The influence of the astrocyte field on neuronal dynamics and synchronization

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Abstract Astrocytes can sense local synaptic release of glutamate by metabotropic glutamate receptors. Receptor activation in turn can mediate transient increases of astrocytic intracellular calcium concentration through inositol 1,4,5-trisphosphate production. Notably, the perturbation of calcium concentration can propagate to other adjacent astrocytes. Astrocytic calcium signaling can therefore be linked to synaptic information transfer between neurons. On the other hand, astrocytes can also modulate neuronal activity by feeding back onto synaptic terminals in a fashion that depends on their intracellular calcium concentration. Thus, astrocytes can also be active partners in neuronal network activity. The aim of our study is to provide a computationally simple network model of mutual neuron–astrocyte interactions, in order to investigate the possible roles of astrocytes in neuronal network dynamics. In particular, we focus on the information entropy of neuronal firing of the whole network, considering how it could be affected by neuron–glial interactions.

Keywords Neuron–glial interactions · Neural dynamics · Synchronization

1 Introduction

In recent years, much effort of the scientific community has been devoted to investigating a possible role for glial cells in the brain. It has been pointed out that astrocytes have an important role in the processing of information in the human brain: they not only provide a trophic support to neurons but they may also respond to neuronal activity and modulate

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it, thus being active partners in neuronal interactions [1]. In this paper, we provide a simple computational model, which consists of two simple blocks, one for astrocytes [2, 3] and the other for neurons [4], together with an interaction between the two.

We first analyze inter-astrocyte communication. Glial cells can communicate with each other by means of Ca^{2+} waves. In this regard, we aim to describe a neuron–glial network. For this purpose, we consider a model for the propagation of these waves. The main process we want to simulate is calcium-induced calcium release (CICR) [5] in order to generate a calcium wave in response to a local increase of inositol 1,4,5-trisphosphate (IP_3). We choose to adopt the model of Atri et al. [2] for its computational simplicity, yet accounting for a cytoplasmic gradient of IP_3 . Furthermore, we extend the Atri et al. model to include intercellular calcium signaling, by modelling intercellular interactions among astrocytes following Wilkins and Sneyd [3]. For the neuronal component of the model, we consider a network of neurons modeled according to Izhikevich [4], basing our choice, once again, on its computational advantages [6]. We therefore build up our neuron–glial network through the coupling of these two models, and we study the different behaviors of the system both when the models are coupled and when they are not. In particular, we will focus on a condition where the Izhikevich model yields a great degree of synchronization, and we still see that switching on the astrocytes decreases the degree of synchronization.

The outline of the paper is as follows. In Sections 2 and 3, we describe the models and provide all parameter values. Section 2 is devoted to a brief description of the Atri–Wilkins–Sneyd [2, 3] model for glial calcium waves, as well as of Izhikevich model for neuron networks [4]. Section 3 describes a glial–neuron network interaction pattern motivated by previous studies [7]. Finally, the results of our study are presented and discussed in Sections 4 and 5, respectively.

2 The models

2.1 The astrocytic syncytium

The dynamics within an astrocyte can be described by the model originally introduced by Atri et al. [2]. This model considers three variables only: these are p , the cytoplasmatic concentration of IP_3 ; c , the cytoplasmatic concentration of Ca^{2+} ; and h , the fraction of IP_3 receptors that are not activated by Ca^{2+} . In a two-dimensional frame, the values of these concentrations depend on their (x, y) position. Therefore, from the physics terminology, we will following refer to $c(x, y)$ as the *calcium field* and the triplet (c, p, h) as the *astrocyte field*. Equations read:

$$\frac{\partial p}{\partial t} = D_p \left(\frac{\partial^2 p}{\partial^2 x} + \frac{\partial^2 p}{\partial^2 y} \right) + \frac{1}{\tau_{\text{IP}_3}} (p_{\text{eq}} - p), \quad (1)$$

$$\frac{\partial c}{\partial t} = D_c \left(\frac{\partial^2 c}{\partial^2 x} + \frac{\partial^2 c}{\partial^2 y} \right) + J_{\text{flux}} - J_{\text{pump}}, \quad (2)$$

$$\tau_h \frac{dh}{dt} = \frac{k_2^2}{k_2^2 + c^2} - h, \quad (3)$$

$$J_{\text{pump}} = \gamma \frac{c}{k_{\gamma} + c}, \quad (4)$$

$$J_{\text{flux}} = k_f \mu(p) \left(b + \frac{(1-b)c}{k_{\gamma} + c} \right) h, \quad (5)$$

where D_p and D_c are the IP_3 and cytoplasmic calcium diffusion coefficients, respectively, J_{pump} describes the rate of Ca^{2+} pumping from the cytoplasm into the endoplasmic reticulum (ER) and into the extracellular space, while J_{flux} describes the rate of release of Ca^{2+} from the ER into the cytoplasm through the IP_3 receptors. The meaning and the value of the other constants are reported in Table 1. Equations (1) and (2) are only valid within the cell, but not at its boundaries in the presence of other cells. Boundary conditions for connected astrocytes can be described following Wilkins and Sneyd [3]. Namely, the diffusive flux of any chemical can be taken proportional to the gradient of the chemical across the boundary. Accordingly, for the sample case of a monodimensional membrane located at $x = 0$, we have:

$$\begin{aligned} D_p \frac{\partial p(0^-, t)}{\partial x} &= D_p \frac{\partial p(0^+, t)}{\partial x} \\ &= F_p [p(0^+, t) - p(0^-, t)] \\ D_c \frac{\partial c(0^-, t)}{\partial x} &= D_c \frac{\partial c(0^+, t)}{\partial x} \\ &= F_c [c(0^+, t) - c(0^-, t)], \end{aligned} \quad (6)$$

Table 1 Parameters for the Atri et al. model

Const	Meaning	Value
b	Fraction of open IP_3 receptors at $[\text{Ca}^{2+}] = 0$	0.111
k_1	Kinetic constant	$0.7 \mu\text{M}$
k_2	Kinetic constant	$0.7 \mu\text{M}$
D_c	Diffusion constant for $[\text{Ca}^{2+}]$	$20 (\mu\text{m})^2/\text{s}$
γ	Maximum value for J_{pump}	$2 \mu\text{M}/\text{s}$
k_f	$[\text{Ca}^{2+}]$ flux when all IP_3 receptors are activated	$16.2 \mu\text{M}/\text{s}$
k_{γ}	Kinetic constant of calcium pumps of ER	$0.1 \mu\text{M}$
k_{μ}	Binding constant of IP_3 to its ER receptors	$0.7 \mu\text{M}$
τ_h	Time constant of IP_3 receptors	2 s
F_c	Ca^{2+} permeability of the cell membrane	$1.1 (\mu\text{m})/\text{s}$
F_p	IP_3 permeability of the cell membrane	$5 (\mu\text{m})/\text{s}$
p_{eq}	IP_3 resting concentration	$0.28 \mu\text{M}$

where F_c and F_p are the Ca^{2+} and IP_3 permeabilities of the membrane, and 0^- and 0^+ stand for the right and left sides of the membrane (refer to Table 1 for details).

Inspection of Eqs. (1)–(5) shows that Eq. 1 is almost decoupled from the other equations and describes a regression to equilibrium of the messenger IP_3 . The nonlinear features of CICR are given by the coupled Eqs. (2) and (3). Both equations resemble the Hodgkin and Huxley formalism [8], with Eq. (2) being a mass balance and Eq. (3) accounting for a refractory time in calcium responses of astrocytes. We are inclined to believe that the results reported here will have a general validity for all models that share features with ours. We further note that, if diffusion is suppressed and the fast equation for IP_3 is adiabatically eliminated (e.g., by assuming steady conditions as in [3]), our model reduces to a couple of nonlinear equations. Notably, in this latter case, Ca^{2+} oscillations may rise through Hopf or saddle-homoclinic bifurcations depending on parameter values, as widely documented in other minimal models for CICR [9, 10]. The whole model (with diffusion) exhibits travelling waves. Detailed analysis showed that inclusion of diffusion makes the system more complex through the coupling of many equations (i.e., a set for each point in the spatial grid), up to the level that the system could not equilibrate even for small values of p_{eq} if strong perturbations on initial conditions are applied: a firm hint of ergodicity breakdown.

2.2 The neural network

We use the simplified version of the Izhikevich model as presented in [4]. Equations read:

$$\frac{dv}{dt} = 0.04 v^2 + 5 v + 140 - u + I \quad (7)$$

$$\frac{du}{dt} = A (B v - u) \quad (8)$$

with the auxiliary condition:

$$\text{if } v \geq 30 \text{ mV} \quad \text{then} \quad \begin{cases} v \rightarrow C \\ u \rightarrow u + D \end{cases}$$

The above condition means that, if the membrane potential v is larger than the threshold value of 30 mV, it is reset to its after-spike value C . Accordingly, the membrane recovery variable u is incremented by D . The parameter A represents the characteristic time for the variable u : the lower the value of A , the slower the dynamics of u . B instead is the sensibility of u to sub-threshold fluctuations.

The Izhikevich model reproduces several behaviors observed in cortical neurons, depending on the choice of parameters A , B , C , and D . Furthermore, the parameter I in Eq. 7 lumps together all the possible external afferent inputs feeding the neuron, among which we shall also include the current that astrocytes inject into neurons [7]. This latter aspect is discussed in the next section.

3 The neuron–glial network

A neuron–glial network can be thought of as three components, namely, the astrocyte syncytium, an overlapping neuronal network, and the mutual astrocyte–neuron interactions

[11]. From a modeling perspective, the astrocytic syncytium can be represented as an array of square cells, each cell being located at a specific point of a regular lattice [2, 3]. The overlapping neuronal network can also be thought of as a regular array of Izhikevich neurons whose synaptic connections are randomly defined by a matrix S_{ij} . Accordingly, when the j -th neuron fires, the membrane potential of the i -th neuron v_i changes according to: $v_i \rightarrow v_i + S_{ij}$. In the present study, we consider a 20×20 regular array of astrocytes overlapping a 7×7 neural network (see Fig. 1). Hence, we consider 49 neurons for 400 astrocytes, namely, about eight astrocytes per neuron, in agreement with experimental data for cortical neurons [12].

The mutual neuron–astrocyte interactions can be modeled as follows. We assume that, at each spike (that is, when $v_i \geq V_{\text{spike}}$), the glutamate released by all the synapses of the i -th neuron is sufficient to spill over the synaptic cleft and bind with astrocytic metabotropic receptors. Accordingly, we account for such spill-over by considering an instantaneous production of IP_3 equal to Q_{IP_3} in the astrocyte that is the closest to the spot of the released glutamate (that is, the ij -th synapse). In this study, the phenomenological quantities V_{spike} and Q_{IP_3} are chosen to be 25 mV and 9 nM, respectively.

The influence of astrocytes on neurons is modeled according to the experimentally-derived relation [7]:

$$I_{\text{astro}} = 2.11 \theta (\ln z) \ln z, \quad (9)$$

Fig. 1 Scheme of the glial–neuron network. The *black dots* represent neurons, whereas the *squares* stand for astrocytes

where

$$z \equiv [\text{Ca}^{2+}] \text{ (in nM)} - 196.69. \quad (10)$$

This current is then rescaled by the inverse of the neuronal capacitance ($C = 3 \mu\text{F cm}^{-2}$) in order to be lumped into I in Eq. (7) (see Section 2.2).

We study the influence of the astrocyte field on a neural network endowed with self-activity, that is, a neural network whose neurons can fire even in the absence of external stimulation. For Izhikevich neurons, this can be obtained by an opportune choice of the value of parameter B . If we set to zero the time derivatives in Eqs. (7) and (8) with $I = 0$ (no external input), the following equilibrium values for v are allowed:

$$v_{\text{eq}}^{(1,2)} = \frac{B - 5 \pm \sqrt{B^2 - 10B + 2.6}}{0.008}. \quad (11)$$

Equation (11) has no real solutions if $0.267 \leq B \leq 9.73$, which is equivalent to saying that, for B within such a range, an Izhikevich neuron has no resting state, or, alternatively, it is endowed with self-activity even without external inputs. In the following, we will set $B = 0.268$. For the other parameters of the Izhikevich neurons, we choose $A = 0.02$ for

Fig. 2 Simulation of a network of 49 neurons without astrocytes. The firing patterns show two synchronization events. The first involves both excitatory (from 1 to 39, below the *horizontal line*) and inhibitory (from 40 to 49, above the *horizontal line*) neurons with a frequency that corresponds to the alpha rhythm, close to 10 Hz. The second one (in *blue*) involves only excitatory neurons (yet with a frequency still close to 10 Hz). The initial instant of the displayed time window is $t_0 = 99$ s (color online)

Fig. 3 Inter-spike interval histogram of a 500-s time window of simulated activity of a neuronal network without astrocytes. The clustering of the majority of the inter-spike intervals around 100–110 ms hints at the existence of a favorite spiking state, which corresponds to the frequency of the two synchronization events observed in the whole network dynamics in Fig. 2

excitatory neurons and $A = 0.01$ for inhibitory ones. In particular, we consider an average ratio between excitatory neurons and inhibitory neurons of four to one. This value agrees with those reported in the literature [4] and provides our model with biological consistency, limiting the highest spiking frequency. Finally, C and D are randomly generated according to [4].

4 Results

4.1 Network dynamics without neuron–glial interactions

In the absence of mutual neuron–astrocyte interactions, the typical firing patterns of the network are shown in Fig. 2. We can clearly distinguish two synchronization events, namely, (1) a global event that involves all the neurons with a frequency of about 10 Hz and (2) a further event at the same frequency that involves excitatory neurons only. Figure 3 shows the unnormalized inter-spike interval distribution obtained by counting, for each neuron, how many times an inter-spike interval appeared during the simulation. We note that there is a favorite state of spike emission that resembles the alpha rhythm frequency (which is normally between 8 and 13 Hz [13]). This is a consequence of the synchronization events,

Fig. 4 Simulation of a network of 49 neurons in the presence of neuron–astrocyte interactions. Eye inspection of the firing patterns does not show any global synchronization events, in contrast to Fig. 2 as discussed in the text (Section 4.2). Initial instant of the displayed time window is $t_0 = 99$ s

which involve the whole network. The entropy associated with the inter-spike interval distribution is given by [14, 15]:

$$S = - \sum_n p_n \ln p_n, \quad (12)$$

where p_n is the frequency of the n -th inter-spike interval. For the network of neurons without astrocytes, we obtain $S = 2.8$. We will discuss the meaning of this value in the following in light of the same measure for a neuron–glial network of neurons interacting with astrocytes.

4.2 The effect of astrocytes on the dynamics of the network

When astrocytes are taken into account, the network dynamics changes considerably with respect to the case without astrocytes (compare Fig. 4 with Fig. 2). In particular, we do not observe any global synchronization event: the results suggest the possibility that perturbation of the network dynamics by an astrocytic field could increase the spiking probability for the neurons within the network. This is indeed supported by the inter-spike distribution in Fig. 5, where, differently from Fig. 3, the neurons interacting with the astrocytes appear to have two equiprobable spiking states instead of only one, as in the case without astrocytes.

Notably, the entropy of the inter-spike interval distribution in Fig. 5 is $S = 3.1$, which is greater than the value obtained for the case without astrocytes (see Section 4.1). This

Fig. 5 Inter-spike interval distribution for a simulated neuron–glia network. Note that, differently from the case in Fig. 3, the existence of neuron–astrocyte interactions seems to shift the frequency of spike-emission states of the network to higher frequencies (i.e., smaller inter-spike intervals)

simple result is somewhat trivial, in the sense that any perturbation of a model is expected to increase its computational complexity. However, if we also look at the firing patterns, it is plausible that an increase of the entropy of the inter-spike interval distribution could be a consequence of the increase of the spike-emission states.

5 Conclusions

The aim of our study was to provide a computationally simple modeling framework to investigate neuron–glia network dynamics. Our approach consists of coupling together two simple models—the Atri–Wilkins–Sneyd model [2, 3] for the astrocyte syncytium and the Izhikevich model for neurons [4]—by means of phenomenological quantities such as V_{spike} , and Q_{IP_3} , namely, the neuronal firing threshold to trigger astrocyte IP_3 -induced CICR and the corresponding IP_3 production, respectively, as well as empirical laws [7]. Our simulations suggest that astrocytes could raise the number of effectively activated spike-emission states of a neural network, allowing the whole system to explore more complex dynamics. Indeed, comparison of the inter-spike interval distribution of the network activity without astrocytes with the case with astrocytes shows a transition from unimodal to bimodal features. As a consequence, the entropy of the distribution increases in the presence of neuron–astrocyte interactions. Since the entropy of the distribution can be related to the computational complexity of the neural signal [16], our study suggests that the perturbation of neuronal network dynamics by an astrocyte field appears to increase the computational

complexity of the neural code. We do not claim that Kolmogorov computational complexity, estimated by a simple entropy measure, mirrors a real biological complexity (although the opposite is often true [17]). Yet, our study shows that a very apparent neural synchronization is effectively broken by neuron–glial interactions. Notwithstanding, the question of if and how complexity increases in “dressed” neurons (i.e., “dressed” by astrocytes) is still open [18, 19].

Preliminary inspection of Ca^{2+} dynamics within an astrocyte syncytium up to a 40×40 cell regular lattice revealed a weak form of turbulence with extremely slow relaxations to equilibrium (> 100 s) (Allegrini et al., unpublished manuscript). This condition is complex in the sense that it can result from the coexistence of order and randomness [20]. This means that, while astrocytes could increase randomness in a neural network that exhibits trivial (too regular) patterns, on the contrary, they could also introduce regularity in a completely chaotic neural network.

Although this possibility will be addressed by future studies, a rationale for glial complexity may already be briefly drawn as follows. The Atri–Wilkins–Sneyd model can be reduced to a simplified model by setting the IP_3 concentration to be homogeneous in both space and time. This corresponds to adiabatic elimination of Eq. (2). If we further neglect the calcium inhomogeneity in space, that is, if we neglect the first term on the right-hand side of Eq. (1), then the simplified model undergoes a supercritical Hopf bifurcation at a concentration of IP_3 slightly above the one found for the set of parameters adopted in the current study. This means that, before the bifurcation point, a fixed point is found, whereas beyond the bifurcation, global oscillations occur [3, 9, 10]. As a matter of fact, allowing for inhomogeneity allows the model to become “active” also for the parameters explored here. Accordingly, glia could behave like an excitable media close to a bifurcation point, which becomes “broader.” This resembles the weak chaotic condition observed theoretically in Landau–Ginzburg models, as well as experimentally in electroconvective liquid crystals, which were recently shown to exhibit inverse-power-law relaxations and breaking of ergodicity [21].

In neuronal networks in vivo, global synchronization events may denote ongoing pathological conditions, such as epileptic seizures [22]. While the effective role of astrocytes in epilepsy is a matter of debate [23, 24], few doubts exist on the correlations between epilepsy and glial pathology [25–27]. Here, we provide theoretical support for this possibility, showing that deficits in astrocytes that could shut down neuron–astrocyte communications might indeed give rise to global synchronization events akin to pathological conditions, such as epileptic seizures.

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