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Title: Astrocytic Based Controller Shifts Epileptic Activity to the Chaotic State

Running Title: Astrocyte controller restores chaos

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Abstract

Investigating effective controller to shift hippocampal epileptic periodicity to normal chaotic behavior will be new hope for epilepsy treatment. Astrocytes nourish and protect neurons as well as maintaining synaptic transmission and network activity. Therefore, this study explores the ameliorating effect of astrocyte computational model on epileptic periodicity.

Modified Morris-Lecar equations were used to model hippocampal CA3 network. Network inhibitory parameters were employed to generate oscillation induced epileptiform periodicity. The astrocyte controller was based on a functional dynamic mathematical model of brain astrocytic cells.

Results demonstrated that synchronization of two neural networks shifted the brain chaotic state to periodicity. Applying astrocytic controller to the synchronized networks returned the system to the desynchronized chaotic state.

It is concluded that astrocytes are probably a good model in controlling epileptic periodicity. However, more research efforts are needed to delineate the effect.

Keywords: Epilepsy, Chaos, Astrocyte, Computational model, Desynchrony

I. Introduction

Modulating the dynamic properties of neuronal networks (Sarkisian, 2001), using the nonlinear techniques is a common method to control seizures (Aihara, 2012; de Paula & Savi, 2008). These methods usually assume a tiny stimulus, applied at an accurate short time, capable of interfering with the dynamics of brain excitability to change the dynamics from a periodic and synchronized activity into a desynchronized neuronal firing (Milton & Jung, 2003). Since the antiepileptic drugs and surgical excision of the seizure focus as the classic controlling methods are ineffective in about one third of epileptic patients (Tsakalis, Chakravarthy, Sabesan, & Iasemidis, 2006), electrical therapeutic methods could be an alternative or, in some cases, supplemental treatment to control seizures through modulating the abnormal neuronal activity (Sunderam, Gluckman, Reato, & Bikson, 2010). The advantage of this method compared with surgery and drugs is that surgery is irreversible and has permanent effects on some parts of the brain, while the stimulation has a transient ameliorating effect on that specific region of the brain. Furthermore, unlike drugs, the variable dosage of stimulation can be easily applied in every region. However, because of unknown epileptic dynamics, duration and accuracy of electrical interference are not completely understood. On the other hand, due to the empirical nature of stimulation paradigm calculation, the intervention may initiate a convulsion in some cases (Sarkisian, 2001). In recent studies, due to the high-frequency of brain waves during the seizure, researchers studied the background mechanism of this high frequency signal to use as a therapeutic intervention (Orban, Kiss, Lengyel, & Erdi, 2001). Chaos anti-control is an application method, based on electrical stimulation and system dynamics, for the treatment and reduction of periodic activity of the nervous system (Christini & Collins, 1995). Schiff et al. introduced the concept of anti-control for the increase of chaos in epilepsy treatment (Schiff et al., 1994).

Due to the unknown equations of the system dynamics, in the case of cerebral seizures, the only available variables are time series. Thus, the methods of nonlinear control systems are used as a model for establishment of chaos (Schiff et al., 1994). Feedback control is used to prevent the transition from chaotic desynchronous state to the synchronized periodicity in CA3 hippocampal neuronal populations. As asynchrony is one of the chaos properties, the effort was reducing the degree of synchronization between two populations of neurons in the hippocampus of the brain to restore chaos. The disappearance of chaos, as the dominant state of activity in the normal brain, will lead to epileptic convulsions. Therefore, restoring the chaotic state means control of epilepsy attack. Astrocytes control the composition of the

extracellular fluid, electrolyte homeostasis and neurotransmitter content (M. Amiri, Bahrami, & Janahmadi, 2010), and hence, regulate the neural synchrony (Fellin et al., 2004; Seiferta, Carmignoto, & Steinhäuser, 2010). They have the potential to reverse the synchrony of two coupled neurons by manipulation of the synchronization threshold (M Amiri, Hosseinmardi, Bahrami, & Janahmadi, 2013). To implement the astrocyte dynamics, Amiri et al. modeled a neuron-astrocyte circuit to alter the pattern of neuronal firing through astrocyte transmission of communication signals (Nazari, Faez, Amiri, & Karami, 2015; Nazari, Faez, Karami, & Amiri, 2014). On the other hand, the failure of astrocytes increases the susceptibility of hypersynchrony and firing of neurons in a regulatory feedback communication (M. Amiri, F. Bahrami, & M. Janahmadi, 2012). Therefore, astrocytes are attractive candidates to be substituted by a controller to control the chaos in the case that two lattice subnetworks are periodically synchronous.

2. Computational Model

In this study, an astrocyte inspired controller (M. Amiri, Montaseri, & Bahrami, 2011) was used to apply a stimulus to two lattice subnetwork of CA3 region developed periodicity due to the epilepsy model. This research focuses on the spatiotemporal behavior of the coupled model of a network in which each node or cell of the network is described by ordinary differential equation model. Introduced network, describes the microscopic, spatiotemporal behavior of a small area of the hippocampal region. Dynamical behavior of this subnetwork, described by the differential equations, is based on two-variable model of Hodgkin–Huxley. These equations were originally introduced by Morris and Lecar (M&L) as a model of Barnacle muscle fiber (Morris & Lecar, 1981), however they were introduced as a tool to model the pyramidal cell functions in a specified network (Fig.1).

Figure1. Interconnections between an excitatory pathway and a population of inhibitory interneurons. The parameter c is the strength of excitatory input to the inhibitory interneurons and the factors α_{exc} and α_{inh} govern the strength of the excitatory and inhibitory synaptic connection, respectively.

Then Larter and her coworkers added an equation to M&L equations to replicate the effect of a population of inhibitory interneurons synapsing onto principle pyramidal cells (Larter, Speelman, & Worth, 1999).

Nonlinear differential equations, described this model, are as following:

$$\begin{aligned} \dot{V}_i = & -g_{ca}m_{\infty}(V_i - 1) - g_KW_i(V_i - V_i^k) \\ & - g_L(V_i - V_i^L) + I \end{aligned} \quad (1)$$

$$- \alpha_{inh}Z_i$$

$$\dot{W}_i = \frac{\phi(w_{\infty} - W_i)}{\tau\omega} \quad (2)$$

$$\dot{Z}_i = b[cI + \alpha_{exc}V_i] \quad (3)$$

The M&L model consists of (1) And (2) without the $\alpha_{inh}Z_i$ term of (1). The first and third variables V_i and Z_i , are the membrane potentials of the pyramidal and inhibitory cells, respectively, while the second variable, W_i , is the fraction of open potassium channels in the pyramidal cell populations of the mentioned subnetwork. The three variables were applied to node “i” in the lattice. The parameters; g_{ca} , g_K and g_L are the total conductance for the Ca, K and leakage channels, respectively. V^K is the Nernst potential for potassium which will be used to link neuronal populations and form a lattice (Larter et al., 1999; Raiesdana & Goplayegani, 2013). The I is the applied current, while $\emptyset$ and b , are temperature scaling factors. The parameter C in (3) is the differential modifier of the current input to the inhibitory interneuron (Raiesdana & Goplayegani, 2013). Parameters of the simulations are summarized in Appendix A. Describing in three-dimensional ordinary differential equations (ODEs) the model is capable of being an effective controlling system, which satisfies the controlling supplies. Such a system is so dynamic that covers different behaviors such as simple limit cycles, complex periodic oscillations and chaotic behaviors (Fig. 2).

Figure2. a) Time series and phase portrait for chaotic state. Where $c = 0.165$, $b = 15$ and $vk = 0.4$, (b. Time series and phase portrait for periodic state, where $c = 135$, $b = 12$ and $vk = 0.5$

Since this lattice model proved to delineate the effects of disinhibition on the model dynamics; this work is going to show how the system's behavior could be altered due to an inhibitory parameter change.

2.1. The dynamics of the model

In this part, dynamical properties of the introduced system will be analyzed. The dynamics of nonlinear systems are mostly illustrated by some graphical tools. The effect of inhibition variation on the dynamic behavior of neural networks in the CA3 region was shown in the below diagrams of time series and phase portraits (Fig.2).

It is illustrated in Fig. (2-a) and Fig. (2-b), system behaviors were altered by changing the parameters of excitation and inhibition and was shifted from chaotic state in part (a) to periodic

state in part (b). Parameters values was selected from Appendix A (Larter et al., 1999), except the amount of V_6 , b , and C which were chosen from Sreenivasan et al. (Nadar & Rai, 2012).

3. Astrocyte based controller

In this part, the astrocyte function and the astrocyte-based controller will be explained.

3.1. The Astrocyte Model

Biological research has confirmed that glial cells function actively in neuronal electrical signaling and information processing (Fellin et al., 2004; Halassa & Haydon, 2010). While astrocytes do not develop electrical activity, they act in response to changes in intracellular calcium concentration (Rosenblum & Pikovsky, 2004). An increase of astrocytic intracellular calcium levels induces the release of glutamate, changes ATP/ADP ratio, and thereby affects nearby synapses and neurons by a feedback mechanism. Astrocytes make synapse-like contact onto pyramidal as well as inhibitory neurons, individually and in a network (M. Amiri et al., 2010).

The main cellular mechanism underly tripartite synapses is as follows: Presynaptic neurons release glutamate as a neurotransmitter following its axon terminal depolarization, and then the released glutamate is bound to its receptor on the astrocyte as well as postsynaptic membrane. Ligand-receptor interaction triggers a series of signal transduction molecules such as IP3 and DAG, which IP3, in turn, induces calcium release from intracellular stores. This concentration change of Ca^{2+} originated from endoplasmic reticulum (ER) source, initiates a calcium wave in astrocytic ensemble via gap junctions and finally induces gliotransmitters (glutamate and ATP) release and regulates the pre to post-synaptic transmission (Fellin et al., 2004; Halassa & Haydon, 2010). A simple and general mathematical model based on the presented equations and signal transmission through the tripartite synapse encompassed the pre- and post-synaptic neurons and the astrocyte, introduced by Amiri and colleagues which is capable of desynchronizing the two coupled synchronized neural oscillators (M Amiri, F. Bahrami, & M. Janahmadi, 2012; M Amiri et al., 2013; M. Amiri et al., 2011; Postnov, Koreshkov, Brazhe, Brazhe, & Sosnovtseva, 2009). Not clear. Please rephrase this part

The proposed model for the mathematical structure of the controller is as follows:

$$\dot{x} = -k_1 x + k_2 + k_3 y \quad (4)$$

$$\dot{y} = (1 + \tanh[k_4(p - k_5)])(1 - y) - k_6 y \quad (5)$$

$$p = a(x_1 + x_2 + y_1 + y_2) \quad (6)$$

The input p triggers the y changes which the y then affects the x dynamics by the term $k_3 y$. The controller output considered x and k_5 is the threshold parameter used for activation and inactivation of the controller. The parameters x_1, x_2, y_1, y_2 are controller input signals received from the neural network. The parameter "a" is input gain. The parameters k_1 - k_6 and a are summarized in Appendix B.

3.2. Closed-loop dynamics

The controller was applied to two subnetworks lattice of the hexagonal neural system, with each subnetwork affected by the controller output, via γX . Schematic illustration of closed-loop system is shown in Fig.3.

Figure3. Schematic illustration of closed loop system.

$$\begin{aligned}
\dot{V}_1 = & -g_{ca}m_{\infty}(V_1 - 1) \\
& - g_k W_1 (V_1 \\
& - V_1^K) \\
& - g_L (V_1 - V_1^L) \quad (7-1) \\
& + I - \alpha_{inh} Z_1 \\
& + \gamma_1 X
\end{aligned}$$

$$\dot{W}_1 = \frac{\phi(W_{\infty} - W_1)}{\tau\omega} + \gamma_1 X \quad (7-2)$$

$$\dot{Z}_1 = b[cI + \alpha_{exc} V_1] \quad (7-3)$$

$$\begin{aligned}
\dot{V}_2 = & -g_{ca}m_{\infty}(V_2 - 1) \\
& - g_k W_2 (V_2 \\
& - V_2^K) \\
& - g_L (V_2 - V_2^L) \quad (8-1) \\
& + I - \alpha_{inh} Z_2 \\
& - \gamma_2 X
\end{aligned}$$

$$\dot{W}_2 = \frac{\phi(W_{\infty} - W_2)}{\tau\omega} - \gamma_2 X \quad (8-2)$$

$$\dot{Z}_2 = b[cI + \alpha_{exc} V_2] \quad (8-3)$$

"X" is the control signal which was applied to the closed loop system capable of desynchronizing the two lattice subnetwork through the terms $\gamma_1 X$ and $-\gamma_2 X$. The positive sign implies to excitation, and the negative sign indicates the inhibition. Input p was considered as ($p = a(V_1 + V_2 + W_1 + W_2)$), an observer that detects the instantaneous change in the membrane potential of the pyramidal neurons and K^+ channels in the two subnetworks and then apply proper controlling signal. Consequently, the closed-loop system was protected from a transition to periodicity.

4. Results

Initial values ($C = 0.13$, $V_6 = 0.6$ and $b = 0.1$) were employed to run the model and a low-dimensional chaotic behavior was resulted, subsequently. This low level of inhibition leads to the reduction of chaotic state and, start of an epileptic seizure (Nadar & Rai, 2012). It is well known that the seizure state (in its pathologic form) precedes the seizure appearance and a gradual development of the seizure dominance will be persued. . Therefore, it seems that this is a proper phase to apply controlling stimulation (Raiesdana & Goplayegani, 2013). This phase is shown in Fig.4.

Figure 4. time series and phase portrates for pre sizure state.

According to section (II. A), initially, we kept the model of low-dimensional chaotic behavior (the simulated state shown in the Fig. 4, pre-seizure state.).

The controller was turned on, in this state, without any manipulating the parameter values. As it is illustrated in the Fig.5, the neural model behavior returned to the chaotic state. The parametric values of closed-loop system are summarized in Appendix B. Results showed that x (controller output) has a strengthening effect on inhibitory cells.

Figure 5. Time series and phase portraits for closed loop system when the controller applied.

5. Discussion

This research aimed to evaluate the effect of astrocyte based mathematical model output onto two CA3 synchronized subnetwork as a convulsion model. The result demonstrated that synchronization was desynchronized and the network was returned to its pre-epileptic chaotic behavior with little effort of astrocyte based controller to maintain the chaotic state.

This study focused on the influence of the astrocyte based controller on two subnetworks of the lattice model of hippocampal CA3 neurons. Upon the mathematical resolving and simulation findings, the controller has the potential to break apart the periodicity in the epileptic model. It seems that feedback controller can be a reliable choice to control this model because of its nonlinear characteristics. It can process the amount of lattice networks output and then apply the controller output to lattice sub-networks. Thus, the network is observing every time, and the controller can intervene every time it is needed.

Altering the dynamic characteristics in epileptogenesis applying by external electrical stimulation, it appears that there exists some confounding factors for a closed-loop control scheme. Results have shown that using a biologically plausible controller, the epileptic periodicity will be resolved. It is well documented that healthy astrocytes will help the network milieu to be cleared of any excitability agent such as, glutamate, which may further provoke another oscillatory activity. Furthermore, as our results showed, the output of the astrocytic model, similar to chemical messenger such as gliotransmitters, may turn down the tuning knob of periodicity. This notion may be helpful regarding the result of a study by Rogawsky et al. that the population of astrocytes increases in the early phases of epileptogenesis which make the epileptic subnetwork a good candidate for the application of the astrocytic based model (Rogawski, 2005). On the other hand, Bedner et al. showed a decrease of the number of gap junction between astrocytes, as key elements of astrocytic synchrony to react to any change of network conditions, on the initial establishment phases of epileptogenesis (Bedner et al., 2015). This type of astrocyte susceptibility to pathologic insult demonstrates the rational behind the inability of endogenous astrocytic function in healing or cessation of epileptogenic development. Therefore, it is proposed that substituting epilepsy induced disabled astrocytes by an astrocyte-based controller could help to prevent from the transition to periodicity or even returning the seizure condition to chaotic conditions. The effectiveness of the model may be related to the direct effects on the neuronal functions and/or activating the regulatory function of remaining healthy astrocytes (M Amiri et al., 2013).

Additionally, simulating the time series of the lattice model showed that the natural complex behavior of the brain will be dominated after restoring the chaotic state. It is expressive for future works to use this controller for models of noisy synchronized epileptic states, as they seem to be more biologically plausible. Furthermore, investigation of this model may be useful in the periodic non-synchronized epileptic state which is a determinant of status epilepticus and other nonstop seizure attacks.

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Author contributions

Mojde Nahtani performed the programmings, computer simulations and wrote the manuscript. Mahdi Siahi and Javad Razjouyan designed the study and helped analyzing the results from engineering and neuroscientific perspectives, respectively.

Declaration of interest

None

Appendix A

Parameter	Description	Value	Value used in the study
V_1	threshold value for m_∞	-0.01	-0.01
V_2	steepness parameter for m_1	0.15	0.15
V_3	threshold value for w	0.0	0.0
V_4	steepness parameter for w	0.30	0.30
V_5	threshold value for α_{exc}	0.0	0.0
V_6	steepness parameter for α_{exc} and α_{inh}	varied	0.4-0.6
V_7	threshold value for α_{inh}	0.0	0.0
g_{ca}	conductance of population of Ca^{+2} channels	1.1	1.1
g_k	conductance of population of k^+ channels	2	2
g_L	conductance of population of leak channels	0.5	0.5
V^k	equilibrium potential of k channels	-0.7	-0.7
V^L	equilibrium potential of leak channels	-0.5	-0.5
τ_∞	time constant for W	1.0	1.0
$\emptyset$	temperature scaling factor	0.7	0.7
I	applied current	0.30	0.30

b	<i>time constant scaling factor</i>	<i>varied</i>	<i>0.12-0.15</i>
c	<i>strength of feed-forward inhibition</i>	<i>varied</i>	<i>0.135-0.165</i>
α_{exc}	<i>strength of excitatory synapse</i>	<i>varied</i>	<i>1</i>
α_{inh}	<i>strength of inhibitory synapse</i>	<i>varied</i>	<i>1</i>

Table A-1. Parametric values for equations (1-3). The used values are from the result of (Nadar & Rai, 2012).

$m_{\infty} = 0.5[1 + \tanh(\frac{v_i - v_1}{v_2})]$	(1)
$W_{\infty} = 0.5[1 + \tanh(\frac{v_i - v_3}{v_4})]$	(2)
$\alpha_{exc} = \alpha_{exc} [1 + \tanh(\frac{v_i - v_5}{v_6})]$	(3)
$\alpha_{inh} = \alpha_{inh} [1 + \tanh(\frac{z_i - v_5}{v_6})]$	(4)
$\tau_w = [\cosh(\frac{v_i - v_3}{2 * v_4})]^{-1}$	(5)

Table A- 2. Variables used in Equations. (1-3) are expressed as follows:

Appendix B

$K_1 = 1$	$K_2 = 0.05$	$K_3 = 1.6$	$K_4 = 1$	$K_5 = 0.03$	$K_6 = 2$
$\gamma_1 = 0.28$	$\gamma_2 = 0.38$	$C = 0.13$	$V_6 = 0.5$	$b = 0.15$	$a = 1.5$

Table B-1. Parametric values for closed loop system for equations. (6-7)

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