MODELS OF NEURAL SYSTEMS
Computer Practical Final Project

Project 2 Report: Action Potential Propagation

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Abstract

This project was done as part of the Computer Practical component Models of Neural Systems course. The aim of this project is simulating the action potential of along the axon of a neuron using the cable equation and the Hodgkin-Huxley model for membrane current. The first section introduces the theoretical basis of this project. The second section explains numerical simulation of the passive steady state cable equation with only passive membrane conductance. The third section deals with the implementation of Hodgkin-Huxley model and using the Crank-Nicholson method to solve the partial differential equation. Also, the discussion of results of initiation of the action potential by current injection in one and both the ends of the axon along with the action potential propagation velocity are discussed in the third section. The fourth section discusses the action potential propagation in a myelinated axon. The final section includes the discussion of the results from this project.

Section 1. Introduction

The modelling of the action potential propagation along an axon involves finding the dynamics of the membrane potential with respect to time and space. The Cable equation given below describes these dynamics.

$$c_m \frac{\partial V}{\partial t} = \frac{1}{2ar_L}\frac{\partial}{\partial x}\left(a^2 \frac{\partial V}{\partial x}\right) - i_m + i_e \tag{1}$$

where,

c_m is the specific membrane capacitance

r_l is the intracellular resistivity

a is the axon radius

i_m is the membrane current

i_e is the external injected current

The cable equation is a second order partial differential equation relating the membrane voltage, the membrane current and the external injected current. The membrane current can give non-linearity to the dynamics if the active conductances from the Hodgkin-Huxley model as shown below are included:

$$i_m = \overline{g_L}(V - E_L) + \overline{g_{Na}} m^3 h (V - E_{Na}) + \overline{g_K} n^4 (V - E_K) \tag{2}$$

To get the membrane potential dynamics in space and time numerically for passive and active membranes, the equations (1) and (2) are combined and solved using numerical methods like forward Euler and Crank-Nicholson Methods are used which will be discussed in the coming sections.

Section 2. Steady state solution to Cable equation

(Problem 1) The project problem 1 asks for comparison of the analytical and numerical solutions of the steady state cable equation when a constant current is injected at the middle of the axon. The solution is obtained in the following way:

The cable equation from equation (1) is:

$$c_m \frac{\partial V}{\partial t} = \frac{1}{2ar_L} \frac{\partial}{\partial x}\left(a^2 \frac{\partial V}{\partial x}\right) - i_m + i_e$$

The passive membrane current is given by:

$$i_m = \frac{(V - E_L)}{r_m}$$

Therefor the equation (1) becomes:

$$c_m \frac{\partial V}{\partial t} = \frac{1}{2ar_L} \frac{\partial}{\partial x}\left(a^2 \frac{\partial V}{\partial x}\right) - \frac{(V - E_L)}{r_m} + i_e$$

Put $V - E_L = v$

$\frac{\partial v}{\partial t} = \frac{\partial V}{\partial t} - 0, as E_L = constant$

$\frac{\partial}{\partial x}\left(a^2 \frac{\partial v}{\partial x}\right) = \frac{\partial}{\partial x}\left(a^2 \frac{\partial V}{\partial x}\right)$

$$c_m \frac{\partial v}{\partial t} = \frac{1}{2ar_L} \frac{\partial}{\partial x}\left(a^2 \frac{\partial v}{\partial x}\right) - \frac{v}{r_m} + i_e$$

$$r_m c_m \frac{\partial v}{\partial t} = \frac{r_m}{2ar_L} \frac{\partial}{\partial x}\left(a^2 \frac{\partial v}{\partial x}\right) - v + r_m i_e$$

$$r_m c_m \frac{\partial v}{\partial t} = \frac{r_m a}{2r_L} \frac{\partial^2 v}{\partial x^2} - v + r_m i_e$$

Considering:

$r_m c_m = \tau_m \qquad \frac{r_m a}{2r_L} = \lambda^2$

For steady state conditions:

$$\frac{\partial v}{\partial t} = 0, \qquad \frac{\partial v}{\partial x} = \frac{dv}{dx}$$

$$i.e.\, v(x,t) \Rightarrow v(x)$$

$$0 = \lambda^2 \frac{d^2 v}{dx^2} - v + r_m i_e$$

$$\lambda^2 \frac{d^2 v}{dx^2} = v - r_m i_e \tag{3}$$

Equation (3) is the steady state cable equation. It is a second order ordinary differential equation. The analytical solution of this ODE is:

$$v(x) = B \exp(-|x|/\lambda)$$

When a point current is injected at x=0,

$$v(x) = \frac{I_e R_\lambda}{2} \exp\left(-\frac{|x|}{\lambda}\right)$$

For solving the second order ordinary differential equations, two boundary conditions are needed. The following boundary conditions are implemented:

At x=0, $v(0) = \frac{I_e R_\lambda}{2}$ $\qquad\qquad$ $\frac{dv}{dx} = -\frac{1}{\lambda}\frac{I_e R_\lambda}{2}$

An axon of 6 mm is considered with a current of 0.5 μA injected in the middle.

A second order Euler scheme is implemented and the following result is obtained:

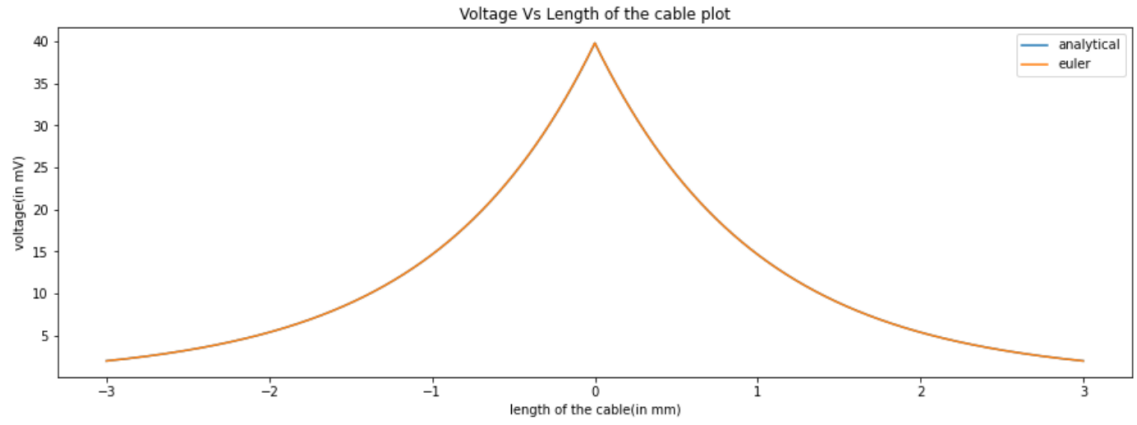

Figure 2. 1 Comparison of the Numerical and Analytical solution

The analytical solution and the solution obtained from the Euler scheme agree well.

Section 3. Hodgkin Huxley Implementation

(Problem 2) The Hodgkin-Huxley model is implemented in a giant squid axon.

The membrane current from equation (2) is included in the equation (1), then equation (1) becomes

$$\frac{dV_\mu}{dt} = -\frac{\overline{g_L}(V_\mu - E_L)}{c_m} - \frac{\overline{g_{Na}}m^3h(V - E_{Na})}{c_m} - \frac{\overline{g_K}n^4(V - E_K)}{c_m} + \frac{i_e^\mu}{c_m A_\mu} + \frac{g_{\mu,\mu+1}}{c_m}(V_{\mu+1} - V_\mu) + \frac{g_{\mu,\mu-1}}{c_m}(V_{\mu-1} - V_\mu)$$

$$\frac{dV_\mu}{dt} = -\frac{\overline{g_L}V_\mu}{c_m} - \frac{\overline{g_{Na}}m^3h(V_\mu)}{c_m} - \frac{\overline{g_K}n^4(V_\mu)}{c_m} + \frac{\overline{g_L}E_L}{c_m} + \frac{\overline{g_K}m^3h(E_{Na})}{c_m} + \frac{\overline{g_{Na}}n^4(E_K)}{c_m} + \frac{i_e^\mu}{c_m A_\mu} + \frac{g_{\mu,\mu+1}}{c_m}V_{\mu+1} - \frac{g_{\mu,\mu+1}}{c_m}V_\mu + \frac{g_{\mu,\mu-1}}{c_m}V_{\mu-1} - \frac{g_{\mu,\mu-1}}{c_m}V_\mu$$

$$\frac{dV_\mu}{dt} = \frac{g_{\mu,\mu-1}}{c_m}V_{\mu-1} - \left(\frac{\overline{g_L}}{c_m} + \frac{\overline{g_{Na}}m^3h}{c_m} + \frac{\overline{g_K}n^4}{c_m} + \frac{g_{\mu,\mu+1}}{c_m} + \frac{g_{\mu,\mu-1}}{c_m}\right)V_\mu + \frac{g_{\mu,\mu+1}}{c_m}V_{\mu+1} + \left(\frac{\overline{g_L}E_L}{c_m} + \frac{\overline{g_K}m^3h(E_{Na})}{c_m} + \frac{\overline{g_{Na}}n^4(E_K)}{c_m} + \frac{i_e^\mu}{c_m A_\mu}\right)$$

This can be written as,

$$\frac{dV_\mu}{dt} = B_\mu V_{\mu-1} + C_\mu V_\mu + D_\mu V_{\mu+1} + E_\mu$$

Where,

$$B_\mu = \frac{g_{\mu,\mu-1}}{c_m} = \frac{a/(2r_L L^2)}{c_m} = \frac{a}{2r_L L^2 c_m}$$

$$C_\mu = -\left(\frac{\overline{g_L}}{c_m} + \frac{\overline{g_{Na}}m^3h}{c_m} + \frac{\overline{g_K}n^4}{c_m} + \frac{g_{\mu,\mu+1}}{c_m} + \frac{g_{\mu,\mu-1}}{c_m}\right) = -\left(\frac{\overline{g_L}}{c_m} + \frac{\overline{g_{Na}}m^3h}{c_m} + \frac{\overline{g_K}n^4}{c_m} + \frac{a/(2r_L L^2)}{c_m} + \frac{a/(2r_L L^2)}{c_m}\right) = -\left(\frac{\overline{g_L}}{c_m} + \frac{\overline{g_{Na}}m^3h}{c_m} + \frac{\overline{g_K}n^4}{c_m} + \frac{a}{r_L L^2 c_m}\right)$$

$$D_\mu = \frac{g_{\mu,\mu+1}}{c_m} = \frac{a/(2r_L L^2)}{c_m} = \frac{a}{2r_L L^2 c_m}$$

$$E_\mu = \left(\frac{\overline{g_L}E_L}{c_m} + \frac{\overline{g_K}m^3h(E_{Na})}{c_m} + \frac{\overline{g_{Na}}n^4(E_K)}{c_m} + \frac{i_e^\mu}{c_m A_\mu}\right)$$

The stability of the method can be improved dramatically by evaluating the membrane potentials on the right side of equation not at time t, but at a later time t + z Δt, so that

$$V_\mu(t+\Delta t) = V_\mu(t) + \Delta V_\mu \tag{4}$$

$$\Delta V\mu = \left(B_\mu V_{\mu-1}(t) + C_\mu V_\mu(t) + D_\mu V_{\mu+1}(t) + E_\mu\right)\Delta t$$

$$\Delta V\mu = \left(B_\mu V_{\mu-1}(t+z\Delta t) + C_\mu V_\mu(t+z\Delta t) + D_\mu V_{\mu+1}(t+z\Delta t) + E_\mu\right)\Delta t$$

$$\Delta V\mu = B_\mu V_{\mu-1}(t)\Delta t + \left(B_\mu z\Delta t\right)\Delta V_{\mu-1} + C_\mu V\mu(t)\Delta t + \left(C_\mu z\Delta t\right)\Delta V\mu + D_\mu V_{\mu+1}(t)\Delta t + \left(D_\mu z\Delta t\right)\Delta V_{\mu+1} + E_\mu\Delta t$$

$$\Delta V\mu = \left(B_\mu z\Delta t\right)\Delta V_{\mu-1} + \left(C_\mu z\Delta t\right)\Delta V\mu + \left(D_\mu z\Delta t\right)\Delta V_{\mu+1} + \left(B_\mu V_{\mu-1}(t) + C_\mu V\mu(t) + D_\mu V_{\mu+1}(t) + E_\mu\right)\Delta t$$

$$\Delta V\mu = b_\mu \Delta V_{\mu-1} + c_\mu \Delta V\mu + d_\mu \Delta V_{\mu+1} + e_\mu$$

Where,

$$a_\mu = \left(B_\mu z\Delta t\right) = \left(\frac{a}{2r_L L^2 c_m} z\Delta t\right)$$

$$b_\mu = \left(C_\mu z\Delta t\right) = \left(-\left(\frac{\overline{g_L}}{c_m} + \frac{\overline{g_{Na}} m^3 h}{c_m} + \frac{\overline{g_K} n^4}{c_m} + \frac{a}{r_L L^2 c_m}\right) z\Delta t\right)$$

$$c_\mu = \left(D_\mu z\Delta t\right) = \left(\frac{a}{2r_L L^2 c_m} z\Delta t\right)$$

$$d_\mu = \left(B_\mu V_{\mu-1}(t) + C_\mu V\mu(t) + D_\mu V_{\mu+1}(t) + E_\mu\right)\Delta t$$

Section 3.1 The algorithm

We are illustrating the method for a single, nonbranching cable that begins with at compartment μ = 1, so that $a_1 = 0$, and ends at compartment μ = N, so $c_N = 0$.

b'_1 and d'_1 are initialised as b_1 and d_1 respectively.

Then, $b'\mu$ and $d'\mu$ are calculated for all the compartments in a given time step:

$$b'_{\mu+1} = b_{\mu+1} + \frac{a_{\mu+1} c_\mu}{1 - b'_\mu}$$

$$d'_{\mu+1} = d_{\mu+1} + \frac{a_{\mu+1} d'_\mu}{1 - b'_\mu}.$$

Then ΔV_N is calculated using:

$$\Delta V_N = \frac{d'_N}{1 - b'_N}$$

All the ΔV_μ are calculated backwards from the last compartment using the following expression:

$$\Delta V_{\mu-1} = \frac{c_{\mu-1}\Delta V_\mu + d'_{\mu-1}}{1 - b'_{\mu-1}}.$$

The change in membrane potential across time is updated using the following expression:

$$V_\mu(t + \Delta t) = V_\mu(t) + \Delta V_\mu$$

The above steps are repeated till we reach the end of time range.

Section 3.1 Parameters taken:

E_K: -77 mV
E_{Na}: 50 mV
g_K: 0.036 * 1e-3 / 1e-6 S/m^2
g_{Na}: 1.2 * 1e-3 / 1e-6, S/m^2
g_l : 0.003 * 1e-3 / 1e-6 S/m^2
E_l: -54.387 mV
r_l: 35.4e-2 ohm-m
r_m: 2 ohm-m^2
I_e: 10e-8 A (injected current)
c_m: 1e-2 F/m^2
a: 238e-6 m (radius of the axon)
compartments=1000
L: 50e-6 m (length of each compartment)
z: 0.5
All compartments are unmyelinated
Maximum time of simulation: 70 ms
Time step size: 1e-5 s

Section 3.2 Results:

(Problem 3) The following heatmap shows the evolution of membrane potential along space(compartments) and time in a giant squid axon with current injection at one end.

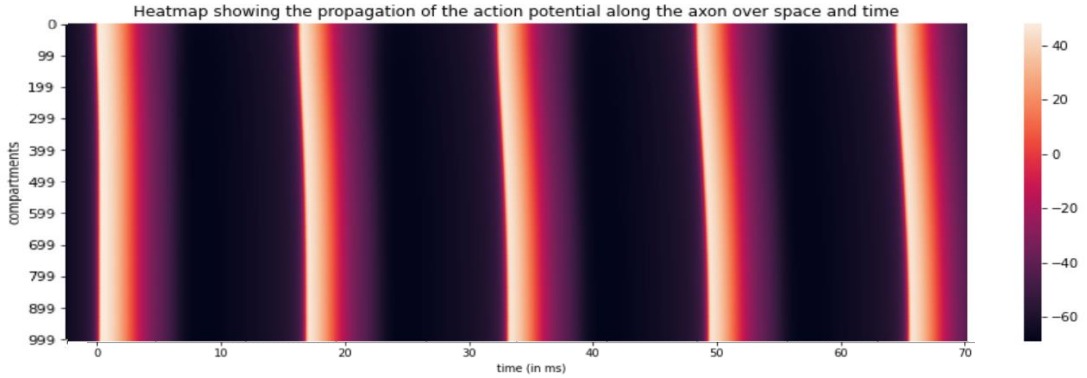

Figure 3. 1 Heatmap of membrane voltage evolution in space and time

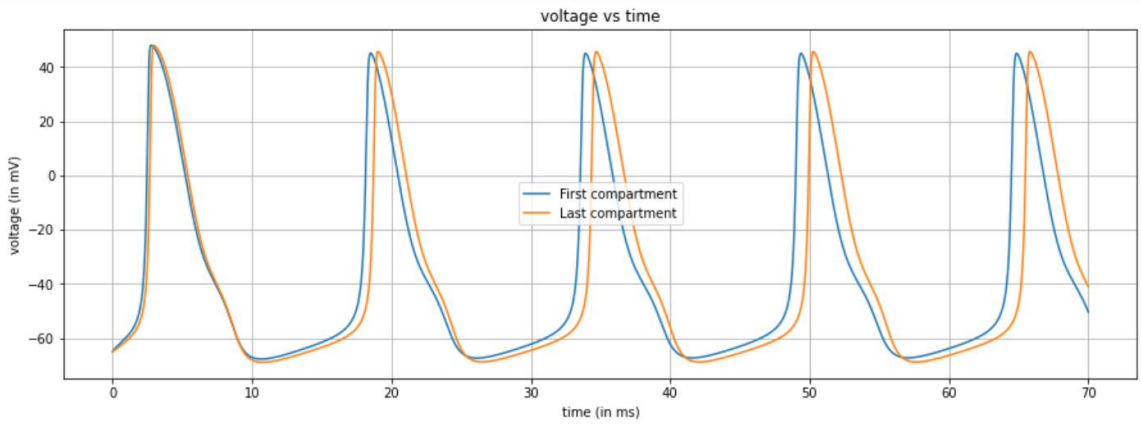

Figure 3. 2 Membrane voltage vs time for the first and last compartment.

(Problem 4) The following figure shows the variation of velocity of action potential propagation in a given axon with respect to the radius of the axon.

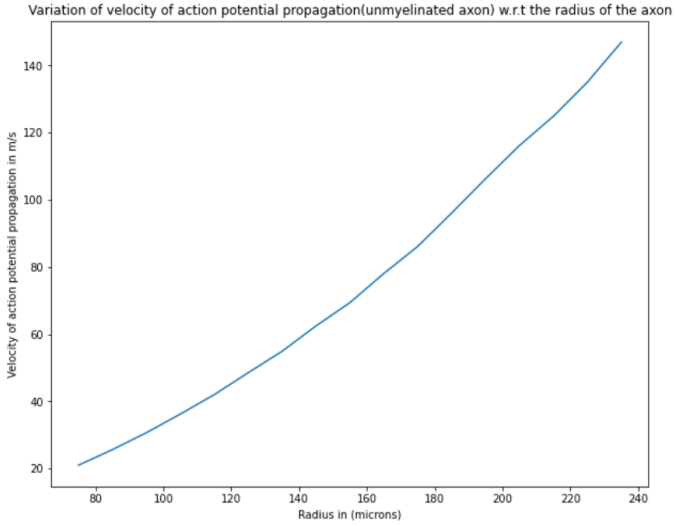

Figure 3. 3 Variation of velocity of action propagation with respect to radius of the axon.

(Problem 5) The following heat map shows the action potential propagation from both ends of the axon due to current injection at both terminal compartments. I_e: 5e-7 A

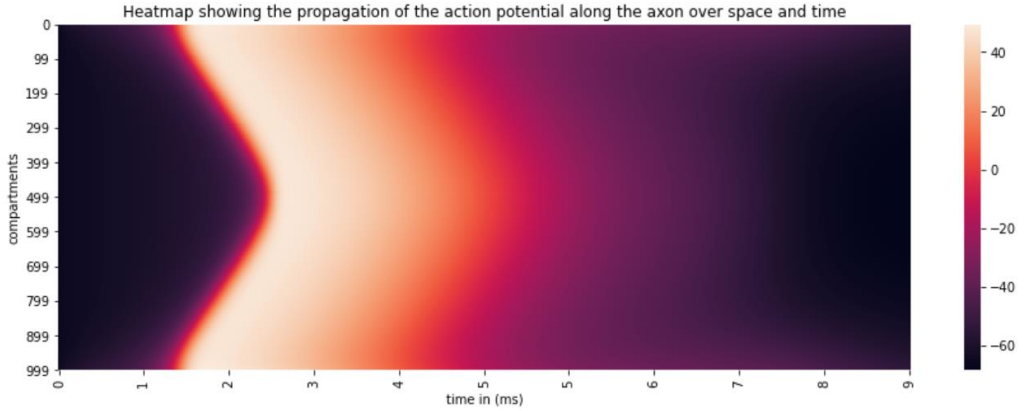

Figure 3. 4 The heatmap of two action potentials propagating towards each other from two ends of the axon.

Section 4. Myelinated Axon

(Problem 6)

The myelinated part of the axons have many layers of (glial cell) membrane wrapped around the axon. In the myelinated region membrane resistance is increases by 5000 times and the membrane capacitance is decreased by 50 times. This causes what is called a saltatory propagation, in which membrane potential depolarization is transferred passively down the myelin- covered sections of the axon, and action potentials are actively regenerated at the nodes of Ranvier.The cell membrane at the nodes of Ranvier has a high density of fast Na+ channels.

Therefore, to model the action potential propagation in a Myelinated axon, the myelinated part of the axon is modelled with compartments having only passive conductances. The nodes of Ranvier are modelled with the active conductances (high density of Na^+ channels). The nodes of Ranvier are 2 μm and Myelinated part is taken as 1 mm.

An axon with 100 nodes of Ranvier is taken with myelinated portions in between them. Each, node of Ranvier is modelled as a compartment and each myelinated portion has 500 compartments.

With the squid axon it was very difficult to notice the difference in the change between the times the action potentials were generated (it was almost instantaneous) in the first and the last compartments of the axon, so the radius was reduced to 9 μm in the myelinated part and the current injected was 1 pA.

Section 4.1 Parameters:

I_e: 1e-12 A (injected current)

The parameters are same as section 3.1 for compartments taken as nodes of Ranvier, except for the following:

- a: 1e-6 m (radius of the axon)
- L: 2e-6 m (length of each compartment)

For the compartments taken as myelinated portion, only the following parameters are modified rest remain same as section 3.1.

- E_K: 0
- E_{Na}: 0
- g_K: 0
- g_{Na}: 0
- g_l : 0.003x10^3/5000 S/m^2
- c_m: 1e-2/50 F/m^2
- a: 9e-6 m (radius of the axon)
- L: 2e-6 m (length of each compartment)

Section 4.2 Result:

The model is run and we obtain the following result:

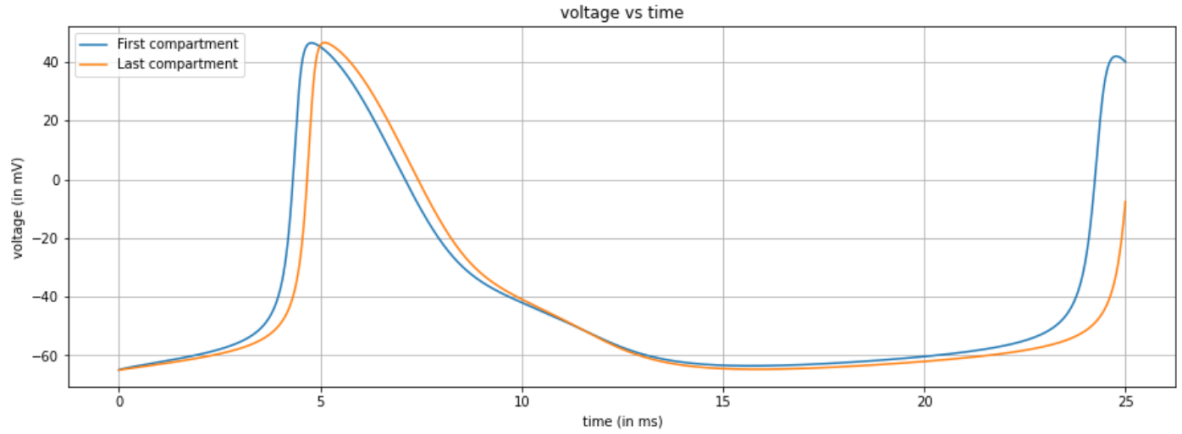

Figure 4. 1 Action potential generation at the in the first and last compartment of Myelinated axon

Velocity of action potential propagation: 300.89 m/s

Section 5 Discussion

(Problem 1): The steady state voltage obtained from the cable equation exponentially decreases away from the point of current injection. The rate of exponential decrease depends on the electrotonic length constant.

(Problem 2): The implementation of the Crank Nicolson numerical scheme in the problem 2 gives better accuracy to the solution but the stability of the numerical scheme largely dependent on the selection of the length of the compartment and the time step size.

(Problem 3): The injection of current at one end of the unmyelinated active axon membrane initiates an action potential in the axon and the action potential reaches its maximum velocity near the middle of the axon.

(Problem 4): The action potential propagation velocity varies directly proportional to square root of the axon radius for unmyelinated axons. So, thicker axons are required for unmyelinated axons to have higher action potential propagation velocity as in case of Giant squid axons which have action potential propagation velocities ranging from 10 to 20 m/s.

(Problem 5): The two action potentials colliding in the same axon will annihilate each other. This is because they cannot pass through each other's trailing refractory regions.

(Problem 6): The action potential propagation in a myelinated axon is very fast compared to the unmyelinated axon. It can be seen that the time gap between an action potential being generated at the first compartment and it being regenerated in the last compartment is almost instantaneous.

This is due to the fact that the myelinated part of the axon acts as an insulator and makes the action potential to jump from one node of Ranvier to another. This has huge biologically significance because this enables an action potential to travel very long distances in axon almost instantaneously for example during reflex actions, when a toe hit something and the muscle suddenly contracts based on the input from the spinal cord.

Also, from a energy consumption perspective, myelinated axons consume way less energy than unmyelinated ones which are full of active ion channels. This reduces the overall energy consumption by the nervous system which already consumes like 20 % of the total energy consumption in a human body[2].

References

1. Theoretical Neuroscience, Laurence F. Abbott, Peter Dayan, MIT Press, 12 Aug 2005
2. Appraising the brain's energy budget, Marcus E. Raichle, Debra A. Gusnard, Proceedings of the National Academy of Sciences Aug 2002, 99 (16) 10237-10239; DOI: 10.1073/pnas.172399499