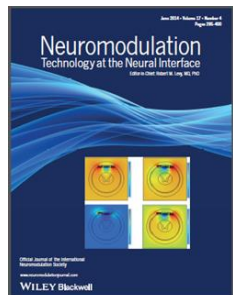


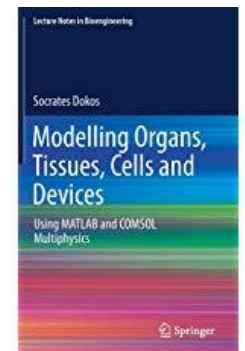
Modeling Electrotaxis of Stem Cells to Stroke Sites in the Human Brain

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



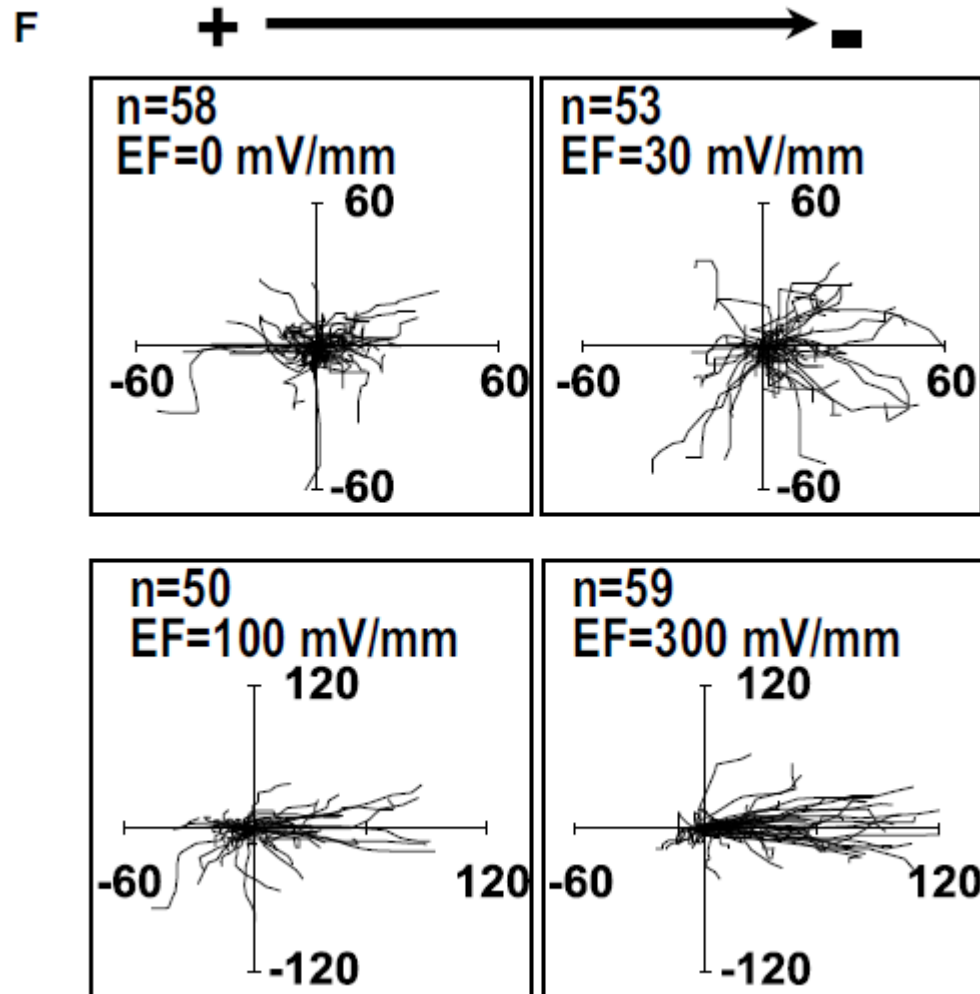
And it quickly turns into this.

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.

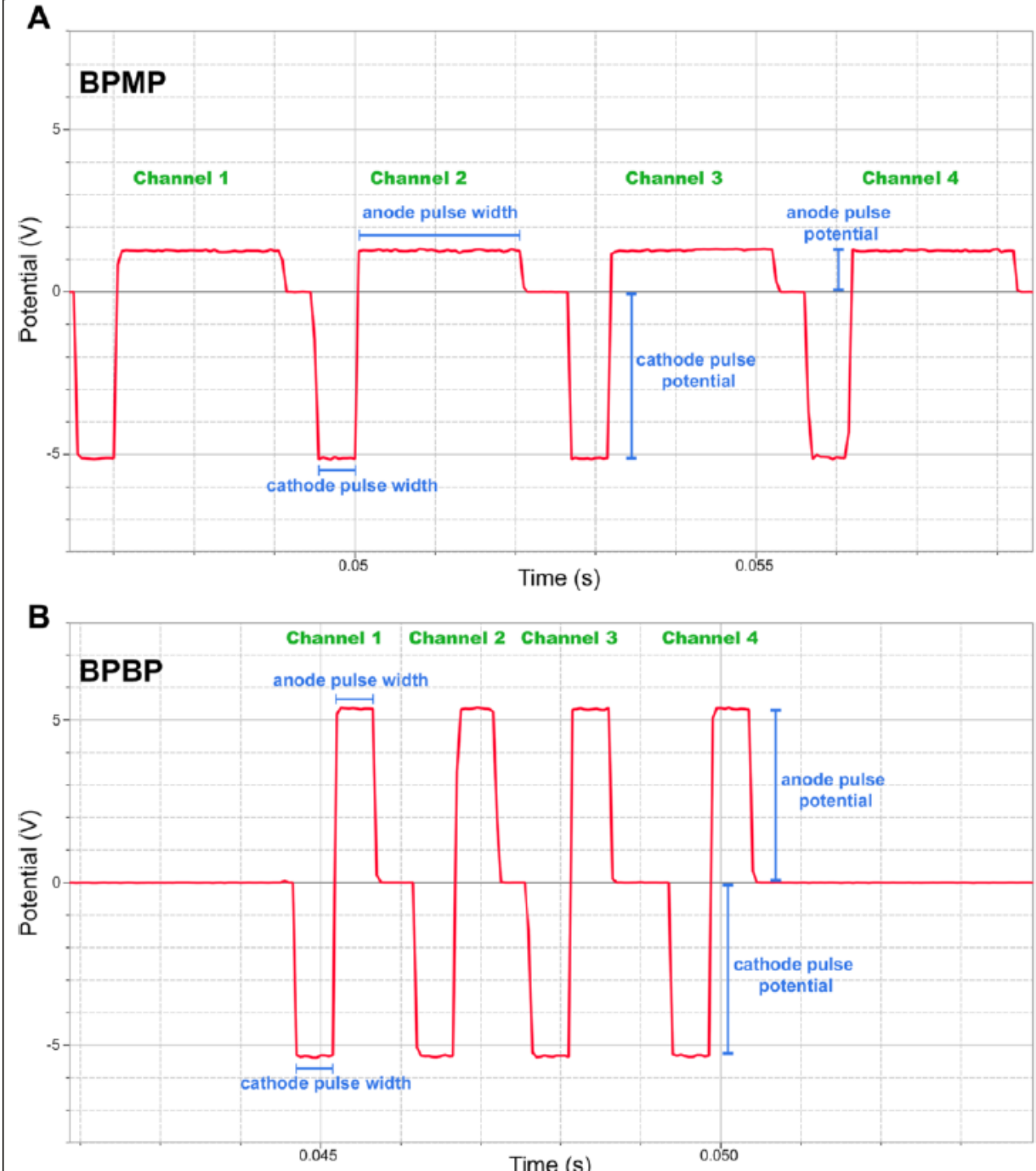
Note: 'Rat brain.'

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 $< 30\mu\text{C}$ (up to $45\ \mu\text{C}/\text{cm}^2$)
- Amplitude $< 10\text{V}$
- Frequency $< 330\ \text{Hz}$
- $< 2000\ \text{mV}/\text{mm}$ near electrodes

Efficacy

- $300\ \text{mV}/\text{mm}$ therapeutic floor ($200\ \text{mV}/\text{mm}$ is okay)

Initial forays with Optimization Module

The screenshot displays the COMSOL Multiphysics software interface, specifically the Optimization Module. The top ribbon includes tabs for File, Home, Definitions, Geometry, Materials, Physics, Mesh, Study, Results, and Developer. The main workspace is divided into three panels:

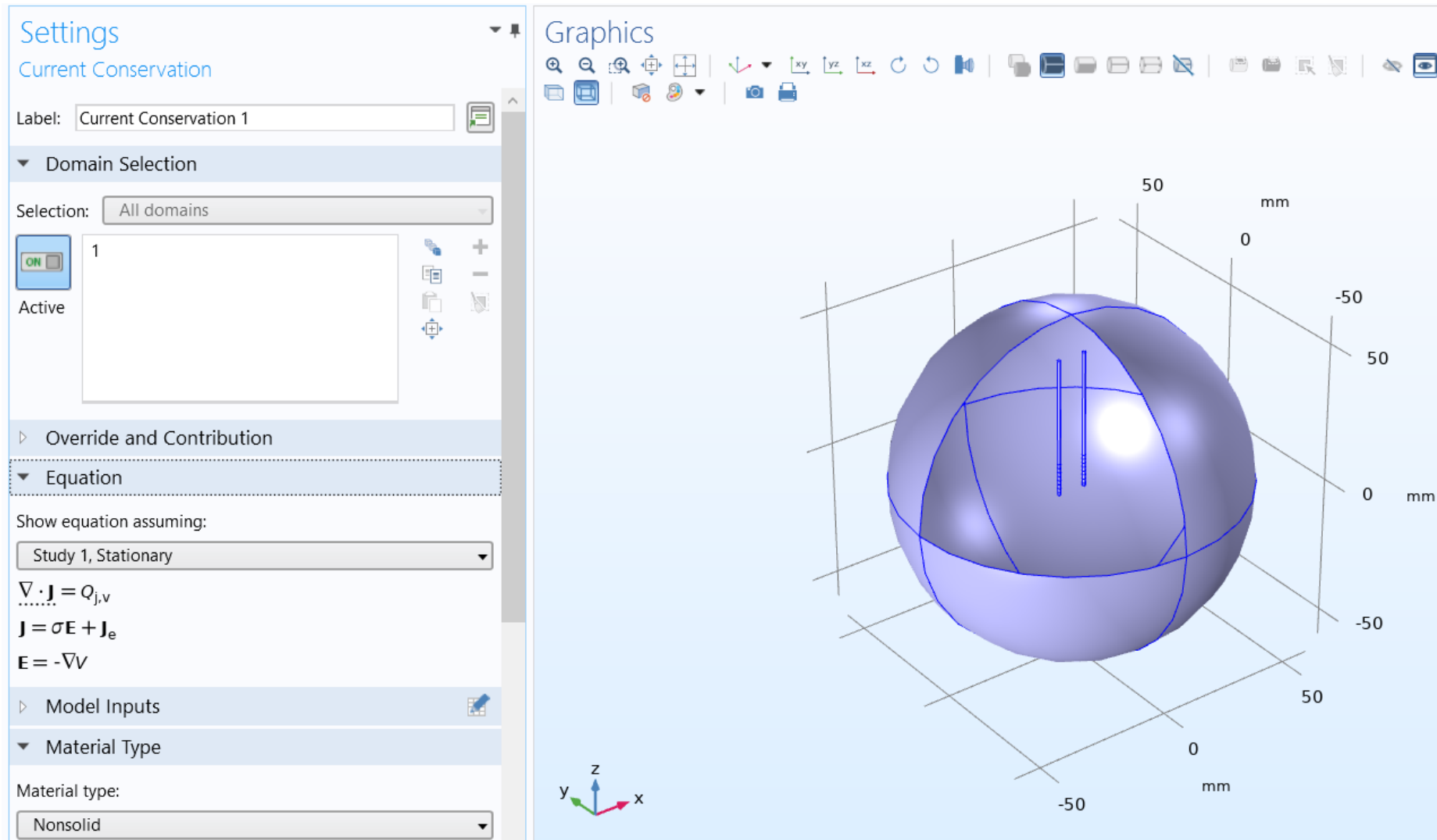
- Model Builder:** Shows a hierarchical tree of the model. The 'Optimization (opt)' node is expanded, showing 'Global Inequality Constraint-Q_density' selected.
- Settings:** Displays the configuration for the selected constraint. The label is 'Global Inequality Constraint-Q_density'. Under the 'Constraint' section, the variable 'Q_density' is specified. The 'Bounds' section is checked, with a lower bound of 0 and an upper bound of $30[\mu\text{C}/\text{cm}^2]$.
- Graphics:** Shows a 3D visualization of the model geometry, which appears to be a cylindrical structure with internal components. The axes are labeled x, y, and z, with dimensions in millimeters (mm) ranging from -50 to 50.

Socrates' home-made Optimization

The screenshot displays the COMSOL Multiphysics interface. On the left is the Model Builder, showing a hierarchical tree for a model named 'VTS_spherical_isotropic_DesignB_non_optimised-full-hem'. The tree includes 'Global Definitions', 'Component 1 (comp1)', and 'Global ODEs and DAEs (ge)'. Under 'Global ODEs and DAEs (ge)', 'Global Equations 1' is selected. On the right is the Settings panel for 'Global Equations 1'. It shows the label 'Global Equations 1' and the equation $f(u, u_t, u_{tt}, t) = 0, u(t_0) = u_0, u_t(t_0) = u_{t0}$. Below this is a table with the following data:

Name	f(u,ut,utt,t) (V/m)	Initial value (u_0) (1)	Initial value (u_t0) (1/s)	Description
u	$ut*(1[s*mV/mm])+target_E-(300[mV/mm])$	1	0	Scaling term for electrode voltages
		0	0	

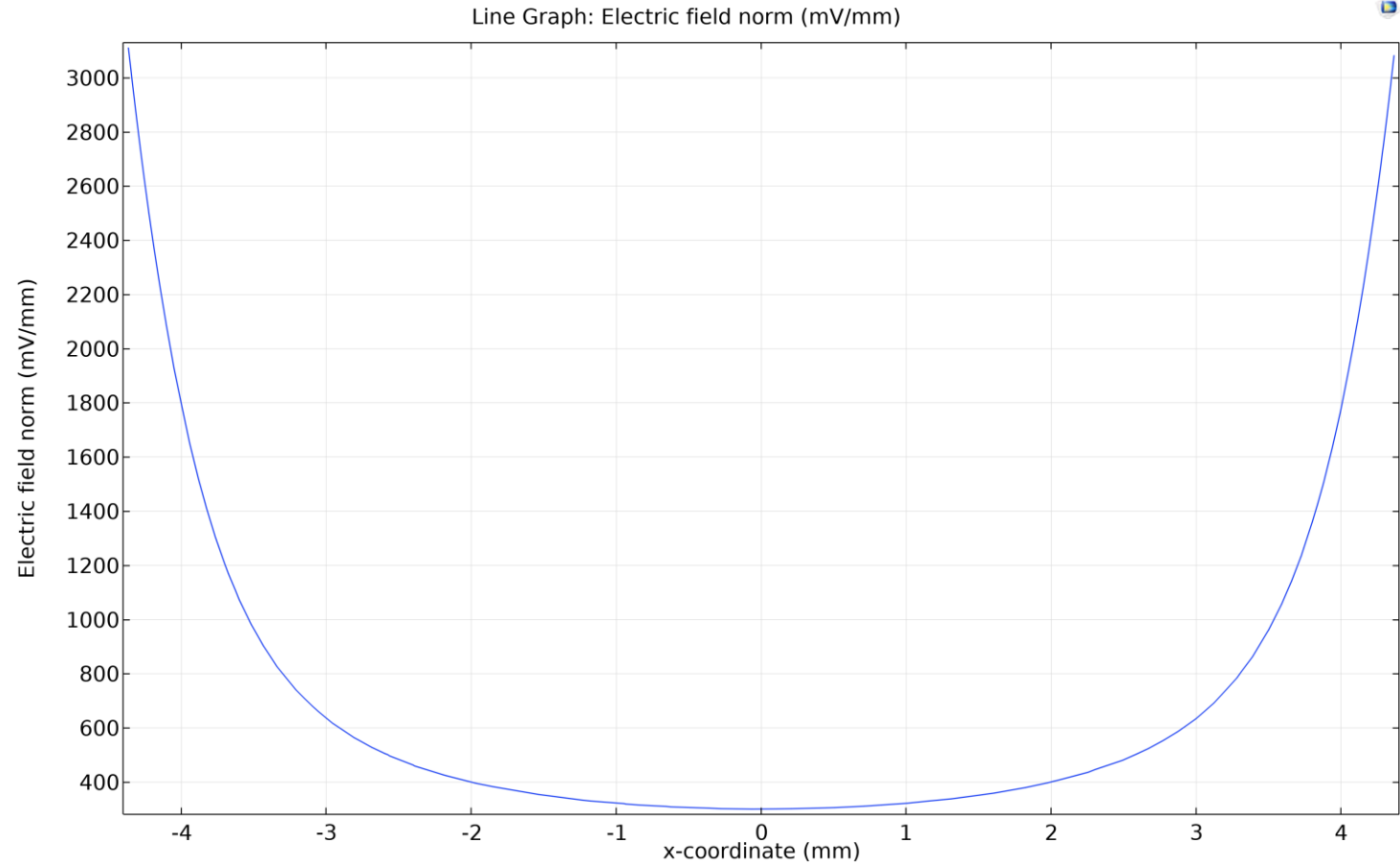
Curve ball was the inverse square law of Efield attenuation



Electric field at Cut Line between probes

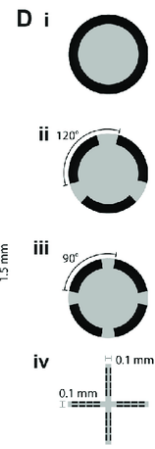
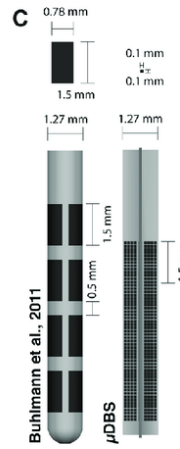
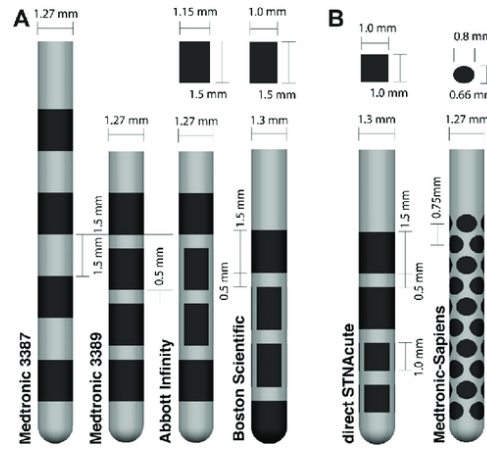
Neural tissue activation ->>>>>

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

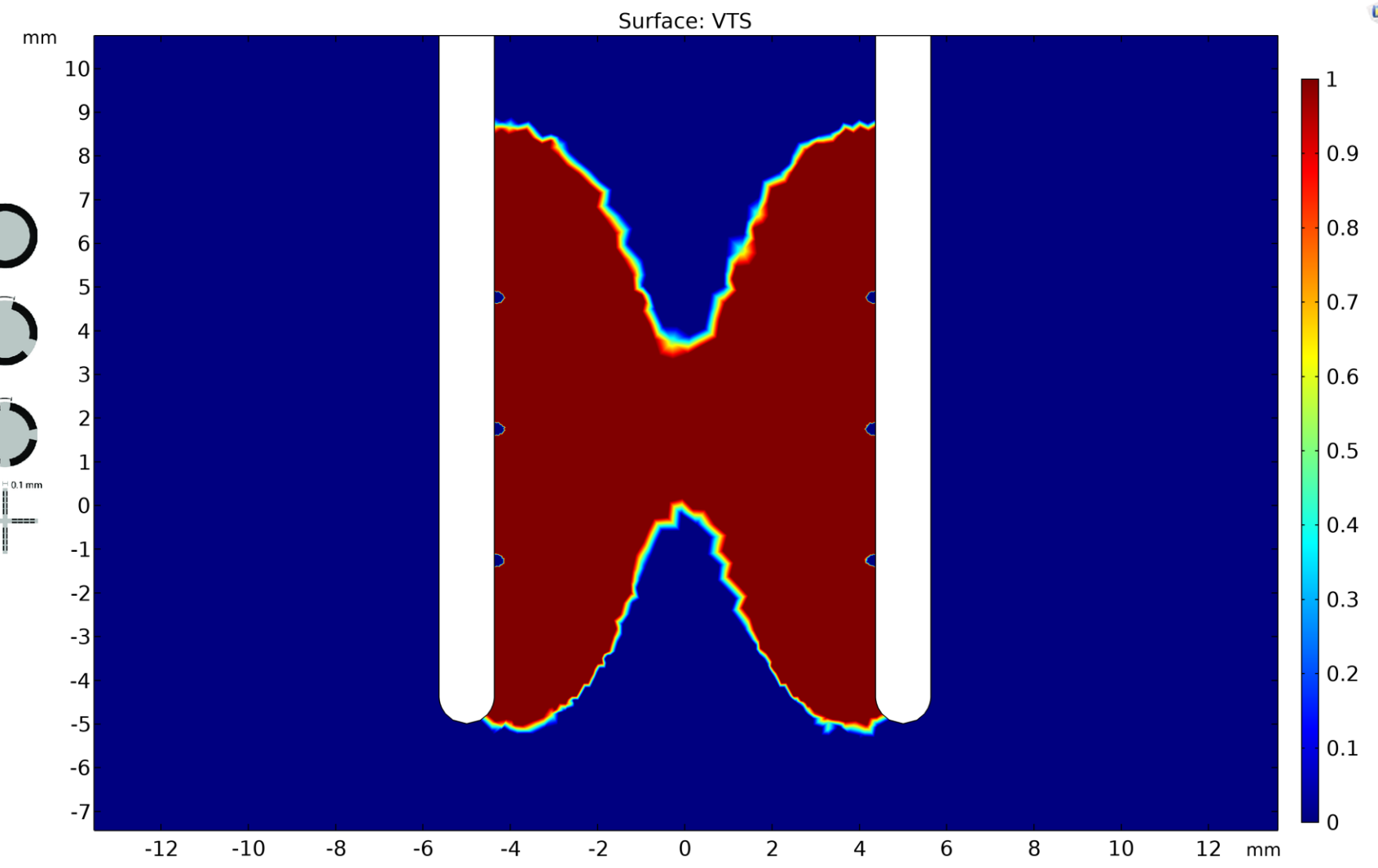


Volume of Tissue Stimulated at probe cut plane

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



Medtronic, Inc.



Hand-tuning through many iterations

The screenshot displays a software interface with three main panels: Model Builder, Settings, and Graphics.

- Model Builder:** Shows a tree view of the model structure. The 'Derived Values' section is expanded, showing 'Global Evaluation-Charge density' selected.
- Settings:** Shows the configuration for 'Global Evaluation-Charge density'. The 'Data' section is set to 'Study 1/Solution 1 (sol1)'. The 'Expressions' table is as follows:

Expression	Unit	Description
Q_density	$\mu\text{C}/\text{cm}^2$	Charge density
VTS	cm^3	Volume of Tissue Stimula...
I_ther	mA	Therapeutic dose (current)
Power	mW	Power
- Graphics:** Shows a 3D visualization of the model geometry, which consists of two vertical cylindrical structures. A coordinate system with x, y, and z axes is visible.
- Messages/Progress/Log:** A table titled 'Table 1' is displayed, containing the following data:

Charge density ($\mu\text{C}/\text{cm}^2$)	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/mm)
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 ($\mu\text{C}/\text{cm}^2$)	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

