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A NEURONS-ASTROCYTE NETWORK MODEL : FROM SYNAPTIC BOOSTING TO EPILEPSY.

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ABSTRACT

Recent findings indicate that astrocytes might play a functional role in triggering epileptic seizures. To test both the role of astrocytes on neuronal firings under normal conditions and the role they could play in epilepsy, we build here a computational model where four neurons and an astrocyte interact.

Based on a mathematical model previously described in the literature, our model allows to investigate the dynamics of neuronal firing in this mini-network. In particular, we describe the conditions that can lead to hypersynchronous firings.

KEY WORDS

. Computational Modelling, Astrocytes, Neural Networks, Epilepsy.

1. Introduction

Ten years after the end of the “Brain Decade”, the human cognitive system still remains a mystery to us. One of the most stable facts that have been discovered is that the brain is highly more complex than meets the eye. After exploring the temporal structure of firing patterns in neural networks, neurobiology is now looking in a new direction to explain how networks in the brain encode and process information. Astrocytes could indeed be of importance for information processing in the brain. Since their first description in 1851 by H. Müller, they were thought to play essentially a supporting role for neural networks. This view is now challenged by a number of recent findings (for example see [1], [2], [3], [4]): astrocytes could have various functional roles, such as extracellular milieu regulation, synaptic information regulation, neuronal synchronization, or feedback to neural activity.

Astrocytes could also be of major importance for explaining epilepsy¹. EEG observations during epileptic

seizures show abnormal prolonged depolarization with a repetitive spiking pattern, called Paroxysmal Depolarization Shift (PDS). Plus, epileptic discharges are partly initiated by a local depolarization shift that drives groups of neurons into synchronous bursting. According to Tian [6], astrocytes could trigger PDS and therefore play a role in the genesis of epileptic seizures.

We propose to build a computational model of a network where neurons and astrocyte interact. This should help to investigate how abnormal astrocyte activity could trigger epileptic simultaneous neuronal firings of multiple neurons.

2. The mathematical model

In this paper, we use a mathematical model of a dressed neuron created by D. Postnov [5]. This model is constituted of a presynaptic neuron, a synaptic terminal, a postsynaptic neuron and an astrocyte cell. It simplifies the biological reality as only four neuron/astrocyte interaction pathways are simulated. Astrocytes can be activated via two different routes:

- The fast route (called α in Postnov’s model) corresponds to the astrocyte sensitivity to extracellular K^+ release after a postsynaptic neuron firing.
- The slow route (called β) corresponds to the astrocyte sensitivity to glutamate release by the presynaptic neuron after firing.

Then, when astrocyte Ca^{2+} concentration is sufficiently high, it can impact on neural activity in two ways:

- Postsynaptic neuron excitation (strength is controlled by γ coefficient). Increasing Ca^{2+} in the astrocyte cytoplasm triggers the production of glutamate and its release into the intercellular space.
- Postsynaptic neuron inhibition (strength is controlled by the δ coefficient). The astrocyte reduces the synaptic strength by releasing a GABA-like inhibition mediator.

We will first describe briefly the mathematical system created by Postnov.

¹Epilepsy is a neurological disorder in which normal brain is disrupted as a consequence of intensive bursts of activity from groups of neurons. Hypersynchronous neuronal firing is typical of epileptic condition.

Neurons are modeled by the FitzHugh-Nagumo model (See eq. (1) and (2) for a presynaptic neuron, and eq. (3), (4) for a postsynaptic neuron).

$$\epsilon_1 \frac{dv_1}{dt} = v_1 + \frac{v_1^3}{3} - w_1 \quad (1)$$

$$\frac{dw_1}{dt} = v_1 + I_1 - I_{app} \quad (2)$$

$$\epsilon_2 \frac{dv_2}{dt} = v_2 + \frac{v_2^3}{3} - w_2 \quad (3)$$

$$\frac{dw_2}{dt} = v_2 + I_2 - I_{syn} - I_{glion} \quad (4)$$

with v_1 and v_2 representing the transmembrane potentials of pre- and post-synaptic neurons, and I_{app} representing the excitatory current applied to the presynaptic neuron. I_{glion} is the astrocyte-induced current. I_{glion} is proportional to the mediator production (eq. (5)).

$$I_{glion} = \delta G_m \quad (5)$$

The γ and δ factors allow controlling the influence of the astrocyte on the synapse and on the postsynaptic neuron.

The synaptic terminal. Only two essential properties of a synapse are described in these (eq. (6) and (7)) first-order differential equations:

- The delayed reponse of the postsynaptic neuron activity
- The synapse threshold activation.

$$\tau_s \frac{dz}{dt} = (1 + \tanh(s_s(v_1 - h_s)))(1 - z) - \frac{z}{d_s} \quad (6)$$

$$z_0 = \frac{2d_s}{1 + 2d_s + \exp(2I_1)} \quad (7)$$

I_{syn} is the synaptic current:

$$I_{syn} = (k_s - \delta G_m)(z - z_0) \quad (8)$$

The astrocyte. An astrocyte is described by four equations, two for the calcium dynamics in the astrocyte, two for the astrocyte glio- and neuro-mediator production. c is the concentration of Ca^{2+} in the cell, c_e is the same in the reticulum endoplasmic. $f(c, c_e)$ represents the exchange between the astrocyte cytoplasm and the reticulum endoplasmic.

$$\tau_c \frac{dc}{dt} = -c - c_4 f(c, c_e) + (r + \alpha w_2 + \beta S_m) \quad (9)$$

$(r + \alpha w_2 + \beta S_m)$ represents the calcium from the extracellular space sensitive to the synapse mediator S_m production (with the factor β) and to the astrocyte depolarization by increasing extracellular potassium (via αw_2).

$$\epsilon_c \tau_c \frac{dc_e}{dt} = f(c, c_e) \quad (10)$$

$$f(c, c_e) = c_1 \frac{c^2}{1 + c^2} - \left(\frac{c_e^2}{1 + c_e^2} \right) \left(\frac{c^4}{c_2^4 + c^4} \right) - c_3 c_e \quad (11)$$

The equations (12) and (13) describe the astrocyte release and production of neuromediator.

$$\tau_{S_m} \frac{dS_m}{dt} = (1 + \tanh(s_{S_m}(z - h_{S_m}))(1 - S_m) - \frac{S_m}{d_{S_m}} \quad (12)$$

$$\tau_{G_m} \frac{dG_m}{dt} = (1 + \tanh(s_{G_m}(c - h_{G_m}))(1 - G_m) - \frac{G_m}{d_{G_m}} \quad (13)$$

In our work, all parameter values are taken from [5].

We propose an equation allowing to build a network of neurons under the influence of an astrocyte. This equation generalizes equation (9) and thus allows the integration of all network synapses information by the astrocyte. This equation is proposed, but not tested in the original paper.

$$\tau_c \frac{dc}{dt} = -c - c_4 f(c, c_e) + \left(r + \sum_{i=1}^N \alpha_i w_i + \sum_{j=1}^M \beta_j S_{m,j} \right) \quad (14)$$

The aim of our work is thus to simulate and test this generalization, on a network of neurons and astrocytes.

3. Our Model

Our astrocyte-neurons network is composed with four neurons and one astrocyte. We used the same components as in Postnov's model : neuron 1 is modeled as a presynaptic neuron, and neurons 2 and 4 are postsynaptic components. Neuron 3 is also modeled like a post-synaptic component as it does not receive any external current. The two synaptic terminals are modeled with equations (6) and (7).

Connections between cells.

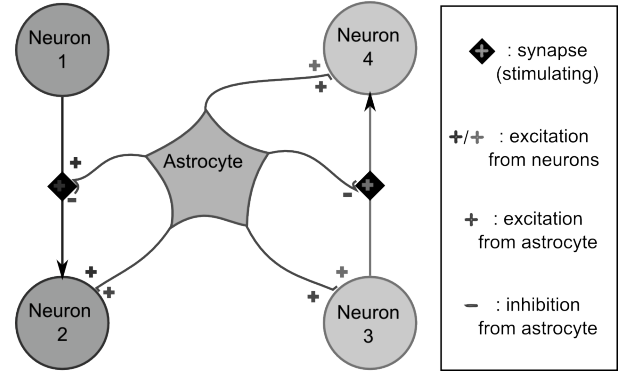


FIGURE 1: The network model, composed of three parts : the active sub-network (neurons 1 and 2), the passive sub-network (neurons 3 and 4), and the astrocyte supervising synaptic connections. Synapses between neurons 1 and 2, and between neurons 3 and 4 are excitatory. The astrocyte receives excitations from all neurons, and, in return, the astrocyte will interact with neurons around the synaptic cleft.

Figure 1 shows the network created. This network is organized in three sub-structures:

- The active sub-network with neuron 1 and neuron 2. His role is to transmit stimulations to the other cells.
- The passive sub-network, with neuron 3 and neuron 4. This network has no connection with the

active sub-network, so that activity in this sub-network depends entirely on the astrocyte.

- The astrocyte is supervising all synaptic connections. In the human brain, an astrocyte can supervise over 10.000 neurons [2, 6]. Here, only four are modeled to keep the model readable and to have reasonable computation time.

Only the astrocyte can propagate activity from neurons 1 and 2 to the sub-network with neurons 3 and 4.

In all our experimentations, we apply a current to the presynaptic neuron 1 (*I_{app}*) and we observe the network behavior. By varying γ and δ coefficients different firing patterns will be observed in the network.

4. Protocol

Our protocol consists in, at first, the activation of neuron 1. The excitation propagates according the synaptic strength to neuron 2 (for clarity's sake all synaptic strengths are fixed in the model, and no learning is done during the simulations). Neurons 1 and 2 excite the astrocyte according to α and β value. If the calcium concentration in the astrocyte reaches a certain threshold, a glutamate exocytosis occurs. The astrocyte then excites or inhibits back neurons 2, 3 and 4, according to δ and γ values. Note that all strengths and all α , β , δ and γ values are equal for all synapses. The neurons/ astrocyte system then forms a closed-loop system, with the astrocyte retroacting on neurons (See fig. 1).

We are fully aware that the limited size and the particular configuration of our model do not mimic biological networks. Our model only aims at simulating behaviors of neurons and groups of neurons.

All neurons in the network are excitatory. We set up synaptic strengths to model information loss as in the original Postnov's paper. Synaptic efficiency between neuron 1 and neuron 2 is around 60% when the astrocyte is deactivated.

5. Results.

First, our model replicates Postnov's results, with an appropriate tuning of each way (α , β , δ and γ). We observe the same firing patterns than the original work.

We will now investigate the impact of modulating δ and γ channels on the network behavior. Note that only γ and δ will be modified in the next experiments, because these parameters represent the effect of the astrocyte on neurons. We believe that these variables are critical and in the following part, we will systematically test them to see in which way neurons will react to the astrocyte emissions.

5.1 The "no effect" mode.

This functioning mode is the standard behavior of the network without astrocytes. Astrocytic means of action on neurons have been suppressed by turning off γ and δ pathways. Information only transmits through the active sub-network, according to synaptic conductivity. None of the neurons 3 and 4 are excited, as shown on figure 2 ($\gamma=0$, $\delta=0$): activation is restricted to the active sub-network.

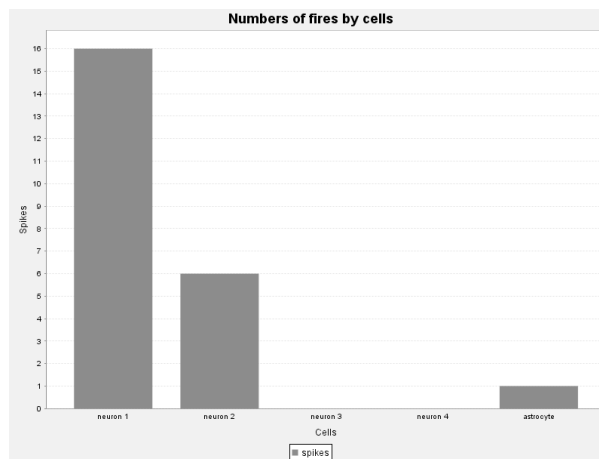


FIGURE 2: An example of functioning for the "no effect" mode. Each column represents a number of spikes by cell, the first four bars are for neurons 1 to 4, the last one is for the astrocyte. Gamma and Delta are set to 0, the astrocyte is withdrawn from the network.

5.2 The "normal mode".

In the "normal mode" simulation, as shown on figure 3, the astrocyte boosts synaptic transmission. The γ/δ couple is set to $\gamma=.05$, $\delta=.1$. The fire rate of neuron 2 is higher in this condition than in the "no effect" condition. This synaptic efficiency boosting is what we call the normal mode.

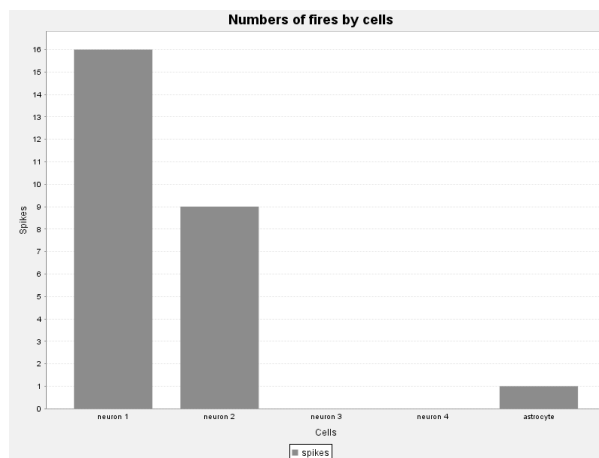


FIGURE 3: An example of functioning in the "normal mode". This figure displays the number of spikes by cell. Here, γ is set to 0.05 and δ is set to 0.1. The effect of the astrocyte is to reinforce the synapses conductivity, especially between neurons 1 and 2. All cells have the same behavior than in the "no effect" condition except neuron 2 (9 spikes vs 6 only in the "no effect" mode).

In the next test, we will increase again γ and δ and see another specific mode called the "forced mode".

5.3 The "forced mode"

In this new condition (fig. 4 and 5) we use the couple ($\gamma=.7, \delta=.25$). Whereas in the normal mode neuron 3 is isolated and has no activity, here, as a result of the astrocytic influence, neuron 3 emits spikes. This means that the exocytosis of the astrocyte is sufficiently powerful to force neurons in distant networks to react.

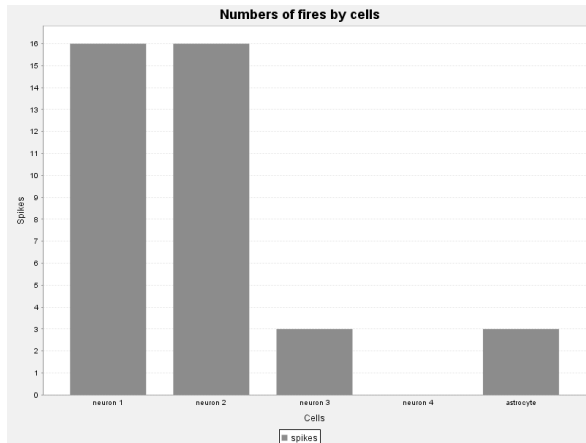


FIGURE 4: An example of the "forced mode" functioning. This figure shows the number of spikes by cell with $\gamma = 0.07$ and $\delta = 0.25$. The effect of the astrocyte is to reinforce synapses conductivity, and to partially transmit information to other neurons under its influence. Neuron 2 emits 16 times (vs 9 times in "normal mode"). Neuron 3 emits 6 times (vs 0 in "normal" condition).

Another important point is the reinforcement of activity in neuron 2, as more spikes are emitted in this new condition (fig. 4) compared to the "normal" condition (fig. 3). The astrocyte allows compensating for the information transmission losses in synapses.

More important, as shown on figure 5, some late spikes of neuron 2 and neuron 3 are synchronized with astrocytic firing. It suggests that the astrocyte could have a possible effect on controlling spike timings in the network.

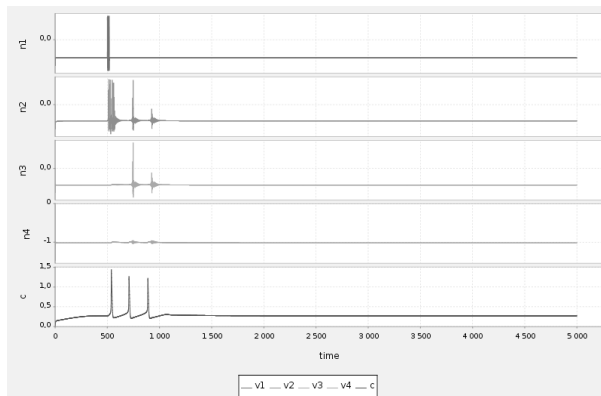


FIGURE 5: Spike timings for neuronal and astrocyte activities in "forced mode" simulation. ($\gamma = .07, \delta = .25$). The first four lines represent activities of neurons 1, 2, 3 and 4. Last line is the astrocytic activity. Neurons 2 and 3 spike in synchrony with the astrocyte.

Indeed, in neural networks, information is encoded by synaptic strength as well as by the temporal firing pattern. Astrocytes could influence both ways of coding.

This observation of a normally functioning system in which the astrocyte releases enough glutamate to excite neurons by itself, forcing isolated neurons to fire is what we call the "forced mode".

This could mean that astrocytes, if receiving enough stimulation, can induce activation of neurons within their influential domain.

5.4 The "epileptic mode"

Our model allows simulating the generation of epileptic firing patterns in the network. When the parameters couple is set to ($\gamma = .07, \delta = .015$), hypersynchronous firing occurs in the network.

Figure 6 shows activity over time of the four neurons (first four plots) and of the astrocyte (last plot). Here, our interest will focus on the passive sub-network behavior. Because the astrocyte excites all neurons (except neuron1), a repeated firing pattern can arise in neurons 2, 3 and 4. This strongly suggests epileptiform neuronal activity.

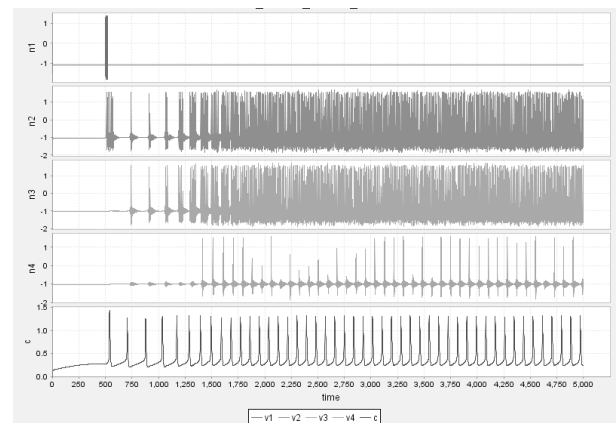


FIGURE 6: An example of the "epileptic mode". Each line represents a cell behavior. The four top lines are neurons 1 to 4. The last line is the astrocyte. The total time is 5000 steps. Here, $\gamma = 0.07$ and $\delta = 0.015$

Larger-scale simulations show that there are four ways for bringing neurons to an epileptic state. These means of action are:

- Successive excitations of neuron N1 in temporal proximity ($\Delta t < 1000$ time steps): the astrocyte needs time to return to a basal activation level.
- A small value for parameter α ($\alpha < 0.02$). This could correspond to a weak reaction of the astrocyte to extracellular K^+ .
- A big value for parameter γ ($\gamma > 0.06$) This could correspond to the astrocyte sending back through exocytosis too much activation to the network.

- And on the opposite, a small value for parameter δ (the upper bound is γ -dependant). This could implement a weak return inhibition from astrocyte to neurons.

The γ/δ ratio also seems to be a crucial parameter for the neurons behavior. γ and δ must be considered in conjunction, as there seems to have a balance to find between these parameter values. More systemic tests need to be performed to have more precise data on this element.

Time seems to be an important factor: as seen in figure 6, when the astrocyte has a high firing rate (*0.012 spikes/time step* or 1 spike/18 time steps) the system becomes unstable and leads to an epileptic mode.

To conclude on epilepsy, the computational model permits us to test more precisely some variables, and to make more precise hypotheses on complex systems behavior.

This model also predicts some interesting behaviors when the system is not epileptic. When parameters γ and δ do not have extreme values, the network works normally. This permits us to learn more about the possible role of astrocytes in the brain.

Numerical results are in line with Tian's view of astrocytes possibly contributing to epileptic seizures by inducing transient synchronous spiking activity in neurons [6].

6. Conclusion.

This model permits us to simulate four possible functioning modes of an astrocyte interacting with neurons: "no effect mode", "normal mode", "forced mode", and "epileptic mode"

These modes depend on the precise values of the model parameters, tuning the Glutamate and GABA production (γ and δ parameters). These results bring up some questions about the role of astrocytes in the brain.

Furthermore, this model matches Tian's results [6] and sheds light on four ways of generating artificial epileptic seizures-like behaviors with an astrocyte. These ways are an exocytosis producing too much Glutamate, a too small GABA production, a long "refractory" period, or a deficient regulation of the extracellular milieu. These results appeal for some new biological in-vivo tests that could verify our assumptions.

7. Discussion.

About information transmission. The "forced mode" described in 5.3 paragraph on neurons 3 and 4 shows that astrocyte certainly has an effect on transmission of information, but also on reinforcement of synaptic strength into the long-term potentiation process. The neurons - astrocytes interaction could be an important

mechanism in Hebbian memory (as discussed for example in [2]).

About the hypersynchronous neuronal firing characterized by groups of neurons into synchronous bursting. This synchronicity could be induced by the astrocyte firing rate.

This questions the role of astrocytes in the brain, but this article would also like to raise the question of astrocytes in artificial neural networks. As stated in [8] astrocytes form networks and are capable of exchanging information: incorporating networks of artificial astrocytes could allow computational neuroscience to go a step further in understanding the brain.

Precisely because of the synaptic modulation and the effect on disconnected networks and as seen in [2, 3], astrocytes could be involved in self-organisation of neural projections.

Moreover, the possible temporal synchronization emerging from astrocyte activity could be involved into a possible polychronization of grapes of neurons [7].

For finishing, our network is more a mini-network than a fully operational model. It offers a good starting point for creating and exploring more complex models, with more sophisticated mathematical description of the basic elements. This is also one of the first attempts to model elements in terms of a system rather than in terms of single elements.

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