Simulating Spiking Neurons Using a Simple Mathematical Model

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Abstract: Evolving studies related to external electrical stimulation of the spinal cord are showing voluntary motor function in paralyzed patients. However, the relationship between stimulus and response is not completely understood, and thus, optimal stimulus parameters are learned through exhaustive trial and error experiments during clinical testing. In this work, finite element analysis is used to provide insight between the electrical stimulation parameters and the resulting neurological responses. COMSOL Multiphysics 5.1 is used to determine the electric field distribution generated by two electrodes placed on the epidural layer of the spinal cord. The electric field results are then used as an input to the mathematically based Izhikevich neural model to simulate the resulting transient action potentials generated in the axons and these results are comparable to data published in the original paper.

Keywords: Spiking, neuron, action potentials

1. Introduction

Recent studies [1, 2] have shown that spinal cord stimulation can enable voluntary motor function in patients with spinal cord injury. However, trial and error methods are frequently used to determine the stimulus parameters needed to activate specific motor neurons. While machine-learning methods can be utilized to help optimize the stimulus parameters, simulations are useful in predicting the response elicited from particular stimulus parameters. Simulations may also aid in an improved understanding of restorative spinal cord stimulation.

One recognized method of simulation is to study the nerve responses for given stimuli. Once the nerve responses are simulated they can be mapped to a muscle response based on a second simulation study. In 1952, Alan Hodgkin and Andrew Huxley published a series of papers describing mathematics behind propagation of action potentials in a squid axon. Their quantitative description of the membrane currents and nerve excitation [3] has since been used as the foundation for modeling action potentials in different biological systems. Although the Hodgkin-Huxley model is widely used and is one of the most comprehensive models available for neural modeling, it becomes a computational challenge when used to model complex systems.

1.1 Hodgkin-Huxley Model

The Hodgkin-Huxley model consists of a series of linear and nonlinear differential equations, which reduce the computational efficiency as the system becomes complex. Specifically, the Hodgkin-Huxley model is given by the following equations,

$$C_m \frac{\partial V}{\partial t} = \frac{r}{2\rho}\frac{\partial^2 V}{\partial x^2} + g_{Na} m^3 h (V_{Na} - V) + g_K n^4 (V_K - V) + g_L (V_L - V) \quad (1)$$

where C_m is the membrane capacitance, r is the radius of the axon, ρ is the resistance of the intracellular space, $V_{Na}, V_K \; and \; V_L$ are equilibrium potentials of sodium and potassium ions and leakage potential and $g_{Na}, g_K \; and \; g_L$ are voltage dependent conductances.

$$\frac{dw}{dt} = \alpha_w (1 - w) - \beta_w w \quad (2)$$

where $w \; is \; m, n \; or \; h$ in equation (1)

$$\alpha_m = \frac{2.5 - 0.1V}{e^{2.5-0.1V} - 1} \quad (3a)$$

$$\alpha_n = \frac{1 - 0.1V}{10(e^{1-0.1V} - 1)} \quad (3b)$$

$$\alpha_h = 0.07 e^{-\frac{v}{20}} \quad (3c)$$

$$\beta_m = 4 e^{-\frac{v}{18}} \quad (3d)$$

$$\beta_n = 0.125 e^{-\frac{v}{80}} \quad (3e)$$

$$\beta_h = \frac{1}{e^{3-0.1V} + 1} \quad (3f)$$

Because the Hodgkin-Huxley model is computationally complex, alternative models are sometimes employed for neural simulations. Although most of these models are computationally efficient compared to Hodgkin-Huxley model, not all of these alternative models have the capability to simulate all of the spiking and bursting patterns that can be simulated using the Hodgkin-Huxley model [4].

2. Izhikevich Model

The Izhikevich model [5] is a recently published simple mathematical model that is both computationally more efficient than the Hodgkin-Huxley model and is also capable of simulating all of the spiking and bursting patterns. It has also been demonstrated that the Izhikevich model can be utilized to simulate a large number of spiking neurons.

The model consists of two, two-dimensional ordinary differential equations of the form

$$\frac{dv}{dt} = 0.04v^2 + 5v + 140 - u + I \quad (4)$$

$$\frac{du}{dt} = a(bv - u) \quad (5)$$

with a voltage spike resetting condition referred to as the "auxiliary condition".

$$if\ v \geq 30mV, then \begin{cases} v \leftarrow c \\ u \leftarrow u + d \end{cases} \quad (6)$$

Here, v and u are dimensionless variables where v represents the membrane potential of the nerve axon and u represents the membrane recovery variable. The parameters a, b, c and d are dimensionless and are used to describe the time scale of the recovery variable u, the sensitivity of the recovery variable u, the after spike reset value of the membrane potential v and after spike reset value of the recovery variable u, respectively.

The auxiliary condition is used to reset the variables v and u after the spike reaches its maximum $(+30mV)$.

The membrane potential v has a mV scale and the time t has ms scale. The resting potential of the model depends on the value of the parameter b and can have a value between $-70mV$ and $-60mV$. The model does not have a fixed threshold potential and can have values as low as $-55mV$ or as high as $-40mV$ depending on the history of the membrane potential.

3. Numerical Simulations with COMSOL Multiphysics® Software

3.1 Geometry

Based on average dimensions of the L1-L5 region of the human spinal cord [6], a two dimensional longitudinal section was modeled. The model consists of multiple domains representing different sections of the spinal cord. Two surface electrodes are modeled on the domain, which represents the epidural fat. Figure 1 shows the average dimensions of the L1-L5 region of the human spinal cord. Figure 2 shows the longitudinal sectional model used in this study.

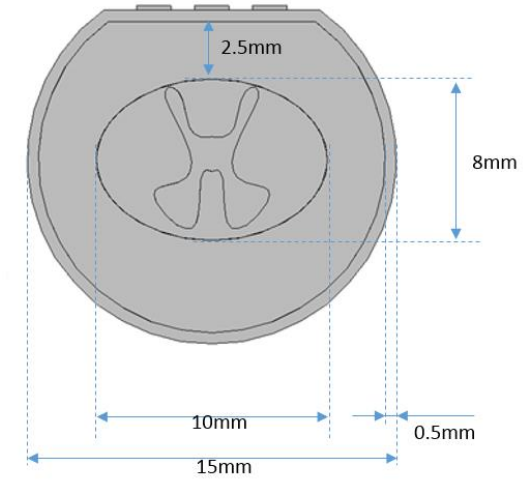

Figure 1. Cross section of the human spinal cord with average dimensions of L1-L5 region.

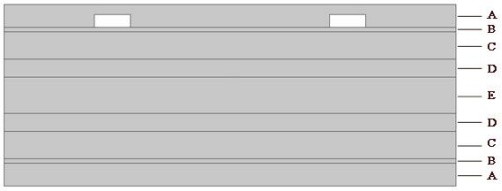

Figure 2. 2D model used for simulations representing the longitudinal section of the spinal cord with two embedded electrode; where A, B, C, D and E represent epidural fat, Dura matter, CSF, white matter and gray matter, respectively.

3.2 Materials and Physics

The simulation process consists of two steps. The first step is to solve the extracellular potentials for a given stimulus. This step requires dielectric properties in order to solve the relevant equations. Table 1 shows the dielectric properties [7, 8] used in this study.

Table 1: Dielectric properties of the spinal cord

Item	Conductivity (S/m)	Permittivity
White matter (longitudinal)	0.6	38.79
White matter (transverse)	0.083	1846.05
Gray matter	0.23	458.89
CSF	2	108.89
Dura matter	0.6	141.25
Epidural fat	0.04	38.72

Once the material properties are set, the electric current module in COMSOL 5.1 is used to calculate the potential distribution in the 2D model. This module utilizes Maxwell's equations to solve for the potential distribution.

$$\nabla \cdot \mathrm{J} = -\nabla(\sigma \nabla V) - \nabla\left(\epsilon_o \epsilon_r \nabla \frac{\partial V}{\partial t}\right) = 0 \qquad (7)$$

The Dirichlet-boundary conditions are applied to the two electrodes such that one of them is grounded while the other is used as the active electrode to provide the electrical stimulus.

'Global equations' nodes within the 'Global ODE and DAE' module are used to model the Izhikevich equations.

Once the physics are set, the model is meshed using a tetrahedral mesh with a finer mesh around the electrodes and a coarser mesh in the extracellular regions. The mesh consists of approximately 5500 domain elements and 800 boundary elements. The number of degrees of freedom solved for in the model is approximately 11,500.

Two transient simulation studies are setup to solve the entire model. The first simulation study solves the electric currents interface to calculate the potential distribution in the 2D model. The second simulation study solves the Izhikevich equations using the calculated potential as an input. Since a geometry is not used to represent nerve axons, a point potential is extracted from the results of the first study and subsequently used as an input to the second study to solve for the action potential in an axon, which would have its dendrite at the point where the potential is extracted.

3.3 COMSOL Application

Multiple variables, different electrical stimuli, and the possibility of extracting time varying potentials at different point locations result in numerous possible variations in the simulations. The management of these options is addressed using a COMSOL application built with the COMSOL application builder utility.

The interface of the application is shown in figure 3. The application provides the ability to change all the variables, change the stimulation pulse, and change the location of the point at which the 2D potential is extracted.

The Izhikevich model has the ability to simulate a variety of spiking and bursting patterns. These patterns are a result of the values taken by the variables in Izhikevich model. Five of these variable value sets are also predefined within the application. The application also allows the user to easily navigate through the simulation process and visualize the resulting potential distributions and the action potentials.

3.4 Simulation

The first step of the simulation is to define an electrical stimulus and apply it to the active electrode. Step potentials are used in this study as the primary stimuli. The COMSOL application allows the user to set the two-step values and time ranges for the stimulus. If the user requires the application of more complex stimuli, it can be achieved within the COMSOL settings; however, the app has a simple interface and does not provide this capability. After the stimulus is set, the 2D potential distribution can be calculated. Once the 2D potential is calculated, the time varying point potential needs to be extracted. The dendrite position in the application defines the location of this point. Next the potential at this point is exported into a file and imported back to

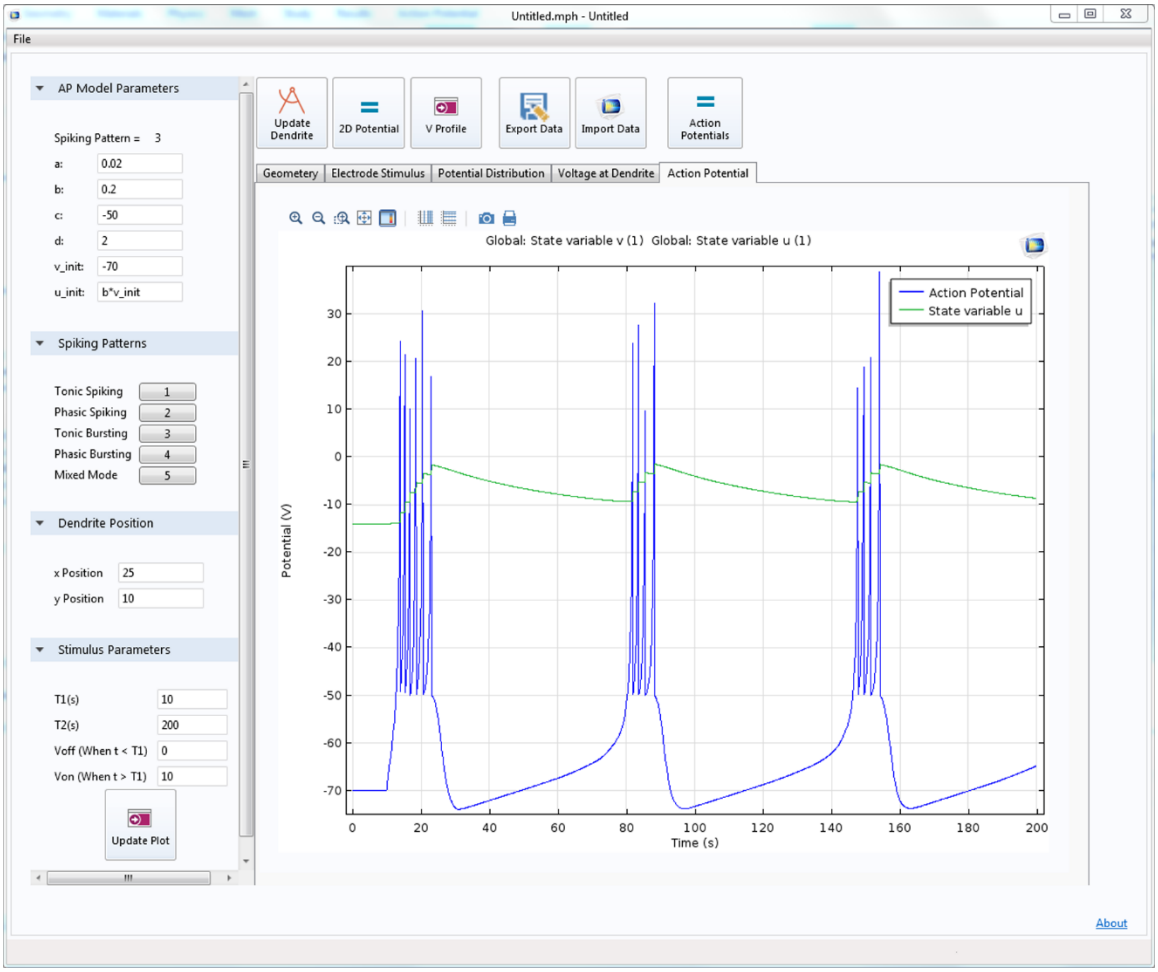

Figure 3. Interface of the COMSOL application

a function to be used in the second step of the simulation. Using predefined parameter sets or manually editing the model parameters, the Izhikevich model is initialized. Finally, the action potential can be calculated.

4. Results

Figure 4 shows the step potential stimulus used to obtain all the results shown here. Applying the stimulus shown in Figure 4 to the active electrode results in a 2D potential distribution as shown in figure 5. From this 2D potential distribution, a point potential is extracted for the second step of the simulation. The point (25mm, 10mm) at which the data is extracted is shown in the figure. This data provides the necessary input for the Izhikevich model. Figures 6-10 shows the resulting spiking and bursting patterns that can be generated using the Izhikevich model. The spiking and bursting patterns shown here are generated using the five predefined parameter sets.

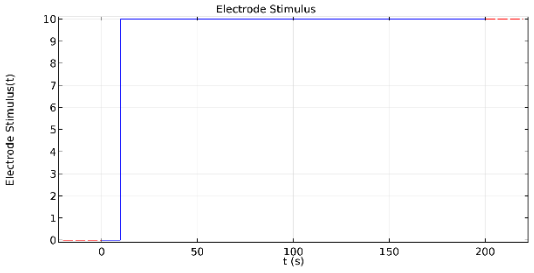

Figure 4. Step potential stimulus

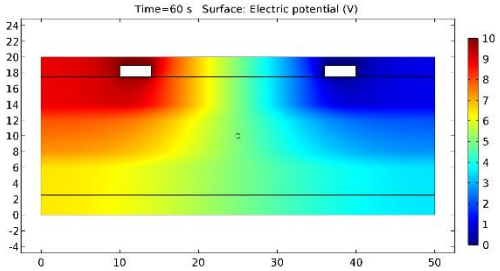

Figure 5. 2D potential distribution

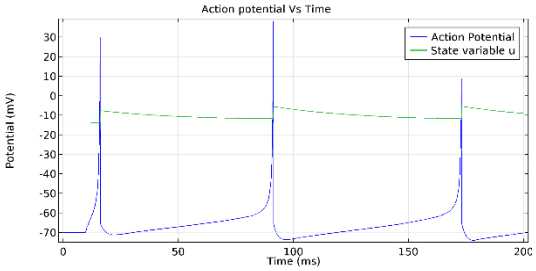

Figure 6. Tonic Spiking

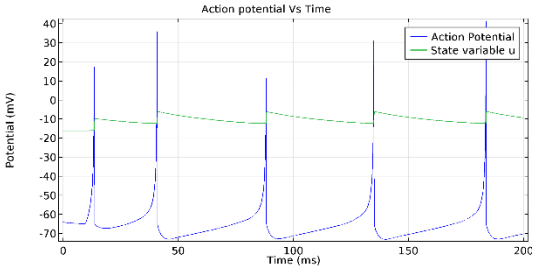

Figure 7. Phasic Spiking

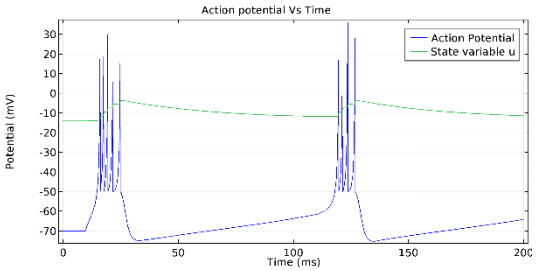

Figure 8. Tonic bursting

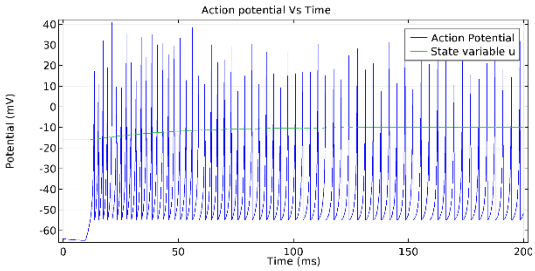

Figure 9. Phasic bursting

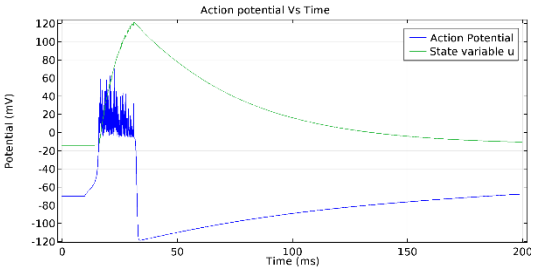

Figure 10. Mixed mode

5. Conclusion

Simulated spiking and bursting patterns generated in nerve axons are computed using the Izhikevich mathematical model. Electrical stimuli provided through an electrode to a 2D human spinal cord model is used to generate a 2D potential distribution. A time varying point potential is extracted from the 2D potential distribution and fed into the Izhikevich model. The flexibility and efficiency of the Izhikevich model provides the ability to simulate a variety of spiking and bursting patterns identified by experimentations. This study can be extended to study multiple neurons, interactions between neurons and to study the impact of action potentials on muscle fibers. These additional conditions will be investigated in future work to better understand the dynamics of the spinal cord stimulation and muscle responses.

6. References

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7. Appendix

The values of the parameters for the five predefined spiking patterns are listed in the table 2.

Table 2: Predefined parameters

Pattern	Variable	Value
Tonic Spiking	a	0.02
	b	0.2
	c	-65
	d	6
Phasic Spiking	a	0.02
	b	0.25
	c	-65
	d	6
Tonic Bursting	a	0.02
	b	0.2
	c	-50
	d	2
Phasic Bursting	a	0.02
	b	0.25
	c	-55
	d	0.05
Mixed Mode	a	0.02
	b	0.2
	c	-5
	d	4

Figure 11 shows the simulation steps followed and the inputs which can be provided to the simulation through the COMSOL app to obtain the final results.

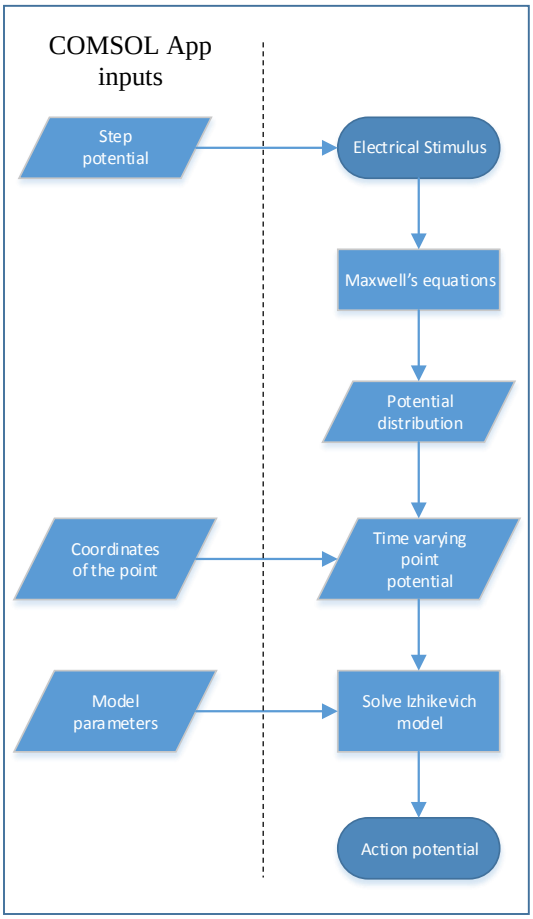

Figure 11. Flow chart of the simulation structure