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External Current Application in a Bidomain Model of Active Neural Tissue

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Abstract

The formal treatment of tissue as two coupled continua is referred to as a bidomain model. Bidomain models have recently been used to describe the properties of neural tissue and nerve fiber bundles [1, 2]. By adapting the Hodgkin Huxley equations in COMSOL Multiphysics, we have investigated the propagation of an action potential through neural tissue by external current stimulation.

I. Introduction

The bidomain model was developed in the late 70s as a generalization of one-dimensional cable theory. It combines the partial differential equations that describe intracellular and extracellular spaces as they are coupled into a simulated cellular membrane. For instance, cardiac tissue has a complex microstructure comprised of coupled cells enveloped by an interstitium made of blood vessels, connective tissue and fluid. This has classically made it difficult to model. However, the bidomain approximation has been used to model cardiac tissue under a variety of circumstances, including different bath conditions and anisotropies. It is particularly well-suited for the myocardium because the anisotropic structure of the tissue can be partially preserved by assigning a conductivity tensor [3]. In the mid-90s, this was expanded to include active tissue, and within the last decade, passive neural tissue and active nerve fiber bundles [4, 1, 2]. More recently, Sadleir [2] adapted the passive neural tissue bidomain model to incorporate reduced Hodgkin Huxley (HH) equations for distributed active tissue. This was assembled in COMSOL Multiphysics, using parameters described by Giugliano [5]. Our current work uses the full set of HH equations to simulate the behavior of specific active neural tissue types. This will be used to validate continuing experimental work in magnetic resonance electrical impedance tomography (MREIT) studies.

II. Methods

The model being used is based on a simplification of the *Aplysia californica* abdominal ganglion (AG), a small body of tissue containing several hundred neural cells [6]. For this paper, it is modeled as a sphere with a diameter of 2 mm. We found that models constructed using short cylindrical AG compartments produced very similar results. It was placed in an

octagonal sample chamber with a width of 6.25 mm. These dimensions were chosen to closely represent those found in our MREIT experimental chamber (Fig. 1).

We adapted the full HH equations [6, 7] in COMSOL Multiphysics in order to study membrane depolarization events as a result of external current application. There are six separate physics domains, each with their own governing equations. V_o was defined in the bath and is governed by:

$$J = \sigma E \quad (1)$$

Boundary conditions were specified as a current applied across two ports, one port for the current source and another for ground. All other physics domains were defined only in the tissue. V_e was the extracellular potential, governed by:

$$\nabla \cdot ((\sigma_i + \sigma_e) \nabla V_e + \sigma_i \nabla V_m) = 0 \quad (2)$$

At the interface of the tissue and bath, V_o equaled V_e . V_m was the membrane potential, governed by:

$$\nabla \cdot ((\sigma_i + \sigma_e) \nabla V_m + \sigma_i \nabla V_e) = \beta_c I_m - I_{amp} I_{src}(t, r) \quad (3)$$

Membrane current was defined as:

$$I_m = \beta(C_m \frac{dV_m}{dt} + (V_m - V_{Na})g_{Na} + (V_m - V_K)g_K + (V_m - V_{lk})g_{lk}) \quad (4)$$

The boundary condition for V_m was insulation on all boundaries. As a part of the active tissue model, the HH parameters m , h , and n are used. These parameters are governed by (5), where η can be m , h or n :

$$\frac{d\eta}{dt} = (\eta_{inf} - \eta)\tau_\eta^{-1} \quad (5)$$

The boundary condition for the HH m , h and n parameters was that there was no flux across the membrane. The effect of HH parameters on membrane conductance is shown in Fig. 2. All other parameters and variables used in the simulation are defined in tables in the appendix.

III. Results

For studies involving current application across the chamber, current was passed between one electrode surface and grounded at the diametrically opposite injection port (Fig. 1). Current was applied as two Gaussian pulses centered at 7 ms (CI1) and 17 ms (CI2). The

Gaussian standard deviation was 0.7 ms. Analysis of membrane potential and membrane conductance was performed at a point on the origin along the path of current injection. This provided a convenient location by which to determine the values for our dependent variables of interest, V_m and G_m . In Fig. 3 and 4, we show membrane voltage and conductance associated with action potentials caused by this scheme of current injection. They are evident by a marked increase in membrane voltage and conductance. For a current of 0.3 mA, no depolarization events occurred. For a current of 0.4 mA, a depolarization event did not occur at CI1, but the persisting increase in membrane voltage allowed an action potential at CI2. For 0.5 mA, an action potential occurred at CI1, but the resulting refractory phase lowered the membrane voltage enough at CI2 so that a second action potential did not occur. This was true for 0.6 mA current injection as well. At 0.7 mA, action potentials were evident at both current injection times. The double action potential scheme resulting from 0.7 mA is nicely detailed in Fig. 5, such that the propagation of the depolarization event can be seen traveling from right to left as current is applied.

For studies in which the current was placed at an angle, all parameters—including the current of 0.7 mA—remained the same, but the current source was moved from 180° to 315° in increments of 45° (using ground as the 0° angle). Fig. 6 demonstrates the described current application schemes and their effect on action potential generation. At 180° , two action potentials were produced, as noted before. At 225° , there was still enough exogenous current to drive membrane voltage above threshold values at both current injection times, resulting again in two action potentials. At 270° , an action potential was generated at CI1, but not at CI2 (due to the lowered membrane voltage during the refractory period). At 315° , current density within the AG was no longer high enough to generate action potentials.

IV. Discussion

Upon evaluating V_m and G_m at the center of the simulated AG, it became evident that the depolarization event (the action potential) was propagating along the x-axis faster than the voltage change induced by the current injection. Because of this, future analysis should either be done closer to the grounded side of the AG or properties of the injected current should be changed, depending on what is investigated. Additional avenues for future research include a combined internal/external source scheme, which would better simulate actual conditions in an MREIT system.

The external current could also be set to a constant frequency and internal sources could then be randomized in time and space within the simulated AG in a way that better approximates *in-vivo* conditions. This would also require lengthening the time in which we are running the simulation. Asymmetric current injections also have potential for investigation, including varying the current to determine the relationship between amperage required for continuous depolarization events and current application along different paths.

V. Conclusion

An active bidomain model of the *aplysia* AG was tested under various external current conditions in order to test its practicality as a theoretical model for *in-vitro* MREIT research.

Active tissue properties similar to those expected *in-vivo* were produced, including nonlinearities associated with the HH model of active neural tissue [8].

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Appendix

TABLE I

Parameters and Constants

Parameter	Value	Description
$G_{Na_{max}}$	1200 S/m ²	Na conductance when all channels are open
$G_{K_{max}}$	36 S/m ²	K conductance when all channels are open
G_{lk}	0.3 S/m ²	Conductance due to leakage
E_{Na}	55 mV	Sodium current reversal potential
E_K	−90 mV	Potassium current reversal potential
E_{lk}	−70 mV	Leakage current reversal potential
σ_i	3.63 S/m	Conductivity in cytoplasm
σ_e	5.8 S/m	Conductivity in extracellular space
σ_o	5.8 S/m	Conductivity of bath
C_m	0.01 F	Membrane specific capacitance
V_r	−70 mV	Membrane resting voltage
β	3.5E5 m ^{−1}	Cellular surface to volume ratio
amp_e	640.2 A/m ²	External current source (flat)
amp_i	0 A/m ³	Internal current source (spherical)

Parameter	Value	Description
m_{inf0}	0.042	Steady state sodium activation
h_{inf0}	0.618	Steady state sodium deactivation
n_{inf0}	0.315	Steady state potassium activation
c_{gauss}	0.0007 s	Standard deviation of amp _e gaussian

TABLE II

Variables

Variable	Expression	Description
I_{Na}	$G_{\text{Na max}} m^3 h (V_m - E_{\text{Na}})$ [A/m ²]	Current density due to Na
I_{K}	$G_{\text{K max}} n^4 (V_m - E_{\text{K}})$ [A/m ²]	Current density due to K
I_{lk}	$G_{\text{lk}} (V_m - E_{\text{lk}})$ [A/m ²]	Current density due to leak
I_{m}	$I_{\text{Na}} + I_{\text{K}} + I_{\text{lk}}$ [A/m ²]	Membrane current density
G_{Na}	$G_{\text{Na max}} m^3 h$ [S/m ²]	Conductance due to Na
G_{K}	$G_{\text{K max}} n^4$ [S/m ²]	Conductance due to K
G_{m}	$G_{\text{Na}} + G_{\text{K}} + G_{\text{lk}}$ [S/m ²]	Membrane conductance
α_{m}	$(2.5 - 0.1 V_{\text{mr}}) / (e^{(2.5 - 0.1 V_{\text{mr}})} - 1)$ [1/s]	Expression for HH m
β_{m}	$4 / e^{(V_{\text{mr}}/18)}$ [1/s]	Expression for HH m
α_{h}	$0.07 / e^{(0.05 * V_{\text{mr}})}$ [1/s]	Expression for HH h
β_{h}	$1 / (e^{(3 - 0.1 * V_{\text{mr}})} + 1)$ [1/s]	Expression for HH h
α_{n}	$(0.1 - 0.01 V_{\text{mr}}) / (e^{(1 - 0.1 V_{\text{mr}})} - 1)$ [1/s]	Expression for HH n
β_{n}	$0.125 / \exp^{0.0125 V_{\text{mr}}}$ [1/s]	Expression for HH n
r	$x^2 + y^2 + z^2$ [m]	Distance from center

Figure 1. Comsol model for the spherical *aplysia* AG in an MREIT sample chamber. a) The *aplysia* AG b) The simulated bath. c) One of eight current application ports.

Figure 2.

From *Bioelectromagnetism*, showing the interplay between membrane conductance and voltage [7]. G_{Na} and G_K are proportional to m^3h and n^4 , respectively.

Figure 3.

Membrane potential measured at the center of the ganglion during external current application of 0.3–0.7 mA in 0.1 mA increments over a period of 28.6 ms. Legend shows injected current values.

Figure 4.

Membrane conductance measured at the center of the ganglion during external current application of 0.3–0.7 mA in 0.1 mA increments over a period of 28.6 ms. Legend shows injected current values.

Figure 5.

A propagation event within the spherical AG. Values of V_m from a slice on the plane $z=0$ are shown at a) 50 ms, b) 70 ms, c) 75 ms, d) 79 ms, e) 90 ms, and f) 105 ms.

Figure 6. V_o (bath) and V_m (AG) distribution contour lines for a) the standard current injection, b) 215° injection angle, c) 270° injection angle, d) 315° injection angle. The associated excitation profile is shown below each contour plot.