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On the role of astrocytes in synchronization of two coupled neurons: a mathematical perspective

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Abstract Based on recent findings, astrocytes, a subtype of glial cells, dynamically regulate the synaptic transmission of neuronal networks. In this research, a biologically inspired neuronal network model is constructed by connecting two Morris-Lecar neuron models. In this minimal network model, neuron–astrocyte interactions are considered in a functional-based procedure. Utilizing the developed model and according to the theoretical analysis carried out in the article, it is confirmed that, the astrocyte increases the threshold value of synchronization and provides appropriate feedback control in regulating the neural activities. Therefore, the healthy astrocyte has the potential to desynchronize the synchrony between two coupled neurons. Next, we investigate malfunction of the astrocyte in the regulatory feedback loop. Mathematically, we verify that pathologic astrocyte is no longer able to increase the synchronization threshold and therefore, it cannot compensate excessive increase in the excitation level. The main reason behind this is the fact that healthy astrocyte can optimally increase the input current of the individual neurons, while the so-called pathological astrocyte is unable to modify correctly the amount of this current. Consequently, disruptions of the signaling function of astrocyte initiate the hypersynchronous firing of neurons. In other words, reduction in neuron–astrocyte cross-talk will lead to synchronized firing of neurons. Therefore, our results propose that the astrocyte could have a key role in stabilizing neural activity.

Keywords Astrocyte · Synchronization · Functional modeling · Mathematical analysis

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1 Introduction

Synchronization is a well-known phenomenon of collective dynamics of interacting oscillators. In normal brain function, synchronization within and between neural populations is an important mechanism for neural signaling and information processing (Hauptmann et al. 2005; Luo et al. 2009). In recent years, synchronization has been extensively studied in different contexts by several researchers. Labouriau and Rodrigues presented a mathematical proof that synchronization in partially coupled Hodgkin-Huxley neuronal model with different parameters is a global behavior when the coupling is strong enough, that is, synchronization will occur regardless of the initial conditions (Rodrigues 1996; Labourian and Rodrigues 2003). Wang and colleagues applied analytical methods to study the synchronization of coupled equations of Morris-Lecar model. They investigated that the dynamical behavior of the coupled Morris-Lecar models changes as the input current changes (Wang et al. 2008). Several attempts have been made to understand when synchronization of neurons coupled via diffusive coupling, that is via gap junctions, occurs (Velazquez et al. 2003; Mancilla et al. 2007; Ermentrout and Wechselberger 2009). Steur and collaborators also studied synchronization

in networks of neuronal oscillators which are interconnected through gap junctions. They presented sufficient conditions for synchronization in these networks using the theory of semi-passive and passive systems (Steur et al. 2009).

On the other hand, there is increasing evidence that an improved understanding of the synchronization process can be achieved through analysis of bidirectional interactions between *astrocytes* and neuronal cells (De Keyser et al. 2008; Amiri et al. 2010). Astrocytes are the most abundant type of *glial cells* and are connected together by gap junctions forming a large functional syncytium. They control the content of extracellular fluid and electrolyte homeostasis, regulate neurotransmitter release, and control synapse formation (Nedergaard et al. 2003). Although astrocytes cannot generate action potentials, they respond to neuronal activities with an elevation of their intracellular calcium levels. In this way, not only astrocytes can *sense* neuronal transmission, but also their calcium elevation leads to the *release* of gliotransmitters such as glutamate or Adenosine Triphosphate (ATP) which can regulate and control the synaptic strengths of neighboring neurons (Hertz and Zielke 2004; Perea and Araque 2005). This fact leads to the concept of the "*tripartite synapse*" (Araque et al. 1999; Haydon and Araque 2002; Fellin et al. 2006) in which the astrocyte, a third active element of the synapse, "*listens and responds*" to the synapse (Newman 2003; Halassa et al. 2009). In light of these findings, one can conclude that the amount of information transmitted across the synapse is modulated by the astrocytic mechanisms.

Concerning important aspects of neuron–astrocyte interactions, few computational models are developed to analyze the relationship between neurons and astrocytes. Nadkarni and Jung proposed a "dressed neuron" model and provided a mathematical framework for the synaptic interactions between neurons and astrocytes in the tripartite synapse (Nadkarni and Jung 2004, 2007; Nadkarni et al. 2008). A generalized and non-dimensional model for the tripartite synapse is proposed by Postnov et al. (2007). Recently, this model was modified in order to be applied to a spatially extended neuron–astrocyte network (Postnov et al. 2009). A minimal model consisting of a pyramidal neuron, an interneuron, and an astrocyte was modeled and simulated by Garbo (2009). He investigated the effect of ATP and the interneuron in the overall neural activity. The release of ATP by the astrocyte influences neural dynamics by modulating firing activity of pyramidal neurons and interneurons. ATP leads to an increase in inhibition by promoting spike generation in the interneurons (Garbo et al. 2007).

In the present study, a pair of biologically inspired neuronal models is coupled considering neuron–astrocyte interactions. We apply a functional approach and exploit the available information from the current literature. Thereby, as a first step, a simple two-neuron network is constructed by connecting two Morris-Lecar neural models. Next, the coupled neuronal models are analyzed mathematically to determine under what conditions two neurons get synchronized. Then, the two-neuron network is extended to include also the fundamental functions of astrocyte in regulation of neuronal dynamics, and is used to provide insights into the role of astrocyte in the neural synchrony. Our mathematical analysis and numerical simulations show that the feedback mechanism, organized by astrocytes, can stabilize normal asynchronous behavior among neurons in spite of being subjected to an abnormal increase in the strength of the excitatory coupling between two neurons. However, reduction in these feedback actions of astrocytes can produce hypersynchronized oscillations. Indeed, the primary reason for this excessive synchronous firing of neurons is the inability of the astrocyte to compensate for the changes in the level of the excitatory coupling.

The rest of the article is organized as follows: In Sect. 2, the dynamic models of the Morris-Lecar neuron, the astrocyte model and coupled neurons with presence and absence of astrocyte are explained. The mathematical analyses of synchronization are discussed in Sect. 3. In this section, we put forward conditions which will result in synchrony of two coupled neurons, and will investigate mathematically the role played by the astrocyte in neural synchrony. Section 4 presents the results of some numerical simulations to shows the correctness of the theoretical deductions. Finally, Sect. 5 concludes the article.

2 Dynamic models of neuron and astrocyte

In this section, we first present the dynamic model of the modified Morris-Lecar (M-L) neuron, two coupled M-L neuron and then mathematical description of the astrocyte and its interaction with two coupled M-L neuron are explained. The modified M-L equations model the flow of potassium and calcium ions and are a three-dimensional description of neuronal spike dynamics. For the astrocyte, a generalized mathematical model which is recently introduced is utilized.

2.1 Neuron model

We use a modified version of the well-known M-L equation as a basic model for each neuron (Morris and Lecar 1981). It includes the contribution of internal ionic fast activity Ca^{2+}, delayed K^{+}, and passive leak currents. In the dimensionless form, the dynamics of the membrane potential, v_j, for a neuron j is as follows (Volman et al. 2007):

$$C\frac{\mathrm{d}v_j(t)}{\mathrm{d}t} = -\bar{g}_{\mathrm{Ca}}\, m_\infty\left(v_j(t)\right)\left(v_j(t)-v_{\mathrm{Ca}}\right) - \bar{g}_{\mathrm{K}} w_j(t)\left(v_j(t)-v_{\mathrm{K}}\right) - \bar{g}_{\mathrm{L}}\left(v_j(t)-v_{\mathrm{L}}\right) + i_j(t) \qquad (1)$$

$$\frac{dw_j(t)}{dt} = \phi[w_\infty\left(v_j(t)\right) - w_j(t)]/\tau_w(v_j(t)) \quad (2)$$

$$i_j(t) = i_j^{\text{const}}(t) + i_j^{\text{noise}}(t) + i_j^{\text{slow}}(t) \quad (3)$$

$$\frac{di_j^{\text{slow}}(t)}{dt} = \varepsilon_j(v^* - v_j(t) - \alpha_j i_j^{\text{slow}}(t)) \quad (4)$$

where w_j is an auxiliary variable and is the fraction of open K^+ channels. The channel conductances $\bar{g}_{\text{Ca}}$, $\bar{g}_{\text{K}}$, and $\bar{g}_{\text{L}}$ for the Ca^{2+}, K^+ and leak currents are constants. The functions $m_\infty\left(v_j(t)\right)$, $w_\infty\left(v_j(t)\right)$ and $\tau_w\left(v_j(t)\right)$ control the dynamics of the ion channels and are defined by the following equations:

$$m_\infty\left(v_j(t)\right) = 0.5\left[1 + \tanh\left(\frac{v_j(t) - \hat{v}_1}{\hat{v}_2}\right)\right] \quad (5)$$

$$w_\infty\left(v_j(t)\right) = 0.5\left[1 + \tanh\left(\frac{v_j(t) - \hat{v}_3}{\hat{v}_4}\right)\right] \quad (6)$$

$$\tau_w\left(v_j(t)\right) = \frac{1}{\cosh\left(\frac{v_j(t)-\hat{v}_3}{2\hat{v}_4}\right)} \quad (7)$$

$i_j(t)$is the applied current to the jth neuron. It consists of a constant background current (i_j^{const}), a slowly varying current (i_j^{slow}) which has been proposed by Rinzel and Ermentrout (1989) as a source of bursting behavior in the individual neurons and a noisy current (i_j^{noise} with amplitude D_n and correlation τ_n) to model the inevitable noise present in real systems (Popovych et al. 2006). ε_j and α_j control the bursting behavior of the jth neuron. It should be mentioned that $i_j(t)$ displays a dynamical behavior due to the presence of i_j^{slow}.

2.2 Two coupled Morris-Lecar neurons

The set of Eqs. 1–7 can be written in the following compact form:

$$\frac{dv_j}{dt} = F(v_j, w_j, i_j) \quad (8)$$

$$\frac{dw_j}{dt} = G(v_j, w_j) \quad (9)$$

where

$$F(v_j, w_j, i_j) = -\bar{g}_{\text{Ca}} m_\infty(v_j(t))(v_j(t) - v_{\text{Ca}}) - \bar{g}_{\text{K}} w_j(t)(v_j(t) - v_{\text{K}}) - \bar{g}_{\text{L}}(v_j(t) - v_{\text{L}}) + i_j(t) \quad (10)$$

$$G(v_j, w_j) = \phi\left(w_\infty(v_j(t) - w_j(t))\right)/\tau_w(v_j(t)) \quad (11)$$

Next, we create a minimal biologically inspired neuronal network model which is consisted of two coupled M-L neurons. The individual neurons are coupled through so called "gap junctions". The mathematical descriptions of two coupled neurons are as follows:

$$\begin{aligned} \frac{dv_1}{dt} &= F(v_1, w_1, i_1) & \frac{dv_2}{dt} &= F(v_2, w_2, i_2) \\ &\quad + g_{\text{se}}(v_2 - v_1) & &\quad + g_{si}(v_1 - v_2) \\ \frac{dw_1}{dt} &= G(v_1, w_1) & \frac{dw_2}{dt} &= G(v_2, w_2) \end{aligned} \quad (12)$$

where $g_{\text{se}}(g_{\text{si}})$ is the maximal conductance for excitatory (inhibitory) gap junctional-based synapses which are positive numbers referred as coupling constants throughout the article. We used g_{se} to change the excitation level. Increase in g_{se} leads to enhancement of the coupling strength between neurons and thereby influences the neural synchrony.

2.3 Astrocyte model

During the last decade, basic research in biology confirmed that glial cells are not only thought to be important for metabolic maintenance and support of the nervous system, but also they are active players in neuronal activity and information processing (Araque et al. 1999; Haydon and Araque 2002; Fellin et al. 2006). The most abundant type of glial cells are star-shaped astrocytes. They have a large number of receptors that are used to get information about synaptic activity. Although astrocytes do not have adequate voltage-gated sodium channels to exhibit electrical excitability, they are excitable with respect to intracellular calcium (Fellin and Carmignoto 2004; Voltarra and Steinhäuser 2004). Increasing the intracellular calcium levels in astrocytes initiates the release of glutamate, ATP, and other neuroactive substances that are capable, by a feedback mechanism, of modulating synaptic strengths between nearby neurons (Newman 2003; Silchenko and Tass 2008).

At the cellular level, the main mechanisms underlying the tripartite synapse are as follows: neurotransmitters such as glutamate, released from presynaptic neuron during its activation, are bound to the metabotropic glutamate receptors (mGluR) of the astrocytes adjacent to synaptic terminals. This triggers the production of the second messenger, inositol (1,4,5)-trisphosphate (IP_3) and release of calcium (Ca^{2+}) into astrocyte cytoplasm from endoplasmic reticulum (ER). These calcium elevations propagate into nearby astrocytes as intercellular calcium waves with the passage of second messengers through gap junctions (Hung and Colicos 2008). As a consequence of the increased intracellular Ca^{2+} concentration, the astrocyte releases gliotransmitters, such as glutamate and ATP into the extracellular space and thereby can regulate pre- and postsynaptic neurons (Araque et al. 1999; Haydon and Araque 2002; Newman 2003; Fellin et al. 2006; Halassa et al. 2009). The aforementioned processes are summarized in Fig. 1.

To model the dynamics of the intracellular Ca^{2+} waves produced by astrocytes, a recently introduced dynamic model of the astrocyte is used (Postnov et al. 2007, 2009). This is a generalized and simplified mathematical model for a small neuron–astrocyte ensemble which considers the main

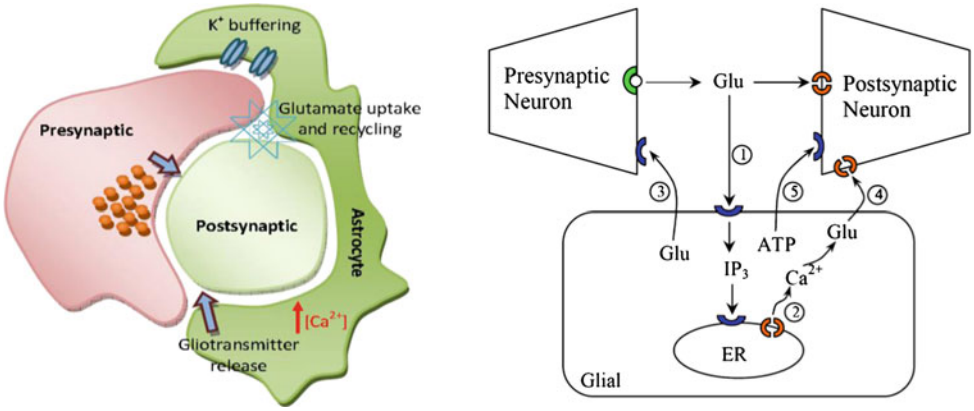

Fig. 1 The main pathways for neuron–astrocyte interactions: (*1*) Release of glutamate from the presynaptic neuron activates astrocytic receptors and (*2*) induces an increase in intracellular Ca^{2+} levels. (*3*) The release of glutamate from astrocyte activates presynaptic receptors and regulates neurotransmitter release, while (*4*) activation of postsynaptic receptors directly depolarizes neurons. (*5*) Stimulation of astrocyte elicits also the release of ATP which, in turn, inhibits nearby neurons (Newman 2003)

pathways of neuron–astrocyte interactions. Consequently, this model will be useful to study the main types of astrocyte response and the resulting dynamical patterns which allow us to predict their changes with varying control parameters. These parameters will be introduced later in this section. This model is explained with the following set of equations (Postnov et al. 2009):

$$\tau_c \frac{dc}{dt} = -c - c_4 f(c, c_e) + (r + \beta\ S_m) \tag{13}$$

$$\varepsilon_c\ \tau_c \frac{dc_e}{dt} = f(c, c_e) \tag{14}$$

$$f(c, c_e) = c_1 \frac{c^2}{1+c^2} - \left(\frac{c_e^2}{1+c_e^2}\right)\left(\frac{c^4}{c_2^4 + c^4}\right) - c_3\ c_e \tag{15}$$

$$\tau_{S_m} \frac{dS_m}{dt} = \left(1 + \tanh\left[S_{S_m}(z - h_{S_m})\right]\right) \times (1 - S_m) - \frac{S_m}{d_{S_m}} \tag{16}$$

$$\tau_{G_m} \frac{dG_m}{dt} = \left(1 + \tanh\left[S_{G_m}(c - h_{G_m})\right]\right) \times (1 - G_m) - \frac{G_m}{d_{G_m}} \tag{17}$$

where c is the calcium concentration in the astrocyte cytoplasm. c_e denotes the calcium concentration within the endoplasmic reticulum. The parameters ε_c and τ_c together define the characteristic time for calcium oscillations. The calcium influx from the extracellular space is sensitive to the production of secondary messenger $S_m(IP_3)$, which is controlled by the factor β. The initial state of the calcium oscillation is controlled by the parameter r. The calcium exchange between the cytoplasm and the endoplasmic reticulum is defined by the nonlinear function $f(c, c_e)$. We set the control parameters $r, \beta, \tau_c, \tau_{S_m}, \tau_{G_m}, s_{S_m}, s_{G_m}, h_{S_m}, h_{G_m}, d_{S_m}, d_{G_m}$ to the values listed in the Table 1 that are taken from (Postnov et al. 2009; Chakravarthy et al. 2007; Popovych et al. 2006). Increase of calcium concentration in the cytoplasm causes release of astrocyte mediator G_m. The interaction between astrocyte and neurons is denoted with the parameter z that shows the synaptic activity of the two coupled neurons.

2.4 Astrocyte interactions with two coupled Morris-Lecar neurons

To have a physiologically inspired network and in order to clarify astrocyte-dependent regulation of neural activities, the initial minimal network model of two-neuron is extended and astrocyte is incorporated into the network. Although for the sake of mathematical simplicity, the two neurons are coupled through a so-called "gap-junction," the interaction between each neuron and the astrocyte is modeled through a chemical synapse in order to form the tripartite synapse.

Table 1 Parameter values used in the simulations

c_1	0.13	c_2	0.9	c_3	0.004	c_4	$1/\varepsilon_c$	r	0.02
β	1	τ_{S_m}	10	h_{S_m}	0.015	d_{S_m}	0.071	τ_c	2
s_{S_m}	100	a	2	ε_c	0.01	D_n	10^{-5}	τ_n	5
$\bar{g}_{Ca}$	1	$\bar{g}_K$	2	$\bar{g}_L$	0.5	ϕ	1.107	$\hat{v}_2$	0.15
$\hat{v}_4$	0.145	v^*	−0.217	σ_s	0.02	β_s	0.05	θ_s	0.2
v_{Ca}	1	v_K	−0.7	v_L	−0.5	$\hat{v}_1$	−0.01	$\hat{v}_3$	0.1
α_i	0.0001	g_{si}	0.0051	C	1	i_j^{const}	0.02	ε_j	0.002

In other words, the synaptic interactions are modeled as suggested by Terman et al. (2002). In this model, depending on the membrane potential, action potential spreading from the neuron causes neurotransmitter release. Concentration of the neurotransmitter in the synaptic cleft is modeled by the following equation:

$$[T]_j = \frac{1}{1+\exp\left(-(v_j(t)-\theta_s)/\sigma_s\right)} \quad j=1,2 \tag{18}$$

where θ_s and σ_s are half-activation voltage and steepness of the sigmoid function, respectively. The input of an astrocyte (z) is concentration of the neurotransmitter ($[T]_j$) released by activated neuron, and it triggers the IP_3 production (see Eq. 16). It is defined as:

$$z = a\sum_{j=1}^{2}[T]_j \tag{19}$$

where $a > 0$ is an amplifying parameter. The output of the astrocyte is

$$i_j^{\text{ast}} = \lambda_j \cdot G_m \quad j=1,2 \tag{20}$$

This value is applied to each individual neuron, separately. Based on numerous physiological findings, astrocytes release ATP that has direct excitatory effects on interneurons through activation of metabotropic P2Y1 receptors and thereby produces a depolarization leading to action potential initiation (Bowser and Khakh 2004; Fellin et al. 2006). On the other hand, astrocytes decrease excitability of the pyramidal neuron due to the interaction of ATP with different purinergic receptors. Consequently, synaptic saturation is prevented (Koizumi et al. 2003; Postnov et al. 2009). This biological fact is modeled by considering positive (negative) sign for excitatory (inhibitory) effects. In this way, to implement the interaction of astrocytes with neighboring neurons "$+i^{\text{ast}}$" and "$-i^{\text{ast}}$" is added to Eq. 12. Therefore, the complete expressions of the current for the neurons are:

$$\begin{aligned} i_1(t) &= i_1^{\text{const}}(t) + i_1^{\text{slow}}(t) + i_1^{\text{noise}}(t) + i_1^{\text{ast}}(t) \\ i_2(t) &= i_2^{\text{const}}(t) + i_2^{\text{slow}}(t) + i_2^{\text{noise}}(t) - i_2^{\text{ast}}(t) \end{aligned} \tag{21}$$

where $i_j^{\text{ast}} = \lambda_j \cdot G_m$ and $\lambda_j > 0$. Consequently, the coupled M-L model (12) is modified as follows by integrating the outputs of astrocyte:

$$\begin{aligned} \frac{dv_1}{dt} &= F(v_1, w_1, i_1 - i_1^{\text{ast}}) \\ &\quad + g_{\text{se}}(v_2 - v_1) + i_1^{\text{ast}} \\ \frac{dw_1}{dt} &= G(v_1, w_1) \end{aligned} \qquad \begin{aligned} \frac{dv_2}{dt} &= F(v_2, w_2, i_2 - i_2^{\text{ast}}) \\ &\quad + g_{si}(v_1 - v_2) + i_2^{\text{ast}} \\ \frac{dw_2}{dt} &= G(v_2, w_2) \end{aligned} \tag{22}$$

3 Mathematical analysis of synchronization

To clarify the results of this section, first a brief introduction to the concept of synchronization is presented. Consider the general case of two coupled first order differential equations depending on some parameters $i \in \Re^q$:

$$\dot{x}_1 = f(x_1, x_2, i_1) \tag{23}$$

$$\dot{x}_2 = f(x_1, x_2, i_2) \tag{24}$$

where x_1 and x_2 belong to $\Re^n$. If $x_1(t) = x_2(t)$ for all t, perfect synchronization occurs. For asymmetric initial conditions, that is $x_1(0) \neq x_2(0)$, the equality holds asymptotically. For asymmetric systems with $i_1 \neq i_2$, perfect synchrony is not expected. A solution $(x_1(t), x_2(t))$ is synchronized if $x_1(t)$ and $x_2(t)$remain close to each other in the future that is $|x_1(t) - x_2(t)| \leq s(t)\xi\,|i_1 - i_2|$, where $s(t) \geq 0$ is a continuous function with $\lim_{t\to\infty} s(t) = 0$ and ξ is a constant (Labourian and Rodrigues 2003).

Then, in the following, a Theorem will be provided. This theorem, in its turn, is a summary of two theorems, one (named Theorem 2) proved by Labourian and Rodrigues (2003) and another theorem (again named Theorem 2) proved by Wang et al. (2008). These researches have mainly focused on the synchronization problems. As an alternative, we developed a Theorem to examine the desynchronization problem. In other words, we utilize this theorem not only to study the synchronization of two coupled neurons in the presence or absence of the astrocyte, but also to investigate the role of astrocyte in desynchronizing the synchronous behavior of two coupled neurons.

According to this theorem, if coupling between two neurons is strong enough, the two coupled neurons can be synchronized regardless of the initial conditions and the parameter values.

Theorem *Consider the two coupled M-L equations* (12) *with parameters* i_1, i_2. *It is supposed that the initial conditions* $w_1(0), w_2(0) \in [0,1]$ *and* $|(v_1(0), v_2(0))| \leq R$ *where*

$$R = \left(\sqrt{2} + 2\sqrt{\frac{\tilde{g}}{\bar{g}_L} + \frac{1}{2}}\right)\left(v_{\text{Ca}} + \frac{I_M}{\bar{g}_L}\right) \tag{25}$$

$$\tilde{g} = \bar{g}_L + \bar{g}_K + \bar{g}_{\text{Ca}} \tag{26}$$

$$I_M = \max_t |i_1(t), i_2(t)| \tag{27}$$

and maxima are taken over the parameter values for the two equations. Let coupling constants satisfy $|g_{\text{se}} - g_{\text{si}}| < \frac{\bar{g}_L}{C}$, *then there exist positive constants* g_0, γ, A, B *and a positive function* γ_g *of* $g = g_{\text{se}} + g_{\text{si}}$ *such that if*

$$g_{\text{se}} + g_{\text{si}} > g_0 \tag{28}$$

where

$$g_0 = C\left(L_1 + \gamma + \frac{L_2 N_1}{\gamma^2} + 1\right) - \bar{g}_L \tag{29}$$

then, all solutions $(v_1(t), w_1(t), v_2(t), w_2(t))$ *of the coupled* M-L *equations* (12) *satisfy the following inequalities for* $t \geq 0$:

$$
\begin{aligned}
&|v_1(t) - v_2(t)| \leq \mathrm{e}^{-(\gamma-\gamma_g)t} \\
&\left[\left(1 + \frac{L_2 N_1}{\eta}\right)|v_1(0) - v_2(0)| + L_2\,|w_1(0) - w_2(0)|\right] \\
&\quad + A\,|i_1 - i_2| \\
&|w_1(t) - w_2(t)| \\
&\leq \mathrm{e}^{-(\gamma-\gamma_g)t}\left[\frac{N_1}{\eta}|v_1(0) - v_2(0)| + |w_1(0) - w_2(0)|\right] \\
&\quad + B\,|i_1 - i_2|
\end{aligned}
\tag{30}
$$

where

$$\eta = g_{\mathrm{se}} + g_{\mathrm{si}} + \bar{g}_{\mathrm{L}} \tag{31}$$

$$L_1 = \frac{2R\bar{g}_{\mathrm{Ca}}}{C} \tag{32}$$

$$L_2 = \frac{2R\bar{g}_{\mathrm{K}}}{C} \tag{33}$$

and N_1 is the Lipschitz constant of the function G; that is for $|v_2| \leq R$

$$|G(v_1, w_2) - G(v_2, w_2)| \leq N_1\,|v_1 - v_2| \tag{34}$$

and the constant γ satisfies $0 < \gamma \leq \frac{\phi}{\tau_w(v)}$ for $|v_1| \leq R$. To have $\gamma - \gamma_g > 0$, γ_g is selected as:

$$\gamma_g = \frac{L_2 N_1}{\gamma(\eta - \gamma - L_1)} \tag{35}$$

This theorem implies that if the coupling constants are sufficiently large (i.e., $g_{\mathrm{se}} + g_{\mathrm{si}} > g_0$), *providing the initial conditions $w_1(0), w_2(0) \in [0, 1]$ and $|(v_1(0), v_2(0))| \leq R$, then $|v_1(t) - v_2(t)|$ and $|w_1(t) - w_2(t)|$ exponentially decrease and finally are bounded by $A\,|i_1 - i_2|$ and $B\,|i_1 - i_2|$, respectively. In other words, considering the definition of synchronization mentioned in the beginning of this section, when coupling constants are sufficiently large, then the difference between the solutions of* (12) *get synchronized with an error proportional to $|i_1 - i_2|$.*

According to this Theorem, after selecting appropriate initial conditions and when $g = (g_{\mathrm{se}} + g_{\mathrm{si}}) > g_0$, the two neurons get synchronized. Thus, g_0 is a threshold for synchronization of two coupled neurons. Now, let us examine how the presence of astrocyte can influence the threshold value g_0. We consider different parameters used in definition of g_0 (see Eq. 29). It is clear that C, g_{L}, γ and N_1 are constants and adding astrocyte does not change the value of these parameters. However, according to Eqs. 25 and 26, L_1 and $L_2$are proportional to R and based on (25), R is a function of I_M. Eq. 19 indicates that astrocyte (i_j^{ast}) alters $i_1(t)$ and $i_2(t)$, and consequently changes I_M (see Eq. 23). Now, two different cases may be considered:

3.1 A. Astrocyte increases the value of I_M. In other words, $I_{M,\mathrm{ast}} > I_M$ where $I_{M,\mathrm{ast}}$ is the value of I_M in the presence of astrocyte

In this case, considering Eq. 25, first R is increased and then based on Eqs. 25 and 26, L_1 and L_2, and subsequently the value of g_0 are increased. If we call the threshold of synchronization when astrocyte exists in the network as $g_{0,\mathrm{ast}}$, then $g_{0,\mathrm{ast}} > g_0$ meaning that the astrocyte enhances the threshold value of synchronization. Therefore, we expect that the new synchronization condition in the presence of astrocytes becomes:

$$g = (g_{\mathrm{se}} + g_{\mathrm{si}}) > g_{0,\mathrm{ast}} \tag{36}$$

Now assume that the two coupled neurons oscillate in the synchronized regime (i.e., $g_0 \leq g$). Then, we continue our analysis by considering two different conditions:

3.1.1 A.1 $g \leq g_{0,\mathrm{ast}}$

This implies that the synchronization condition (30) is not satisfied, that is the coupling constant between neurons does not exceed the new synchronization threshold created by astrocyte. Hence, we expect the astrocyte to have the potential to desynchronize the synchrony between two coupled neurons.

3.1.2 A.2 $g > g_{0,\mathrm{ast}}$

Since the coupling between two neurons is so strong that is still greater than the new synchronization threshold, we expect that the two coupled neurons remain synchronized and astrocyte is not able to break their synchrony. In short, we claim that the astrocyte is capable of removing the neural synchrony only when the new synchronization threshold ($g_{0,\mathrm{ast}}$) is greater than the coupling strength between neurons (g).

3.2 B. Astrocyte decreases or does not change the value of I_M namely $I_{M,\mathrm{ast}} \leq I_M$

In this situation $g_{0,\mathrm{ast}} < g_0$ and since $g_0 \leq g$, we have $g_{0,\mathrm{ast}} \leq g$. Consequently, the coupled neurons continue to remain synchronized.

In the next section, Eqs. 1–7 and 12–22 are used for numerical simulations to verify the obtained theoretical deductions of this section.

4 Simulation results

In this section, the simulation results are presented to explore the role of astrocytes in normal and pathological conditions.

Figure 2 shows the effect of increased interaction between neurons. It should be mentioned that in this case, no astrocyte is present in the network model. We used g_{se} to change the coupling strength between neurons and thereby influencing the neural synchrony (Chakravarthy et al. 2007). Figure 2 clearly shows that increasing g_{se} at $t = 2000$ s from 0.001 to 0.05 (top panel) leads neurons to get synchronized. This is illustrated in the middle panel by the obvious synchronized oscillations of the membrane potentials. Therefore, changing g_{se} alters the behavior of the coupled models significantly since the astrocytic functions, which are essential for the normal brain function, are not modeled. The bottom panel illustrates the synchronization index. To calculate the synchronization index, we follow the procedure implemented by Tass and colleagues (2007). We define the phase φ_j of neuron j by the standard interpolation (Pinsky and Rinzel 1995):

$$\varphi_j = 2\pi \frac{t - t_k}{t_{k+1} - t_k} \tag{37}$$

where $t \in [t_k, t_{k+1}]$, and t_k is the onset time of the kth burst of the jth neuron. In this way, it is possible to assess the extent of in-phase synchronization of neurons with the standard order parameter:

$$\Re(t)\, e^{i\Theta(t)} = \frac{1}{N} \sum_{j=1}^{N} e^{i\varphi_j(t)} \tag{38}$$

where $\Theta(t)$ is the mean phase and $\Re(t)$ is the time-dependent synchronization index. It is clear that $0 \leq \Re(t) \leq 1$ holds for all times t. $\Re(t) = 0$ corresponds to complete absence of in-phase synchronization and perfect in-phase synchronization is characterized by $\Re(t) = 1$.

Next, we consider the more realistic situation in which the role of astrocyte in regulation of synaptic transmissions is considered. In this case, synaptic properties are tuned through release or/and uptake of neurotransmitters and ions and stable ongoing activity in the neuronal circuit is maintained. Results of simulations are shown in Fig. 3. Similar to Fig. 2, the top panel shows the increase of coupling level, g_{se}, and the middle panel demonstrates the membrane potential of the coupled neurons. In this simulation, it is assumed that the astrocyte begins to interact with the coupled neurons at $t = 7000$ s. It is obvious that the astrocyte modifies the synaptic currents by providing appropriate feedback actions. Consequently, runaway excitation is compensated and normal asynchronous behavior is again resumed quickly. For the simulations shown in Fig. 3, $\lambda_1 = 0.15$ and $\lambda_2 = 0.23$. In line with these simulations, recent studies about communications between astrocytes and neurons reveal that glutamate release from single astrocyte may control the excitability of several neighboring cells simultaneously (Silchenko and Tass 2008). Indeed, physiological evidence suggests that astrocytes can act as local controllers of the synaptic function (Araque et al. 1999;

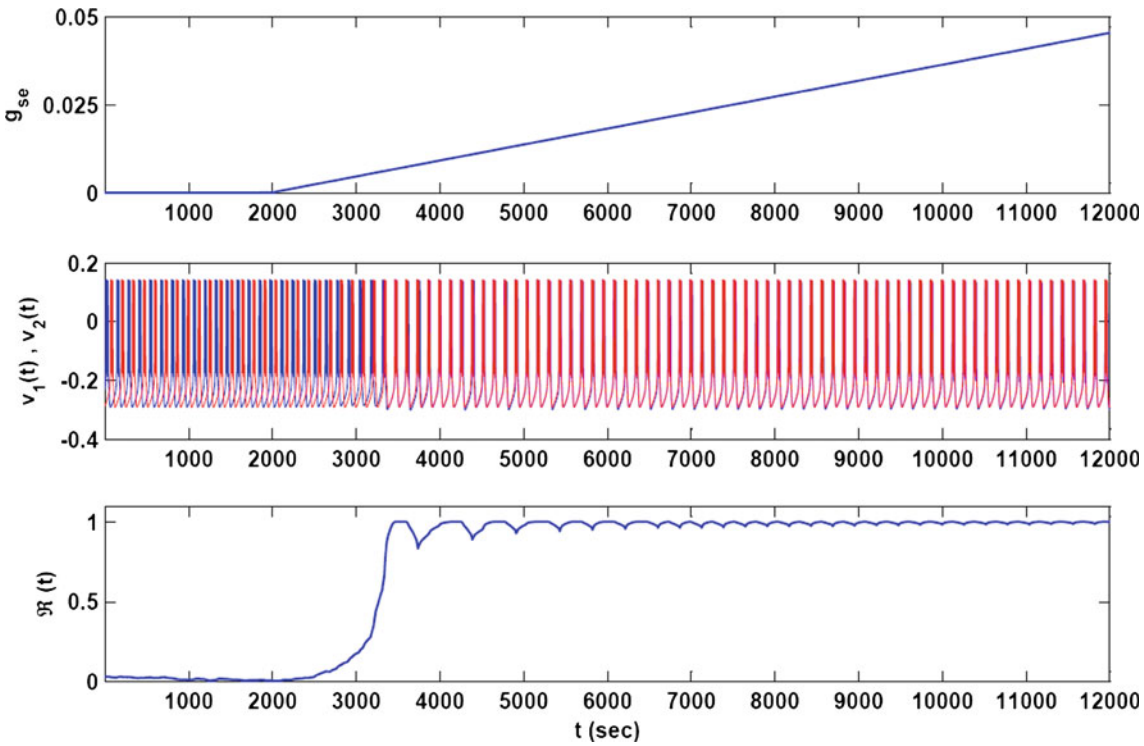

Fig. 2 The effect of varying coupling strength g_{se} in the two coupled M-L neurons. Increasing the g_{se} (*top panel*), the neurons are becoming synchronized. This can be observed from simultaneous firing of neurons (*middle panel*). The *bottom panel* illustrates the synchronization index

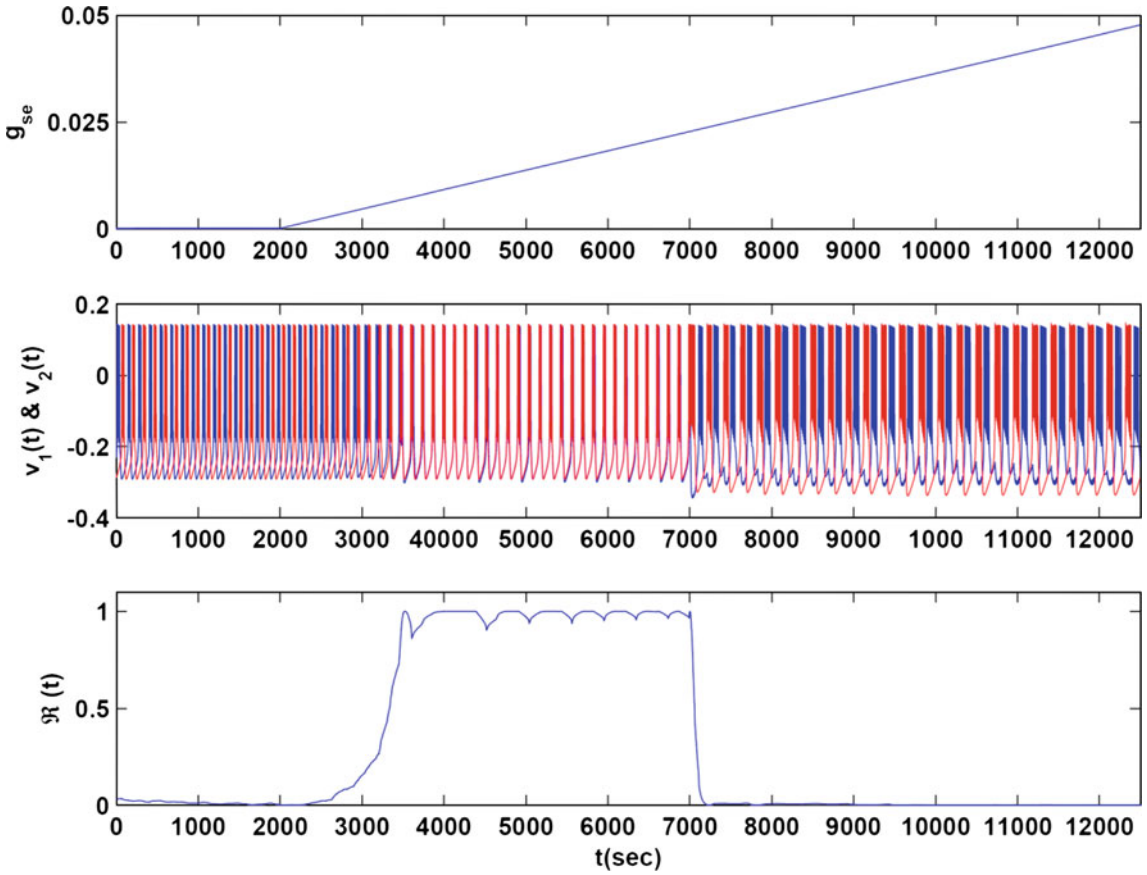

Fig. 3 The effect of varying coupling strength g_{se} in two coupled neurons in which the interaction of astrocyte with the individual neurons is included for $t > 7000$ s. In spite of increasing g_{se} (*top panel*), the neurons are not synchronized any more (*middle panel*) for $t > 7000$ s. In this case, astrocyte provides balanced excitation and inhibition to coordinate synaptic interactions. The *bottom panel* illustrates the synchronization index. It is apparent that the concurrent firing of neurons is disturbed by feedback from astrocyte

Haydon and Araque 2002; Voltarra and Steinhäuser 2004; Fellin et al. 2006).

In this case, the output of astrocyte to individual neurons is shown in Fig. 4a (top and bottom panels). For $0 < t < 7000$ s, no astrocyte exists in the model and therefore, the output is zero for this time interval. However, for the interval $t > 7000$ s, astrocyte produces appropriate control signal to desynchronize the two coupled neurons. Figure 4b (top and bottom panels) illustrates the total input current (19) of the individual neurons. It is apparent that the amplitude of oscillations for the time interval of $t > 7000$ s is greater than that of $0 < t < 7000$ s. Thus, in the presence of healthy astrocyte, the peak value of i_1 and i_2 namely $I_{M,\text{ast}}$ is increased; in other words $I_{M,\text{ast}} > I_M$. In this way, the astrocyte is able to desynchronize the two coupled neurons by applying appropriate feedback. This is in agreement with the mathematical analysis performed in the Sect. 3.1.1 A.1 and our claims.

In addition to the role of normal astrocytes in control of neuronal excitability and synaptic transmission, they can contribute to some of the disorders of the nervous system (Seifert et al. 2010). In this research, role of a pathological astrocyte is also studied, that is, when it is not able to properly perform its normal role in the neuronal network. *One* way to simulate pathological astrocyte is simply to reduce the capability of astrocyte in regulating synaptic transmission. This corresponds to a deficit in astrocyte function and reduction of gliotransmitter release and/or decrease of neurotransmitter uptake. This fact is replicated in our simulations by decreasing the numerical values of λ_1 from 0.15 to 0.08 and λ_2 from 0.23 to 0.05. The results of simulation under new conditions are shown in Fig. 5. These simulations imply that although astrocyte tend to desynchronize the two coupled neurons (in the time interval $7000 < t < 11200$ s), due to pathology in its feedback structure (reduction of λ_1 and λ_2) astrocyte is not able to fulfill its function and consequently hypersynchronization appears (the time interval $11200 < t < 12500$ s). For the simulations that are shown in Fig. 5, the output of the astrocyte and the total current (19) for the individual neurons are illustrated in Fig. 6a, b, respectively. For

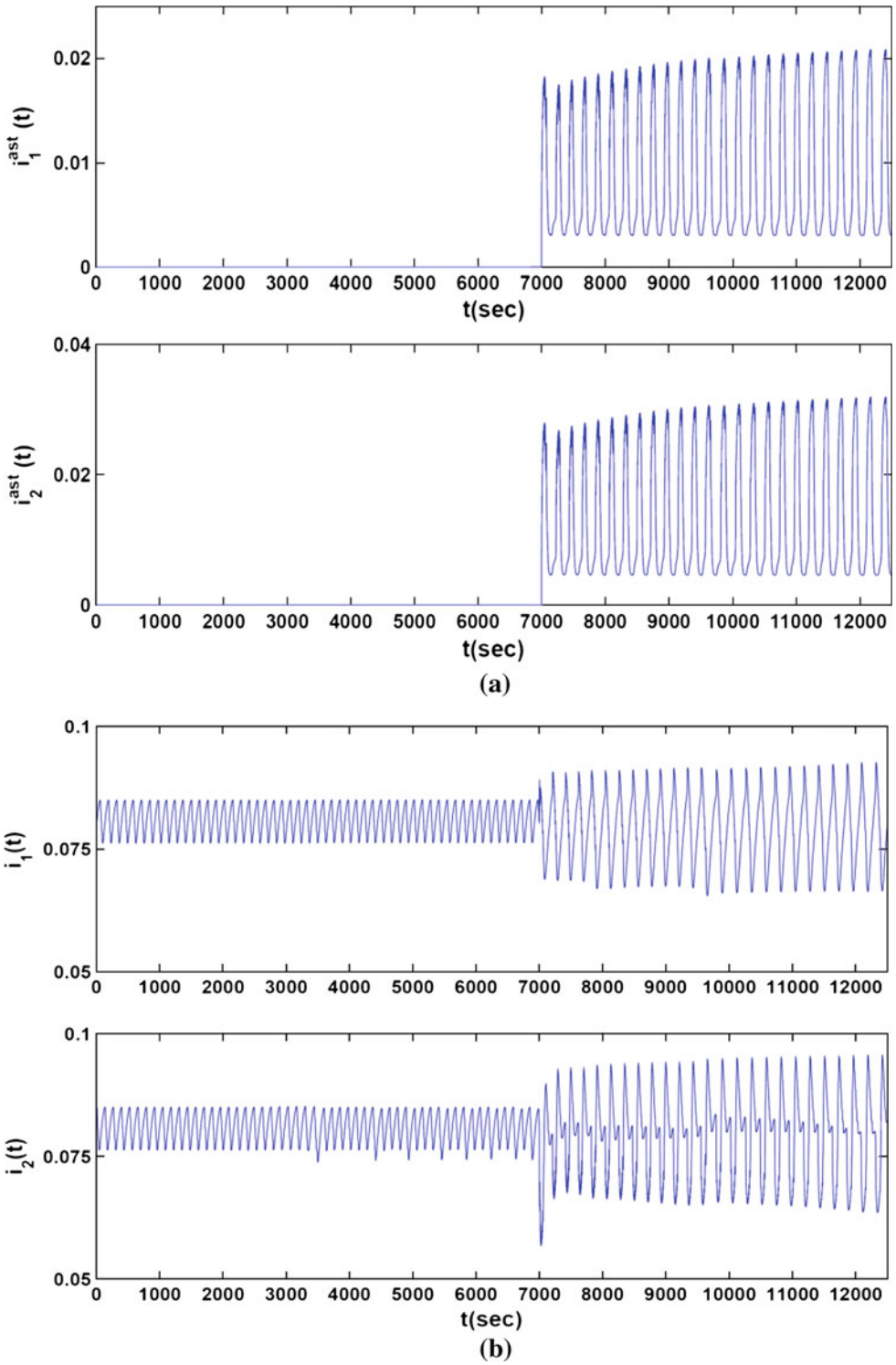

Fig. 4 **a** The output of astrocyte applied to individual neurons. **b** The total current (19) sketched for each neuron. This figure clearly demonstrates that after incorporating the astrocyte in the network ($t > 7000$ s), the oscillation amplitude of i_1 and i_2 is increased

$0 < t < 7000$ s, no astrocyte exists in the model and therefore, the output is zero for this interval. However, for the time interval $7000 < t < 11200$ s, astrocyte creates a control signal (Fig. 6a) with an attempt to desynchronize the two coupled neurons. As the bottom panel of Fig. 5 shows, the synchronization index decreases for this time interval. Moreover, considering the Fig. 6b, $I_{M,\text{ast}} > I_M$ and based on the mathematical analysis carried out in the Sect. 3.1.1 A.1, the asynchronous oscillations of the coupled neurons are expected. In the time interval $11200 < t < 12500$ s, more interesting phenomena are observed. Despite the initial success of astrocyte in disturbing the synchrony between two neurons,

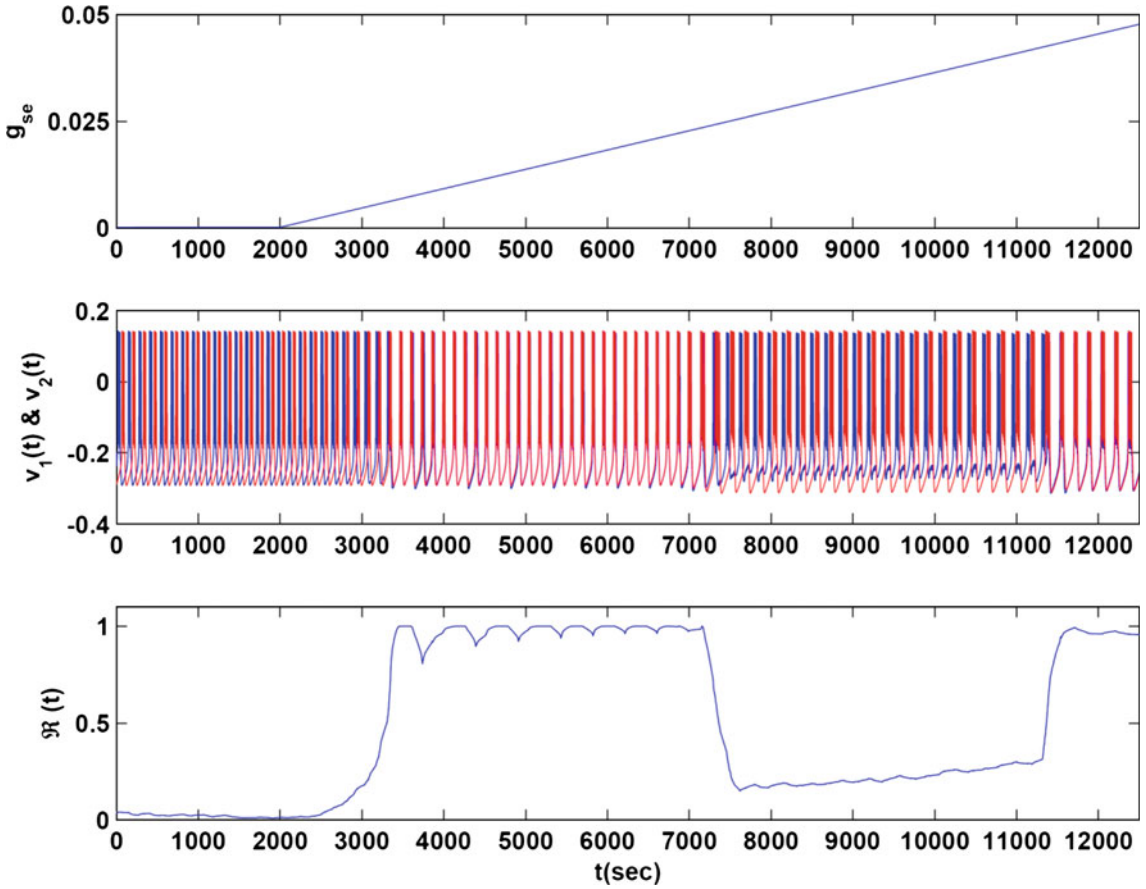

Fig. 5 The effect of altering coupling strength g_{se} (*top panel*) in the two coupled neurons with pathological astrocytes. The *middle panel* shows the membrane potentials of the two neurons. Due to infection of astrocyte, despite the initial success in disturbing the synchrony between two neurons, synchronized oscillations finally emerged. The bottom panel displays the synchronization index

synchronized oscillations finally emerged. This occurs as a result of the incremental coupling strength between neurons (g) becomes greater than the new synchronization threshold ($g_{0,\mathrm{ast}}$), that is $g > g_{0,\mathrm{ast}}$. Hence, the two coupled neurons get synchronized and astrocyte is not able to preserve the asynchronous behavior. Such observations are also expected based on the theoretical analysis carried out in the Sect. 3.1.2 A.2. It is interesting to draw attention to Fig. 6b (top and bottom panels) for this time interval. It is apparent that the peak value of total current (19) namely $I_{M,\mathrm{ast}}$ is reduced and this agrees with the mathematical analysis conducted in the Sect. 3.2 B. In this way, astrocyte cannot regulate and/or compensate excessive increase in the synaptic strengths through release of gliotransmitters and/or uptake of neurotransmitters to break the synchronization and this leads to the emergence of synchronous oscillations.

Finally, we consider a more realistic and physiological case where the astrocyte interacts with the coupled neurons for *all* the duration of the simulation that is the astrocyte is present all times from the beginning of the simulations. Results are shown in Fig. 7a, b for the healthy and pathological astrocyte, respectively. As can be observed, in the case of healthy astrocyte the asynchronous activity between neurons is maintained in spite of being subjected to the increase of coupling level. On the other hand, when the astrocytes are considered to be pathological and for the same level of interaction, the coupled neurons finally get synchronized. It is interesting to compare Fig. 7 with Fig. 2. Figure 2 shows the results for the behavior of the coupled neurons in the absence of the astrocytes. A pathologic astrocyte is able to preserve asynchronous behavior until 10000 s, whereas when there is no astrocyte to supervise the neuronal connections, the synchronous behavior begins around 3000 s. Therefore, we can conclude that variations in the coupling between neurons and astrocyte lead to the emergence of synchronous/ asynchronous patterns in neural responses. That is, astrocyte actively contributes in the information processing mechanisms which are carried out primarily by neurons.

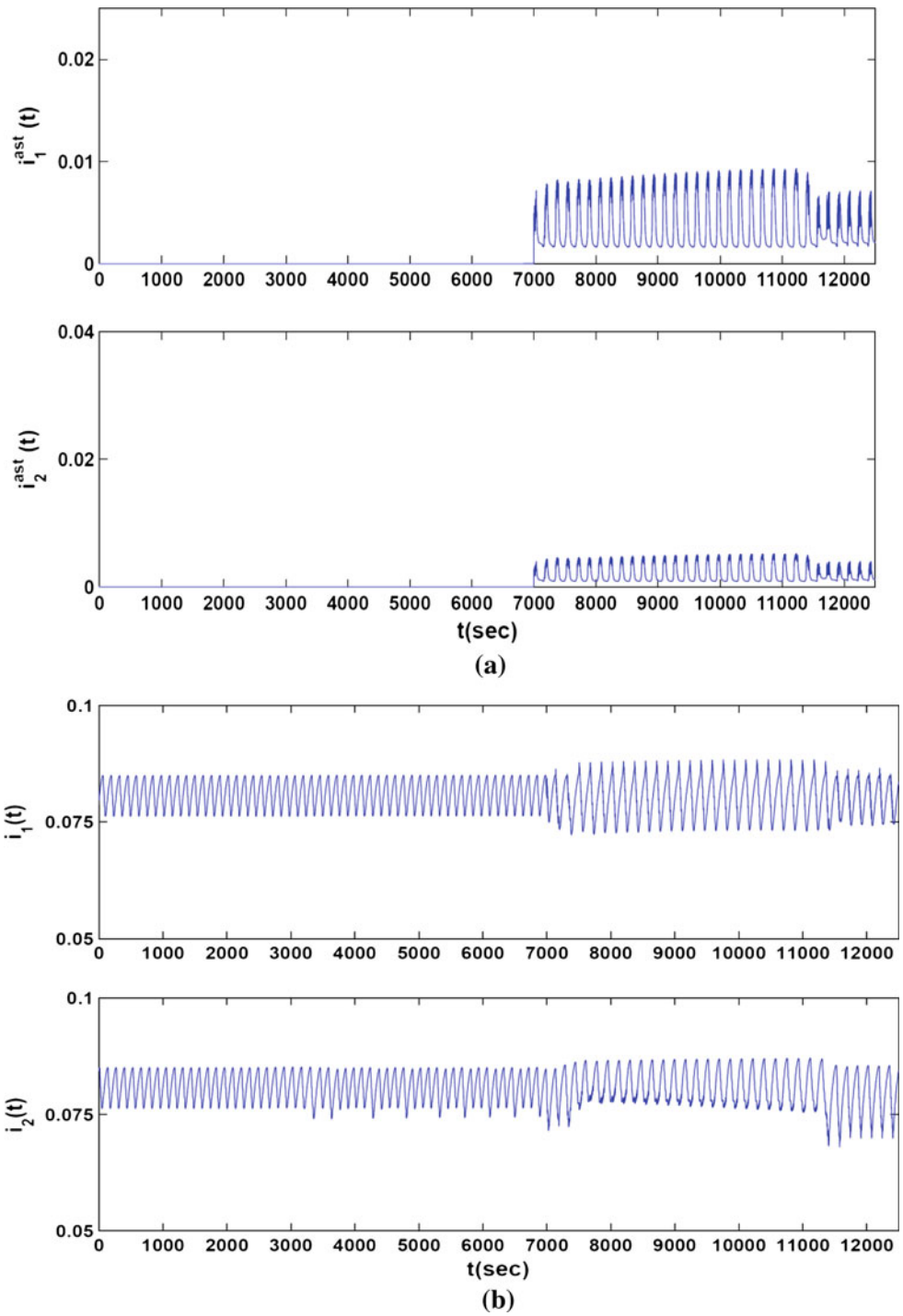

Fig. 6 **a** The output of pathological astrocyte applied to the individual neurons. **b** The total current (19) sketched for each neuron. This figure clearly demonstrates that for $7000 < t < 11200$ s, the oscillation amplitude of i_1 and i_2 is increased however for $11200 < t < 12500$ s, the amplitude of oscillations are decreased

5 Conclusions

Bidirectional communication between neurons and astrocytes are necessary for normal functioning of the nervous system during signal processing (Newman 2003; Halassa et al. 2009). Recent experimental findings show that astrocytes are involved in the hypersynchronous firing of neurons (Pereira Jr and Furlan 2009). Hence, it is essential to develop models which consider neuron–astrocyte interactions.

In one of our previous works (Amiri et al. 2010), we discussed neural synchronization in the context of epilepsy. In that study, the thalamocortical neural population model (TCM) originally proposed by Suffczynski and colleagues (2004) was extended by integrating the functional role of

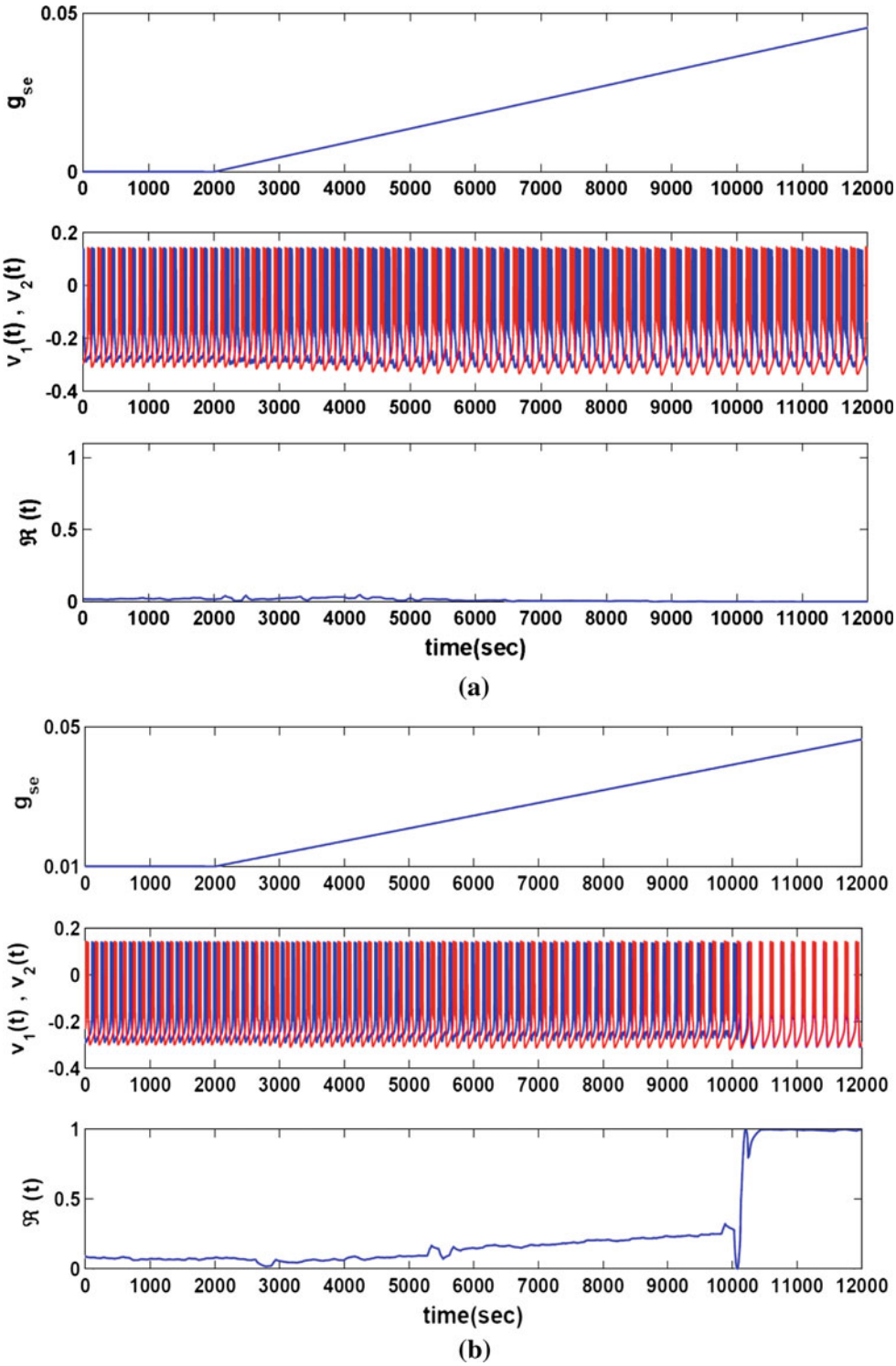

Fig. 7 The effect of varying coupling strength g_{se} in the behavior of the two coupled neurons. In this case, the astrocyte is present all the time and its interactions with individual neurons are included from the beginning of the simulations. **a** For healthy astrocyte, in spite of increasing g_{se}, the asynchronous behavior of neurons continues. **b** The pathological astrocyte is not able to preserve the asynchronous activities of the neurons and ultimately they become synchronized

astrocytes in the regulation of synaptic transmission and the model was called modified TCM or MTCM. The TCM and MTCM were constructed in a macroscopic level and consider the basic components involved in absence seizures. They describe the electrophysiology of cortical and thalamic neural populations while the explicit behavior of the individual neurons is not simulated. The thalamic module consists of reticular thalamic and thalamocortical subpopulations, and the cortical module consists of pyramidal cell and interneuron subpopulations. The output of both models is the mean membrane potential of the pyramidal cells and simulates experimental recordings of the local field potentials.

In the MTCM, astrocytes dynamically regulate the synaptic strengths between pyramidal and interneuron subpopulations. This modified model helps us to understand one of the basic functional mechanisms that can cause epileptic seizure.

On the other hand, in the present research a biologically inspired neuronal network model was developed by connecting two M-L neural models and one astrocyte dynamic model. It should be mentioned that, Di Garbo (2009) has also considered a minimal network model consisting of a pyramidal neuron, an interneuron, and an astrocyte. The main focus of his study was to investigate the dynamical properties of the model describing calcium dynamics in the astrocyte. Nevertheless, he did not investigate the effect of neuron–astrocyte interactions on the neuronal synchronization. Whereas in this research, we focused on the synchronization question both from mathematical and numerical perspectives with emphasizing on the role of astrocyte in controlling synchronization level through regulation of synaptic transmissions. In this way, using a minimal model and based on the mathematical analysis and the results of the numerical simulations reported in the article, we demonstrated that the astrocyte is able to change the threshold value of transition from synchrony to asynchrony.

It should be emphasized that desynchronization is also important for specific kinds of neural processing (Ackert et al. 2006). In other words, variations in the degree of synchrony, shifting from synchrony to asynchrony or vice versa, can be interpreted as signals for neural information processing. This suggests a novel mechanism by which cell groups can encode specific information (Benda et al. 2006). In other words, the function of astrocyte, when changing the synchronization level between two coupled neurons, can be considered as a mechanism to encode information. Therefore, variation in the strength of neuron–astrocyte interactions can be used as an important signal for the next level of information processing besides variations in the neuron–neuron interactions in the brain. This is a current topic of interest in neuroscience to discover the putative role of astrocytes for stabilizing neural activity.

Although in this article, we focused on the role of astrocyte in synchronization of two coupled neurons and explain the potential of the approach, this is an interesting point to consider a neuronal population model and construct a network which integrates the role of astrocytes in the synaptic transmission as well as in the regulation of neuronal dynamic. This procedure will help us to understand how astrocytes affect the dynamics of synchronization from a network-level point of view, which in turn will bring to light some important aspects of neuron–astrocyte interactions. Finally, it will be interesting to model the direct neuronal interactions via the synaptic release mechanism especially given the fact that they are anyway computing something similar to neurotransmitter release. In this way, it is possible to examine if the basic mechanism would survive even without gap-junction coupling. This presents new opportunities for further investigation of the model and pertinent applications including involvement of astrocytes in brain disorders such as epilepsy. These issues will be addressed in future study.

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