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Modeling Inhibitory and Excitatory Effect of Astroglia in Synaptic Plasticity and Learning

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Abstract— **Unlike past, scientific researches in recent years have shown that glial cells actively play various important roles in the nervous system. Because of difficulty in experimental study of glia a suitable method to investigate various aspects of its function is mathematical modeling. In this paper we attempt to illustrate inhibitory and excitatory aspects of astrocyte cells in producing Central Pattern Generators (CPG) and predict their role in some diseases by using modeling approach. We extracted CPG model from biological based data and then modeled sensitivity of glia cell to changes of the potassium equilibrium (α parameter), effect of synaptic activation on the secondary messenger production (inositol 1, 4, 5-trisphosphate (IP3)) (*β* parameter), Increasing [Ca^{2+}] in the glial cytoplasm triggers the production of a mediator (glutamate) and its release into the intercellular space (δ parameter) and effect of glial mediator (glutamate and adenosine 5'-triphosphate (ATP)) on postsynaptic neuron (γ and η respectively). To evaluate the model, first a simple 2 layer neural astrocyte network was simulated. Then results were compared with experimental evidence. Analysis of the waveforms showed the effect of astrocyte cell in modulating the synaptic transmission especially generation of patterns of rhythmic signals that can be used as CPG, changing neural network structure, acquisition of memory via impulse repetition which may be considered as long-term potentiation (LTP). We propose that glia have important effect on optimal intrinsic subthreshold oscillations (ISO) functionality. Finally, the model predicted the effects of astrocyte in some neurological disorders.**

Keywords: Astrocyte; neuron; neural network; LTP; learning; modeling; simulation; hippocampus

I. INTRODUCTION

The nervous system basically consists of two major types of cells, the neuron and the glia. Although it is without doubt that neurons play pivotal role in the nervous system function, studies over the past decade are raising our awareness about the diversity of roles played by various glial cells in nervous system function. Among them, astrocyte cells are active associates for neurons in information processing and therefore study of the interactions between these two cell types is important in neurophysiology, cellular biophysics and modeling studies. Computer assisted modeling of the various biological functions of neurons and astrocyte cells can help us understand and predict neural behavior and the role of these cells under normal range of conditions as well as in neurological diseases [1]. Several models of astrocyte cells have been reported that focused on one or several aspects of their physiological characteristics and functions. It is generally thought that neural oscillatory circuits in the spinal cord, called as central pattern generators (CPG), underlie the production of rhythmic motor behavior such as locomotion in several species of animals [2]. Astrocyte cells have been proposed to modulate and synchronize neuronal activity via secretion of glutamate, adenosine 5'-triphosphate (ATP) and D Serine [3]. CPG is considered to be the base of many movements and biologic phenomena including respiration, chewing, digesting and rhythmic movements, such as swimming, walking, and hopping. Investigation of the relationship between CPG and astrocyte cells can lead to better understanding of relevant biological phenomena such as locomotion and various aspects of motor function in health and disease.

In this regard, a computational model of a pathway in the cat subcortical auditory system was initially proposed and this pathway extended from the basilar membrane of the cochlea and its inner hair cells to the principal auditory nuclei in the cat brainstem. However, this model did not consider glial cell [4].

New evidences indicate that astrocyte generate synaptogenesis-promoting signals [5]. They influence both pre and post-synaptic function and play important role in synapse maturation and elimination, secrete soluble and contact-dependent factors that influence the composition of the postsynaptic density and also synaptic connections appear to require astrocyte to support their structural stability[6]. Additionally, astrocyte perform a wide range of physiological actions in synaptic signaling and regulate neuronal integration and regulate their both excitatory and inhibitory signals necessary for neuronal function under various states [7].

Nadkarni and Jung first proposed the idea of a dressed neuron [8]. They described the role of astrocyte (astrocyte), which plays important role in producing Long Term Potentiation (LTP), the cellular basis of memory, leading to spontaneous oscillations in the dressed neuron [8]. This was further confirmed by other investigators [7].

A completed model of the tripartite synapse was then proposed that included a presynaptic neuron, the synaptic terminal itself, a postsynaptic neuron, and an astrocyte cell [9]. Additionally, the role of astrocyte cells in synaptic plasticity, synaptic regulation in hippocampus and neuromuscular interactions was later described [9]. In 2007 Nadkarni et al. proposed a complex model for the tripartite neuron. They

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interpreted the role of astrocyte cell in conveying the frequency of oscillation from the presynaptic to the postsynaptic neuron.

Most of models and studies carried out so far describe the dynamics of one tripartite synapse [10], simulations of networks of neurons and astrocytes focusing on the propagation of calcium waves [11] and modeling of one aspect of astrocyte function [12]. In this study we modeled four different physiological aspects of astrocyte cells in a neural glia network which also comprised of presynaptic and postsynaptic neurons and synapse. By alteration in these modeled astrocyte functions, we were able to study their effects on variations in neuronal output and its possible impact on central pattern generator for rhythmic movements. The corresponding dynamical properties were mainly investigated by using numerical simulations. In this way by modifying the model employed by Postnova [13] which incorporates subunits of the tripartite synapse that includes a presynaptic neuron, the synaptic terminal itself, a postsynaptic neuron, and a astrocyte cell, we simulated a section of neural glia network and by choosing the proper parameters of the model, we generated different signaling patterns with variable frequencies and pulse width and finally analyzed theses pattern in pathologies and normal situations and predict effect on astrocytes in these diseases.

This paper is organized as follows: First we will present the main pathway for neural-astrocyte interaction and the underlying principles for modeling. In part 3 the mathematical model and control parameters are introduced and in part 4 numeric simulation of astrocyte activity in a neural glia network is presented.

II. Methodology

A. Neural-glial interaction mechanism

Here first we present basic information about the series of events related to the dynamics of a neural-astrocyte set as follows: Astrocyte cells do not produce action potentials by themselves but show permeability to calcium and have a spontaneous oscillatory behavior with a specific frequency[14]. These cells monitor the activity related variations of ions and produce exocytose release of three classes of gliotransmitters: (i) amino acids, such as glutamate; (ii) nucleotides, such as ATP; and (iii) peptides, such as ANP (atrial natriuretic peptide) in synaptic cleft [15].Potassium concentration is very important because the intracellular concentration is much higher than the extracellular concentration and during synaptic transmission; the instantaneous increase of extracellular K^+ depolarizes the astrocyte cell. The calculated potential difference caused by this effect is close to experimental results. Neuronal activity depolarizes glial cells, which induces an alkaline shift in glial pH. The glial cells therefore extrude acid and the acid shifts in pH result in a decrease in neuronal excitability by changes in the receptor proteins[16].

Astroglial cells have voltage dependent Ca^{2+} channels that allow flow of calcium ions inside the cell in response to the membrane depolarization. When the synaptic terminal is activated by the presynaptic neuron, a mediating substance (e.g. glutamate) can escape the synaptic cleft and act on the astrocyte receptors which in turn activate the second messenger inositol 1, 4, 5-trisphosphate (IP3). Increase of IP3 triggers the release of free calcium ions from the endoplasmic reticulum (ER) which may lead to calcium oscillation seen in astroglial cells. Calcium increase in the cytoplasm initiates release of glutamate and ATP which also acts on the synaptic terminal along with increased calcium and lead to the depolarization or hyperpolarization of postsynaptic neurons. Glutamate also inhibits the presynaptic potentials [17].

Figure 1 shows a schematic view of the model for neural-astrocyte interactions. There is a slow and a fast mechanism for the activity of astrocyte (single astrocyte cell). The fast mechanism of astrocyte depolarization is caused by increase in extracellular K^+ and the slow mechanism is due to synaptic mediator (glutamate or ATP) [18]. The response of both presynaptic and postsynaptic neurons to the astrocyte cell is considered in model.

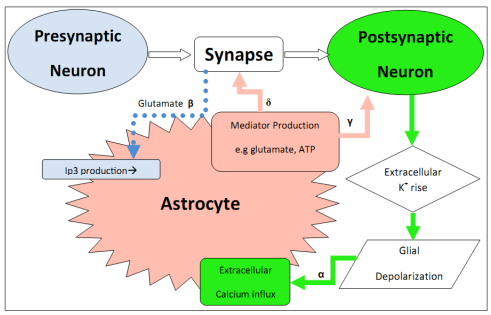

Figure 1. A schematic view of the model for neural-astrocyte interactions comprising of 4 sections [astrocyte cell, presynaptic and postsynaptic neurons and synapse] and 4 parameters [α, β, δ, γ] presented in this paper

B. Model

To model the neural glia network, we assume that it is formed by parallel of blocks where each block is comprised of a presynaptic pyramidal neuron which kind of input layer, a synapse, an astrocyte cell and a postsynaptic neuron which kind of output layer. Figure 2 shows a schematic view of such network. Network is simplified and just direct connection between pre and postsynaptic is considered.

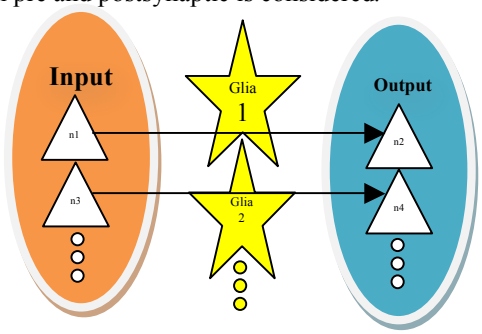

Figure 2. A schematic view of the simulated model of the neural glia network comprising of several basic blocks used for studying the astrocyte function.

According to the well-known FitzHugh–Nagumo's model for neuron and Kopell's model for synapse, by combination of these equations and assuming that presynaptic neuron stimulate postsynaptic neuron, following equations can be derived for the nth block: Where n>2. The parameters can vary from block to block.

$$\begin{cases} \varepsilon_n \frac{dv_n}{dt} = v_n - \frac{v_n^3}{3} - \omega_n \\ \frac{d\omega_n}{dt} = v_n - I_n - I_{syn(n-1)} - I_{glion(n-1)} + I_{ATP(n-1)} \\ I_{glion(n)} = \gamma_n G_m \quad , \; I_{ATP(n)} = \eta_n G_a \end{cases} \tag{1}$$

$$\begin{cases} \tau_s \frac{dz_n}{dt} = \left(1 + tanh\left(s_s(v_n - h_s)\right)\right)(1 - z_n) - \frac{z_n}{d_s} \\ I_{syn(n)} = \left(k_{s_n} - \delta G_m\right)(z_n - z_0) \end{cases} \tag{2}$$

Where v is relatively fast variable which represents the transmembrane potentials and ω is the slow variable and representing the potassium current. z is a synaptic activation variable and τ_s describes the time delay. The synaptic activation parameters such as h_s, s_s, and d_s are shown as activation and relaxation state of z. For more information about parameters see [13].

According the modified model of the calcium dynamics of the astrocyte cells with additional term (I_{Ca}) which describes the different synaptic functions [13], these equations can be derived for the Pth astrocyte as follows:

$$\tau_c \frac{dc^p}{dt} = -c^p - c_4 f(c^p, {c_e}^p) + {I_{Ca}}^p \quad (3)$$

$$\varepsilon_c \tau_c \frac{d{c_e}^p}{dt} = f(c^p, {c_e}^p) \quad (4)$$

$${I_{Ca}}^p = r^p + \alpha^p \omega_{p+1} + \beta^p {s_m}^p \quad (5)$$

$$\tau_{s_m} \frac{d{s_m}^p}{dt} = \left(1 + tanh\left(s_{s_m}(z^p - h_{s_m})\right)\right)(1 - {s_m}^p) - \frac{{s_m}^p}{d_{s_m}} \quad (6)$$

These equations represent the calcium influx from the extracellular space into the cytoplasm of Pth glia. Extracellular space sensitive to the synapse mediator production with the factor β^p and to the astrocyte depolarization by increasing extracellular potassium with the factor α^p. Parameter $r^p = 0.31$ represents a constant transmembrane current which controls the initial state of the calcium oscillator with no external influence (at $\alpha^p = 0$ and $\beta^p = 0$). The term $\alpha^p \omega_{p+1}$ is the implementation of the K^+ activation pathway. Namely, it qualitatively describes the potential-dependent inward calcium current that is activated by the depolarization of the glial cell caused by the elevation of the extracellular K^+.

Base of the Keener's model for describing the Ca^{2+} exchange between the cytoplasm and ER, the following equations can be derived for the Pth astrocyte as follows:

$$f(c^p, {c_e}^p) = c_1 \frac{{c^p}^2}{1+{c^p}^2} - \left(\frac{{c_e}^{p2}}{1+{c_e}^{p2}}\right)\left(\frac{{c^p}^4}{{c_2}^4+{c^p}^4}\right) - c_3 {c_e}^p \quad (7)$$

Where c_p denotes the Ca^{2+} concentration within the Pth astrocyte, ${c_e}^p$ is the calcium concentration in the internal store ER, τ_c defines the characteristic time for Ca^{2+} oscillations together with time separation parameter c_ε which are same for all astrocyte cells.

The five parameters considered in our model that are related to various aspects of astrocyte function that affect neuronal output are: α [effect of increase in extracellular K^+ on glial depolarization and Ca^{2+} influx], β [effect of presynatpic glutamate that influences glial IP3 production], γ (Gamma) [strength of the astrocyte influence on the postsynaptic neuron via glial mediator], δ (delta) [strength of the astrocyte excitatory influence on synapse], η (eta) [strength of the astrocyte inhibitory influence on synapse]

In order to model the inhibitory and excitatory roles of astrocytes we consider two gliotransmitters that are sensitive to calcium concentration, glutamate as excitatory and ATP as inhibitory. We used

$$\begin{cases} \tau_{G_m} \frac{dG_m}{dt} = \left(1 + \tanh\left(s_{G_m}(c - h_{G_m})\right)\right)(1 - G_m) - \frac{G_m}{d_{G_m}} \\ \tau_{G_a} \frac{dG_a}{dt} = \left(1 + \tanh\left(s_{G_a}(c - h_{G_a})\right)\right)(1 - G_a) - \frac{G_a}{d_{G_a}} \end{cases} \quad (8)$$

For modeling these gliotransmitters which G_m denotes glutamate and G_a denotes ATP.

III. SIMULATIONS AND RESULTS

In this part we examine the effects of parameter variation in the model and analyze the results. We used α, β, γ, η and δ as the main control parameters which regulate the activation of astrocyte and its response. I_{app} is used as a variable external current that triggers spontaneous activity of the first presynaptic neuron and, thus, allows us to consider the transient dynamics of the neural–astrocyte ensemble. For other neurons we use I_{syn} instead of I_{app}.

A. Frequency and Stimulation interval increase

The complex model for a tripartite neuron proposed by Nadkarni and Jung (2007) illustrates astrocyte cell's influence on transferring the oscillation frequency from presynaptic neuron to the postsynaptic neuron [8]. In this section this event is elaborated further.

It is apparent from Figure 3 that changing the astrocyte cell's parameters changes the frequency and stimulation interval in addition to the signal transfer. This means that for a neural glia network with at least 4 neurons, the frequency of the signal is modulated by the β parameter. Figure 4 shows the amplitude of frequency response of calcium dynamics of astrocyte cell. This shows that increasing β parameter leads to increase of the amplitude of high frequencies and also shifts the main frequency towards higher frequency range.

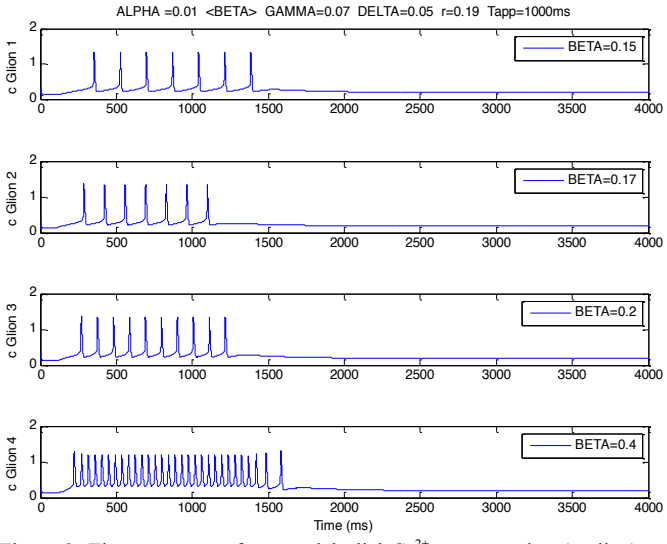

Figure 3. Time response of sequential glial Ca^{2+} concentration (c glion) are plotted for different values of β parameter for each glial. Period of Ca^{2+} oscillation is decrease by increasing β from 0.15(top panel) to 0.4 (bottom panel). So by crossing signal from sequential neuron, it's frequency may be decreed or increased. We describe it as frequency multiplier which is a CPG characteristic.

Thus the astrocyte cell here acts as frequency multiplier. This characteristic of astrocyte cell may be used by the brain to generate high frequency signals through a neural glia network. In this way, the initial signal is a low frequency signal and its frequency can be gradually increased along the pathway. Additionally, this mechanism might be useful for generating variable frequency signals.

B. Glial cells as inhibitors

In Figure 5 a scheme of a branched neural pathway is shown. In this case the synaptic space of neurons 1 and 2 is common and therefore the stimulating signal is same for both neurons and their difference is only in the value of the alpha (α) parameter of their corresponding astrocyte. Effect of increasing extracellular potassium on the astrocyte depolarization is regulated with α parameter in our model.

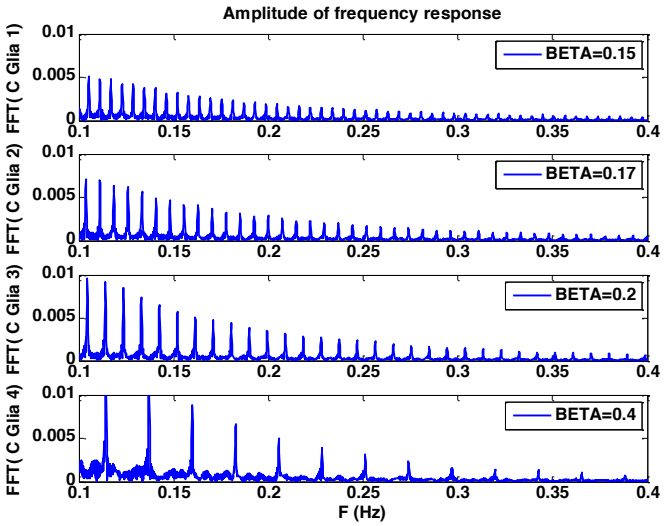

Figure 4. Amplitudes of Frequency response of Glia Ca^{2+} oscillation (FFT(C Glia)) for different β values. The amplitude of some low frequencies is increased by increasing β from 0.15 to 0.4. So effect of low frequencies is more observed in stimulation patterns. There for we can say glia cell capable of changing frequencies of stimulation pattern which is seen in CPG.

As can be seen in Figure 6, the signal has passed neuron 2; however, it's blocked by neuron 3. One of the consequences of this observation is that a glial cell can affect the connection between neurons in different neural network layers and therefore cause changing network structure.

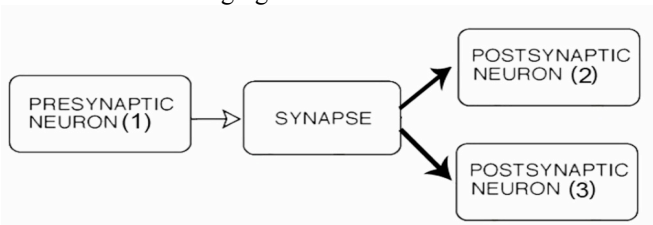

Figure 5. A schematic view of a branched neural pathway is shown. The synaptic space of neurons 2 and 3 is common and therefore the stimulating signal is same for both neurons and their difference is only in the value of the alpha (α) parameter of their corresponding astrocyte.

C. *Alzheimer's disease*

Recent studies shown that intercellular communication via gap junctions is an important modulator of learning and memory performance [19]. Also addresses select metabolic interactions between neurons and astrocytes and emphasizes the role of astrocytes in mediating and amplifying the progression of several neurodegenerative disorders, such as Parkinson's disease, hepatic encephalopathy, hyperammonemia, Alzheimer's disease and ischemia [20].

In this section, the effect of parameters γ and δ variation is analyzed. As shown in Figure 7, by increasing γ in second astrocyte and increasing δ in third astrocyte, the stimulation interval has increased and has become patchy. In reality, if this signal is intended to be the response of human to the action which was completed in 1200 ms, but its effect still remained from 0 to 500 ms after it which may mean irregular function of memory which may appear or not after the stimulation.

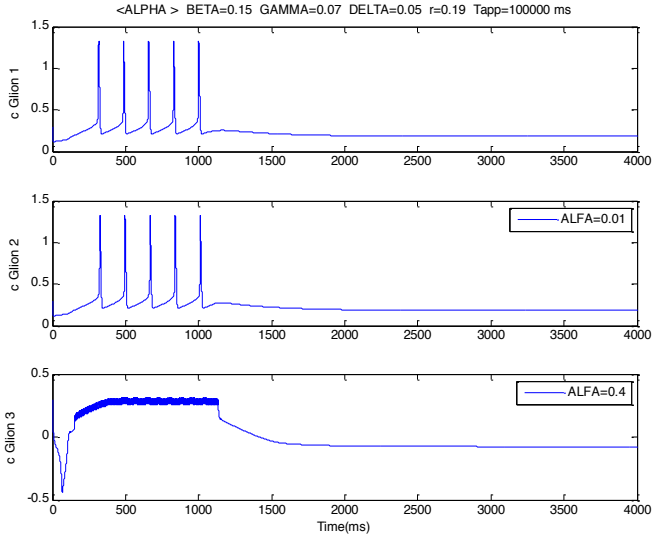

Figure 6. From top to bottom, diagram shows Ca^{2+} oscillatory patterns of the first, second and third glia cells. The signal has passed astrocyte cell 2 which leads to stimulate its corresponding neuron because of increasing α parameter from 0.01 to 0.4; however the astrocyte cell 3 didn't oscillate. As a result presynaptic neuron stimulated neuron 2 and lead to producing action potential by neuron2 and it will stimulate next neuron and so on. So the signal crossed from top pathway which beginning with neuron 2.

It depends on the effect of glia cell. In some disease like Alzheimer, glia cell can play such role.

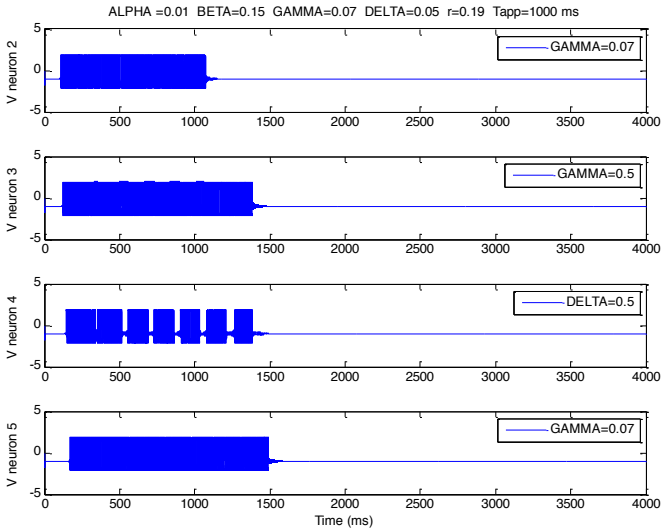

Figure 7. Increase in the γ parameter of second and third neurons of pathway from 0.07 to 0.5 led to an increase in the interval and number of Ca^{2+} spikes of fourth neuron which is seen in bottom panel.

D. *Glia preserve stability of synaptic space*

Brain cortex activity probably reflects the basic strategy of brain information processing; the most popular hypotheses have been advanced to interpret this phenomenon is that suitable combinations of excitatory and inhibitory neurons behave as assemblies of oscillators susceptible to synchronization and desynchronization [21]. Astrocytes are now known to be directly involved in the generation of neuronal synchrony in different areas of brain [22]. One mechanism of the synchronization of neuronal activity is the spontaneous release of glial glutamate [23]. Furthermore recent studies suggest that astrocyte cells regulate certain aspects of synapse development. Neurons can form synapses without glia, however, require glia-derived cholesterol to form numerous and efficient synapses. Synaptic connections appear to require glia to support their structural stability.

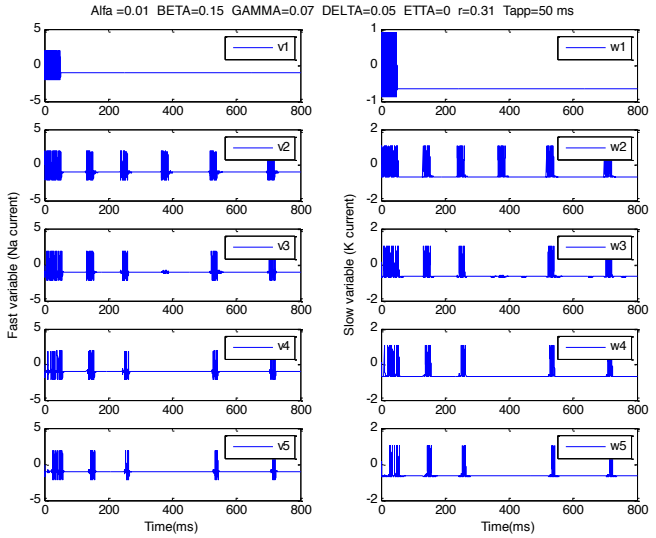

Figure 8. Over stimulation and unstable excitability was observed by omitting the effect of ATP (η=0) which has inhibitory effect on synaptic space.

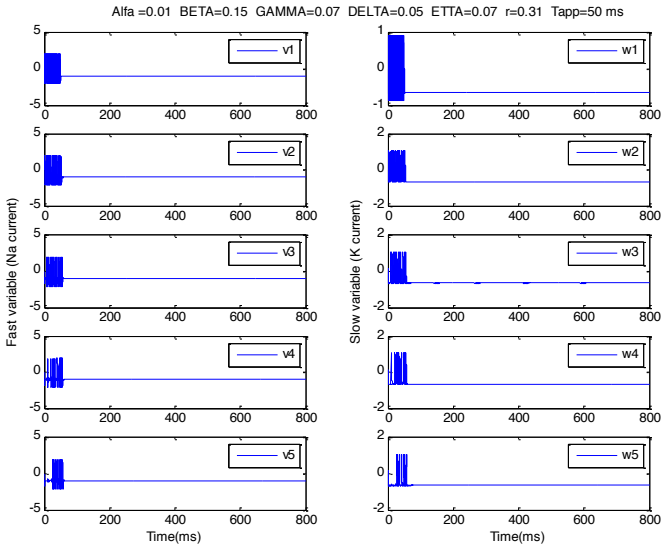

Figure 9. Synaptic stability by adding ATP effect (η=0.7), which has inhibitory effect on synaptic synapse, the noises and over stimulation seen in Figure 8 were omitted and synaptic output was stabilized.

In this section, the effect of parameters η, which reflect effect of inhibitory glial transmitter on synaptic space, is analyzed. As shown in Figure 8, by omitting the effect of ATP (η=0) unwanted stimulation current in synaptic space was observed; however, as shown in Figure 9, by adding ATP effect (η=0.7), the noises are omitted and synaptic output was stabled. This shows that the inhibitory effect of astrocyte with excitatory effect causes stability of synaptic synapse.

We propose that because of capability of astrocyte in controlling the working conditions of neurons, they have important effect on optimal intrinsic subthreshold oscillations (ISO) functionality. Note that ISO have important effect in starting and stopping synchronized firing, and has effective role in brain information processing [21].

IV. Discussion

In summary, we have proposed a functional mathematical model for neural network which concentrates on Astrocyte effects. This modeling approach shows how astrocyte can have inhibitory and excitatory effect on neuronal signal. Despite being qualitative and simplified, it nevertheless reproduces the most typical glial responses and patterns of signal transmission. Furthermore we proposed that glia has important effect on optimal ISO functionality.

This model preserves the essential features of astrocyte such a functional unit: fast and slow activation pathways as well as a dual response of the glia to synaptic and neuronal activities. The model dynamics clearly resembles experimental observations. Namely their ability to exocytotic release of various classes of gliotransmitters such as amino acids like glutamate which have stimulatory effect or nucleotides like ATP which has inhibitory effect [15] and control the synaptic balance with them.

According to the results of modeling presented in this study, astrocyte cells may be regarded as inhibitory and excitatory modulators of the neuronal activity which can have impact in normal as well as abnormal states of brain function. Interactions of these cells with each other have received little attention. By accounting for these interactions, role of astrocyte cells in changing neural network structure and its probable influence on diseases such as Alzheimer's disease can be studied more precisely. By completion of complex models and matching the parameters to biological observations, role of these cells and their influence in biological phenomena will be better understood. Additionally, better models which can present more neurotransmitter of glia and more receptor of it may be used in future to predict diagnosis and treatment of specific neurological disorders.

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