Electroceutical Modeling with Advanced COMSOL Techniques

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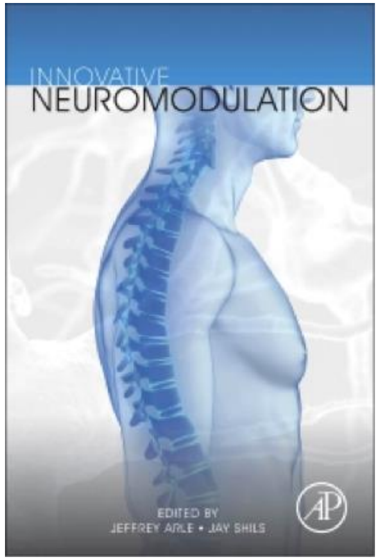
Neuromodulation and Electroceutical Goals

- Neuromodulation: Applying an electromagnetic field to the central or peripheral nervous system
  - Spinal cord for chronic back pain
  - Deep brain for Parkinson’s disease
  - Vagus nerve for epilepsy, depression
  - Transcranial (thru the scalp and skull) for cognitive decline and many others
- Electroceuticals
  - $2.5B and 10+ years to get a drug through the FDA
  - BUT medical device regulatory process ~1/10 of that
  - Electroceuticals (GlaxoSmithKline, DARPA): modify any part of the nervous system


INNOVATIVE
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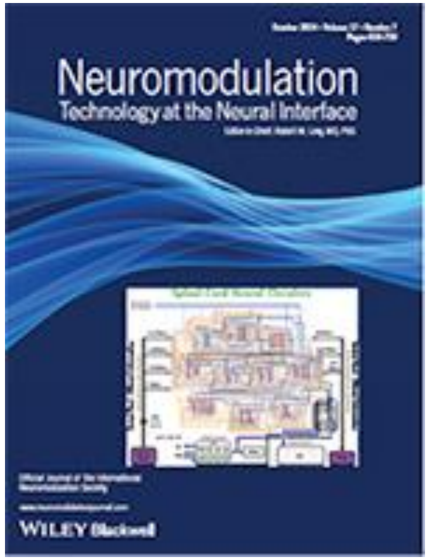
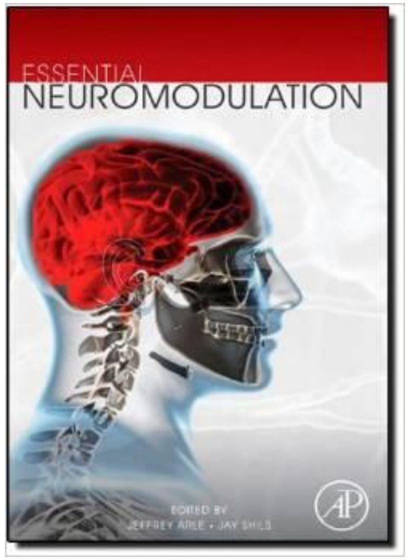

Neuromodulation
Technology at the Neural Interface
WILEY Blackwell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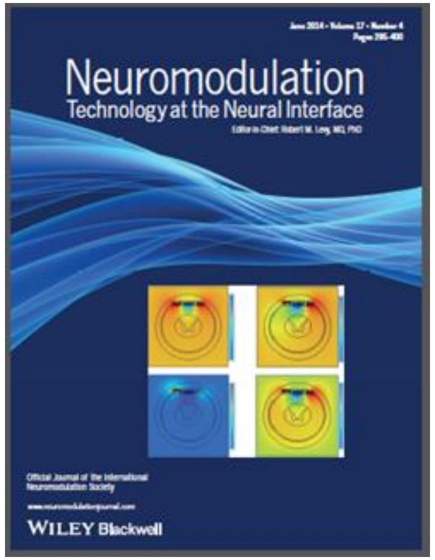
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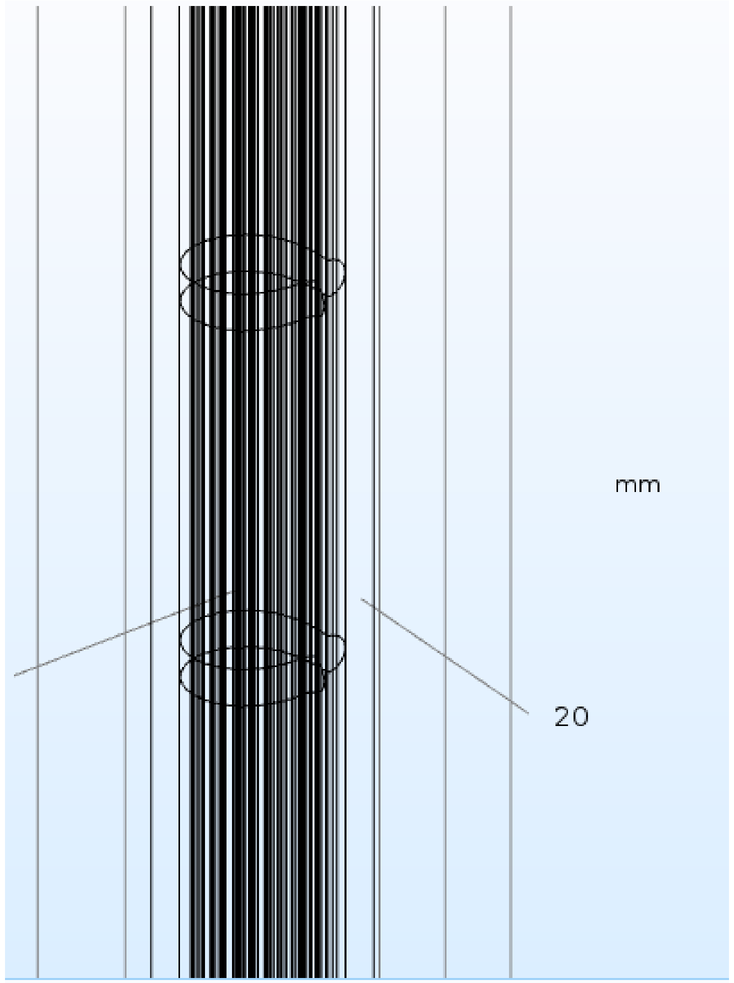
Vagus nerve with helical electrodes



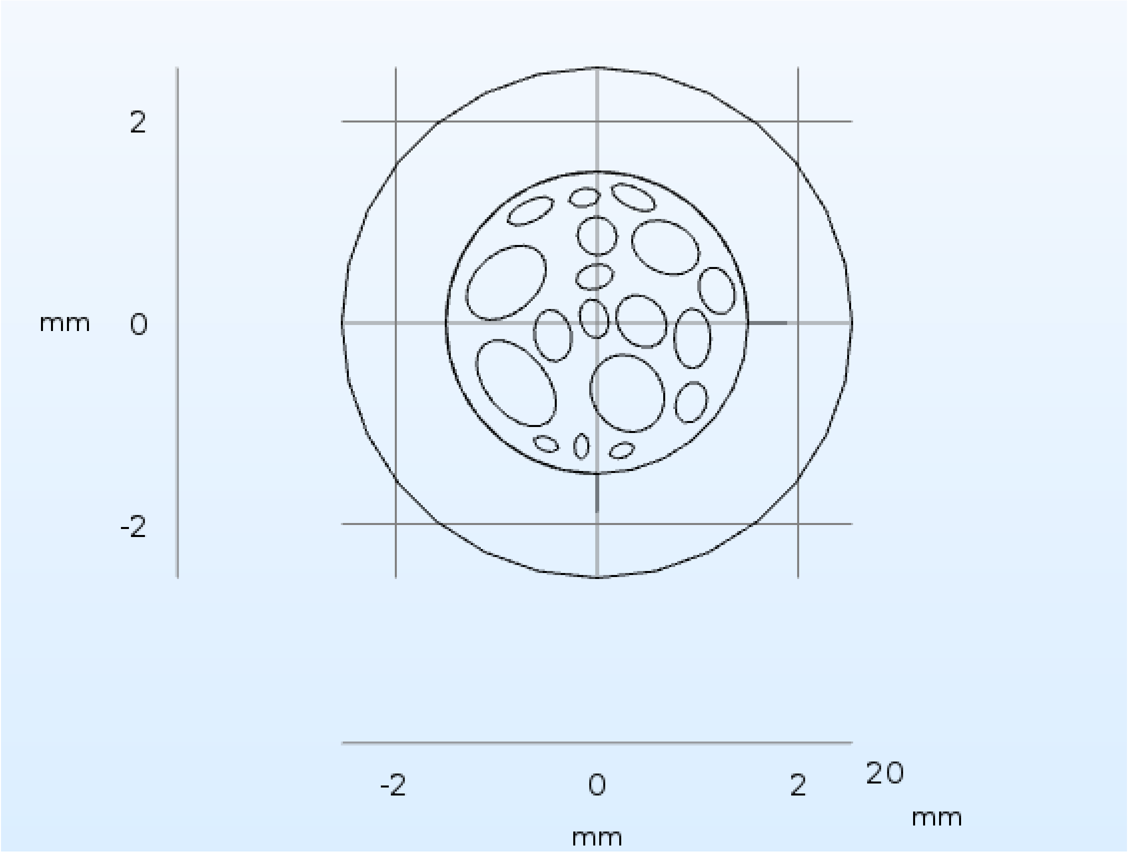
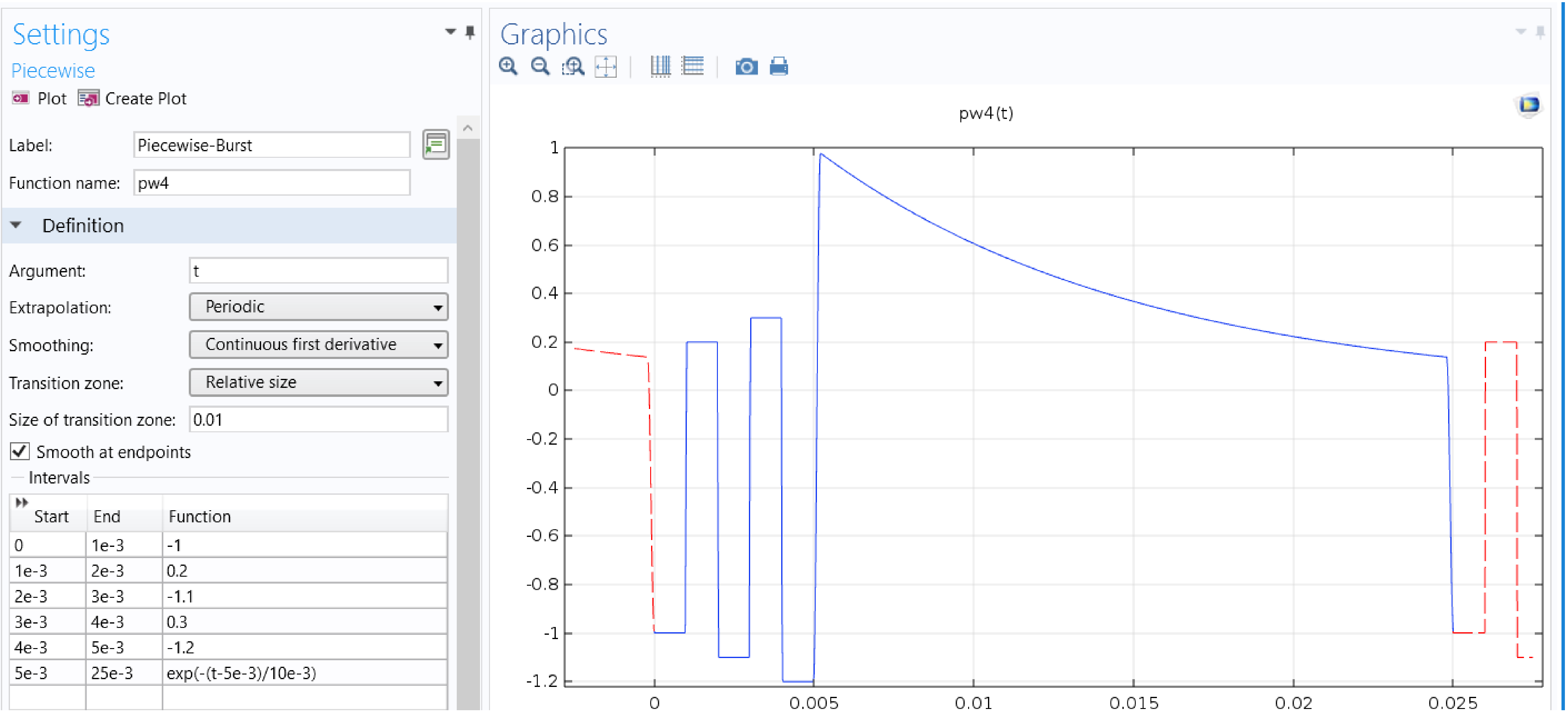
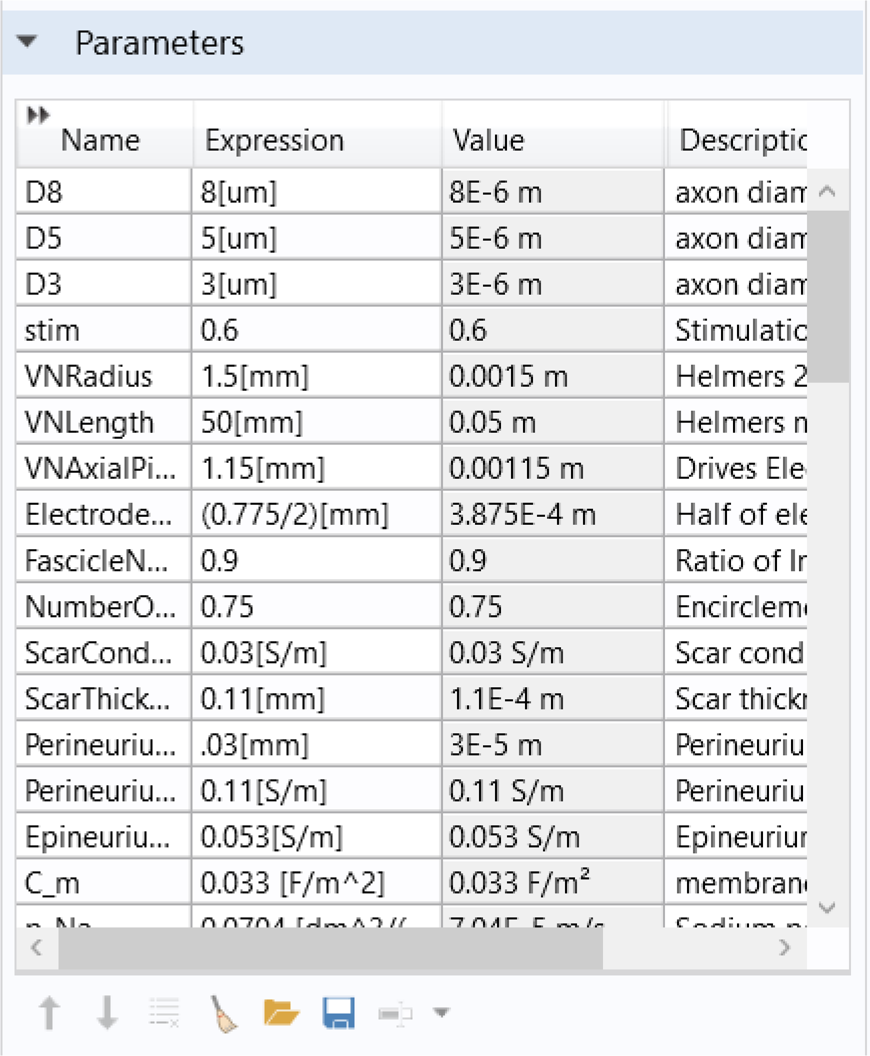


Table 1. COMSOL techniques used in model.

- Rectangular and piecewise stimulation waveforms
- Managing parameters and variables using external files
- Anisotropic material properties
- COMSOL's units consistency check
- COMSOL CAD functions (e.g. helix, Boolean operations, thin layers)
- Contact impedance to save solve time
- Infinite element domains to avoid edge effects
- Mapping an operator onto data with the General Extrusion Component Coupling to calculate running 2^{nd} differences along an edge
- General Form Edge PDE to calculate transmembrane potential over time
- Edge ODEs and DAEs interface to calculate probabilities that ion channel gates are open or closed
- Formulas in local Variables to calculate, e.g., ion channel open and closing rates
- Solving Laplace's equation with a Stationary solver, then using that solution in a Time-Dependent solver
- Separating the physics solved by each solver so that each can be run independently of the other to save solve time
- Study Extensions as alternative to Parameter Sweep to sweep parameters of each study individually
- Multiplying the electric potential along the axon by the waveform amplitude over time to drastically reduce solve time


Settings
Piecewise
Plot
Create Plot
Label: Piecewise-Burst
Function name: pw4
Definition
Argument: t
Extrapolation: Periodic
Smoothing: Continuous first derivative
Transition zone: Relative size
Size of transition zone: 0.01
Smooth at endpoints
Intervals
Start End Function
0 1e-3 -1
1e-3 2e-3 0.2
2e-3 3e-3 -1.1
3e-3 4e-3 0.3
4e-3 5e-3 -1.2
5e-3 25e-3 exp(-(t-5e-3)/10e-3)
Graphics
pw4(t)
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
-1.2
0
0.005
0.01
0.015
0.02
0.025



Parameters

Name	Expression	Value	Descriptio
D8	8[um]	8E-6 m	axon diam
D5	5[um]	5E-6 m	axon diam
D3	3[um]	3E-6 m	axon diam
stim	0.6	0.6	Stimulatic
VNRadius	1.5[mm]	0.0015 m	Helmers 2
VNLength	50[mm]	0.05 m	Helmers n
VNAxialPi...	1.15[mm]	0.00115 m	Drives Ele
Electrode...	(0.775/2)[mm]	3.875E-4 m	Half of ele
FascicleN...	0.9	0.9	Ratio of In
NumberO...	0.75	0.75	Encircleme
ScarCond...	0.03[S/m]	0.03 S/m	Scar cond
ScarThick...	0.11[mm]	1.1E-4 m	Scar thickr
Perineuriu...	.03[mm]	3E-5 m	Perineuriu
Perineuriu...	0.11[S/m]	0.11 S/m	Perineuriu
Epineuriu...	0.053[S/m]	0.053 S/m	Epineuriur
C_m	0.033 [F/m^2]	0.033 F/m²	membran

D8 8[um] "axon diameter 8 um"
D5 5[um] "axon diameter 5 um"
D3 3[um] "axon diameter 3 um"
stim 0.6 "Stimulation factor (see stim_wf in Variables)"
VNRadius 1.5[mm] "Helmers 2mm diam 6.05mm 270degree electrode model"
VNLength 50[mm] "Helmers nerve length"
VNAxialPitch 1.15[mm] "Drives Electrode Length"
ElectrodeMinorRadius (0.775/2)[mm] "Half of electrode width-Livanova"
FascicleNerveRatio 0.9 "Ratio of Inner Fascicle to Nerve Diameter"
NumberOfTurns 0.75 "Encirclement of electrode around nerve"
ScarConductivity 0.03[S/m] "Scar conductivity"
ScarThickness 0.11[mm] "Scar thickness"
PerineuriumThickness .03[mm] "Perineurium thickness"
PerineuriumConductivity 0.11[S/m] "Perineurium conductivity"
EpineuriumConductivity 0.053[S/m] "Epineurium conductivity"
C_m "0.033 [F/m^2]" "membrane capacitance"
p_Na "0.0704 [dm^3/(m^2*s)]" "Sodium permeability"
rho_i "0.33 [ohm*m]" "membrane resistance"
C_d 0.76 ""
dl "1.5 [um]" "nodal width"
D_d "1.81 [um]" ""
D_L "3.44 [um]" ""
r8 (C_d*D8-D_d)/2 "axon radius-8um"
r5 (C_d*D5-D_d)/2 "axon radius-5um"
dx8 C_L*log(D8/D_L) "internodal length 8um-Wesselink"
dx5 C_L*log(D5/D_L) "internodal length 5um-Wesselink"
gamma8 dl/dx8 "internodal / nodal length-8um axon"
gamma5 dl/dx5 "internodal / nodal length-5um axon"
L 50[mm] "axon length"
V_K "-132 [mV]" "Potassium reversal potential"
Na_o "154 [mM]" "extracellular sodium concentration"
Na_i 30[nM] "intracellular sodium concentration"
g_K 300[S/m^2] "potassium conductance"
T 310.5[K] temperature
g_L 600[S/m^2] "Leak conductance"
C_L 7.86[um] ""
V_L -84.14[mV] "leakage reversal potential"
I_output 300[A/m^2] "Output current to electrode"
i_current 1.5[mA] "Current to electrode"
OutputCurrent0.3 64[A/m^2] "Threshold of VN A fiber"
OutputCurrent0.75 160[A/m^2] ""
OutputCurrent1.5 320[A/m^2] ""
OutputCurrent2.25 480[A/m^2] ""
electrode_Area 2*ElectrodeMinorRadius*NumberOfTurns*pi*2*VNRadius "Area of electrode"
dx1 0.093[um]+0.076*D "internodal length-Murray linear"
dx2 "0.0037[um] + 0.098*D- 0.00103*D^2[1/um]" "internodal length-Murray quadratic"
R2 3000[ohm] "typical chronic resistance"
CC 10[uF] "coupling cap"
discharge 2/(CC*R2) "discharge factor"
electrode_area2 7.3042E-6[m^2] "constant electrode area for greater than 360 deg coverage"
D14 14[um] "axon diameter 14 um"
r14 (C_d*D14-D_d)/2 "axon radius-14 um"
dx14 C_L*log(D14/D_L) "internodal length 14um-Wesselink"
gamma14 dl/dx14 "internodal / nodal length-14um axon"
dxs 1.4[mm] "A standardized nodal center-to-center length to use in 2nd finite difference calc"
internodal_length "2354*(1-exp(-D14/16.26))[m]" ""
delta_8 dx8+dl "Internode+node length 8 um"
delta_5 dx5+dl "Internode+node length 5 um"
delta_14 dx14+dl "Internode+node length 14 um"
ambient_factor_width 2.5 "Ambient cylinder/VN radius. Set to 2.5 for infinite elements domains to accommodate electrodes."
ambient_factor_length 1.3 "Ambient cylinder/VN length. Set to 1.6 for infinite elements domains."
sigma_fat 0.04 "From Veltink I tink"

Solve Laplace's equation once

Show equation assuming:

Study 1, Stationary

$$\nabla \cdot \mathbf{J} = Q_{j,v}$$

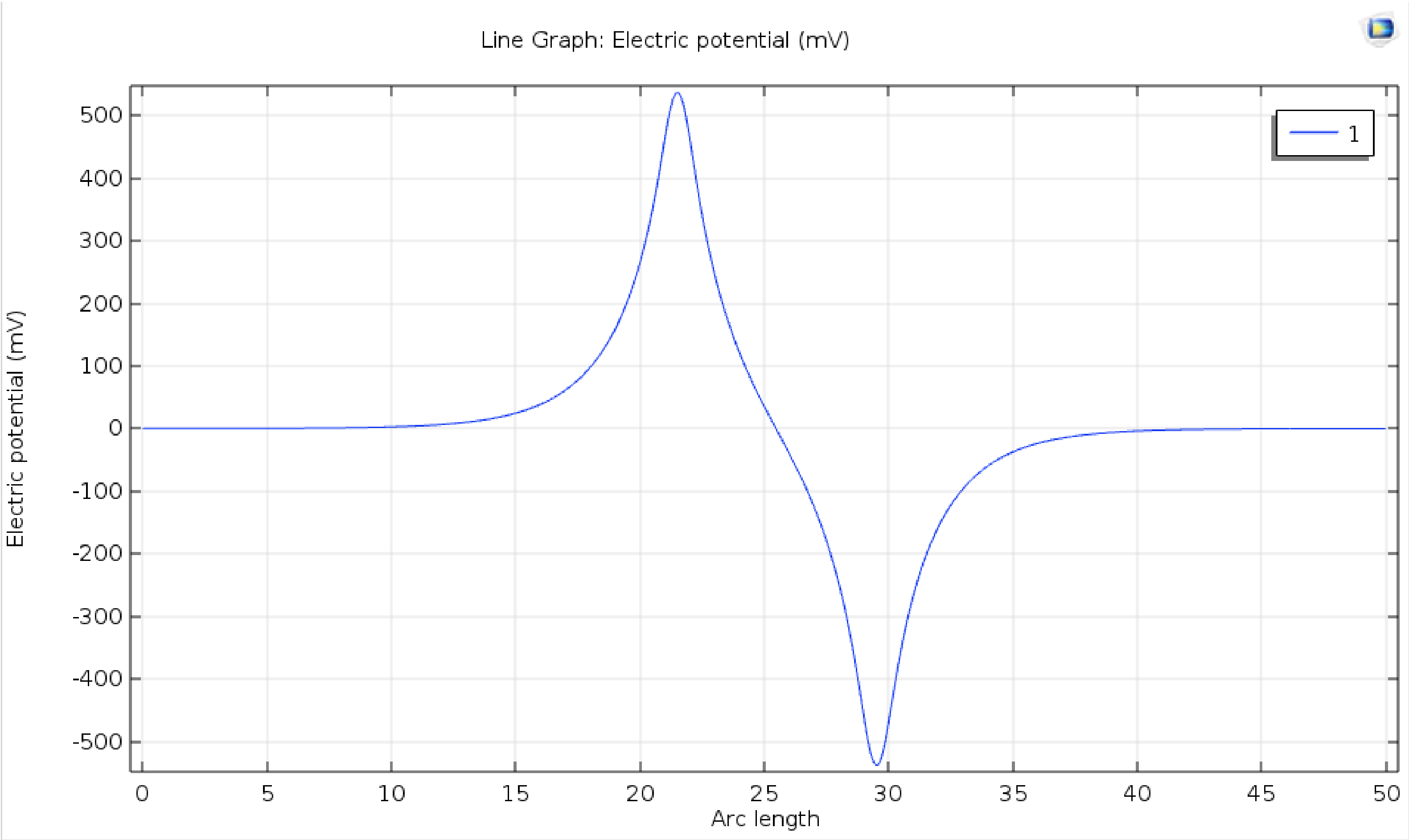
$$\mathbf{J} = \sigma \mathbf{E} + \mathbf{J}_e$$

$$\mathbf{E} = -\nabla V$$

Physics and Variables Selection

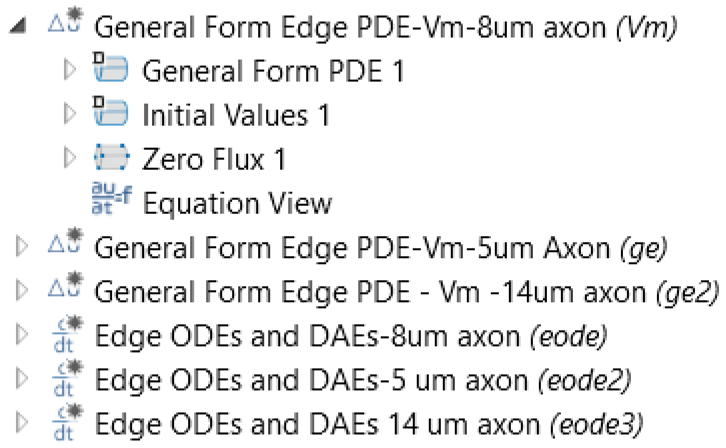
☐ Modify physics tree and variables for study step

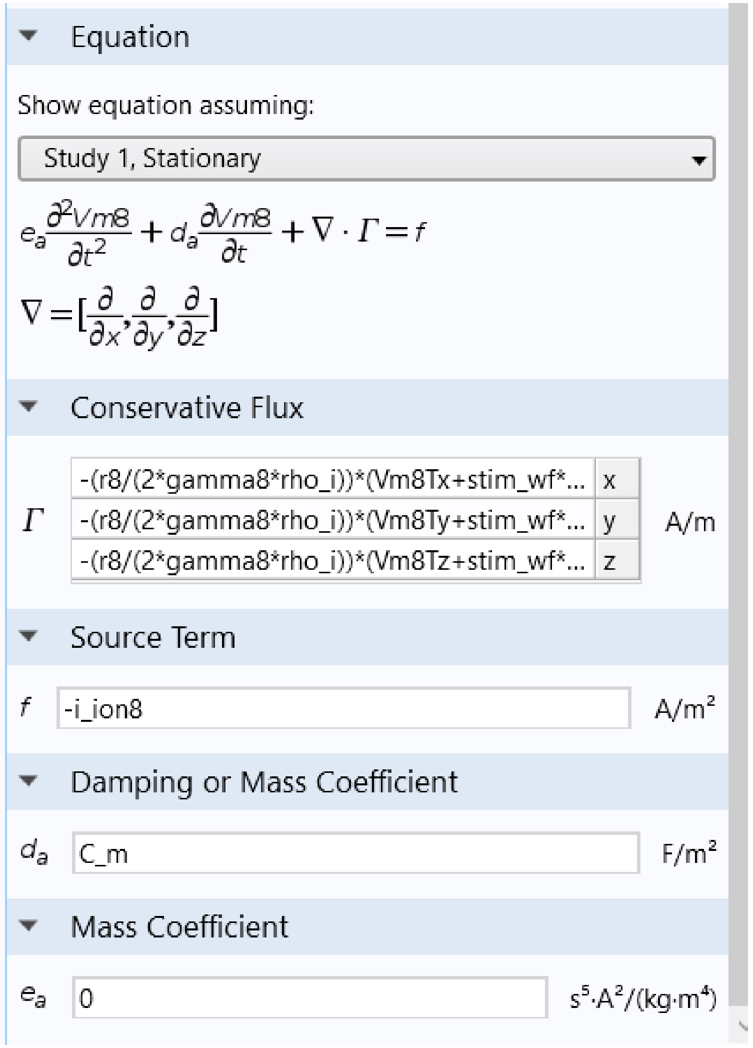
Physics interface	Solve	Discretization
Electric Currents (ec)	☑	Physics settings
General Form Edge PDE-...	☐	Physics settings
General Form Edge PDE-...	☐	Physics settings
General Form Edge PDE -...	☐	Physics settings
Edge ODEs and DAEs-8u...	☐	Physics settings
Edge ODEs and DAEs-5 u...	☐	Physics settings
Edge ODEs and DAEs 14...	☐	Physics settings



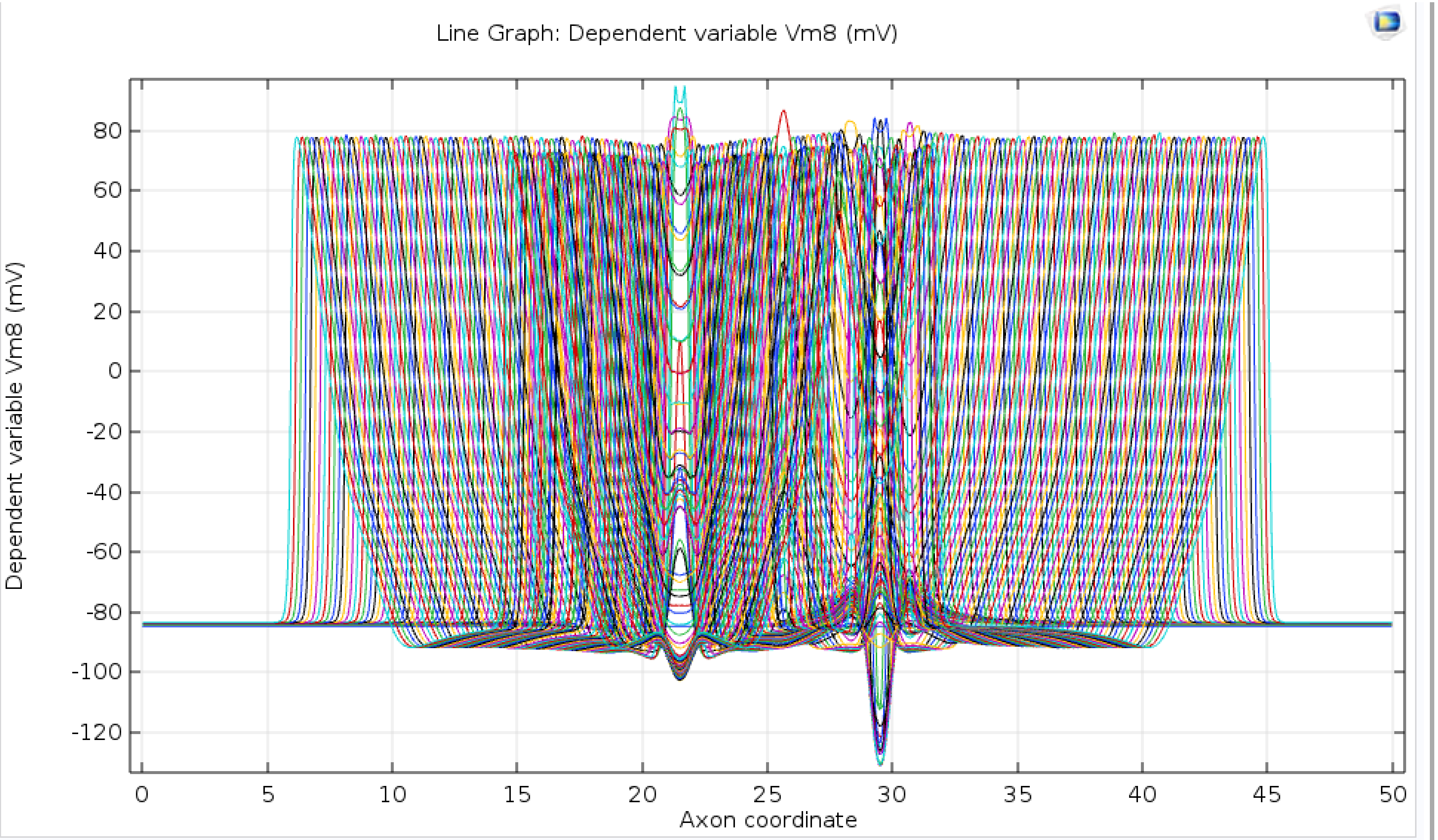
Multiply V by waveform time series in PDE

stim_wf stim*pw4(t[1/s]) "Stim amplitude over waveform"



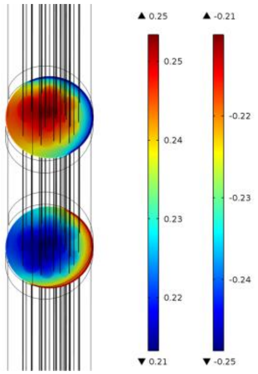


Plot of membrane potential over time - spikes



Key Findings

- Identified ~5 fiber diameter groups implicated in VNS: ~8, 7, 5, 3, 2.5 µm
- Proposed correlations between fiber groups and functional fascicles responsible for efficacy and side effects
  - 8, 7 µm: Recurrent laryngeal fascicle (hoarseness)
  - 3 µm: P2ry1 pulmonary fascicle (cough, forced exhalation)
  - 5 µm: Aortic baro/chemoreceptors (efficacy)
- Estimated numbers of fibers involved
- Proposed which fiber groups are activated at different amplitude levels
- Proposed a 'bandpass' paradigm where both rostral activation and caudal blocking are considered as stim tools[1]
- At clinical stim amplitudes consistently found activation gaps in the nerve due to the <360 degree (270 degree) encirclement by the cathode



1. Anholt et al. Recruitment and blocking properties of the CardioFit stimulation lead. 2011 J. Neural Eng. 8