35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

A Continuum Neuronal Tissue Model Based on a Two-Compartmental Representation of Cells

Amr Al Abed, *Member*, Nigel H. Lovell, *Fellow, IEEE*, Gregg J. Suaning, *Senior Member, IEEE*, Socrates Dokos, *Member, IEEE*

***Abstract*—Although significant advances have been made in continuum modeling of cardiac and smooth muscle tissue, the progress in neuronal continuum modeling has been slower. In this paper, a continuum neuronal tissue model based on a two-compartmental representation of cells is presented. Each neuron is described using both a somatic compartment modeled by the classical Hodgkin-Huxley current kinetics and a dendritic compartment based on a passive RC formulation. In addition, a synaptic current is fed into the dendritic compartment to account for the presynaptic influence of cells located within the dendritic field of each soma. A number of cases are simulated, including intracellular current injection into either the dendritic or somatic compartments, as well as extracellular current stimulation with and without synaptic input into neurons. The model incorporates a number of parameters controlling neuronal excitability which can be adjusted to validate each neuron's responses against experimental data, allowing for the modeling of different neuronal cell types and behaviors.**

I. Introduction

Computational modeling is a valuable tool for quantitative analysis of the function of neuronal systems under healthy and diseased conditions and to aid in the testing of pharmacological therapies, the design of neuroprostheses, as well as the development of optimal signal processing and stimulation strategies for use in such devices.

It is crucial that such models do include a representation of the neural network under consideration, rather than simulating the behavior of a single neuron under physiological conditions and in response to electrical stimulation or pharmacological treatment. For example, initial modeling studies on the effects of electrical stimulation of the retina have focused on the responses of retinal ganglion cells (RGCs) to electrical stimulation but have largely ignored the presence of the retinal network. Some groups have attempted to incorporate these presynaptic inputs by modeling the retina as a discrete network [1, 2]. Efforts are underway to reconstruct discrete neuronal micro- and macro-circuits as part of the Blue Brain Project [3]. Cells are reconstructed from neuronal tracing images and connected using circuit building tools that obey rules for synaptic connections. Distributions of ion channels and membrane proteins, obtained experimentally, are incorporated into the resulting geometries to generate anatomically-accurate and functionally-realistic neuronal circuits. However the simulation and geometry-reconstruction algorithms are computationally expensive and require the use of supercomputers [3].

Alternatively a continuum approach to neuronal tissue modeling has been proposed. It has been utilized to model the retina [4], incorporating both passive retinal neuronal properties, active ganglion cell behavior and synaptic inputs from bipolar and amacrine cells to RGCs, which modulate the spiking activity of RGCs. The model was used to simulate both epiretinal and suprachoroidal electrical stimulation of the retina using bipolar electrodes as well as RGC responses to light stimulation [5, 6]. A method based on spatial averaging of the extracellular potential was also proposed to estimate the effect of the extracellular stimulus on the dendritic fields of RGCs [7]. Continuum neuronal modeling has also been employed in the study of direct brain activation following transcranial current stimulation in order to gain a better quantitative understanding of the mechanisms and effects of electroconvulsive therapy for the treatment of psychiatric disorders [8].

All the previous examples are case specific, and each neuron was represented by a single compartment describing the soma. It will be advantageous if neuronal cells in such continuum models were described using a multi-compartmental formulation, as commonly done in discrete neuronal modeling, in order to account for the heterogeneous distribution of ion channels in different parts of the neuron, for example dendrites, axon, and soma. Such an approach would allow a plethora of discrete neuronal model formulations to be incorporated into continuum simulations of the brain, spinal cord or retina. As a preliminary investigation, this study describes and tests a two-compartmental representation of neuronal cells in a simplified tissue under a number of intracellular and extracellular electrical stimulation conditions.

II. Mathematical Formulation

A 2D finite-element continuum model of electrical stimulation of a neuronal tissue (Fig. 1) was formulated in COMSOL Multiphysics (v4.3a, COMSOL AB, Sweden) and solved on an office workstation (CPU: i7 3.2GHz, RAM: 24GB). A 1mm thick layer (1mm x1mm) of neuronal cells was embedded in a conductive extracellular domain, whereby each point in the neural tissue is represented by a two-compartmental model: an active soma compartment and a passive dendritic compartment, coupled by a linear conductor. The change in transmembrane potential ($V_{m,s}$) of the somatic compartment (eq. 1) is formulated using the classical Hodgkin-Huxley kinetics [9] and currents (eq. 2):

This research was supported by the Australian Research Council (ARC) through its Special Research Initiative (SRI) in Bionic Vision Science and Technology grant to Bionic Vision Australia (BVA).

A. Al Abed, N. H. Lovell and G. J. Suaning, and S. Dokos are with the Graduate School of Biomedical Engineering, University of New South Wales, Sydney, NSW 2052, Australia (email: g.suaning@unsw.edu.au).

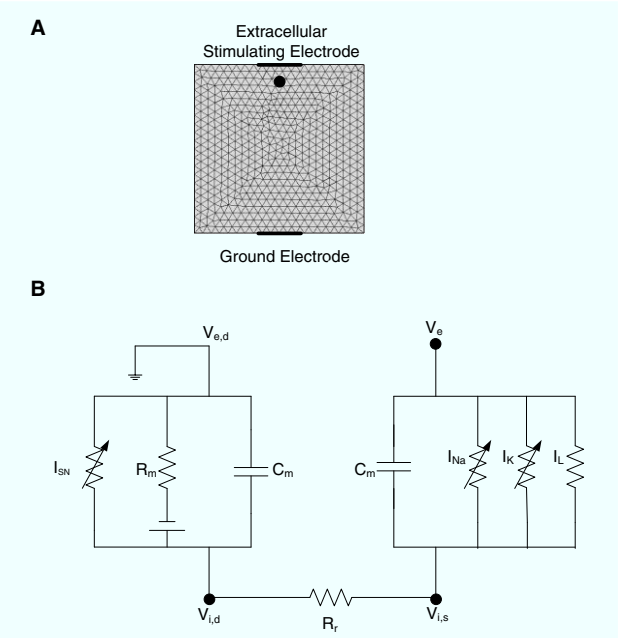

Figure 1. A. Setup of the 2D continuum neuronal model showing the locations of the extracellular stimulation and ground electrodes and probe point (solid circle), 100µm from the stimulating electrode. B. Circuit diagram of the two-compartment cell model implemented at each point in the 2D rectangular geometry.

$$V_{m,s} = V_{i,s} - V_e \tag{1}$$

$$C_m\left(\frac{\partial V_{i,s}}{\partial t} - \frac{\partial V_e}{\partial t}\right) = i_{Na} + i_K + i_L + \frac{1}{p} i_r + \frac{1}{p} i_{stim,s} \tag{2}$$

where $V_{i,s}$ (mV) is the intracellular potential of the somatic compartment and i_{Na}, i_K, i_L, i_r, $i_{stim,s}$ (nA.cm^{-2}) are the sodium, potassium, leakage, intracellular inter-compartmental and stimulus currents respectively. C_m is the specific membrane capacitance (µF.cm^{-2}) and p is the percentage of the total cell surface area taken up by the soma. On the other hand, the membrane potential of the dendritic compartment is formulated based on a passive RC model:

$$C_m \frac{\partial V_{m,d}}{\partial t} = \frac{V_{m,d} - V_{r,d}}{R_{m,d}} + \frac{1}{1-p} i_r + \frac{1}{1-p} i_{stim,d} + i_{sn} \tag{3}$$

where $V_{m,d}$ and $V_{r,d}$ are the transmembrane and resting transmembrane potentials (mV) of the dendritic compartment. $R_{m,d}$ is the specific membrane resistance (MΩ.cm^2) of the dendritic compartment, and $i_{stim,d}$ and i_{sn} (nA.cm^{-2}) are the stimulus current injected into the dendritic compartment and the synaptic current respectively. The model is constrained by setting the extracellular potential of the dendritic compartment to zero and hence its transmembrane potential ($V_{m,d}$) is equal to its intracellular potential ($V_{i,d}$). This condition is commonly used in discrete neuronal models. Also it is well known that neurons express a higher density of inward channels in the soma relative to their dendrites and therefore the somatic membrane is significantly more sensitive to changes in the extracellular potential, following external stimulation, relative to the dendrites.

In one simulation an excitatory synaptic current i_{sn}, described based on the formulation of Yin et al. [5], was fed into the dendritic compartment of each cell:

$$i_{sn} = p_{sn} g_{sn}\left(V_{m,d} - V_{sn}\right) \tag{4}$$

where p_{sn} a first-order state variable representing the delayed response from the presynaptic input, g_{sn} (µS.cm^{-2}) the synaptic conductance, and V_{sn} (mV) is the reversal potential of the synaptic channel. p_{sn} was determined by the synaptic transfer function (5, 6) with a center operating point of V_{50} and steepness parameter β_{50}:

$$\frac{dp_{sn}}{dt} = \frac{p_\infty - p_{sn}}{\tau} \tag{5}$$

$$p_\infty = \frac{e^{(V_{pre} - V_{50})/\beta_{50}}}{1 + e^{(V_{pre} - V_{50})/\beta_{50}}} \tag{6}$$

where V_{pre} (mV) is calculated from the convolution average of the $V_{m,s}$ of neighboring cells within a radius r (set to 200 µm in this study) and area a, around each soma (x_i,y_i).

$$V_{pre} = \frac{1}{a}\iint V_{m,s}\phi(x,y)dxdy \tag{7}$$

where

$$\phi(x,y) = \begin{cases} 1 & if \quad \left((x-x_i)^2 + (y-y_i)^2\right) < r^2 \\ 0 & otherwise \end{cases}$$

The inter-compartmental current [10] from the dendritic compartment to the somatic compartment is defined by

$$i_r = \frac{1}{p} g_r\left(V_{i,s} - V_{i,d}\right) \tag{8}$$

And from the somatic to the dendritic compartment as

$$i_r = \frac{1}{1-p} g_r\left(V_{i,d} - V_{i,s}\right) \tag{9}$$

The neuronal tissue was electrically stimulated with a boundary electrode, of size 200µm, and the current returned via a ground electrode of the same size on the opposite boundary (Fig. 1A). The current distribution in the extracellular domain V_e (V) was described by the Poisson equation:

$$\nabla \cdot \left(-\sigma \nabla V_e\right) = 0 \tag{10}$$

where σ (S/m) is the extracellular conductivity of the bulk neuronal tissue. Because of the necessity of constraining the model by setting the extracellular dendritic potential to zero, it is assumed that extracellular stimulation *directly* affects the transmembrane potential of the somatic, but not the dendritic, compartment of each cell. A second assumption of the model is that neighboring neurons can only electrically interact together and influence each other's transmembrane potential through the synaptic current feeding into the dendritic compartment of a particular cell. In other terms only the potential of the extracellular space of the bulk neuronal tissue was continuous across elements in the finite element model. No such continuity existed between the intracellular somatic and dendritic compartments of adjacent elements.

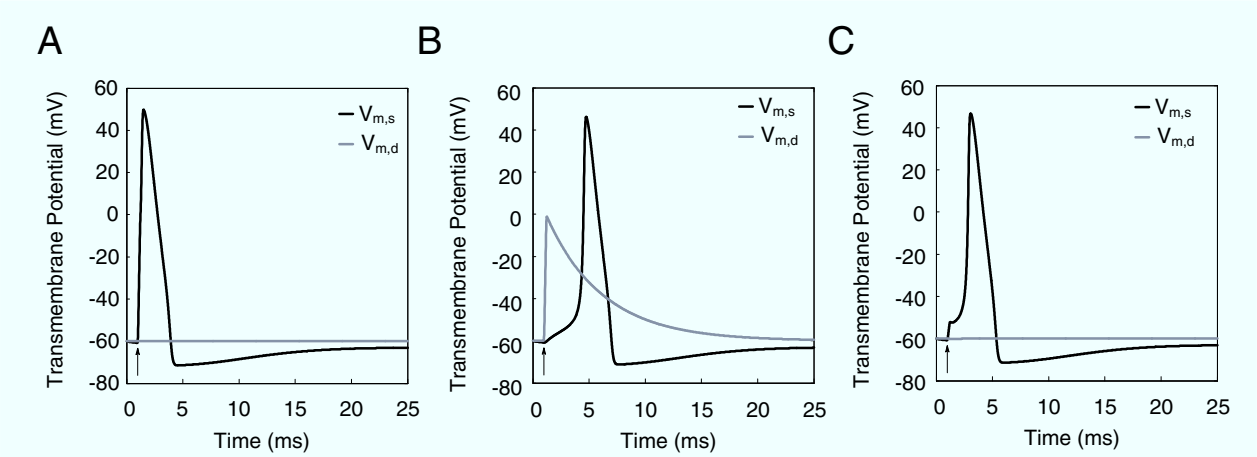

Figure 2. Transmembrane potential of the somatic and dendritic compartments recorded at the probe point indicated on Fig1A. Three cases are considered. (A) intracellular stimulation of the somatic compartment, (B) intracellular stimulation of the dendritic compartment, and (C) extracellular stimulation of the neuronal tissue domain. The arrow indicates the onset of the 200 µs stimulus pulse for each case.

III. Results

Three simulation scenarios were considered to test the feasibility of the proposed continuum neuronal model formulation.

A stimulus pulse of 3 µA.cm^{-2} amplitude and 200 µs duration was injected intracellularly into the somatic compartment of each cell (Fig. 2A). The current was sufficient to generate an action potential (AP). An intracellular coupling current passed between the somatic and dendritic compartments. However its magnitude was not sufficient to elicit any significant passive response in the dendritic compartment, resulting in a transmembrane depolarization of only 0.9mV.

On the other hand, a much larger stimulus pulse of 300µA.cm^{-2} amplitude and 200 µs duration was required to be injected intracellularly into the dendritic compartment of each neuron to generate a sufficient transmembrane depolarization leading to an inter-compartmental coupling current capable of bringing the somatic transmembrane potential above the threshold for generating an AP (Fig.2B).The latency between the peak dendritic and somatic transmembrane potentials was 3.5ms.

To test the performance of the model under extracellular stimulation conditions, the bulk neuronal tissue was stimulated from a boundary electrode (Fig.1A) using a monophasic pulse of 500A.m^{-2} in amplitude and 200 µs duration. This current was sufficient to excite neurons across a region as illustrated in Fig.3. Note at t = 51ms, the recovery from depolarization of neurons close to the stimulation electrode (middle top part of the domain) while the somatic compartments of neurons at the activation wavefront are still depolarized. An example response recorded from a point 100µm away from the stimulus electrode is presented in Fig.2C. The stimulus-response latency is 2.1ms from the onset of the stimulus pulse to the time of peak somatic transmembrane potential. The dendritic compartment depolarized by 100µV following the AP in the soma.

It should be noted that in all the above simulations, no synaptic input into the dendritic compartments of neurons were considered.

Fig. 4 illustrates the effect of enabling an excitatory synaptic current into the dendritic compartment, on the responses of neurons to extracellular current stimulation of identical pulse characteristics to the one used for the previous case. The stimulus pulse directly excited the somatic compartment of the probed neuron (Fig.1A). Similar to the previous case, the latency between the stimulus onset and the peak somatic transmembrane potential is 2.1ms. In addition, the transmembrane potential of the dendritic compartment depolarized to -37mV, a response that was absent when the synaptic input into the dendritic compartment was not considered. The latency between stimulus onset and peak dendritic depolarization was 43ms.

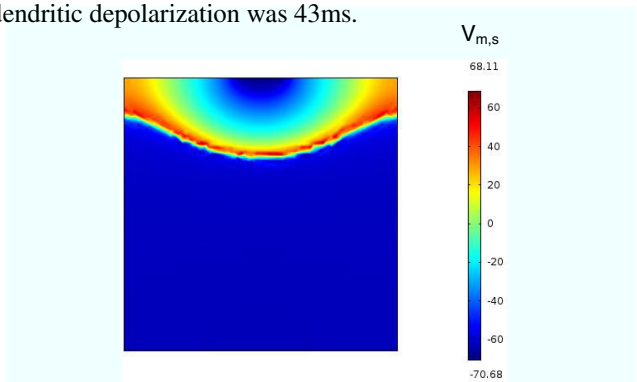

Figure 3. An instantaneous electrical activation map of the continuum tissue domain. The transmembrane potential ($V_{m,s}$) of the somatic compartments of neurons is plotted at t=51ms, 41 ms following the stimulus onset. The activation wavefront is at its maximal reach at this time point.

The model was verified by inspection of the currents underlying the changes in transmembrane potential (results not shown). In all cases tests, currents in the somatic and dendritic compartments displayed classical Hodgkin-Huxley and RC current waveforms respectively. A further verification step was conducted to test for the absence of electric leakage in the system and whether the model is properly constrained and numerically stable. The error was estimated from the maximum deviation of the summation of currents in eq. 2 from zero. At the probe point (Fig. 1A) the error relative to the peak of the ionic and capacitive currents in the soma was less than 10%.

IV. Discussion

A two-compartmental continuum representation of neuronal tissue was implemented in a simplified 2D model of an idealized neuronal mass. The formulation incorporated a somatic compartment described by Hodgkin-Huxley currents and kinetics, connected to a passive RC dendritic compartment via a coupling resistance. A synaptic current was added to the dendritic compartment to incorporate neuronal network effects. Although in this study the presence of a synaptic excitatory current did not have a significant effect on the area of neuronal tissue activated by extracellular current stimulation, the authors speculate that the contribution of presynpatic inputs on the excitability of neurons will become obvious when a train of pulses are used for stimulation, especially if they are delivered at a high frequency.

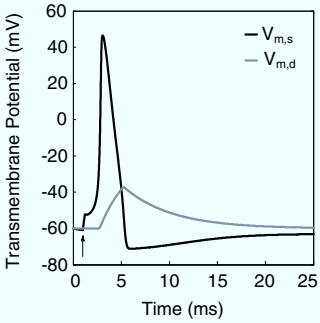

Figure 4. Membrane potential of somatic and dendritic compartments at the probe point indicated in Fig. 1A. Arrow: stimulus onset.

The addition of a dendritic compartment represents an improvement on previous continuum neuronal models [5, 8] which employed a single active compartment tied to a fixed resting potential. The model formulation outlined in this paper incorporates a number of parameters that can be modified to simulate different types of neuronal responses. The percentage of total membrane area occupied by the soma allows the electrotonic source/sink effect between the soma and dendritic tree to be taken into account. A value of 1% was used in this study and its effects are demonstrated by the lack of electrotonic current flow into the dendritic compartment when the soma was stimulated intracellularly, or during extracellular stimulation without any synaptic input into the dendrites. However, when a stimulus current was injected intracellularly into the dendritic compartment, electrotonic current passed to the somatic compartment and activated the soma. Other parameters include the conductivity of the bulk neuronal tissue (set to 0.31 S/m) and the inter-compartmental conductivity g_r ($1\mu S.cm^{-2}$) which contribute to determining the excitability of the neurons, particularly following extracellular stimulation. The continuum approach is used extensively in cardiac electromechanical [11] as well as smooth muscle and gastrointestinal electrophysiology [12] modeling. However its use in neuronal modeling is less widely adopted because, in general, neurons are not connected by gap junctions and therefore neuronal networks do not behave as electric syncytia. Therefore, interactions between neurons and between different compartments of the one neuron need to be modeled using a set of synaptic inputs and linear conductivities. As a result, the classical bidomain or monodomain formulation of the neuronal cable equation of electric propagation no longer hold and the model needs to be constrained to prevent the potential of each of the compartments from floating relative to one another. In this study, the model was constrained by fixing the extracellular potential of the dendritic compartment to zero.

V. Future Work

The current description of the extracellular potential of the dendritic compartment is the main limitation of this study and a more physiologically-realistic formulation needs to be developed. A sensitivity study would quantify the effect of the mesh element size and choice of grid. Model parameters controlling cell excitability in the proposed continuum neuronal model can be more accurately obtained by validating the model against discrete simulations reconstructed from a realistic neuronal geometry and experimentally-derived electrophysiological properties. Such a procedure will allow different neuron types, each with heterogeneous biophysical properties at their dendritic and somatic compartments, to be incorporated into a continuum tissue model to simulate the network interactions between different cell types and the results from such simulations can be validated against experimental data. This approach is ideal for simulating the retinal response to high-frequency electrical pulses in order to test the efficacy of various stimulation strategies used in vision prosthetic devices.

References

[1] R. J. Greenberg, T. J. Velte, M. S. Humayun, G. N. Scarlatis, and E. de Juan, Jr., "A computational model of electrical stimulation of the retinal ganglion cell," *IEEE Trans Biomed Eng,* vol. 46, pp. 505-14, May 1999.

[2] J. Teeters, A. Jacobs, and F. Werblin, "How neural interactions form neural responses in the salamander retina," *J Comput Neurosci,* vol. 4, pp. 5-27, Jan 1997.

[3] H. Markram, "The blue brain project," *Nat Rev Neurosci,* vol. 7, pp. 153-60, Feb 2006.

[4] S. Dokos, G. J. Suaning, and N. H. Lovell, "A bidomain model of epiretinal stimulation," *IEEE Transactions on Neural Systems and Rehabilitation Engineering,* vol. 13, pp. 137-146, Jun 2005.

[5] S. Yin, N. H. Lovell, G. J. Suaning, and S. Dokos, "A continuum model of the retinal network and its response to electrical stimulation," *Conf Proc IEEE Eng Med Biol Soc,* vol. 2010, pp. 2077-80, 2010.

[6] S. Yin, N. H. Lovell, G. J. Suaning, and S. Dokos, "Continuum model of light response in the retina," *Conf Proc IEEE Eng Med Biol Soc,* vol. 2011, pp. 908-11, 2011.

[7] A. Al Abed, S. Yin, G. J. Suaning, N. H. Lovell, and S. Dokos, "Convolution based method for calculating inputs from dendritic fields in a continuum model of the retina," *Conf Proc IEEE Eng Med Biol Soc,* vol. 2012, pp. 215-8, Aug 2012.

[8] S. W. Bai, C. Loo, A. Al Abed, and S. Dokos, "A computational model of direct brain excitation induced by electroconvulsive therapy: Comparison among three conventional electrode placements," *Brain Stimulation,* vol. 5, pp. 408-421, Jul 2012.

[9] A. L. Hodgkin and A. F. Huxley, "A quantitative description of membrane current and its application to conduction and excitation in nerve," *J Physiol,* vol. 117, pp. 500-44, Aug 1952.

[10] K. A. C. Ferguson, Sue Ann, "A two compartment model of a CA1 pyramidal neuron," *Canadian Applied Mathematics Quarterly,* vol. 17, pp. 293-302, 2009.

[11] A. V. Panfilov and A. V. Holden, *Computational biology of the heart*. Chichester ; New York: Wiley, 1997.

[12] P. Du, G. O'Grady, J. B. Davidson, L. K. Cheng, and A. J. Pullan, "Multiscale modeling of gastrointestinal electrophysiology and experimental validation," *Crit Rev Biomed Eng,* vol. 38, pp. 225-54, 2010.