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A Proposed Mathematical Model for Tripartite Synapse to Enhance Artificial Model for Artificial Neuron-Astrocyte Networks

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ABSTRACT
An ongoing challenge in machine learning is to advance general and biological inspired artificial models of neural networks which are compatible with the spatial and temporal constraints of the brain. For instance, deep neural networks represent the state-of-the-art for a wide spectrum of applications in machine learning inspired by deep hierarchies of biological cortex, conventional artificial neural networks are inspired by how the biological neuron fires action potentials, and spiking neural networks utilized the neural code that incorporates the concept of timing of individual action potentials. The proposed model in this work concerns the appropriate astrocyte abstractions that capture essential computational principles to advance a biologically inspired model. Therefore, we propose mathematical models based on kinetic model for tripartite synapse to advance a new artificial model for artificial neuron-astrocyte networks. The simulation results showed that such model could change the behavior of LIF and Izhikevich.

Key words: Tripartite synapse, Artificial Neural Network, Mathematical Model Astrocyte.

1. INTRODUCTION

Artificial Neural Networks (ANNs) are powerful tools to perform modelling and to solve non-linear problems inspired by the biological neural networks that compose brains. Asrocytes, the predominant glial cell type in the brain, were traditionally considered as merely passive supportive cells without any important roles in synaptic information processing. In contrast, the contemporary view was given rise to show that astrocytes play active roles such as synaptic Processing [2] , [14] , [16] , [19]neurotransmission [8] , [9] , [16], Long Time Potentiation / Depression (LTP/LTD) [10], Short Term Potentiation/Depression (STDP) [21],[22],[23] and learning or synaptic plasticity [3], [5] , [15] , [18]. Therefore, two concepts have been come forth, the Artificial Neuron-Glial Networks (ANGNs) and Spiking Neuron-Astrocyte Network (SNAN) to incorporate astrocyte in conventional ANN and SNN, respectively. The mechanisms underlying the molecular basis of tripartite synapse and the bidirectional interaction between astrocytes and neurons should be considered[4]. Firstly, when presynaptic neurons release neurotransmitter, e.g. Glutamate, spill to the synaptic cleft to communicate with other neurons, some of such glutamate could also spill out of the cleft and bind to receptors on the neighboring astrocyte. In turn, this stimulates the release of second messenger inositol 1,4,5-trisphospate (IP3) into the astrocytic cytoplasm, then IP3 opens channels to trigger calcium (ca^{+2}). When ca^{+2} levels increase above a threshold [20], the gliotransmitter (glutamate) is released from the astrocyte. In turn, the gliotransmitter glutamate can be released to synaptic cleft to modulate the synaptic activities by different mechanisms.However, in current study we propose mathematical models based on kinetic dynamics to mimic the communication between astrocytes-to-neurons (*tripartite synapse*). One of the pioneer researches in this context, a study by [1]whoimplemented different neuron-glia algorithms for multilayer ANGN to investigate the different astrocyte-neuron interactions by computational models for classification problem. Another study in context of learning algorithms to ANGN, [13] proposed a learning rule for ANGNs that fully automates the learning process based on coevolutionary Genetic Algorithms (GA) and can learn all parameters of the feed- forward, multilayer and fully connected ANGN without back propagation or lateral connections.In the current study, we propose mathematical modelbased on kinetic model for tripartite synapse to advance a new artificial model for artificial neuron-astrocyte networks

2Tripartite Synapse Model (TSM)

The proposed model based on the two-state kinetic models to create a coherent neuron-astrocyte model in which subcellular, cellular, and network properties are described within the same formalism. As illustrated in Figure 1, which represents the proposed three pathways in tripartite synapse,

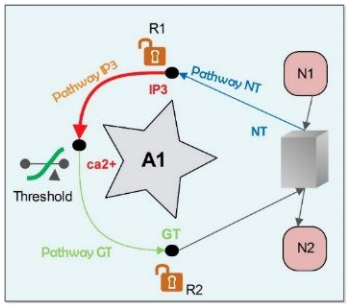

Figure 1: Proposed Pathways for Artificial Tripartite Synapse Model

In this simple model where N1 for presyanptic neurons and N2 postsynaptic neuron, the interaction between astrocyte A1 and the presynaptic neurons N1 and N2 has three pathways: pathway NT with blue dots arrow which represents the pathway between the neurontransmitter NT and the astrocytic second messanger IP3, pathway IP3 with red bold arrowwhich represents the pathway between IP3 and calcium ca^{2+} and the pathway GT is represented by green arrow between $ca^{2+}$and GT. At the intersections of pathway IP3 and pathway GT, there are two channels R1 and R2, respectively. And at the intersection between pathway IP3 and calcium there is a threshold symbole to indicate that calcium has threshold to activate the pathway GT. We first consider that the relationship between the elements of the interaction: the neurotransmitter NT, the second messenger IP_3, the calcium ca^{2+} and the gliotranmitter GT across the two channels (R_1 and R_2) is stimulus-response relationship.

TSMdemonstrate how this relationship will elicit the channels considering that each channel has two states either close or open and the response of the channel changes its state depending on the stimulus. In the description of the model, there are three componants of tripartite synapse (T_1): an astrocyte A, population of presynaptic neurons N_1, and one postsynaptic neuron N_2. We propose to define the three pathways by the following terms: the pathway between neurotranmitter (NT) and the second messenger (IP_3) is termed P_{NT-IP3}, the pathway between IP_3 and the calcium(ca^{2+}) is called P_{IP3-ca} and the pathway between $ca^{2+}$and gliotranmitter (GT) is named P_{ca-GT}. The model has two channels: channel 1 (R_1) between pathways P_{NT-IP3} and P_{IP3-ca}, and the channel 2 (R_2) between pathways P_{IP3-ca} and P_{ca-GT}.
However, to explain the model more clearly and in detail, we break the equations of the proposed astrocyte modelinto three steps based on the interactive pathways and they will be the focus of this section:

2.1 Neurotransmitter Pathway (P_{NT-IP3}): The initiation of $IP_3$is dependent on the amount of the neurotransmitter released to astrocyte which considered as the quanta of total amount of the neurotransmitter released into the synaptic cleft. The synaptic efficacy has been typically defined as the distinctive feature of synapse determined by relevant factors such as the transmitter amount released to synaptic cleftor its simple definition as synaptic weight (single scalar,w_{ij}) to present the strength of the connection between neuron $j$and neuron i. One of the most important subtleties is to quantify the synaptic efficacy. Hence, we propose to utilize any synaptic input equation to calculate the quanta of the neurotranmitter released to astrocyte by modifying the synaptic efficacy term, let assume the synaptic efficacy denoted as T_{syn}. Apparently, this proposed model of ATSM is not confined to SNN, it can be applied to any ANN architecture by calculating the amount of neurotransmitter released into synapse through any term represents the synaptic strength or the efficacy. However, [7] proposed the relationship between the neurotransmitter concentration and the presynaptic voltage by kinetic models. Hence, we generalize this relationship to be applicable to astrocyte, and we propose the following equation to calculate the quanta of neurotransmitter concentration to stimulate astrocyte:

$$NT = \frac{r_{NT} * T_{syn}}{1+\exp(-v(t)-v_P/k_P)} \quad (1)$$

Where r_{NT} is the rate at which neurotransmitter interacts with astrocyte in order to control the quanta of the neurotransmitter, $v(t)$ is the presynaptic voltage,k_P represent the steepness of the sigmoid function, and v_P is the half activation voltage. Mainly, the effective rate of IP_3 production depends on the quanta of neurotransmitter NT that is being released to astrocytes. The neurotransmitter NT governs the state across the respective channel, The first-order kinetic scheme was introduced by [6]. The notation has been modified and simplified by [7]. We propose the kinetic model to represent the probability of the response (IP_3) given the stimulus of neurotransmitter (NT), can be written as:

$$IP3 + NT \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} IP_3' \quad (2)$$

When spike is ON because $NT > 0$, The fraction of open gate IP3 for each time step Δt is proposed as the following equation:

$$IP3 = r + (IP3 - r)\exp\left(\frac{-\Delta t}{\tau_r}\right) \quad (3)$$

Where Δt is time step, τ_r and r, are control variables where $\alpha, \beta, \beta', and\ T_{max}$ are constants. To calculate the change of the second messenger we propose the following equation:

$$\frac{dIP3}{dt} = \alpha\,[NT](1 - IP3) - \beta\, IP3 \quad (4)$$

The variables r and τ_r are defined as follows:

$$r = \frac{\alpha\, T_{max}}{\alpha T_{max} + \beta}, \quad \tau_r = \frac{1}{\alpha T_{max} + \beta'} \quad (5)$$

When spike is off and $S_{NT} = 0$

$$IP3 = IP3 * \exp\left[-\beta\,(\Delta t)\right] \quad (6)$$

IP_3 will be maintained whenever there is an input stimulus to the synapse. On the other hand of this spectrum, IP_3 depend on the stimulus frequency proportionally, i.e. the higher the input stimulus frequency, the higher the level of IP_3 [20].

2.2 Second Messenger Pathway (P_{IP3-ca}): The channel R_2has the stimulus input of IP_3 (output of R_1) and the response output is calcium. The state diagram that represents the gating of calcium ion channel can be expressed as:

$$Ca2 + IP3 \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} Ca2' \quad (7)$$

To compute the change of the calcium in which the increased IP_3 concentration triggers the calcium release from the ER and can, thus, evoke Calcium (Ca^{2+}) oscillations, hence, we propose the following equation:

$$\frac{d\,[Ca2]}{dt} = \alpha\,[\mathrm{IP3}](1 - Ca2) - \beta\,Ca2 \quad (8)$$

The fraction of open gate ca2+ for each time step Δt is proposed as the following equation:

$$[ca2] = s + ([ca2] - s)\exp\left(\frac{-\Delta t}{\tau c}\right) \quad (9)$$

Where

$$s = \frac{\alpha IP3}{\alpha IP3 + \beta} \quad (10)$$

2.3 Gliotransmitter Pathway (P_{ca-GT}): Increasing calcium concentration in the astrocyte cytoplasm triggers the production of astrocyte gliotransmitter (Glutamate) when ca^{+2} crosses a threshold value ca_{thr}[20]. We assume that gliotransmitter GT is some amount of calcium ca^{2+} is defined as:

$$GT = \begin{cases} \gamma * \left(\frac{1}{1 + \exp\left[(-[ca2] - \theta)/\sigma\right]}\right), if \quad ca^{2+} \geq ca_{thr}, \\ 0\ otherwise \end{cases} \quad (11)$$

Here, γ is a control variable, $\theta$is the value at which the function is half activated, σ is the steepness. the calcium diffused from gap junction channels. Finally, to calculate the term I_{astro}, the astrocyte will release the gliotransmitter glutamate to the synapse as given in:

$$I_{astro}(t) = \sigma\,\mathrm{GT} \quad (12)$$

Here, σ is a control parameter to control the strength of astrocyte.

3. SIMULATIONS AND RESULTS

The simulations have been performed for ATSM in MATLAB. We have used two neuron models,leaky integrate and fire (LIF) and Izhikevich model. Leaky Integrate and Fire (LIF) neuron model usually takes the form of the voltage when the current injection is constant over time as given:

$$V(t) = E_L + R_m I_e + (V(t_\circ) - E_L - R_m I_e)\exp\left(-\frac{t - t_\circ}{\tau_m}\right) \quad (13)$$

We simulate the following parameters values: membrane resistance $R_m = 10\,M\Omega$, time constant $\tau_m = 10\,ms$, the current injection I_e was 1.55, $t_\circ$is any reference time, t is a single time-step $\Delta t = 0.1\,ms$. When the cell receives current injection, the membrane voltage increases with time until it reaches the AP threshold $V_{th} = -55$, the voltage spikes and then immediately reset to its resting potential level $V_{reset} = -75\,mV$, where $V = E_L = -70\,mV\ at\ t = 0$. We run our simulations for $1000\,ms$ total (the initial current pulse of I_o=0 starts at time $t = 0$ to $t_{pulse} = 200\,ms$, the period of $600\,ms$ with $Ie = 1.55$ and the last $200\,ms$ with $I_e = 0$), the firing rates between 1 and $100\,Hz$. Firstly, we ran the LIF alone without astrocyte given the parameters above, the average firing rate was 25 (number of spikes per second) and the number of spikes fired was 16. Secondly, we run the LIF with the proposed TSM based on the assumption that the input of the injected current ($I_e = 1.55$) is equal the term T_{syn} in Equation 1and then we run our model with three pathways equations with the following parameters (fine tuning): r_{NT}=0.1, $t - t_i^f \Delta t = 0.1$, $\tau_1 = 0.2$, $S_\infty = NT$, $S_\circ = 0$, $I_\infty = IP_3$, $I_\circ = 0.3$, $IP_{thr} = 0.3$, $ca_{thr} = 0.6$, $ca_{external} = 0.2, \gamma = 1, \sigma = 1$.

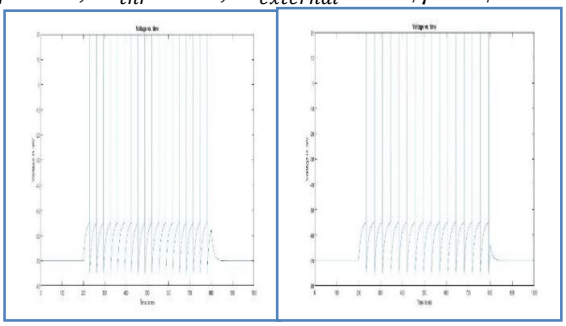

Figure 2: Number of spikes with two simulations: LIF with TSM (left) and without TSM (right)

The results showed that astrocyte has changed the average rate of firing to 30 and the number of the fired spikes to 18 as depicted in **Error! Reference source not found.**: LIF without TSM (right), LIF with TSM (left).

The second neuron model we have used in our simulation is Izhikevich model [11] , [12] , which is based on the following two-dimensional system of ordinary differential equations of the form: $v' = 0.04v^2 + 5v + 140 - u + I$ and $u' = a(bv - u)$, $if\ v \geq 30\,mV, then \begin{cases} v \leftarrow c \\ u \leftarrow u + d \end{cases}$.

The variable v refers to the membrane potential and u refers to the membrane recovery (v and u will be reset when the spike reaches its highest value with +30 mV), the variable I refers to synaptic currents, the resting potential is between -70 and $-60\,mV$ depending on b, the threshold potential can be between $-55\,mV$or and -40 mV, the parameter a represents the time scale of the recovery variable u and the parameter b represents the sensitivity of u to the subthreshold fluctuations of v, the parameter c represents the after-spike reset value of v, and the parameter d represents after-spike reset of u. (the following parameters values were chosen (fine tuning): $a = 0.02, b = 0.2, c = -65\,mV, and\ d = 2$). Simulation has been done on sparse network of 10 000 spiking neurons with 1 000 000 synaptic connections in real time (resolution 1 ms). The synaptic

connection weights between the neurons are given by the matrix $S = (s_{ij})$, so that firing of the jth neuron instantaneously changes variable v by s_{ij} as shown in Figure 3 (left panel). Here we assumed that term T_{syn} in Equation 3.1is equal to the matrix $S = (s_{ij})$ term in Izhikevich model which is represented by a random number between 0 and 1 multiplied by 0.5 for excitatory neurons and by -1 for inhibitory neurons. The following parameters have been chosen for the TSM (fine tuning): r_{NT}=0.1, $t - t_i^f = \Delta t = 0.1$, $\tau_1 = 0.2$, $S_\infty = NT$, $S_\circ = 0$, $I_\infty = IP_3$, $I_\circ = 0.3$, $IP_{thr} = 0.9$, $ca_{thr} = 0.18$, $ca_{external} = 0.2, \gamma = 1, \sigma = 1$.

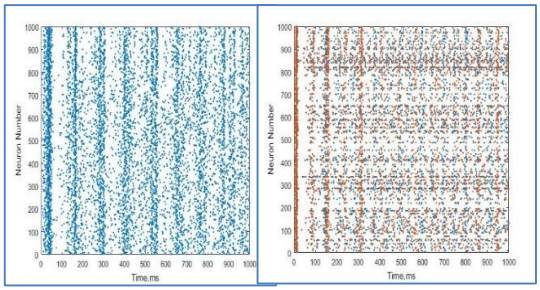

Figure 3: represents spiking activity (blue dots for Izhikevich model in left panel, red dots for TSM in right panel).

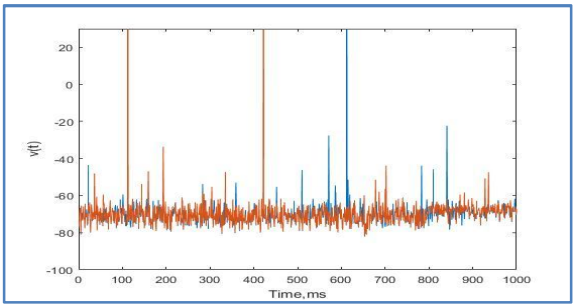

Figure 4: Spiking activity with Izhikevich model, red line for TSM

The simulation results showed that using of TSM has changed the spike behavior (rate and firing pattern) of Izhikevich model as shown in Figure 3 and Figure 4.

4. DISCUSSION

The simulations have been performed for TSM in two neuron models,leaky integrate and fire (LIF) as and Izhikevich model. The performance of the TSM was compared to standard LIF and Izhikevich model. We run our simulations for 1000 ms total and the results showed that using astrocyte (TSM) in the spiking neural network models such as LIF and Izhikevich has changed the average rate of firing (greater) and the number of the fired spikes (greater) or changed the spike behavior (rate and firing pattern) of the SNN models. Consequently, astrocytes increase the postsynaptic potential, in other words, astrocytes may help PSPs to reach the activation threshold to evoke the postsynaptic neuron to fire a spike and this indicates that the results of the simulation of real time astrocyte is matching the biological property related to the relationship between the amount of neuron stimuli (neurotransmitter) and the degree of astrocytic response: the greater the stimuli, the higher the level of functionality by astrocytes or the versatility of astrocytic functions.

Furthermore, the results matched the biological property related to the contribution of gliotransmission in the regulation of the release probability and their influence on the synaptic efficacy (weights) as illustration of the increase in the mean amplitude of excitatory postsynaptic activities. Moreover, the results matched the biological property which states that astrocytes represent an additional neuro-modulatory system that acts in complement to the neuronal ones but with its own time and space domains. Finally, the results matched the biological properties which state that the astrocyte Ca2+ signal is not a stereotyped ‘‘on-off’’ response and can results in large, slow inward currents (SICs) able to significantly depolarize the cells and even to trigger their firing which has been proposed to induce their synchronous firing and enhance the frequency of spontaneous and evoked synaptic currents. In summary, the influence is typically changes in either (1) the frequencies of Excitatory Post Synaptic Potential (EPSP) or Inhibitory PSP (IPSP), (2) SICs, (3) rate of synaptic failure.

5. CONCLUSION

We proposed a model for the interaction between astrocyte and neurons in tripartite synapse to construct the tripartite synapse model (TSM) based on two- state kinetic model. We proposed three pathways to represent the interactions in tripartite synapse and label them as follows: firstly, the pathway from presynaptic neuron to astrocyte called *neurotransmitter-second messenger pathway*. Secondly, the pathway inside astrocyte at which the second messenger IP_3 elicits calcium ca^{+2} named *the second messenger-calcium pathway*. Finally, the pathway at which calcium reaches the threshold and elicits the gliotransmitter to be released to synaptic cleft called *calcium-gliotransmitter pathway*. However, for the first two pathways, there are channels with gate probability to be opened subject to stimuli of the channel. For instance, second messenger (IP_3) and calcium (ca^{+2}) are two channels for the pathways: neurotransmitter-second messenger pathway and second messenger-calcium pathway, respectively. Whereas for the calcium-gliotransmitter pathway, the probability of releasing gliotransmitter is subject to calcium threshold, if calcium crossed the threshold, amount of gliotransmitter will be released to synaptic cleft, presynaptic neuron, or postsynaptic neuron. Therefore, we proposed mathematical model for the tripartite synapse to mimic the channel gating mechanism based on the two-state kinetic model for neurotransmission proposed by [6] , [7]. Furthermore, we simulated the TSM with two neurons model: leaky integrate and fire (LIF) and Izhikevich model. We concluded that TSM model is biological inspired model by matching the results of the simulation with the biological properties presented in section 3. 2. Moreover, we concleded that TSM changed the behaviour of neuron models such as LIF and Izhikevich.

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