# Epileptiform activity in a neuron-astrocyte network model

Yuliya Tsybina
*Lobachevsky University*
Nizhny Novgorod, Russia
*Sechenov University*
Moscow, Russia
lotarevaj@gmail.com

Innokentiy Kastalskiy
*Lobachevsky University*
Nizhny Novgorod, Russia
*Moscow Institute of Physics and Technology*
Moscow, Russia
*Samara State Medical University*
Samara, Russia
kastalskiy@neuro.nnov.ru

Andrey Andreev
*Lobachevsky University*
Nizhny Novgorod, Russia
*Immanuel Kant Baltic Federal University*
Kaliningrad, Russia
andreevandrei1993@gmail.com

Nikita Frolov
*Immanuel Kant Baltic Federal University*
Kaliningrad, Russia
phrolovns@gmail.com

Susanna Gordleeva
*Lobachevsky University*
Nizhny Novgorod, Russia
*Samara State Medical University*
Samara, Russia
gordleeva@neuro.nnov.ru

Alexander Hramov
*Immanuel Kant Baltic Federal University*
Kaliningrad, Russia
hramovae@gmail.com

***Abstract*—In this paper, we propose a spiking neuron-astrocyte network model to study the mechanisms of epileptic activity in the brain. This model allows for the implementation of a self-organized bistability regime - spontaneous switching of network activity between two states: desynchronization and synchronization. These states simulate the resting state and pathological state of the brain, respectively. In other words, under the dominant stability of the asynchronous state, rare and short-lived occurrences of extreme synchronization of action potential generation by neurons are possible. Numerical investigation of this model has shown that the recurrence of transitions to the synchronization regime in this network model exhibits the same statistical properties as the interictal intervals observed in numerous experimental studies. This confirms the relevance of the model and the correctness of the basic physical principles underlying it.**

***Index Terms*—Epilepsy, Neuron-astrocyte network, Extreme synchronization, Neuron-astrocyte interaction**

## I. Introduction

Epilepsy is a neurological disorder characterized by recurrent episodes of involuntary seizures, which are caused by abnormal brain activity. The study of epilepsy involves various aspects, including its causes, mechanisms of development, diagnostic methods, and treatments [1] - [3]. The causes of epilepsy can be diverse and may include hereditary factors, injuries, infections, tumors, stroke, disorders in the development of the cerebral cortex, and others. However, despite extensive research, the exact causes of epilepsy remain unknown.

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Mathematical modeling methods play a significant role in studying the functioning of the brain under both normal and pathological conditions. They enable the development of computer models that mimic the complex dynamics of brain activity, thereby aiding in the understanding of its characteristics. Furthermore, these models allow for the exploration of potential mechanisms involved in the generation and propagation of epilepsy [4] - [6]. By manipulating the parameters of the model, it becomes possible to identify how alterations in neurons or their connections can contribute to the emergence or suppression of epileptiform activity. This knowledge has the potential to assist in the development of novel treatment strategies and the prediction of the effectiveness of various therapies.

Astrocytes, a type of brain cells, possess the capacity to detect and respond to neuronal activity. Recent studies have demonstrated the significant roles played by astrocytes in normal physiology [7] - [13] as well as in epilepsy [14] - [17]. Investigations involving patients with epilepsy have revealed dysfunction in glutamate transporters and the enzyme glutamine synthetase, which participate in glutamate metabolism; and also changes in the expression, localization, and function of astrocytic $K^+$ and water channels. These findings suggest that impaired astrocytes contribute significantly to epilepsy and could be potential targets for innovative therapeutic approaches.

Therefore, in this work, we developed a biologically plausible model of a neuron-astrocyte network to investigate the effects of neuron-astrocyte interaction and their role in pathologically altered brain activity associated with epilepsy. The model integrates a biophysical depiction of astrocytic

regulation of synaptic transmission, with consideration given to calcium dynamics in astrocytes.

Continued research in the field of epilepsy is imperative to enhance diagnosis, treatment, and overall quality of life for individuals living with this condition.

## II. Methods

The developed network model consists of 1000 neurons, with each neuron engaging in bidirectional interaction with one astrocyte (the total number of astrocytes in the network is 1000).

Among the available biologically plausible neuron models, we chose the Izhikevich model [18] to represent the dynamics of membrane potential. The Izhikevich model is a simplified version of the Hodgkin-Huxley neuron [19] and was selected due to its computational efficiency in modeling large-scale networks while still capturing the dynamics of various types of cortical neurons. This model characterizes the changes in neuron membrane potential by considering the currents flowing through membrane ion channels.

The Barabasi-Albert algorithm [20] was utilized to generate the scale-free (SF) synaptic connection topology in the network model. In this algorithm, the network grows by adding a new node connected to $m$ = 6 new edges with $n_0$ = 6 existing nodes. However, in the SF graph implemented using the Barabasi-Albert algorithm, the connections between elements are bidirectional, which does not align with the principles of brain neural networks. In the brain, chemical synapses are unidirectional. To address this inconsistency, the procedure for generating the SF graph was initially performed, and then one direction of each synapse was randomly removed.

The synaptic current of each neuron represents the total current received from all its presynaptic neurons, averaged over the number of synapses. It is calculated according to the formula presented in works [21] - [22].

To simulate the dynamics of a single astrocyte, we employed the Ullah model [23]. This model consists of three differential equations that describe the intracellular concentrations dynamics of two main active substances: calcium ions ($Ca^{2+}$) and inositol 1,4,5-trisphosphate molecules ($IP_3$).

During the generation of action potentials by a neuron, a neurotransmitter glutamate is released into the synaptic cleft. The dynamics of extracellular concentration of released neurotransmitter $X$ is described by the following equation:

$$\frac{dX}{dt} = -\alpha_x X + k_0 H(V - 30mV), \tag{1}$$

where $\alpha_x$ = 10 $s^{-1}$ represents the neurotransmitter clearance constant, $k_0$ = 100 $\mu M{\cdot}s^{-1}$ denotes the effective rate of neurotransmitter release, and $H$ represents the Heaviside function. When glutamate comes into contact with the mGluRs receptors located on the astrocyte membrane, it triggers the initiation of $IP_3$ production, which is followed by the generation of an astrocytic calcium elevation.

During the generation of a calcium impulse in an astrocyte (a brief increase in intracellular calcium concentration above the threshold value $[Ca^{2+}_{thr}]$ = 0.2 $\mu$M), a gliotransmitter is released from the astrocyte. This gliotransmitter can modulate the efficacy of synaptic transmission in the presynaptic and postsynaptic terminals associated with astrocyte-neuron interaction. Specifically, the model incorporates the experimentally verified effect of astrocytic suppression of neurotransmitter release. In this case, the strength of the synaptic input connection $\lambda$ for the neuron interacting with the astrocyte decreases proportionally to the amplitude of the calcium impulse in the astrocyte. The model describes this astrocytic regulation of synaptic transmission as follows:

$$\frac{d\lambda}{dt} = \alpha(\lambda_0 - \lambda) - \beta[Ca^{2+}], \tag{2}$$

where $\alpha$ = 0.01, $\beta$ = 0.02, $[Ca^{2+}]$ represents the intracellular calcium concentration in the astrocyte. According to experimental data, after the completion of the calcium impulse, the effect of the gliotransmitter on the synaptic connection lasts for approximately 5 seconds. The strength of astrocyte-mediated modulation is equal to $\beta[Ca^{2+}_{thr}]$.

To estimate the degree of synchronization in the activity of network neurons, we calculated the global time order parameter $S(t)$:

$$\begin{aligned} S(t) &= \frac{1}{N(N-1)} \sum_{i \neq j} cos^2 \left( \frac{\phi_i(t) - \phi_j(t)}{2} \right) \\ \phi_i(t) &= 2\pi(t - t_i^k)/(t_i^{k+1} - t_i^k) \end{aligned} \tag{3}$$

Here, $t$ represents time in ms, $N$ is the size of the neural network, $\phi_i(t)$ and $\phi_j(t)$ are the instantaneous phases of the $i$-th and $j$-th neurons in the network, respectively, at time $t$. The indices $i$ and $j \in$ [1,$N$], representing the indices of the network neurons. Additionally, $t_i^k$ and $t_i^{k+1}$ denote the time points of the $k$-th and $(k+1)$-th membrane potential spikes of the neuron, respectively.

The value of $S$ = 1 corresponds to complete synchronization of the entire network, while $S$ = 0.5 corresponds to complete asynchrony of the network activity.

## III. Results

Figure 1 illustrates an example of the dynamics of the global order parameter $S(t)$ of the network, as well as the temporal realizations of the dynamics of one neuron and its corresponding astrocyte. These dynamics are shown at a maximum synaptic connection weight value of $\lambda_0$ = 3.8.

The drawings indicate that the neuron-astrocyte network operates in a bistable regime, exhibiting spontaneous switches between extreme synchronization and asynchrony. During synchronization episodes, there is an increase in extracellular neurotransmitter concentration. When this concentration surpasses the threshold $X_{thr}$, it triggers brief and abrupt increases in intracellular $IP_3$ concentration within the astrocyte. Consequently, calcium impulses are generated. Astrocytic activation, characterized by exceeding the threshold value of intracellular calcium concentration $[Ca^{2+}_{thr}]$, leads to the modulation of synaptic connection weights. Eventually, this

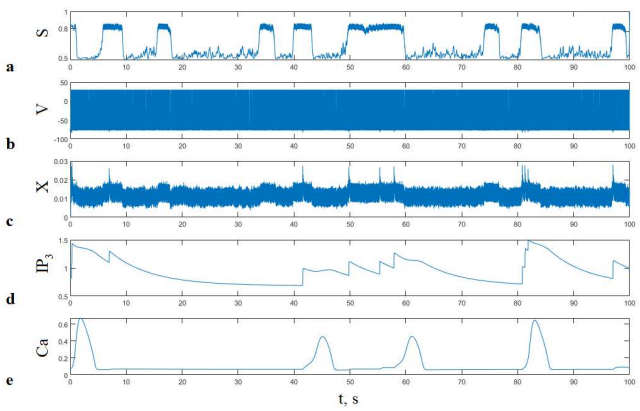


Fig. 1. Temporal realizations: (a) - global order parameter $S$; (b) - membrane potential $V$ of a single neuron in the network; (c) - extracellular concentration of neurotransmitter $X$ released by this neuron; (d) - concentration of $IP_3$ molecules in the astrocyte interacting with this neuron; (e) - intracellular calcium concentration in the astrocyte.

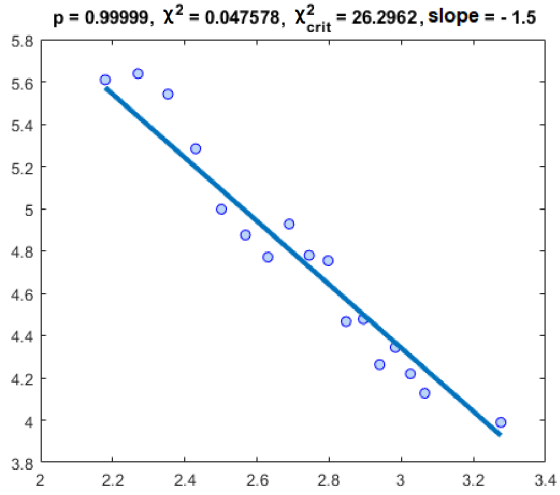


Fig. 2. The histogram of durations of asynchronous states in the neuron-astrocyte network. The histogram is presented on a double logarithmic scale, with the return time intervals represented by blue dots. Additionally, a theoretical line is shown, fitting the intervals distribution.

modulation results in the suppression of synaptic connections, which disrupts network synchronization due to the reduced efficiency of interaction between neurons.

Then, we investigated the distribution of intervals between consecutive synchronization events in the network. To accomplish this, we simulated a long temporal realization of network dynamics. From the resulting network switching statistics, we constructed a histogram of the asynchronous state periods (i.e., periods between synchronization events). The histogram, presented on a double logarithmic scale (Figure 2, blue dots), was subsequently approximated by a linear dependence. We assessed the approximation quality using the Pearson $\chi$-square criterion. According to the obtained results (Figure 2), the calculated chi-square value $\chi^2$ = 0.0476 $\ll$ $\chi^2_{krit}$ = 26.296. Additionally, the calculated $p-value$ for this study is 0.99999, which is close to 1. This indicates an extremely high probability that the theoretical line accurately fits the experimental data. The power law coefficient was found to be -3/2.

## IV. Conclusion

It has been demonstrated that the proposed model of the neuron-astrocyte network is capable of exhibiting activity synchronization akin to pathological processes. The mechanisms underlying the spontaneous and induced emergence of synchronous clusters of activity were investigated. The analysis of network synchronization involved examining the dependence of the global order parameter on the maximum weight of synaptic connections. Within certain parameter ranges, the system exhibited synchronous, asynchronous, and bistable states, with transitions occurring between these states.

Furthermore, an investigation was conducted regarding the distribution of return time intervals between neighboring synchronization events. It was found that this distribution obeys a power law relationship, with the slope of the fitting line equal to -3/2. This result is of fundamental importance, as the exponent -3/2 has been observed in various experiments, particularly in empirical observations of epileptic activity in rodent brains [24] - [27].

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