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A phase plane analysis of neuron–astrocyte interactions

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ABSTRACT

Intensive experimental studies have shown that astrocytes are active partners in modulation of synaptic transmission. In the present research, we study neuron–astrocyte signaling using a biologically inspired model of one neuron synapsing one astrocyte. In this model, the firing dynamics of the neuron is described by the Morris–Lecar model and the Ca^{2+} dynamics of a single astrocyte explained by a functional model introduced by Postnov and colleagues. Using the coupled neuron–astrocyte model and based on the results of the phase plane analyses, it is demonstrated that the astrocyte is able to activate the silent neuron or change the neuron spiking frequency through bidirectional communication. This suggests that astrocyte feedback signaling is capable of modulating spike transmission frequency by changing neuron spiking frequency. This effect is described by a saddle–node on invariant circle bifurcation in the coupled neuron–astrocyte model. In this way, our results suggest that the neuron–astrocyte crosstalk has a fundamental role in producing diverse neuronal activities and therefore enhances the information processing capabilities of the brain.

1. Introduction

Intensive research in the past decade not only revealed new crucial roles for the glial cells and specifically astrocytes, but it also increased evidence about the importance of bidirectional interactions between astrocytes and neuronal cells in maintaining normal neural activity (Amiri, Bahrami, & Janahmadi, 2011, 2012c; Fellin, 2009; Halassa, Fellin, & Haydon, 2009). Astrocytes are the most abundant type of glial cells and perform a variety of tasks. They control the content of extracellular fluid and electrolyte homeostasis, regulate neurotransmitter release and control synapse formation (Fellin, Pascual, & Haydon, 2006; Halassa et al., 2009). By transporting ions and other substances, they provide structural, metabolic, and functional support for differentiation, proliferation, and survival of neurons (Araque, Parpura, Sanzgiri, & Haydon, 1999; Voltarra & Steinhäuser, 2004). On the other hand, a considerable amount of evidence obtained by several groups during the last few years has demonstrated that astrocytes are active partners in the control of synaptic transmission (Haydon & Araque, 2002; Nimmerjahn, 2009). Although astrocytes cannot generate action potentials, they respond to neuronal activities through elevation of their intracellular calcium levels (Giugliano, 2009). Therefore, astrocytes not only can *sense* neuronal transmission but also their calcium elevation will lead to the *release* of gliotransmitters such as Adenosine Triphosphate (ATP) or glutamate which regulate and control the synaptic strengths of the adjacent neurons (Fellin et al., 2006; Hertz & Zielke, 2004). In this way, astrocytes provide reciprocal signals to neighboring neurons. The concept of the "tripartite synapse" recapitulates these features (Araque et al., 1999; Halassa et al., 2009; Haydon & Araque, 2002). The notion emphasizes that the astrocyte is a third signaling element at a synapse with a pre- and a post-synaptic terminal (Fellin et al., 2006; Newman, 2003).

The interest in understanding the biophysical mechanisms of communication between neuron and astrocyte as well as the computational modeling of the neuron–astrocyte signaling, is continuously increasing (Amiri, Montaseri, & Bahrami, 2011; Ullah, Cressman, Barreto, & Schiff, 2009). 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 & Jung, 2004, 2007). Cressman and collaborators constructed a mathematical model consisting of a single conductance-based neuron together with intra- and extracellular ion concentration dynamics to study the role of potassium dynamics on the stability of the activity of a

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single neuron (Cressman, Ullah, Ziburkus, Schiff, & Barreto, 2009). Volman and colleagues presented a simple biophysical model for the coupling between synaptic transmission and the local calcium concentration on an enveloping astrocytic domain. They concluded that the astrocyte acts as a gatekeeper for the synapse (Volman, Ben-Jacob, & Levine, 2007). A generalized and nondimensional model for the astrocyte is proposed by Postnov and colleagues (Postnov, Ryazanov, & Sosnovtseva, 2007). Recently, this model was modified in order to be applied to a spatially extended neuron–astrocyte network (Postnov, Koreshkov, Brazhe, Brazhe, & Sosnovtseva, 2009). A minimal model consisting of a pyramidal neuron, an interneuron and an astrocyte was developed and simulated by Garbo (2009). He investigated that the presence of ATP and the interneuron affects the overall neural activity (Garbo, Barbi, Chillemi, Alloisio, & Nobile, 2007). Silchenko and Tass presented a simple mathematical model of the interaction between an astrocyte and neuron that is able to numerically reproduce the experimental results concerning the initiation of the paroxysmal depolarization shifts (PDS) in the neighboring neuron (Silchenko & Tass, 2008). Wade and colleagues developed a detailed model of bidirectional signaling between astrocytes and neurons and provide evidence which shows that astrocytes have a role to play in Long Term Potentiation/Depression (LTP/LTD; Wade, McDaid, Harkin, Crunelli, & S Kelso, 2011). De Pitta and collaborators explored a plausible form of modulation of short-term plasticity by astrocytes using a biophysically realistic computational model (De Pittà, Volman, Berry, & Ben-Jacob, 2011). Nevertheless, a characterization of how astrocyte actively shapes the dynamics of neuronal function, from the dynamical system point of view, remains largely unstudied. This standpoint increases our understanding of the dynamical mechanisms of neuron–astrocyte interactions and helps to find out more about the astrocyte function and what it does in regulation of neural activities. Therefore, in the present study, in order to investigate these issues a physiologically-inspired model was developed. We have implemented a functional approach, and the Morris–Lecar formalism of the neuronal ionic currents synapse to the Postnov model of the astrocyte dynamics. Then, the developed model was analyzed from the viewpoint of dynamical system theory. Through numerical simulations and bifurcation analyses, we have shown that the feedback mechanism organized by astrocyte could turn on the silent neighboring neuron or alter the neuronal firing rate. This means that the neuron–astrocyte crosstalk can enhance the information processing capabilities of the brain.

The rest of the paper is organized as follows. In Section 2, the biological description of the Morris–Lecar neuron model, the dynamic model of the astrocyte and its interaction with the neuron are covered. Section 3 presents quantitative and qualitative analyses of the astrocyte–neuron model. Also in this section, the results of some simulations are presented to investigate the role played by the astrocyte in regulation of neuronal firing from the dynamical system point of view. In Section 4, the importance, limitations and some future directions of the present research are discussed. Finally, Section 5 concludes the paper.

2. Dynamic models of neuron and astrocyte

In this section, we first present the dynamic model of the Morris–Lecar neuron and then a mathematical description of the astrocyte is explained. The Morris–Lecar equations model the flow of potassium and calcium ions and are a two-dimensional description of neuronal spike dynamics. For the astrocyte a generalized mathematical model which is recently introduced is utilized.

Table 1
Parameter values used in the simulations. The first five rows show the parameter values of the M–L neuron, the next four rows are the parameter values of the astrocyte dynamic model and the last four rows shows the parameter values of the synapse.

C	$20\,\mu F/cm^2$	v_L	-60 mV	$\hat{v}_3$	12 mV
$\bar{g}_K$	$8\ mS/cm^2$	v_{Ca}	120 mV	$\hat{v}_4$	17.4mV
$\bar{g}_L$	$2\ mS/cm^2$	$\hat{v}_1$	-1.2 mV	ϕ	$1/15\ s^{-1}$
$\bar{g}_{Ca}$	$4\ mS/cm^2$	$\hat{v}_2$	18 mV	v_K	-80 mV
D_n	0.8	τ_n	5	i^{const}	35
β	3	τ_{Sm}	10	h_{Sm}	0.015
s_{Sm}	100	ε_c	0.2	τ_c	2
c_1	0.13	c_2	0.9	c_3	0.004
c_4	$1/\varepsilon_c$	r	0.2	d_{Sm}	0.1
σ_s	0.02	θ_s	0.2		

2.1. Neuron model

We use the well-known Morris–Lecar (M–L) equations as a basic model for the neuron (Morris & Lecar, 1981). It includes the contribution of internal ionic fast activity Ca^{2+}, delayed K^+ and passive leak currents. The dynamics of the neuron membrane potential, v, is as follows (Hauptmann & Tass, 2009):

$$C\frac{dv(t)}{dt} = -\bar{g}_{Ca}\, m_\infty(v(t))\,(v(t)-v_{Ca}) - \bar{g}_K\, w(t)\,(v(t)-v_K) - \bar{g}_L\,(v(t)-v_L) + i(t) \quad (1)$$

$$\frac{dw(t)}{dt} = \phi[w_\infty(v_j(t)) - w(t)]/\tau_w(v(t)) \quad (2)$$

$$i(t) = i^{const}(t) + i^{noise}(t) \quad (3)$$

where $w \in [0, 1]$ is an auxiliary variable and is the fraction of open K^+ channels. The channel conductances $\bar{g}_{Ca}$, $\bar{g}_K$ and $\bar{g}_L$ of the Ca^{2+}, K^+ and leak currents are constants. $i(t)$ is the applied current to the neuron. It consists of a constant background current (i^{const}) and a noisy current (i^{noise} with amplitude D_n and correlation τ_n) to model the inevitable noise present in real systems (Popovych, Hauptmann, & Tass, 2006). The functions $m_\infty(v(t))$, $w_\infty(v(t))$ and $\tau_w(v(t))$ control the dynamics of the ion channels and are defined by Eqs. (4)–(6):

$$m_\infty(v(t)) = 0.5\left[1 + \tanh\left(\frac{v(t)-\hat{v}_1}{\hat{v}_2}\right)\right] \quad (4)$$

$$w_\infty(v(t)) = 0.5\left[1 + \tanh\left(\frac{v(t)-\hat{v}_3}{\hat{v}_4}\right)\right] \quad (5)$$

$$\tau_w(v(t)) = \frac{1}{\cosh\left(\frac{v(t)-\hat{v}_3}{2\hat{v}_4}\right)}. \quad (6)$$

The parameter values of the M–L model are taken from Tsumoto, Kitajima, Yoshinaga, Aihara, and Kawakami (2006) and are listed in Table 1.

2.2. Astrocyte model

During the last decade, the numerous *in vitro* and *in vivo* studies suggest that astrocytes play an active role in synaptic transmission, which is mediated via calcium-dependent release of neurotransmitters (Perea & Araque, 2005; Voltarra & Steinhäuser, 2004). 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., 2009, 2007). This is a generalized and simplified mathematical model for a small neuron–astrocyte ensemble which considers the main pathways of neuron–astrocyte interactions. Consequently, this model will be useful to study the main types of astrocyte response to neural activities and the resulting dynamical patterns and thereby it will

allow us to predict their changes with varying control parameters. These parameters will be introduced later in this section. The model is explained with the following set of equations (Postnov et al., 2007):

$$\tau_c \frac{dc}{dt} = -c - c_4 f(c, c_e) + (r + \beta S_m) \tag{7}$$

$$\varepsilon_c \tau_c \frac{dc_e}{dt} = f(c, c_e) \tag{8}$$

$$f(c, c_e) = c_1 \frac{c^2}{1 + c^2} - \left(\frac{c_e^2}{1 + c_e^2}\right)\left(\frac{c^4}{c_2^4 + c^4}\right) - c_3\, c_e \tag{9}$$

$$\tau_{Sm} \frac{dS_m}{dt} = (1 + \tanh[S_{Sm}(z - h_{Sm})]) \times (1 - S_m) - \frac{S_m}{d_{Sm}} \tag{10}$$

where c and c_e are the calcium concentration in the astrocyte cytoplasm and within the endoplasmic reticulum, respectively. 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, β, τ_c, τ_{Sm}, S_{Sm}, h_{Sm}, h_{Gm}, d_{Sm}, to the values listed in Table 1. The values are taken from Amiri, Bahrami, and Janahmadi (2012a) and Postnov et al. (2007). As a result of augmentation of calcium concentration in the cytoplasm, astrocyte mediator is released. The interaction between astrocyte and neuron is denoted with the parameter z (astrocyte input) that shows the synaptic activity of the neuron.

2.3. Neuron–astrocyte interactions

Bidirectional communication between neurons and astrocytes are necessary for normal functioning of the nervous system during signal processing (Fellin, 2009; Halassa et al., 2009). To develop a physiologically inspired model and in order to clarify astrocyte-dependent regulation of neural activities, astrocyte is connected to the neuron model. We proceed in a phenomenological manner and utilized a *functional* approach to describe the loop of information exchange between neuron and astrocyte rather than a detailed biophysical and biochemical model.

The relative number of astrocytes per neuron varies between species and differs across the central nervous system. Indeed, the brain is a localized organ in the sense that the ratio of neurons and glial cells, their relative volumes, morphology and their functioning depend strongly on the regionality (Occhipinti, Somersalo, & Calvetti, 2009). In the human frontal cortex, the ratio of glia to neurons is about 1.65 (Oberheim, Wang, Goldman, & Nedergaard, 2006; Sherwood et al., 2006). Given that astrocytes comprise about 50% of the total number of glial cells, a 1:1 ratio seems to characterize an acceptable approximation (Reato, Cammarota, Parra, & Carmignoto, 2012).

The synaptic interactions are modeled in the same way as suggested by Terman, Rubin, Yew, and Wilson (2002). Depending on the membrane potential ($v(t)$), action potential spreading from the neuron causes neurotransmitter release whose concentration in the synaptic cleft, $[T]$, is modeled by the following equation:

$$[T] = \frac{1}{1 + \exp(-(v(t) - \theta_s)/\sigma_s)} \tag{11}$$

where θ_s and σ_s are the half-activation voltage and steepness of the sigmoid function, respectively. It is now well-documented that astrocytes are able to sense transmitters released by neurons, that is $[T]$. Following Volman et al. (2007), we assume that the rate of IP_3 production depends on the concentration of neurotransmitter which is released to the synaptic cleft. Therefore, the input of the astrocyte (z) which triggers the IP_3 production is defined as:

$$z = \lambda\,[T] \tag{12}$$

where $\lambda > 0$ is an amplifying parameter. Astrocytes contribute to synaptic signaling by performing a physiological feedback. This gives rise to depolarization or hyperpolarization of nearby neurons (Smith, 2010). Specifically, astrocytic glutamate release in the hippocampus can activate NMDA (N-methyl-D-asparate) type glutamate receptors, leading to so-called slow inward currents (SIC) in neighboring neurons (Fellin et al., 2009; Min, Santello, & Nevian, 2012; Perea & Araque, 2005). Consequently, the output of the astrocyte is modeled as:

$$i^{ast} = \gamma \cdot c \tag{13}$$

where γ is the feedback strength from astrocyte to neuron. Therefore, the full expression of the input current of the neuron is modified as follows to integrate the feedback of the astrocyte:

$$i(t) = i^{const}(t) + i^{noise}(t) + i^{ast}(t). \tag{14}$$

3. Phase plane analysis

In this section, the neuron–astrocyte interaction is analyzed from the dynamical system point of view. It should be emphasized that we analyze the full model of the astrocyte and neuron together. Specifically, the neuron affects the astrocyte dynamics through $\bar{z}$, where $\bar{z}$ is the steady state of neurotransmitter concentration (z). On the other hand, the effect of astrocyte dynamics on the neuron in the steady state is $i^{ast} = \gamma\,\bar{c}$ where $\bar{c}$ is the steady state of the calcium concentration inside the astrocyte (Eq. (17)). The $\bar{c}$ also depends on $\bar{S}_m$ (the steady state of the second messenger inside the astrocyte) and finally $\bar{S}_m$ is determined by the steady state of the neuron membrane potential ($\bar{v}$). Therefore, the closed loop system of neuron–astrocyte signaling is analyzed.

3.1. Quantitative analysis

The steady state values of the neuron model (or the equilibrium points of the neuron model), i.e., $(\bar{v}, \bar{w})$, are obtained by solving:

$$\begin{cases} \dfrac{dv(t)}{dt} = \dfrac{1}{C} f_1(\bar{v}, \bar{w}) = 0 \\ \dfrac{dw(t)}{dt} = f_2(\bar{v}, \bar{w}) = 0 \end{cases} \tag{15}$$

where $f_1(\bar{v}, \bar{w})$ and $f_2(\bar{v}, \bar{w})$ are:

$$\begin{cases} f_1(\bar{v}, \bar{w}) = -\bar{g}_{Ca}\, m_\infty(\bar{v})\,(\bar{v} - v_{Ca}) - \bar{g}_K\, \bar{w}\,(\bar{v} - v_K) \\ \qquad\qquad - \bar{g}_L\,(\bar{v} - v_L) + i^{const} + i^{noise} + i^{ast} \\ f_2(\bar{v}, \bar{w}) = \phi\,[w_\infty(\bar{v}) - \bar{w}]/\tau_w(\bar{v}). \end{cases} \tag{16}$$

In (16), i^{ast} should be replaced by its steady state value as $i^{ast} = \gamma\,\bar{c}$, where:

$$\begin{aligned} &\bar{c} = r + \beta\,\bar{S}_m, \\ &\bar{S}_m = \frac{\bar{M}}{\bar{M} + \frac{1}{d_{Sm}}}, \quad \bar{M} = 1 + \tanh[S_{sm}(\bar{z} - h_{sm})] \end{aligned} \tag{17}$$

and

$$\bar{z} = \lambda\,[\bar{T}], \qquad [\bar{T}] = \frac{1}{1 + \exp(-(\bar{v} - \theta_s)/\sigma_s)}. \tag{18}$$

Using Eqs. (15)–(18), we can investigate the role of the feedback strength from astrocyte to neuron (γ). As we will observe, variation in γ can change the number of equilibrium points and their stability.

Computing the bifurcation point γ^*:

To obtain the bifurcation point, we determine *nullclines* of the 2nd order neural system defined by Eqs. (16)–(18). The v-nullcline associated with the variable v is described by the following function:

$$w = \frac{-\bar{g}_{Ca}\, m_\infty\,(v)\;(v - v_{Ca}) - \bar{g}_L\;(v - v_L) + i}{\bar{g}_K\,(v - v_K)}. \tag{19}$$

Similarly, the w-nullcline associated with the variable w is a monotonically increasing function of v as follows:

$$w = w_\infty\;(v) = 0.5\left[1 + \tanh\left(\frac{v - \hat{v}_3}{\hat{v}_4}\right)\right] \tag{20}$$

v and w nullclines are depicted by green and brown colors in Fig. 1, respectively. The nullclines partition the phase plane into four quadrants. The asymptotically stable (*attractor*), the saddle and the unstable equilibrium points are illustrated by the filled, half-filled and empty circles in Fig. 1, respectively. In the simulation results shown in Fig. 1, the value of λ is fixed at 0.5. However, the feedback strength from astrocyte to neuron (γ) varies and takes on three values of (a) $\gamma = 0$, (c) $\gamma = 18$ and (e) $\gamma = 35$.

When $\gamma = 0$, and according to Fig. 1(a), the minimum point of the v-nullcline, $v_{\min}$, is between the stable and the saddle equilibrium points. Using (19), we can obtain the corresponding $w_{\min|\gamma=0}$:

$$w_{\min|\gamma=0} = \frac{\bar{g}_{Ca}\, m_\infty\,(v_{\min})\;(v_{\min} - v_{Ca}) - \bar{g}_L\;(v_{\min} - v_L) + i^{const} + i^{noise}}{\bar{g}_K\;(v_{\min} - v_K)}. \tag{21}$$

Considering (19), and (20), the variations of γ affect only the v-nullcline and move it vertically in the w-axis direction. This is illustrated in Fig. 1(a), (c) and (e). At the bifurcation point ($\gamma = \gamma^*$) and for $v_{\min}$ the $w_{\min|\gamma=\gamma^*}$ is:

$$w_{\min|\gamma=\gamma^*} = \frac{\bar{g}_{Ca}\, m_\infty\,(v_{\min})\;(v_{\min} - v_{Ca}) - \bar{g}_L\;(v_{\min} - v_L) + i^{const} + i^{noise} + \gamma^*\bar{c}}{\bar{g}_K\;(v_{\min} - v_K)}. \tag{22}$$

Considering Fig. 1(c), when $\gamma = \gamma^*$ the v-nullcline is tangent to the w-nullcline at $v_{\min}$. Because γ does not affect the w-nullcline, at $v_{\min}$, the values of the w-nullcline for $\gamma = 0$ and $\gamma = \gamma^*$ are equal. From the numerical simulations shown in Fig. 1(a), it can be *measured* that $v_{\min} = -31.77$ and at this point the distance between v- and w-nullclines is approximately equal to 0.0101. Therefore, $w_{\min|\gamma=\gamma^*} - w_{\min|\gamma=0} \approx 0.0101$. Subtracting (21) from (22) leads to:

$$\frac{\gamma^*\bar{c}}{\bar{g}_K\;(v_{\min} - v_K)} \approx 0.0101. \tag{23}$$

Replacing $v_{\min} = -31.77$ and the parameter values listed in Table 1, we obtain:

$$\gamma^*\bar{c} \approx 3.8939. \tag{24}$$

Substituting $\bar{c}$ from (17) and the other parameter values listed in Table 1 leads to:

$$\begin{aligned} [T] &= \frac{1}{1 + \exp\left(-(-31.77 - 50)/15\right)} = 0.0043,\\ \bar{z} &= 0.5\,[\bar{T}] = 0.0021\\ \bar{M} &= 1 + \tanh[100(0.0021 - 0.02)] = 0.0546\\ \bar{c} &= 0.2 + \frac{3 \times 0.0546}{0.0546 + 10} = 0.2163 \end{aligned} \tag{25}$$

and finally,

$$\gamma^* = \frac{3.8939}{0.2163} = 18.00. \tag{26}$$

Now, we consider three different cases:

Case 1. $\gamma = 0$

Solving (16)–(18) results in three equilibrium points for the system as:

$$\begin{aligned} Eq_1 &: \begin{pmatrix}\bar{v}_1\\ \bar{w}_1\end{pmatrix} = \begin{pmatrix}-36.8802\\ 0.0036\end{pmatrix},\\ Eq_2 &: \begin{pmatrix}\bar{v}_2\\ \bar{w}_2\end{pmatrix} = \begin{pmatrix}-23.2933\\ 0.0170\end{pmatrix},\\ Eq_3 &: \begin{pmatrix}\bar{v}_3\\ \bar{w}_3\end{pmatrix} = \begin{pmatrix}5.1496\\ 0.3127\end{pmatrix}. \end{aligned} \tag{27}$$

The stability properties of these equilibrium points can be investigated by analyzing the linearized system at the equilibrium points. The Jacobean matrix is calculated by:

$$A = \left.\begin{pmatrix}\dfrac{\partial f_1(v,w)}{\partial v} & \dfrac{\partial f_1(v,w)}{\partial w}\\ \dfrac{\partial f_2(v,w)}{\partial v} & \dfrac{\partial f_2(v,w)}{\partial w}\end{pmatrix}\right|_{v=\bar{v}_i,\, w=\bar{w}_i} \tag{28}$$

where $i = 1, 2$. The eigenvalues of A at Eq_1 are: $\lambda_1 = -0.0527$, $\lambda_2 = -0.1327$. These eigenvalues demonstrate that Eq_1 is a stable node. For Eq_2 we obtain: $\lambda_1 = 0.0853$, $\lambda_2 = -0.0800$ and therefore it is a saddle point. Finally, for Eq_3, $\lambda_{1,2} = 0.0689 \pm j0.1961$ which imply that it is an unstable focus.

Case 2. $\gamma^* = 18$

At the bifurcation point, i.e., $\gamma^* = 18$, two equilibrium points exist:

$$\begin{aligned} Eq_1 &: \begin{pmatrix}\bar{v}_1\\ \bar{w}_1\end{pmatrix} = \begin{pmatrix}-29.6248\\ 0.0083\end{pmatrix},\\ Eq_2 &: \begin{pmatrix}\bar{v}_2\\ \bar{w}_2\end{pmatrix} = \begin{pmatrix}5.9364\\ 0.3325\end{pmatrix}. \end{aligned} \tag{29}$$

The eigenvalues of A at Eq_1 are: $\lambda_1 = 0.0000$, $\lambda_2 = -0.1013$, and thus it is a saddle–node. For Eq_2 we obtain: $\lambda_{1,2} = 0.0653 \pm j0.2041$, that is, it is still an unstable focus. Based on a phase portrait of the system (Fig. 1(c)) we see that an invariant circle has also emerged at the bifurcation instant.

Case 3. $\gamma = 35$

For $\gamma = 35$, there is one unstable focus $Eq_1 : \begin{pmatrix}\bar{v}_1\\ \bar{w}_1\end{pmatrix} = \begin{pmatrix}6.6599\\ 0.3512\end{pmatrix}$ whose eigenvalues are: $\lambda_{1,2} = 0.0596 \pm j0.2123$. The phase portrait show also the stable limit cycle of the system.

3.2. Qualitative analysis

Fig. 1(a), (c) and (e) correspond to the phase plane of the neuronal system (Eqs. (1)–(2)), and Fig. 1(b), (d) and (f) illustrate the relevant time responses and the astrocyte outputs for each case. According to Fig. 1(a) and the stability analysis performed in the previous subsection, when we open the astrocyte feedback (that is $\gamma = 0$), the M–L model has one stable, one saddle and one unstable equilibrium point. In this case, depending on the initial conditions, only a single action potential or sub-threshold responses could be observed. Some examples are shown in the top panel of Fig. 1(b). It should be mentioned that since $\gamma = 0$, the astrocyte output (i^{ast}) is zero for this condition. Next, we consider the more realistic situation and integrate the role of astrocyte in the regulation of synaptic transmissions. When the astrocyte feedback strength (γ) is increased, the stable and the saddle equilibrium points get

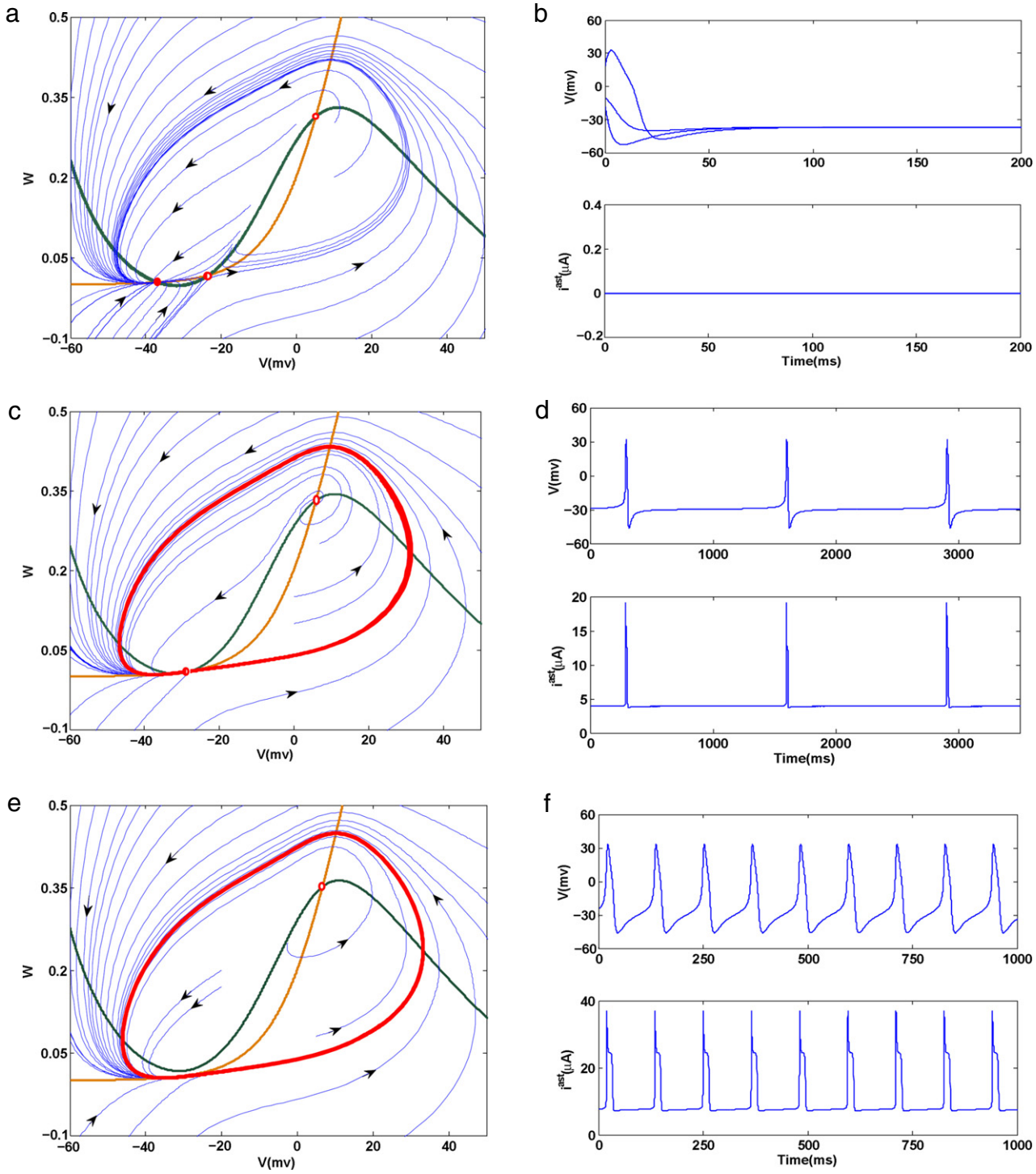

Fig. 1. The phase plane and equilibrium points of the dynamical system (1)–(2). (Left panels), filled, half-filled and empty circles denote stable, saddle and unstable equilibrium points, respectively. Arrows indicate directions of trajectories. The red closed curve denotes the stable limit cycle. The green and brown curves indicate v and w-nullclines. The right panels show the time response of the neuron (v) and the astrocyte output (i^{ast}). In these simulations $\lambda = 0.5$ and in (a) and (b) $\gamma = 0$, in (c) and (d) $\gamma = 18$ and in (e) and (f) $\gamma = 35$. It is evident that increasing the feedback strength from astrocyte to neuron first activates the silent neuron and then increases its firing frequency. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

closer to each other and finally, as Fig. 1(c) shows, at $\gamma = 18$, the two equilibrium points come together and at the same time an *invariant circle* is formed. In other words, a stable limit cycle appears via a *saddle–node on invariant circle* (SNIC) bifurcation (Izhikevich, 2007). The time response of the neuron and the astrocyte output are demonstrated in the top and bottom panels of Fig. 1(d), respectively. Due to the presence of the invariant circle and right after and very close to the bifurcation point, the neuron generates very low frequency spikes. This implies that if the feedback strength from astrocyte to neuron is strong enough, then the silent neighboring neuron can be turned on and generate a few spikes. Next, we increased the astrocyte feedback beyond the critical point ($\gamma > 18$) and investigated the resulting dynamical behavior of the neuron. For $\gamma = 35$, the phase portrait of the system, the time response of the neuron and the astrocyte output are shown in Fig. 1(e) and (f). In the phase plane, the stable limit cycle corresponds to the repet-

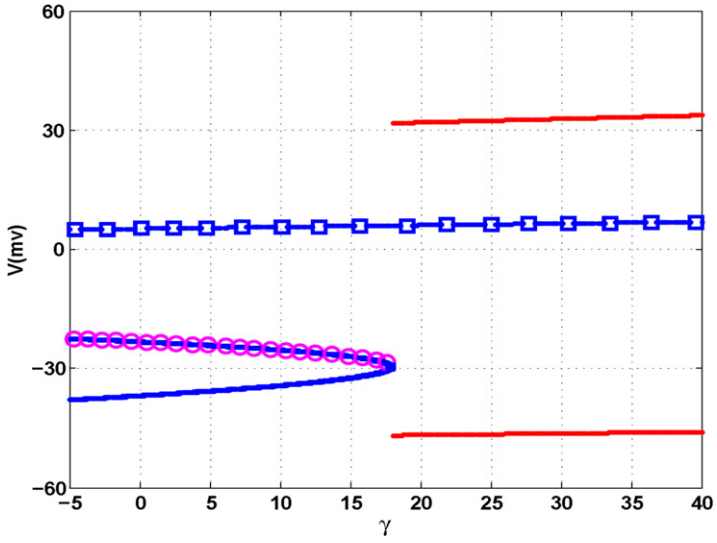

Fig. 2. One-parameter bifurcation diagram for equilibrium points shows that at $\gamma = 18$ SNIC bifurcation occurs and a stable limit cycle emerges. All parameters, except for γ, are fixed to the values shown in Table 1. In this figure, the unstable, stable and the saddle equilibrium points are indicated by empty squares, blue line and pink circles, respectively. The red lines show the stable limit cycle. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

itive firing of the neuron. Comparing the simulation results shown in Fig. 1(d) and (f) together, we will notice that the firing frequency of the neuron is considerably increased as the astrocyte feedback is increased from 18 to 35. In other words, the frequency of oscillation depends on the bifurcation parameter which is in accordance with the results mentioned in (Izhikevich, 2007). Therefore, the astrocyte modulates neuronal excitability by providing feedback action. It is noteworthy the astrocyte output is biphasic and consists of a large initial peak followed by a sustained plateau with smaller amplitude. This is in agreement with the response obtained by the experimental results and reported by Garbo et al. (2007, Fig. 2). As Fig. 1(b), (d) and (f) show, increasing the feedback strength from astrocyte to neuron leads to the emergence of different neuronal responses. In other words, the astrocyte is able to turn on the silent neuron or change the neuron spiking frequency. Moreover, based on different neural coding paradigms, the firing activity of a neuron is a key component of information processing. In the "temporal code", the precise timing of action potentials is important and in the "rate code", the information is represented by a modulation of the firing rate (Quilichini & Bernard, 2012). Thus, variation in the strength of astrocyte–neuron interactions can be considered as a mechanism for information encoding. In this way, the astrocyte dynamically contributes to the information processing mechanisms. Indeed, the astrocyte is capable of modulating the output of the neuron and thus the neuron–astrocyte interaction can facilitate the diversity of responses produced by the neuron. In line with these simulation results, recent studies about communications between astrocytes and neurons reveal that glutamate release from a single astrocyte may control the excitability of neighboring cells (Silchenko & Tass, 2008), that is, the astrocytes can act as local controllers of the synaptic function (Fellin, 2009; Fellin et al., 2006).

To have a general view of how the variation of γ affects the dynamical behavior of the neuron and summarize the results observed in Fig. 1, a one-parameter (γ) bifurcation diagram is plotted in Fig. 2. It can be seen that when γ is increased, the stable (blue line) and the saddle equilibrium points (pink circles) move towards each other and finally coalesce and disappear and a stable limit cycle emerges (red lines), which corresponds to the SNIC bifurcation mentioned earlier. Regardless of the value of γ, the stability property of the unstable point (empty squares) remains unchanged.

Next, let us consider the effect of variation of λ in (13), that is, in neuron to astrocyte feed-forward strength. To study this relation, in Fig. 3, we fixed $\gamma = 28$ and changed the value of λ. It can be seen that changing λ from 0.1 (blue curve) to 0.5 (green curve) and finally to 1 (pink curve) alters the v-nullcline insignificantly. In other words, due to the change of λ no bifurcation occurs and only the position of the unstable equilibrium point moves slightly upward. This is illustrated in the enlarged diagram at the left side of Fig. 3. In Fig. 4, the top panel shows the time response of the neuron and the bottom panel the astrocyte output corresponding to the individual values of λ in Fig. 3. Fig. 4 shows that changing the value of λ also alters the firing rate of the neuron. To investigate the effect of changing λ and γ on the neuronal behavior simultaneously, we calculated the neuron spiking frequency (that is, the inverse on inter-spike intervals) and then plotted it versus λ and γ. The results are shown in Fig. 5. It should be mentioned that in this figure, the minimum value of γ is considered to be 18, since first at this point the limit cycle (tonic behavior) is appeared. As shown in Fig. 2, repetitive firing is caused by the SNIC bifurcation, and therefore starts with the zero frequency. This region is indicated by the dark blue in Fig. 5. However, for the large value of λ and γ the frequency is increased considerably. Two important results are derived from this figure. First, we observe a transition in the neuron firing frequency as the strength of the neuron–astrocyte interactions changes. Second, the locus of the constant frequency points has an *arc* shape. This observation suggests that there is a nonlinear relationship between the feed-forward (from neuron to astrocyte) and feedback (from astrocyte to neuron) gains in the neuron–astrocyte communication. In this way, to have a specific firing activity, the interaction of both parameters is required which reveals the fundamental role of the astrocytes to regulate the neuronal excitability.

4. Discussion

Neuronal firing activity, which includes both the frequency and the timing of action potentials, is an essential component in information processing in the brain. Understanding neuronal computation requires knowledge about how neurons can switch from one firing pattern to another and how neuronal networks can switch from one mode of oscillation to another (Quilichini

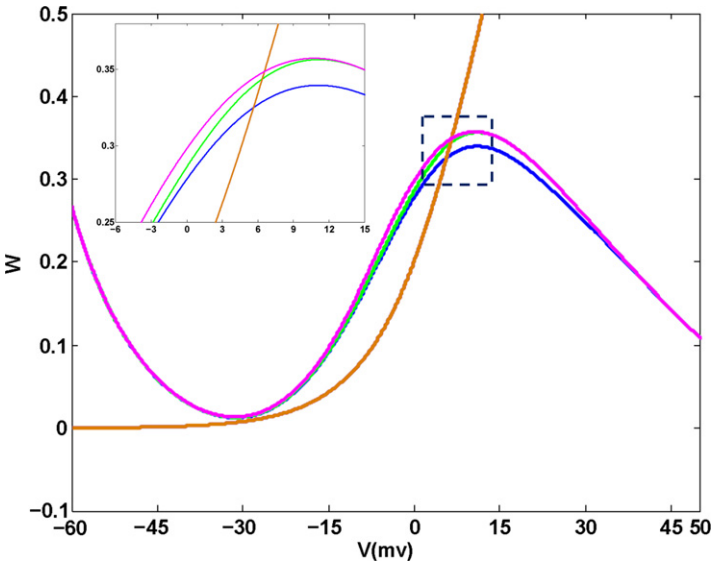

Fig. 3. The phase plane of the dynamical system (1)–(2) for different values of λ. The brown curve indicates w-nullcline. In these simulations γ was fixed at $\gamma = 28$ and λ was changed and took on three different values of $\lambda = 0.1$ (blue curve), $\lambda = 0.5$ (green curve) and $\lambda = 1$ (pink curve). It is evident that increasing λ, the position of the unstable equilibrium point will move upward and the firing frequency of the neuron will increase. The inset is the enlargement of the selected part. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

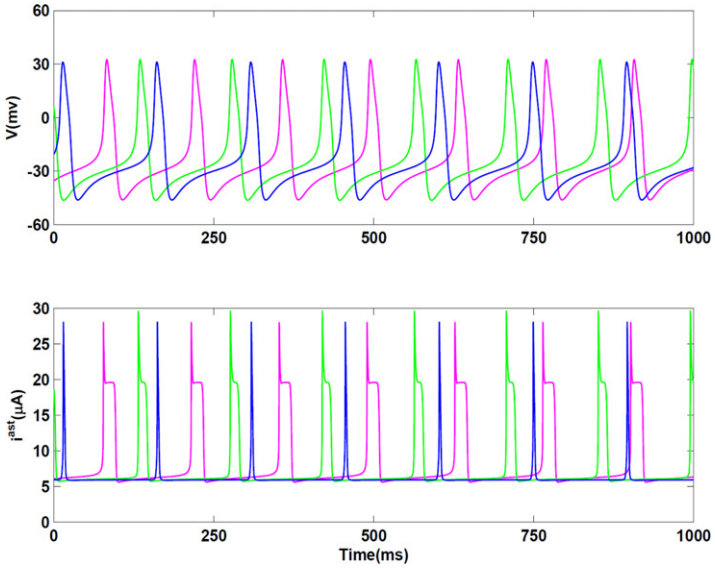

Fig. 4. Top panel illustrates the time response of the neuron and the bottom panel shows the astrocyte output for the fixed value of $\gamma = 28$ and three different values of $\lambda = 0.1$ (blue, $T = 147$ ms), $\lambda = 0.5$ (green, $T = 143$ ms) and $\lambda = 1$ (pink, $T = 138$ ms). The values of λ are chosen consistent with Fig. 3. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

& Bernard, 2012). Considering the results of this paper which implies that the astrocyte is able to change the neuron spiking frequency, suggests the possibility that the astrocyte has an active role in neuronal synchronization. Synchronization is an important mechanism for neural signaling, whereas a hallmark of several neurological diseases such as epilepsy is excessively synchronized discharges of neurons (Amiri, Bahrami, & Janahmadi, 2012b; Amiri, Davoodi, Bahrami, & Raza, 2011; Seifert, Carmignoto & Steinhäuser, 2010). Indeed, *in vitro* experiments have demonstrated that astrocytes control the frequency of cortical up-states (Min et al., 2012; Poskanzer & Yuste, 2011). In addition, experimental evidence shows that astrocytically released gliotransmitters has a role in the neural synchrony (Fellin et al., 2009; Pereira & Furlan, 2009). One explanation for local synchronization of neurons is that neighboring synapses are coordinated by signals from a single astrocyte. In other words, one astrocytic glutamate release event can induce SICs simultaneously in adjacent neurons. This led to the assumption that they play a role in the local neuronal synchronization (Angulo, Kozlov, Charpak, & Audinat, 2004; Fellin et al., 2004; Min et al., 2012).

Also, based on the results of this paper, it is expected that not only variations in the neuron–astrocyte interactions, but also variation in the strength of astrocyte–neuron interactions can be considered as a mechanism to encode information besides variations in the neuron–neuron interactions in the brain. This can provide a layer of information processing that could be in parallel with, and/or interacting with, the information processing in neuronal cells (Amiri, Hosseinmardi, Bahrami, & Janahmadi, 2013; Hamilton & Attwell, 2010). Based on the structural relationship between astrocytes and nerve cells, it has been reported that not only an astrocyte has the potential to coordinate small clusters of neurons, but also one astrocyte has the potential to regulate

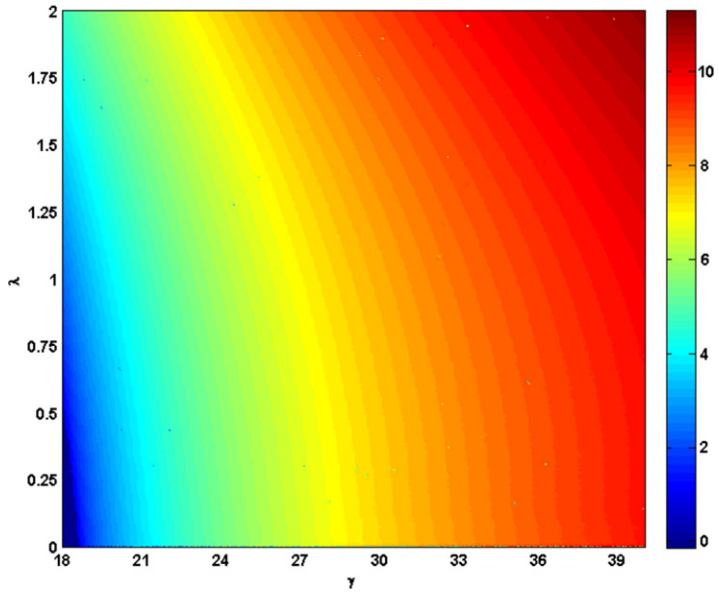

Fig. 5. The neuron firing frequency as a function of γ and λ with different colors to investigate the effect of bidirectional communication between neuron and astrocyte on the neuronal behavior. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the function of hundreds of synapses (Halassa, Fellin, Takano, Dong, & Haydon, 2007). Given that the results of this paper highlight the importance of astrocyte–neuronal coupling, it is an interesting point to consider a neuronal population model and construct a network in which astrocytes can dynamically modulate neuronal excitability and synaptic transmission. This procedure also provides new opportunities for further investigation of the model and pertinent applications including involvement of astrocytes in brain disorders such as epilepsy.

It should be pointed out that the procedure used in this paper to model neuron–astrocyte interactions is a *functional* approach rather than a detailed structural and biophysical modeling. The proposed model was developed by applying simplifications to the underlying biophysical mechanisms. Hence, although changing the model alters the *quantitative* analysis performed in the paper, the obtained *qualitative* responses are the same. In this way, the absolute values of the obtained results are less significant and thus the simulation results are qualitatively discussed and compared with experimental observations. Finally, the phase plane analysis of the model carried out in this paper is a starting point for dynamical analysis of the realistic neuron–glia networks.

5. Conclusion

Over the past two decades, the knowledge about the diverse role of astrocytes in many facets of synaptic transmission has considerably expanded (Rusakov, Zheng, & Henneberger, 2011). The present study puts forward a new perspective to analyze the loop of information exchange between the neuron and astrocyte. First, a biologically inspired model was developed by connecting the Morris–Lecar neuron and astrocyte dynamic models. Then, utilizing dynamical system theory and based on the stability analysis of the equilibrium points and the bifurcation diagram, the neuron–astrocyte crosstalk was analyzed. In this way, it was demonstrated that the astrocyte could apply feedback action to regulate neuronal excitability. Through SNIC bifurcation, it was shown that the astrocyte is able to turn on the silent neighboring neuron or change the neuron spiking frequency. This means that the bidirectional signaling between neuron and astrocyte could facilitate the diversity of responses produced by the neuron. Consequently, the feedback signaling through the activation of astrocytes modulates spike transmission frequency by increasing or decreasing neuronal firing. This suggests that astrocyte actively contributes in the information processing mechanisms which are carried out primarily by neurons. It should be pointed out that the state-of-the-art experimental techniques will require further investigation of the astrocyte's role in the understanding of brain function.

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