the steady state voltage for this value of I_e? Compute these answers analytically.

$I_e = 0.5\ nA$

$V(t) = -60\ mV$

The equation is rewritten in terms of time t as

$$\boxed{t = \tau_m \ln\left(\frac{R_m I_e}{R_m I_e - V(t) + V_{rest}}\right)}$$

On substituting the values, we get

$$\boxed{t = 23.5\ ms}$$

The steady state voltage formula is

$$\boxed{V_\infty = V_{rest} + R_m I_e}$$

On substituting the values, we get

$$\boxed{V_\infty = -58.9476\ mV}$$

Q2.13

Let's add an extra channel to our neuron. The extra channel has a resistance R_{extra} and is added in parallel to the other components. Does this new channel make the membrane time constant slower or faster? Show calculations to support your conclusion.

The resistance in parallel (R_p) is added as follows to the original resistance R

$$\text{Combined membrane resistance } \boxed{R_m = \frac{R \times R_p}{R + R_p}}$$

Any addition of resistance in parallel causes the total resistance of the membrane to drop.

Since the time constant $\boxed{\tau_m \propto R_m}$

A decrease in membrane resistance causes the time constant to decrease i.e the time constant becomes faster.

PROBLEM 3: Nernst Potential

Ions will drift across the membrane down their concentration gradient from areas of high concentration to areas of low concentration. However, this creates a charge gradient in the opposite direction, since ions are charged. These two opposing forces balance at the Nernst potential where the net flow across the membrane for a given ion species is zero. The Nernst potential is given by the following formula:

$$E = \frac{kT}{q}\log\left(\frac{C_e}{C_i}\right) \tag{2}$$

where k is the Boltzmann constant with value $1.38 \times 10^{-23}(J/K)$, T is the temperature in Kelvins $(T(K) = T(C) + 273.15)$, and q is the charge of a monovalent ion with value $1.6 \times 10^{-19}(C)$.

For this problem let's consider a neuron with the following intra- and extra-cellular ionic concentrations:
$[K^+]_{in} = 186mM, [K^+]_{out} = 4.8mM, [Ca^{++}]_{in} = 50nM, [Ca^{++}]_{out} = 1.5mM.$

Q3.1

Complete the starter code provided below (or in .py file pset1_functions.py) so that it calculates the Nernst potential in mV, for ions of any arbitrary valence at a specified temperature in degrees Celsius.

Q3.2

Calculate the Nernst potentials of K^+ and of Ca^{++} for this cell at 37^oC, using the function you wrote in question 1.

K ion: -97.8298 mV

Ca ion: 137.8845 mV

PROBLEM 4: Ionic Fluxes and Nernst Potential

A spherical cell of radius $0.06mm$ cell with a specific membrane capacitance of $10nF/mm^2$ is sitting in a bath at 37^oC. The only channel present in this cell is a Potassium conductance and the concentration of this is: $186mM$ intracellularly Potassium and $4.8mM$ extracellularly. (Note that these numbers are the same as in problem 2 and 3). This cell starts at $0mV$ with all the potassium channels closed. At time t_0 the channels are suddenly opened.

Q4.1

Calculate the initial (before the channels open) number of potassium ions inside the cell.

In [11]:
```
import numpy as np

r = 0.06 # in mm
K_in = 186e-3
K_out = 4.8e-3
C = 0.45 #nF, taken from problem 2

# cell volume
Vol = (4/3)*np.pi*(r**3) #in mm3


# add your code here:
# First, find moles inside cell, moles:

moles = Vol *(1e-6)* K_in  #Volume is in mm3 hence converting to liter

# Second, Convert to ions
initial_ions = moles * 6.023e23


print("There are %.2e potassium ions inside the cell" %initial_ions)
```

```
There are 1.01e+14 potassium ions inside the cell
```

Q4.2

What is the steady state membrane potential a long time after the channels open?

In [9]:
```
# From Q3.2, the Potassium Nernst potential is the steady
# state membrane potential (mV):

# enter your answer here
Vss = -97.8298 # in mV
```

Q4.3

Calculate how much net charge must accumulate for the cell to reach steady state. Remember that the charge accumulated by a capacitor is $q = CV$.

In [13]:
```
# add your code to calculate charge, q:
q =C *1e-9* Vss *1e-3   # as C is in nF and Vss is in mV, converting to F and V respectively

print("At steady state, we accumulate %.2e C of charge." %q)
```

```
At steady state, we accumulate -4.40e-11 C of charge.
```

Q4.4

Calculate the net change in number of potassium ions. In which direction is this net flux?

In [15]:
```
# add your code here for n_ions:

n_ions = abs(q) /(1.6e-19) # number of potassium ions is given as the total charge divided by charge on one monovalent ion

print("The net change is %.2e potassium ions." %n_ions)
```

```
The net change is 2.75e+08 potassium ions.
```

Answer:

direction of flux : As the steady state potential is negative, it implies more K+ on ions inside. Hence the ions flow from **intracelluar space to extracellular space**

Q4.5

How much does this flux of K^+ ions change the cell's potassium concentration? Would this change affect the physiological properties of the neuron?

In [18]:
```
# The potassium concentration inside the neuron decreases

n_ions_final = initial_ions - n_ions
K_in_final = n_ions_final / (6.023e23 * Vol *(1e-6))
print("The potassium concentration inside the cell is finally", K_in_final * 1e3 ,"mV")
```

```
The potassium concentration inside the cell is finally 185.99949509639313 mV
```

Answer: **Yes it should as the concentration and membrane potential changes. I do not know what happens though.**

The physiological properties: