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Astrocyte Stimulation as a New Technique to Desynchronize Two Coupled Neurons

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Abstract- **Experimental researches in recent years have proven that glial cells and specifically astrocytes play several important roles in the central nervous system. Due to difficulties in investigation of astrocyte's functions in neural information processing mechanisms, an appropriate method is computational modeling approach. In this paper, we use the Li-Rinzel model for astrocyte and Izhikevich model for neurons to create a tripartite synapse model and then the role of astrocyte in neural synchronization is explored. Next, the new mechanism of stimulating astrocyte to support impaired astrocyte to maintain normal neural oscillations is proposed. Simulation results show that the malfunction of astrocyte which in turn induces hyper synchronization of the coupled neurons could be compensated by stimulating the astrocyte using an external stimulator.**

Keywords: Tripartite synapse, Astrocyte stimulation, synchronization

I. Introduction

15 years after the end of the "Brain Decade", the human cognitive system still remains a mystery to us. One of the most stable facts that have been found is that our brain is the most complex machine that ever existed. After exploring the structure of firing patterns in neural networks, neurobiology is now looking in a new direction to explain how networks in the brain encode and process information. For a long time after the first description of astrocyte in 1851, it was believed that the only role of glial cells in brain functions is to prepare structural support for the neurons [1]. This view has changed now by a number of several findings that astrocytes could have various functional roles, such as extracellular milieu regulation, synaptic information modulation, neuronal synchronization or feedback to neural activities [2,3]. Astrocytes can sense neuronal transmissions and respond with releasing gliotransmitters and thus "listen and respond" to the synapses and locally regulate neural information processing which leads to propose the concept of "tripartite synapse" [4]. Synchronization processes have the crucial importance for brain functions. Well-coordinated synchrony within and between neuronal populations appears to be an important mechanism for neuronal signaling and information processing [5]. On the other hand, epilepsy and Parkinson have been historically seen as the functional brain disorders that have associated with excessive synchronization of large neuronal cortical populations leading to a hyper-synchronous state [6]. In recent years, there is increasing evidence that a better understanding of the synchronization process can be achieved through analysis of mutual relation between astrocyte and neurons [3,5,7]. Here we attempt to build a computational model of a network where neurons and astrocyte have bidirectional interactions. First, we consider a network with two coupled neurons and without astrocyte in order to reflect synchronous activities of pre- and post-synaptic neurons. Next, we investigate the role of strong and weak astrocyte in de-synchronization of the synchronized neurons.. Nevertheless, the main focus of this study is to compensate the malfunction of weak astrocyte by stimulating the astrocyte using an external stimulator. Results confirm that, astrocyte stimulation using the external stimulator with linear feedback from membrane potential of neurons is able to suppress synchronized oscillations of the coupled neurons.

In addition to investigate the behavior of biological systems from the perspective that will be discussed in this article, recent studies have been concentrated on the digital and analog implementation of similar biological systems [8-12] that can be considered in the future works.

The rest of paper organized as follows: In Section. 2, the network model consisted of dynamic models of the Izhikevich neuron and Li–Rinzel model to describe the calcium exchange in the astrocyte are explained. In Section

3 results of simulation and proposed stimulation technique are presented and finally, Section 4 concludes the article.

II. Network Model

A. Mathematical Neuron Model

In this paper, we use a mathematical model of a neuron that created by Izhikevich [13]. This model reproduces spiking and bursting behavior of known types of cortical neurons. The equations of the model are as follows:

$$v' = 0.04v^2 + 5v + 140 - u + I \quad (1)$$

$$u' = a(bv - u) \quad (2)$$

With the auxiliary after-spike resetting

$$\text{If} \quad v \geq 30mv \begin{cases} v \leftarrow c \\ u \leftarrow u + d \end{cases} \quad (3)$$

Where *a*, *b*, *c*, *d* are neuron parameters and their values are listed in the Table I. *v* represents the membrane potential of the neuron and *u* represents a membrane recovery variable [13]. After the membrane voltage reaches +30 mV, the membrane voltage and the recovery variable are reset according to Eq.3.

B. Astrocyte Mathematical Model

Astrocytes cannot generate action potentials, i.e., the astrocytes are non-excitable electrically but, they can be considered as an active processing element, which communicate closely with neurons [14]. Recent studies have demonstrated that astrocyte is capable of changing the threshold value of transition from synchronous to asynchronous behavior among neurons [5,7]. Astrocytes respond to the neurotransmitter release in the synaptic cleft through IP3 production. Subsequently, elevation of IP3 concentration induces the release of calcium from endoplasmic reticulum (ER), and then more calcium is released depending on the IP3 induced calcium elevation. The elevation of calcium above a certain threshold triggers the release of glial transmitters, which, in turn, will influence the dynamics of the neurons. Here we use Li–Rinzel model to describe the calcium exchange in the astrocyte [15].

$$\frac{d[IP_3]}{dt} = \frac{(IP_3^* - IP_3)}{\tau_{ip3}} + r_{ip3}[T] \quad (4)$$

$$\frac{d[ca^{2+}]}{dt} = J_{chan} - J_{pump} + J_{leak} \quad (5)$$

$$\frac{dq}{dt} = \alpha_q(1 - q) - \beta_q q \quad (6)$$

According to Eq.4, production of IP_3 depends on the amount of neurotransmitter that is released to the synaptic cleft ($[T]$). $[ca^{2+}]$ is the cytosolic calcium concentration, q is the fraction of activated IP_3 receptors and IP_3^* is the equilibrium concentration of IP_3. J_{chan}, J_{pump} and J_{leak} are the calcium flux from the ER to the cytosol, the pump flux from cytoplasm to ER and the leakage flux from the ER to cytosol, respectively. These parameters are given in the following relations:

$$J_{chan} = c_1 v_1 p_\infty^3 n_\infty^3 q^3([ca^{2+}]_{ER} - [ca^{2+}]) \quad (7)$$

$$J_{leak} = c_1 v_1([ca^{2+}]_{ER} - [ca^{2+}]) \quad (8)$$

$$J_{pump} = \frac{v_3[ca^{2+}]^2}{[ca^{2+}]+k_3^2} \quad (9)$$

$$p_\infty = \frac{[IP_3]}{[IP_3]+d_1} \quad (10)$$

$$n_\infty = \frac{[ca^{2+}]}{[ca^{2+}]+d_5} \quad (11)$$

$$\alpha_q = a_2 d_2 \frac{[IP_3]+d_1}{[IP_3]+d_3} \quad (12)$$

$$\beta_q = a_2[ca^{2+}] \quad (13)$$

$$[ca^{2+}]_{ER} = \frac{c_0 - [ca^{2+}]}{c_1} \quad (14)$$

The values of all constants are taken from [5] and given in Table I.

C. Tripartite Synapse Model

In the recent years, we had witnessed an increasing interest in study of neuron-glia interaction. The expression 'tripartite synapse' refers to a concept in synapse based on the demonstration of the bidirectional communication between astrocytes and neurons [4]. Based on this description, in addition to the 'bipartite' information exchange between the pre- and postsynaptic neurons [16], astrocytes exchange information with the synaptic neuronal elements, respond to synaptic activity and, in turn, regulate synaptic transmission. Our model, which is schematized in Fig.1 contains two neurons and one astrocyte.

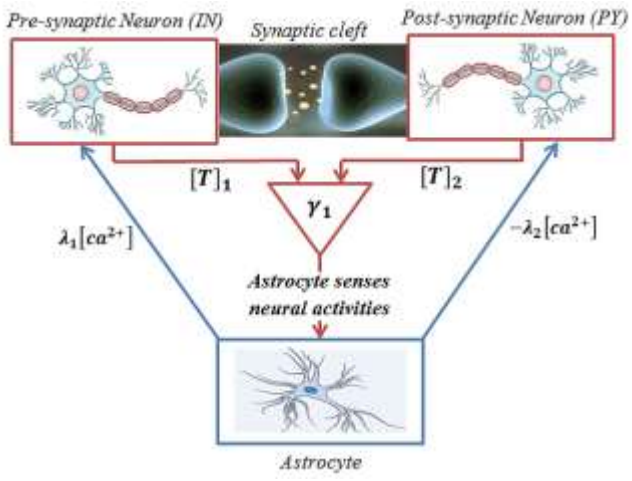

Fig.1: The tripartite synapse in which astrocyte regulates the synaptic transmission via uptake of neurotransmitters or release of gliotransmitters.

With spreading action potential from each neuron, neurotransmitter concentration in the synaptic cleft is modeled by the following equation [17]. In this equation $v(t)$ is the membrane potential.

$$[T] = \frac{1}{1+\exp(-\frac{v(t)-0.2}{0.02})} \quad (15)$$

Pre- and postsynaptic neurons are coupled with the first order differential equation that is utilized to explain the effect of the neurotransmitter release ($[T]_j$) on the nearby j_{th} neuron:

$$\frac{dg(t)_j}{dt} = \alpha_s[T]_i\left(1 - g_j(t)\right) - \beta_s g_j(t) \quad (16)$$

The values of the constant parameters are given in Table I. In order to couple two neurons, we should add "$g_{se}(v(t) - v_{se})g_2$" to Eq.(1) for presynaptic neuron and we have added "$g_{si}(v(t) - v_{si})g_1$" to Eq.(1) for the postsynaptic neuron. On the other hand, the concentration of the neurotransmitter ($[T]_j$) in the synaptic cleft triggers the IP_3 production and is considered as an input of the astrocyte (z) that is defined by the following equation:

$$z = \gamma_1 \sum_{j=1}^{2}[T]_j \quad (17)$$

So that γ_1 is a constant parameter and the output of the astrocyte is defined as:

$$i_j^{ast} = \lambda_j[ca^{2+}] \qquad j = 1,2 \quad (18)$$

This amount is added separately in each neuron equation. So, to implement the interaction between astrocyte with pre- and postsynaptic neurons "$+i^{ast} = \lambda_1[ca^{2+}]$" is added to Eq.1 for pre synaptic neuron (Inter Neuron) and "$-i^{ast} = -\lambda_2[ca^{2+}]$" is added to Eq.1 for post synaptic neuron (Pyramidal Neuron). Therefore, the membrane potential of the pre synaptic neuron ($v_1(t)$) and post synaptic neuron ($v_2(t)$) in the tripartite synapse are defined as follow:

$$\frac{dv_1(t)}{dt} = 0.04v^2 + 5v + 140 - u + i_{constant} + g_{se}(v(t) - v_{se})g_2 + \lambda_1[ca^{2+}] \quad (19)$$

$$\frac{dv_2(t)}{dt} = 0.04v^2 + 5v + 140 - u + i_{constant} + g_{si}(v(t) - v_{si})g_1 - \lambda_2[ca^{2+}] \quad (20)$$

Table I*:* Parameter values of the tripartite synapse network model.

Parameter	Value	Parameter	Value	Parameter	Value
A	0.02	IP_3^*	0.16	v_3	0.9
B	0.2	τ_{ip3}	7	k_3	0.1
C	-50	r_{ip3}	7.2	d_1	0.13
D	1.5	v_1	6	d_5	0.082
d_2	1.05	c_1	0.185	γ_2	0.0004
a_2	0.2	α_s	0.1	g_{si}	0.1
d_3	0.94	β_s	0.05	v_{se}	-0.85
c_0	2	γ_1	1	v_{si}	0

III. Simulation Results

The network in Fig. 1, illustrates the configuration that we used for the first set of simulations. In this case, we want to show the role of astrocytes in neuronal synchronization. Regarding [3,4,7], astrocyte has a key role in controlling synchronization level through intermediacy in synaptic transmissions. In order to synchronize neural firing, we increase the interaction between neurons by increasing the coupling coefficient (g_{se}) according to the first panel of Fig.2. As shown in the second panel of Fig.2, with increasing g_{se} at t=1500ms from 0 to 0.0001, two neurons become synchronized. In this case, we have considered open loop system in Fig.1 which means that astrocyte has no interaction with neurons ($\lambda_1 = \lambda_2 = 0$). In the third panel of the Fig.2, we show LFP as the sum of the membrane voltage of the neurons [18]. When two neurons are synchronized, increasing in the amplitude of the LFP can be observed [3,5].

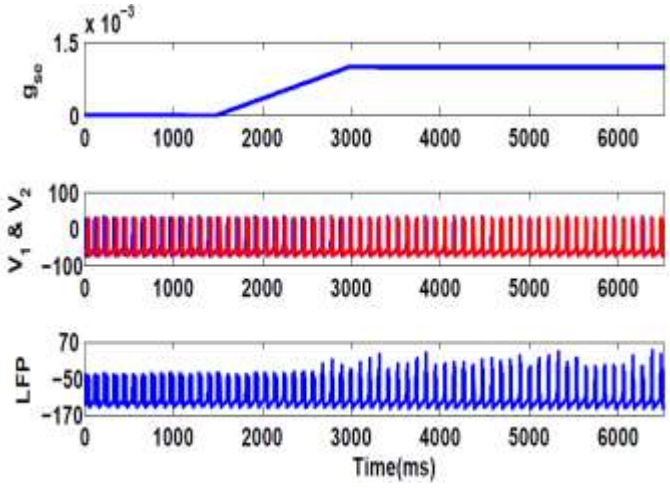

Fig.2: The effect of increasing coupling coefficient (g_{se}) in synchronizing two coupled neurons when astrocyte has not any interaction with neurons ($\lambda_1 = \lambda_2 = 0$).

Next, we consider the close loop system in Fig.1 in which astrocyte has bidirectional interaction with pre- and postsynaptic neurons. In this case, synaptic transmissions are regulated via uptake of neurotransmitters or release of

gliotransmitters. To show the effect of the astrocyte in firing activity of the neurons, the astrocyte begins its interaction with the coupled neurons at t = 6500ms with $\lambda_1 = 1.2$ and $\lambda_2 = 0.9$. As can be seen from Fig.3, astrocyte can provide appropriate feedback signal to return normal asynchronous neuronal firing.

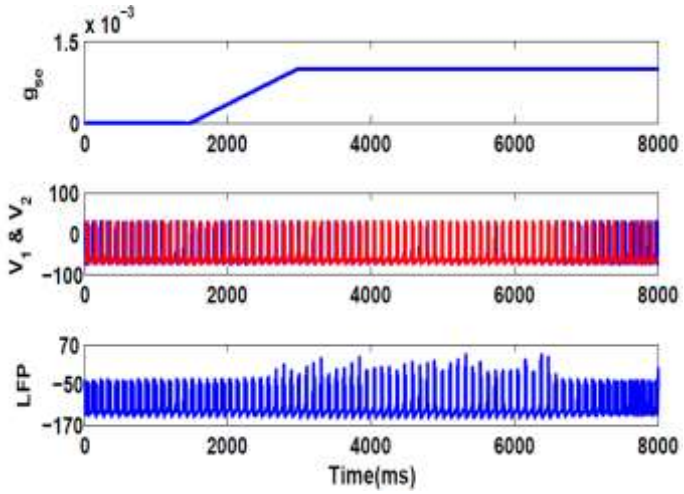

Fig.3: The effect of astrocyte in tripartite synapse. When astrocyte has active interaction with neurons (t>6500ms), it can provide appropriate feedback signal to shift firing of neurons from a synchronized state to the asynchronous state. The amplitude of LFP is also reduced, when astrocyte begins its interaction with neurons.

In the second set of simulations, we consider the effect of the weak astrocyte. In this situation, astrocyte cannot regulate synaptic transmission and provide weak feedback to neurons [7]. To simulate weak astrocyte, we decrease λ_1 from 1.2 to 0.15 and λ_2 from 0.9 to 0.08. Despite of the effort of astrocyte in de-synchronizing coupled neurons, due to weak feedback signal, astrocyte is not able to accomplish its work properly. So, after the astrocyte starts its interaction with the coupled neurons at t = 6500ms, the synchronous firing of neurons still persist. The simulation results under these conditions, has shown in Fig.4.

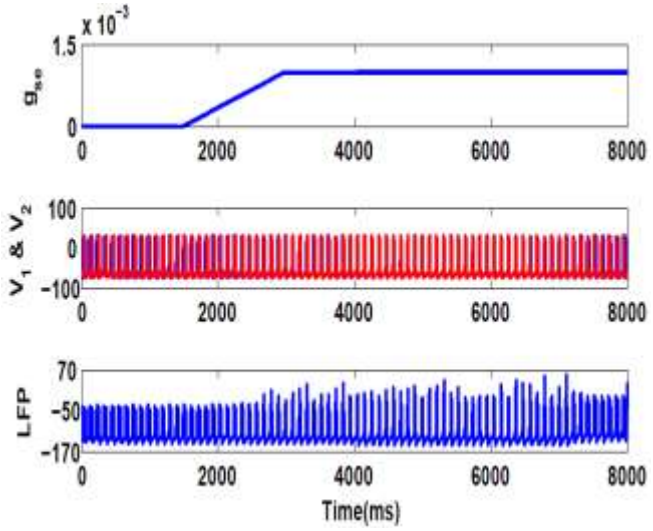

Fig. 4: The effect of weak astrocyte in tripartite synapse. When astrocyte has weak interaction with neurons ($\lambda_1 = 0.15, \lambda_2 = 0.08$), the normal activity cannot be reoccurred.

Considering, Figures 2-4, while the strong astrocyte is able to adjust the synaptic transmission to keep on the normal asynchronous neural activities, the weak one cannot. To deal with this problem, we present new stimulation technique to compensate the malfunction of weak astrocyte performance. So, we consider the close loop system of Fig.5, in order to study the interaction between neurons and weak astrocyte in tripartite synapse.

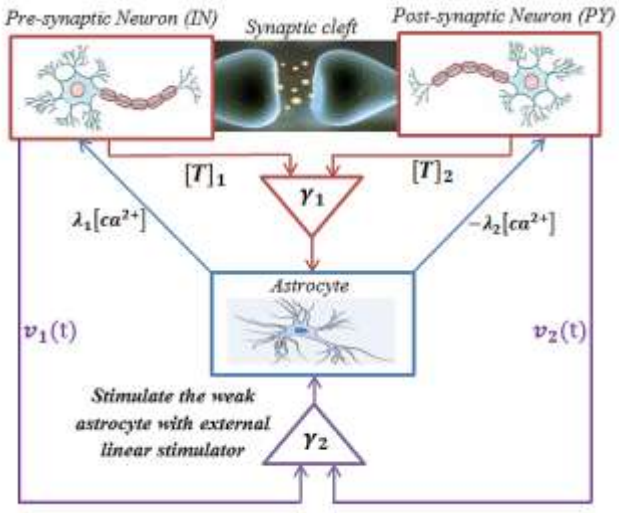

Fig.5: The tripartite synapse with weak astrocytes. In this close loop system, the weak feedback strength from astrocyte to neuron will be compensated by stimulate the weak astrocyte with external linear stimulator. Astrocyte stimulation is proportional to the membrane voltage of neurons.

According to the second panel of Fig.3, by increasing the strength of coupling between neurons at t=1500ms, two

neurons are synchronized. Strong astrocyte that starts its interaction at t=6500ms, can break the synchronization and create an appropriate control signal. As can be observed from the second panel of Fig.4, weak astrocyte cannot perform its function properly. In Fig.5, we proposed a new configuration to assist the impaired astrocyte by astrocyte stimulation according to the neuron's membrane voltage of ($i_{stim} = \gamma_2(v_1(t) - v_2(t))$). To demonstrate the proper performance of the proposed system in Fig.6, we set $\lambda_1 = 0.15$, $\lambda_2 = 0.08$ (weak astrocyte) and then assume that weak astrocyte starts its interaction with neurons at t=6500ms. At t=6500ms, we begin to stimulate astrocyte in order to restore natural asynchronous neural firing. Simulation results are shown in Fig.6. According to this figure, we can conclude that with the proposed system in Fig.5, in spite of having impaired astrocyte, we can preserve normal neuronal activity.

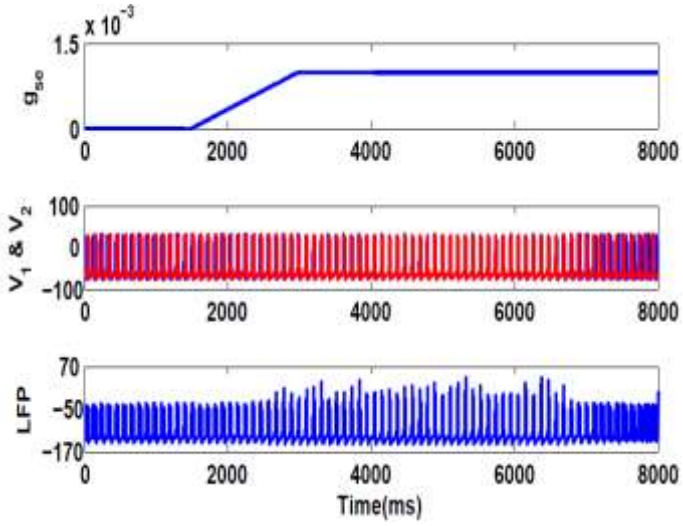

Fig.6: The tripartite synapse in Fig.5 with weak astrocyte and external stimulator with linear feedback from membrane potential of neurons to stimulate the astrocyte. It is obvious that, we can suppress synchronized oscillations of the coupled neurons by stimulating the weak astrocyte.

IV. Conclusion

Synchronization process has crucial importance for brain function in neural signaling and information processing. But excessively synchronized discharge of neurons impaired normal brain performance with several neurological diseases such as Parkinson and epilepsy [19]. In the present work, we have provided a biologically inspired synaptic model based on [7], which the model is made up of pyramidal neuron, interneuron and astrocyte. In recent years, the old view of astrocyte as a simple supportive cell for neurons has changed, so that astrocytes have been known as the active elements of the brain, especially in bidirectional communication with neurons at synaptic level [20]. Astrocyte senses neuronal transmission in tripartite synapse and regulates neurotransmitter release, so that controls synapse activity with providing appropriate feedback signal to neurons. Amiri et al [7] investigated the role of astrocyte in controlling synchronization level. They demonstrated that astrocyte can change the threshold value of transition from synchrony to asynchrony. However, the weak astrocyte cannot adjust input signal of individual neurons in order to desynchronize coupled neurons. To deal with this problem, in this study, the impaired astrocyte has been stimulated using an external linear stimulator. Results showed that the proposed mechanism can suppress synchronized oscillation of the coupled neurons in the tripartite synapse model with impaired astrocyte and is able to return normal neural activities. Future works should be conducted to investigate the performance of the proposed technique using more realistic neuronal models and authenticate the proposed system performance using quantitative criteria.

Acknowledgments

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