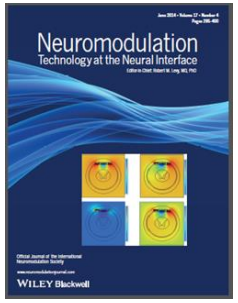
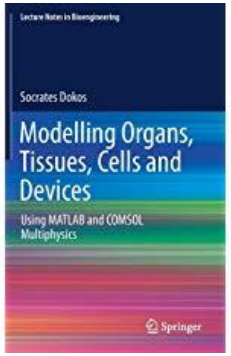
Modeling Electrotaxis of Stem Cells to Stroke Sites in the Human Brain

Socrates Dokos[1], Trisha Pfluger[2], and Kristen W. Carlson[3]

1. University of New South Wales, Sydney, Australia 2. Juno Biomedical, Inc., Los Angeles, CA 3. BIDMC/Harvard Medical School, Boston, MA



COMSOL Conference 2019



COI: Funding by Juno Biomedical

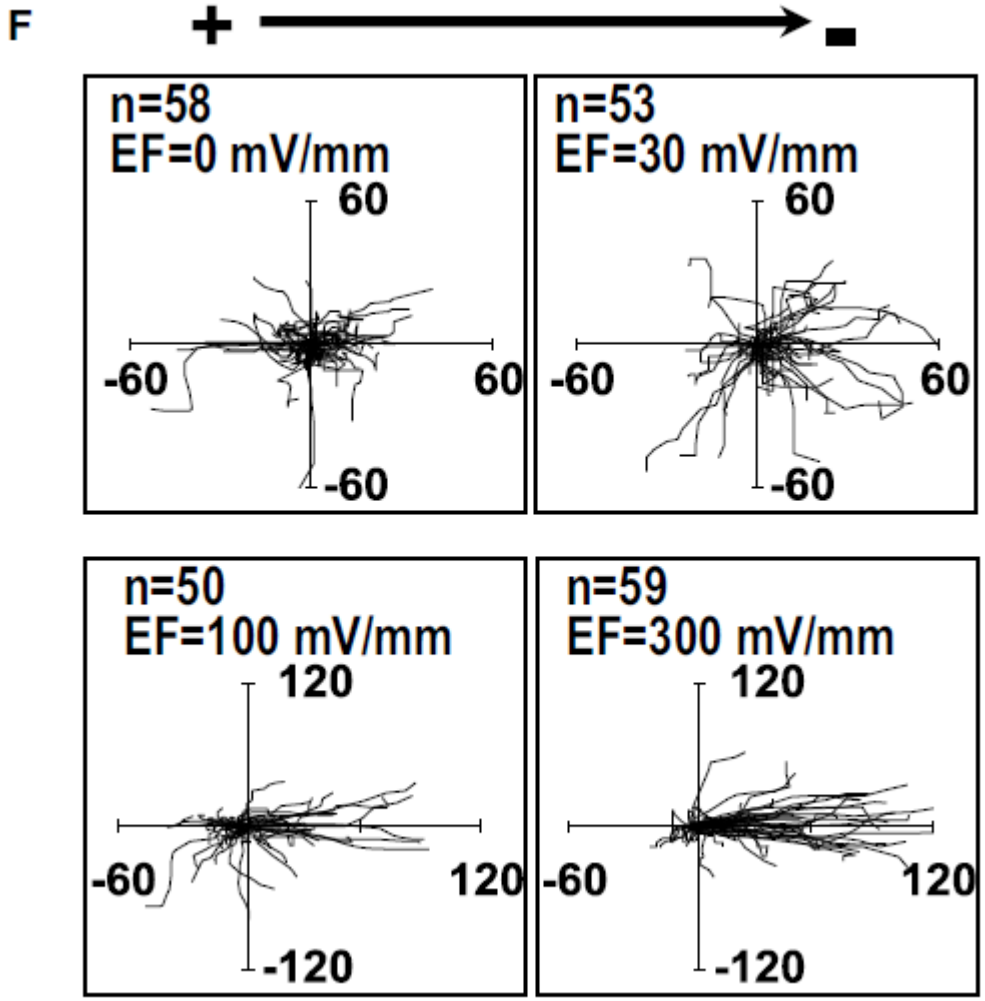
Getting all octopus arms in the pail. You start with a nice friendly octopus…

And it quickly turns into this.

What was the curve ball in this project?

And how did we get it back on track?

Electrotaxis: Cells move from cathode -> anode



Feng, J. F., Liu, J., Zhang, L., Jiang, J. Y., Russell, M., Lyeth, B. G., Nolta, J. A., and Zhao, M. Electrical Guidance of Human Stem Cells in the **Rat Brain**, *Stem Cell Reports,* ***2017, 9, 177-189.***

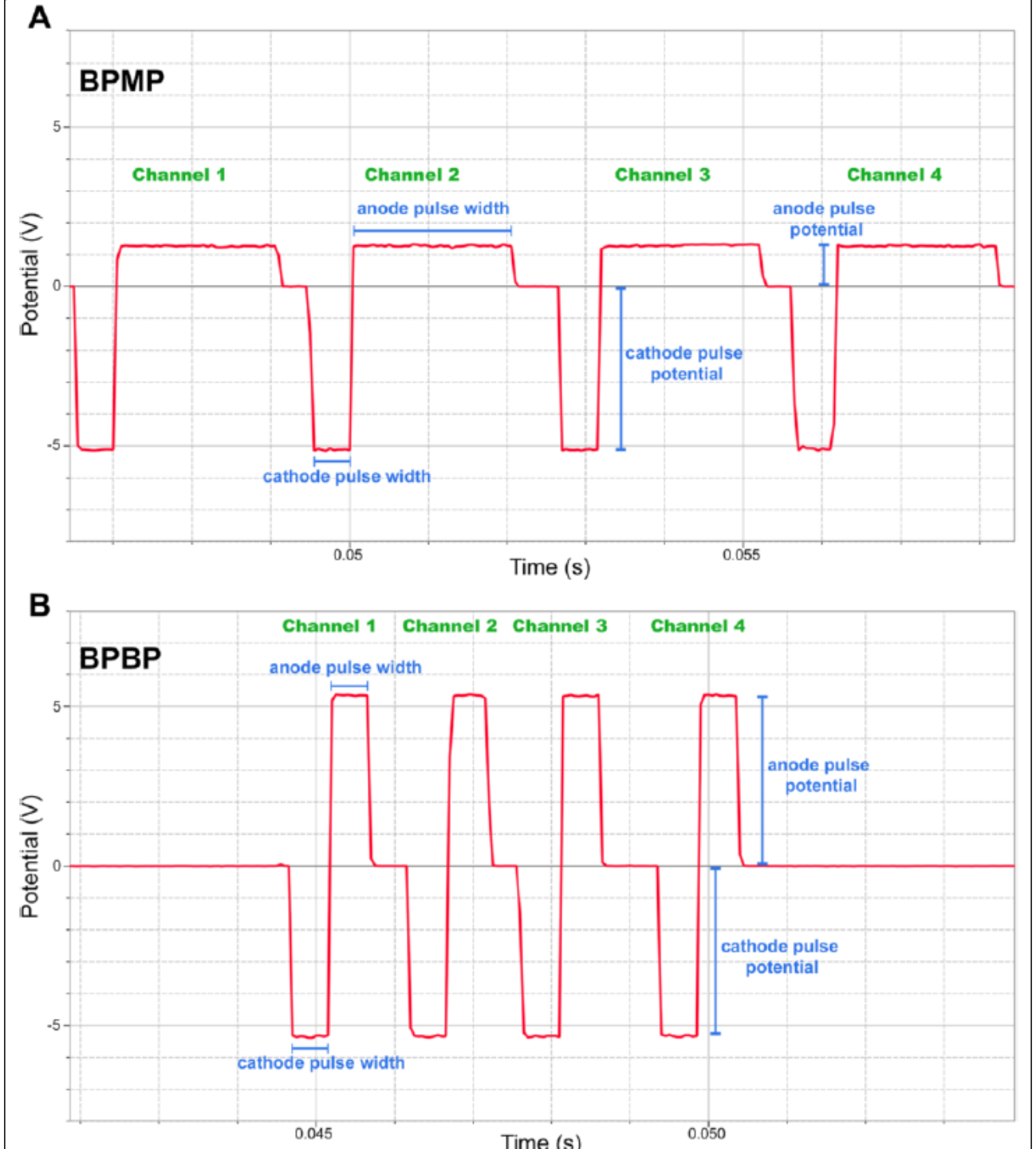
Note: 'Rat brain.'

Cathodic pulses drive undifferentiated neural stem cells down a potential gradient (‘electrotaxis’).

Anodic pulses negate electrotaxis.

Babona-Pilipos, R., Pritchard-Oh, A., Popovic, M. R., and Morshead, C. M. Biphasic monopolar electrical stimulation induces rapid and directed galvanotaxis in adult subependymal neural precursors, *Stem Cell Res Ther,* ***2015, 6, 67.***

Note: In vitro study (petri dish).



Arms of the octopus (constraints)

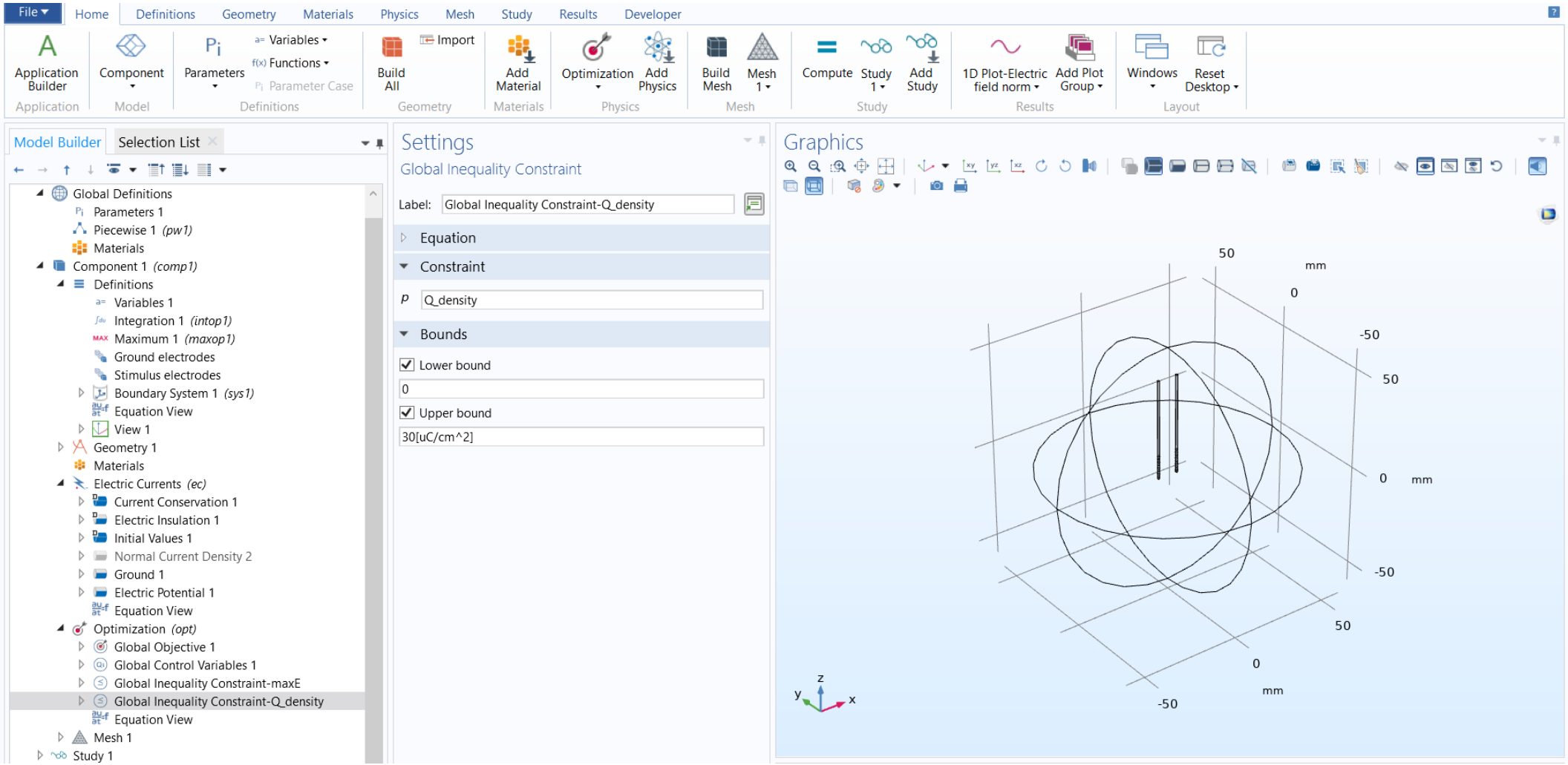
Safety

- Surface charge density < 30uC (up to 45 uC/cm^2)
- Amplitude < 10V
- Frequency < 330 Hz
- < 2000 mV/mm near electrodes

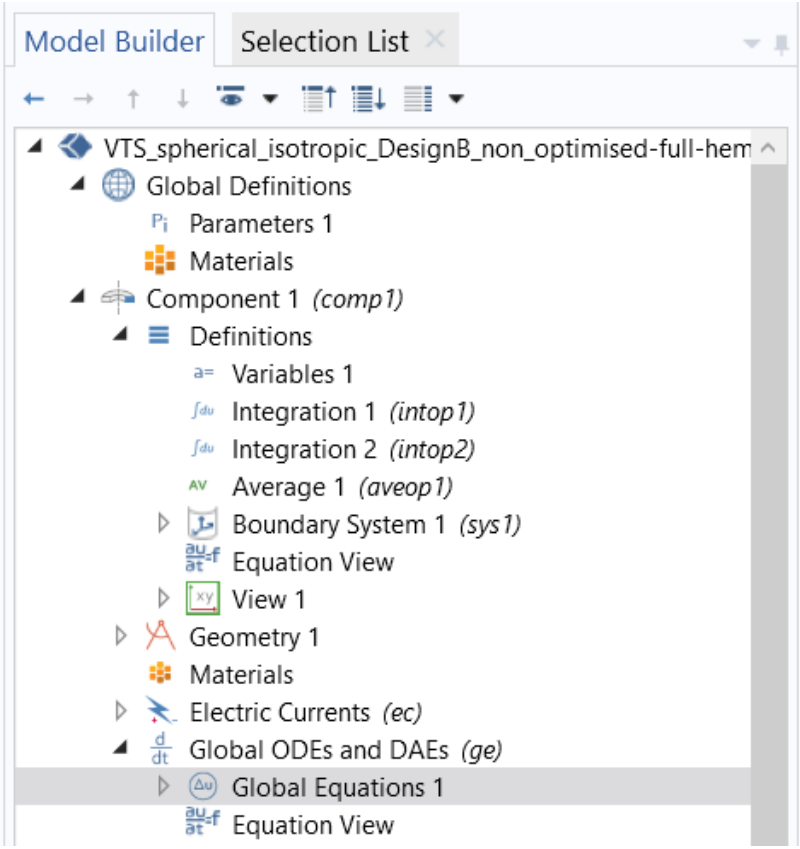
Efficacy

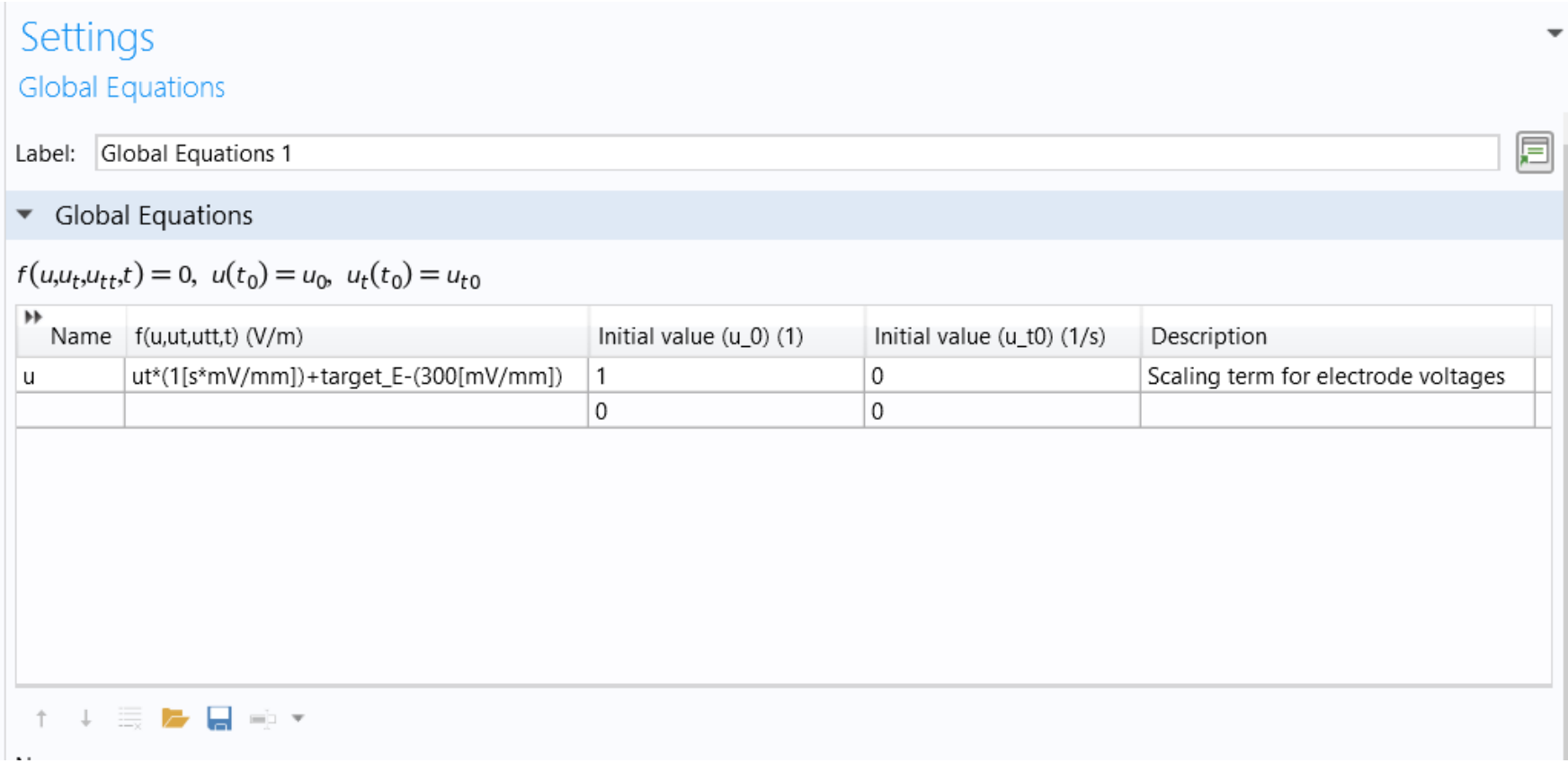
- 300 mv/mm therapeutic floor (200 mV/mm is okay)

Initial forays with Optimization Module

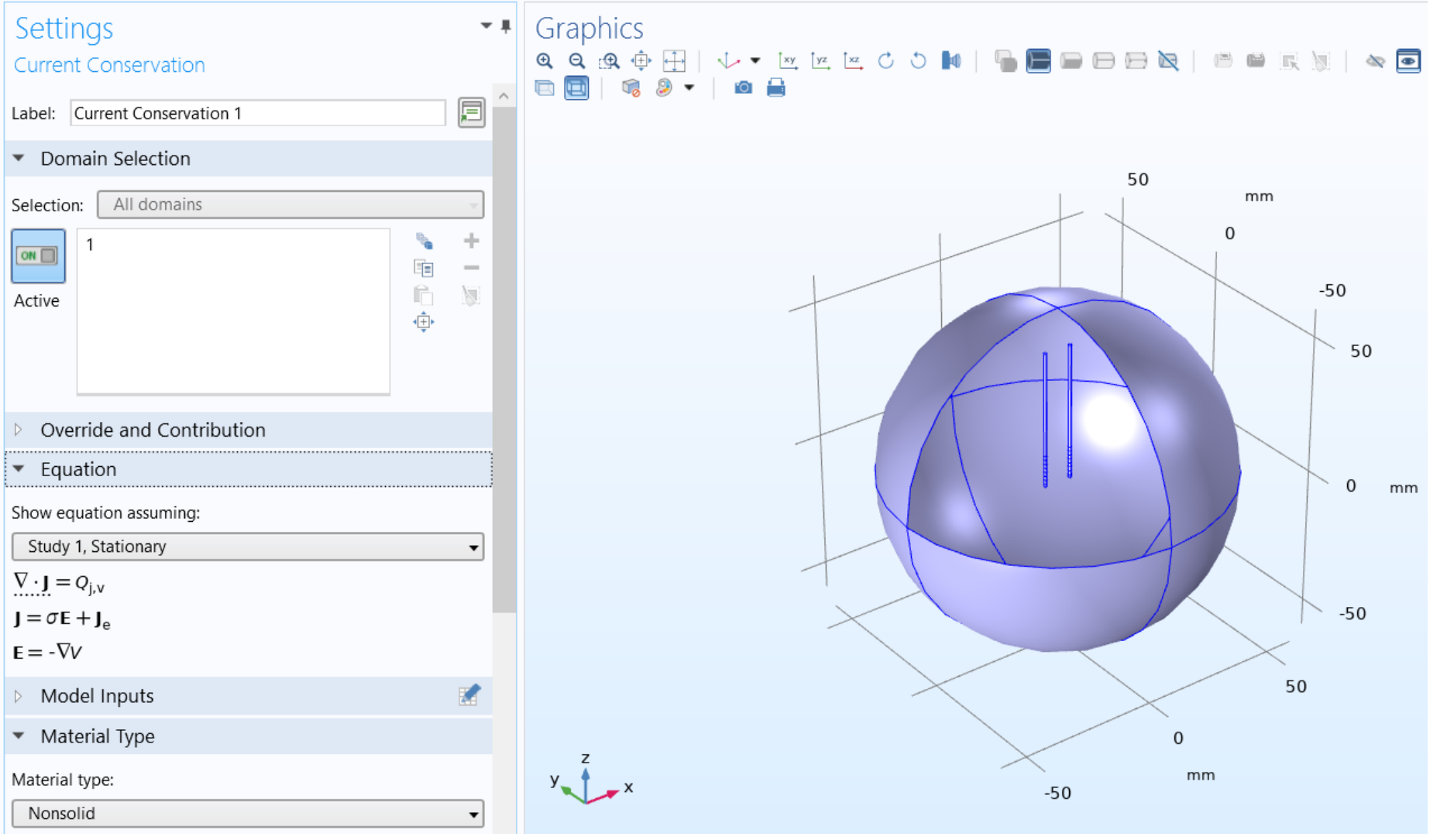


Socrates' home-made Optimization





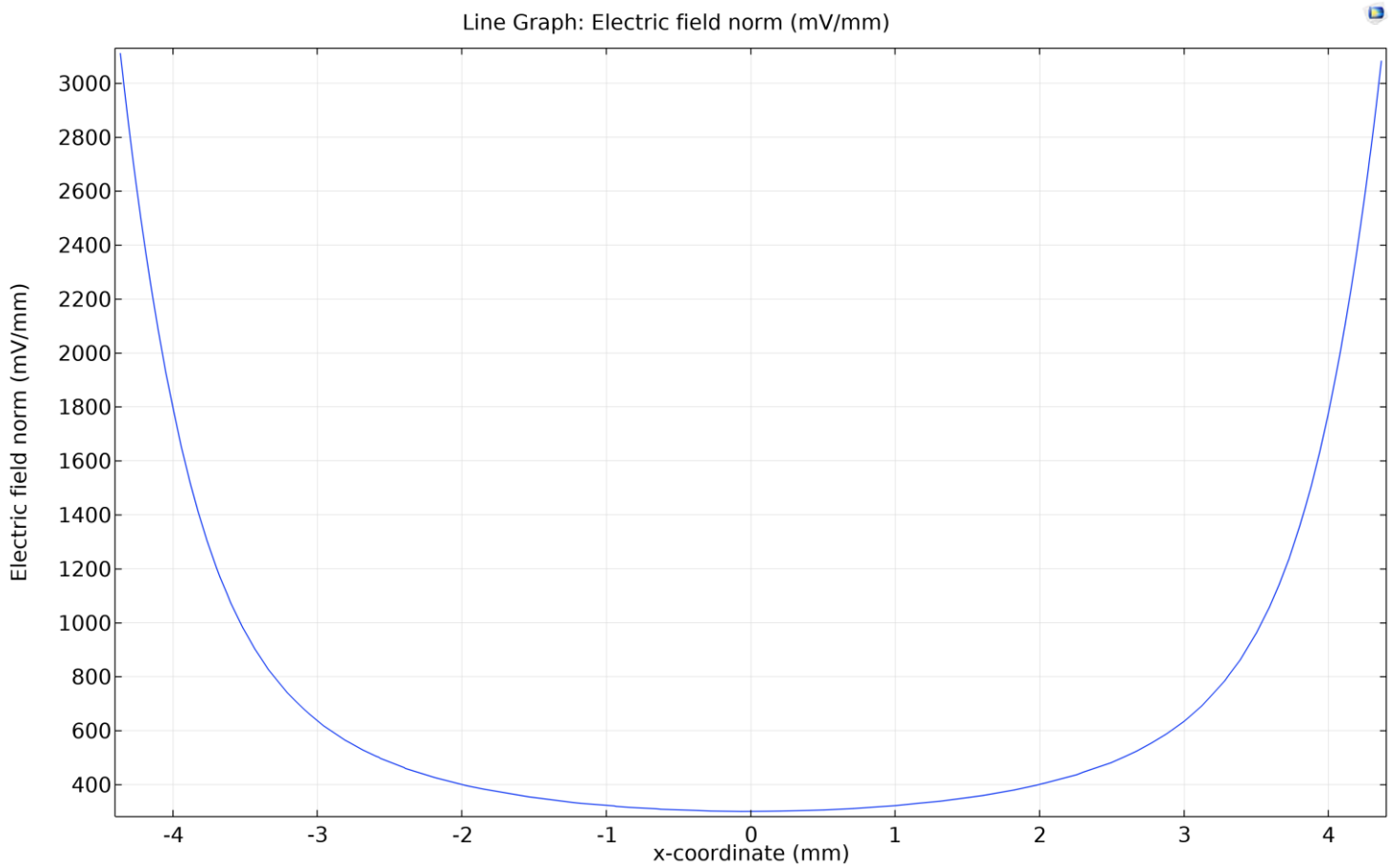
Curve ball was the inverse square law of Efield attenuation



Electric field at Cut Line between probes

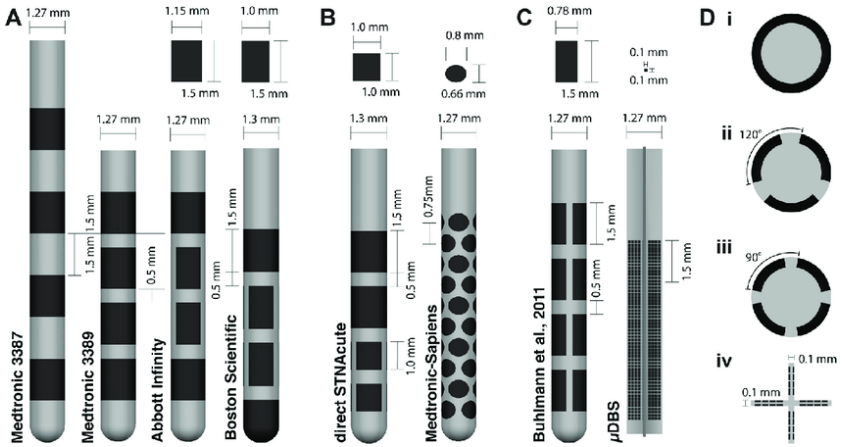
Neural tissue activation ->>>>>

Floor of efficacy (electrotaxis) ->>>>>

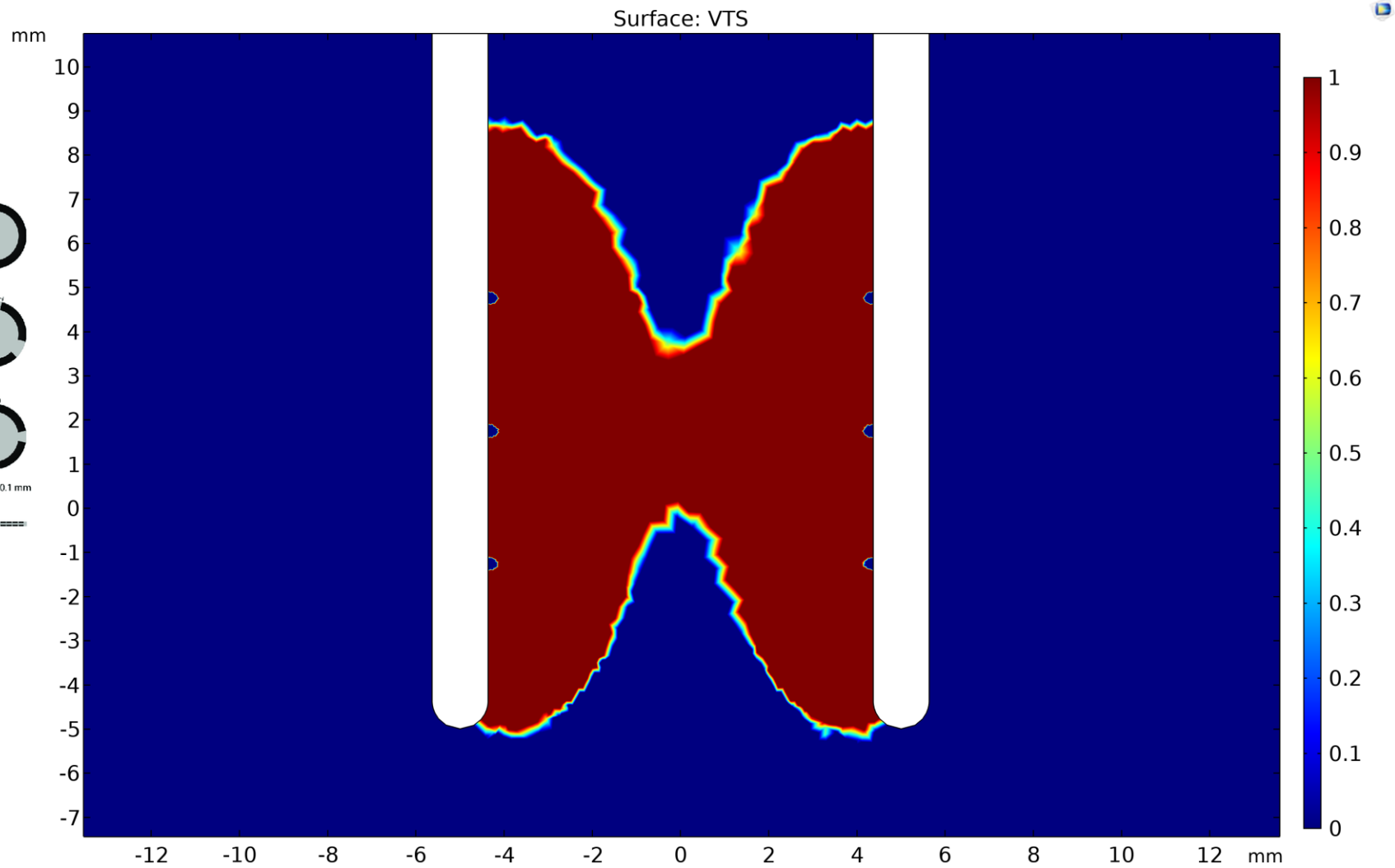


Volume of Tissue Stimulated at probe cut plane

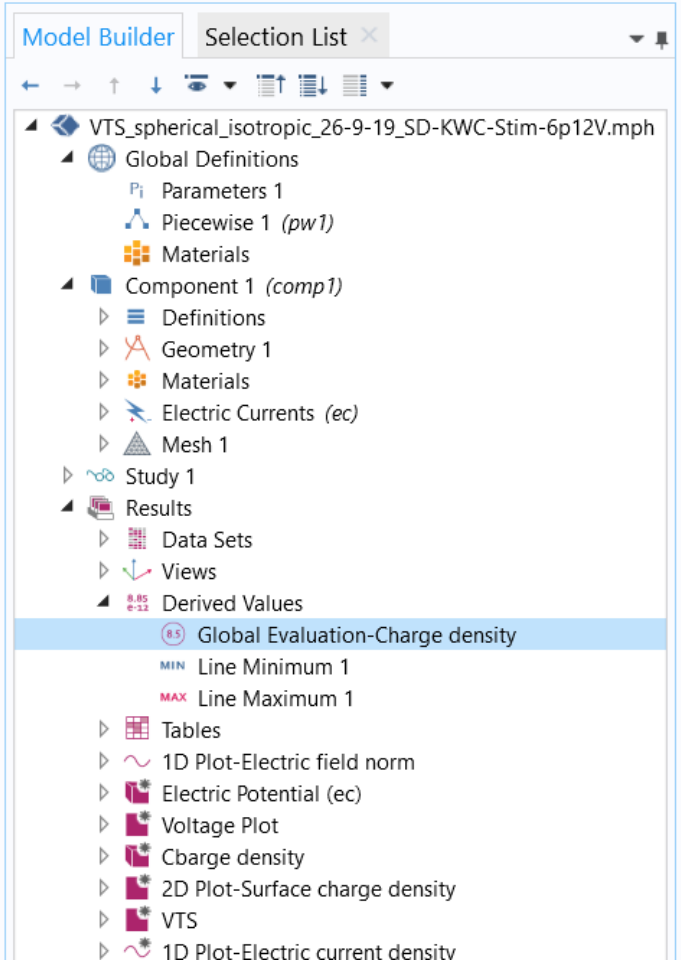
(ec.normE>300[mV/mm])

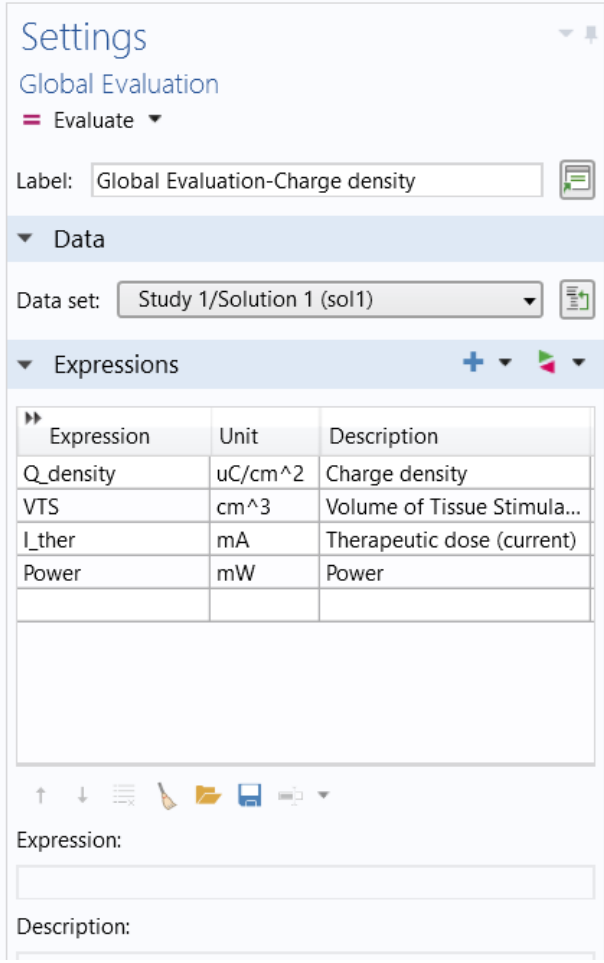


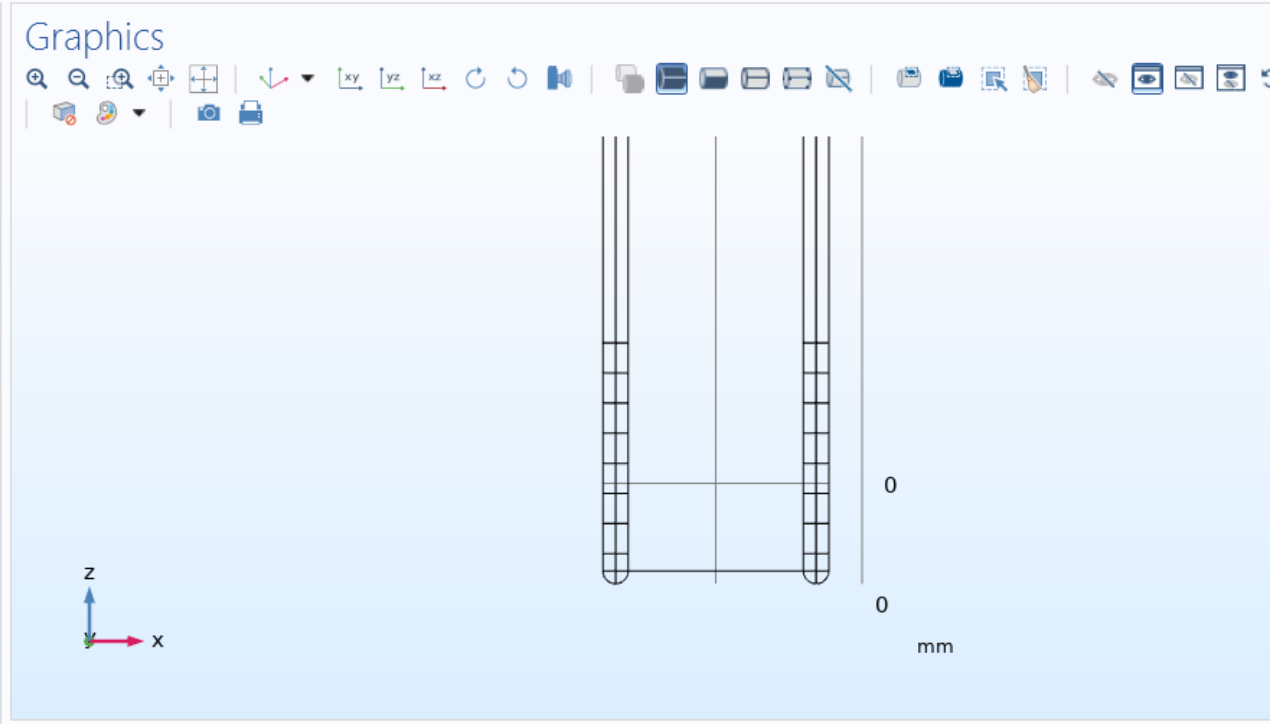
Medtronic, Inc.



Hand-tuning through many iterations







Messages | Progress | Log | Table 1

Charge density (uC/cm^2)	Volume of Tissue Stimulated (>300 mV/mm) (cm^3)	Therapeutic dose (current) (mA)	Power (mW)
19.809	0.21212	23.711	11.974

Electric field norm (mV/mm)	Electric field norm (mV/mm)	Electric field norm (mV/mm)	Electric field norm (mV/mm)	Electric field norm (mV/m
206.13	343.40	294.35	300.23	300.23

Electric field norm (mV/mm)	Electric field norm (mV/mm)	Electric field norm (mV/mm)	Electric field norm (mV/mm)
3111.4	3111.4	2053.9	3111.4

Penultimate results: Sacrifice Efield at electrodes to get other arms (mostly) in the pail

Probe Separation (mm)	Surface Charge Density ($\mu C/cm^2$)	Voltage | Current (V, mA)	Power at 100% Duty Cycle (mW)	Field Strength Min | Max (mV/mm)
10	39.6	4.08 | 23.7	12.0	198.2 | 2054
10	58.8	6.12 | 35.2	26.4	300.2 | 3111

Further tuning via waveform design

Relax cathode/anode amplitude from 8:1 to 4:1

Decrease duty cycle from 100% to 90 – 80 – 70 – 60% to reduce power consumption

Use longer cathodic pulses to drive fiber thresholds up (‘accommodation’)

Further wet lab experiments on electrotaxis are needed to refine protocols