Proceedings of The National Conference
On Undergraduate Research (NCUR) 2013
University of Wisconsin La Crosse, WI
April 11 – 13, 2013

A Dynamic Computational Study of the Role of Ion Channels in a Neuron

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Abstract

Neurons are specialized cells that exchange information across connections, called synapses, using electrical signals. These signals are formed by a potential difference (a voltage) across the cell membrane. This voltage changes as ion channels, specialized protein pores, open and close to allow ions to flow across the membrane. The region of a neuron which typically receives signals is called the dendrite. Synaptic signals propagate along the dendrite to the cell body, which adds together all the individual synaptic signals in a process called synaptic integration. It is expected that as synaptic input is added to a neuron, the effect of each additional input on the integration process will be less than the previous input. However, a process known as linear synaptic integration is observed, whereby additional synaptic inputs have the same effect as the previous inputs. Linear synaptic integration is possible due to the presence of voltage-gated ion channels that modify the strength of these synaptic signals. The goal of this research is to study the role of three types of dendritic voltage-gated ion channels in the context of linear synaptic integration. We constructed a time-dependent computational model of a single dendritic compartment using available physiological data. We studied the effect of the voltage-gated ion channels individually and in combinations to identify the conditions required for linearization. Physiological studies show that neurons express different types of ion channels in varying amounts in different regions of the neuron. Our results help demonstrate one possible reason why this occurs: individual channels and their combinations are active at different levels of synaptic activity and over different voltage ranges. By utilizing multiple types of ion channels, the neuron is able to function under a much greater range of conditions. By expressing the right combination of voltage-gated ion channels, the neuron can achieve linear synaptic integration over the entire voltage range between rest and threshold.

Keywords: Computational Neuroscience, Synaptic Integration, Biophysics

1. Introduction

Neurons are specialized cells within the nervous system that transmit information in the form of electrical signals.[1] A neuron is divided into multiple specialized regions. The dendrites receive signals at points of information exchange called synapses. The cell body (also known as the soma) evaluates received signals in a process called synaptic integration. These electrical signals are constructed by varying the potential difference across the cell membrane; if we arbitrarily define the extracellular fluid to be at zero volts, the cell interior is at a more negative potential at rest (that is, the membrane is polarized). The membrane potential changes as the cell receives electrical signals, becoming either more positive (a depolarization) or more negative (a hyperpolarization), depending on the signal. The neuron makes decisions based on these changes in potential. If the sum of the signals causes the cell to depolarize enough to reach a certain value, called the threshold voltage, the cell will initiate a signal of its own, an action potential, which is transmitted to other neurons via the axon. The membrane potential then returns to the resting membrane potential, allowing the integration process to begin anew.

The electrical signaling properties of neurons are based entirely on the movement of ions in and out of cells. The cell membrane is selectively permeable, meaning that ions cannot travel freely across the membrane. This results in a concentration gradient and a potential difference across the membrane. Electrical signals, changes in the membrane potential, are caused by the flow of ions across the membrane through specialized protein pores known as ion channels. In physical terms, the channel conductance varies as channels open and close, altering the ionic current flow, according to Ohm's Law:

$$I_{ion} = g\,(V_M - E_{ion}) \tag{1}$$

where g is the conductance (the inverse of resistance), measured in units of siemens (S) or inverse ohms, and I_{ion} is the ionic current, with units of amperes (A). The membrane potential, given in volts (V), is denoted by V_m, while E_{ion} is the reversal potential for that ion. For a specific ion, the difference between the membrane potential and the reversal potential for that particular ion is called the driving force. It is this voltage difference that causes ions to move across the membrane.

The reversal potential, E_{ion}, of an ion refers to the voltage difference across a membrane at which the force due to the concentration gradient is exactly equal and opposite to the force due to the electric potential. There is no net ionic flow at the reversal potential. The reversal potential is found from the Nernst Equation:

$$E_{ion} = \frac{RT}{zF} \ln \frac{[ion\ out]}{[ion\ in]} \tag{2}$$

where R is the universal gas law constant, T is the temperature, z is the charge on the ion considered, F is Faraday's constant, and the brackets indicate ion concentrations inside and outside the membrane.

There is an amazing amount of diversity among the types of ion channels in the human body,[1] yet these channels can be classified into several categories, including ligand-gated and voltage-gated channels. Ligand-gated channels, which open in response to neurotransmitter binding, are present at synapses. Voltage-gated channels, the type considered in this research, open and close in response to changes in membrane potential.

The dendrites play an extremely important role in neuron function. The earliest studies considered dendrites to be merely passive signal receivers, and it is still from this perspective that they are considered at the introductory level.[2] Wilfrid Rall was the first person to develop a computational description of dendrites, using cable theory to describe dendrites as passive conductors.[3]

In its simplest form, cable theory assumes an isopotential unbranched dendrite. This situation, in which all membrane properties are uniform, is described by equation (3):

$$\Sigma I_{m=} C_m \frac{dV_m}{dt} + gV_m \tag{3}$$

where the total membrane current ΣI_m is uniform across the surface; C_m and g represent the membrane capacitance and total effective membrane conductance, respectively, while V_m represents the membrane potential.

Rall's model showed an important property of passive dendritic conduction: a passive dendrite sums synaptic input in a nonlinear fashion. As additional synaptic input is added to a dendrite, the effect of each additional input is less than the previous input. This attenuation effect is analogous to the creation of a circuit with resistors in parallel; as resistors are added, a constant current has additional paths across which to flow, and the voltage drop (equivalent to signal strength) across each resistor is decreased. This nonlinear relationship is evident when considering Ohm's Law, equation (1). As synaptic channels open, ions flow into and out of the cell, causing the membrane potential to move closer in value to the synaptic reversal potential. This in turn decreases the driving force on those ions, which reduces the effect of subsequent synaptic signals on the membrane potential. This assumes a passive, constant conductance value.

A passive dendrite raises important issues for the function of a neuron. Neurons are uniquely tuned to be able to receive many thousands of synaptic inputs. A passive neuron could become saturated at high levels of synaptic activity, causing the vast majority of synaptic signals to have a negligible effect and limiting the effectiveness of the

complex network of connections among neurons in the nervous system. However, it is now known that dendrites are active conductors that can modulate synaptic signals as they propagate towards the soma. As a result, linear integration can occur, whereby additional synapses have the same effect on the membrane potential as previous synapses; there is no saturation. Active conductance, in the context of this research, means that the conductance value of dendritic ion channels, instead of remaining constant, is itself a function of voltage. Cash and Yuste provide an exceptionally persuasive demonstration of linear integration in CA1 pyramidal hippocampal neurons (in a brain slice experiment).[4] Studies of the visual processing system in higher mammals have also demonstrated linear integration.[5] In effect, the dendrite is making use of two nonlinear mechanisms (the varying driving force and the voltage-based conductance) to achieve a linear solution. This is not to say that dendrites universally operate as active conductors, only that active conductance can play an important role in certain situations. Linear summation allows the neuron to take full advantage of the vast network of connections that characterize the nervous system of higher-level organisms.

The purpose of this research is to study the role of dendritic voltage-gated ion channels in linear synaptic integration, with the particular goal of examining the ability of these channels to allow integration to be linear from the resting membrane potential to the threshold voltage. This voltage range is the most interesting to study and arguably the most important because it is here that neural information processing occurs.

2. Methods

A computational model of a single dendritic compartment was constructed using the *NEURON* software.[6] The model was built using available physiological data, incorporating passive mechanisms, voltage-gated ion channels, and excitatory (depolarizing) synapses. The dendrite contains a variable number of excitatory synapses, each with a conductance of 0.1 nS (0.1×10^{-9} S). The model can be visualized by the following electrical circuit diagram.

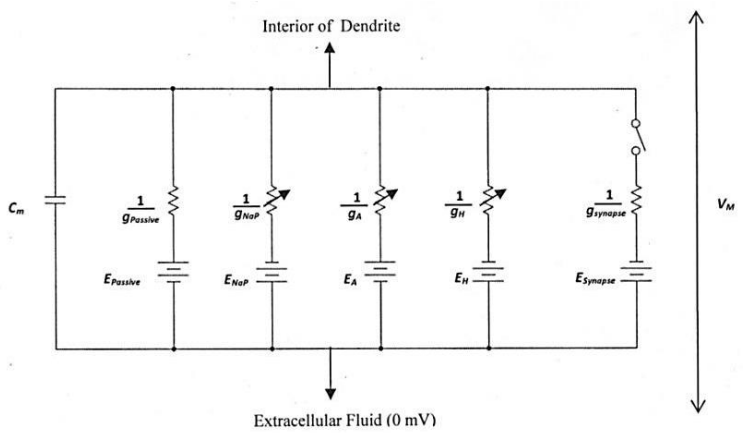

Figure 1: Circuit diagram of a dendritic compartment

In Fig. 1, a capacitor is included because the membrane has the ability to store charge.[1] The dendrite has passive ion channels which are continually open and determine the resting membrane potential. These channels are represented in Fig. 1 by $\frac{1}{g_{Passive}}$. The membrane potential is shown by V_m, while the batteries represent the reversal potential for the respective mechanisms involved. One synapse is shown for simplicity, but a dendrite can receive many thousands of synaptic inputs, each of which can be switched on and off. Channels which have a voltage-gated conductance are represented by potentiometers. The parameters of the model are given in Table 1. The various time constants τ describe the kinetics of channel opening and closing.

Table 1: Model parameters

Parameter:	**Value**:	**Parameter:**	**Value:**
R_m	28000 Ω-cm^2	E_H	1 mV
$g_{Passive}$	16.1 nS	E_A	-95 mV
Dendrite Length	120 μm	E_{NaP}	55 mV
Dendrite Diameter	120 μm	τ_m (*NaP* Activation)	0.025 ms
$E_{Passive}$	-80 mV	τ_h (*NaP* Inactivation)	2000 ms
$E_{Synapse}$	0 mV	τ_n (*A* Activation)	1 ms
Temperature	37 ℃	τ_l (*A* Inactivation)	5 ms
R_a	50 Ω -cm	τ_{lh} (*H* activation)	20 ms
C_m	1 μF/cm^2		

In Table 1, the membrane resistance R_m is the resistance of the cell membrane itself, while the axial resistance R_a represents the ability of current to flow along the length of the dendrite. Membrane parameters are uniform for the model. Calculations are performed using *NEURON*, which numerically solves a version of equation (3). The differential equations involved (equations 3, 6-8) are continuous, which *NEURON* approximates by discretizing space and time with time steps of 0.025 ms. This is a dynamic model, meaning channel properties and membrane potential are both functions of time. The results are collected at a time of 200 ms after synaptic activation, when the system has reached steady-state.

This work considered three different types of voltage-gated channels found in the human brain: a persistent sodium channel[7,8] (I_{NaP}), an A-type potassium channel[9,10,11] (I_A), and a hyperpolarization-activated mixed cation current[12] (I_H). The properties of these channels were modeled based on available physiological data. To understand how these channels work, we must return to the version of Ohm's Law given in equation (1), with a modification to account for the voltage-dependence of the channel conductance. That is,

$$I = g_{channel}(V_m, t) \cdot (V_m - E) \tag{4}$$

Instead of the conductance remaining constant, $g_{channel}$ is now a function of voltage and time, which can in turn be described by an equation of the type (here shown for I_{NaP}):

$$g_{NaP}(V_m, t) = \bar{g}_{NaP} \cdot m \cdot h \tag{5}$$

where $\bar{g}$ is the maximum possible conductance for that channel, and m and h are the activation and inactivation variables, respectively, which are themselves functions of voltage and time (see equation 6 for I_{NaP}).[3] These variables describe the kinetics of channel opening and closing, with their product representing the fraction of channels that are open at any membrane voltage. In physiological terms, $\bar{g}$ represents the channel density, the amount of a certain type of channel that is embedded within the cell membrane. The reversal potential and time constants for each channel are given in Table 1. Experimental data for the activation and inactivation variables were fitted to Boltzmann functions, yielding steady-state activation and inactivation curves (see Fig. 2 for I_{NaP}). The time derivatives represent the time-dependence of channel kinetics,

$$I_{NaP} = g_{NaP}(V_m, t) \cdot (V_m - E_{NaP}) \text{ where } g_{NaP} = \bar{g}_{NaP} \cdot m \cdot h \tag{6}$$

$$\frac{dm}{dt} = \frac{m_{inf} - m}{\tau_m} \qquad \frac{dh}{dt} = \frac{h_{inf} - h}{\tau_h}$$

$$m_{inf} = \frac{1}{1 + e^{-\left[\frac{-37.6\ \text{mV} - V_m}{7.4\ \text{mV}}\right]}} \qquad h_{inf} = \frac{1}{1 + e^{\left[\frac{-48.8\ \text{mV} - V_m}{10\ \text{mV}}\right]}}$$

while the "*inf*" subscript represents the steady-state value for the respective variable.

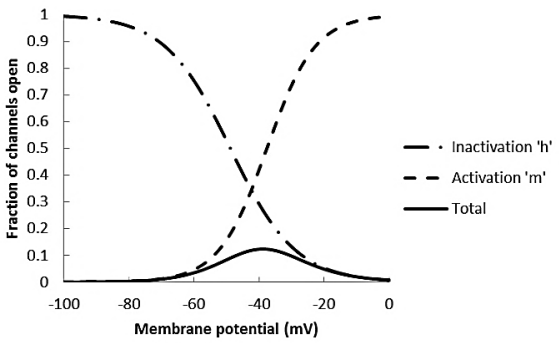

Figure 2: I_{NaP} steady-state activation/inactivation curves and total channel availability

Curves for the I_A and I_H channels (not shown) were similar to those for I_{NaP}, with certain exceptions. First, each channel is maximally active at a different value of the membrane potential. Second, each channel type has a different maximum fraction of $\bar{g}$ that is active. In particular, a lower fraction of A-type potassium channels are open than either of the other two channels at all values of the membrane potential. Finally, while I_{NaP} and I_A allow only a single type of ion to flow, I_H is a non-inactivating channel which allows both sodium and potassium to flow. I_H becomes more active as the membrane potential becomes more negative, unlike I_{NaP} and I_A. The equations for the I_A channel can be seen below,

$$I_A = g_A(V_m, t) \cdot (V_m - E_A) \text{ where } g_A = \bar{g}_A \cdot n \cdot l \tag{7}$$

$$\frac{dn}{dt} = \frac{n_{inf} - n}{\tau_n} \qquad \frac{dl}{dt} = \frac{l_{inf} - l}{\tau_l}$$

$$n_{inf} = \frac{1}{1 + e^{\left[\frac{11\text{ mV} - V_m}{18\text{ mV}}\right]}} \qquad l_{inf} = \frac{1}{1 + e^{-\left[\frac{-56\text{ mV} - V_m}{8\text{ mV}}\right]}}$$

where *n* and *l* are the activation and inactivation variables, respectively, and the "*inf*" subscript represents the steady-state. The equations describing I_H are very similar,

$$I_H = g_H(V_m, t) \cdot (V_M - E_H) \text{ where } g_H = \bar{g}_H \cdot k \tag{8}$$

$$\frac{dk}{dt} = \frac{k_{inf} - k}{\tau_{kh}} \qquad k_{inf} = \frac{1}{1 + e^{-\left[\frac{-90\text{ mV} - V_m}{8.5\text{ mV}}\right]}}$$

where *k* represents the activation variable for I_H, and the "*inf*" subscript once more is used to describe the steady-state value of *k*.

Parameter sweeps over the maximum available conductance $\bar{g}$ were performed to find the channel densities required for linear synaptic integration. Each linear range was obtained first by visual inspection, after which its limits were quantified by a region where the depolarization per synapse varied by less than two percent from the

central value. These limits were then mapped to a graph of membrane potential to determine the voltage range of linearity.

3. Results

In a purely passive system, each additional synapse has a decreased effect on the membrane potential relative to preceding synapses. This can be seen in the dotted line of Fig. 3a, where signal strength is expressed in depolarization per active synapse and that depolarization decreases as more synapses become active (that is, higher total synaptic conductance). However, the incorporation of a specific amount of voltage-gated conductance (for I_{NaP}, $\bar{g}_{NaP}$ = 5.20 nS) leads to a limited range of linearity. The solid line of Fig. 3a shows that, between 6.4 nS and 9.9 nS of active synaptic conductance, each additional synapse equally depolarizes the membrane by about 0.3 mV. I_{NaP} is an example of an amplifying channel, boosting the signal strength above that of the passive system.

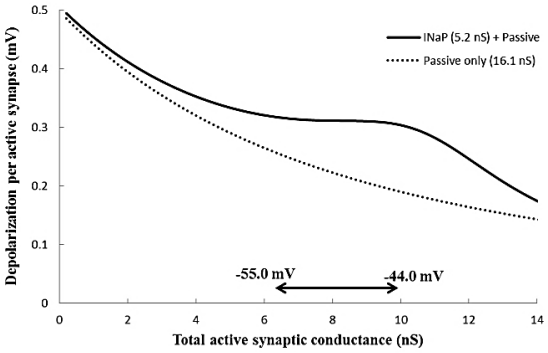

Figure 3a: Depolarization of the membrane potential by each additional synapse in a passive system and in the presence of I_{NaP}

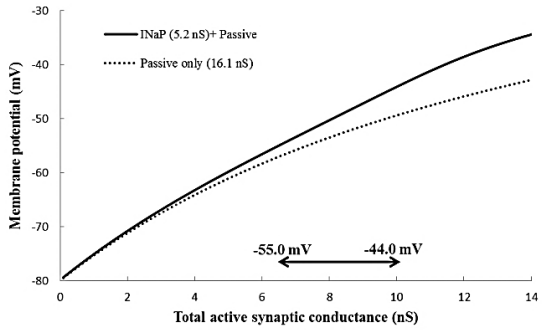

Figure 3b: Linearizing effect of voltage-activated I_{NaP} conductance on the membrane potential

Figure 3b depicts the effect on the membrane potential of incorporating a specific amount of I_{NaP} voltage-gated conductance. The passive system membrane potential (dotted line in Fig. 3b) is seen to increase non-linearly as total synaptic conductance increases. The addition of I_{NaP} (solid line in Fig. 3b) further depolarizes the membrane potential relative to the passive system. However, over a short voltage range mapping to the range of synaptic conductance seen in Fig. 3a (-55.0 mV to -44.0 mV), the membrane potential is changing linearly.

Figures 3a and 3b show that the linearizing effect of I_{NaP} is limited, both in terms of voltage range and synaptic conductance (-55.0 mV to -44.0 mV; 6.4 nS to 9.9 nS) but synaptic signals are amplified relative to the passive dendrite.

Each voltage-gated ion channel studied requires a different value of $\bar{g}$ to create the conditions for linearity: for I_A it is 2261.9 nS, while for I_H it is 6.79 nS. As expected, a much higher value of $\bar{g}$ is required for I_A because it has a

much lower probability of being open, based on the gating variables. As seen in Fig. 4 (dashed-dotted curve), I_A gives rise to a lengthy linear range (-58.4 mV to -42.3 mV; 14.4 nS to 29.2 nS), but this is offset by a weak signal strength. In contrast to I_{NaP}, I_A is an attenuating channel, because it decreases the signal strength compared to that of the passive system for part of its linear range. I_H (dashed curve in Fig. 4) displays intermediate properties (-72.1 mV to -60.1 mV; 0 nS to 4.6 nS). I_H is most active at more negative membrane potentials and therefore low levels of synaptic activity. None of the channels are individually capable of achieving linear integration over the entire voltage range between rest and threshold.

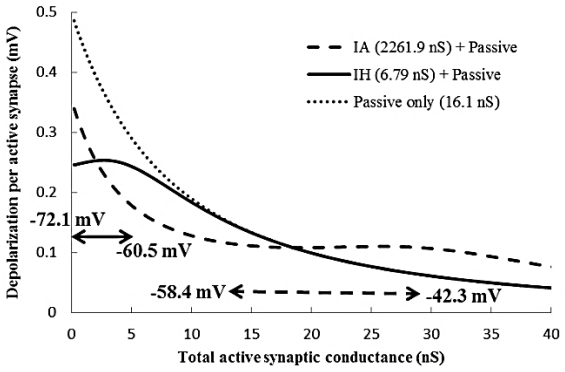

Figure 4: Depolarization of the membrane potential by each additional synapse in the presence of I_H and I_A individually

Channel combinations can also be used to achieve linearity. Both of the combinations allow for much longer ranges of linear synaptic integration, both in terms of membrane potential and synaptic activity. The I_H and I_A combination (solid line in Figs. 5a and 5b) allows for the longest linear range, (-71.6 mV to -42.9 mV; 0 nS to 24.9 nS), but with a weaker signal strength than the I_H and I_{NaP} combination (-73.5 mV to -46.7 mV; 0 nS to 9.9 nS; dashed line in Figs. 5a and 5b). I_A once again required a much higher level of conductance than did the other channel types. Both of these combinations allow for linearity over the entire voltage range between rest and threshold, with the I_H and I_A combination being most active at low levels of synaptic activity.

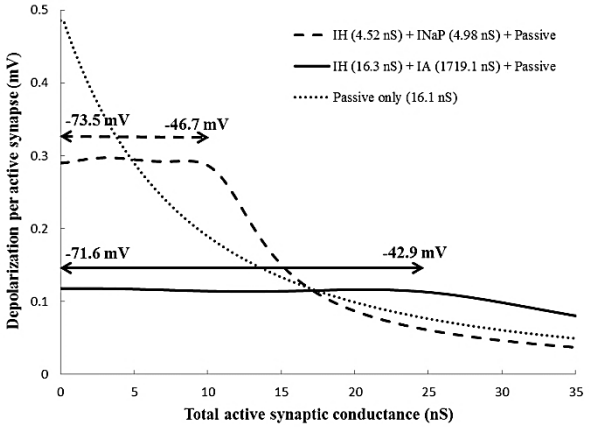

Figure 5a: Depolarization of the membrane potential by each additional synapse in the presence of combinations of dendritic voltage-gated ion channels

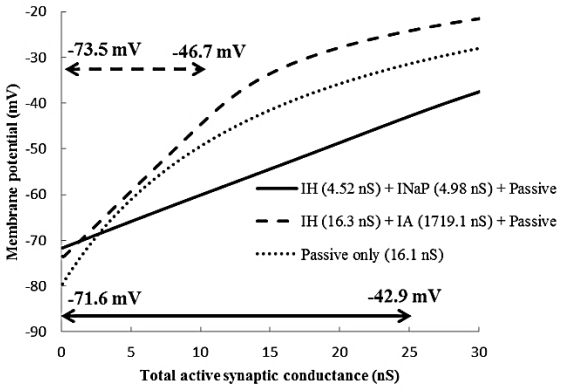

Figure 5b: Linearizing effect of combinations of dendritic voltage-gated ion channels on the membrane potential

A summary of the results is presented in Table 2. All three channels individually yielded linearity over different levels of synaptic conductance and over different ranges of membrane potential. None of the channels individually were capable of achieving linear synaptic integration over the entire voltage range between rest and threshold, although combinations could accomplish this. The total available channel conductance required for linearity was different for each type of channel, as expected based on the different activation and inactivation variables governing channel kinetics.

Table 2: Linearizing synaptic conductance values and voltage ranges

$\bar{g}_{NaP}$ (nS)	$\bar{g}_{A}$ (nS)	$\bar{g}_{H}$ (nS)	Linearizing synaptic conductance range (nS)	Voltage range of linear region (mV)
5.20	0	0	6.4 – 9.9	-55.0 – -44.0
0	2261.9	0	14.4 – 29.2	-58.4 – - 42.3
0	0	6.79	0 – 4.6	-72.1 – -60.5
4.98	0	4.52	0 – 9.9	-73.5 – -46.7
0	1719.1	16.3	0 – 24.9	-71.6 – -42.9

4. Conclusion

Previous research explored the issue of linear synaptic integration using time-independent, point-like dendritic models.[13,14] In an effort to move toward a more biologically realistic model, this research uses a time-dependent, one-compartment dendritic model to demonstrate that it is possible for a neuron to not only achieve linearity, but to do so over the entire voltage range between rest and threshold. This is of great interest, as it is over this range that neural information processing occurs. In the subthreshold voltage range, a neuron consolidates thousands of incoming synaptic inputs and then decides whether or not to initiate an action potential. Understanding this process is crucial to understanding neural information processing and transmission, as linear synaptic integration permits the neuron to evaluate each input individually, rather than becoming saturated at high levels of synaptic activity. This in turn allows for the complex network of connections that characterize the nervous system of higher-level organisms.

This work additionally shows that the neuron can select between multiple combinations of ion channels to accomplish linear synaptic integration over the full voltage range between rest and threshold. There are, however, trade-offs between these mechanisms. The I_H and I_{NaP} combination requires lower levels of synaptic activity but produces a stronger signal strength (depolarization per synapse). This would be desirable for synaptic signals coming from far away from the soma. In contrast, the I_H and I_A combination is seen to operate at higher levels of synaptic activity, but with a weaker signal strength. This would work well for synapses near the soma. Experimental data indicate that ion channel densities vary over different regions of the dendrite[15] and that conditions, such as the

resting membrane potential, are variable as well. The level of synaptic activity is also known to greatly influence the integrating properties of neurons.[16] The differences among dendritic ion channels explored here can be seen as necessary to facilitate different types of synaptic integration which take place over the spatial extent of the dendrite.

A passive dendrite displays nonlinear, saturating integration, which poses several issues for the integration process and limits the ability of a neuron to function under high levels of synaptic activity. The most important conclusion of this present research is that it is possible for a neuron to achieve linear synaptic integration over the entire voltage range between rest and threshold through the judicious use of voltage-gated channels.

Extensions of this work will consider other combinations of dendritic ion channels using multi-compartment models of a dendrite in an effort to deepen our understanding of the complex process of synaptic integration.

5. Acknowledgements

The author would like to thank Dr. Danielle Morel and Dr. Kevin Riggs for all of their help, as well as the Stetson University Physics Department and the Stetson University Dean's Fund for their financial support of this project.

6. References

1. Purves, D., Augustine, G.J., Fitzpatrick, D., Hall, W.C., LaMantia, A-S., McNamara, J.O., & White, L.E. (2008). *Neuroscience*, 4th Edition. Sinauer Associates. Sunderland, Mass.

2. Yuste, R., & Tank, D. W. (1996). Dendritic integration in mammalian neurons a century after Cajal. *Neuron*, **16**, 701–716.

3. Johnston, D. & Wu, S.M. (1995). *Foundations of Cellular Neurophysiology*. The MIT Press. Cambridge, MA.

4. Cash, S., & Yuste, R. (1999). Linear summation of excitatory inputs by CA1 pyramidal neurons. *Neuron*, **22**, 383–394.

5. DeAngelis, G. C., Ohzawa, I., & Freeman, R. D. (1993). Spatiotemporal organization of simple-cell receptive fields in the cat's striate cortex. II. Linearity of temporal and spatial summation. *Journal of Neurophysiology*, **69**, 1118–1135.

6. Carnevale, N.T., Hines, M.L. (2006). *The NEURON book*. Cambridge, UK: Cambridge UP. Additionally, see http://www.neuron.yale.edu/neuron/

7. Agrawal, N., Hamam, B. N., Magistretti, J., Alonso, A., & Ragsdale, D. S. (2001). Persistent sodium channel activity mediates subthreshold membrane potential oscillations and low-threshold spikes in rat entorhinal cortex layer v neurons. *Neuroscience*, **102**, 53–64.

8. Magistretti, J., & Alonso, A. (1999). Biophysical properties and slow voltage-dependent inactivation of a sustained sodium current in entorhinal cortex layer-II principal neurons. *The Journal of General Physiology*, **114**, 491–509.

9. Hoffman, D. A., Magee, J. C., Colbert, C. M., & Johnston, D. (1997). K^+ channel regulation of signal propagation in dendrites of hippocampal pyramidal neurons. *Nature*, **387**, 869–875.

10. Klee, R., Ficker, E., & Heinemann, U. (1995). Comparison of voltage-dependent potassium currents in rat pyramidal neurons acutely isolated from hippocampal regions CA1 and CA3. *Journal of Neurophysiology*, **74**, 1982-1995.

11. Migliore, M., Hoffman, D., Magee, J., & Johnston, D. (1999). Role of an A-type K^+ conductance in the back-propagation of action potentials in the dendrites of hippocampal pyramidal neurons. *Journal of Computational Neuroscience*, **7**, 5-15.

12. Magee, J. C. (1998). Dendritic hyperpolarization-activated currents modify the integrative properties of hippocampal CA1 pyramidal neurons. *The Journal of Neuroscience*, **18**(19), 7613–7624.

13. Morel, D., & Levy, W. (2009). The cost of linearization. *Journal of Computational Neuroscience*, **27**, 259-275.

14. Bernander, O., Koch, C., & Douglas, R. J. (1994). Amplification and linearization of distal synaptic input to cortical pyramidal cells. *Journal of Neurophysiology*,**72**, 2743-2753.

15. Migliore, M. & Shepherd, G. M. (2002). Emerging rules for the distributions of active dendritic conductances. *Nature Reviews Neuroscience*, **3**, 362-370.

16. Destexhe, A., Rudolph, M., & Pare, D. (2003). The high-conductance state of neocortical neurons *in vivo*. *Nature Reviews Neuroscience*, **4,** 739-751.