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RESEARCH ARTICLE

SYMMETRIC BIPHASIC PATTERNED STIMULATION OF RETINAL GANGLION CELLS

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ABSTRACT

Vision is the complex information processing which relies on the neural processing of the retina. Light incident on the tissue layer of retina which is sensible to light, produces a series of electrical and chemical synapses which creates the nerve impulses. The light passing the pupil gets focused by the lens presents an inverted image to the photoreceptors called the rods and cones. Neural signals from the rods and cones are processed in the retinal ganglion cells (RGC) whose axons form the optic nerve. These nervous messages are mostly associated with an electrical change known as the action potential. An all active Fohlmeister – Coleman – Miller (FCM) model with five nonlinear ion channels is modelled for the RGC, with an intracellular resistance (R_a), a membrane mechanism in parallel with a membrane capacitance and also a gap junction conductance (G) in between the compartments. The simulations were done for the above mentioned FCM neuron model and are analysed by stimulating with a constant dc current and also with a patterned biphase current stimulation with Inter Phase Gap (IPG). The action potential of the designed RGCs and the electrotonic current flowing across the boundaries were figured out for different patterned stimulating current and gap junction conductances.

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INTRODUCTION

Vision is a complex processing of information depending on a neuro-processor of the eye called the retina. When light passing through the pupil of the eye is focused by the lens onto the retina's sensory neuroepithelium which leads to the projection of a reduced, inverted image of the object onto the millions of photoreceptor cells called the rods and cones present in the outermost layer of the retina. These rods and cones convert the local luminance and the color patterns of the projected image into electrical signals as action potentials and chemical signals. Visual information from the retina's photoreceptors is compressed into electrical signals carried by the ganglion neurons, whose axons form the optic nerve. The optic nerve transmits the visual information via the lateral geniculate nucleus to the primary visual cortex of the brain (Zrenner 2002). Nerve cells communicate via a combination of electrical and chemical signals. Individually neurons are completely separated from one another by their outer cell membranes and cannot directly share the electrical or chemical signals (David M. Lovinger 2008). The exceptional are the electrical synapses, in which the ion-conducting pores made from proteins called connexins connect the intracellular compartments of adjacent neurons, allowing direct ion flow from cell to cell (Kandel *et al.*, 2000). Within the neuron, electrical signals driven by the charged particles allow rapid conduction from one end of the cell to the other end. The membrane potential changes and if it changes enough in the positive direction (i.e., depolarizes to threshold), an action potential is initiated. The RGCs remain intact even if there is blindness due to the loss of photoreceptor function. Even without consistent stimulation, the RGCs experience some transsynaptic degeneration. As a first attempt to explore the effect of the gap junction conductance over the retinal ganglion cell, a computational model has been developed for electric field stimulation of the RGC. No models have studied RGC with active membrane properties and gap junction conductance between the RGCs. The simulations are done to stimulate a neuron by extracellular electrical fields with active channels with gap junction conductances between the two cells. This stimulation study stands the first in the area of analyzing the effect of gap junction conductances between two cells with extracellular electrical stimulus.

The action potential of the designed retinal ganglion cell and the electrotonic current flows across the boundaries between the neighboring compartments. The action potentials for the RGC's and their membrane currents for different values of stimulating current I_{stim} and gap junction conductances are manipulated. The parameters of the symmetric biphasic stimulation current such as cathodic amplitudes, anodic

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amplitudes, cathodic durations, anodic durations, Interphase gap delay and frequency of the stimulating pulses are adjusted for an unfired RGC to get stimulated for the efficient spiking. If these superficial passing fibers were preferentially stimulated, groups of ganglion cells from large areas of the retina would be excited. Moreover, since the visual world is mapped onto the surface of the retina such that the area of stimulated RGC's corresponds spatially to the visual image perceived, this response is logical.

Action Potential

Nervous messages are mostly associated with an electrical change known as the action potential. This potential arises at a membrane which is situated between the axoplasm, medium inside the axon and the external medium of the neurons (AL Hodgkin and AF Huxley 1939). The description of electrical phenomena in nerves was problematic and so well analysed. Galvani (Galvani 1791) noticed that the legs of dissected frogs made active movements when their nerves were connected to a battery. He called this phenomenon "animal electricity". Later, Volta (1900) stated that the nerve pulses are electrical conduction phenomena. Helmholtz (1852) performed the first measurements of the propagation velocity of nerves. Ostwald (1890) and others developed the theory of osmosis and electrochemistry, and attempts for relating the flux of ions through the nerve membranes to the propagating action potential (Bernstein 1912). This finally resulted in the model by Hodgkin and Huxley (Hodgkin and Huxley 1952) from 1952 that is the presently accepted model for the nerve pulse which relies on ionic currents and the membrane capacitance. In 1976, Neher and Sakmann described these channels microscopically (Neher and Sakmann 1976). In 1998, MacKinnon and collaborators crystallized the potassium channel and suggested a pathway for the potassium through a pore within the protein (Doyle *et al.,* 1998). Thus, the Hodgkin-Huxley model seemingly finds support in independent experiments which is a purely electrical description based on conductors (ion channels and the cytosol of the nerve axon) and on a capacitor, which is the lipid membrane.

MATHEMATICAL MODELING OF RGC

Millions of people suffer from retinitis pigmentosa, a type of blindness characterized by photoreceptor degeneration (Greenberg *et al.,* 1999), (Wyatt and Rizzo 1996; Perlman *et al.,* 1996; Roush 1995). Visual information processing takes place in various locations of the cortex, and surgical access of the brain imposes its own risks, also the complexity in the connections of photoreceptors and technical challenges in the treatment all which frames the limitation. The retinal ganglion cells remain intact even if there is blindness due to the loss of photoreceptor function. Even without consistent stimulation the retinal ganglion cells experience either some or no transsynaptic degeneration (Humayun *et al.,* 1996). The impulse-encoding mechanism of intact retinal ganglion cells recently was explored on the basis of a series of models (Fohlmeister and Miller 1997), (Fohlmeister and Miller 1997), the five nonlinear ion channels of which were identified from voltage-clamp data (Kaneda and Kaneko 1991; Kaneda and Kaneko 1991b; Lasater and Witkovsky 1990; Lipton and Tauk 1987; Lukasiewicz and Werblin 1988). There is some evidence that such approach also benefit patients with severe age-related macular degeneration (AMD) (Greenberg *et al.,* 1995). Though these patients are blind, their ganglion cells are functioning and transmit the retinal input to the brain (Flannery *et al.,* 1989; Stone *et al.,* 1992; Potts *et al.,* 1968; Miyake *et al.,* 1981; Kato *et al.,* 1983). In this research work, a model has been developed for electric field stimulation of the RGC. The responses of the axons or somas for the electrical stimulation are analysed by many models (Coburn 1989). Mostly models have represented the cell membrane as a resistor and capacitor connected parallel. Rubinstein and Spelman have explained the electrical stimulation of a passive model for unmyelinated axons (Rubinstein and Spelman 1988). Plonsey and Barr performed the analysis including Hodgkin–Huxley active membrane properties (Plonsey and Barr 1995). The analysis of a passive model of cortical pyramidal cells model for extrinsic electrical stimulation was done in 1975 by Hause (Hause 1975). No models have studied the RGC with active membrane properties with gap junction conductance.

The RGC is represented by dividing the cell into compartments as described by Rall (1977). Stimulation studies are experimented on the RGC by stimulating it with an external electric field. This stimulation study stands the first in the area of analyzing the effect of gap junction conductances between two cells with extracellular electrical stimulus.

A. FCM models

Neuron was written using a fully implicit method of integration i.e. backward Euler method of integration. The value for membrane capacitance, C_m ($1\mu F/cm^2$), membrane resistance, R_a ($50{,}000\Omega cm^2$) (Coleman and Miller 1989), and cytoplasmic resistance ($110\Omega cm$) (Coleman and Miller 1989). These values are assumed to be uniform throughout the cell. The simulations were modelled at room temperature (22°C) (Rattay 1990). Each compartment is modelled with an intracellular resistance (R_a), a membrane mechanism in parallel with a membrane capacitance (C_m) and a gap junction conductance (G) in between the compartments as shown in Fig.1. The membrane mechanism model were applied an all active model (FCM) with five nonlinear ion channels distributed at varying densities.

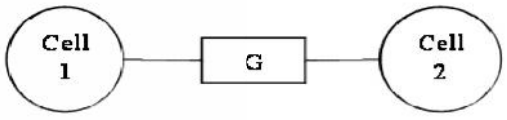

Fig. 1. Model representing connections between two neuron cells

The membrane mechanisms were modeled in parallel with a leak conductance which consisted of a battery in series with a conductance. The passive membrane mechanism consisted of a simple conductance. The active membrane mechanisms consisted of variable conductances in series with batteries. The conductances were defined by the Hodgkin–Huxley formulations for each ionic channel. The batteries were defined

by the corresponding reversal potential of the ion they represent. An all active model (FCM) with five nonlinear ion channels was modeled. The linear passive mechanism reduces each cell membrane to a simple parallel RC circuit with a leak. The leak conductance was modeled as a battery at 70mV in series with a conductance of 20μS/cm^2. The membrane potential everywhere was initialized to a resting potential of -70mV. The HH mechanism is the classic nonlinear description of unmyelinated axons by Hodgkin and Huxley (Hodgkin and Huxley 1952) — a leak conductance, sodium and potassium channels ($\bar{g}_{Na}$=120mS/cm^2, E_{Na} =50mV, $\bar{g}_K$ = 36mS/cm^2, E_K = -77mV, $\bar{g}_l$ = 0.3mS/cm^2, E_l = -54.3 mV). The FCM model is a complex five channel model based on work by (Fohlmeister *et al.*, 1990; Fohlmeister and Miller 1995; Fohlmeister and Miller 1997). It includes the following conductances: $\bar{g}_{Na}$ (a sodium conductance), $\bar{g}_{Ca}$ (a calcium conductance), $\bar{g}_K$ (a delayed rectifier potassium conductance), $\bar{g}_A$ (an inactivating potassium conductance), and $\bar{g}_{K,Ca}$ (a non inactivating calcium activated potassium conductance) (Fohlmeister *et al.*, 1990). All channels are modeled as simple voltage - gated conductances except $\bar{g}_{K,Ca}$, which is modeled as a calcium - gated conductance. This unique combination of channel kinetics which best emulated the firing pattern of ganglion cells (Fohlmeister *et al.*, 1990). The $\bar{g}_{K,Ca}$ served to shape the finer properties of the action potential including the ability to produce slow repetitive firing which is impossible using the Hodgkin–Huxley channels completely. The model for membrane potential takes the familiar Hodgkin/Huxley form (Fohlmeister *et al.*, 1990):

$$C_m \frac{dE}{dt} = -\bar{g}_{Na} m^3 h (E - E_{Na}) - \bar{g}_{Ca} c^3 (E - E_{Ca}) - \bar{g}_K n^4 (E - E_K) - \bar{g}_A a^3 h_A (E - E_K) - \bar{g}_{K,Ca} (E - E_K) \quad (1)$$

Where the rate constants for *m*, *h*, *c*, *n*, *a*, and h_A all solve the first order kinetic equation (40):

$$\frac{dx}{dt} = -(\sim_x + \ _x) \cdot x + \sim_x \quad (2)$$

B. Electrotonic current

The instantaneous membrane potential varies in the compartments from other and also the electrotonic current across the boundaries between them. Except the injected stimulus current into the compartment, there are no current sources or sinks within the compartments. So to maintain the conservation of current, the sum of all currents flowing across the entire boundary of any individual compartment must always be zero or equal to I_{stim}. So the net electrotonic current is the residual current that equals in magnitude of the sum of all instantaneous membrane currents, including ion channel, capacitive, and leak deducing I_{stim}.

C. Stimulation Current

The neuron cells are stimulated with a constant dc current and are also analyzed with a patterned biphase current stimulation. An intracellular stimulation current I_{Stim}, was a symmetric bi-phasic current injection as shown in Fig. 2. The pattern stimulation current consists of two phases: the cathodic phase and the anodic phase. The durations of the cathodic and anodic phases are ω- and ω+ respectively. The Inter Phase Gap (IPG) delays; separates the pulses and also avoids the reversal of the earlier physiological effect of the previous pulse (Humayun *et al.*, 1996). An increasing interphase gap leads to a decrease in the charge required to cause a neuron to spike (Fohlmeister and Miller 1997).

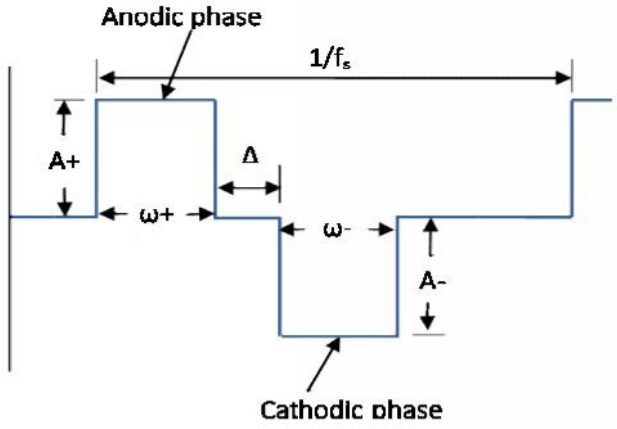

Fig. 2. The biphasic stimulation current waveform

RESULTS

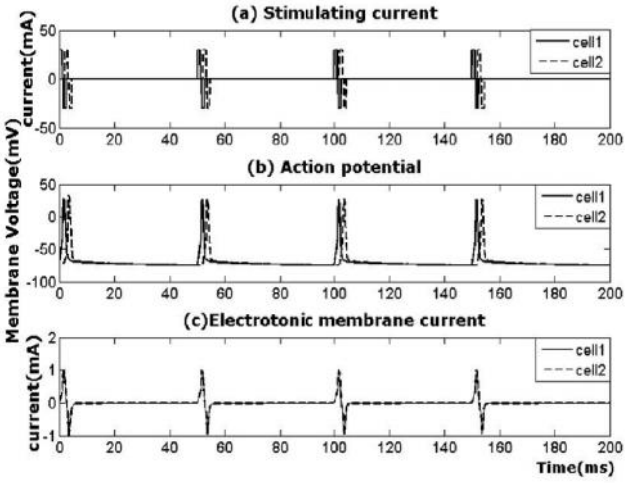

Fig. 3. (a) Symmetric biphasic stimulating current with Δ = 0.5ms (b) Action potential evoked from two RGCs. (c) Electrotonic current flowing across the boundaries between the neighbouring compartments.

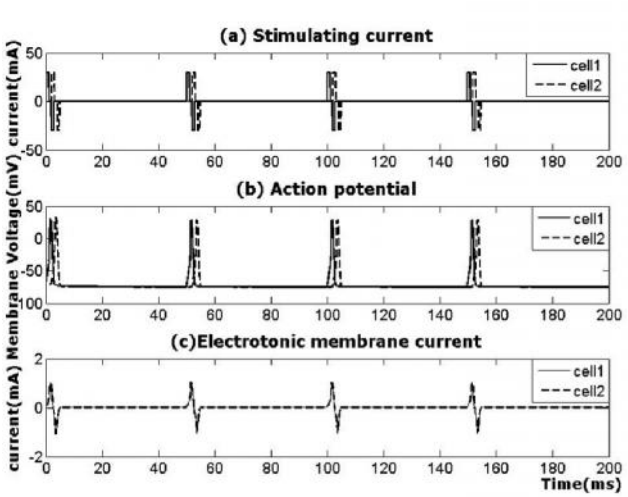

Fig. 4 (a) Symmetric biphasic stimulating current with Δ = 0.9ms
(b) Action potential initiated from the two RGCs by increasing the IPG.
(c) Electrotonic current flowing across the boundaries.

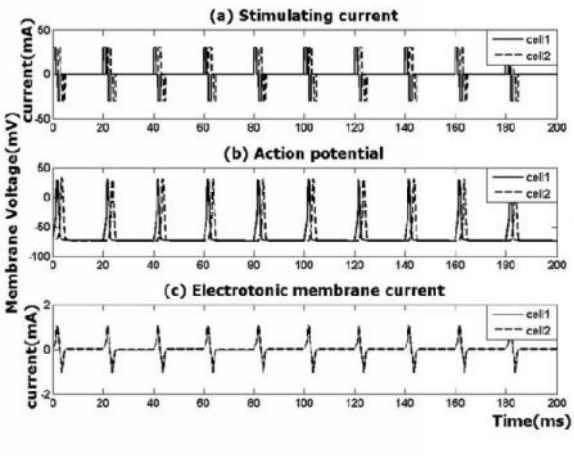

Fig. 5 (a) Symmetric biphasic stimulating current
(b) Action potential spikes from the two RGCs by increasing the simulating current pulse frequency to 50Hz.
(c) Electrotonic current flowing through the boundaries.

DISCUSSION

The action potential of the designed neuron cell and the electrotonic current flows across the boundaries between the neighboring compartments were analysed for the constant dc stimulus current bounding up to 20mA (Padma priya *et al.*, 2013). Though the stimulating current is applied continuously the action potential is provoked in the neurons only when the RGC crosses the threshold and it is not generated in the refractory period. The spike potentials for the cells were inspected for different values of gap conductances (G) ranging from $1x10^{-30}$mS/cm^2 to 1.4mS/cm^2 and stimulating current I_{stim} up to 10mA which leads to the observation, that when the amplitude of I_{stim} is increased the spiking rate of the neuron increases (Padma priya *et al.*, 2013). The increasing conductance of the cells increases the spiking rate of the neuron and gets collapsed for higher values of G greater than 1 and the current through the membrane increases (Padma priya *et al.*, 2013). The Fig.3 manifests the symmetric biphasic stimulation current with the pulse frequency of 20Hz i.e. a pulse for each 50ms and the corresponding action potential developed. The frequency can bound from 20Hz to 100Hz (Padma priya *et al.*, 2013).

A symmetric biphasic stimulation current with the anodic and cathodic phase duration, ω+ and ω– is 1ms and the Anodic amplitude (A+) of 30mA and Cathodic amplitude (A–) with –30mA is applied with an inter phase delay (Δ) as 0.5ms as presented in Fig. 3(a). The action potential originated with such a symmetric biphasic stimulation current and the electrotonic current produced in the boundaries between the neighboring compartments is depicted in Fig. 3(b), and 3(c) respectively. The fig.4 narrates the action potential evoked in Fig. 4(b) and the electrotonic current developed in Fig. 4(c) with the biphasic stimulating current with the pulse duration i.e. Anodic phase duration, ω+ = 1ms, and Cathodic phase duration, ω– = 1ms, Δ = 0.9ms as in fig. 4(a). The Fig. 5 depicts the action potential spiking of the RGCs and the electrotonic current initiated in Fig. 5(b) and Fig. 5(c) correspondingly for the symmetric biphasic stimulating current by increasing the pulse frequency to 50Hz as in 5(a). From the stimulation studies, it is perceived that the parameters of the symmetric biphasic stimulation current such as cathodic amplitudes, anodic amplitudes, cathodic durations, anodic durations, Interphase gap delay and frequency of the stimulating pulses can be adjusted so that the stimulating current can make an unfired RGC to get stimulated for the efficient spiking.

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