ISSN (Print) : 0974-6846
Indian Journal of Science and Technology, *Vol 8(35), DOI: 10.17485/ijst/2015/v8i35/67158, December 2015* ISSN (Online) : 0974-5645

Analysis of Primate Retinal System for Better Computational Modeling

T. Alavanthar[1*], K. Manikanda Raja[2] and S. K. Pandiyan[3]

[1]School of Electrical and Electronics Engineering, SASTRA University, Thanjavur - 613401, Tamil Nadu, India; alavanthar.t@ece.sastra.edu;
[2]School of Chemical and Biotechnology, SASTRA University, Thanjavur - 613401, Tamil Nadu, India; kmanikandaraja@live.com
[3]Centre for Nonlinear Science and Engineering, SASTRA University, Thanjavur - 613401, Tamil Nadu, India; krishpandiyan@ece.sastra.edu

Abstract

Photo transduction in human eye can be segmented into different electrical components by proper analysis of their work on the action potential with electrophysiological studies. J. H. Van Hateren, designed a computational model of primate retinal system with the aim of mimicking the human visual system as an electrical device for retinal implants in the future, but the model suffered from chromaticity adaptation and the existence of after images. This article concentrates in studying the model by simulating with different values and stating why generic value fit is taken into consideration, while others are not. The choice of generic value for the inactivation reaction of photopigment and phosphodiesterase is reasoned in greater detail. This paper states the flaws present in the previous mentioned computational model and put forth that photoreceptor works as a band pass filter and not as low pass filter which might help to overcome chromotacity adaptation in the given model.

Keywords: Computational Model, Chromaticity Adaptation, ERG, Photoreceptor, Primate Retinal System, Photopigment, Phosphodiesterase

1. Introduction

Light plays a significant role in the regulation of image-forming photoreceptor function in the genome of mammalian species and animal reproduction of some nonmammalian species. Recent advancement in fish, shows brain itself is a photoreceptive organ; brain expresses non-visual photoreceptors to regulate reproduction by light[1]. There are several components that contribute to the early phase of the Electro-Retinogram (ERG) at the molecular level in human photoreceptors. Incoming light ray has been taken as an optical parameter in estimating the retinal response and the spatial distribution of photon absorption in the photoreceptors of a human eye[2]. These kinds of studies and measure of the wavefront will lead to significant correlation between the right and left eye's aberrations[3]. The data mining is one of the computation method used to predict the abnormality in human retina like diabetic retinopathy using[4]. The data mining is also useful for prediction of the normal retina by estimating the electrical behavior of the retina. Various electrochemistry processes causing cascade of reactions in the retina. The electrochemistry involved in retina contributes to the ERG waveform. Here we have attempted to compute a model of a normal ERG wave contributed by various electrochemistry processes in human retina. The values of ERG amplitudes and the time period of a normal eye vary according to the type and intensity of the flash.

As retina acts like a photodiode in general, it receives light and produce electrical pulse which are rectified by different cells. The light affects the retinal system in exponential form of saturation, resulting in cascade of

* *Author for correspondence*

reactions. Different stages of the cascade are also called as stages of amplification. The retinal model proposed lately[5], mainly differs from the number of filters used with different gain factors and the reactions taken into consideration for modeling. By having Electro-Retinogram (ERG) waveform of an ideal eye as reference, the retinal system was sorted out into different electrical components. By simulation of the retinal model[6] using Matlab, the perfect values for each parameter were studied mathematically and values were obtained from the output. The image is processed using two methods they are Auto-Regressive Moving Average filters (ARMA) and Ordinary Differential Equation (ODE).

Each bio-chemical reaction was converted into low-pass filter equations of ODE form. These equations were coupled together and the output was simultaneously compared with the reference ERG waveform and the values were "fitted". ODE method is slow but accurate. It is depicted with blue line in the plots. A generalized low pass filter equation is given below, where 'a' is input and 'b' is output. Each low pass filter equation contains a gain and a time constant.

$$R_X \frac{db}{dt} = a - b \tag{1}$$

ARMA method is fast and accurate. It is depicted with red line in the plots. General equation of ARMA method is:

$$b(\mathrm{n}) = f_1 b(n-1) + f_2 a(n) + f_3 a(n-1) \tag{2}$$

$$f_1 = \exp\left(-\frac{1}{X'}\right) \tag{2a}$$

$$f_2 = X' - \left(1 + X'\right) f_1 \tag{2b}$$

$$f_3 = 1 - X' + X' f_1 \text{ where } X' = \frac{X}{\Delta t} \tag{2c}$$

In photo transduction process each reaction is coupled linear or feedback controlled in order to overcome the nonlinearities present in the model, so both are taken for comparison. Different gain control mechanisms were implemented in the model for sensitivity regulation[7].

2. Photo-transduction and its Electrical Equivalence

2.1 In photoreceptors

Rods and cones are almost similar in their process in photo-transduction wise. The difference in rods is that, it has greater contact with Extra Cellular Matrix (ECM) rather than cones which make rods, behave like low-pass filter in order to mimic the capacitance effect of extensive cone membrane. This result in stating that, rod's a-wave fit better than cone's a-wave fit by saturating exponentially. Hence, both the receptors are going to be discussed under the same heading "photoreceptors"[8].

Light (L) incidents on the pigment, i.e., rhodopsin (M) present in the top most retinal layer which changes from 11-Cis conformation to all Trans-conformation, i.e., M*. The above active form is inactivated and this reaction can be considered under 1st order kinetics with a rate constant R_M and a scaling constant S_M that acts in the form of 1st order low pass filter[6]. This reaction happens with time constant T_M.

$$T_M \frac{dM}{dt} = T_M S_M L - M^* \tag{3}$$

where $T_M S_M$ is the gain and $T_M = 1/R_M$. G-protein (H) have 3 subunits (alpha, beta, gamma) of which Transducin (alpha subunit) part gets activated by M* which leaves from G-protein this reaction happens fast and so rate constant does exist but ignored in order to reduce mathematical problems.

Activated G-protein (H^*) binds to phosphodiesterase forming complex N^*, in similar way reversal of this reaction to its original form has a rate constant which is denoted by R_N scaling constant S_N. These two reactions are coupled with the third reaction in which, it acts like 1st order low pass filter.

$$T_N \frac{dN}{dt} = T_N S_N M^* - N^* \tag{4}$$

where $T_N = 1/R_N$ and $T_N S_N$ is gain. cGMP (P) production by guanylate cyclase is given by the rate constant ^ . N^* reduces the concentration of Cyclic-Guanosine Monophosphate (cGMP). Activity of N^* is given by μ which has constant dark activity (D). R_D shows inactivity of N*.

$$\mu = D + R_D N^* \tag{5}$$

$$\wedge = \frac{1}{\left(1 + \left\{S_N Z\right\}^{n_Z}\right)} \tag{6}$$

$$\frac{dP}{dt} = \wedge - \mu P \tag{7}$$

$$T_P \frac{dP}{dt} = \frac{\wedge}{\mu - P} \tag{8}$$

Input for cGMP reaction is assumed to be inverse, in-order to attain the same biological action in the electrical circuit. cGMP binds to the cyclic nucleotide-gated calcium receptor in a forward reaction and release Ca+ ions.

$$T_Z \frac{dZ}{dt} = T_Z \Omega I_O - Z \tag{9}$$

where $T_Z=1/R_Z$ and $T_Z \Omega$ is the gain. Calcium on the Na+/Ca+ channel activation, acts in "negative feedback" sense. Simultaneously, much of Ca+ influx acts as a "Negative feedback" which affects ^9. Ω Indicates the scaling constant which is proportional to the current exiting the photoreceptor. T_Z shows the time constant for the Ca+ influx. The calcium influx does depend on the cGMP presence as discussed above and which is denoted by J_X. The higher concentration of calcium results in strong negative feedback which would affect the pulse propagating to the inner segment of the receptor and in total, it is represented using the divisive feedback gain circuit to control its gain[10]. The opening of cGMP nucleotide gated channels is dependent on which camp is represented by

$$I_O = Z^{J_x} \tag{10}$$

There are Ca-independent reactions in which cGMP dissociation from PDE increases G-protein's activity. The inner segment is voltage sensitive and it helps to alter the response of the system. Propagation of pulse from the outer segment to the inner segment can be represented with respect to conductance equation, as it helps in studying the response of the cone. The conductance behaves more like scaling constant.

$$\text{Steady-state membrane Conductance} = \frac{\text{steady state current}}{\text{receptor potential}} \tag{11}$$

Steady state membrane conductance is a nonlinearity function of the retinal model. Additional filtering action is carried, as when the signal transcends from the inner region of photoreceptors to its pedicle, with a time constant $\mathbf{T_S}$. This step of reaction is gain controlled by using a divisive feedback circuit. G represents immediate conductance, G_S represents steady state conductance and V_S represents steady state receptor potential.

$$T_S \frac{dG}{dt} = G_S(V_S) - G \tag{12}$$

As the current is transmitted from inner segment to the pedicle, additional low-pass filtering happens which is denoted by T_W. The response for photo-current generated by photoreceptors is fast and monophasic. The scaling factors help to get a good fit without disturbing the parameter values.

2.2 In Horizontal Cell (H Cells)

The photoreceptors transmit signal to H cells, which is represented by a subtractive feedback circuit in order to control the gain. Oscillatory potential is mainly difficult to achieve at high intensities and this fact were achieved by analyzing ERG's b-wave[11]. The Frequency of these oscillations decreases proportionally with intensity as mentioned before. By using larger time constant in the series of low pass filters this will produce oscillations. Two, low pass filters are enough for the production of oscillations, but three or more allows the peak to "fit". The signal is transmitted to bipolar cells and is low pass filtering is more when compared with photoreceptors. For better understanding: When calcium channels are closed the photoreceptor gets hyper polarized and generates a pulse which is propagated through bipolar cell without neurotransmitter release. Without neurotransmitter release, bipolar cell depolarizes and neurotransmitter is released at the synapse, between ganglion cell and bipolar cell, which generates an action potential. This action potential is propagated to brain through the optic nerve.

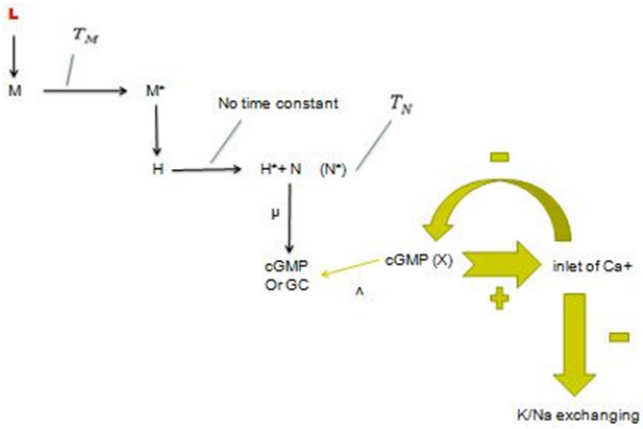

Figure 1. Primate's visual photo-transduction.

3. Results and Discussion

Using rectangular flash as a function with constant background intensity 60 troland (td), different stimulating intensities (5 td, 12 td, 23 td, 38 td, 69 td, 141 td, 331 td)

is given to the retinal circuit and values were fitted with respect to the reference ERG. The rectangular flash is depicted with a green line in the outputs. As ODE is a slow processing method, relative tolerance or fractional error of 10^{-6} is utilized. When one parameter is varied to study, all the other parameters are set at their respective generic values.

Parameter: T_M Unit: ms Generic value: 3.4 Range: 0.5-6.5

T_M is the rate at which photo pigment gets deactivated. The choice of generic value 3.4 ms is because it does best fitting delayed Gaussian curve at high intensities. When T_M considered 0.5 ms, activation of photo-pigments (M) is fast which results in sharp peak rather than the other two extreme ranges. When T_M considered 6.5 ms, activation of photo-pigments is slow and it takes more time after the flash to exponentially saturate the reaction which is depicted from Figure 2 (Left).

Parameter: T_N Unit: ms Generic value: 9.6 Range: 3.0-16.8

The choice of generic value 9.6 ms is because it shows least peak response to the voltage amplitude. This is to bring the fact that maximum rate constant of PDE hydrolysis is required to support the data that T_M maximum is required to attain the reference ERG. When this fact is compared with both the limits, generic value only suits. This can be understood from Figure 2 (Right). Generic value 3.4 ms of T_M and 9.6 ms of T_N does satisfy with energy barrier activation values of the corresponding proteins which tell that hundred photo pigments are required to activate ten G-proteins and these ten G-proteins can activate only one PDE. These two time constants determine the

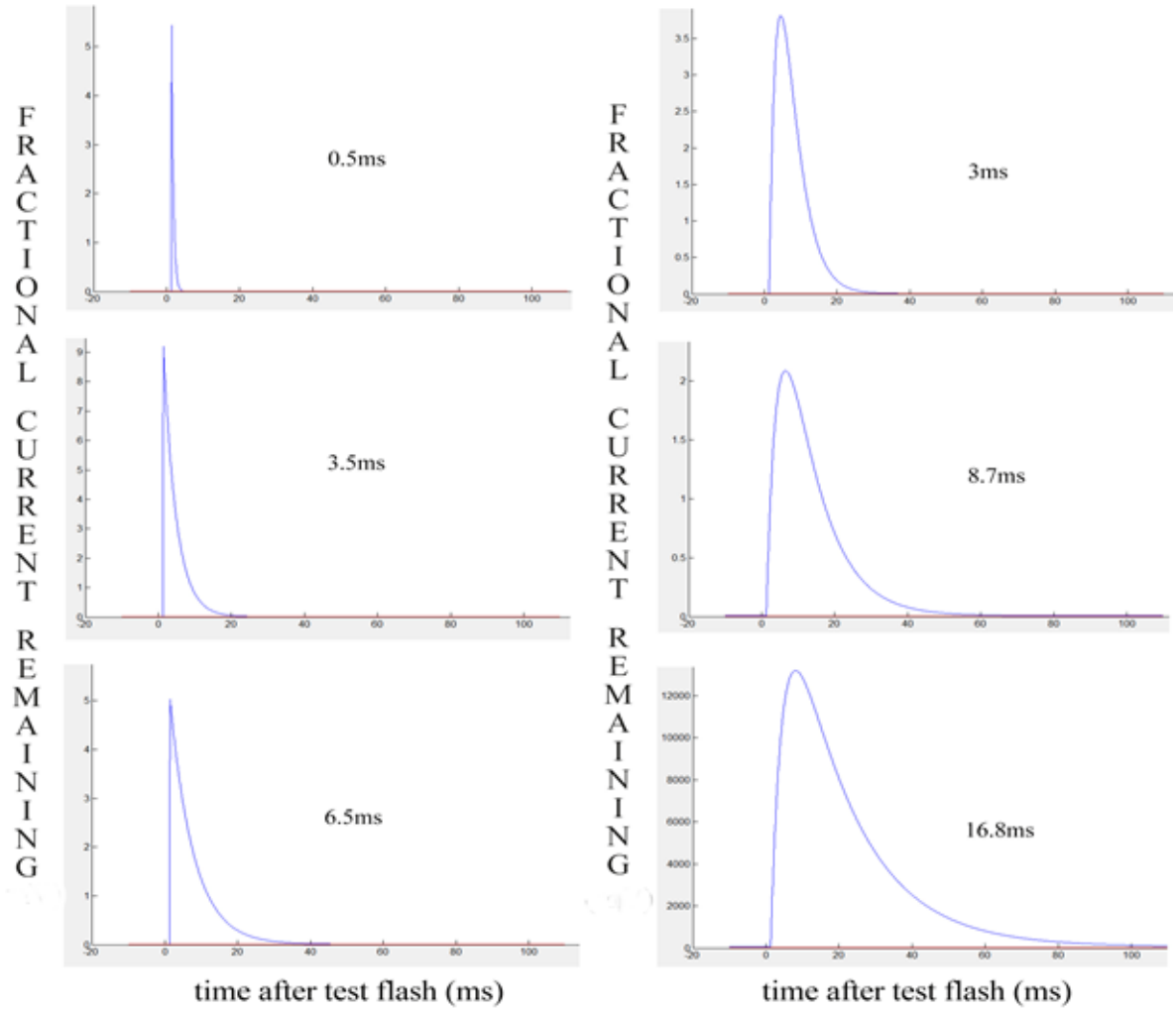

Figure 2. Y-axis contains arbitary values. T_M (Left) shows: Least range value, generic value and highest range value. Out of which generic value 3.5 ms can alone attain T_M maximum, which helps to support the fact for genreic value of T_N (Right) using the energy barrier activation ratio of the proteins.

"time constant" of the whole transduction. If any one of the two constants is increased, we can see the increase in the response with time in the output ERG and that's why, they are called as "dominant time constants" of photo transduction[12].

Parameter: R_D Unit: $(ms.td)^{-1}$ Generic value: 10^{-4} Range: 4.9×10^{-5} – 3.9×10^{-4}

R_D is the parameter which couples the light gain to the cGMP hydrolysis. The choice of generic value 10^{-4} $(ms.td)^{-1}$ shows almost similar fit to that of macaque's R_D value (i.e. 1.6×10^{-4})[12] but when R_D value is increased greater than the generic value, the a-wave's maximum gets to be same for all the stimulus intensities, refer Figure 4. Also when R_D value is below generic value, it gives low a-wave maximum. This implies that coupling of light to the cGMP hydrolysis is slow. That is depicted in Figure 3.

Parameter: T_Z Unit: ms Generic value: 3 Range: 2-6.3

T_Z is the time constant for Ca+ extrusion from the neuron. 3 ms is not the only generic value that can make perfect fit, as after many experiments any value of $T_Z<12$ ms makes similar fit. When the value increases, the system is prone to RMS errors in the fits and lead to biphasic response[12] which is implicated in Figure 3. As said before, the photocurrent produced should only have monophasic response. When T_Z is lesser than generic value, the fit is not perfect.

Parameter: J_X Unit: nil Generic value: 1 Range: FIXED

J_X indicates the proportionality of amount of cGMP required to activate cyclic nucleotide-gated channel. When J_X is 3[5], it plays main role in sensitivity regulation, and the proper fit is only attained only by 1. When J_X is 1, the Equation 9 will imply direct proportionality of the total photo-current generated at the receptors pedicle to the cGMP concentration and regulate the sensitivity of the cell.

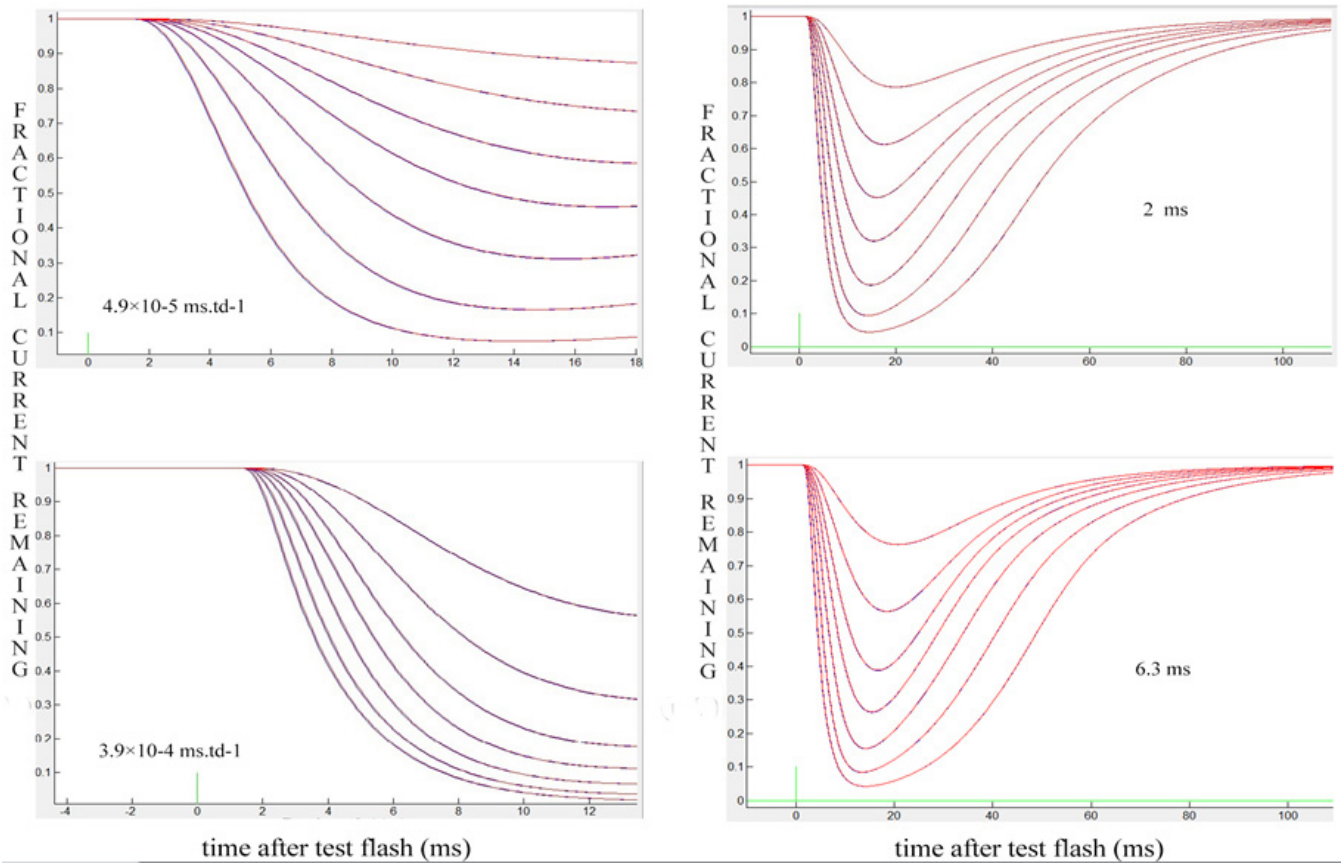

Figure 3. Y-axis contains arbitary values. R_D (Left); 1st panel: when R_D is 4.9×10-5 ms.td-1 it gives minimum a-wave which will affect the output and it does not help in getting the perfect fit. 2nd panel: when R_D is 3.9×10-4 ms.td-1 it gives maximum a-wave which gets to be the same for all the stimulating intensities 5 td, 12 td, 23 td, 38 td, 69 td, 141 td, 331 td. T_Z (Right); 1st panel and 2nd panel: when T_Z is varied there is no difference between both the extremes of the range as illustrated before, any value greater than 2 ms can satisfy the reference fit. But do increase RMS errors along with increase in T_Z value.

Parameter: n_Z Unit: nil Generic value: 4 Range: FIXED

n_Z is the major coefficient of cGMP conversion to Guanyulate cyclase. When, n_Z is increased greater than generic value 4, b-wave's maximum decreases due to the conversion process which leads the system to excess GMP concentration. This will reduce the photocurrent generated. When a-wave decreases, simultaneously b-wave also decreases[13]. It is taken as 4[14]. Values less than 4 does fit but no good as 4 can.

Parameter: T_W Unit: ms Generic value: 2.3 Range: FIXED

T_W is the outer segment capacitive time constant or the additional low pass filter which arises when current is transmitted form inner segment to the pedicle of the receptor. Apart from the generic value 2.3 ms, 1 and 3 ms gives perfect fit. This fit can be achieved by modifying the values of $T_{N,}$ R_D and T_{delay}[5]. When T_W is more than 3, it would make the b-wave linear to the time after flash. This is due to excessive low pass filtering which is not mostly seen in normal working eyes.

Parameter: T_{delay} Unit: ms Generic value: 1.3 Range: FIXED

It is the same with respect to many constituents. In the photoreceptor-H cell bridge, the low pass filters in the loop produces a delay which produces the oscillations. The input for the calcium feedback is delayed using low pass filters, which energize temporal frequencies and plays important role in regulating the sensitivity. There is an effective time delay in the model to have the series of amplification reactions. In an unclamped cell, extra time delay is present due to cell's electrical time constant[5].

The value given to the parameters are used in the retinal model and the output is studied. The values given are not accurate and varying for each case. Mostly, they are successful in attaining the required reference ERG but do give unsteady output for certain stimulating and background intensities, because of the presence of nonlinearity in the system. The generic values used for T_M, T_N are perfect. But generic values of T_{delay}, T_Z and T_W are used for computation to only attain the best "fit". Later J. H. Van Hateren added three new components to the computational system which where adaptive temporal filtering, a two-component spatial receptive field and adaptive feedback gain[15]. The model suffered from problems like chromaticity adaptation and after-images. The model should be corrected, by changing the low pass filter equations into band pass filter equations as the low pass filtering effect is carried to mimic the capacitance effect of the cone surface which will be one of the reasons why the retinal model suffered from color adaptation problem[16].

It was proved that rod behaves like a band pass filter and not as low pass filter[17]. But according to J. H. Van Hateren, he modeled the photoreceptors as low pass filters and said they act like band pass filters only during hyperpolarization state. When there is more Ca+ influx it would show additional depolarization effects which will mediate slow hyper-polarization by K+ current, this would result in dynamic net current fluctuation leading to complex behavior by recurring back- and forth-crossings of bifurcation boundaries. The above mentioned phenomenon will occur when T_Z value exceeds 12 ms, which is shown in the Figure 4. When T_Z value exceeds more than 12 ms, this will be the point specified by J. H. Van Hateren mentioning that receptors act as band pass filters only at hyperpolarized conditions. But as this will increase the RMS errors which can be overcome by using modified Tustin's method in the negative feedback circuit as modified Tustin's method[7]. Sensitivity regulation mechanisms act independent on the cones[18].

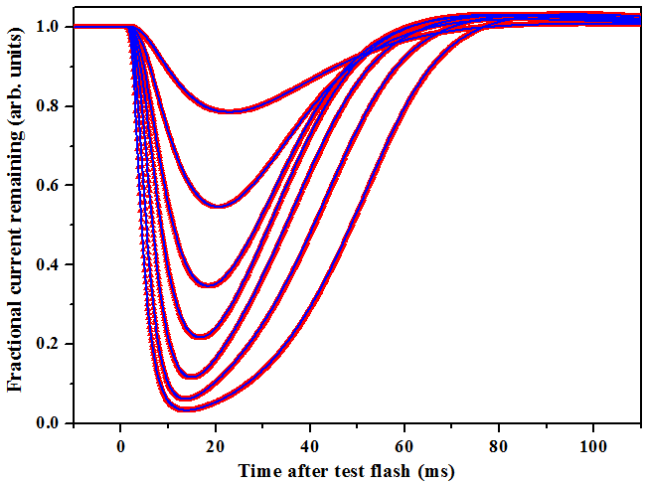

Figure 4. The output ERG for T_M = 3.4 ms, T_N = 9.6 ms, R_D = 10-4 (ms.td)-1, J_X = 1, T_Z = greater than 12 ms (13 ms), n_Z = 4, T_W = 2.3 ms, T_{delay} = 1.3 ms.

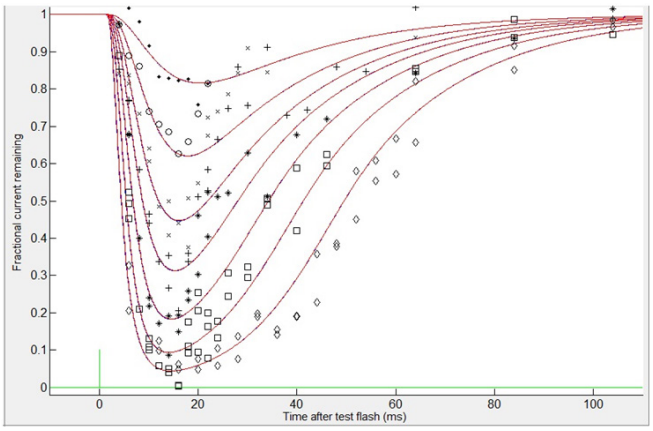

Figure 5. The output ERG for T_M = 3.4 ms, T_N = 9.6 ms, R_D = 10^{-4} $(ms.td)^{-1}$, J_X = 1, T_Z = 3 ms, n_Z = 4, T_W = 2.3 ms, T_{delay} = 1.3 ms.

4. Conclusion

The retinal model was simulated with different range of values and they show good response only to the generic value. The choice of generic value for inactivation reaction of photopigment and phosphodiesterase are perfect as they support with energy barrier activation ratio described above. T_Z does plays main role in determining the actual reason why J. H. Van Hateren's view on low-pass filters as a replacement for the bio-chemical reactions in the photoreceptors. The reasons will be feasible to prove the choice of value, but still the nonlinearities have to be varied in order to attain the perfect 'fit'. As proved before, low pass filter acts as band pass filter when there is extensive Ca+ influx. The problems can be overcome by changing the low pass filters into band pass filters which will suffice our problems in the computational model.

5. References

1. Kitahashi T, Parhar IS. Expression of deep-brain photoreceptor, vertebrate ancient long opsin, in the Japanese. Indian Journal of Science and Technology. 2014; 9.
2. Sharma NK. Coherent response of a human eye: An Apodization model of stiles crawford effect of the first kind. Indian Journal of Science and Technology. 2015; 8(10):906–12.
3. Lee S-D, Kim M-H, Kim C-G. Similarity of aberrations between right and left eyes. Indian Journal of Science and Technology. 2015; 8(S8):79–82.
4. Ananthapadmanaban KR, Parthiban G. Prediction of chances - Diabetic retinopathy using data mining classification techniques. Indian Journal of Science and Technology. 2014; 7(10):1498–503.
5. Breton ME, Schueller AW, Lamb TD, Pugh EN, Jr. Analysis of ERG a-Wave Amplification and Kinetics in Terms of the G-Protein Cascade of Phototransduction. Invest Ophthalmol Vis Sci. 1994; 35(1):295–309.
6. van Hateren H. A cellular and molecular model of response kinetics and adaptation in primate cones and horizontal cells. Journal of Vision. 2005; 5(5):331–47.
7. van Hateren JH. Fast recursive filters for simulating nonlinear dynamic systems. Neural Computation. 2008; 20(7):1821–46.
8. Hood DC, Birch DG. Phototransduction in human cones measured using the a-wave of the ERG. Vision Res. 1995; 35(20):2801–10.
9. Koch, Stryer. Highly cooperative feedback control of retinal rod guanylate cyclase by calcium ions. Nature. 1988; 334:64–6.
10. Snippe HP, van Hateren JH. Dynamics of nonlinear feedback control. Neural Computation. 2007; 19(5):1179–214.
11. Fujimura K, Tsuchida Y, Jacobson JH. Oscillatory potential of the human electroretinogram evoked by monochromatic light. Invest Ophthalmol. 1972; 11(8):683–90.
12. van Hateren JH, Lamb TD. The photocurrent response of human cones is fast and monophasic. BMC Neuroscience. 2006; 7:34.
13. Brown KT, Wiesel TN. Localization of origins of electroretinogram components by intraretinal recording int he intact cat eye. J Physiol. 1961; 158:257–80.
14. Burns ME, Mendez A, Chen J, Baylor DA. Dynamics of cyclic GMP synthesis in retinal rods. Neuron. 2002; 36(1):81–91.
15. van Hateren JH. A model of spatiotemporal signal processing by primate cones and horizontal cells. Journal of Vision. 2007; 7(3):1–9.
16. Hood, DC, Birch DG. Human cone receptor activity: The leading edge of the a-wave and models of receptor activity. Neuroscience. 1993; 10(5):857–71.
17. Kamiyama Y, Wu SM, Usui S. Simulation analysis of bandpass filtering properties of a rod photoreceptor network. Vision Research. 2009; 49(9):970–8.
18. Smith VC, Pokorny J, Lee BB, Dacey DM. Primate horizontal cell dynamics: An analysis of sensitivity regulation in the outer retina. J Neurophysiol. 2001; 85(2):545–58.