Effect of L and T - type Calcium Channels in Retinal Ganglion Cells stimulation

K. Padma priya, J. Krishnan and R. Malathi

***Abstract*—**Visual system compose of image-forming pathways in which the retinal ganglion cells (RGCs) depend on the photoreceptors, rods and cones whereas non-image-forming pathways involves intrinsically photosensitive retinal ganglion cells (ipRGCs), which express the photopigment melanopsin. 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 FCM RGC model and the ionic currents are analysed for single RGC and two RGCs with gap junction conductance in between them. By valuing up the vitality of the calcium ions in RGC apoptosis of diabetic retinopathy and glaucoma patients, the model was adapted by including the L- and T-type calcium channels and the ionic currents in the RGCs were analysed for single RGC and two RGCs with the effects of gap junction conductance.

***Keywords*—**Action potential, Calcium channels, FCM model, Ionic currents, Retinal Ganglion cell.

I. Introduction

PEOPLE suffering from retinitis pigmentosa, a type of blindness characterized by the degeneration of photoreceptors, which are primarily responsible for the sensing of light [1]–[4]. Visual information processing is at various locations of the cortex, and surgical access of them imposes its own risks, also the complex interconnections of photoreceptors and technical challenges in the treatment, all which frames the limitation. The retinal ganglion cells (RGCs) remain intact though there is blindness due to the loss of photoreceptor function [5]–[7]. Transsynaptic degeneration is in the RGCs without sufficient stimulation [8].

Along with the rod and cone photoreceptors in the image-forming pathways, a third type of photoreceptor for the non-image-forming pathways has been revealed in the mammalian retina, namely intrinsically photosensitive retinal ganglion cells (ipRGCs) expressing the photopigment melanopsin [9], [10] and are less than 2% of the overall RGC population in mammals [10]–[13]. These ipRGCs de-polarize in response to light [9] and form an electrically coupled network in the ganglion-cell layer [14]. In adult retinae, 56% of the light responses were due to electrical coupling[15]. The impulse-encoding mechanism of intact RGCs was explored on the basis of a series of models[16], [17]. The presence of five nonlinear ionic intrinsic membrane current channels were identified from voltage-clamp data[18]–[22]. Such approach benefitted patients with severe age-related macular degeneration(AMD)[23] and retinitis pigmentosa(RP).

Though these patients are blind, their ganglion cells are functioning and transmit the retinal input to the brain[24]–[28] due to the presence of actively functioning inner retina with ipRGCs[29] which are responsible for the non-imaging functions like circadian-clock resetting, pupillary constriction, and other non-image-forming photic responses[30]–[33], and also a part of imaging functions too in neonatal stage[15]. The ipRGC subtypes contribute differently to non-image and image-forming functions[34]. It has been explored that by electrically stimulating the surviving neurons with a retinal prosthetic, vision could be partially restored[35]–[37]. Trials with human has succeeded[38]–[40]. Unlike the hyperpolarizing light responses of rods and cones, light depolarizes ipRGCs and induces action potential firing [9], [13], [41]. If these superficial passing fibers were preferentially stimulated, groups of ganglion cells from large areas of the retina would be excited.

The responses of the axons or somas for the electrical stimulation are analysed by many models [42]. 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[43]. Plonsey and Barr performed the analysis including Hodgkin–Huxley active membrane properties[44]. Single-compartment models such as the classic Hodgkin-Huxley model [45] focus on how its various ionic currents contribute to subthreshold behavior and spike generation[46]. These models have led to a quantitative understanding of many dynamical phenomena including phasic spiking, bursting, and spike-frequency adaptation[47]. The analysis of a passive model of cortical pyramidal cells model for extrinsic electrical stimulation was done in 1975 by Hause [48]. The RGC is represented by dividing the cell into compartments as described by Rall [49]. No models have studied the RGC with active membrane properties with gap junction conductance

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between the RGCs.

In this research work, a model has been developed for electric field stimulation of the RGC as an all active Fohlmeister–Coleman–Miller(FCM) model with five non-linear ion channels. Studies are experimented on the RGCs by varying the gap conductances between the cells and the gap conductances of the ionic channels of the RGCs. This stimulation study stands the first in the area of analyzing the effect of gap junction conductances between two cells.

The voltage gated calcium channels (VGCCs) are divided into two major classes of Ca^{2+} channels based upon the membrane potential that opens them. There are low-voltage activated (LVA) and high-voltage activated (HVA) channels. These channels can be further divided into T-type which is the LVA and L, N, P/Q, and R type which are all HVA. The voltage clamp data details the presence of low–threshold, Low voltage activating (LVA), T–type Calcium current($I_{Ca,T}$) [50]–[52] and a high–threshold, high voltage activating (HVA), L–type Calcium current($I_{Ca,L}$) [16], [51]–[53]. The voltage-gated Ca^{2+} currents were exclusively of a LVA type at the embryonic stage E17, composed of HVA and LVA at the postnatal stage, and solely of a HVA type in adult RGCs[54].

In ipRGCs, the depolarization of the membrane potential, resulting in the activation of voltage gated Na^{+} channels (VGNCs). The Na^{+} flux through VGNCs during action potential firing makes the membrane further depolarized, leading to the activation of L-type VGCCs. The Ca^{2+} influx and most of the Ca^{2+} signal in the ipRGCs was the result of the depolarization-induced opening of VGCCs[55]. Spontaneous electrical activity has been described as rhythmic bursts of action potentials that spread between adjacent cells and produce transient elevations in internal calcium concentration [56]. Three discrete classes of light-induced Ca^{2+} change were observed in ipRGCs: Sustained response, Transient response, Repetitive firing without recovery[14].

Glaucoma is an optic neuropathy, characterized by selective death of RGCs and a progressive loss of vision. Elevated intraocular pressure (IOP) is the most important risk factors for developing glaucoma [57]. Increased IOP may lead to reduced blood flow in the capillaries of the optic nerve, because of a irregular blood flow in the optic disk. Astrocytes also induce vasoconstriction of regional small capillaries by the release of vasoactive peptides during stress, associated to increased intracellular Ca^{2+} [58]. This isquemic condition and the depletion of energy stores affects the axonal Na^{+}/K^{+} ATPase, that would increase intracellular Na^{+}, leading to an overload of intracellular Ca^{2+} due to a greater Na^{+}/Ca^{2+} exchanger activity. This vascular initial damage and mechanical damage due to compression of the axons because of increased intraocular pressure estimulate axon degeneration [59], which leads to RGC's death through a final common pathway (apoptosis) [60], [61].

Patients with diseases of the inner retina result in RGC death (e.g., glaucoma) are at particular risk and should be counseled about the effects of ipRGCs loss[29]. Chronic progressive loss of RGCs is considered biphasic. The damage is initiated by a primary injury associated with elevated IOP, cardiovascular risk factors, age, vasospasm etc.. There's a delayed (secondary) degeneration of partially damaged neurons as an outcome of a hostile environment created by damaged neurons. The high levels of potassium and calcium ions in the RGC is also one of the main factor for the secondary neuronal degeneration [55],[62]. Calcium channel blockers are useful in the management of low-tension glaucoma [63],[64].

RGCs undergo apoptosis early in diabetic retinopathy via N-methyl-D-aspartate (NMDA) receptor overstimulation. The RGC death mediated by overstimulation of NMDA subtype of glutamate receptor leads to excessive levels of intracellular calcium[65]. The increase in intracellular Ca^{2+} acts as a second messenger that cascades leading to cell death[66].

The simulations are done to stimulate a neuron by extracellular electrical fields with active channels with gap junction conductances between the two cells. Later the calcium channels are modified by including the L and T-type calcium channels valuing their crucial roles in RGCs for glaucoma patients.

II. FCM Model

Neuron was written using a fully implicit method of integration i.e. backward Euler method of integration. 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.

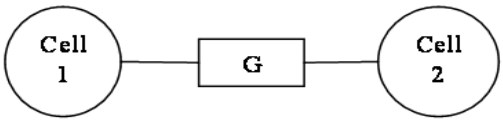

Fig. 1 Model representing connections between two neuron cells

The passive membrane mechanism consisted of a simple conductance. The active membrane mechanisms consisted of variable conductances in series with batteries for each ionic channels. 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 membrane potential everywhere was initialized to a resting potential of -70mV[67].

The FCM model is a complex five channel model based on work by Fohlmeister *et al.* [68]–[70]. It includes the following maximal conductances: $\overline{g}_{Na}$ (a sodium conductance), $\overline{g}_{Ca}$ (a calcium conductance), $\overline{g}_{K}$ (a delayed rectifier potassium conductance), $\overline{g}_{A}$ (an inactivating potassium conductance), and

$\bar{g}_{K,Ca}$ (a non inactivating calcium activated potassium conductance) [68]. 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 [68]. 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[68]:

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

where the values of maximal conductance and the reversal potentials of sodium channels, calcium channels, delayed rectifier potassium channels, A type potassium channels, Ca-activated potassium channels, are given respectively $\bar{g}_{Na}$=50mS/cm^2, E_{Na}=50mV, $\bar{g}_{Ca}$=2.2mS/cm^2, E_{Ca}=70mV, $\bar{g}_K$=12mS/cm^2, $\bar{g}_{K,A}$=36mS/cm^2, $\bar{g}_{K,Ca}$=0.05mS/cm^2, E_K = -75mV, C_m = 1μF/cm^2, and the rate constants for *m*, *h*, *c*, *n*, *a*, h_A all solve the first order kinetic equation [71]:

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

Na^+ Activation channel :

$$\alpha_m = \frac{-0.6(E+30)}{e^{-0.1(E+30)} - 1}; \quad \beta_m = 20 e^{-(E+55)/18}; \quad (3)$$

Na^+ Inactivation channel:

$$\alpha_h = 0.4 e^{-(E+50)/20}; \ \beta_h = \frac{6}{e^{-0.1(E+20)} + 1}; \quad (4)$$

K^+ channel:

$$\alpha_n = \frac{-0.02(E+40)}{e^{-0.1(E+40)} - 1}; \ \beta_n = 0.4 e^{-(E+50)/80}; \quad (5)$$

A–Type K^+ Activation channel:

$$\alpha_A = \frac{-0.006(E+90)}{e^{-0.1(E+90)} - 1}; \ \beta_A = 0.1 e^{-(E+30)/10}; \quad (6)$$

A–Type K^+ Inactivation Channel:

$$\alpha_{h_A} = 0.04 e^{-(E+70)/20}; \ \beta_{h_A} = \frac{0.6}{e^{-0.1(E+40)} + 1}; \quad (7)$$

Ca^{2+} Activation channel :

$$\alpha_c = \frac{-0.3(E+13)}{e^{-0.1(E+13)} - 1}; \ \beta_c = 10 e^{-(E+38)/18}; \quad (8)$$

The Intracellular calcium was calculated according to the following equation,

$$\frac{d[Ca^{2+}]_i}{dt} = \frac{-3 I_{Ca}}{2Fr} - \frac{([Ca^{2+}]_i - [Ca^{2+}]_{res})}{\tau_{Ca}} \quad (9)$$

where F is the Faraday constant, 3/*r* is the surface to volume ratio and the valency is 3.

In the FCM model, the currents I_{Na}, I_K, $I_{K,A}$ and I_{Ca} were modeled as voltage-gated, whereas Calcium activated potassium was gated by Ca concentration. Gating of $I_{K,Ca}$ was modeled as follows:

$$g_{K,Ca} = \bar{g}_{K,Ca} \frac{([Ca^{2+}]_i / [Ca^{2+}]_{diss})^j}{1 + ([Ca^{2+}]_i / [Ca^{2+}]_{diss})^j} \quad (10)$$

where Ca^{2+}-dissociation constant, $[Ca^{2+}]_{diss}$=10^{-6} molar, residual internal Ca concentration, $[Ca^{2+}]_i$ = 10^{-7} molar, and Ca-activated potassium conductance depends on calcium concentration.

The Calcium channels play a vital role in the RGCs and ipRGCs and its vitality with glaucoma is still more essential. So the designed model was modified by including the L- and T-type Calcium channels and analysed. After including both types of calcium channels the model for membrane potential takes the form:

$$C_m \frac{dE}{dt} = -\bar{g}_{Na} m^3 h (E - E_{Na}) - \bar{g}_{Ca,L} m^2 (E - E_{Ca,L}) - \bar{g}_{Ca,T} n h (E - E_{Ca,T}) - \bar{g}_K n^4 (E - E_K) - \bar{g}_A a^3 h_A (E - E_K) - \bar{g}_{K,Ca} (E - E_K) + I_{stim} \quad (11)$$

The L-type calcium current, $I_{Ca,L}$ and the T-type calcium current $I_{Ca,T}$ were computed[16]:

$$I_{Ca,L} = \bar{g}_{Ca,L} \ m^2 (E - E_{Ca,L}) \qquad I_{Ca,T} = \bar{g}_{Ca,T} \ n h (E - E_{Ca,T}) \quad (12)$$

where the values of maximum conductance for the L-type calcium channels and T-type calcium channels are $\bar{g}_{Ca,L}$=1mS/cm^2, $E_{Ca,L}$=45mV, $\bar{g}_{Ca,T}$=1mS/cm^2, $E_{Ca,T}$=45mV [16].

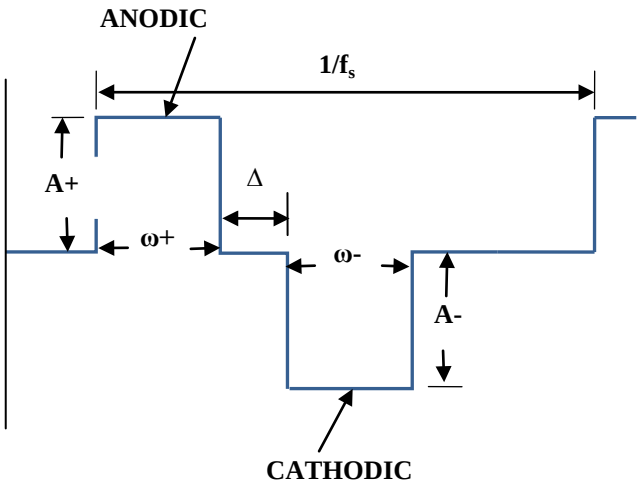

Fig.2. The biphasic stimulation current waveform

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 cathodic and anodic amplitudes are A- and A+ respectively, and the durations of the cathodic and anodic phases are ω- and ω+ respectively. The intra phase gap(IPG), Δ, delays; separates the pulses and also avoids the reversal of the earlier physiological effect of the previous pulse[72]. An increasing interphase gap leads to a decrease in the charge required to cause a neuron to spike [73].

III. Results

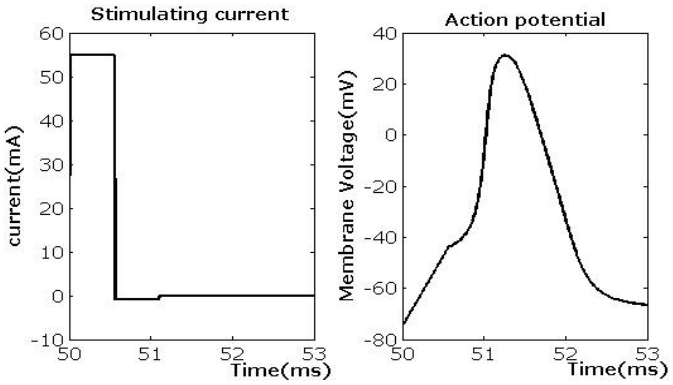

Fig. 3. (a) Biphasic stimulating current.
(b) Action potential evoked from the RGC.

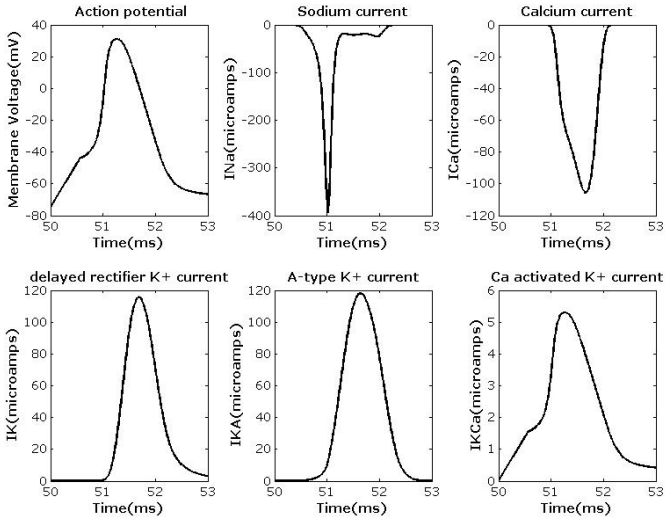

Fig. 4. Action potential initiated from the RGC and the five non-linear ionic currents in the RGC.

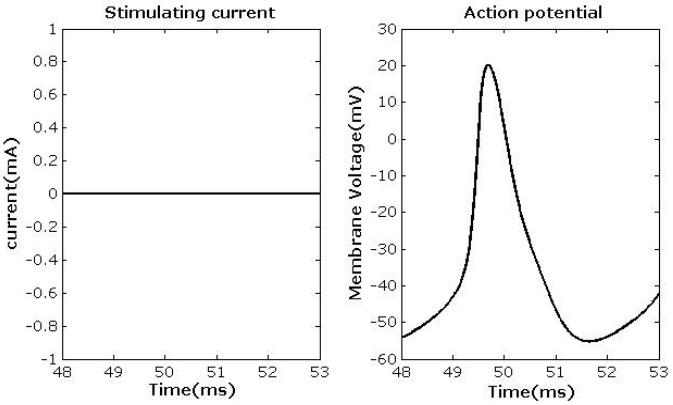

Fig. 5 (a) Stimulating current.
(b) Action potential spike from the RGC with L and T - type Calcium channels.

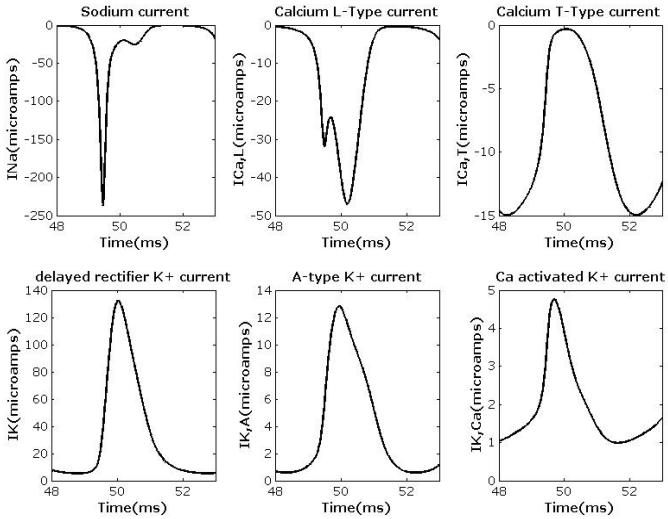

Fig. 6. Ionic currents in the RGC model with L and T - type Calcium channels.

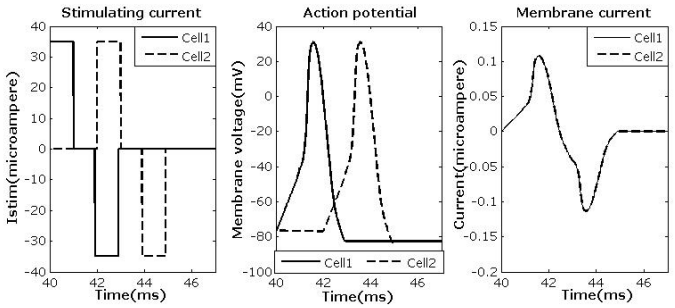

Fig. 7. (a) Symmetric Biphasic stimulating current.
(b) Action potential evoked from the two RGCs.
(c) Electrotonic current flowing across the boundaries between the neighbouring compartments

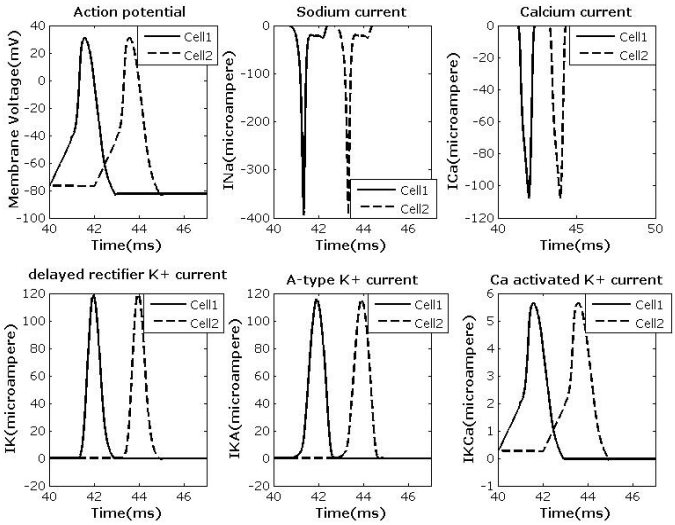

Fig.8. Action potential and the five non-linear ionic currents in the two RGCs

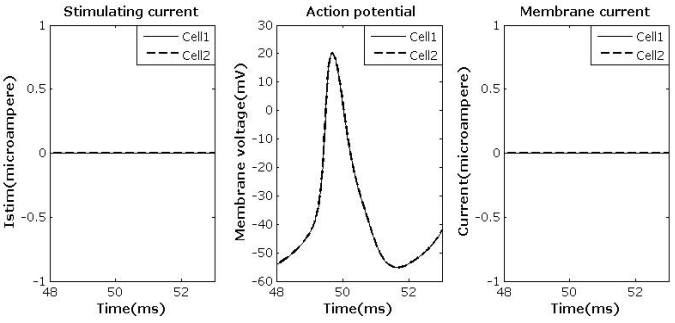

Fig. 9. (a) Symmetric Biphasic stimulating current.
(b) Action potential evoked from the RGC model with the L and T-type Calcium channels.
(c) Electrotonic current flowing across the boundaries between the neighbouring compartments

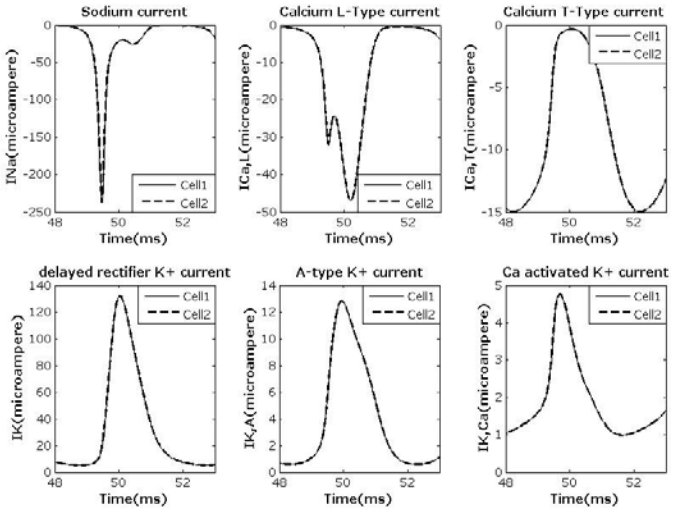

Fig.10. Non-linear ionic currents in the two RGCs L and T - type Calcium channels.

IV. Discussion

The action potential of the designed retinal ganglion cell and the electrotonic current flows across the boundaries between the neighboring compartments were analysed for constant dc current, symmetric biphasic stimulating current, I_{stim} and gap junction conductances [74], [75]. 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 were adjusted and analysed for the efficient spiking [74], [75].

The action potential evoked from a RGC for the I_{stim} with anodic amplitude, A+ of 55µA for the anodic duration, ω+ of 550µs, cathodic amplitude, A- of -1µA for a cathodic duration, ω+ of 550µs and IPG, Δ = 0ms is manifested in Fig.3. The action potential in the RGC and the five non-linear ionic currents of sodium channels, calcium channels, delayed rectifier potassium channels, A type potassium channels, and Ca-activated potassium channels for the model in (1) are depicted in Fig.4. The RGC model in (1) was modified to (11) by adding L type and T type calcium channels. The action potential spikes were obtained in this model of RGC without application of the I_{stim} due to the depolarization of the RGC which leads to the repetitive firing of RGCs. The action potential originated is represented in Fig.5 and the ionic currents flowing in the RGC are presented in Fig.6. In ipRGCs, the depolarization of the membrane potential, resulting in the activation of voltage gated Na^+ channels (VGNCs). The Na^+ flux through VGNCs during action potential firing makes the membrane further depolarized, leading to the activation of L-type VGCCs. The Ca^{2+} influx and most of the Ca^{2+} signal in the ipRGCs was the result of the depolarization-induced opening of VGCCs[55]. Spontaneous electrical activity has been described as rhythmic bursts of action potentials that spread between adjacent cells and produce transient elevations in internal calcium concentration [56]. The action potential spikes of two RGCs connected with a gap conductance of 0.001mS/cm^2 were stimulated with I_{stim1}

with A+ = 35μA, ω+ = 1ms, A- = -35μA, ω+ = 1ms, Δ = 0.9ms is pictured in Fig.7. The I_{stim2} for the second RGC is of same amplitude and duration as I_{stim1} but with a delay of 1ms after the application of I_{stim1}. The ionic currents flowing are characterized in Fig.8. The action potential initiated without stimulation from Istim is revealed in Fig.9. With the adaptation done as in (11) by the inclusion of L-type and T-type Calcium channels, the ionic currents are illustrated in Fig.10.

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