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Astrocyte-induced intermittent synchronization of neurons in a minimal network

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ABSTRACT

We investigate the impact of mixed coupling on synchronization in a minimal multiplex neuro-astrocytal ensemble, inspired by physiological systems. We find that calcium activity in astrocytes can effectively mediate neural interactions and control cooperative dynamics of neurons. In particular, astrocytes can induce the intermittent synchronization of a pair synaptically coupled fast spiking Hodgkin-Huxley neurons on the slow timescale of calcium oscillations.

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1. Introduction

Synchronization phenomenon plays a crucial role in neural communication [1], information processing [2] and coordination of motor activity [3]. There is evidence that brain rhythms (alpha, theta, and gamma oscillations) associated with memory organization [4] are formed due to partial synchronization of neural groups. It has also been demonstrated that synchronous firing of large neuronal networks underlies pathological processes, in particular epileptiform activity [5]. At the cellular level, the persistent synchronized firing of presynaptic and postsynaptic neurons induces the long-term changes in the strength of interaction between them. This phenomenon is called synaptic plasticity and is thought to stand behind learning and memory [6].

Synchronization of neural activity in the brain is never perfect. Imperfect or intermittent synchronization has been extensively studied in nonlinear dynamics for generic oscillators, including chaotic [7–10]. Some aspects of intermittent synchronization in ensembles of spiking neuronal oscillators were addressed [11–13], but its understanding remains far from complete (for a recent review see [14]). In particular, the dynamical role of astrocytes, a type of glial cells, in which neurons are embedded, is yet to be clarified.

Recent experimental findings have shown that astrocytes can participate in synaptic signal transmission [15]. In particular, the activation of synaptic transmission evokes Ca^{2+} elevations in astrocyte. Importantly, the duration of astrocytic calcium signals (1–2 s) is three orders of magnitude longer than the time scale of action potential in neuron (1 ms). Calcium elevations in astrocytes induce release of gliotransmitters resulting in stimulation of synaptic receptors and acute synaptic modulation [16]. Experimental studies [17–20] revealed that astrocyte-induced modulation of synaptic transmission leads to synchronous neuronal activation.

A number of papers investigated the dynamical effects of astrocytes in neuronal ensembles. It was shown that astrocytes can stabilize neural activity, while disruption of their signaling can lead to abnormal neural synchrony [21]. Synchronization in the two-layer network of phase oscillators with multiplex topologies, mimicking architecture of a neural-astrocyte network was studied in [22]. Although there remained a far stretch to a physiological model, the results suggested that synchronization of fast oscillations can be effectively controlled by the slow oscillating subnetwork. In [23], it was demonstrated that Ca^{2+} signalling in spatially extended astrocyte model can coordinate (e.g., synchronize) networks of neurons and synapses. Interestingly, [24] revealed astrocytic influence on a generation of positive integrated information in neuron-astrocyte ensembles.

Despite these insights, the fundamentals of signal processing in neuron-astrocytic networks still remain largely undisclosed. In this study we make use of physiologically relevant Hodgkin-Huxley (HH) and Ullah-Jung (UJ) models to investigate the astrocytal

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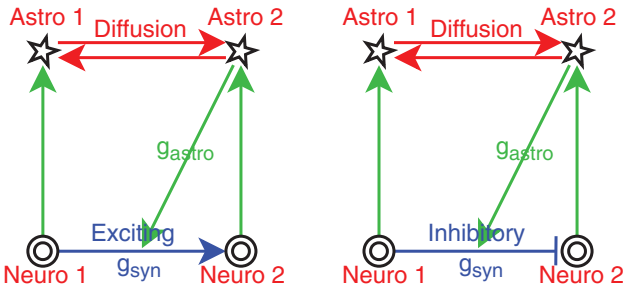

Fig. 1. [Color online] Schematic illustrations of the neuron-astrocyte ensemble for the two investigated cases: with exciting and inhibitory synaptic neuronal coupling. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

influence on the dynamics of a pair of synaptically coupled spiking neurons. We find that spiking activity in neurons induces the slow oscillatory activity in astrocytes, which in turn modulates strength of synaptic connectivity. That leads to the novel regime of intermittent synchronization between spiking neurons on a timescale of slow calcium oscillations.

2. Model and methods

We study a minimal model of a neuron-astrocyte ensemble that consists of two pairs of reciprocal neurons and astrocytes. A schematic view of the neuron-astrocyte ensemble topology is shown in Fig. 1. Dynamics of intracellular Ca^{2+} concentration in astrocyte is described by the Ullah-Jung model [25] and the membrane potential of a neuron evolves according to the Hodgkin-Huxley model [26] with Mainen modification for mammals brain [27,28].

The dynamics of membrane potential is described by the HH model [26]:

$$\begin{cases} C\frac{dV_i}{dt} = \mu(g_{Na}m_i^3h_i(E_{Na}-V_i) + g_K n_i(E_K - V_i) + \\ \quad + g_{Leak}(E_{Leak}-V_i) + I_{app_i} + I_{syn_2}); \\ \frac{dx_i}{dt} = \mu(\alpha_x(1-x_i) - \beta_x x_i), \quad x = m,n,h;\ i = 1,2; \end{cases} \tag{1}$$

where V is the membrane potential, m and h the activation and inactivation variables of the sodium current and n the activation variable of the potassium current. The subscripts 1 and 2 mark the master (presynaptic) and slave (postsynaptic) neurons, respectively. The applied currents I_{app_i} determine the constant depolarization level of neurons and the dynamic regime (excitable, oscillatory, or bistable). They also control the neuron's spiking frequency in the oscillatory and bistable regimes.

Nonlinear functions for gating variables α_x and β_x, are taken as the follows [27]:

$$\begin{aligned} \alpha_m &= \frac{0.182(V_i+35)}{1-e^{\frac{-(V_i+35)}{9}}}; & \beta_m &= \frac{-0.124(V_i+35)}{1-e^{\frac{(V_i+35)}{9}}}; \\ \alpha_n &= \frac{0.02(V_i-25)}{1-e^{\frac{-(V_i-25)}{9}}}; & \beta_n &= \frac{-0.002(V_i-25)}{1-e^{\frac{(V_i-25)}{9}}}; \\ \alpha_h &= 0.25e^{\frac{-(V_i+90)}{12}}; & \beta_h &= 0.25\frac{e^{\frac{V_i+62}{6}}}{e^{\frac{V_i+90}{12}}}; \end{aligned} \tag{2}$$

An excitatory or inhibitory unidirectional nonlinear coupling from presynaptic (master) neuron to postsynaptic (slave) neuron is realized by the synaptic current, I_{syn_2}. This current reflects the kinetics of chemical synapse and is expressed as follows:

$$I_{syn_2} = \frac{\tilde{g}_{syn}(E_{syn}-V_2)}{1+e^{(-V_1/k_{syn})}}; \tag{3}$$

where parameter $\tilde{g}_{syn}$ describes the synaptic weight. The reversal potential equals $E_{syn} = -90\ mV$ for the inhibitory synapse and $E_{syn} = 0\ mV$ for excitatory.

The concentration of neurotransmitter that was released from the synapse of the (i)-neuron, can be expressed as follows [23]:

$$\frac{dG_i}{dt} = -\alpha_G G_i + \frac{\beta_G}{1+e^{\frac{-V_i}{0.5}}}; \tag{4}$$

Biophysical meaning of parameters in Eqs. (1)–(4) and their values are detailed in Appendix.

The state variables of the ith astrocyte include Ca^{2+} intracellular concentration, Ca_i, the fraction of activated IP_3 receptors on the endoplasmic reticulum, z_i, and intracellular concentration of inositol 1,4,5-trisphosphate (IP_3), $IP3_i$. They evolve according to the following equations [25]:

$$\begin{cases} \frac{dCa_i}{dt} = J_{ch} - J_{pump} + J_l + J_{in} - J_{out} + D_{Ca}\Delta Ca_i; \\ \frac{dIP3_i}{dt} = \frac{IP3^* - IP3_i}{\tau_{IP3}} + J_{PLC} + J_{Glu} + D_{IP3}\Delta IP3_i; \\ \frac{dz_i}{dt} = a_2(d_2\frac{IP3_i+d_1}{IP3_i+d_3}(1-z_i) - Ca_i z_i); \end{cases} \tag{5}$$

Equations for the currents describing the biochemical processes inside the astrocyte read:

$$\begin{aligned} &J_{ch} = c_1 v_1 IP3_i^3 Ca_i^3 z_i^3\left(\frac{c_0}{c_1} - \left(1+\frac{1}{c_1}\right)Ca_i\right)/ \\ &/[(IP3_i+d_1)(Ca_i+d_5)]^3; \\ &J_{PLC} = v_4(Ca_i + (1-\alpha)k_4)/(Ca_i+k_4); \\ &J_l = c_1 v_2\left(\frac{c_0}{c_1} - \left(1+\frac{1}{c_1}\right)Ca_i\right); \\ &J_{pump} = v_3 Ca_i^2/\left(k_3^2 + Ca_i^2\right); \\ &J_{in} = v_5 + v_6 IP3_i^2/\left(k_2^2 + IP3_i^2\right); \\ &J_{out} = k_1 Ca_i; \\ &J_{Glu} = \frac{\alpha_{Glu}}{1+e^{\frac{-(G_i-0.25)}{0.01}}}; \end{aligned} \tag{6}$$

The terms $(D_{Ca}\Delta Ca_i)$ and $(D_{IP3}\Delta IP3_i)$ in Eq. (5) account for Ca^{2+} and IP_3 diffusion via gap junctions between astrocytes. D_{Ca} and D_{IP3} are the diffusion coefficient for Ca^{2+} and IP_3, respectively; Δ denotes the discrete Laplace operator. Biophysical interpretation of all nonlinear functions and parameters in Eqs. (5) and (6) and their values that are determined experimentally can be found in Refs[25]. For parameters values used in this study refer to Appendix.

Calcium elevations in astrocytes trigger the release of gliotransmitters, such as glutamate, GABA, ATP and D–serine. Gliotransmitter can modulate the synaptic strength by binding with pre- or postsynaptic terminals. Among the variety of experimental manifestations of different gliotransmitters [29], we focus on the effect of the astrocyte-induced enhancment of synaptic transmission. It can be described with the simple model proposed in [24]:

$$\tilde{g}_{syn} = \begin{cases} g_{syn}(1+g_{astro}Ca_i), & \text{if } Ca_i > 0.3\ \mu M, \\ g_{syn}, & \text{otherwise}, \end{cases} \tag{7}$$

where parameter g_{astro} is the impact of the astrocyte to the synaptic transmission and Ca_i is astrocytic calcium concentration (5). Detailed biophysical description of the neuron-astrocyte interaction can be found in [30,31].

Nonlinear analysis of dynamics of the non-coupled HH neuron and astrocyte (5), (6) and described in [32] and [33], respectively. Here we present the analysis of autonomous dynamics of neuron described by the Mainen modification of HH model (1), (2). From the Fig. 2a it can be seen that the bifurcation diagram of the Mainen neuron is qualitatively similar to the HH neuron diagram. With an increasing value of applied current, I_{app}, the oscillations appear through the saddle-node limit cycle bifurcation (Fig. 2a). More precisely, the bifurcation leads to the emergence of stable and unstable limit cycles, that coexist with the stable fixed point,

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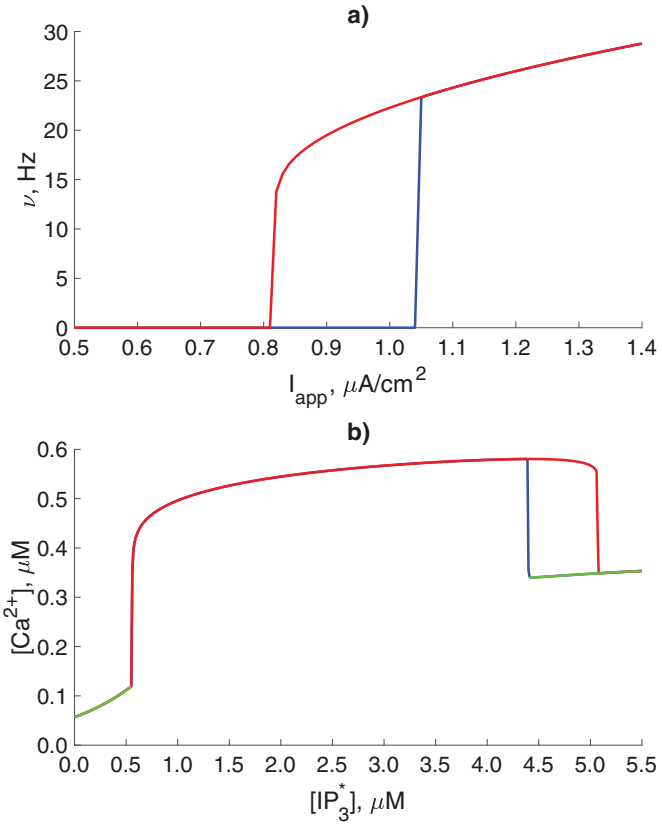

Fig. 2. (a) Bifurcation diagram of a single neuron. The dependence of spiking frequency on the value of applied current is shown. Zero frequency corresponds to the stable fixed point. Nonzero frequency corresponds to the periodic spiking. There is a bistability region in the middle. (b) Single astrocyte bifurcation diagram. The dependence of Ca^{2+} concentration on the steady state concentration of IP_3 is shown. Green line corresponds to the Ca^{2+} concentration in the steady state. Red line - to the amplitude of Ca^{2+} oscillations. Note the presence of bistability. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

in other words, bistability sets on. With the further increase of I_{app} the subcritical Andronov-Hopf bifurcation takes place, where the unstable limit cycle merges with stable fixed point. Then only stable limit cycle remains in the phase space (the oscillatory mode). For the purpose of study, we choose I_{app} in the oscillatory mode and set the initial conditions of each neuron at the limit cycles (see Appendix).

Parameter values and initial conditions for the astrocytes correspond to the stable equilibrium (Fig. 2b). As IP_3 increases, oscillations can emerge through the supercritical Andronov-Hopf bifurcation. These oscillations disappear at high concentrations of IP_3 through the tangent bifurcation of limit cycles. When IP_3 changes in the opposite direction, transition to oscillations follows the hard route through the subcritical Andronov-Hopf bifurcation.

Fig. 3 illustrates astrocyte activation by the neuronal activity, as modeled by Eqs. (1)–(6). When neuron oscillates (Fig. 3a), the concentration of neurotransmitter, G (4), changes periodically (Fig. 3b). In result, the intracellular concentration of IP_3 increases in response to the synaptic release. In other words, the increase of the IP_3 induced by the neuronal activity shifts the operating point from green part on the Fig. 2b to the red part, corresponding to Ca^{2+} oscillations in astrocyte (Fig. 3c).

To characterize the neural frequency response and synchronization, we calculate an instantaneous firing rate, $\nu(t)$, calculated as the inverse of the interspike interval (ISI):

$$\nu(t) = (ISI(t))^{-1}; \tag{8}$$

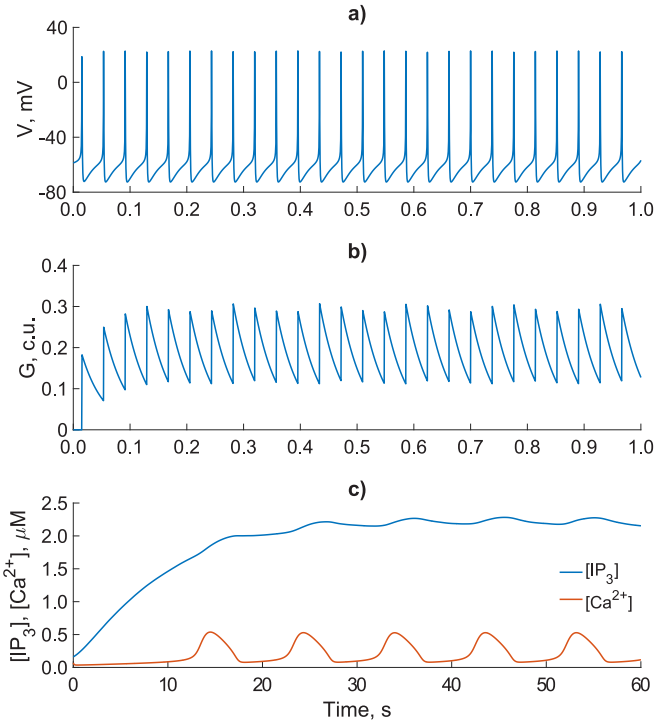

Fig. 3. The dynamics of astrocyte activation induced by the neuronal activity in Eqs. (1)–(6). (a) Spike train in HH neuron in the oscillatory mode. (b) The concentration of the neurotransmitter, $G(t)$. (c) The astrocytic concentrations of Ca^{2+}, $Ca(t)$ and IP_3, $IP3(t)$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Also we define the relative spiking phase, $\Delta\phi_{1,2}$, as the time shift between the response (postsynaptic) spike $t_{post}(n)$ and the corresponding preceding spike in the presynaptic neuron $t_{pre}(n)$:

$$\Delta\phi_{1,2} = 2\pi \frac{t_{post}(n) - t_{pre}(n)}{T}; \tag{9}$$

where T is the largest oscillating period between pre- or postsynaptic neurons, and $n = 1, 2, \ldots$ stand for the index of the postsynaptic spike. We define that neurons are synchronized in a given time interval, t_s, if phase slips on this interval are absent and the difference between neuronal instantaneous firing rates is less then 1%, that is $|\nu_2(t_i) - \nu_1(t_i)| < 0.2$. The sum of all time intervals when neurons are synchronized, t_s, normalized by the total observation time, t_{tot}, gives the relative time of synchronization, $\frac{t_s}{t_{tot}}$. In particular, when the relative synchronization time $\frac{t_s}{t_{tot}}$ is equal to 1, the two neurons are synchronized all the time.

3. Results

We find that astrocytic modulation of neuronal synaptic connectivity can lead to the emergence of a special regime of intermittent synchronization between spiking neurons. In a generic system of coupled oscillators, intermittent synchronization is observed as an intermediate regime between the phase locking mode and asynchronous mode [34]. Typically, this regime is restricted to a narrow parameter interval, where the frequency of phase slips changes gradualy. Strikingly, we show that astrocytes can induce the intermittent synchronization of neurons in a wide range of system parameters, and its characteristics remain robust under variation of parameters.

The mechanism behind astrocyte-mediated intermittent synchronization is disclosed in Fig. 4. First, spiking neurons induce calcium oscillations in astrocytes, that originally resided in the steady

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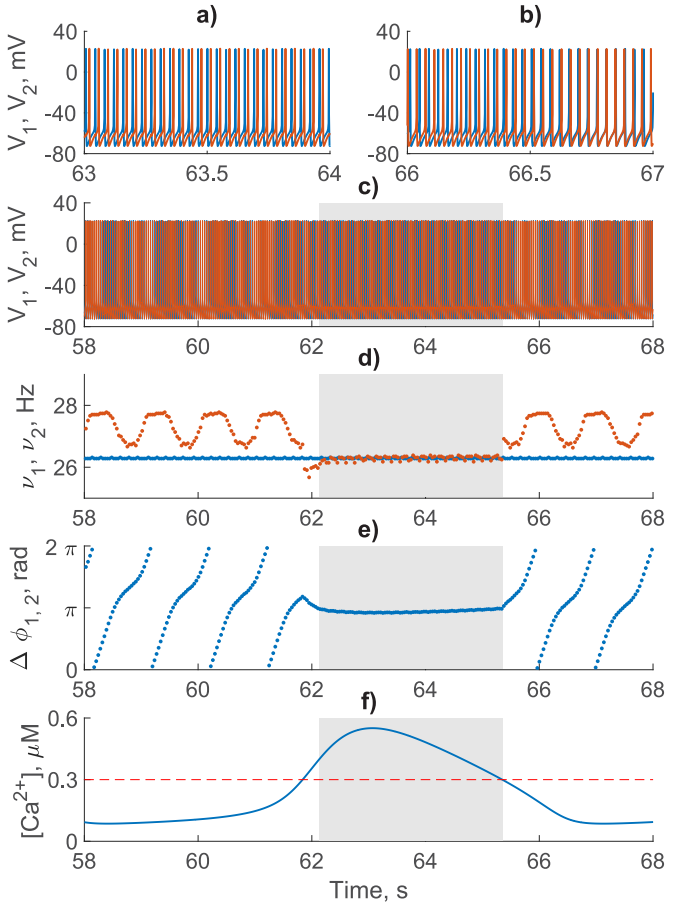

Fig. 4. Dynamics of two inhibitory synaptically coupled oscillating neurons with astrocytic influence. Grey areas show the time intervals of synchronization (t_s). a) Phase locking mode. b) Asynchronous mode (beating). c) Spike trains in two coupled neurons. d) Instantaneous firing rates of neurons. For (a-d) blue and red colors correspond to presynaptic and postsynaptic neurons, respectively. e) Relative spiking phase. f) A single elevation of intracellular calcium concentration in the astrocyte. The red-dotted line shows the activation threshold for astrocytic modulation of synaptic connectivity. Here $g_{syn} = 0.06$, $g_{astro} = 3.0$, $I_{app_1} = 1.20\ \mu A/cm^2$, $I_{app_2} = 1.30\ \mu A/cm^2$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

state (Fig. 3). Thus, a new slow time scale appears in the system, shaped by the astrocytic calcium dynamics. When intracellular Ca^{2+} concentration comes over a certain threshold, the synaptic strength between the neurons gets enhanced. Eventually, they become synchronized in anti-phase on the time interval equal to duration of calcium pulses in astrocyte. In absence of the astrocytic influence, the system stays in the beating regime, as prescribed by the frequency detuning between coupled oscillators (Fig. 4b).

To investigate the phenomenon in more detail, we calculate the dependence of the relative time of synchronization, $\frac{t_s}{t_{tot}}$, on the frequency detuning of the oscillators and the synaptic strength for the two cases: without and with astrocytic influence, Fig. 5) and Figs. 6, 7), respectively.

Fig. 5 indicates that for greater frequency detuning between neurons the greater coupling strength is required to establish synchronization. It is observed both for excitatory and inhibitory coupling. We also note that the synchronization region on the plane (frequency detuning × coupling strength) is not symmetrical. Such non-classical shape of synchronization map is determined by a specific type of synaptic connectivity between HH neurons (3). That is, the master neuron with higher oscillation frequency increases the firing rate of the slave neuron through an excitatory unidirectional pulse coupling, and vice a versa in the case of inhibitory coupling. In the opposite direction, the excitatory connection can reduce the firing rate of the fast slave neuron, but to a limted extent. This phenomenon is sensitive to the phase shift relation between post- and presynaptic pulses [35,36].

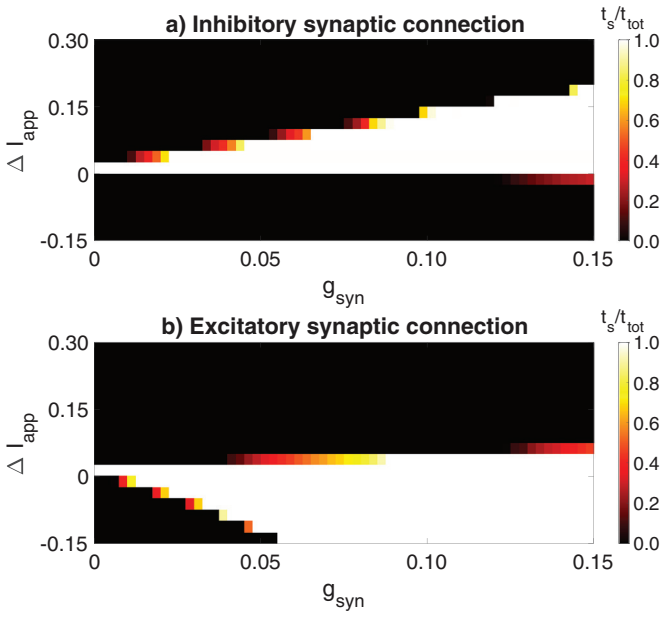

Fig. 5. [Color online] The relative time of synchronization in the absence of astrocyte-induced modulation synaptic connection ($g_{astro} = 0.0$). For (a) inhibitory and (b) excitatory types of synapse. $\Delta I_{app} = I_{app_2} - I_{app_1}$, $I_{app_1} = 1.20\ \mu A/cm^2$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 6 demonstrates that the regions of complete synchronization for excitatory and inhibitory coupling are not affected by the astrocyte-induced modulation of synaptic coupling. In other words, astrocytes neither facilitate complete synchronization, nor

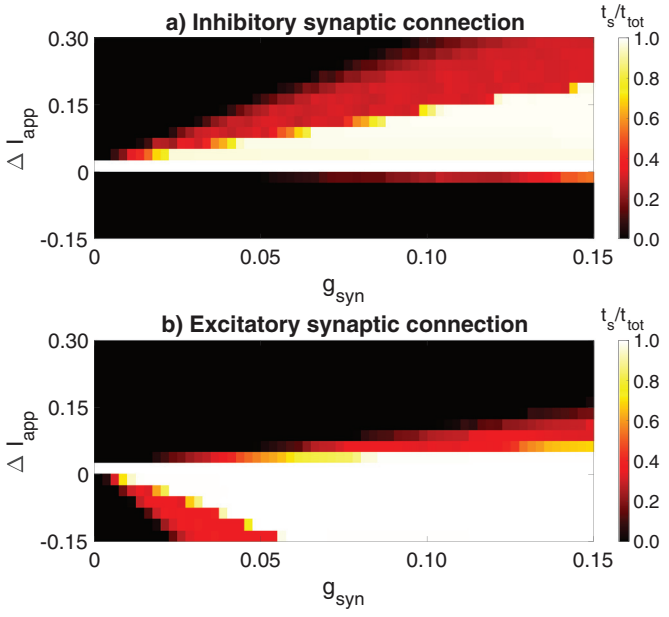

Fig. 6. [Color online] The relative time of synchronization in the presence of astrocyte-induced modulation synaptic connection ($g_{astro} = 3.0$). For (a) inhibitory and (b) excitatory types of synapse. $I_{app_1} = 1.20\ \mu A/cm^2$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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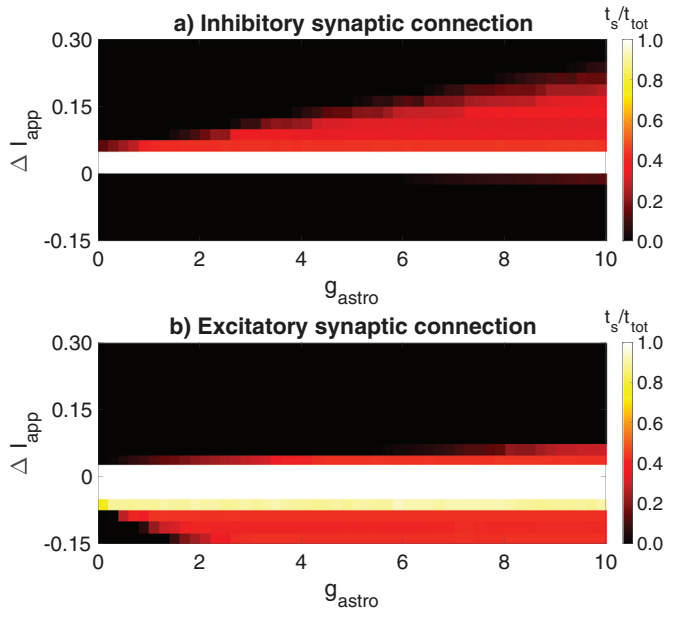

Fig. 7. [Color online] The dependence of relative time of synchronization on the strength of astrocyte-induced modulation of synaptic coupling. For (a) inhibitory and (b) excitatory types of synapse. Parameter $g_{syn} = 0.03$, $I_{app_1} = 1.20\ \mu A/cm^2$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

detriment it. However, synchronization is extended by the emerging regions of intermittent synchronization, induced by astrocytes. As calcium elevations in astrocytes enhance the effective synaptic strength, it becomes possible to achieve synchronization of the two neurons for a greater detuning, temporarily, on the timescale of calcium events. Numerical simulations show, that the relative duration of intermittent synchronization intervals can take up to a half of observation time.

Note that the duration and frequency of Ca^{2+} oscillations in astrocytes are not sensitive to the degree of synchrony between neurons, being determined only by the average of activity. Due to this, the characteristics of intermittent synchronization, such as frequency and duration of synchronization intervals, are determined only by the slow astrocytic dynamics and do not essentially depend on the neuronal detuning or coupling. Fig. 7 confirms it, that amplification of the strength of astrocytic influence expands the regions of intermittent synchronization, while the characteristics of this regime remain unchanged.

4. Conclusion

In summary, we investigated the influence of the astrocytic modulation on the synchronization of a pair synaptically coupled spiking HH neuronal oscillators for excitatory and inhibitory synaptic connectivities. We showed that astrocytes do not noticeably modify the region of complete synchronization between spiking neurons, but induce an extended region of intermittent synchronization. The characteristics of intermittent synchronization, such as frequency and duration of synchronization intervals, are determined essentially by the slow calcium dynamics in astrocytes and do not dependent on neuronal frequency detuning or coupling.

The effect may be decisive for network dynamics. On the one hand, astrocytes can affect signal transmission in thousands of synapses. Thus, a single astrocyte can induce spatial synchronization of a neuronal circuit defined by the morphological territory of astrocyte. The spatial synchronization of the neural ensembles is thought to play a critical role in information processing [2]. Further, Ca^{2+} signals propagating through astrocytic network via gap junctions can lead to modulation of signal transmission in distant neuronal networks and induce remote synchronization [37]. On the other hand, the synchronous activation of a pair of neurons with constant phase shift on the timescales of a seconds can induce long-term changes in the efficiency of synaptic transmission (long-term potentiation or depression). Such synaptic plasticity explains many aspects of brain network structure organization and function [38]. Thus, despite the numerous models describing the neuron-astrocyte communications, the heterogeneous networks of cells have the higher level of complexity and the actual influence of astrocytes on the neuronal network activity is still the subject of further studies.

Declaration of Competing Interest

A conflict of interest occurs when an individual's objectivity is potentially compromised by a desire for financial gain, prominence, professional advancement or a successful outcome. ASJSUR Editors strive to ensure that what is published in the Journal is as balanced, objective and evidence-based as possible. Since it can be difficult to distinguish between an actual conflict of interest and a perceived conflict of interest, the Journal requires authors to disclose all and any potential conflicts of interest.

CRediT authorship contribution statement

S Yu Makovkin: Formal analysis, Writing - original draft, Writing - review & editing. **I V Shkerin:** Formal analysis. **S Yu Gordleeva:** Formal analysis, Writing - original draft, Writing - review & editing. **M V Ivanchenko:** Conceptualization, Writing - original draft, Writing - review & editing.

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Appendix A. Constants value

Astrocytes parameters: $c_0 = 2\ \mu M$; $c_1 = 0.185$; $\nu_1 = 6\ s^{-1}$; $\nu_2 = 0.11\ s^{-1}$; $\nu_3 = 2.2\ \mu M/s$; $\nu_5 = 0.025\ \mu M/s$; $\nu_6 = 0.2\ \mu M/s$; $k_1 = 0.5\ s^{-1}$; $k_2 = 1\ \mu M$; $k_3 = 0.1$; $k_4 = 1.1\ \mu M/s$; $a_2 = 0.14\ \mu M/s$; $d_1 = 0.13\ \mu M$; $d_2 = 1.049\ \mu M$; $d_3 = 0.9434\ \mu M$; $d_5 = 0.082\ \mu M$; $\alpha = 0.8$; $\tau_{IP3} = 7.143\ s$; $IP3^* = 0.16\ \mu M$; $d_{Ca} = 0.001\ s^{-1}$; $d_{IP3} = 0.12\ s^{-1}$; $\alpha_{Glu} = 2$.

Neurons parameters: $C = 1\mu F$; $g_{Na} = 40\ mS/cm^2$; $g_K = 35\ mS/cm^2$; $g_{Leak} = 0.3\ mS/cm^2$; $E_{Na} = 55\ mV$; $E_K = -77\ mV$; $E_{Leak} = -54.4\ mV$; $E_{syn_i} = -90\ mV$; $k_{syn} = 0.2\ mV$; $I_{app_1} = 1.2\ \mu A/cm^2$.

Initial conditions for astrocytes: $Ca_i(t = 0) = 0.07$; $IP3_i(t = 0) = 0.16$; $z_i(t = 0) = 0.67$; $G_i(t = 0) = 0.0$.

Initial conditions for Limit Circle neurons: $V_i(t = 0) = -58.7085$; $m_i(t = 0) = 0.0953$; $n_i(t = 0) = 0.000913$; $h_i(t = 0) = 0.3662$.

Initial conditions for Stable Focus neurons: $V_i(t = 0) = 14.8409$; $m_i(t = 0) = 0.9174$; $n_i(t = 0) = 0.0140$; $h_i(t = 0) = 0.0539$.

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