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

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INTRODUCTION: Research has shown electric fields (EFs) induce directional migration in stem cells along an electrical potential gradient, a process known as cell electrotaxis, or cell galvanotaxis[1,2,3]. We built a COMSOL model of two probes directing stem cells to brain tissue damaged by stroke (Fig.1).

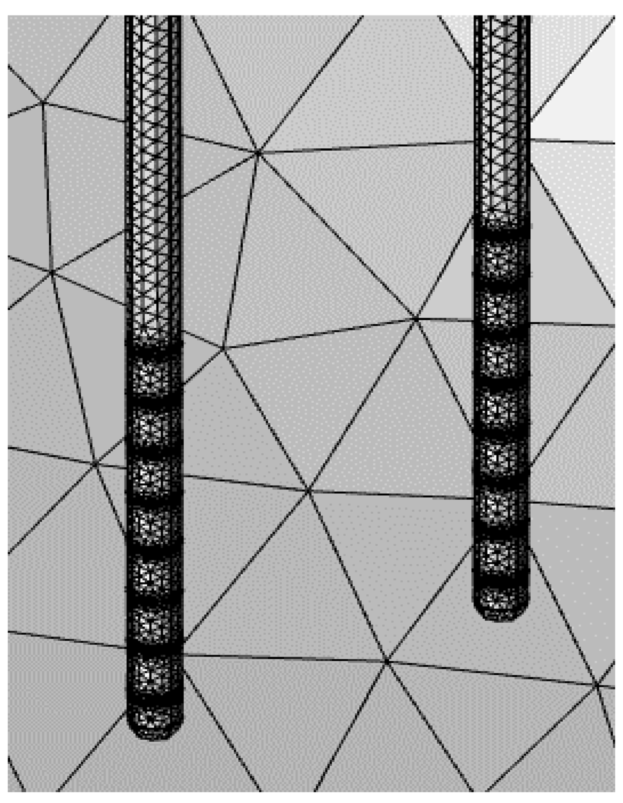

Figure 1. Mesh view of two probes with electrode arrays to control an electrical potential gradient.

Equations and Optimization Module. COMSOL's Electric Currents interface solved the steady-state current conservation equations[4]:

$$\nabla \cdot \boldsymbol{J} = 0 \qquad (1)$$

$$\boldsymbol{J} = \sigma \boldsymbol{E} + \boldsymbol{J_0} \qquad (2)$$

$$\boldsymbol{E} = -\nabla V \qquad (3)$$

where $\boldsymbol{J}$ is current density (A/m2), $\boldsymbol{E}$ is electric field (V/m), V is voltage (in V), and σ is conductivity (S/m).

A minimum of 100mV/mm EF strength is required for efficacy, i.e. directed cell migration[1]. Initial simulations used Global Inequality Constraints in the Optimization Module of 300 mV/mm as the optimal therapeutic EF strength[4]. Further, FDA-recommended safety limits for tissue stimulation include a maximum charge density of 30 μC/cm^2 at electrode surfaces. Taken together, these values establish an initial 'therapeutic window.'

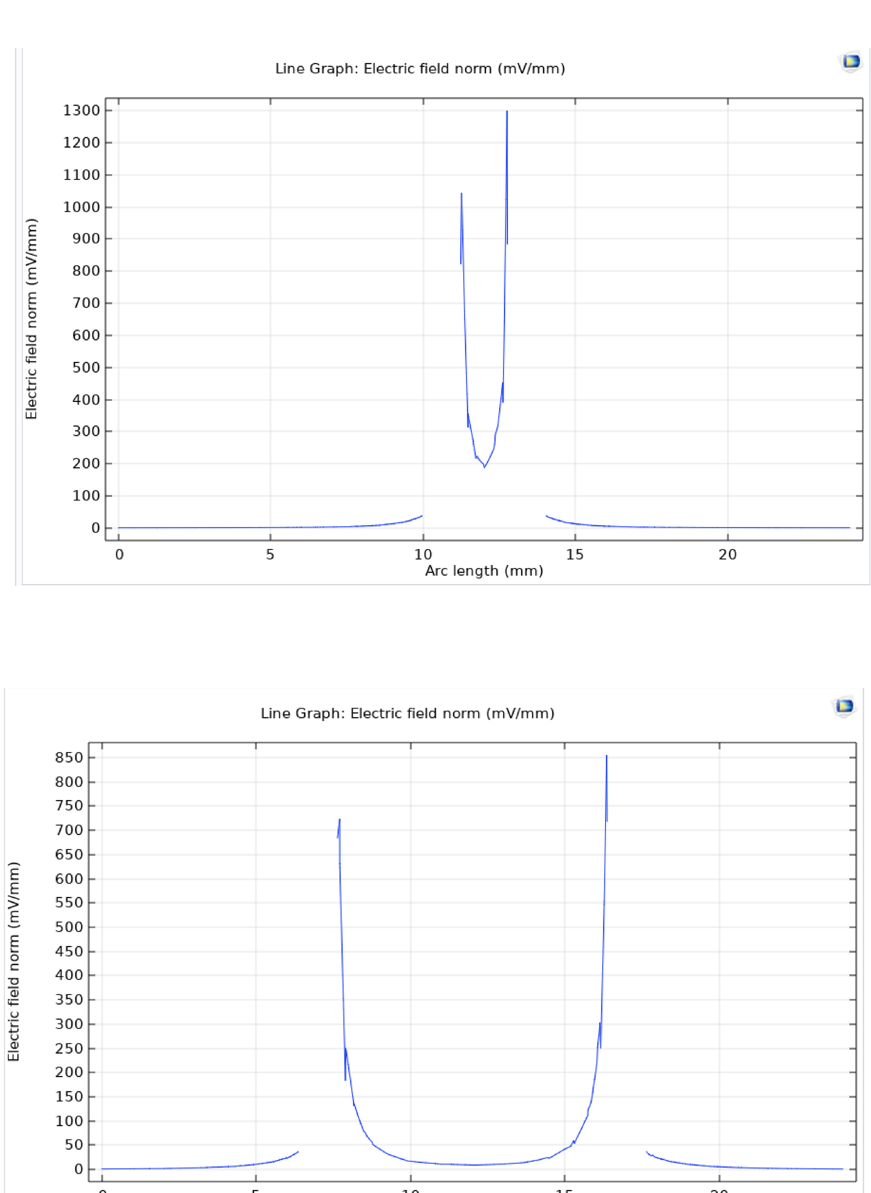

Figure 2. Comparing electric field strength with 6mm^2 electrode surface area. Top: 2.8 mm probe separation used in rats. Bottom: 10mm probe separation as would be used in humans.

RESULTS AND DISCUSSION: At an electrode separation of 2.8 mm used in rodent studies, a therapeutic value of 200 mV/mm was reached, replicating empirical results, with EF values increasing to 1300 mV/mm near the probes (Fig.2, top). Off-the-shelf deep brain stimulation probes used for initialing modeling did not perform well at 10 mm probe separation intended for human patients, showing a rapid 1/r^2 drop in EF strength (Fig.2, bottom), while current density stayed 80% below safety limits.

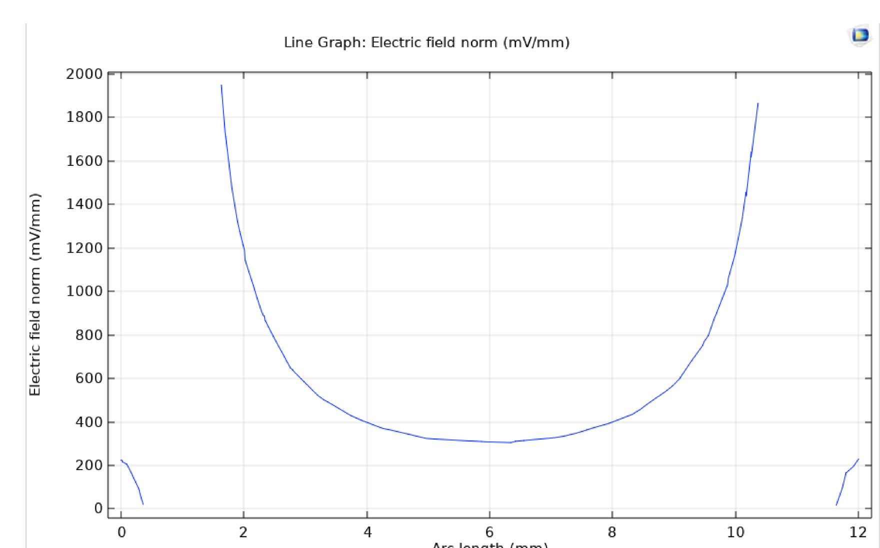

Figure 3. EF strength with 10mm probe separation using 48 mm^2 electrode surface area

However, increasing electrode surface area produced more uniform field strength between probes (Fig. 3). We created a metric, Volume of Tissue Stimulated (VTS), to clarify and compare probe configurations' ability to produce electrotaxis and predict the path cells may take between probes (Fig. 4).

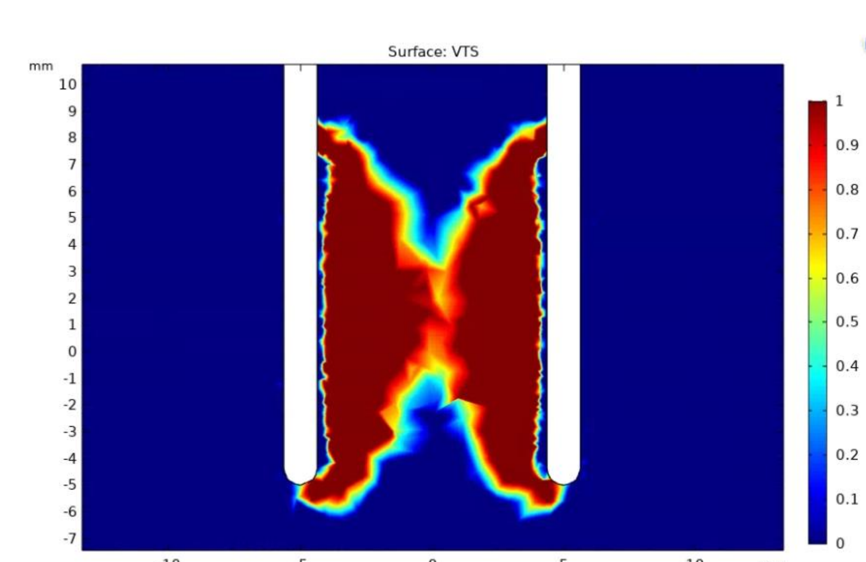

Figure 4. Volume of Tissue Stimulated (2D view) is a useful metric to gauge electric field strength between probes and the path stem cells will take between probes.

CONCLUSIONS: The goal is attaining field strength of 300 mV/mm at a probe separation of 6-10 mm while staying within FDA safety limits. Novel, specialized electrode designs are often required for new applications. Further modeling will analyze if *directional* electrodes may improve electrotaxis.

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