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Research Article

Keywords: dynamic transition, epileptic seizures, random networks, gap junction, inositol triphosphate

Posted Date: June 12th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-231281/v1>

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Version of Record: A version of this preprint was published at Nonlinear Dynamics on August 5th, 2021.
See the published version at <https://doi.org/10.1007/s11071-021-06737-0>.

Channel block of the astrocyte network connections accounting for the dynamical transition of epileptic seizures

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Abstract Epilepsy has been found to be modulated by the astrocyte systems in experiments, and tremendous modeling studies have unveiled the roles of astrocyte cellular functions such as the calcium and potassium channels in the epileptic seizures. However, little attention has been paid to the structure changes of astrocytes in the epileptic seizures in the scale of networks. This paper first constructs a neuron-astrocyte network model to explain the experimental observation that astrocytes mainly induce epilepsy by blocking the channels of the astrocyte gap junction in the network scale. Such model is used to discuss potential seizure induction process in the network by changing the connection intensity of the astrocyte gap junction. The simulation results show that a decrease of

the gap junction intensity changes the firing pattern of the population of neurons from slow periodical firing to high-frequency epileptic seizures, featuring epileptic patterns of depolarization blocks. This further verifies that epileptic seizures are experimentally induced via the channel block of the astrocyte gap junctions. Because of the heterogeneous structure of the real neuron-astrocyte network, the effect of changing astrocyte network structures on the seizure activities is then studied in two typical network structures: the regular neighboring connection and the random connection. The results show that an increase of the number of regular connections of the regular neighboring astrocyte network could inhibit the induction and spread of the epileptic seizures. The epileptic inhibition can be achieved similarly by increasing the connection probability of the random astrocyte network. These findings further provide evidence for the experimental phenomena of the protective response of gliosis to epilepsy with increasing gap junctions. Above all, the simulation results suggest a potential pathway of epilepsy treatment by targeting the astrocyte gap junctions.

Keywords dynamic transition, epileptic seizures, random networks, gap junction, inositol triphosphate

1 Introduction

Epilepsy has long been accepted as a refractory brain disorder, characterized by recurrent seizures. However, the underlying mechanisms of its induction are not fully understood, which negatively affects anti-epileptic clinical trial [1]. Initial experimental studies merely focused on abnormal states of different types of neuronal cells and their connection structures [2–4], and modeling studies investigated the same topics [5–11]. For instance, in modeling studies, epilepsy was demonstrated to be mainly caused by the abnormality in synaptic topology such as network hubs [5] and abnormal ganglia [6]. Wang et al. constructed a mass model of excitatory and inhibitory neurons and found

that defects in inhibitory chemical synapses between interneurons contributed to epilepsy [7]. Furthermore, epilepsy has also been shown to be highly sensitive to changes of connections of both electrical synapses [8,9] and chemical synapses [10] among neurons [9,10]. The synchronized firing among population neurons was reported to be crucial for experimental induction of epilepsy [11]. However, epilepsy not only involves different types of neurons and synapses, but also astrocytes [12–15]. How astrocytes affect epilepsy at the network scale has not been reported to date.

Astrocytes are star-shaped glial cells in the central nervous system (CNS), the proportion of which ranges within 20–40% in different regions in the brain [16]. Astrocytes were understood as supporting topology and energy provision for neurons. Then, they were found to be excitable with oscillations of the calcium concentration (Ca^{2+}) in the cytoplasm [17–19]. The activated Ca^{2+} oscillation was found to induce neuronal discharges by releasing chemical neurotransmitters such as glutamate, gamma-aminobutyric acid, and adenosine triphosphate [20–22]. This neuron-astrocyte loop forms specific circuits of neurons and astrocytes termed “tripartite synapses” [14].

Utilizing the concept of “tripartite synapses”, many researchers have utilized modeling tools to investigate the dynamic transitions of seizures modulated by astrocytes and their released chemicals in single cells as well as networks of astrocytes and neurons [23–29]. Ullah and his colleagues constructed the neuron-astrocyte model in the scale of single cell [23] and network [24] to have unveiled that the astrocytes play significant role in modulating extracellular potassium concentration to ease epileptic seizures. Wei et al. have unfold the intrinsic mechanisms of astrocytes modulating the blood oxygen that is related to brain epilepsy or cerebral stroke spread[25], Our team have modeled the gliotransmitter dynamic model to have proved a specific epileptic pathway dominated by the degradation abnormality of the astrocyte-released glutamate[26]. Moreover, the experiment

has found that the astrocyte gap junction can induce epileptic seizures in its channel blocking state [27]. Some modeling studies have given evidence to prove that the astrocyte network inhibit epilepsy mainly by buffering the potassium ions through their connecting gap junctions [23,29]. While the inositol triphosphate (IP3), the main chemical flux in the gap junctions, has also been addressed to show the potential protective role of astrocyte for neurons in epilepsy [30], but has received little attention.

To unravel the effects of IP3-flux gap junctions of the astrocyte network and its topology on the neuronal network firing dynamics, this paper constructs a neuron-astrocyte network model. This model includes pyramidal cells with electrical connections and astrocytes coupled with gap junctions. Based on this model, the network seizure phenomena were investigated by discussing the intensity and topology changes of astrocyte gap junctions. The mechanism underlying the astrocyte gap junction modulation of seizure activities has been identified.

2 Model and Scheme

2.1 Neuron-astrocyte models

The present study constructed a ring-shape network of neurons (each two-compartment neuron (TCN) includes a pyramidal soma and a dendrite) and astrocytes in consideration of the *in vivo* common ring-shaped networks of neurons and astrocytes [17]. Astrocytes are coupled by IP3-flux gap junctions [17] and neurons are coupled with electrical synapses [9], as shown in Fig. 1. Each astrocyte receives neuronal glutamate stimulation, and in return, imposes excitatory feedback by releasing astrocytic glutamate [14].

The astrocytes were modeled so that the IP3-induced Ca^{2+} oscillation in the cell body increased.

The dynamic Ca^{2+} model is described as [31]:

$$\frac{d[Ca^{2+}]_i}{dt} = c_1 v_1 p_\infty^3 n_\infty^3 q^3 ([Ca^{2+}]_{ER} - [Ca^{2+}]_i) + c_1 v_2 ([Ca^{2+}]_{ER} - [Ca^{2+}]_i) - \frac{v_3 [Ca^{2+}]_i^2}{[Ca^{2+}]_i^2 + k_3^2}, \quad (1)$$

$$\frac{dq_i}{dt} = \alpha_q (1 - q_i) + \beta_q q_i, \quad (2)$$

$$p_\infty = \frac{[IP_3]_i}{[IP_3]_i + d_1}, n_\infty = \frac{[Ca^{2+}]_i}{[Ca^{2+}]_i + d_5}, \quad (3)$$

$$\alpha_q = a_2 d_2 \frac{[IP_3]_i + d_1}{[IP_3]_i + d_3}, \beta_q = a_2 [Ca^{2+}]_i,$$

where $[Ca^{2+}]_{ER} = (c_0 - [Ca^{2+}]_i)/c_1$ represents the equilibrium concentration of Ca^{2+} in the astrocyte (i.e., its endoplasmic reticulum (ER)). The increase of the astrocyte second messenger $[IP_3]_i$ in each astrocyte is modulated by pyramidal dendrite action potentials, which were modeled as [31]:

$$\frac{d[IP_3]_i}{dt} = \frac{1}{\tau_{ip3}} ([IP_3]^* - [IP_3]_i) + r_{ip3} \Theta(V_{d,i} - 35) + g_{A-A} ([IP_3]_{(i+1)} + [IP_3]_{(i-1)} - 2[IP_3]_i), \quad (4)$$

where g_{A-A} represents the coupling intensity between astrocytes. This coupling intensity (or permeability) g_{A-A} depends on the number of gap junction channels and their unitary permeability.

The decrease of g_{A-A} represents the channel block of the gap junction, and the smaller g_{A-A} which is close to 0 represents a higher degree the channel block.

Astrocytes release a constant glutamate flux into the extracellular space when $[Ca^{2+}]_i > 0.2$. During this synaptic-like exocytosis process, the astrocyte release glutamate in the Extracellular Space(ECS) is modeled by a dynamical form of astrocyte glutamate defined in our previous work in [26]:

$$\frac{d[Aglu]_i}{dt} = \frac{([Aglu]^* - [Aglu]_i)}{\tau_{aglu}} + r_{aglu} \Theta([Ca^{2+}]_i - 0.2), \quad (5)$$

$$I_{astro,i} = \lambda_{aglu} [Aglu]_i, \quad (6)$$

where λ_{aglu} corresponds to the expression level of the neuronal receptor that binds to glutamate, and $[Aglu]^*$ represents the equilibrium concentration of the astrocyte glutamate which is mainly dependent on the expression of the astrocyte glutamate intaking function— the astrocyte glutamate transporter[26]. $I_{astro,i}$ represents the feedback current induced by the glutamate from the astrocyte [32–34].

In the neuronal network, each pyramidal soma was subjected to Gaussian noise to simulate the heterogeneous condition among neurons. The neuron model is a two-compartment model of a CA-3 pyramidal neuron [31]. The original model describes three basic dynamical types of responses to either somatic or dendritic stimulation: very low frequency bursting (<8 Hz) (VLF), low frequency bursting (8–20 Hz) (LF), and periodic somatic spiking. The amplitude of the voltages varies among about [−20 80] mV according to the bifurcation map of the voltage versus external current in [31].

The pyramidal soma models are shown as follows [31]:

$$C_m \frac{dV_{s,i}}{dt} = I_{leak}(V_{s,i}) - I_{Na}(V_{s,i}, h_i) - I_{K-DR}(V_{s,i}, n_i) + \frac{g_c}{p} (V_{d,i} - V_{s,i}) + I_{astro,i} + g_{n-n}(V_{s,(i-1)} + V_{s,(i+1)} - 2V_{s,i}) + S\xi_i(t), \quad (7)$$

where g_{n-n} represents the coupling intensity among neurons. The variable $\xi_i(t)$ is a Gaussian white noise with a mean value of zero, defined by $\langle \xi(t) \rangle = 0$, and the noise correlations are described by $\langle \xi(t) \xi(t') \rangle = \delta(t-t')$ [9]. S corresponds to the intensity of the Gaussian noise. $I_{astro,i}$ represents the slow inward current induced by the astrocytic glutamate ([Aglu]) released from the astrocyte. The variable $I_{astro,i}$ and [Aglu] have been described by the Eqs. (6) and (5) respectively.

The ions channel currents are defined as:

$$\begin{aligned} I_{Leak}(V_{s,i}) &= g_L(V_{s,i} - V_L), \\ I_{Na}(V_{s,i}, h_i) &= g_{Na}m_{\infty}^2(V_{s,i})h_i(V_{s,i} - V_{Na}), \\ I_{K-DR}(V_{s,i}, n_i) &= g_{K-DR}n_i(V_{s,i} - V_K), \end{aligned} \quad (8)$$

The dendrite action potential is modeled as [31]:

$$C_m \frac{dV_{d,i}}{dt} = -I_{Leak}(V_{d,i}) - I_{Ca_{neuron}}(V_{d,i}, s_{d,i}) - I_{K-AHP}(V_{d,i}, w_{d,i}) - I_{K-C}(V_{d,i}, c_{d,i}) + \frac{g_c}{1-p} (V_{s,i} - V_{d,i}), \quad (9)$$

$$\begin{aligned} I_{Leak}(V_{d,i}) &= g_L(V_{d,i} - V_L) \\ I_{Ca_{neuron}}(V_{d,i}, s_i) &= g_{Ca_{neuron}}s_i^2(V_{d,i} - V_{Ca_{neuron}}) \\ I_{K-AHP}(V_{d,i}, w_i) &= g_{K-AHP}w_i(V_{d,i} - V_K) \\ I_{K-C}(V_{s,i}, c_i) &= g_{K-C}c_i\chi([Ca_{neuron}]_i)(V_{d,i} - V_K), \end{aligned} \quad (10)$$

$$\chi([Ca_{neuron}]_i) = \min(\frac{[Ca_{neuron}]_i}{250.0}, 1.0),$$

$$\frac{dy}{dt} = \frac{y_{\infty}(x) - y}{\tau_y(x)}, \quad (11)$$

$$x = \begin{cases} V_{s,i} & y = h_i, n_i, m_i \\ V_{d,i} & y = s_i, c_i \\ [Ca_{neuron}]_i & y = w_i \end{cases}, \quad (12)$$

$$y_{\infty} = \frac{\alpha_y}{\alpha_y + \beta_y}, \tau_y = \frac{1}{\alpha_y + \beta_y}, \quad (13)$$

$$\alpha_m = \frac{0.32(13.31 - V_{s,i})}{\exp((13.31 - V_{s,i})/4) - 1}, \beta_m = \frac{0.28(V_{s,i} - 40.1)}{\exp((V_{s,i} - 40.1)/5) - 1},$$

$$\alpha_n = \frac{0.016(35.1 - V_{s,i})}{\exp((35.1 - V_{s,i})/5) - 1}, \beta_n = 0.25 \exp(0.5 - 0.025V_{s,i}),$$

$$\alpha_h = 0.128 \exp((17 - V_{s,i})/18), \beta_h = \frac{4}{1 + \exp((40 - V_{s,i})/5)},$$

$$\alpha_s = \frac{1.6}{1 + \exp(-0.072(V_{d,i} - 65))}, \beta_s = \frac{0.02(V_{d,i} - 51.1)}{\exp((V_{d,i} - 51.1)/5) - 1},$$

$$\alpha_c = \begin{cases} (\exp((V_{d,i} - 10)/11 - (V_{d,i} - 6.5)/27))/18.975 & V_{d,i} < 50 \text{ mV} \\ 2 \exp(V_{d,i} - 6.5)/27 & V_{d,i} > 50 \text{ mV} \end{cases},$$

$$\beta_c = \begin{cases} 2 \exp(V_{d,i} - 6.5)/27 - \alpha_c & V_{d,i} < 50 \text{ mV} \\ 0 & V_{d,i} > 50 \text{ mV} \end{cases},$$

$$\alpha_w = \min(0.00002[Ca_{neuron}]_i, 0.01), \beta_w = 0.001,$$

At the end of the dendrite, the dynamic activity of the neuronal calcium concentration is modulated by the dendrite action potential $V_{d,i}$, which is described by:

$$\frac{d[Ca_{neuron}]_i}{dt} = -0.13 g_{Ca_{neuron}} s_i^2 (V_{d,i} - V_{Ca}) - 0.075[Ca_{neuron}]_i, \quad (14)$$

where V_{Ca} represents the reversal potential of the calcium channel at the dendrite terminal.

2.2 Synchronization factor

Neuronal population synchronization has long been discussed in previous dynamical studies [32–34]. Amiri also emphasizes the significance of neuronal synchronization under the modulation of astrocytes [35–37]. The present study introduces the spike synchronization factor [38]. To alleviate the noisy signals, the voltages of each neuron were firstly transformed into the new form V^* of 1 for $V > 50 \text{ mV}$, and 0 for $V < 50 \text{ mV}$. The threshold 50mV was selected based on the actual voltages

scale shown in Fig.2 upper firing figures, where 50mV is efficient to get rid of the low-amplitude noisy voltages. The fundamental equation of the synchronization factor has the basic form of:

$$R_{ij}^* = \frac{\sum_1^{Ts} V_i^* \times V_j^*}{\sqrt{\sum_1^{Ts} V_i^* \times \sum_1^{Ts} V_j^*}}, \quad (15)$$

Where R_{ij}^* represents the synchronization degree between the i^{th} and j^{th} neuronal voltages for the total step number (Ts) = 100 00000 in the entire time of 100 seconds. Each V_i (or V_j) is the discrete instantaneous voltage at time t . To describe the changing trend of the synchronization factor across time, we have performed a non-overlap time window ($bin=250*100$, simulation time step =0.01ms) for Equation(15) by replacing the “1” and “ Ts ” with “ $(\tau-1)*bin+1$ ” and “ $(\tau)*bin$ ” respectively, and $\tau = 1, 2, 3, \dots, Ts/bin(400)$. Finally, we assigned the center time of each time window, that is $((\tau-1)*bin+1+ (\tau)*bin)/2*0.00001$ seconds, to the time t , then $R(t)$ is obtained by an average of all synchronization degrees cross all the pairs of neurons in the corresponding time t window.

Table 1 The parameters of the formulas above are listed below, the parameters of the two-compartment neuron and astrocyte are selected from the original single neuron-astrocyte model [31], and the astrocyte glutamate-related parameters were selected from astrocyte glutamate dynamical model in [26].

Parameters	Value	Parameters	Value
IP_3^*	0.16 $\mu\text{M}^{[31]}$	g_{K-DR}	15 mS $\text{cm}^{-2[31]}$
τ_{IP_3}	7.14 s ^[31]	g_{K-AHP}	0.8 mS $\text{cm}^{-2[31]}$
r_{IP_3}	0.8 $\mu\text{M s}^{-1[31]}$	g_{K-C}	15 mS $\text{cm}^{-2[31]}$
[Aglu] [*]	0.5 $\mu\text{M}^{[26]}$	$g_{Ca_{neuron}}$	10 mS $\text{cm}^{-2[31]}$
τ_{aglu}	6 s ^[26]	g_c	2.1 mS $\text{cm}^{-2[31]}$
r_{aglu}	1 $\mu\text{M s}^{-1[26]}$	V_{Na}	115 mV ^[31]
λ_{aglu}	2.11 ^[26]	V_K	-15mV ^[31]
C_m	3 $\mu\text{F cm}^{-2[31]}$	V_{Ca}	140 mV ^[31]
g_L	0.1mS $\text{cm}^{-2[31]}$	V_L	0 mV ^[31]
g_{Na}	30 mS $\text{cm}^{-2[31]}$	p	0.5 ^[31]

3 Results of Numerical Simulations

3.1 Glutamate released by the astrocyte network sustains seizure induction

In the numerical studies, we have applied the constant-step fourth-order Runge-Kutta algorithm to simulate the neuron-astrocyte network models directly in the original platform of C++ for saving the simulation time. Also, for the simplification of the coding process in this platform, the form of the fourth-order Runge-Kutta algorithm has been chosen as the constant step type with time step. Although the constant step algorithm involves limitation in solving some abrupt changes in fast-slow dynamics, we have set constant step as small as 0.01ms to reduce the potential computation error. The total integration time was as long as 100 000 ms to guarantee obtaining complete slow dynamics of astrocyte signals. The initial conditions were given as: $V_{s,i}=-4.6$, $n_i=0.001$, $h_i=0.999$, $V_{d,i}=-4.5$, $s_i=0.009$, $w_i=0.6$, $c_i=0.007$, $[Ca_{neuron}]_i=0.2$ [31]. The initial gaps between dendrite and somas simulate the biological condition referred in [31]. The astrocyte initial conditions for systems are all the same as: $[Ca^{2+}]_i=0.1$, $[IP3]_i=0.2$, $q_i=0.1$.

The astrocytes have been found to explain the epileptic seizures when their functions come into abnormality [39–44], the blocked gap- junction channels between astrocytes emerges to be one of the main causes for the astrocyte-related epilepsy [45,46]. However, there remains to be unknown how the IP3-dependent gap junctions modulate the epileptic seizures. For unfolding underlying mechanisms of the blocked gap- junction channels in epilepsy, we have studied the decreases of the astrocyte gap junction intensity g_{A-A} on epileptic seizures. The relevant results are shown in Fig. 2.

As is shown in Fig. 2, when g_{A-A} decreases from 0.3, 0.2, and 0.1 to 0.025, the firing pattern of the neuronal population transits into seizure-like firing from regular spiking. This is termed seizure-like

firing, as shown in the upper right panel of Fig. 2, for the reason that it involves epileptic depolarization blocks as well as the high-frequency characteristics discussed below. Fig. 2 shows that the smaller g_{A-A} is, the earlier the epileptic seizures are induced in the neuronal network. In other words, the less gap junctions among astrocytes are active, the more this contributes to the presence of seizures in the neuronal networks. This explains the experimental phenomena well, i.e., that the channel blocking state of astrocyte gap junctions contributes to epilepsy *in vitro* [27].

Moreover, the population firing rate of the neuronal network f_{neuron} as g_{A-A} decreases was analyzed by averaging the firing rates of all neurons in the network. The firing frequency of the neuronal population firing is the mean of the firing frequency for all the neurons. For each neuron, the firing frequency is obtained by dividing the entire time of 100 s by the peaking number. Here, the peaking number is the filtered one by introducing a proper voltage threshold to get rid of the noisy low-amplitude waves. Fig. 3 shows that when $g_{A-A} < 0.175$, the population firing rate remains lower than 10 Hz. However, when the epileptic seizures emerge at $g_{A-A} = 0.175$, the firing rate of the neuron population abruptly increases to about the gamma band of 40-100 Hz. The human Electroencephalography (EEG) seizure signals were observed to be significant in the gamma band firing oscillation [47,48]. Therefore, the simulated results still portray the characteristic epileptic seizures and shows reasonable frequency.

Although the relationship of astrocyte Ca^{2+} and neuronal epileptic seizures has been addressed by many studies [39–44], little attention has been focused on the statistical relationship between the astrocyte Ca^{2+} frequency and the neuronal state. Therefore, this study also investigated the Ca^{2+} population peaking rate f_{astro} of the astrocyte network, and the mean and standard deviation of all astrocytes were computed and contrasted with the epileptic region of the Ca^{2+} peaking rate *in vitro*

[40]. The population peaking rate of astrocyte f_{astro} is the mean peaking rate for all the peaking rate of each astrocyte. In order to get rid of the initial instantaneous Ca^{2+} resting state, for each astrocyte, the peaking rate is obtained by using the peaking number to divide the peaking duration rather than the whole time. We have presented the mean peaking rate and the corresponding standard deviations in Fig. 4(b), together with the astrocyte population map in Fig. 4(a) to show the properties of the astrocyte population Ca^{2+} oscillations. It can be seen that as the gap junction intensity increases, the mean peaking rate of the astrocyte population Ca^{2+} oscillations gradually decrease until $g_{\text{A-A}} = 0.175$ at which it becomes 0. f_{astro} being close to 0 means that the astrocytes remain in resting mode and the neurons show slow periodical spiking. Meanwhile, the astrocyte population map shows a transition from oscillating state to the resting state when $g_{\text{A-A}}$ increases from 0.025 to 0.275. This suggests that astrocytes play a critical role in maintaining the epileptic seizure of neurons during active Ca^{2+} oscillation that was found in experiments [39]. Furthermore, the simulated f_{astro} of the seizure state was compared with the state *in vitro* [40]. We can see from the figure that the seizure state- Ca^{2+} peaking rate stays higher than the Ca^{2+} peaking rate during seizure in *in vitro* mice (0.4 ± 0.05 peak/min, selected from the most active astrocyte by referring the Fig. 3 and Table 2 of ref. [40]). Because the *in vitro* Ca^{2+} peaking rate was obtained by averaging in a ROI (Region of interest), therefore, it should include some astrocytes in resting state, therefore, the actual Ca^{2+} peaking rate should be bigger. Then the simulated Ca^{2+} peaking rate would be closer to the *in vivo* condition.

Furthermore, a previous experiment showed that astrocyte aberrance causes neuronal seizure activity that highly depends on neuronal synchronization [35]. However, the underlying mechanism is not clear. Generally, epileptic seizures were observed in human brain EEG signals, where they showed synchronized population firing [5], in addition to the depolarization block (DB)-type firing

of single neurons [23]. Therefore, to statistically analyze the neuronal synchronization trend of the neuronal population in the conditions of DB-type firing of single neurons, the spike synchronization index is introduced as described in Eq. (15). $R(t)$ represents the synchronization time series of the neuronal population. Fig. 5 shows the spiking patterns of neuronal populations and the corresponding synchronization time series as g_{A-A} decreases.

The upper panel of Fig. 5 presents the corresponding spiking patterns using the threshold $V_s > 50$ mV. Because there are some noisy voltages during the block depolarization of the epileptic seizures, a relatively high value of 50mV was selected to get rid of the noisy part based on the certain firing shown in Fig.2 upper figures. Here, changes of the neuronal spiking map are consistent with the neuronal firing shown in Fig. 2. Therefore, spiking map-based synchronization not only retains the original firing information, but also can clean the noisy low-amplitude firing. By analyzing these spikes, the time series of the synchronization $R(t)$ are shown in the lower panel of Fig. 5 when $g_{A-A} = 0.3, 0.2, 0.1$ and 0.025 respectively. The results show that regular firing corresponds to a very low $R(t)$ value, while seizure-like bursting phases have a very high $R(t)$ value. These results suggest that the astrocyte gap junction channel blocking process causes the epileptic state of neuronal networks not only with their high frequency and depolarization block characteristics, but also with the synchronized trends. This has been accepted as the typical characteristic of epileptic seizures [5, 11].

3.2 Epileptic seizure of changed astrocyte network structure and connection intensity

The astrocyte network is heterogeneous in different regions, even in different brain states. For example, epilepsy is associated with the typical gliosis, implying increases of astrocyte gap junction topology. There is still no direct evidence for how the astrocyte network modulates this epileptic

state. Therefore, this study focuses on the regular network topology, and the neighboring connections with more than one connection number. Fig. 6 presents the astrocyte network connection forms under different network connection numbers($K_{A-A} = 2, 4$, and 6).

When $K_{A-A} = 2$, the IP3-flux gap junction model can be written as:

$$\frac{d[IP_3]_i}{dt} = \frac{1}{\tau_{ip3}}([IP_3]^* - [IP_3]_i) + r_{ip3} \Theta(V_{d,i} - 35mV) + g_{A-A}([IP_3]_{(i+1)} + [IP_3]_{(i-1)} - 2[IP_3]_i). \quad (16)$$

when $K_{A-A} = 4$, the IP3-flux gap junction model can be written as:

$$\frac{d[IP_3]_i}{dt} = \frac{1}{\tau_{ip3}}([IP_3]^* - [IP_3]_i) + r_{ip3} \Theta(V_{d,i} - 35mV) + g_{A-A}([IP_3]_{(i+1)} + [IP_3]_{(i+2)} + [IP_3]_{(i-1)} + [IP_3]_{(i-2)} - 4[IP_3]_i). \quad (17)$$

when $K_{A-A} = 6$, the IP3-flux gap junction model can be written as:

$$\begin{aligned} \frac{d[IP_3]_i}{dt} = \frac{1}{\tau_{ip3}}([IP_3]^* - [IP_3]_i) + r_{ip3} \Theta(V_{d,i} - 35mV) + g_{A-A}([IP_3]_{(i+1)} + [IP_3]_{(i+2)} + [IP_3]_{(i+3)} + [IP_3]_{(i-1)} + [IP_3]_{(i-2)} \\ + [IP_3]_{(i-3)} - 6[IP_3]_i). \end{aligned} \quad (18)$$

Because the astrocyte connection is sparse, based on the experimental observations [16,17], a larger K_{A-A} over six was not further discussed. Then, this was studied under different K_{A-A} to identify how gap junction channel blocks (i.e., a decrease of g_{A-A}) affect epileptic seizures. The results are shown in Fig. 7. From Fig. 7 we can see that under different network connection numbers K_{A-A} , gap junction channel blocks of decreasing g_{A-A} can consistently induce epileptic seizures. Representative population firing patterns are shown in detail in the inserted panels of Fig. 7. The three cases of K_{A-A} differ in that denser astrocyte junctions obtain a larger K_{A-A} , while slower neuronal population firing transits into an epileptic state when g_{A-A} decreases. This suggests that the increase of astrocyte gap junction topology protects the neuronal network firing from the epileptic state. In fact, an epileptic brain always shows increasing gap junctions, which is commonly termed gliosis in clinical trials [49]. This has been termed as the protective response of the brain to epilepsy [50]. However, if the gliosis grows beyond a certain threshold, other studies demonstrated that gliosis still contributes to a more severe epileptic brain state [51,52].

The above astrocyte topology has been discussed in relation to regular networks, but not close to the real physiological state of the brain astrocyte network topology. Therefore, this study further introduces a random connection into the astrocyte network with the connection probability P_{A-A} .

$$\frac{d[IP_3]_i}{dt} = \frac{1}{\tau_{ip3}} ([IP_3]^* - [IP_3]_i) + r_{ip3} \Theta(V_{d,i} - 35) + g_{A-A} \sum_{j=1}^{50} p_{ij} ([IP_3]_j - [IP_3]_i). \quad (19)$$

Where $p_{ij}=1$ with the probability P_{A-A} and $p_{ij}=0$ with the probability $1-P_{A-A}$, consequently, a larger P_{A-A} represents an increasing gap junction topology density. Based on the random astrocyte network, the effects of increasing the connection probability on the epileptic states of the neuronal network have been studied. First, the case of fixed g_{A-A} when K_{A-A} increases was studied. The results are shown in Fig. 8. The decrease of P_{A-A} induces transitions of neuronal population firing into the epileptic state (e.g., the epileptic firing of the 20th single neuron in the inserted figure panels). This suggests that the increasing topology of astrocyte network gap junctions could protect the brain from epilepsy. However, the location of the boundary of transitions of the neuronal population as both P_{A-A} and g_{A-A} change remains unknown. To identify this boundary, the variation in statistical neuronal population rate f_{neuron} was analyzed as P_{A-A} and g_{A-A} changes. The choice of f_{neuron} as detection parameter of epileptic state arises from the reason that the firing rate represents the neuronal population firing state: high gamma frequency 40-100 Hz represents the epileptic state and the population firing lower than 10 Hz corresponds to regular state of neuronal firing. As Fig. 9 depicts, the frequency of high gamma and slow oscillations region are distinguishable. The slope of this boundary is steep, but rapidly becomes zero as $g_{A-A} > 0.075$. This indirectly suggests that increasing the number of gap junctions of the astrocyte network makes the emergence of epileptic state more difficult. Although we have obtained the boundary for the epileptic seizures in the two-

dimensional space of P_{A-A} and g_{A-A} , some critical factors such as the electromagnetic induction effect were not included[53,54], there must be some gaps between the simulation results and the real ones. Therefore, these factors should be considered in the future studies.

4 Conclusions and Discussions

Previous experimental and modeling studies [26–30,55,56] showed that astrocytes exert an inevitable effect on epilepsy. However, whether astrocytes modulate epileptic seizures into severer or lesser strength remained unknown. In this paper, we have constructed a network model of neurons and astrocytes, and investigated the effect of intensity changes of the astrocyte IP3-depedent gap junction on the epileptic seizures. The results showed that decreasing the intensity of astrocyte gap junctions more easily induces a dynamic transition of neuronal population firing into epileptic seizures. The simulated epileptic seizure patterns involve not only the depolarization blocks [23,39] but also the high frequency ripple firing [47]. Therefore, our model has been proved to be reasonable to study the effect of astrocyte gap junction block on the epilepsy. Moreover, by taking advantages of the synchronization theory, we have investigated the dynamical evolution of the synchronization of the neuronal population firing, another epileptic characteristic. The results support the experimental observation that the epileptic seizures arise with an abrupt synchronization degree increase of the neuronal population firing [5].

Based on this constructed model, the dynamic transition of epileptic seizures was further investigated under different connection forms of the gap junctional astrocyte network: the regular neighboring connection and the random connection with the changes of the corresponding connection parameters. The results showed that both the increase of the regular neighboring connection number and the random connection probability could respectively inhibit the transition

of the neuronal population firing into epileptic seizures. The above increases of the astrocyte network connection also reflect the phenomena of the gliosis, one specific brain protective response to the epileptic induction [50]. Therefore, the simulated results have consistently supported the protective role of gliosis by showing the inhibitory effect of gap junctions on the epileptic induction. Moreover, because the real neuronal network is complex and contains both regular and random astrocyte networks, this comprehensively suggests the astrocyte gap junction as a promising target for epilepsy inhibiting treatment.

Moreover, because the energy metabolism in brain plays critical role in brain function [57], the gap junctional astrocyte network has been shown to not only buffer IP3 [30,40], but also transferred energy metabolism substances, such as glucose [58–60]. This will be further investigated in the future. Moreover, to further identify the network topology effect on seizure dynamics, the potential intervention of the inter-networks among various subnetworks should also be considered in the topological networks of astrocytes [61–63].

Acknowledgements We thank Dr. Yeyin Xu for helpful comments. This work is supported by the National Natural Science Foundation of China (Grant Nos. 11772242, 1197020421, and 12002251), the Natural Science Basic Research Plan in Shaanxi Province of China (2020JM-472, and 2020JM-473).

Data Availability Statement Some or all data, models, or code generated or used during the study are available from the corresponding author by request.

Conflict of Interest The authors declare that they have no conflict of interest.

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Fig. 1 Network scheme of astrocytes and neurons, including 50 astrocytes and 50 two-compartment neurons (TCNs) in a ring-shape network in (a); the astrocytes are connected by the astrocyte gap junction to diffuse IP3 in (b); each TCN includes an pyramidal soma and its dendrite in (c).

Fig. 2 Neuronal population firing versus decrease of the gap junction intensity g_{A-A} . The single neuron firing pattern, presented at the upper panel, is selected from the 20th neuron.

Fig. 3 Evolution of the firing frequency of the neuronal population versus the astrocyte gap junction intensity. g_{A-A} . The increment of g_{A-A} is 0.025 for x-axis.

Fig. 4 The evolutions of astrocyte Ca^{2+} population in response to the increase of g_{A-A} . (a) Astrocyte population Ca^{2+} oscillating map versus decrease of the gap junction intensity g_{A-A} ; (b) Statistical evolution of the mean and standard deviation of astrocyte Ca^{2+} population peaking rate versus g_{A-A} . The astrocyte Ca^{2+} rate during *in vivo* is 0.4 ± 0.05 peak/min[40], and the astrocyte population map in (a) were selected based on the g_{A-A} parameters of the red rectangles in (b).

Fig. 5 Spiking patterns and the dynamical synchronization of the neuron populations versus $g_{A-A} =$

0.3, 0.2, 0.1 and 0.025 (i.e., channel blocking states for the astrocyte network), in Fig. 5 upper panel,

the updated firing series are: 1 for $V_{s,i} > 50\text{mV}$ with black area, 0 for other cases with white area.

Fig. 6 The changed connection number of the regular neighboring connection astrocyte network

with $K_{A-A} = 2, 4, 6$. The black lines represent the gap junctions between pairs of astrocytes.

Fig. 7 Astrocyte population peaking rate under different neural network structural topologies with different $K_{\text{A-A}} = 2, 4, 6$. The inserted maps represent the neuronal threshold-spiking firing patterns at the relevant initial parameter point.

Fig. 8 Neuronal population firing rates under different neural network connection probabilities P_{A-A} .

A. The mean firing rate of the neuronal population in the upper panel were computed by counting the firing peaks that exceed 50 mV to exclude the noise.

Fig. 9 Neuronal population firing frequency distribution versus the random astrocyte network parameters P_{A-A} and g_{A-A} .