ISSN: 0976-3031

Available Online at http://www.recentscientific.com

International Journal of Recent Scientific Research
Vol. 4, Issue, 10, pp.1538-1544, October, 2013

International Journal of Recent Scientific Research

RESEARCH ARTICLE

COMPUTATIONAL STUDY ON THE EFFECT OF PATTERNED ELECTRICAL STIMULATION IN RETINAL GANGLION CELLS

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ARTICLE INFO

Article History:

Received 17th, September, 2013
Received in revised form 27th, September, 2013
Accepted 13th, October, 2013
Published online 28th October, 2013

Key words:

Action potential, Biphasic stimulation current, FCM model, Inter phase gap, Retina, Retinal Ganglion cell, synapses.

ABSTRACT

Vision is the complex information processing which depends on the neural processing of the retina. The retina is a layer of tissue sensible to light. Light incident on the retina produces a series of electrical and chemical synapses which creates the nerve impulses. The retina has multi layered neurons interconnected by the synapses. 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 is a computational model with five nonlinear ion channels is modeled for the electric field stimulation of the RGC, with an intracellular resistance (R_a) and a membrane mechanism in parallel with a membrane capacitance and also a gap junction conductance in between the compartments. The simulations were done for the above mentioned FCM neuron model and are analyzed 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 RGC and the electrotonic current flowing across the boundaries were figured out for different values of stimulating current and gap junction conductances.

INTRODUCTION

Vision is a complex processing of information depending on a neuro-processor of the eye called the retina. Vision is initiated, 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. The cones provide the chromatic vision or photopic vision i.e. the three types of pigment (color) information with a high spatial resolution, and the rods are highly sensitive to light and required for achromatic vision or scotopic vision (one type of pigment) with less spatial resolution in dim light. Rods responses to light even from a single photon whereas cones require tens to hundreds of photons to become activated. 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. These signals activate the complex circuit of retinal neurons comprising of horizontal cells, bipolar cells, amacrine cells, and ganglion cells. The nerve pulses are electrical conduction phenomena. When one neuron receives input from another neuron, its membrane potential changes and if it changes enough in the positive direction (i.e., depolarizes to threshold), an action potential is initiated. 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 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. The responses of the axons or somas for the electrical stimulation are analyzed by many models. No models have studied RGC with active membrane properties and gap junction conductance. This proposed approach was to represent a RGC by dividing the cell into compartments. The simulations are done to stimulate a neuron by extracellular electrical fields with active channels with gap junction conductances between the two cells. Each compartment is modeled with an intracellular resistance (R_a) and a membrane mechanism in parallel with a membrane capacitance and a gap junction conductance in between the compartments (Fig.1). Fohlmeister-Coleman-Miller model (FCM model), an all active model 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 instantaneous membrane potential varies from each compartment to the other and also the "electrotonic current," which is the current flowing across the boundaries between the neighboring compartments. The action potential of the designed retinal ganglion cell and the electrotonic current flows across the boundaries between the neighboring compartments is shown in Fig 3. The action potentials for three RGC's and their membrane currents for different values of stimulating current I_{stim} and gap junction conductances are manipulated.

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Neuron Communication of Eye Through Action Potential

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, 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.

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 (Hodgkin and Huxley, 1939). The description of electrical phenomena in nerves was problematic and so well analyzed. 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 (Volta, 1900) stated that the nerve pulses are electrical conduction phenomena. Helmholtz (Von Helmholtz, 1852) performed the first measurements of the propagation velocity of nerves. In the second half of the 19th century Ostwald (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 the context of their model, the conductance displays rather complex voltage and time dependences that enter the differential equation via a set of empirical parameters. 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. The model by Hodgkin and Huxley 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 Modelling Of Action Potential

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). The treatment depends on the use of sensory modalities with audition and touch to compensate the loss of vision and experimentation has been done in grafting functioning photoreceptors into the retina. Due to the complexity in the connections of photoreceptors and technical challenges in the treatment, it becomes unfeasible and so few portions of the visual cortex are stimulated as an alternate solution (Humayun *et al*., 1996). Visual information processing takes place in various locations of the cortex, and surgical access of the brain imposes its own risks 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, 1997a, b), the five nonlinear ion channels of which were identified from voltage-clamp data (Kaneda, M. and Kaneko, A. 1991a, b), (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 analyzed 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 (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.

FCM Model

Neuron was designed using a fully implicit method of integration i.e. backward Euler method of integration. Each compartment in the simulation was modeled with an intracellular resistance (R_a) and a membrane mechanism in parallel with a membrane capacitance and a gap junction conductance (G) in between the compartments. Several constants were specified based on whole-cell recording data which included the value for membrane capacitance ($1\mu F/cm^2$), membrane resistance ($50{,}000\Omega cm^2$) (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 modeled at room temperature (22°C) (Rattay, 1990). Each compartment is modeled with an intracellular resistance (R_a) and a membrane mechanism in parallel with a membrane capacitance and a gap junction conductance (G) in between the compartments. 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 -70 mV in series with a conductance of 20μS/cm^2. The membrane potential everywhere was initialized to a resting potential of -70 mV. 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} = 50 mV, = 36 mS/cm^2, E_K = -77 mV, $\bar{g}_l$ = 0.3 mS/cm^2, E_l = -54.3 mV). The FCM model is a complex five channel model based on work by Fohlmeister *et al.* (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. It was this unique combination of channel kinetics which best emulated the firing pattern of ganglion cells (Fohlmeister *et al.*, 1990). The calcium and potassium conductances 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):

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

Where the rate constants for *m, h, c, n, a,* and h_A all solve the first order kinetic equation (Plonsey and Barr, 1988):

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

Electrotonic Current

The instantaneous membrane potential varies from each compartment to the other and also the "electrotonic current," flowing across the boundaries between the neighboring compartments. Except the injected stimulus current into the compartment, there are no current sources or sinks within the compartments. So in order 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}. Each compartment's boundary consists of its plasma membrane and its intercompartmental interfaces i.e. the cytoplasmic cross sections across which all the currents are electrotonic. 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}. With regard to the algebraic sign, we define positive electrotonic current as the net positive charge flowing into the compartment from its neighboring compartments. The positive Na^+ ions flowing into the compartment produce the negative Na current which is counter to the convention for membrane currents.

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 bi-phasic current injection as shown in Figure 2. The pattern stimulation current consists of two phases: the cathodic phase and the anodic phase. The duration 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, 1997a).

RESULTS

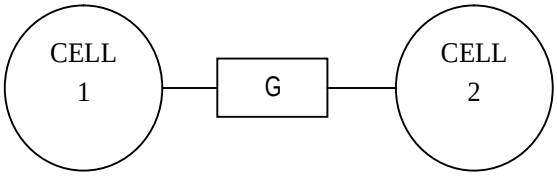

Fig.1 Model representing connections between two neuron cells

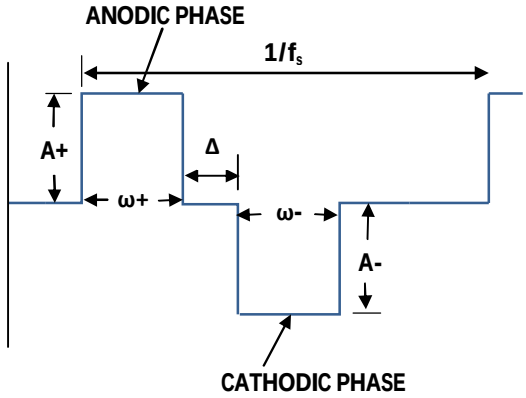

Fig.2 The biphasic stimulation current waveform

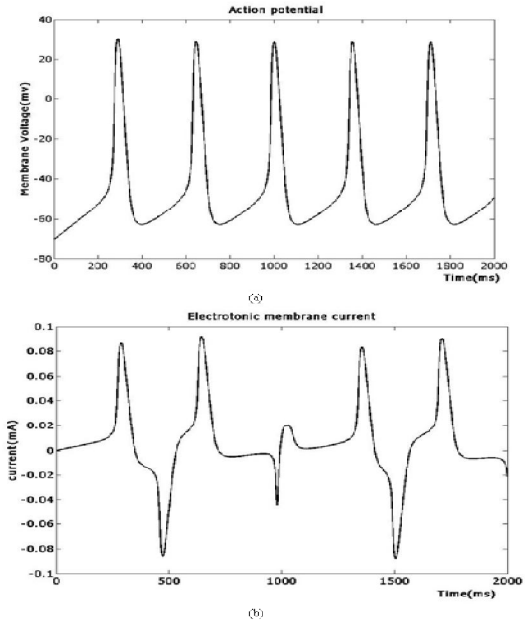

Fig. 3 (a) Action potential of a neuron cell
3. (b) Electrotonic current flowing across the boundaries between the neighboring compartments.

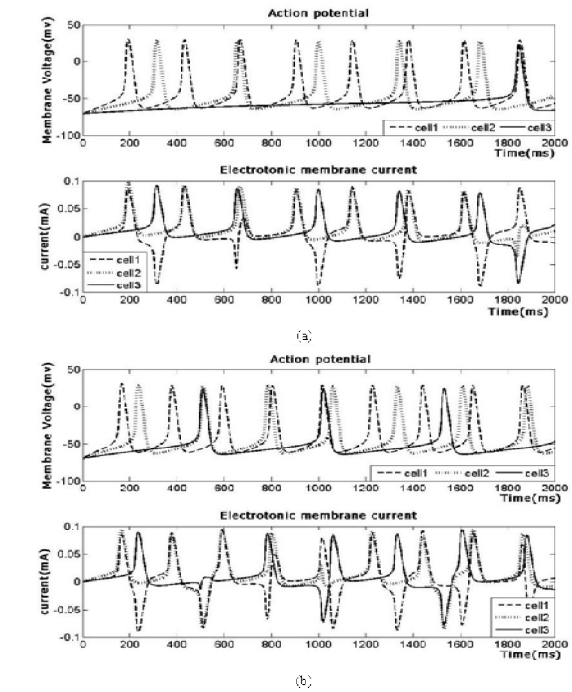

Fig.4 Action potential of a cell and Electrotonic current flowing across the boundaries between the neighboring compartments for different values of stimulating current I_{stim}.
(a) I_{stim} = [5 3 1], and G_1, G_2= 0.001.
(b) I_{stim} = [6 4 2], and G_1, G_2= 0.001.

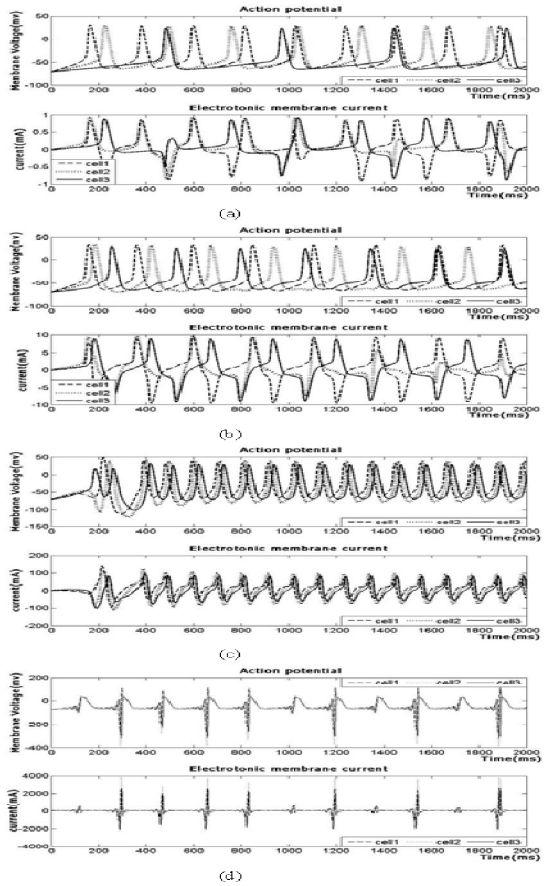

Fig.5 Action potentials of three cell compartments and the electrotonic current flowing through their cell membranes for the given values of stimulating current I_{stim} = [6 4 2] and different values of gap conductances with G1= G2. (a)G_1, G_2= 0.01, (b) G_1, G_2= 0.1, (c) G_1, G_2= 1, (d) G_1, G_2= 10.

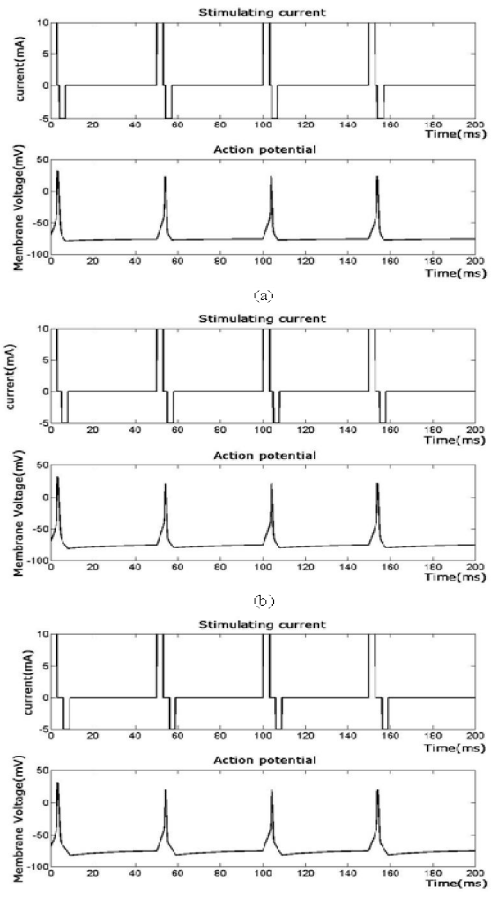

Fig.6 Biphasic stimulating current and the action potential evoked by varying the IPG (a) Δ = 1ms (b) Δ = 2ms(c) Δ = 3ms.

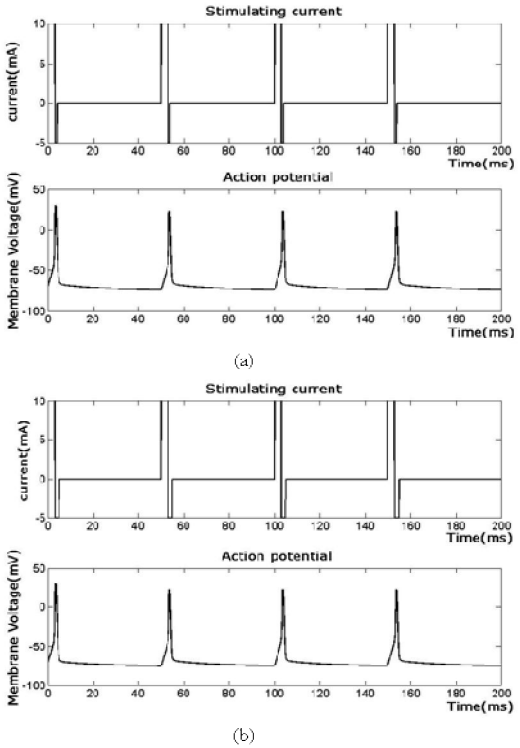

Fig.7 Biphasic stimulating current and the action potential produced with non-uniform pulse duration.

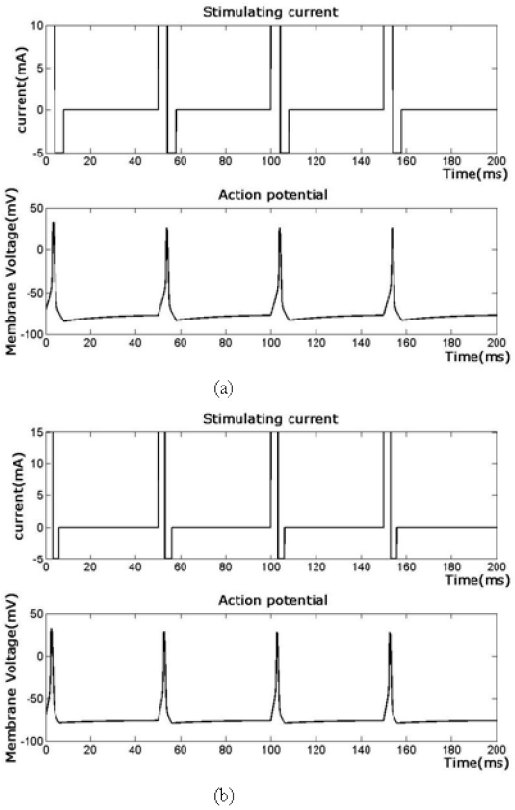

Fig.8 Biphasic stimulating current and the action potential originated by increasing the pulse duration, cathodic pulse amplitude respectively.

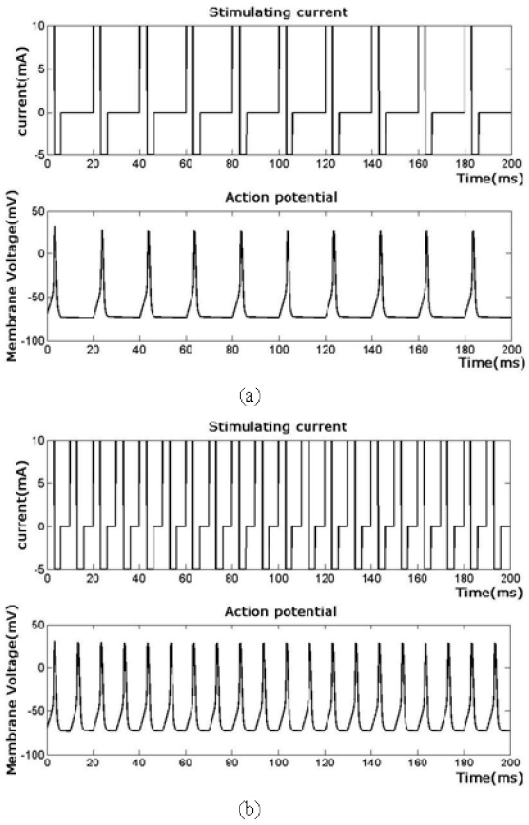

Fig.9 Biphasic stimulating current and the action potential developed by increasing stimulating frequency.

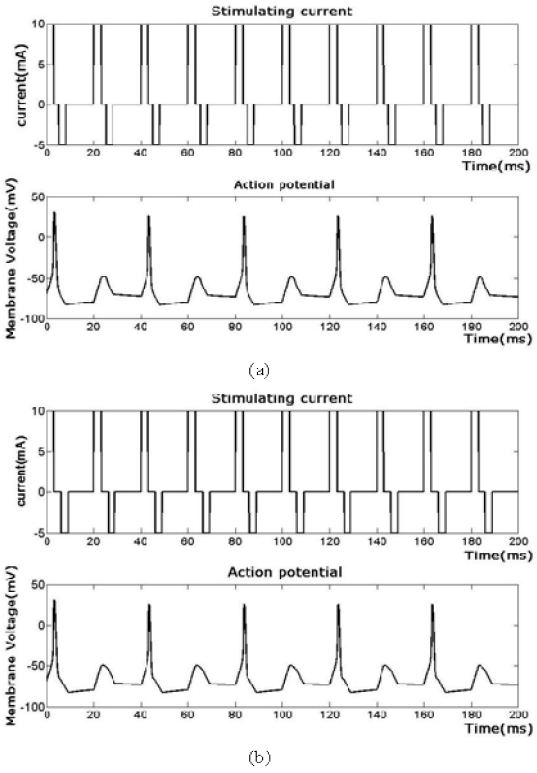

Fig.10 Biphasic stimulating current and the action potential initiated by increasing stimulating amplitude and IPG for 50Hz frequency pulse.

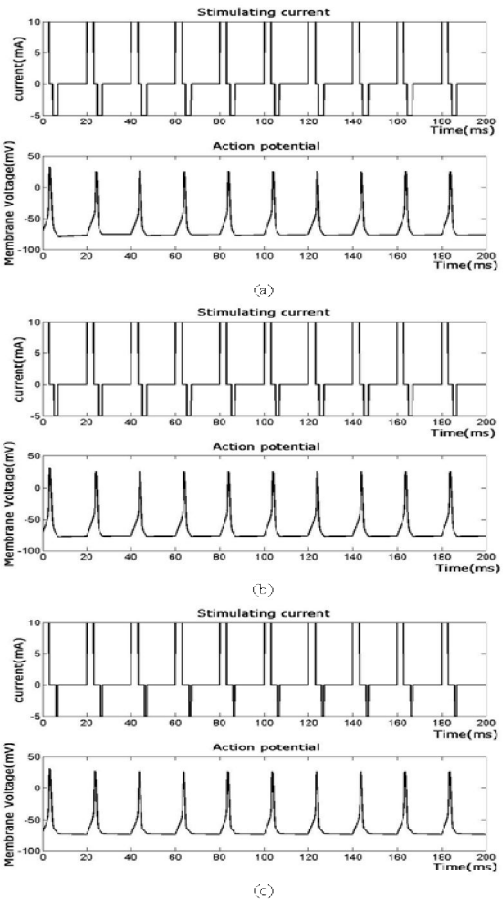

Fig.11 Biphasic stimulating current and the action potential generated by increasing stimulating amplitude and IPG.

DISCUSSION

The action potential of the designed Retinal Ganglion Cell (RGC) and the electrotonic current flows across the boundaries between the neighboring compartments is illustrated in Fig.3. (a) and 3. (b) respectively. Though the stimulating current is applied continuously the action potential is provoked in the neurons, only when the nerve cell crosses the threshold and also it is not generated in the refractory period of the neurons. The spike potentials of the three RGCs are depicted in Fig.4 with equal gap conductances G_1, and G_2 = 0.001 between the cells and with different values of stimulating current, I_{stim} = [5 3 1], and I_{stim} = [6 4 2] in Fig. 4(a) and Fig. 4(b) respectively which leads to the observation that when the amplitude of Istim is increased the spiking rate of the neuron increases. In Fig. 5, the conductances of the membrane are increased and the action potential and the membrane currents are sketched. 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. The Fig.6 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 anodic and cathodic phase duration ω+ and ω- is 3ms. The Anodic amplitude, A+ of 10mA and Cathodic amplitude, A- of -5mA is applied with an inter phase delay, Δ as 0ms. The action potential originated with such a biphasic stimulation current with the IPG for 1ms, 2ms and 3ms is presented in Fig. 6(a), 6(b), and 6(c) respectively. The fig.7 narrates the action potential produced with the biphasic stimulating current with non-uniform pulse duration i.e. Anodic phase duration, ω+ = 3ms, and Cathodic phase duration, ω- = 1ms in fig. 7(a) and the Cathodic phase duration, ω- = 2ms in fig. 7(b). The Fig. 8 pictures the action potential initiated and the biphasic stimulating current by increasing both the anodic and cathodic pulse duration to 4ms in 8(a), and by increasing the Anodic pulse amplitude to 15mA in Fig. 8(b). The Fig. 9 characterizes the spiking of the neuron for the pulse frequency 50Hz and 100Hz in Fig. 9(a) and 9(b) respectively. The spiking of the neuron with the IPG as 2ms and 3 ms are presented in Fig. 10(a) and 10(b) respectively. The Fig. 10 reveals that the action potential is not initiated for certain pulses in the biphasic current waveform with 50Hz frequency, anodic phase duration, ω+ = 3ms, anodic pulse amplitude, A+ = 10mA, cathodic phase duration, ω- = 3ms, and cathodic pulse amplitude, A- = -5mA. These parameters of the biphasic stimulation current could be adjusted to develop the action potential. The stimulating current parameters are adapted as, Cathodic phase duration, ω- = 2.5ms, 2ms, 1ms, and Inter Phase Delay, Δ = 1.5ms, 2ms, 3ms, so as to provoke the action potential and is represented in Fig. 11(a), 11(b) and 11(c) respectively. The stimulation pattern can be changed and the observation studies may be extended and is in current progress.

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