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Two Suggested Probabilistic and Kinetic Models for Astrocytic Network in Spiking Neural Networks

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ABSTRACT

Astrocytes, 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 in synaptic neurotransmission and information processing. Hence, recently two terms have been emerged, tripartite synapse, to describe the communication between an astrocyte and two neurons, and the term astrocytic syncytium or astrocytic network to describe the communication among the astrocytes by gap junction. Therefore, we propose mathematical models for tripartite synapseand astrocytic syncytium based on two-state kinetics models, several probabilistic methods and Spiking Neural Network (SNN) to introduce new Artificial Astrocytic Syncytium (AAS) model. The simulation results have shown that proposed model could represent the cellular intrinsic properties of astrocyte based on the spatial and temporal aspects to emulate the astrocytic network functions related to cognitive, learning and memory.

Key words: Astrocytic Syncytium, Gap Junction,Spiking Neural Network, Tripartite synapse.

1. INTRODUCTION

The remarkable characteristic for astrocytes is the ability to connect with other astrocytes by gap junction to allow different molecules and ions to propagate between cells depending on the number of gap junction channels and the probability to open these channels [5], [8],[16], [17]. The gap junction communication is controlled by neurons through neurotransmitters and other related substances [5], [8], [16]. Gap junction related to mediating of calcium signaling in syncytium [3] , [18]and any increase in calcium in one astrocyte, it has relation with increasing calcium in tens of neighboring cells because propagating of calcium waves throughout these astrocyte cells [15]. A sequence of events in the syncytium: The increase in Ca2+ in an astrocyte, the passage of IP3, and/or Ca2+ ions and finally an increase in Ca2+in the neighboring cells [8].However, the calcium is considered the message which transmitted to other cells to control the astrocytes gap junction communication [8] and the calcium is the threshold in syncytium[8].Astrocytic networks are dynamic, perform remodeling, show some plasticity, selective [9]and astrocytes can communicate in a network of 30-100 cells [8] where a single astrocyte may be in contact with thousands of synapses from tens of neighboring neurons where a single astrocytic domain can contact up to 105 synapses [2], [10]and hundreds of dendrites [10]. Finally, Astrocyte signaling is not confined to the active tripartite synapse but can be externalized to adjacent synapses. For this reason, the functional tripartite synapse concept is not the elementary unit in processing information, instead, the interactions between the tripartite synapses must be considered [4]. The global changes in ca2+ might lead to lateral signaling between distant synapses [4], [11]. For instance, an elegant study by [4] suggested the term “lateral astrocyte synaptic regulation” that appears like heterosynaptic modulation which was dependent exclusively on neuronal activity with several shared properties but different mechanisms, this lateral regulation exhibits specific signaling, such as gliotransmission, calcium signaling and intercellular communication between astrocytes by gap junction. Moreover, the propagating astrocytic intercellular calcium waves are considered the excitability way for astrocytes. Therefore, it is noteworthy to understand the mechanisms that underlying the propagation of intercellular calcium waves which may involve eitherthe direct intercellular diffusion of IP_3via gap junctions which can be summarized as follows: In response to the stimulation by neurotransmitter released from presynaptic neuron to the synaptic cleft, astrocyte cell initially activates second messenger (IP_3) receptors. Subsequently, the activated IP_3 will trigger calcium to initiate calcium ca^{2+} oscillations in the cell. These ca^{2+} oscillations can only be initiated when the IP3 concentration is within a specific value [13]. Hence, the IP_3 from the stimulated cell can verify the junctional permeability to communicate with astrocytes within a specific zone based on their IP_3gradients to diffuse and permeate to surrounding cells and trigger the release of their intracellular calcium. Eventually, an intercellular ca^{2+} wave propagates to adjacent cells. Recently, 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.Therefore, we propose mathematical models for tripartite synapse and astrocytic syncytium based on two-state kinetics models, several probabilistic methods and Spiking Neural Network (SNN) to introduce new Artificial Astrocytic Syncytium (AAS) model.

2. TRIPARTITE SYNAPSE BASED ON KINETICS MODELS

The signaling components of the tripartite synapse are neurotransmitter, $IP_3, ca^{2+}$and gliotransmitter, and these components are highly spatially and temporally organized in which they transmit and receive information from one cellular zone in the cell to another causing localized events or global activities. In this section, we introduce the proposed model of the tripartite synapse based on the two state kinetic model of the neurotransmission by [7].The Proposed Model For Tripartite Synapse Pathways can be summerized as following:

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}. However, [7] proposed the relationship between the neurotransmitter concentration and the presynaptic voltage by kinetic models. Hence, we generalize this relationship to be applied to astrocyte, and we propose the following equation to calculate the quanta of neurotransmitter concentration to stimulate astrocyte:

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

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 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 $S_{NT} = 0$

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

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 [19].

Second Messenger Pathway (P_{IP3-ca}): This pathway has the stimulus input of IP_3 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:

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

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

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

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} [19]. We assume that gliotransmitter GT is some amount of calcium ca^{2+} is defined as:

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

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:

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

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

3.ASTROCYTIC NETWORK MODEL BASED ON KINETICS MODELS

In the present section, we propose simple and dynamic astrocyte network model based on kinetics modelsextending the tripartite synapse pathways dynamics of the second messenger, calcium and gliotransmitter kinetics as introduced in last section.[14]Introduced a combined algorithm based on a biophysically-inspired simplified Markov model of the synapse proposed by [6] to optimize the synaptic conductance calculation for the network simulation. Suppose that we have multiple astrocytes, say N, which are connecting in a network of astrocytes receiving from N synapses. For each astrocyte, the fraction of open gate for the second messenger at astrocyte i at each time step Δt was considered in Equation 2.3, and second messenger IP3 is dependent on the neurotransmitter, so IP3 can be split to ON or OFF based on the neurotransmitter, and can sum their values over N astrocytes as follows:

$$\sum_{i=1}^{N_{on}} IP3_{on} = r + \left(\sum_{i=1}^{N_{on}} IP3 - r\right)\exp\left(\frac{-\Delta t}{\tau}\right) \qquad (13)$$

The second messenger can be merged into two groups for active ($[T_{syn}]_i > 0$) and inactive ($[T_{syn}]_i = 0$)

$$IP3_{on} = \sum_i R^i{}_{IP_3} \quad (such\ that\ all\ [S_{NT}]_i > 0) \qquad (14)$$

$$IP3_{off} = \sum_i R^i{}_{IP_3} \quad (such\ that\ all\ [S_{NT}]_i = 0) \qquad (15)$$

And can be written as

$$IP3_{on} = r + (n * IP3_{on} - r)\exp\left(\frac{-\Delta t}{\tau}\right) \qquad (16)$$

$$IP3_{off} = IP3_{off} * \exp\left[-\beta\, \Delta t\right] \qquad (17)$$

n is number of active astrocytes. At each time a pulse of transmitter begins or ends, the variables $IP3_{on}$, and $IP3_{off}$must be changed accordingly. This is easily done because the value of any $\frac{dIP3}{dt}$ at any time can be calculated from its value at the time it last changed. If a spike occurs at a synapse *i*, the following computations are performed:

$$IP3_{on} = IP3_{on} + \frac{dIP3}{dt} \qquad (18)$$

$$IP3_{off} = IP3_{off} - \frac{dIP3}{dt} \qquad (19)$$

where $t_\circ$ is the time of the preceding event that occurred at synapse i. When the pulse of transmitter ends, the following computations are performed:

$$IP3_{on} = IP3_{on} - \frac{dIP3}{dt} \qquad (20)$$

$$IP3_{off} = IP3_{off} + \frac{dIP3}{dt} \qquad (21)$$

where $t_\circ$is the time at which the pulse of transmitter started.

4.ASTROCYTIC NETWORK MODEL BASED ON PROBABILISTIC

Figure 1 shows two tripartite synapses connected by gap junction channels which consist of two astrocytes for each denoted as *A* and *B*, two presynaptic neurons refer to as $N1$ and $N3$ and two postsynaptic neurons $N2$ and $N4$. The following terms have been assigned to the parameters: neurotransmitters *NTA* and *NTB*, second messengers *IPA* and *IPB*, calcium *caA* and *caB*, gliotransmitters *GTA* and *GTB*. The gap junction between the two astrocytes are regulated by *IPA* since the astrocyte *A* is assumed to be an active cell.

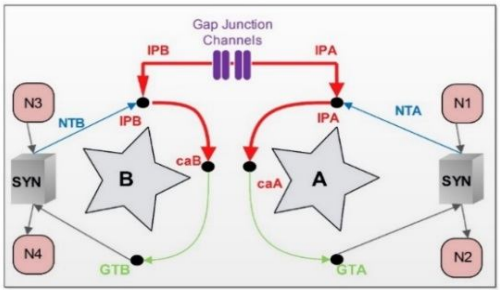

Figure 1: Gap junction between two astrocytes

We propose that astrocyte has four possible phases which represent the relation between the state of astrocyte (spatial and temporal domains of bound and processes) to be in consistent with the proposed pathways of the tripartite synapse:

Silent phase: The none-active state either because the astrocyte enters a refractory period [20],[21] and [22], or there is no spike to activate astrocyte. This phase represents the case when astrocyte is either after pathwayP_{Ca-GT}(entering refractory period) or before pathway between P_{NT-IP3} (spikes are OFF). This phase can be expressed in temporal interval $(t_\circ > t \geq t_{rf})$ where $t_\circ$ is the initial time of neurotransmitter release $(t_\circ = 0)$ and t_{rf} refers to time of refractory.

Stimulating IP_3 Phase: This phase represents the case when astrocyte is within pathway P_{NT-IP3} where the neurotransmitter *NT* has induced IP_3 but the IP_3 threshold has not been reached yet. This phase can be expressed in time domain $(t_\circ \leq t < t_1)$. (t_1) is the time when IP_3 reaches its threshold.

Stimulating ca^{2+}Phase: This phase represents the state when astrocyte within pathway P_{IP3-ca} from the time when IP_3 threshold is reached to the time before ca^{2+} reaching its threshold $(t = t_2)$. This phase can be expressed in temporal intervals $(t_1 \leq t < t_2)$.

Active phase: Represents the case when astrocyte within pathway P_{ca-GT}). Hence, the astrocyte considered to be an active state after the time t_2 (the time when calcium reaches its threshold) to the time when astrocyte enters the refractory period (t=t_{rf}). This state can be expressed as time interval ($t_2 \leq t < t_{rf}$). The phases of astrocyte can be summarized as:

$$S = \begin{cases} silent & t_\circ \geq t \geq t_{rf}, No\ spikes \\ stiumlating \mathrm{IP_3} t_\circ < t < t_1, \text{pathway } P_{NT-IP3} \\ stiumlating\ ca^{2+} t_1 \leq t < t_2, pathway\ P_{IP3-ca} \\ Active & t_2 \leq t < t_{rf}, \text{pathway } P_{ca-GT} \end{cases}$$

Here, S refers to the phases of the spatial and temporal aspects to represent the dynamics of tripartite synapse and they are particularly significant due to the extremely strong relationship between tripartite synapse and gap junction. Moreover, and most excitingly, these phases will serve as parametrization samples from the set of coordinates (silent, stimulating and active) to pick up the needed samples for the comparison between probability distributions of IP_3 concentrations. The Probabilistic behavior for biological molecular communication systems has been intimated in neuroscience. Particularly, in regard to the communication between cells through gap junction [1]. In the current study, we propose an artificial model for the communication between two astrocytes through gap junction by probabilistic methods based on the spatial and temporal phases introduced above. For instance, the following is an illustrative example to represent the spatial and temporal phases for two astrocytes to decide upon the open probability of gap junction channel: if astrocyte A is in active phase and we suggest making assumptions regarding the phase of astrocyte B:

1. When astrocyte B is Silent and astrocyte A is Active: in this case, we assume that astrocyte A will open the gap junction channels and allow the diffuse of IP_A to astrocyte B triggering ca_B to release GT_B to synaptic cleft regulating the synaptic activity.
2. Figure 2 shows an illustrated example of the states of two astrocytes, A and B. In this example we made assumptions regarding their states, astrocyte A is active and astrocyte B is stimulating. First case "A", when astrocyte A is active and astrocyte B is silent, we assumed that the astrocyte A can open the gap junction channels and diffuse IP3. In the second case "B", astrocyte A is active and astrocyte B is stimulating, then in this case, the proposed probabilistic model will be applied. The last case" C", astrocyte A is active and astrocyte B also active, in this case apply standard linear model for gap junction.

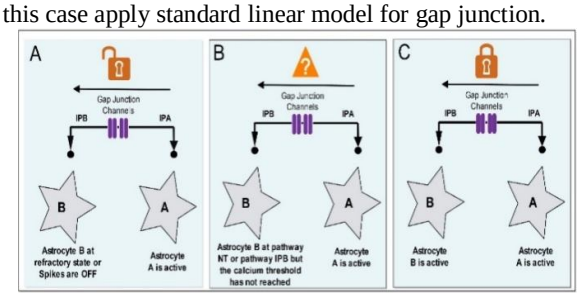

Figure 2: Illustrative example to represent the spatial and temporal phases

3. When astrocyte B is active and astrocyte A is Active: In this case, we propose that the standard linear model will be applied as the following: we assume that the intracellular IP_3 concentrations are given terms IP_{A} and IP_{B} for astrocytes A and B, respectively. The net flux $J_{IP_{\mathrm{A}} \to IP_{\mathrm{B}}}$ is proportional to the concentration difference between IP_{A} and IP_{B} as given by:

$$J_{A \to B} = \varsigma\ (IP_{\mathrm{A}} - IP_{\mathrm{B}}) \qquad (22)$$

Here, ς is the coupling strength. However, the biological justification for such assumption using the standard linear model rather than the proposed probabilistic model is that both astrocytes are active and their IP_3 levels have reached values to start degradation, the aim to make linear comparison between their IP_3 constants values is to examine if they belong to the same functional domain or not.

4. When astrocyte B is in Stimulating IP_3 phase or Stimulating ca^{2+} phase and astrocyte A is Active: we propose probabilistic based model of gap junction to compare between the probability distribution of IP_3 concentrations for both astrocytes (IP_A and IP_B) instead of comparison between constant values of IP_3 as it will be shown in what follows.

The steps of the proposed probabilistic based model of gap junction can be summarized as the following:

1. Choose the population sample of IP_3 values from the concerned pathway: if astrocyte B is in Stimulating IP_3 phase, then the comparison with the probability distributions of active astrocyte A will take place between samples of IP_3 values in pathway P_{NT-IP3} for both astrocytes. Otherwise, if astrocyte B is in Stimulating ca^{2+}phase, then the comparison with the probability distributions of active astrocyte A will take place between samples of IP_3 values in pathways P_{NT-IP3} and pathway P_{IP3-ca} for both astrocytes.

2. Use maximum likelihood estimation (MLE) to fit the data (IP_3 samples) with suitable distribution (normal distribution, exponential distribution or others). Let assume a sample of IP_3 data as$X = X_1, \dots, X_n$, and θ refers to the parameter where $f(x|\theta), x = (x_1, \dots, x_n)$ denotes the density function for the data when θ is the true state of nature. In this case the likelihood function is density function given by $L(\theta|x) = f(x|\theta)$ and the maximum likelihood estimator (MLE) is given by:

$$\hat{\theta} = arg \max_{\theta} L(\theta|x) \qquad (23)$$

3. Compute the probability distribution function (pdf) for the distributedIP_3 values in the concerned samples for both astrocytes.

4. Use one of the comparison methods to define a similarity measure between the probability distribution of A and probability distribution of B such as Kullback-Leibler (KL) divergence (also related to relative entropy). The K–L divergence from $P(B)$to $P(A)$ is often denoted

$D_{KL}\big(p(\mathrm{A}) \parallel p(B)\big)$, and the goal is to calculate $D_{KL}\big(p(\mathrm{C}) \parallel p(D)\big)$ which is defined as:

$$D_{KL}\big(p(\mathrm{A}) \parallel p(B)\big) = \int_{-\infty}^{\infty} p(\mathrm{A})\, Ln\frac{\mathrm{p(A)}}{p(B)}\, d\mathrm{C} \qquad (24)$$

5. Although the KL divergence measures the distance between two distributions, it is not a distance measure and not symmetric (KL from $p(\mathrm{A})$ to $p(B) \neq$ the KL from $p(B)$ to $p(\mathrm{A})$). $D_{KL}\big(p(\mathrm{A}) \parallel p(B)\big)$ is always positive and $D_{KL}\big(p(\mathrm{A}) \parallel p(B)\big) = 0\ if\ and\ only\ if\ p(\mathrm{A}) = p(B)$.

6. Now, our goal is to infer if the active astrocyte A will open the gap junction channels to diffuse IP_3 to astrocyte B based on diffusion equilibrium by which the molecules spread from areas of high concentration to low concentration. In other words, we want to infer if astrocyte A and astrocyte B belong to the same functional domain. Otherwise, astrocyte A has completely different functional domain of astrocyte B. Nevertheless, the ultimate motivation is to establish astrocytic network based on characterizing astrocytes to sub-networks (domains) dependent on the probability distributions of the IP_3 of different cells.

5. SIMULATION AND RESULTS

To illustrate the astrocyte network model by probability distribution comparison, we have used Izhikevich model [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}. Here we assumed that term T_{syn} in Equation 2.1is 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 tripartite synapse pathways kinetic equations (fine tuning):four different parameter values of neurotransmitter stimulation rate ($r_{NT} = 0.1, 0.2, 0.4, 1$), $t - t_i^f = \Delta t = 0.1$, $\tau_1 = 0.2$, $S_\infty = NT$, $S_\circ = 0$, $I_\infty = IP_3$, $I_\circ = 0.3$, $IP_{thr} = 0.9$, $ca_{thr} = 0.18$, $ca_{external} = 0.2, \gamma = 1, \sigma = 1$.

We used the steps of the probabilistic based model of gap junction for the simulation as the following:

- *Choose the population of IP_3 samples:* we have made three PDF comparisons of IP_3 samples in pathway P_{NT-IP3} and time domain ($t_\circ \leq t < t_1$): firstly between astrocyte B with r_{NT}=0.1 and astrocyte A with r_{NT}=0.2, second comparison was between astrocyte B with r_{NT}=0.1 and strocyte A with r_{NT}=0.4 and the last comparison between astrocyte B with r_{NT}=0.1 and astrocyte A with r_{NT}=1. However, the astrocyte B with r_{NT}=0.1 have passed the thrshold of IP_3 at time = 302 ms, astrocyte A with r_{NT}=0.2 at time = 149 ms, astrocyte A with r_{NT}=0.4 at time = 95 and astrocyte with r_{NT}=1 at time=36 ms.
- *Use maximum likelihood estimation (MLE):* to fit the data (IP_3 samples) with suitable distribution we used the maximum likelihood estimation (MLE) with normal distribution and exponential distribution because they were the best distributions fitted our data as depicted in **Error! Reference source not found.**, Figure and **Error! Reference source not found.**

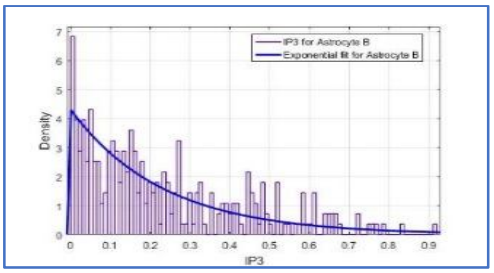

Figure 3: Exponential Fit for PDF of Astrocyte B

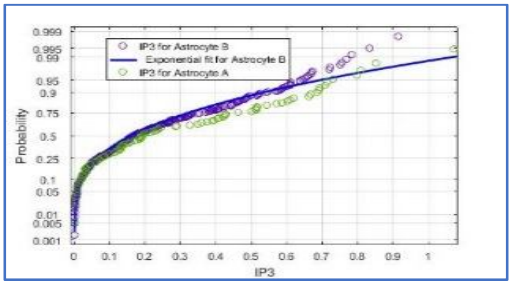

Figure 4: Probability plotting of two astrocytes with differentr_{NT}

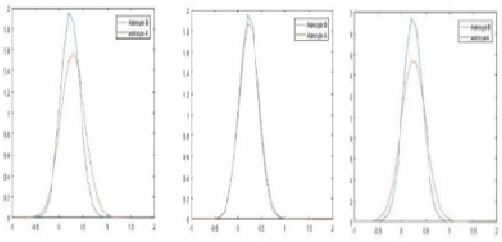

Figure 5: Three different pdf comparison

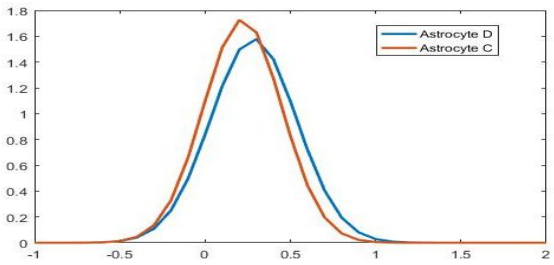

Figure 6: PDF comparisons between two astrocytes

Compute the Probability Distribution Function (pdf) for the distributed IP_3 values: As shown in **Error! Reference source not found.**, the plot between Pdfs of the stimulating astrocyte B and the active astrocyte A (with different values of r_{NT}= 0.2, 0.4, 1). The figure at the left panel is a plot between astrocyte B and astrocyte A with r_{NT}=0.4. In this case, astrocyte A can open the gap junction channel with astrocyte B because the astrocyte A has higher probability than B based on diffusion equilibrium by which the molecules spread from areas of high concentration to low concentration. Whereas the figure at the middle panel, between astrocyte B and astrocyte A with r_{NT}=0.2, the probability distribution of the two astrocytes are so close, but the active astrocyte still able to open the gap junction channel since its probability is higher than the probability of astrocyte B. In the figure at the right panel, the plot between astrocyte B and active astrocyte A with r_{NT}=1, in this case also, the active astrocyte has higher probability and it can open the gap junction.

• *Use one of the comparison methods to define a similarity measure* To measure the similarities and dissimilarities of the pdfs we have used K-L divergence to compare between astrocyte B and different values of the active astrocytes $A.D_{KL}(p(\mathrm{A}=0.2) \parallel p(B=0.1)) = 0.0019$, $D_{KL}(p(\mathrm{A}=0.4) \parallel p(B=0.1)) = 0.0883$, and $D_{KL}(p(\mathrm{A}=1) \parallel p(B=0.1)) = 0.0658$. Let assume that Astrocyte D is an active astrocyte, and astrocyte C is stimulating astrocyte as shown in Figure 3.4, in this case astrocyte D has less probability than astrocyte C, because the probability distribution of IP_3 for Astrocyte C is less than the probability distribution of IP_3 for Astrocyte D. and it couldn't open the gap junction channels based on the diffusion equilibrium. In other words, astrocyte D and C have different domains.

4. CONCLUSION

We introduced a model to mimic the communication between two cells of astrocytes by so-called Gap Junction. This model of Artificial Astrocytic Syncytium (AAS) is dependent on tripartite synapse pathways kinetic model. The steps we have taken to represent the gap junction between two cells can be summarized as follows: consider two astrocytes connected by gap junction, the goal is to illustrate how calcium ions will be diffused from one cell to another. Therefore, we proposed to identify four phases to represent the temporal and spatial states of the astrocyte: The *silence phase* when astrocyte is inactive, the *stimulating IP_3 phase* when the astrocyte at neurotransmitter-second messenger pathway spatially and temporally, *stimulating ca^{2+}phase* when astrocyte at the second messenger-calcium pathway spatially and temporally. Finally, the *active phase* when astrocyte at calcium-gliotransmitter pathway spatially and temporally. In the second step, we proposed probabilistic methods based on the spatial and temporal phases introduced above to compare between two astrocytes based on Probability Distribution Functions (PDFs) to decide upon the open probability of gap junction channel. Then we used one of the comparison methods to define a similarity measure between the probability distributions of these two astrocytes such as: *Kullback-Leibler (KL) divergence.* Finally, to infer if one astrocyte will open the gap junction channels to diffuse IP_3 or calcium to other astrocyte, we suggested the diffusion equilibrium mechanism by which the molecules spread from areas of high concentration to low concentration. The ultimate motivation is to establish astrocytic network based on characterizing astrocytes to sub-networks (domains) dependent on the probability distributions of the IP_3 of different cells. The other method that was used to represent the network of astrocytes was not only through two adjacent cells connected by jap junction, but also by a group of cells that are communicating in the same functional domain. Hence, we proposed "Multiple Domains of Astrocytes", inspired by multiple synapses [14].We have used the simulation of Izhikevich model with tripartite synapse pathways kinetic model and to illustrate the gap junction model by probability distribution comparison, we used the maximum likelihood estimation (MLE) with normal distribution and exponential distribution because they were the best distributions fitted our data. The results showed that astrocyte *with* higher probability can open the gap junction channel based on diffusion equilibrium by which the molecules spread from areas of high concentration to low concentration. We conducted a simulation of Izhikevich model with tripartite synapse model to represent the gap junction model by PDF. We utilized the Maximum Likelihood Estimation (MLE) and we concluded that the proposed gap junction model matched the biological properties related to astrocytic syncytium in terms of the probability of opening gap junction channels by which the molecules spread from areas of high concentration to low concentration.

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