

BME515 gammaCore Sapphire PTSD Final Report

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I. INTRODUCTION

The goal of our study was to perform a simplified computational simulation of the gammaCore Sapphire – a transcutaneous cervical vagal nerve stimulator – and verify its efficacy in stimulating the vagus nerve to treat PTSD, or post traumatic stress disorder¹. Using models in COMSOL and NEURON, we determined that the stimulation parameters used by the gammaCore Sapphire are not sufficient to stimulate vagal nerve fibers. Based on the lack of activation, we recommend that J&J should not acquire this technology.

II. BACKGROUND

A. Device Components and Operation

The gammaCore Sapphire device consists of 3 main components: a handheld stimulator, a charging case, and electroCore-approved gel². There are two electrodes located at the top of the handheld stimulator, through which a bipolar, biphasic current can travel. The stimulator also has a display that indicates the intensity of stimulation, battery life, as well as the number of stimulations left within a 24 hour period.

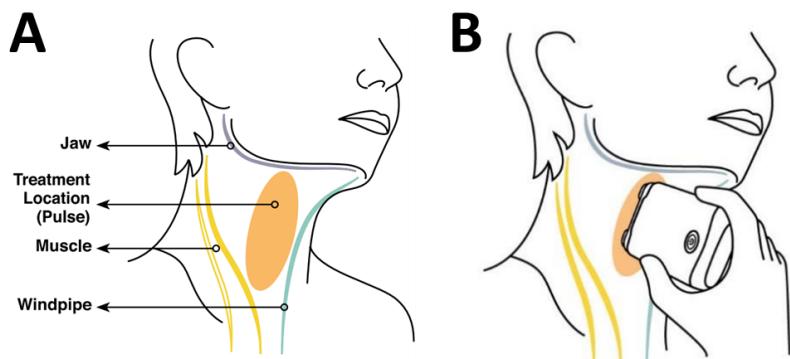


Figure 1. Diagrams from FDA guidelines² depicting use of gammaCore Sapphire CV.

To use the device, the patient first identifies the treatment location by finding their pulse on the side of the neck, as the vagus nerve is located in the same area, indicated by the orange section in Figure 1A. A small amount of electroCore-approved gel is applied to both stimulation electrodes, and then the device is turned on and positioned over the treatment location (Figure 1B). The device allows patients to increase stimulation intensity to the maximum level they are able to tolerate and requires patients to hold the device at the same location for the 2 minute duration of stimulation.

The pivotal clinical trial for the use of transcutaneous cervical vagus nerve stimulation (tcVNS) in treatment of PTSD specifies that VNS should be administered via the gammacore Sapphire immediately following a potential PTSD stressor or trigger³.

B. Safety, Efficacy, and Clinical Utility of the Device, Benefits and Risks of the Device, and Peer Reviewed Publications

The stimulation is delivered transcutaneously and does not require any invasive procedures. One advantage is that patients can utilize the device at home without physician supervision. Some common side effects include muscle twitching, discomfort, or pain during the treatment^{2,3}. The efficacy of tcVNS treatment for reducing the

sympathetic responses in PTSD stress responses was evaluated in a double-blind, randomized, sham controlled trial by Gurel et. al⁴. The results of this publication showed beneficial effects of stimulation with the gammaCore device, with a decreased heart rate by 5.7%, increased peripheral vasodilation by 30.8%, and increased pulse arrival time by 6.3%. A second, randomized sham controlled study by Wittbrodt et. al found that tcVNS also had significant downstream effects in manipulating brain activity⁵. Increased neural activity was found within the anterior cingulate, which is associated with decreased arousal levels and inhibition of the amygdala, leading to improved emotional regulation.

C. Regulatory status and Intellectual Property

The device was FDA-approved for various treatment purposes including the treatment of pain caused by episodic cluster headache and migraine headache, and Paroxysmal Hermicrania and Hermicrania Continua⁶. The device's latest FDA-approval was given in January 2022 for the treatment of PTSD⁷. Due to its plethora of uses and as one of the few existing FDA approved noninvasive cervical vagus nerve stimulators on the market, the gammaCore Sapphire has a competitive advantage within its field. The gammaCore Sapphire and its aforementioned uses are covered under 21 different patents⁸.

III. METHODOLOGY

A. Vagus Nerve Fibers⁹

The vagus nerve controls a wide variety of both motor and sensory functions, although it is primarily composed of sensory fibers. There are three main categories of nerve fibers A, B, and C that make up a larger nerve bundle such as the vagus nerve, two of which are shown in Figure 2.

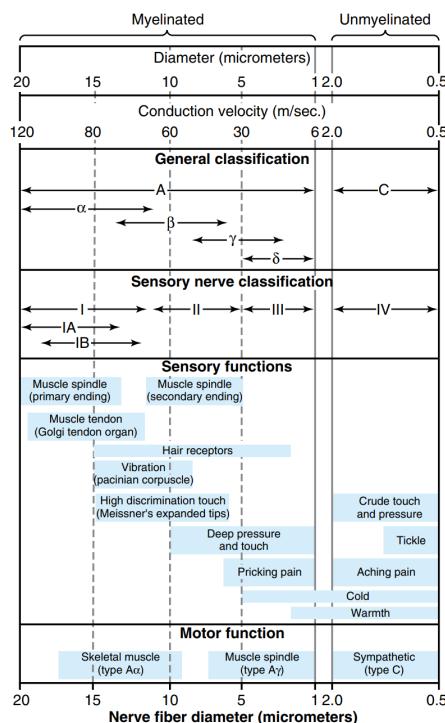


Figure 2. Classification of nerve fibers per diameter¹⁰

A fibers are large, myelinated fibers that are typically subdivided into A α , A β , A γ , and A δ . A α fibers are efferent fibers that control motor functions in the skeletal muscle, muscle spindle, and muscle tendon, ranging from around 10-20 μm . A β fibers range from 6-14 μm and are primarily efferent fibers that control motor function in muscle spindles. There are also afferent Type II A β fibers which relay sensations for vibration and touch that range in size from 6-11 μm . A γ fibers are also primarily efferent fibers

ranging from 2-9 μm that control motor function in muscle spindles. These fibers also include Type II (ranging from 5-9 μm) and Type III (ranging from 2-5 μm) afferent sensory fibers controlling the sensation of deep pressure. Lastly, A δ fibers are the smallest of the A fibers, ranging from 1-5 μm and are primarily Type III afferent sensory fibers detecting pain and cold.

B fibers are small, moderately myelinated fibers and control autonomic functions, making these fibers an ideal target for stimulation in treating PTSD stress symptoms. B fibers range from 1-3 μm .

C fibers are small, unmyelinated fibers ranging in size from 0.5-1.5 μm . These are primarily afferent fibers that control sensations of pain, touch, and warmth.

When performing further analysis with these fibers, the upper value of each fiber's diameter range is used. We chose the maximum diameter values as they would stimulate first, meaning that activation implies at least some of the fibers within the group are being stimulated and carrying out the intended function.

B. Modeling the cervical vagus nerve in COMSOL

We started by constructing a simplified, 3D model of the human cervical vagus nerve region at the level of the C5 spinal cord and implemented a bipolar, biphasic current source in COMSOL. This model consists of the cervical vagus nerve and layers of connective tissue, muscle, fat, and skin between the nerve and electrodes, simplified as a rectangular shape.

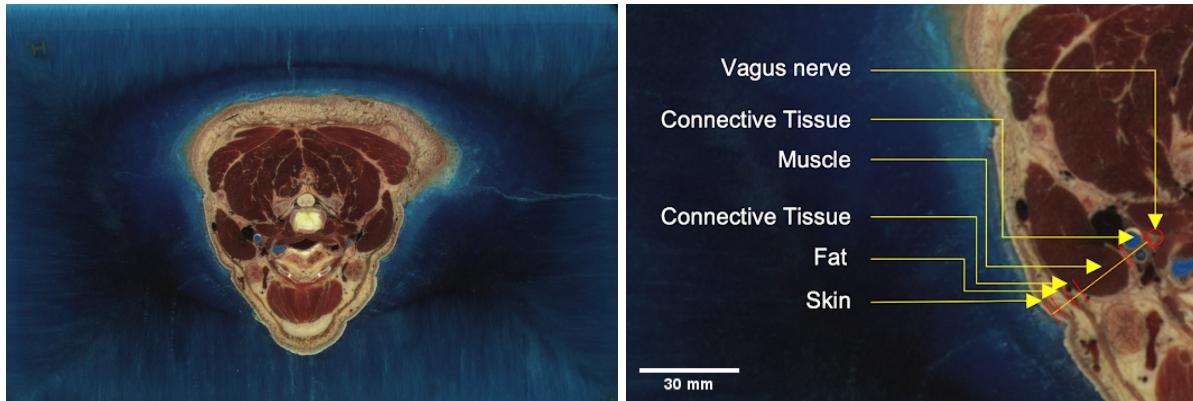


Figure 3. Left: Cross-section of human neck at approximately the C6 region taken from the Visible Human Project¹¹. Right: close-up of how each tissue layer was measured using ImageJ.

The model utilizes literature values of skin to vagus nerve distance, averaging 3.62 cm¹², and the diameter of cervical vagus nerve, averaging 4.6 mm in diameter¹³. Using the distance between the outer skin and vagus nerve as a scale, we measured the thickness of each tissue component (Table 1) from an image found in the NIH's Visible Human Project¹¹ database (Figure 3) using ImageJ software. We found tissue conductivity values reported in literature as well and inputted the tissue thicknesses and material conductivities into COMSOL^{14,15,16}.

Table 1: Thicknesses and conductivity of each tissue layer.

Layer	Thickness (cm)	Conductivity (S/m) ¹⁷
Electrode	-	1E6
Skin	0.272	0.148
Fat	0.452	0.0776
Muscle	1.645	0.461
Connective Tissue	11.97***	0.0792
Vagus Nerve	0.46	0.348

***Connective tissue layer was extended until voltages converged.

After conducting a review of the twenty-one patents available for the gammaCore Sapphire device, we were unable to find the exact measurements of the device as they were not disclosed within these patents. Thus, we estimated the electrode geometry from device descriptions and images of the device fitting in the palm of the hand and a quote from the Chief Medical Officer in a 2018 interview with the Medical Device Network describing the device as “a hand-held device the size of a small cell phone¹⁸.” Looking at cell phones of 2018, the iPhone 8 is a common phone of the time and measured 67.3 mm in width¹⁹. Thus, we estimated the total width of the gammaCore Sapphire device as 7 cm. The electrode contacts are spaced approximately one electrode apart, so we estimated the electrode diameters to be around 2 cm, thus making the distance between electrodes 5 cm. We acknowledge that these estimates are not precise, but are suitable for our simplified modeling purposes.

C. Simulating electrical stimulation in COMSOL

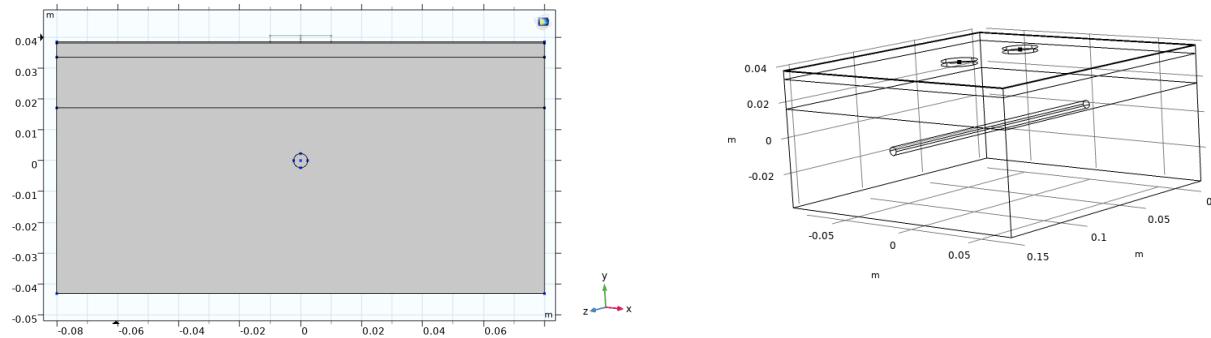


Fig. 4: Cross-section and isometric view of rectangular COMSOL model. From top to bottom: electrode, skin, fat, muscle, vagus nerve encased in connective tissue.

We have kept our model simple as a rectangular 2D cross-section into the neck (Figure 4, left) until the vagus nerve is reached and extruded the model into 3D to accommodate the distance of the electrodes. The model is extruded 16 cm to represent the general region of tissue affected by transcutaneous cervical vagus nerve stimulation

(Figure 4, right). After building the physical model in COMSOL, we placed two point current sources in the center of each electrode with amplitudes of 1 mA and -1 mA and grounded along the bottom surface of our model, with the intention of scaling by the sinusoidal max amplitudes from the output of the device, due to the linearity of the model.

To ensure that the COMSOL model was stable and the voltages converge, we initially measured voltages at 17 evenly spaced points along the center of the vagus nerve. We then increased the connective tissue layer thickness until the voltages converged, which we identified as the point at which the voltage distribution did not change with an increase in model size. These voltages are shown in Table 2 and Figure 5.

Table 2: A comparison of voltages along the modeled vagus nerve at two depths. The voltages remain the same across all points with a 1 and -1 mA current source.

Model Height	Point 1	Point 2	Point 3	Point 4	...	Point 17
7.66 cm	5.642 mV	5.831 mV	6.371 mV	7.131 mV	...	-5.644 mV
15.28 cm	5.642 mV	5.831 mV	6.371 mV	7.131 mV	...	-5.644 mV

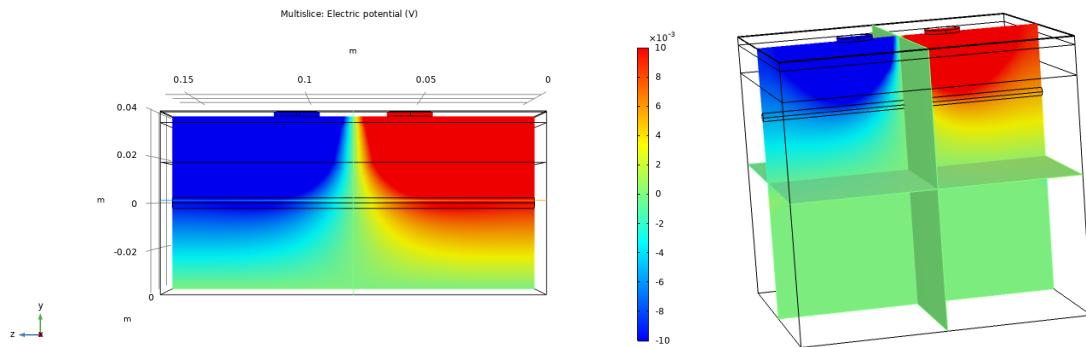


Fig. 5: Electric Potential Distributions throughout the model at two depths resulting from 1 and -1 mA current source.

Once the dimensions of the model were set, we collected extracellular voltage distributions for the six fiber types. To do so, more points were added along the nerve, with the specific number calculated by the internodal length of each fiber measured using the result of the following equation.

$$\frac{\text{Axon Length}}{\text{Internodal Length} + \text{Nodal Length}} = \frac{16\text{cm}}{100 \times \text{Diameter} + 1.5\mu\text{m}}$$

D. Modeling activation in NEURON

After the voltage distributions were collected, they were exported into NEURON for further analysis.

The NEURON model used is based on the Sweeney Model of electrical stimulation. This model targets myelinated peripheral nerves in mammals and is different from typical models because of the absence of voltage-dependent potassium channels that are typically found in frogs (often used as a basis for models) but not in human peripheral nerves.

In NEURON, the extracellular voltages were scaled by the max current output of 35 mA and a sinusoidal wave with a burst frequency of 5 kHz. The stimulation is applied with an envelope frequency of 25 Hz, or 1 ms on and 39 ms off. The program was then run to record the membrane potential in the middle of the axon through time and plotted to check for nerve activation. It is a non-linear model, with voltage-dependent sodium channels, voltage-independent leakage channels, and nodal capacitance.

II. RESULTS

A. Validation of voltage calculation from COMSOL

$$V = \frac{I}{4\pi r\sigma}$$

The electrical potential at distance r from a point current source I can be described by the equation above. Our model represents multiple layers of materials, and COMSOL calculates the potential using multiple values of conductivities (σ). The voltage output from COMSOL can be verified by hand-calculation of voltage using the equation above. Among different conductivities, the smallest and biggest conductivity values (fat = 0.0776 S/m, muscle = 0.461 S/m) can be used to find the upper and lower bounds of the actual voltage. At $(x,y,z) = (0,0,0)$, voltage was measured to be 9.48 mV. y-axis distance from the origin to the two electrodes was 0.04m. The x-axis distances from the origin to the electrode 1 and electrode 2 are $r_1 = 0.055\text{m}$ and $r_2 = 0.105\text{m}$. Therefore, the distances from the origin to the electrode 1 and 2 are 0.068m and 0.1124m. The electrode 1 has current of +1mA and the electrode 2 has current of -1mA.

Lower Bound: $\sigma_{muscle} = 0.461 \text{ S/m}$

$$V = \frac{I_1}{4\pi r_1 \sigma_{muscle}} + \frac{I_2}{4\pi r_2 \sigma_{muscle}} = \frac{+1\text{mA}}{4 \times \pi \times 0.055\text{m} \times 0.461 \text{ S/m}} + \frac{-1\text{mA}}{4 \times \pi \times 0.105\text{m} \times 0.461 \text{ S/m}} = 1.49\text{mV}$$

Upper Bound: $\sigma_{fat} = 0.0776 \text{ S/m}$

$$V = \frac{I_1}{4\pi r_1 \sigma_{fat}} + \frac{I_2}{4\pi r_2 \sigma_{fat}} = \frac{+1\text{mA}}{4 \times \pi \times 0.055\text{m} \times 0.0776 \text{ S/m}} + \frac{-1\text{mA}}{4 \times \pi \times 0.105\text{m} \times 0.0776 \text{ S/m}} = 8.87\text{mV}$$

The COMSOL output of 9.48mV at $(0,0,0)$ was between the calculated lower and upper bounds, which gives validation to the voltage calculation using COMSOL.

B. Simulation of Cervical Vagus Nerve Stimulation in NEURON

When we simulated the cervical vagus nerve stimulation in NEURON using the voltages from COMSOL, none of the vagus nerve fibers tested with diameters in the range of $1.5\mu\text{m}$ to $20\mu\text{m}$ showed activation. We scaled the extracellular voltages to find the

threshold current required to activate each of the vagus nerve fibers in the same environment (Table 3 and Figure 6, Figure). The current-diameter relationship obtained from the model shows a downward curve following the relationship $I_{th} \propto 1/\sqrt{D}$, showing that the NEURON model used follows known neuronal properties. In addition, the thresholds are significantly larger than the maximum current output allowed by the device and tolerated by patients, showing that it would be unfeasible to stimulate these nerves without modifications to the gammaCore Sapphire device.

Table 3: The minimum threshold needed to stimulate the nerve for each diameter

Nerve Diameter (μm)	1.5	3	5	9	11	14	20
Threshold Current Amplitude (mA)	3.5E4	9.8E3	3.5E3	1.08E3	7.35E3	4.55E2	2.27E2

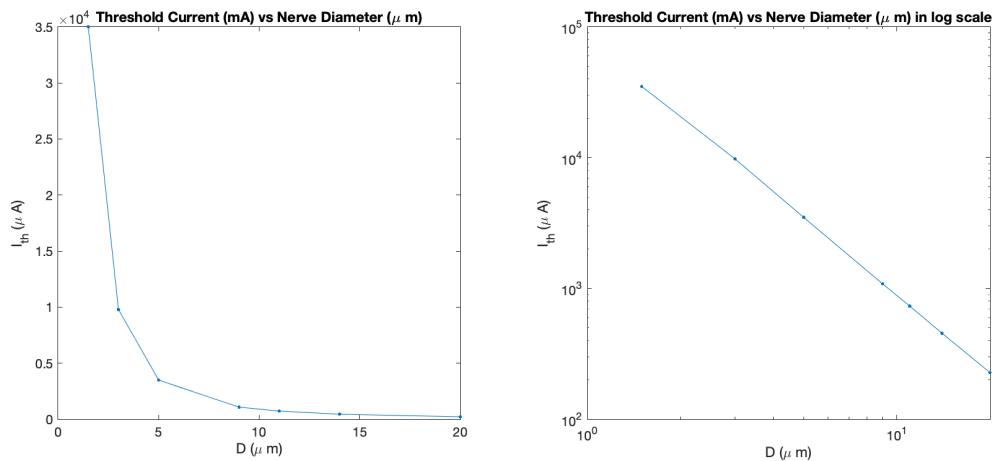


Figure 6: The current-diameter relationship obtained from the model shows a downward curve following the relationship $I_{th} \propto 1/\sqrt{D}$. With a log-log relationship, this becomes linear.

IV. DISCUSSION OF MODEL

Due to a variety of approximations, the model developed for this simulation has inherent flaws. The geometry of the anatomy was grossly simplified into a rectangular model of the tissue with combined individual flat layers rather than a more complex model of the neck that would not only have irregular shapes, but also additional tissues, such as blood and fluids between tissues. Additionally, the vagus nerve was approximated as a non-branching cylinder with uniform diameter throughout the nerve with the target fiber directly in the center of the nerve, while a better model would account for changes in diameter, internodal length, and distance along the vagus nerve that would affect how voltage is propagated from node to node. The electrode contact sizes and distance to the nerve were also approximated off vague imagery due to a lack of available dimensions.

Another major flaw in the model is the singular use of the Sweeney model, intended for mammalian peripheral myelinated nerves, typically motor axons. This model is satisfactory for the larger myelinated fibers within the vagus nerve, such as the A fibers, but does not apply to unmyelinated fibers, such as the C fibers. To improve on this flaw, a new model would have to be used in addition to the Sweeney model or in place of the Sweeney model to properly evaluate the membrane potentials of the C fibers in addition to the A and B fibers.

V. CONCLUSION

Based on the results of our model, the gammaCore Sapphire is a technically unsound device despite promising data in human clinical trials in the treatment of PTSD

stress symptoms. The scientific basis behind these results claimed activation of the vagus nerve, specifically afferent A fibers, leads to the release of biomarkers and immune functions that help to mitigate the PTSD response. However, none of the fibers of the vagus nerve were activated, suggesting alternative mechanisms or a strong placebo effect from self-stimulation at a perceivable level of electrical stimulation.

We advise that it is premature for Johnson and Johnson to consider the acquisition of the gammaCore Sapphire device technology, as it is highly unclear whether the treatment efficacy can be attributed to the treatment itself or other confounding factors. Some R&D efforts can be made to improve the likelihood of the acquisition. Currently, our computational simulation shows that even the maximum tolerable level of current fails to trigger activation in the targeted nerve fibers. Adjusting stimulation parameters other than current amplitude, such as stimulation cycle or burst frequency, may improve the activation intensity without further increasing the current amplitude. Also, continued effort should be made to validate that the treatment is stimulating the A fibers in cervical vagus nerve and can be attributed to the desired treatment outcome.

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NEURON Simulation Script

```
# -*- coding: utf-8 -*-
"""
Created on Tue Feb 22 12:38:02 2022

Created by Eric Musselman January 29, 2021
@author: Winnie Lu, Philjae Chang, Celina Zhou

"""

# %% import NEURON library
from neuron import h
import matplotlib.pyplot as plt

# other imports
import numpy as np
import csv

# %% load run controls
h.load_file('stdrun.hoc')

# %% MODEL SPECIFICATION
# time params
=====
h.tstop = 10 # [ms]: simulation time
h.dt = 0.001 # [ms]: timestep

# cell params
=====
h.celsius = 37
# [mV]: Vm @ rest for initializing membrane potential at start of simulation
V0 = -80
n_nodes = 81 # []: (int) number of sections, make this an odd number
D = 20 # [um]: fiber diameter
inl = 100*D # [um]: internodal length
rhoa = 54.7 # [Ohm]: axoplasmic/axial resistivity
cm = 2.5 # [uF/cm**2]
L = 1.5 # [um]
nseg = 1 # []: (int)
g = 1/2000 # [S/cm**2]

# stim params
=====
delay = 0.5 # [ms]: start time of stim
dur = 1 # [ms]: pulse width of (monopolar) stim
# [mA]: amplitude of (intracellular) stim object -- but we are applying this
extracellular (negative cathodic, positive anodic)
```

```

vol = []
# change this filename for different diameters
filename = "20um_fiber.txt"
f = open(filename, "r")
lines = f.readlines()
vol = []
for x in lines:
    if x[0:1] != "%":
        vol.append(float(x.split(" ")[-1].strip("\n")))
f.close()

# %% MODEL INITIALIZATION
# define nodes for cell
=====
nodes = [h.Section(name=f'node[{i}]') for i in range(n_nodes)]

# insert extracellular/mechanisms part of the circuit
=====
# connect the nodes
=====
for node_ind, node in enumerate(nodes):
    node.nseg = nseg
    node.diam = 0.6*D
    node.L = L
    node.Ra = rhoa*((L+inl)/L)
    node.cm = cm
    node.insert('sweeney')
    node.insert('extracellular')
    for seg in node:
        seg.extracellular.e = 0
    if node_ind > 0:
        node.connect(nodes[node_ind-1](1))

# %% INSTRUMENTATION - STIMULATION/RECORDING

vol_mem = [h.Vector().record(sec(0.5)._ref_v) for sec in nodes]
tvec = h.Vector().record(h._ref_t)

# %% SIMULATION CONTROL
# compute extracellular potentials from point current source (call this from
my_advance to update at each timestep)

def update_field():
    phi_e = []
    for node_ind, node in enumerate(nodes):
        phi_e.append(vol[node_ind])
        node(0.5).e_extracellular = 10000 * phi_e[node_ind] * \
            35 * np.sin(2 * np.pi * 5000 * h.t * 0.001)

# time integrate with constant time step - this just defines method, called by proc
advance() below

def my_advance():
    update_field()
    h.fadvance()

h.finitialize(Vo)

```

```

# this is somewhat of a "hack" to change the default run procedure in HOC
=====
h(r"""
proc advance() {
    nrnpython("my_advance()")
}""")
=====

# run until tstop
=====
h.continuerun(h.tstop)

# %% DATA POST PROCESSING / OUTPUT
# plot things
=====
print(vol_mem)

plt.figure(num=1, clear=False)
plt.plot(tvec, vol_mem[40]) # plot membrane potential at node 10
plt.xlabel('time (ms)')
plt.ylabel('Vm (mV)')
plt.title("gammaCore Activation at 20 um")
plt.show()

print('===== DONE =====')
print('===== DONE =====')

```