Electroceutical Modeling with Advanced COMSOL Techniques

K. Carlson[1], J. Begnaud[2], S. Dokos[3], J. L. Shils[4], L. Mei[1], J. E. Arle[1]

1. Beth Israel Deaconess Medical Center, Boston, MA USA. 2. Livanova Neuromodulation, Houston, TX USA.
3. University of New South Wales, Sydney, Australia. 4. Rush Medical Center, Chicago, IL, USA.

Introduction: The average R&D for one successful drug is a staggering $2.5B – and it takes 10 years to get approval. But the cost and timeline for medical devices is *80% less*. These economics drive a global push, led by DARPA and Glaxo, to create the *electroceutical paradigm* — an ambitious program to modulate any part of the human nervous system, anywhere, anytime, for any reason — to treat disease, disorders, or enhance, or interface with, the nervous system. Using advanced custom equation-based modeling techniques, we created an exemplar finite element model for electroceuticals: vagus nerve stimulation for epilepsy.

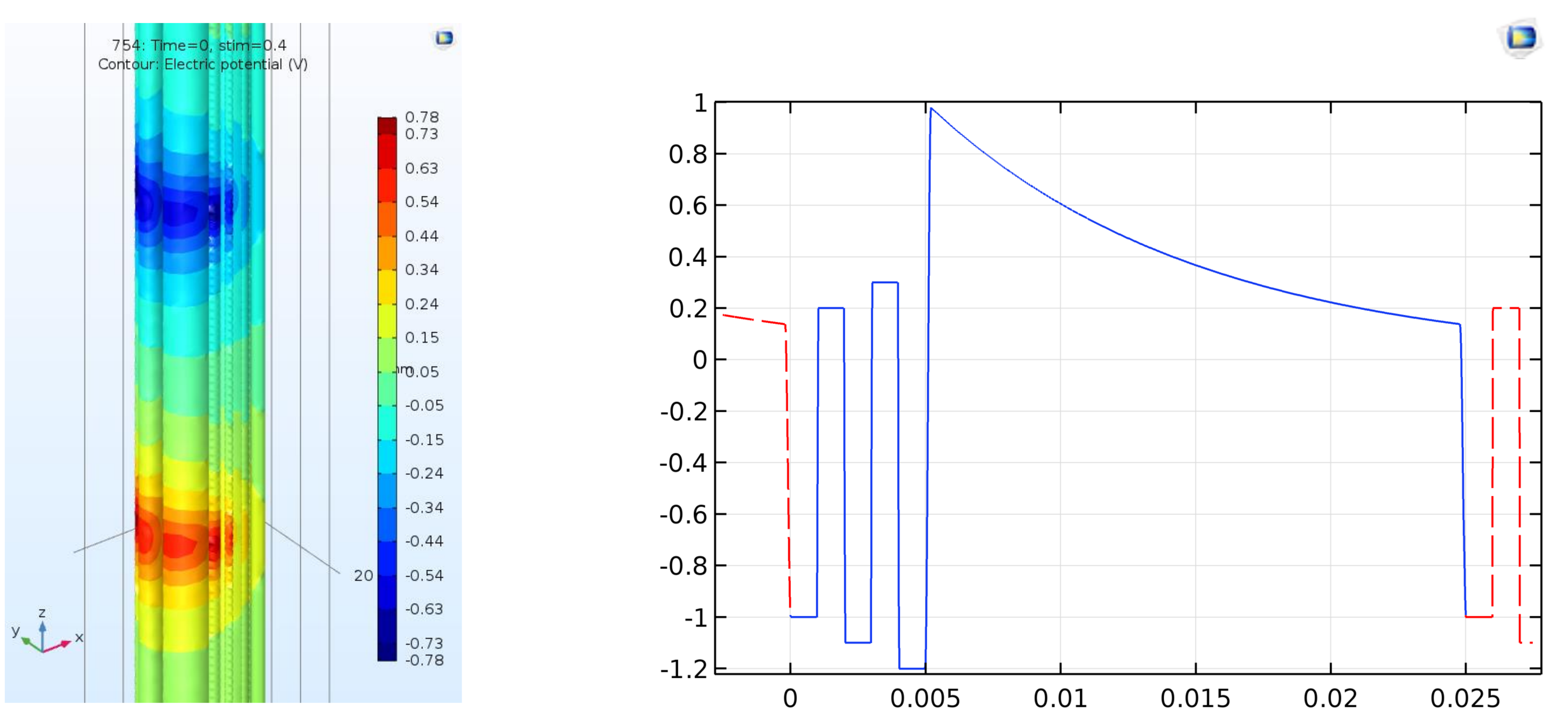

Figure 1. Left: Contour plot of electric potential distribution on the surface of vagus nerve bundles. Right: 'Burst' stimulation waveform made with Piecewise function.

COMSOL Techniques: A variety of COMSOL techniques are used to implement the complex electroceutical model (Table 1). The AC-DC module models the applied electric stimulation on the tissue. We first solve Laplace's equation for electric potential distribution with a Stationary solver. Ampere's law reduces to Laplace's equation when we eliminate the magnetic term by taking the divergence:

$$-\nabla \cdot \left(\sigma \vec{\nabla} \varphi\right) = 0$$

Then the last value of the stationary solver is used as an initial condition of the Time dependent solver, which solves a complex set of differential equations, the Hodgkin-Huxley equations for nerve fiber activation, re-calibrated to human data, modeled in Variables, General Form Edge PDE, and Edge ODEs and DAEs nodes (Fig. 2). In this way we can solve each physics separately to save time, yet they are coupled.

Summary: The COMSOL model was instrumental in identifying fibers causing efficacy and side effects, their probably locations within the nerve, their activation and blocking thresholds, and a variety of known and new effects of electrical nerve stimulation (ref 2). The model is leading example of the exploration required to realize the electroceutical paradigm.

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 2nd 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

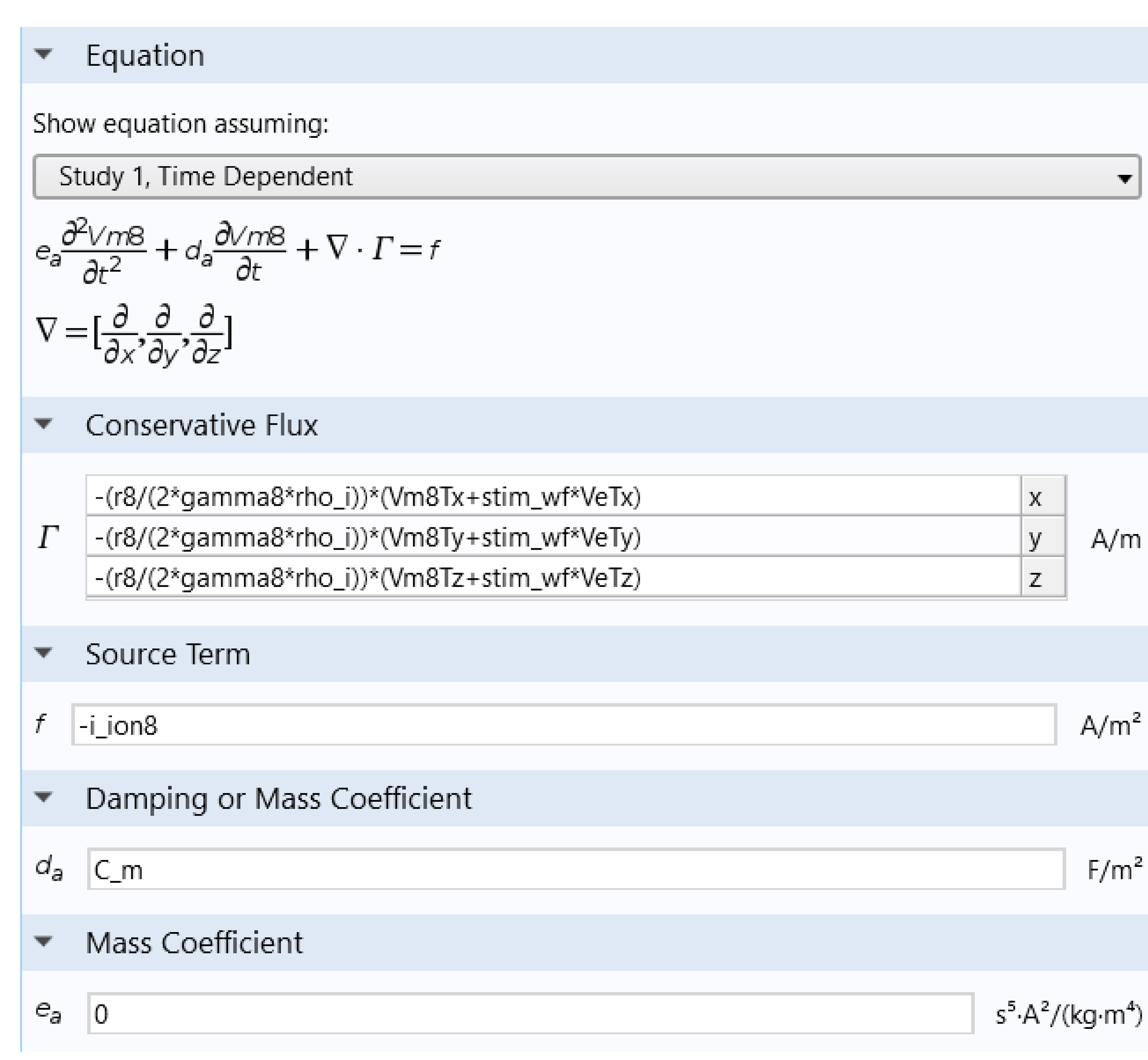

Figure 2. Portion of custom equation-based modeling of nerve fiber activation by an external electric field.

References:

Arle, J. E., Carlson, K. W. (2016). "The use of dynamic computational models of neural circuitry to streamline new drug development." Drug Discovery Today: Disease Models **19**: 69-75..

Arle, J. E., Carlson, K. W., Mei, L. (2016). "Investigation of mechanisms of vagus nerve stimulation for seizure using finite element modeling." Epilepsy Res **126**: 109-118.

Dokos, S. (2017). *Modelling Organs, Tissues, Cells an Devices Using MATLAB and COMSOL.* Berlin: Springer-Verlag.