Homework Assignment 2

**Part 1 – Binary search algorithm in NEURON**

A binary search algorithm starts at the middle element of an ordered array and checks whether the middle element is greater or less than the search element. If the elements match, usually the index or position is returned. Otherwise, this process is repeated on the upper or lower half of the ordered array based on whether or not the array is ordered in ascending or descending value.

For pseudo code of a binary search algorithm for an ascending array (i.e. array=[1 2 3]), the following recursive method can be used to identify the index of the search value given that the search value exists within the array.

binarySearch(array, value)

define midpoint

if midpoint==value

return index of midpoint

if midpoint > value

return binarySearch(array[0:midpoint],value)

if midpoint < value

return binarySearch(array[midpoint:end],value)

Unfortunately, it was difficult to implement a function in hoc that allowed for an array as an input so the following iterative method was used to determine the index of a value in an array.

// ---- ITERATIVE BINARY SEARCH ALGORITHM ----

// (implemented w/ zero-indexed programming)

vector = [0:0.1:10]

key = 4.3

minimumIndex = 0

maximumIndex = vector.size()-1

while (maximumIndex >= minimumIndex){

middleIndex = (maximumIndex - minimumIndex) / 2 + minimumIndex

middleValue = vector[middleIndex]

if (middleValue == key){ return middleIndex }

else if (middleValue < key) { minimumIndex = middleIndex + 1 }

else if (middleValue > key) { maximumIndex = middleIndex - 1 }

}

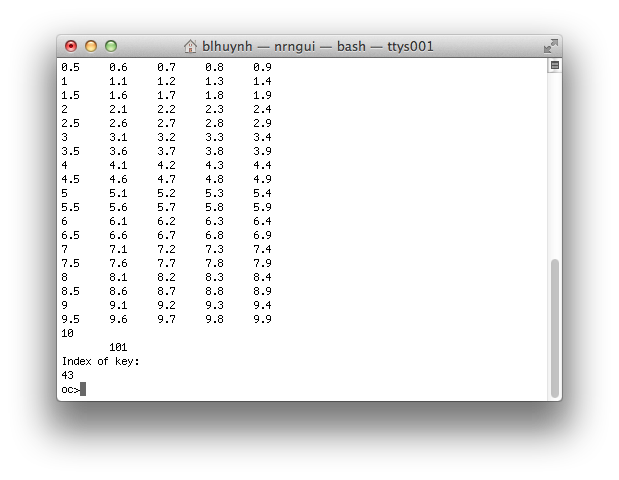


Figure 1: Binary Search Algorithm implemented in NEURON

**Part 2 – Model axon in NEURON**

Given – Fiber diameter

Diameter of node:

Length of myelin:

Based on with , or mV by inspection.

The internodal or axoplasmic resistance, , is calculated using the equation

where is the axoplasmic resistivity, is the internodal length, is the node diameter, and is the myelin diameter. Since consecutive nodes of Ranvier are separated by internodal spaces, the internodal resistance, , can represent these spaces if the myelin is assumed to be a perfect insulator and the internode is modeled as a tube of axoplasm. Therefore, the product of the axoplasmic resistivity and internodal length can be divided by the cross-sectional area of the nerve fiber to calculate the internodal resistance. In Neuron, the myelin is constructed by connecting nodes of Ranvier with resistors by modeling the intracellular space that represent not just the length of the node but also the length of the myelin as well.

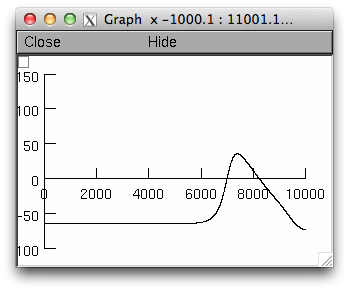


Figure 2: Vm(t) at 45th node

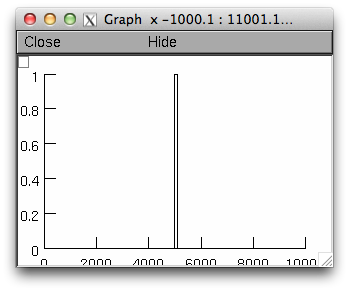


Figure 3: Istim(t)

**Part 3 – Intracellular threshold with PW = 0.1ms**

The binary search algorithm was paired with the modeled axon to determine the minimum threshold to stimulate the axon. Using a resolution of 1 pA, the minimum threshold was calculated to be . The upper bound of 1 nA was determined to be superthreshold and the final value of pA was also determined to be superthreshold. A screenshot of NEURON is shown in Figure 4.

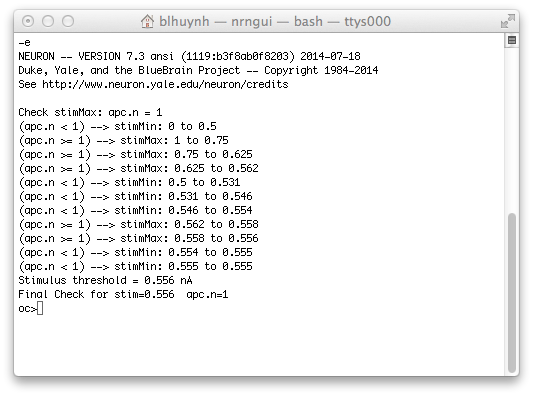


Figure 4: Threshold Finder via NEURON Binary Search Algorithm

**Part 4 – Extracellular threshold with PW = 0.1 ms**

A binary search algorithm was applied to the same modeled axon but with extracellular stimulation with extracellular resistivity . A cathodic stimulus was also used with a pulse width of 0.1 ms from an electrode 1 mm away in the perpendicular direction from the middle node of Ranvier. A screenshot of NEURON finding the threshold to be pA is shown in Figure 5.

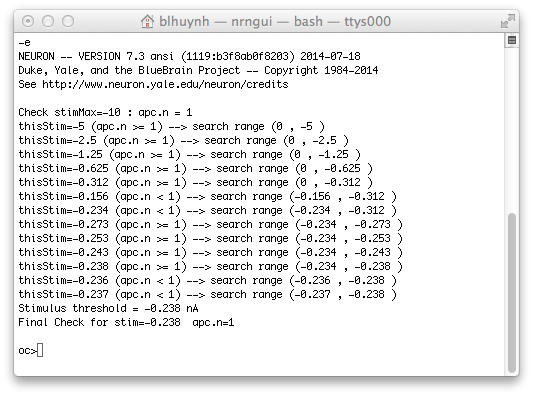
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Figure 5: Extracellular Threshold with PW = 0.1 ms

**Part 5 – Threshold-fiber diameter**

Fibers with a diameter of 1-15 in 2 increments were stimulated extracellularly. With increasing fiber diameter, the spacing between the nodes of Ranvier also increased, resulting in larger transmembrane potential differences and resulting in a lower activation threshold. The threshold-diameter curve can be approximated by

where the two constants, *a* and , are determined empirically. The recorded data is listed in Table 1 and plotted in Figure 6.

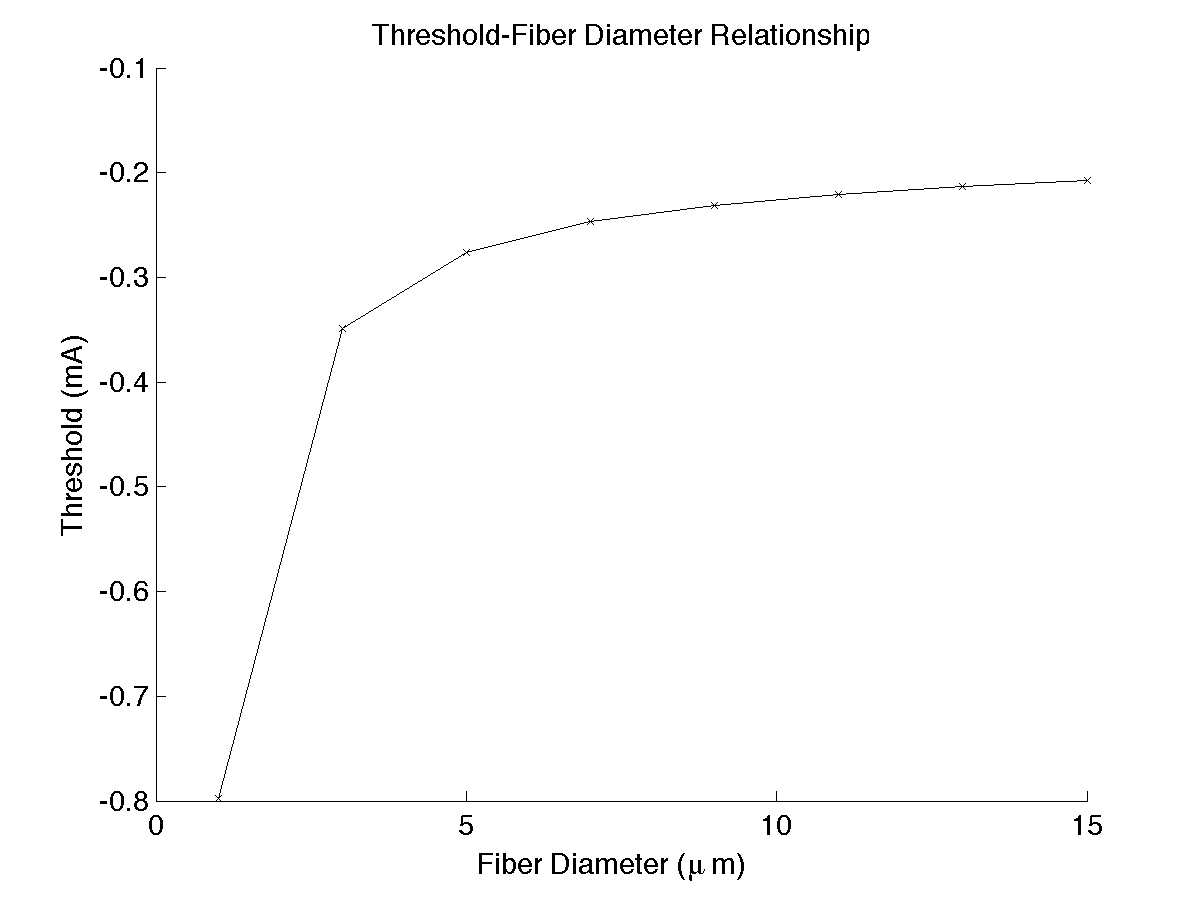


Figure 6: Threshold-Fiber Diameter Relationship

Table 1: Threshold-Fiber Diameter Data

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Fiber Diameter (m) | 1 | 3 | 5 | 7 | 9 | 11 | 13 | 15 |
| Threshold (nA) | -0.798 | -0.349 | -0.276 | -0.247 | -0.231 | -0.221 | -0.213 | -0.207 |

**Part 6 – Threshold-distance relationship**

Using an diameter axon and PW=0.1 ms, the current thresholds for the 7 following electrode-fiber distances were recorded: {0.1, 0.2, 0.5, 1, 2, 5, 10} mm. Transmembrane potentials generated by extracellular stimulation are larger when the electrode is closer to the neuron. As the distance between the neuron and electrode increases, the stimulation amplitude required to activate the neuron increases by

for the offset which determines the absolute threshold, slope which determines the threshold difference between fibers at different distances, stimulation threshold , and electrode-neuron distance . The recorded data is listed in Table 2 and shown in Figure 7.

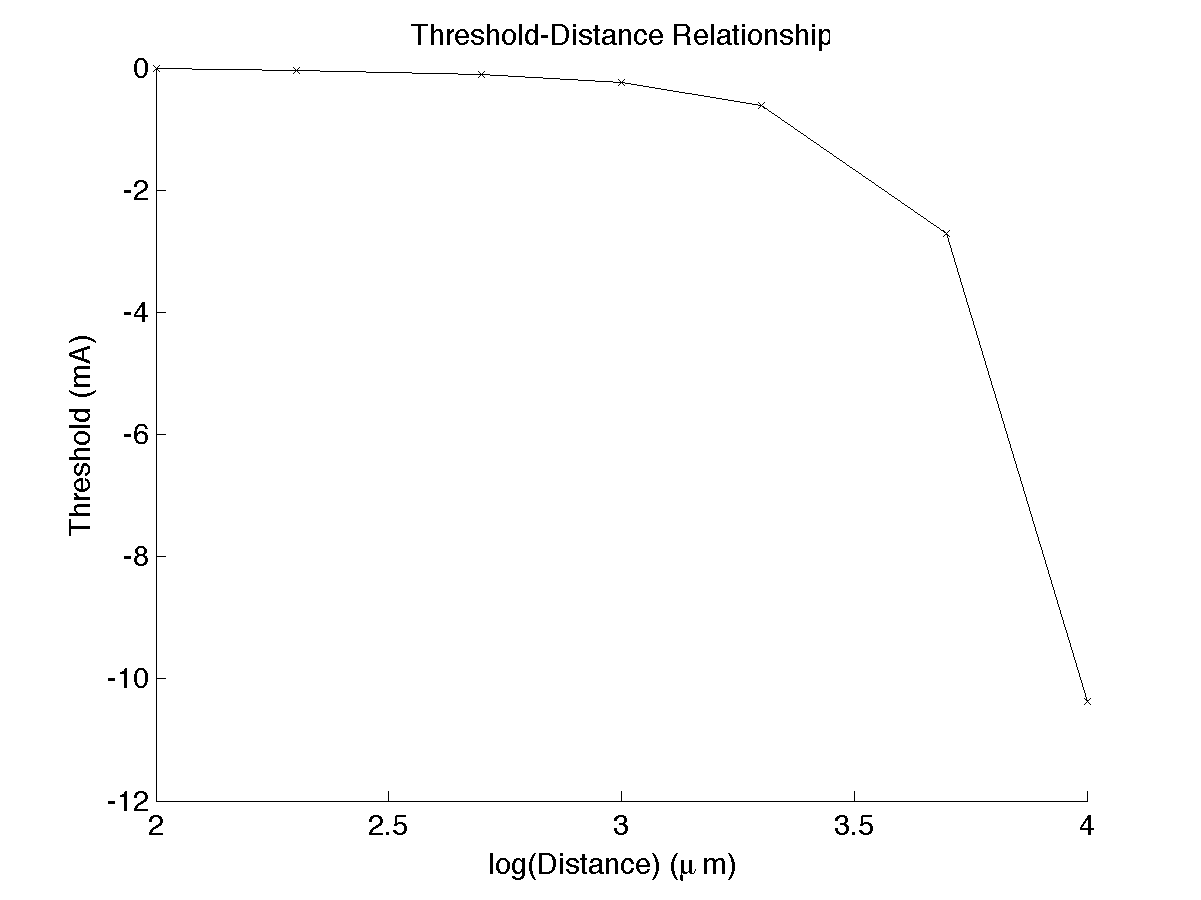


Figure 7: Threshold-Distance Relationship

Table 2: Threshold-Distance Data

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Electrode-Fiber  Distance (mm) | 0.1 | 0.2 | 0.5 | 1 | 2 | 5 | 10 |
| Threshold (nA) | -0.016 | -0.034 | -0.099 | -0.236 | -0.609 | -2.702 | -10.366 |

**Part 7 – Application**

Shannon and colleagues investigated the threshold-distance relationship for electrical stimulation using an auditory prosthesis to compare with postmortem threshold-distance measurements. This allows for a better estimation of current spread to better understand localization effects of electrical stimulation. Using an auditory brainstem implant (ABI), electrical stimulation is directly applied to the auditory structures in the brainstem of patients who have lost hearing ability due to large, bilateral, eighth nerve tumors. Threshold data were obtained from a single subject with sinusoidal and biphasic pulses and electrode position data were determined postmortem. As stimulation amplitudes are increased, there is a higher likelihood of activating non-relevant structures that are not related to auditory processes. It was concluded that the distances between the electrode to the nonauditory nuclei were sufficiently large enough such that presently used stimulation amplitudes would not activate those regions. The relationship between electrical stimulation threshold and electrode-fiber distance was consistent with the function first postulated by Ranck in 1975. The consistency despite varying models of the brain and stimulation waveforms is encouraging and provides confidence in the ability to predict regions of activation for future methods in electrical stimulation for better selectivity and patient comfort.

Shannon, R., Moore, J., Mccreery, D., & Portillo, F. (1997). Threshold-distance measures from electrical stimulation of human brainstem. *IEEE Transactions on Rehabilitation Engineering,* *5*(1), 70-74. Retrieved October 1, 2014, from http://ieeexplore.ieee.org/stamp/stamp.jsp?tp=&arnumber=559351

**Code & Output**

**Part 1 – Binary Search Algorithm in NEURON** (binarySearchAlgorithm.hoc)

load\_file("nrngui.hoc")

func round(){

if ($1>0){

return int($1+0.5)

} else {

return int($1-0.5)

}

}

objref v1

proc createVector(){

startVal = $1

stopVal = $2

stepVal = $3

numel = (stopVal-startVal)/stepVal

v1 = new Vector(numel+1)

v1.x[0] = startVal

for i=1,numel{

v1.x[i] = v1.x[i-1]+stepVal

}

}

// Create list of numbers 0:0.1:10 to search from

createVector(0,10,0.1)

findValue = 4.3

v1.printf()

// ---- ITERATIVE binary search ----

proc iterative(){

key = $1

imin = 0

imax = v1.size()-1

while (imax >= imin){

imid = round((imax-imin)/2 + imin)

midValue = v1.x[imid]

if (midValue == key){

// print imid

break

} else if (midValue < key) {

imin = imid + 1

} else if (midValue > key) {

imax = imid - 1

}

// print "\n"

}

if (midValue != key) {

print "Key not found."

} else {

print "Index of key: "

print imid

}

}

iterative(findValue)

**Part 2 – Model axon in NEURON**

//load\_file("nrngui.hoc")

//load\_proc("nrnmainmenu")

// \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* Model specification \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

proc params() {

// Geometrical properties

D = 8

num\_nodes = 51 // number of nodes [unitless]

node\_diam = D\*0.7 // node diameter [um]

node\_length = 1 // node length [um]

myelin\_length = 100\*D // internodal length [um]

// Electrical properties

node\_cm = 2 // specific membrane capacitance [uF/cm^2]

rhoa = 200 // intracellular resistivity [ohm-cm]

node\_Rm = 1500 // specific membrane resistance [ohm-cm^2]

ap\_thresh = 0 // action potential threshold

// Stimulus parameters

mydel = 5 // start at t=5ms [ms]

myamp = 1.0 // amplitude [nA]

mydur = 0.1 // duration, aka pulsewidth [ms]

// Temporal parameters

dt = 0.001 // [ms]

tstop = 10 // [ms]

num\_timesteps = int(tstop/dt) + 1

// Other parameters

v\_init = -65 // [mV]

celsius = 6.3 // [deg C]

}

params()

// \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* Model initialization \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

create axon[num\_nodes]

proc initialize() {local i

for i = 0, num\_nodes - 1 {

axon[i] {

nseg = 1

diam = node\_diam

L = node\_length

Ra = rhoa \* ((node\_length+myelin\_length)/node\_length)

cm = node\_cm

// Insert passive channel

insert hh

g\_hh = 1/node\_Rm // do we need to change this from g\_pas -> g\_hh?

}

}

for i = 0, num\_nodes - 2 {

connect axon[i](1), axon[i+1](0)

}

}

initialize()

// \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* Instrumentation \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

// Intracellular stimulation

objref stim

proc int\_stim() {

axon[int(num\_nodes/2)] { // changed stimulus location to center of the axon (10 -> )

stim = new IClamp()

stim.loc(0.5)

stim.del = mydel

stim.amp = myamp

stim.dur = mydur

}

}

int\_stim()

// Record Vm(t) at all nodes

objref Vm\_vec[num\_nodes], Istim\_vec

Istim\_vec = new Vector(tstop/dt)

for i = 0, num\_nodes - 1 {

Vm\_vec[i] = new Vector(num\_timesteps,0)

Vm\_vec[i].record(&axon[i].v(0.5),dt)

}

// add APCount object to node 20

objref apc

axon[19] apc = new APCount(0.5)

apc.thresh = 20

// \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* Simulation control \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

proc stimul() {

finitialize(v\_init)

while(t<tstop) {

fadvance()

Istim\_vec.x[t/dt-1] = stim.i

if (stim.i > 1){

print stim.i

}

}

}

stimul()

print "apc.n = ",apc.n

// \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* Data analysis & output \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

// Plot Vm(t) at the 45th node

objref g1

proc plot\_data() {

g1 = new Graph()

g1.size(0, num\_timesteps, -100, 150)

// Vm\_vec[int(num\_nodes/2)].plot(g1)

Vm\_vec[44].plot(g1)

}

plot\_data()

// Plot I\_stim(t)

objref g2

proc plot\_Istim(){

g2 = new Graph()

g2.size(0, num\_timesteps,0,1)

Istim\_vec.plot(g2)

}

plot\_Istim()

// plot Vm(t) at 20th node

// objref g3

// proc plot\_data\_node20() {

// g3 = new Graph()

// g3.size(0, num\_timesteps, -100, 150)

// // Vm\_vec[int(num\_nodes/2)].plot(g1)

// Vm\_vec[19].plot(g3)

// }

// plot\_data\_node20()

// plot\_data()

**Part 3 – Intracellular threshold with PW = 0.1 ms (threshold procedure)**

proc iterative(){

count=0

while (1) {

thisStim = cutoff((stimMax-stimMin)/2+stimMin)

myamp = thisStim

int\_stim()

stimul()

if (apc.n >= 1){

print "(apc.n >= 1) --> stimMax: ",stimMax,"to ",thisStim

stimMax = thisStim

} else if (apc.n < 1){

print "(apc.n < 1) --> stimMin: ",stimMin,"to ",thisStim

if (stimMin == thisStim) { print "Stimulus threshold = ",thisStim+0.001,"nA" }

stimMin = thisStim

}

count+=1

if (count>10){break}

}

}