Astrocyte-Mediated Neuronal Irregularities and Dynamics: The Complexity of the Tripartite Synapse

Den Whilrex Garcia

den-whilrex.garcia@universite-paris-saclay.f

Université Paris-Saclay, CNRS, Institut des Neurosciences Paris-Saclay

Sabir Jacquir

Université Paris-Saclay, CNRS, Institut des Neurosciences Paris-Saclay

Research Article

Keywords: neuron, astrocyte, tripartite synapse, calcium dynamics, gliotransmission

Posted Date: December 20th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3772780/v1

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Biological Cybernetics on September 14th, 2024. See the published version at https://doi.org/10.1007/s00422-024-00994-z.

Astrocyte-Mediated Neuronal Irregularities and Dynamics: The Complexity of the Tripartite Synapse

Den Whilrex Garcia[1,2*] and Sabir Jacquir[1*†]

[1*]Université Paris-Saclay, CNRS, Institut des Neurosciences Paris-Saclay, Saclay, 91400, France.

[2]Department of Engineering, Lyceum of the Philippines University - Cavite, Philippines.

*Corresponding author(s). E-mail(s): den-whilrex.garcia@universite-paris-saclay.fr; sabir.jacquir@universite-paris-saclay.fr;

†These authors contributed equally to this work.

Abstract

Despite significant advancements in recent decades, gaining a comprehensive understanding of brain computations remains a significant challenge in neuroscience. Using computational models is crucial for unraveling this complex phenomenon and is equally indispensable for studying neurological disorders. This endeavor has created many neuronal models that capture brain dynamics at various scales and complexities. These models range from highly detailed multi-compartmental models like the Hodgkin-Huxley model to simpler models like the leaky integrate-and-fire model. However, most existing models do not account for the potential influence of glial cells, particularly astrocytes, on neuronal physiology. This gap persists even with the emerging evidence indicating their critical role in regulating neural network activity, plasticity, and even neurological pathologies. While some literature focuses on modeling interactions between neurons and glial cells, these approaches are often sophisticated, mimicking the complexity of the physiological phenomenon. In our work, we aim to propose a simplified tripartite synapse model encompassing the presynaptic neuron, postsynaptic neuron, and astrocyte. This model is more straightforward yet still includes the primary astrocytic calcium dynamics. We defined the tripartite synapse model based on the Adaptive Exponential Integrate-and-Fire neuron model and a simplified scheme of the astrocyte model previously proposed by Postnov. Our results demonstrate the model's ability to replicate essential synaptic transmission dynamics attributed to astrocytic calcium dynamics within the context of the tripartite synapse. Through our simulations, we propose that astrocytes can modify and shape the behavior and can introduce irregularities in the firing pattern of both presynaptic and postsynaptic neurons.

Keywords: neuron, astrocyte, tripartite synapse, calcium dynamics, gliotransmission

1 Introduction

Glial cells were traditionally considered passive elements in brain physiology. Their sole roles were primarily believed to be in supporting and maintaining suitable environmental conditions for the nervous system, such as neurotransmitter homeostasis, structural scaffolding, and ionic and metabolic supports (Han, Kim, Molofsky, & Liddelow, 2021; Kater, Badia-Soteras, van Weering, Smit, & Verheijen, 2023; Perea & Araque, 2009). It

was generally thought that they do not keenly participate in information processing within the nervous system (Perea, Navarrete, & Araque, 2009). However, over the last few decades, numerous experimental pieces of evidence have given rise to the notion that glial cells have more active roles in synaptic information processing and transmission within neural networks. Astrocytes, in particular, are now recognized as a crucial third component of the synapse due to their proximity to neurons and their bidirectional communication with them (Oschmann, Berry, Obermayer, & Lenk, 2018). Recent studies utilizing calcium imaging techniques have revealed a correlation between neuronal communication and astrocytic signaling, providing concrete evidence for their interplay (Goenaga, Araque, Kofuji, & Herrera Moro Chao, 2023). Furthermore, they have been recognized for their roles in memory formation (Zorec, Horvat, Vardjan, & Verkhratsky, 2015), regulation of synaptic plasticity (De Pittà, Brunel, & Volterra, 2016), decision making (Wang et al., 2017), attention (Guimarães, Madureira, & Madureira, 2018), cognitive processes (Brockett et al., 2018), behavioral regulation (Hwang, Lee, Seo, & Lee, 2021), working memory encoding (De Pittà & Brunel, 2022), generation of up and down states (Joshi, Joshi, & Joshi, 2023), and neurovascular coupling (Tesler, Linne, & Destexhe, 2023).

These findings have led to numerous studies suggesting that astrocytes indeed play a role in modulating local neural circuits, networks, and complex behaviors (Kastanenka et al., 2020). Similar to studying neurons, where different models were proposed to describe their dynamic features (Brunel, 2010; Brunel, Hakim, & Richardson, 2014) , computational and mathematical models have developed to describe astrocytic activities on various scales in response to the increasing number of experimental findings highlighting astrocytes'influence on neuronal network dynamics (Oschmann et al., 2018). Such modeling endeavors offer valuable insights into understanding the functional role of calcium (Ca^{2+}) waves in regulating synaptic transmission and allow for the investigation of relevant nonlinear mechanisms (Postnov, Koreshkov, Brazhe, Brazhe, & Sosnovtseva, 2009). However, it is essential to note that because astrocytes have been the subject of extensive research relatively later than neurons, models describing their functions are still inadequate compared with those of neurons (Oschmann et al., 2018).

Given the considerable variability in animal and cell-dependent traits and the broad spectrum of signaling pathways engaged in bidirectional neural-glial signaling, the application of a generalized computational model may serve as a valuable tool in studying the primary operational patterns and underlying nonlinear mechanisms of neural-glial ensembles (Postnov et al., 2009). Therefore, this work presents a concise, straightforward tripartite synapse model that successfully captures the primary astrocytic calcium dynamics. The presynaptic and postsynaptic neurons are based on the Adaptive Exponential Integrate-and-Fire (AdEx) model, while the astrocyte dynamics are inspired by the model proposed by Postnov (Postnov, Ryazanova, & Sosnovtseva, 2007).

It has been well-established that the release of gliotransmitters has a profound impact on neuronal function, potentially exerting excitatory and inhibitory effects (Calim, Longtin, & Uzuntarla, 2021; De Pittà, Goldberg, Volman, Berry, & Ben-Jacob, 2009; De Pittà et al., 2012). In light of this, our investigation primarily focuses on elucidating only astrocytes' excitatory influences on neuronal functions. Specifically, our attention is directed toward the Glu-Ca^{2+}-Glu signaling pathway, recognizing that the functional implications within real astrocytic-neuronal networks are significantly more complex. Furthermore, in our computational approach, we grapple with the challenge of integrating a dimensional model of neuron activity with a non-dimensional model that mimics astrocytic dynamics, encompassing calcium activities and gliotransmitter release.

This paper is organized as follows: In Section 2, we offer a concise overview of astrocytes, their functions, and their interactions with neurons. Section 3 is dedicated to presenting our proposed model and describing its connection to biological aspects. We discuss our model's key features and components, emphasizing its relevance to understanding astrocyte-neuron interactions. Continuing in Section 4, we present the *in silico* results obtained from our model and provide a comprehensive analysis. Here, we explore the implications and significance of our findings. Finally, in Section 5, we draw meaningful conclusions based on our

results and offer suggestions for future research directions.

2 Related Literature and Studies

2.1 Astrocytes and Their Functions

Astrocytes are specialized glial cells characterized by their bushy and star-shaped morphology (Han et al., 2021) and are abundantly found in the central nervous system (CNS) of mammals (Kater et al., 2023). The active participation of astrocytes in brain physiology is becoming increasingly evident (Perea & Araque, 2009; Perea et al., 2009). Although they do not generate action potentials, they are known to have a signaling mechanism, which relies on intracellular Ca^{2+} oscillations (Oschmann et al., 2018). These oscillations are capable of propagating as Ca^{2+} waves within astrocytes, to neighboring astrocytes (Perea & Araque, 2009), and even to the relatively distant synapses with no existing direct neuronal communication between them through a process termed as lateral astrocyte regulation (Covelo & Araque, 2016). These variations in intracellular Ca^{2+} levels within astrocytes can arise spontaneously or be regulated by synaptic activity within specialized microdomains. These microdomains represent spatially confined regions within astrocyte processes (Perea et al., 2009), influenced by neurotransmitters released from synaptic terminals and mechanical stimulation (Perea & Araque, 2009). Notably, the synaptically evoked astrocytic Ca^{2+} signal plays a crucial role in facilitating bidirectional signaling between neurons and astrocytes, making a significant contribution to overall brain function (Palabas, Longtin, Ghosh, & Uzuntarla, 2022; Perea & Araque, 2009).

Astrocytes also establish physical contact with synapses through specialized extensions known as perisynaptic astrocytic processes (PAPs) or leaflets, enabling their communication and functional integration (Kater et al., 2023). Furthermore, they serve as the primary source for uptake and buffering of biomolecules released by active neurons, facilitating the regulation of ion homeostasis and the levels of various large molecules, including glutamate, in the extracellular and synaptic space (Han et al., 2021; Oschmann et al., 2018).

Additionally, astrocytes sense synaptic activity and respond to neuronal signaling by releasing neuroactive biomolecules called gliotransmitters (in analogy with neurotransmitters), which include glutamate, D-serine, adenosine triphosphate (ATP), lactate (Kater et al., 2023; Oschmann et al., 2018), adenosine, tumor necrosis factor α (TNFα), prostaglandins, proteins, peptides (Perea, Navarrete, & Araque, 2009), and γ-aminobutyric acid (GABA) (Goenaga et al., 2023). Through the release of these biomolecules into the synaptic cleft, astrocytes can actively regulate neuronal excitability, synaptic transmission, plasticity, and the transfer of neuronal information (Goenaga et al., 2023; Oschmann et al., 2018; Perea & Araque, 2009).

Furthermore, astrocytes may also have pathological implications, as studies suggest that astrocyte dysfunction could potentially contribute to the development of various neurodegenerative disorders (Han et al., 2021; Preman, Alfonso-Triguero, Alberdi, Verkhratsky, & Arranz, 2021). Astrocytes are thought to be significantly involved in diseases like epilepsy and Alzheimer's disease. For instance, astrocytes alter neuronal excitability and synaptic transmission, which causes synchronized firing of neurons and is linked to epilepsy. In the case of Alzheimer's, GABA is being released in more significant amounts due to the impairment of astrocytes (Oschmann et al., 2018). When this happens, a portion of the network's neurons go completely quiet, which lowers the network's overall activity and influences other neurons to go quiet. This phenomenon could be linked to memory impairment. Some works strengthened these claims, like in the work of (Kater et al., 2023), where they proposed that changes in how astrocytes interact with synapses can affect how memories are formed and processed in the brain. Furthermore, in instances such as inflammation, neurodegenerative diseases, and acute injury, astrocytes enter a reactive state and exhibit marked changes in morphology, molecular composition, and function. These rapid modifications disrupt the capacity of the astrocyte to sustain brain homeostasis and can have far-reaching consequences for the viability and rehabilitation of other cells in the central nervous system (Han et al., 2021).

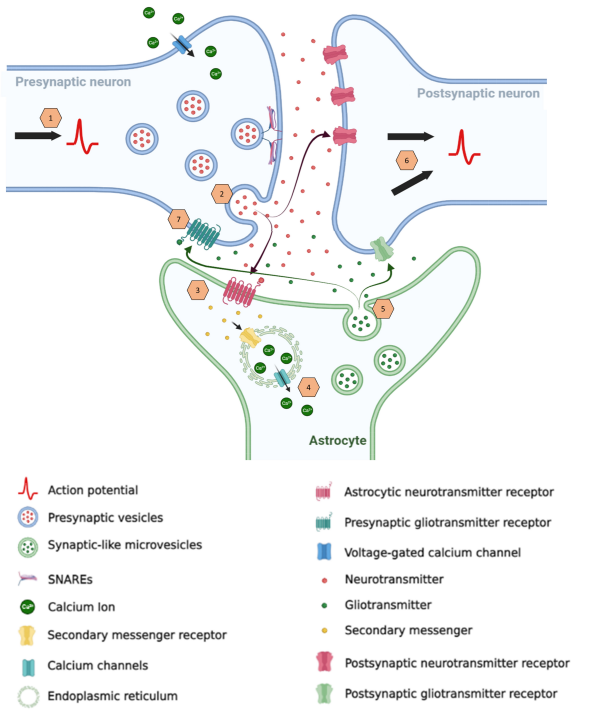
Advancements in scientific investigation have unequivocally demonstrated that astrocytes possess multifaceted roles within the CNS, actively contributing to information processing, the modulation of neuronal functions, and the overall functionality of neural networks. Their ability to exhibit excitability, establish physical connections with synapses, and release gliotransmitters underscores their significance in synaptic transmission, plasticity, and the underlying mechanisms of brain physiology. Understanding the intricate interactions between astrocytes and neurons is paramount for unraveling the complexities of brain function and deciphering their involvement in physiological and pathological conditions.

2.2 Tripartite Synapse

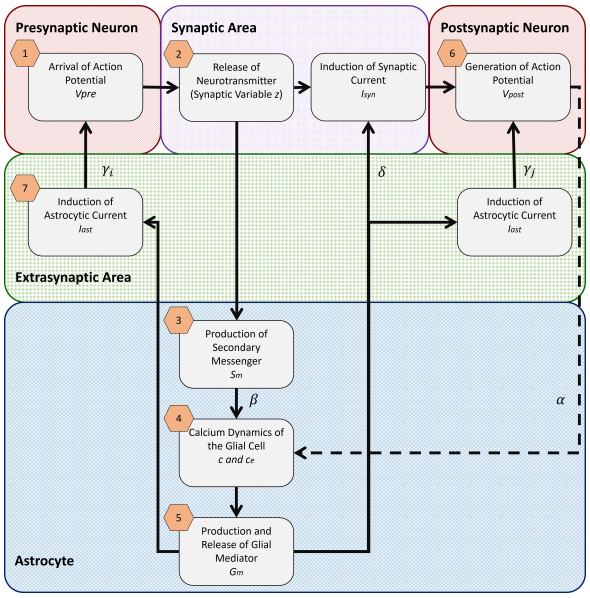
Astrocytes demonstrate a remarkable ability to enwrap around 140,000 hippocampal synapses (Bushong, Martone, Jones, & Ellisman, 2002) and to contact 300 to 600 neuronal dendrites in the cortex (Halassa, Fellin, Takano, Dong, & Haydon, 2007), intricately intertwining their processes with synaptic elements. This precise control over intracellular Ca^{2+} signal propagation significantly influences brain function, delineating the spatial extent of astrocyte impact on synaptic terminals. This complex interaction underscores a fundamental concept in synaptic physiology known as the 'tripartite synapse,' representing the structural and functional connections between presynaptic and postsynaptic neurons and adjacent astrocytic networks. This framework fosters bidirectional signaling between astrocytes and neurons (Perea & Araque, 2009; Postnov et al., 2009), wherein information not only travels between presynaptic and postsynaptic elements but also involves astrocytes as integral components in synaptic functioning (Goenaga et al., 2023).

To provide a comprehensive visualization of the intricate interplay between astrocytes, presynaptic neurons, and postsynaptic neurons, Figure 1a illustrates the communication pathway involved in the tripartite synapse. The arrival of action potential (AP) opens the voltage-gated calcium channels, which allows calcium ions (Ca2+) from the extracellular fluid to enter the presynaptic terminal. These calcium ions activate the proteins called Soluble N-ethylmaleimide-sensitive factor Attachment Protein Receptors (SNAREs), which promote the fusion of the neurotransmitter-containing synaptic vesicles with the presynaptic membrane, leading to the release of the neurotransmitters to the synaptic cleft. Upon neurotransmitter release, typically glutamate (Glu), activation occurs both at glutamate ionotropic receptors (i-GluRs) on the postsynaptic membrane and glutamate metabotropic receptors (m-GluRs) on astrocytes. Interaction with m-GluRs leads to IP3 production, triggering Ca^{2+} release from the endoplasmic reticulum (ER) and Ca^{2+}-dependent Ca^{2+} release from the ER. The extent of the increase of Ca^{2+} concentration in the astrocyte cytoplasm depends on synaptic activity levels. This mechanism is also known as the slow activation pathway (Postnov et al., 2007). Other than this, whenever neurons fire often, potassium builds up in the extracellular region. The glial cells get depolarized due to the elevated potassium content, and voltage-dependent Ca^{2+} channels open (Oschmann et al., 2018). This is known as the fast activation pathway (Postnov et al., 2007). Once the Ca^{2+} level surpasses a specific threshold, it prompts the release of gliotransmitters, such as glutamate, adenosine triphosphate (ATP), or D-serine. The released glial glutamate then interacts with i-GluRs, resulting in additional depolarization of the postsynaptic neuron. Furthermore, the astrocyte's Ca^{2+} concentration may undergo oscillations due to Ca^{2+} uptake into the ER and repetitive Ca^{2+}-dependent Ca^{2+} release (Postnov et al., 2009).

Mathematical models can be employed to simulate astrocytic networks integrated with synaptically bound neurons, offering insights into the functional role of Ca^{2+} waves in regulating synaptic transmission and allowing investigation of pertinent nonlinear mechanisms, like in (Lorenzo, Binczak, & Jacquir, 2022; Lorenzo, Vuillaume, Binczak, & Jacquir, 2020; Vuillaume, Lorenzo, Binczak, & Jacquir, 2021). However, these models were sophisticated, mimicking the complexity of the physiological phenomenon. Therefore, employing a generalized computational model can be highly beneficial for dissecting the fundamental operational patterns and nonlinear mechanisms that govern neural-glial ensembles. Following this, we propose a simple yet able to generate the crucial Ca^{2+} dynamics and the interplay between neural-glial ensembles.



(a) The tripartite synapse showing the intricate interplay between astrocyte, presynaptic neuron, and postsynaptic neuron.



(b) The functional diagram of the proposed model based on neurophysiological facts and hypothesis.

Fig. 1: Illustration of the tripartite synapse. [1] Arrival of action potential (AP). [2] Neurotransmitter release. [3] Production of secondary messenger (Sm). [4] Ca^{2+} exchange between the endoplasmic reticulum (ER) store and the cytoplasm of the astrocyte. [5] Release of glial mediators (Gm) or gliotransmitters. [6] Generation of action potential in the postsynaptic neuron due to currents induced by the synapse and the astrocyte. [7] Modulation of the neuronal activity of the presynaptic neuron due to gliotransmitters. The variables α, γ_i, γ_j, and δ are the main control parameters responsible for regulating the strength of influence of the astrocyte in the tripartite synapse. On the other hand, the variable β is the main control parameter that regulates the strength of influence of the secondary messenger to the concentration of Ca^{2+} in the cytoplasm of the astrocyte.

3 Methods

The dynamics and the different physiological interactions at the level of the tripartite synapse are depicted in Figure 1a. Inspired by this, we define a functional diagram of our proposed model shown in Figure 1b. Compared to the previous work (Postnov et al., 2007), our framework includes a feedback loop from the astrocyte to the presynaptic neuron. This feedback mechanism adds a layer of complexity to the interaction dynamics and is considered crucial, as discussed in (De Pittà & Brunel, 2022; Tewari & Majumdar, 2012; Theodosis, Poulain, & Oliet, 2008).

3.1 Neuron Model

Our model is based on the Adaptive Exponential Integrate-and-Fire (AdEx) model, formerly known as aEIF (Brette & Gerstner, 2005), for simulating the presynaptic and postsynaptic neurons. The choice of this model is motivated by its high biological accuracy, computational efficiency, and versatility (Brette & Gerstner, 2005; Naud, Marcille, Clopath, & Gerstner, 2008). It has demonstrated accurate prediction of spike timing, achieving 96% precision within a 2-ms window, for detailed regular spiking (RS) neuron models subjected to realistic (noisy) conductance-based

synaptic inputs (Brette & Gerstner, 2005). Moreover, it accurately replicates the spiking patterns of cortical pyramidal neurons (Naud et al., 2008).

The differential equations describing the dynamics of both presynaptic and postsynaptic neurons were:

$$C\frac{dV_{i,j}}{dt} = -g_L(V_{i,j} - E_L) + g_L\Delta_T \exp\left(\frac{V_{i,j} - V_T}{\Delta_T}\right) + Istim_i + Isyn_j + Iast_{i,j} - w_{i,j} \tag{1}$$

$$\tau_w\frac{dw_{i,j}}{dt} = a(V_{i,j} - E_L) - w_{i,j} \tag{2}$$

with a reset condition:

$$\begin{cases} V_{i,j} \rightarrow & V_r \\ w_{i,j} \rightarrow & wr_{i,j} = w_{i,j} + b \end{cases} \tag{3}$$

Here, variables with subscripts i and j correspond to parameters specific to the presynaptic and postsynaptic neurons, respectively. Conversely, variables without subscripts are common to both neurons and have fixed values. The membrane potential is V, C is the membrane capacitance, g_L is the leak conductance, E_L is the effective rest potential, Δ_T is the slope factor, V_T is the effective threshold potential, $Istim_i$ is the stimulating current, $Isyn_j$ is the synaptic current, w is the adaptation current, τ_w is the adaptation time constant, a is the level of subthreshold adaptation, V_r is the reset potential, and b is the spike-triggered adaptation.

The influence of the current from the astrocytic cell to the neuron was modeled as

$$Iast_{i,j} = \gamma_{i,j}G_m \tag{4}$$

where $\gamma_{i,j}$ is a parameter of proportionality that controls the astrocytic influence on the neuronal dynamics and G_m is the rate of glia mediator production. If there is no influence of the astrocytic cell, we can put $\gamma_{i,j} = 0$, otherwise $0 < \gamma_{i,j} \leq 1$. If we would like to consider a complete model of the tripartite synapse, as depicted in Figure 1b, the proportion of the gliotransmitter released in the synapse and uptake by the postsynaptic and presynaptic neurons is bounded by the equation (5). This last one means that the distribution of G_m from the astrocyte can not be greater than the quantity of G_m released by the astrocyte:

$$\gamma_i + \gamma_j + \delta = 1 \tag{5}$$

A detailed discussion follows in the subsequent subsections. It is important to note that, unlike in the presynaptic neuron, no additional external current is applied to the presynaptic neuron. The only currents influencing the behavior of the postsynaptic neuron are the currents induced by the synapse and by the astrocytic cell itself.

Neurons were configured to exhibit various firing patterns to explore the intricate interplay between presynaptic and postsynaptic neurons and the astrocyte. This deliberate choice aims to reveal the potential impact of neuronal firing patterns on the interaction dynamics. Refer to Table 1 for specific parameters governing these firing patterns.

3.2 Synapse Model

The synaptic dynamics and the neurotransmitter (or gliotransmitter) production have been modeled by an event-driven approach instead of the threshold activation approach commonly used in some works. This choice was driven by the fact that when an action potential arrives at the presynaptic neuron, a vesicle of neurotransmitters is released in the synaptic cleft (Stimberg, Goodman, Brette, & De Pittà, 2019). Subsequently, when the synaptic vesicle is released, it triggers the promotion of secondary messenger production. Similarly, we only need the glial messenger's values when the cytoplasm's calcium concentration reaches the threshold. This modeling approach provided simplified and efficient models, facilitating a more concise and intuitive representation of synaptic dynamics.

The synaptic current ($Isyn_j$) integrates two components. The first one, derived from the conductance-based synapse (Abbott & Dayan, 2001), is governed by this equation:

$$\tau_x\frac{d_{gx}}{dt} = -g_x, \tag{6}$$

where the subscript x indicates the excitatory e or inhibitory i, τ_x is the synaptic time constant, g_x is the synaptic conductance and the synaptic current is given by:

$$I_{gx} = g_x(E_x - V), \tag{7}$$

Table 1: Parameters used to generate various firing patterns using AdEx model (Gerstner et al., 2014; Naud et al., 2008)

Firing Pattern	C (pF)	g_L (nS)	E_L (mV)	V_T (mV)	Δ_T (mV)	a (nS)	τ_w (ms)	b (pA)	V_r (mV)	I (pA)
Tonic Spiking with Sharp Reset	200	10	-70	-50	2	2	30	0	-58	500
Tonic Spiking with Broad Reset	40	2	-70	-50	2	0	30	60	-51	65
Adaptation	200	12	-70	-50	2	2	300	60	-58	500
Initial Burst	130	18	-58	-50	2	4	150	120	-50	400
Regular Bursting	200	10	-58	-50	2	2	120	100	-46	400
Delayed Accelerating	200	12	-70	-50	2	-10	300	0	-58	210
Delayed Regular Bursting	100	10.5	-65	-50	2	-10	90	30	-47	110
Irregular Spiking	100	12	-60	-50	2	-11	130	30	-48	160

where E_x is the synaptic reversal potential. In this current work, we only considered the excitatory effect from the presynaptic neuron.

The second one arises from the release of neurotransmitters from the presynaptic neuron, represented as the synaptic variable z, and is modeled as an event. This means that the biomolecules will be released to the synaptic cleft whenever an action potential arrives at the presynaptic neuron. The equation governing this model is:

$$\tau_s \frac{d_z}{dt} = -z \tag{8}$$

Here z is the synaptic event and τ_s is the time delay. The corresponding synaptic current is expressed as:

$$I_z = \delta G_m (z_0 - z) \tag{9}$$

where δ is the proportionality parameter which could be equal to 0 if there is no release of glia mediator G_m in the synaptic clef or $0 < \delta \leq 1$ in otherwise. z_0 is determined by the sigmoïd activation-relaxation function:

$$z_0 = \frac{1}{1 + \exp(V_i)}, \tag{10}$$

with V_i is the action potential at the presynaptic neuron.

Consequently, the total synaptic current (I_{syn_j}) is the sum of these components:

$$I_{syn_j} = I_{gx} + I_z \tag{11}$$

Here, I_{syn_j} is the synaptic current applied to the postsynaptic neuron.

3.3 Astrocyte Model

3.3.1 Calcium Dynamics

The astrocytic activity is mainly based on the calcium dynamics. The model proposed by Postnov *et al* (Postnov et al., 2007) has been chosen due to its availability, its reproducibility, its ease of implementation, and its capability to simulate the dynamics of multi-synapse and multi-neuron structures.

$$\tau_c \frac{dc}{dt} = -c - c_4 f(c, c_e) + (r + \alpha w + \beta S_m) \tag{12}$$

$$\varepsilon_c \tau_c \frac{d_{c_e}}{dt} = f(c, ce) \tag{13}$$

$$f(c, c_e) = c_1 \frac{c^2}{1 + c^2} - \left(\frac{{c_e}^2}{1 + {c_e}^2} \right) \left(\frac{c^4}{{c_2}^4 + c^4} \right) - c_3 c_e \tag{14}$$

where c is the calcium concentration within the cytoplasm, c_e is the calcium concentration in the endoplasmic reticulum, τ_c is the characteristic time for calcium oscillations and transients, ε_c is the time separation parameter, r is the initial state of the calcium oscillator without external influence, αw is the extracellular potassium affecting the depolarization of the astrocyte, S_m is the synapse mediator controlled by the factor β; and, c_1, c_2, c_3, and c_4 are control parameters. The function $f(c, c_e)$ describes the nonlinear function of the Ca^{2+} exchange between the endoplasmic reticulum (internal storage) and the cytoplasm.

This model of the intracellular Ca^{2+} dynamics involved in the generation of the astrocytic and synaptic current, I_{ast} and I_{syn}, has relied on a deterministic approach, excluding various local and global processes within the cellular medium.

This one simplifies the models while still allowing them to generate crucial Ca^{2+} dynamics.

3.3.2 Mediator production

The secondary mediator S_m and glial mediator G_m (gliotransmitter) productions have been modeled using the following equations:

$$\tau_{S_m} \frac{dS_m}{dt} = -\frac{S_m}{d_{S_m}} \tag{15}$$

$$\tau_{G_m} \frac{dG_m}{dt} = -\frac{G_m}{d_{G_m}} \tag{16}$$

where τ_{S_m} and τ_{G_m} are the time scales, and d_{S_m} and d_{G_m} are control parameters to determine the steepness of the sigmoid functions. These were modeled as an event, similar to the synaptic variable z. This means that whenever a neurotransmitter is released, it will bind with the receptors on the postsynaptic membrane and promotes the production of the secondary messenger. In contrast, the glial mediator will be released in the synaptic cleft whenever the calcium oscillation in the cytoplasm reaches the threshold. The time scales of the synaptic variable z, the secondary messenger production S_m and the gliomediator production G_m need to respect this condition $\tau_{S_m} > \tau_{G_m} > \tau_s$. This is du to the glial and neuronal modulation functions which occur impresively at different time scales, with the former in the scale of submilliseconds to few milliseconds, while the latter at milliseconds to minutes (Araque et al., 2014; Goenaga et al., 2023; Savtchouk & Volterra, 2018) depending on the brain region.

The α, β, γ_i, γ_j, and δ are the main parameters responsible for the activation and influence of astrocyte. Specifically, the parameter α controls the fast activation pathway corresponding to the depolarization of the astrocyte due to the increasing extracellular potassium; the parameter β controls the slow activation pathway corresponding to the depolarization due to the production of secondary messenger S_m, hence, in other words, this is the one that controls the production rate of S_m (Amiri, Montaseri, & Bahrami, 2011); the parameters γ_i and γ_j control the coupling strength of the astrocyte to the presynaptic and postsynaptic neuron, respectively, through the production of gliotransmitters; and the parameter δ controls the strength of the influence of astrocyte to the synapse though the release of gliotransmitters.

Table 2: Parameters used for the rest of the model (Postnov et al., 2009, 2007; Stimberg et al., 2019)

Synapse Model Parameters		
Parameter	**Value**	**Description**
τ_s	10ms	Time delay for synaptic activation variable z
τ_e	5ms	Excitatory synaptic time constant
w_e	0.05nS	Excitatory synaptic conductance
E_e	0mV	Excitatory synaptic reversal
Calcium Dynamics Model Parameters		
τ_c	8ms	Characteristic time for Ca^{2+} oscillations
ϵ_c	0.04	Time separation parameter
r	0.31	Initial state of the Ca^{2+} oscillation
c_{peak}	1.2	Cytosolic Ca^{2+} concentration threshold
c_1	0.13	Parameter 1 for Ca^{2+} concentration in the cytoplasm
c_2	0.9	Parameter 2 for Ca^{2+} concentration in the cytoplasm
c_3	0.004	Parameter 3 for Ca^{2+} concentration in the cytoplasm
c_4	$2/\epsilon_c$	Parameter 4 for Ca^{2+} concentration in the cytoplasm
Mediator Production Model Parameters		
τ_{S_m}	100ms	Time scale for S_m
τ_{G_m}	$5 \times \tau_s$	Time scale for G_m
d_{S_m}	3.0	Deactivation rate for S_m
d_{G_m}	3.0	Deactivation rate for G_m
U_{S_m}	0.6	Secondary mediator release probability
U_{G_m}	0.6	Gliotransmitter release probability

Table 2 summarizes the parameters governing the synaptic and astrocytic models.

4 Results and Discussions

Our results are derived from a 14 seconds simulation, with a 6 second step current injection introduced after the first second. As highlighted in (Postnov et al., 2009), astrocytes predominantly employ the slower β-controlled pathway, crucial for simulating astrocytic–neural network interactions. Therefore, our primary focus lies in exploring dynamic patterns regulated by β, as they are pivotal for accurately simulating astrocyte–neural

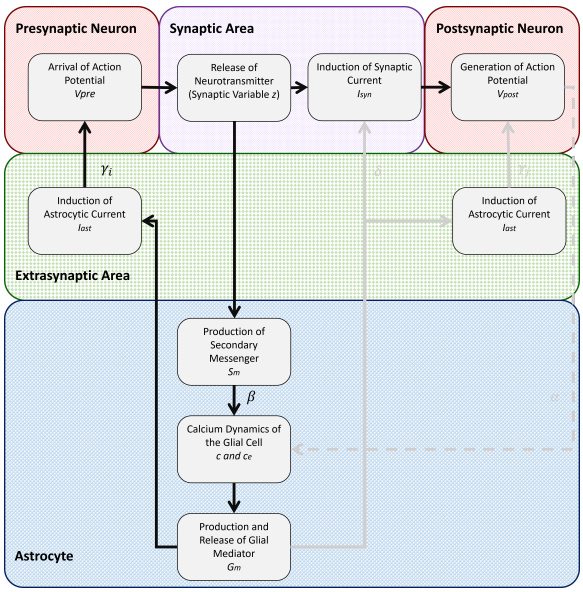


Fig. 2: The functional diagram of the simulations varying the control parameters β and γ_i.

network interactions. In each simulation, we maintain consistent parameter values for the postsynaptic neuron, which, in theory, should result in similar behavior to the presynaptic neuron. However, our results reveal unexpected temporal dynamics exhibited not only by the postsynaptic neuron but also by the presynaptic neuron. These dynamics arise due to the activation and influence of the glial feedback pathway.

4.1 Temporal Dynamics through the Variations of Control Parameters β and γ_i

In these simulations, we blocked the control parameters α, γ_j, and δ, setting them to zero, as shown in the functional diagram in Figure 2. Consequently, no glial feedback influenced the postsynaptic neuron and the synapse.

Figure 3 illustrates how varying the control parameters β and γ_i impacts the behavior of the presynaptic neuron. Notably, in panels 3 and 6, the influence of the astrocyte on the presynaptic neuron has minimal to no effect. Therefore, regardless of the strength of the production rate of S_m, as long as the coupling strength between the presynaptic neuron and astrocyte remains weak, the temporal dynamics of the presynaptic neuron are unaffected.

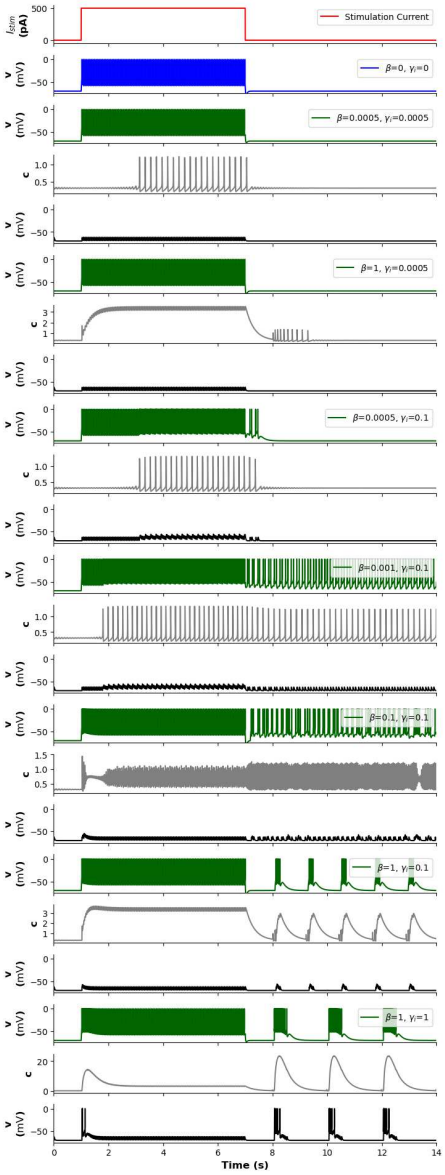


Fig. 3: *Top two panels:* The injected stimulating current and the dynamics of the presynaptic neuron when the control parameters β, γ_j, and δ were set to zero, respectively. *Remaining panels:* The temporal dynamics of the presynaptic neuron's membrane potential (in green), the Ca^{2+} oscillations in the astrocyte's cytoplasm (in gray), and the postsynaptic neuron's membrane potential (in black) influenced by various conditions of control parameters β and γ_i. In these simulations, the presynaptic neuron was set to have a tonic spiking with broad reset behavior.

However, when γ_i is high, even with low β, the presynaptic neuron exhibits firing activity

briefly after the stimulating step current injection. Increasing β further prolongs this activity after the stimulating current ceases. Moreover, a substantial increase in β introduces a fascinating alternation of firing and quiescence periods reminiscent of the mechanisms underlying neuronal up and down states (see the panels 18 and 21 in the Figure 3). These observations were not limited to this firing behavior; they were consistent across various firing patterns. We can also seen that this up and down state is modulated by the calcium spiking activity of the astrocyte (equations (12),(13) and (14)) and the glio mediator production G_m. These results suggest that if the timescale of the calcium spiking activity in the astrocyte is slow, the up and down state appears at presynaptic neuron and also at postsynaptic neuron (see the panels 21, 22 and 23 in the Figure 3). We observed at a tripartite synapse level the results published by (Blum Moyse & Berry, 2022). In this paper, the authors worked on the modulation of cortical up and down state switching by astrocytes.

The observed results in this part suggest also that when there is a strong coupling between the presynaptic neuron and the astrocyte, combined with moderate to high values of the production rate strength of S_m, the tripartite synapse exhibits self-sustaining behavior. The panels displaying black traces in the Figure 3 depict the temporal dynamics of the postsynaptic neuron. Notably, all panels, except the last one, exhibit subthreshold activities, indicating an absence of firing. This observation suggests that alterations in behavior resulting from glial feedback to the presynaptic neuron are likely to induce firing in the postsynaptic neuron, particularly when the control parameters β and γ_i are set to high values.

A box plot has been plotted in order to quantify further the effects of varying these control parameters, as shown in Figure 4. This figure illustrates the distribution of Inter-Spike Intervals (ISIs) observed in the presynaptic neuron under different combinations of control parameters, β and γ_i. Each box represents a distinct parameter setting, and the whiskers extend to show the range of ISIs. The central line within each box represents the median ISI for that configuration. Individual data points beyond the whiskers indicate the

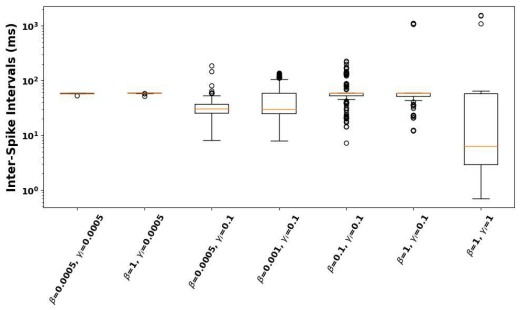


Fig. 4: InterSpike Intervals (ISIs) of the presynaptic neuron across varied β and γ_i settings.

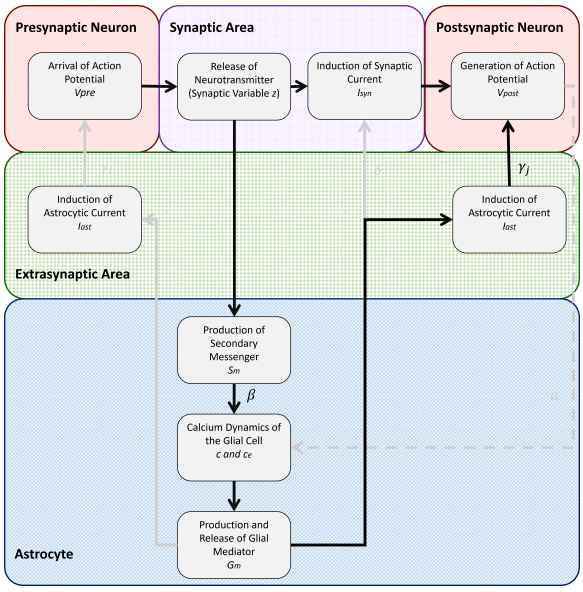


Fig. 5: The functional diagram of the simulations varying the control parameters β and γ_j.

presence of outliers. Notably, for the last two settings (when β were 0.05 and 1, respectively), we observed a considerable difference between the top outliers and the interquartile range, representing intervals between bursting behavior, which were observed after removing the stimulating current.

4.2 Temporal Dynamics through the Variations of Control Parameters β and γ_j

In these simulations, we deliberately set the control parameters α, γ_i, and δ to zero, as shown in the functional diagram in Figure 5. This will effectively block any glial feedback that could

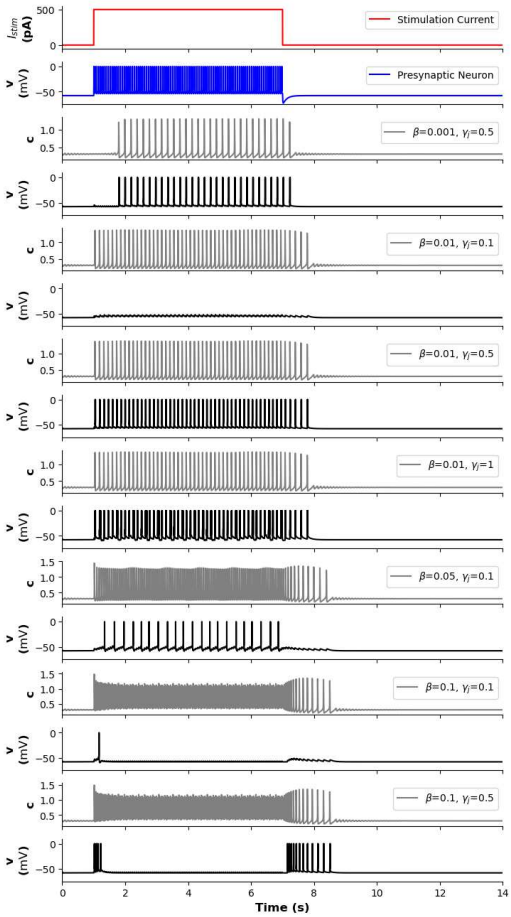


Fig. 6: *Top two panels:* The injected stimulating current and the dynamics of the presynaptic neuron, respectively. *Remaining panels:* The temporal dynamics of the Ca^{2+} oscillations in the astrocyte's cytoplasm (in gray) and the postsynaptic neuron's membrane potential (in black) influenced by various conditions of control parameters β and γ_j. In these simulations, both the presynaptic and postsynaptic neurons were set to have an initial busting behavior. Because of the influence of astrocyte, the postsynaptic neuron exhibited various firing behavior depending on the condition of the control parameters: regular bursting (Panels 4 and 8), irregular spiking (Panel 10), tonic spiking (Panel 12) or transient spiking (Panels 14 and 16). These results underscore the significant impact of glial factors on shaping the behavior of the postsynaptic neuron.

influence the presynaptic neuron and the synapse.

Figure 6 reveals the complex temporal dynamics of the postsynaptic neuron under the influence of varying control parameters, specifically β and

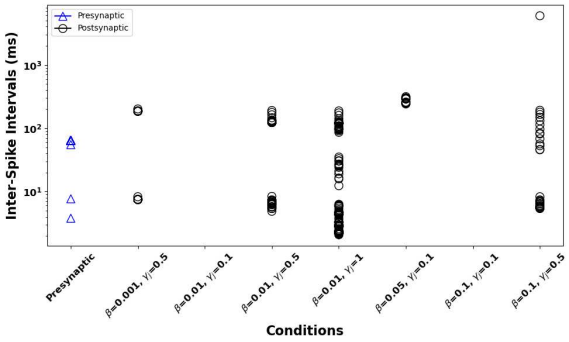


Fig. 7: InterSpike Intervals (ISIs) of the postsynaptic neuron across varied β and γ_j settings.

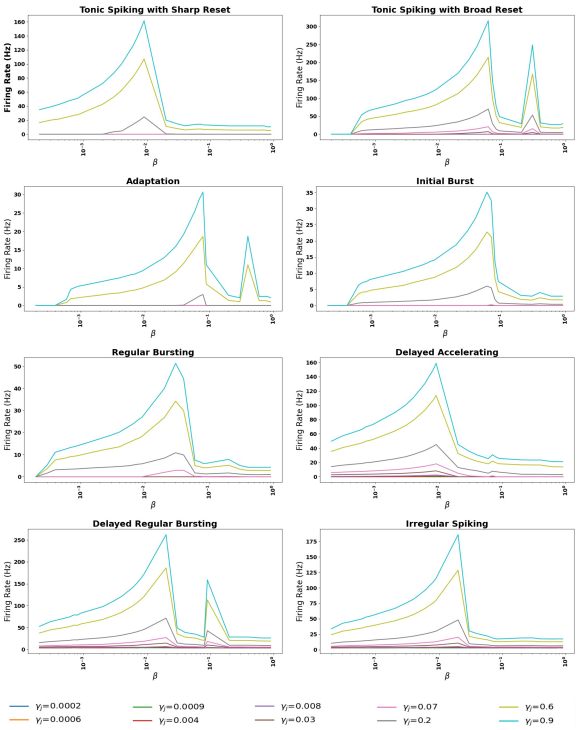


Fig. 8: The firing rate in the postsynaptic neuron when varying the control parameters β and γ_j

γ_j. This figure provides insight into the intricate responses exhibited by the postsynaptic neuron due to the influence of glial factors, with these responses varying based on the values of these control parameters. Remarkably, the behavior of the postsynaptic neuron can exhibit a range of firing patterns based on the conditions of these control parameters. For instance, when β is set to 0.001

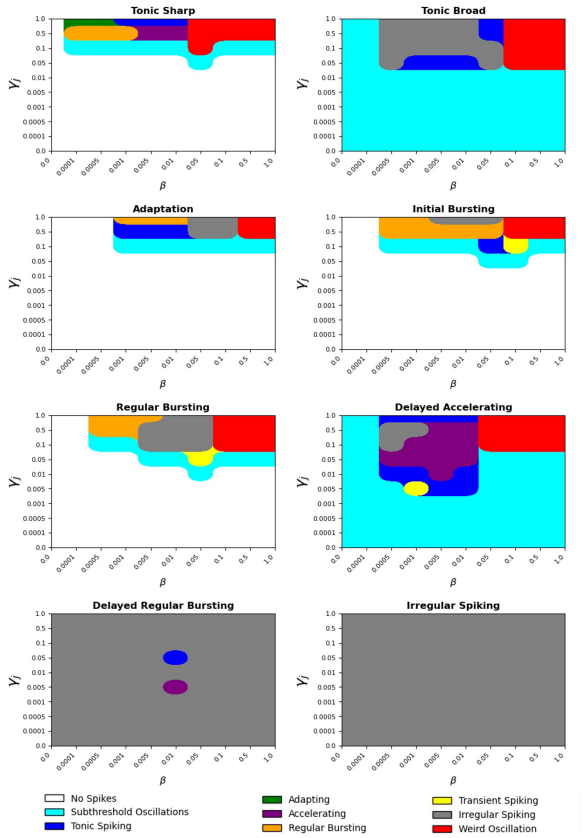


Fig. 9: Parameter space exploration to determine the firing behavior exhibited by the postsynaptic neuron through varying the control parameters β and γ_j. The title of each panel indicates the behavior of the presynaptic neuron.

and γ_j to 0.5, the postsynaptic neuron demonstrates a regular bursting behavior (Panel 4). However, increasing β to 0.01 while concurrently reducing γ_j to 0.1 results in the postsynaptic neuron falling into complete silence (Panel 6). Conversely, maintaining the strength of β while elevating γ_j to 0.5 again leads to the postsynaptic neuron exhibiting regular bursting behavior (Panel 8). However, increasing γ_j to 1 leads to irregular firing patterns (Panel 10), and increasing β to 0.05 while simultaneously decreasing γ_j to 0.1 results in tonic spiking behavior but with fewer action potentials (Panel 12). These findings underscore the intricate interplay between these control parameters and the evoked responses. In order to validate the diverse firing behaviors resulting from different sets of control parameters, a scatterplot of Inter-Spike Intervals (ISIs) was generated, as presented in Figure 7. This scatterplot visually represents the intricate relationship between ISIs, reflecting neuronal firing patterns and the control parameters β and γ_j. Furthermore, to have better insights, we computed the firing rate, the ratio between the number of neuron spikes, and the chosen time window, which in this case is the entire simulation. The results are shown in Figure 8. Our findings indicate that irrespective of the presynaptic and postsynaptic neuron behaviors, there is a peak in spike ratio at intermediate β values. This phenomenon can be attributed to the saturation or blockade of calcium ions when β is excessively high. Finally, in the Figure 9, we conducted a comprehensive parameter exploration to uncover the postsynaptic neuron's behavior across varying combinations of control parameters β and γ_j. In this case, at the initial state, the presynaptic and the postynaptic neurons have been configured to have the same dynamics (as example tonic sharp behavior, see the panel 1 in the Figure 9). We can observe that depending on the influence of the astrocytic activity (second messenger and glio mediator productions, calcium activity), the dynamics of the postsynaptic neuron is variable. Through this, we can predict the behavior of the postsynaptic neuron given the conditions of β and γ_j.

4.3 Temporal Dynamics through the Variations of Control Parameters β and δ

In these simulations, the control parameters α, γ_i, and γ_j were blocked, hence set to zero, as shown in the functional diagram in Figure 10. Thus, no glial feedback could influence the presynaptic and postsynaptic neurons.

In Figure 11, we can see as well that the postsynaptic neuron's behavior was influenced by the glial dynamics even though they were configured to behave as tonic spiking. And similarly, like when varying the parameters β and γ_j (see section (4.2)), when β is too high, the Ca^{2+} will be blocked, hence, no spiking activity during this period.

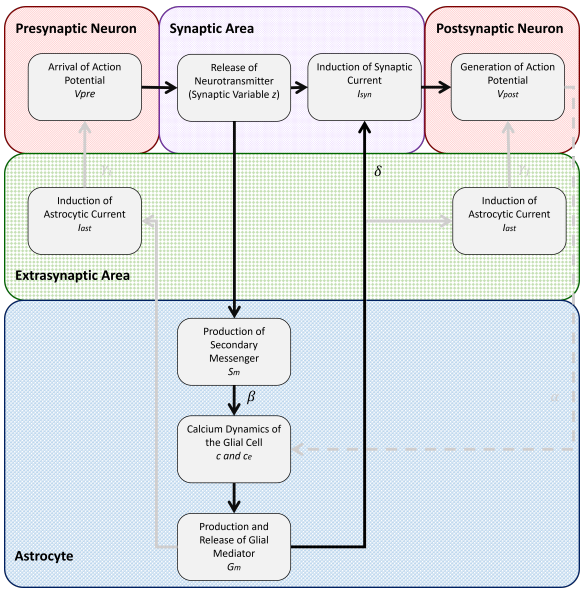


Fig. 10: The functional diagram of the simulations varying the control parameters β and δ.

4.4 Temporal Dynamics of the Calcium Oscillations in the Astrocyte's Cytoplasm

We also investigated the temporal dynamics of the calcium oscillations of the astrocyte's cytoplasm, and we have observed that the calcium concentration is tuned by the control parameter β (see the Figure 12). As we can see, β should maintain a low to mid value; otherwise, this saturates the calcium concentration on the cytoplasm and, in return, inhibits the release of the gliotransmitter to the synaptic cleft. Hence, no excitation was observed during the period when the calcium concentration was too high.

We then calculated the average frequency of calcium peaks, and as shown in Figure 13, this is when the neuron is set to behave as tonic spiking with sharp reset, and it strengthens the claim that when the control parameter β is too high, the calcium concentration stops oscillating. Hence, we can infer that when there is too much release of secondary messenger like IP3, there will be a high concentration of calcium ions in the cytoplasm and hence inhibit the activity of the postsynaptic neuron.

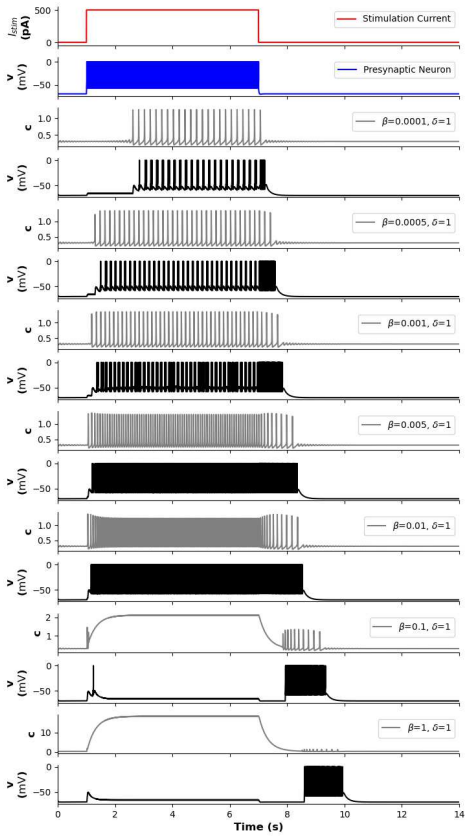


Fig. 11: *Top two panels:* The injected stimulating current and the dynamics of the presynaptic neuron, respectively. *Remaining panels:*The temporal dynamics of the Ca^{2+} oscillations in the astrocyte's cytoplasm (in gray) and the postsynaptic neuron's membrane potential (in black) influenced by various values of control parameters β and δ. Both the presynaptic and postsynaptic neurons are configured to behave as tonic spiking with sharp reset.

4.5 Irregular Firing Behavior due to Astrocyte

Spontaneous neural spiking activity in most brain regions is highly irregular, as observed in both *in vivo* and *in vitro* recordings (Shadlen & Newsome, 1998; Zierenberg, Wilting, & Priesemann, 2018). This irregularity has attracted significant attention in recent decades, with researchers attempting to discern its nature, origins, and potential functional significance. While various factors, such as inherent neural dynamics and environmental influences, have been proposed as potential causes of spiking irregularity, the underlying mechanism

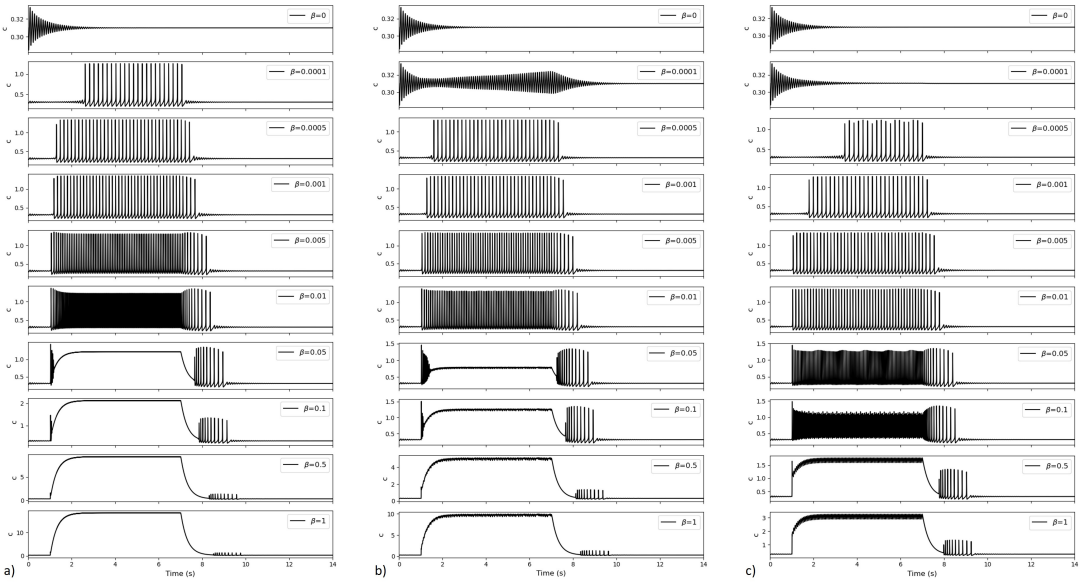


Fig. 12: The temporal dynamics of the calcium oscillations of the astrocyte's cytoplasm through the variation of the control parameter β when the neuron is configured to behave as a) tonic spiking with sharp reset, b) initial burst, and c) irregular spiking.

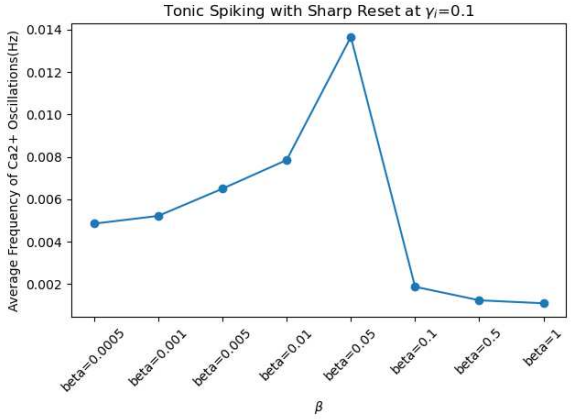


Fig. 13: The average frequency of calcium oscillations of the astrocyte's cytoplasm at various values of control parameter β when γ_i is 0.1, and the neuron is behaving as tonic spiking with sharp reset.

remains unknown. As a result, there is a particular focus on investigating the role of astrocytes in shaping these irregular firing patterns (Palabas et al., 2022). To investigate, we rigorously simulated our tripartite synapse model, explored astrocytic factors that may influence the neural activity of neurons, and assessed this impact using the Coefficient of Variation (CV) of spike trains, a widely accepted metric for measuring spiking irregularity. The CV is computed by dividing the standard deviation by the mean of the interspike intervals (ISIs), and it is formally defined as (Ozer, Perc, & Uzuntarla, 2009; Schmid, Goychuk, & Hänggi, 2001) with N the total number of ISI :

$$CV = \frac{\sqrt{\sum \left(ISI_i - \mu\right)^2 / N}}{\sum ISI_i / N}; \quad i = 1, 2, \ldots, N \tag{17}$$

It should be emphasized that elevated CV values are linked to higher irregularity in spike trains (Palabas et al., 2022). In contrast, smaller values indicate more structured spike trains and approach negligibility in the case of purely deterministic signals (Ozer et al., 2009).

We first investigated the effect of varying the control parameters on the activity of the presynaptic neuron. Figure 14 shows how CV changes with different conditions of control parameters γ_i and β. As evident from the results, it was expected that no irregularities would be generated when altering the control parameters γ_j and δ, as they respectively pertain to the astrocytic influence on the postsynaptic neuron and the synapse. However, a notable change in CV is observed when

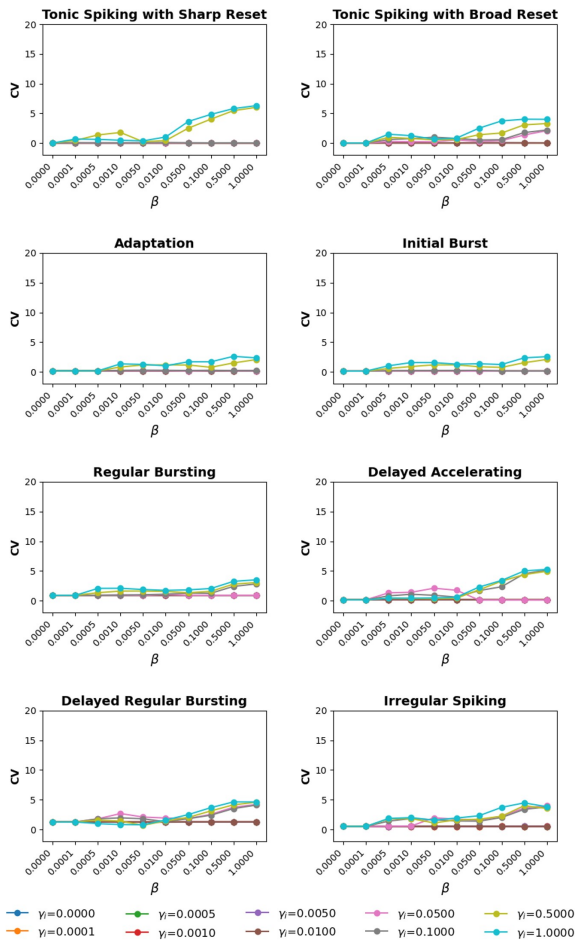


Fig. 14: The coefficient variation of the presynaptic neuron during the entire simulation when varying the control parameters β and γ_i.

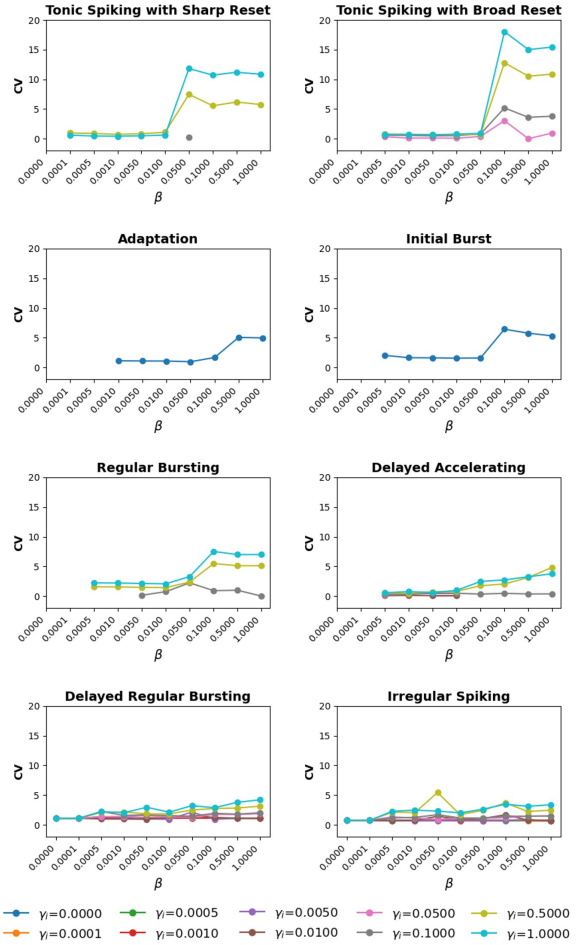


Fig. 15: The coefficient variation of the postsynaptic neuron during the entire simulation when varying the control parameters β and γ_j.

γ_i is varied. This indicates that the behavior becomes more irregular as the coupling strength between the astrocyte and the presynaptic neuron strengthens (represented by an elevated γ_i). Conversely, the relationship is not linear for β. For example, when the neuron exhibits delayed accelerating behavior, and the value of γ_i is relatively low, such as 0.05, instead of experiencing increased irregularity as β rises, the presynaptic neuron becomes more regular. This illustrates the intricate interaction between neurons and astrocytes. The influence depends on the neuron's firing behavior and the astrocytic influence's strength on and by the coupled network. The same analysis was performed to assess irregularities in the firing behavior of the postsynaptic neuron. Figure 15 illustrates the trend of irregularities in the postsynaptic neuron's behavior. In this context, beyond observing the Coefficient of Variation (CV) trend, we also observed that not every case has a corresponding CV value, indicating that there are specific conditions for the parameters β and γ_j that must be met to generate an action potential in the postsynaptic neuron.

5 Conclusion

In this study, we focused on unraveling the intricate interplay between neurons and astrocytes at the synapse level. Our investigation is based on a dimensional model (AdEx model for the neuron) in conjunction with the non dimensional

model (astrocytic calcium activity model) proposed by (Postnov et al., 2007). Additionally, we introduced simplified models for the synapse and the production of secondary and glial messengers, adopting an event-driven approach for a more concise and intuitively understandable representation of synapse and neuro-glial transmitters production dynamics. Despite the simplicity inherent in our proposed framework, we achieved successful replication of the essential synaptic transmission dynamics linked to astrocytic Ca^{2+} dynamics within the tripartite synapse.

The simulation results underscored the intricate complexity of glial influence and feedback mechanisms. Notably, these dynamics were found to be highly reliant on specific control parameters, particularly β, γ_i, γ_j, and δ. These parameters represent the production rate of the secondary messenger, the coupling strength between the astrocyte and the presynaptic and postsynaptic neurons, and the strength of the astrocyte to the synapse through the release of gliotransmitters, respectively. Despite configuring both presynaptic and postsynaptic neurons with predetermined firing patterns, the astrocyte exhibited the capacity to modulate the behavior of the neurons. Astrocytes can also introduce firing irregularities on both presynaptic and postsynaptic neurons. In some conditions, the astrocytic dynamics induce a "pseudo up and down state" in presynaptic and postsynaptic neurons. This result is inline with the recent work focused on modelling the modulation of cortical up-down state switching by astrocytes (Blum Moyse & Berry, 2022).

Our research introduces an alternative theoretical framework, underscoring the considerable impact of astrocytes on neural activity. Nevertheless, it is crucial to note that our work predominantly centered on the tripartite synapse level. Delving into additional studies at the network level would yield insightful perspectives, enriching our understanding of these interactions within expansive neural networks. In addition, such investigations can potentially unveil the broader ramifications of astrocyte-neuron interactions in the domain of neural information processing, and even in the context of predictive coding (Koch & Poggio, 1999; Rao & Ballard, 1999; Spratling, 2017). Moreover, pursuing further validation, mainly through comparisons with experimental data, would fortify the robustness and relevance of our findings.

Acknowledgments. This work has been supported by the Department of Science and Technology-Science Education Institute, Philippines (DOST-SEI) and the Embassy of France to the Philippines and Micronesia through the PhilFrance-DOST Fellowship of DWG.

Author contributions. Conceptualization: SJ. Formal analysis: DWG, SJ. Funding acquisition: DWG, SJ. Investigation: DWG, SJ. Methodology: DWG, SJ. Software: DWG, SJ. Validation: DWG, SJ. Visualization: DWG, SJ. Writing – original draft: DWG, SJ. Writing – review & editing: DWG, SJ.

Code availability. All the code used to generate the data of this article is freely available upon request to the authors.

Declarations

Conflict of interest. The authors declare no conflicts of interest in this paper.

References

Abbott, L.F., & Dayan, P. (2001). Theoretical neuroscience. *Comput Math Model Neural*, *60*, 489–95,

Amiri, M., Montaseri, G., Bahrami, F. (2011). On the role of astrocytes in synchronization of two coupled neurons: a mathematical perspective. *Biological cybernetics*, *105*, 153–166,

Araque, A., Carmignoto, G., Haydon, P.G., Oliet, S.H., Robitaille, R., Volterra, A. (2014). Gliotransmitters travel in time and space. *Neuron*, *81*(4), 728–739,

Blum Moyse, L., & Berry, H. (2022). Modelling the modulation of cortical up-down state switching by astrocytes. *PLoS Computational Biology*, *18*(7), e1010296,

Brette, R., & Gerstner, W. (2005). Adaptive exponential integrate-and-fire model as an effective description of neuronal activity. *Journal of neurophysiology*, *94*(5), 3637–3642,

Brockett, A.T., Kane, G.A., Monari, P.K., Briones, B.A., Vigneron, P.-A., Barber, G.A., ... others (2018). Evidence supporting a role for astrocytes in the regulation of cognitive flexibility and neuronal oscillations through the ca2+ binding protein s100β. *PLoS One*, *13*(4), e0195726,

Brunel, N. (2010). *Modeling point neurons: From hodgkin-huxley to integrate-and-fire.* MIT Press.

Brunel, N., Hakim, V., Richardson, M.J. (2014). Single neuron dynamics and computation. *Current opinion in neurobiology*, *25*, 149–155,

Bushong, E.A., Martone, M.E., Jones, Y.Z., Ellisman, M.H. (2002). Protoplasmic astrocytes in ca1 stratum radiatum occupy separate anatomical domains. *Journal of Neuroscience*, *22*(1), 183–192,

Calim, A., Longtin, A., Uzuntarla, M. (2021). Vibrational resonance in a neuron–astrocyte coupled model. *Philosophical Transactions of the Royal Society A*, *379*(2198), 20200267,

Covelo, A., & Araque, A. (2016). Lateral regulation of synaptic transmission by astrocytes. *Neuroscience*, *323*, 62–66,

De Pittà, M., & Brunel, N. (2022). Multiple forms of working memory emerge from synapse–astrocyte interactions in a neuron–glia network model. *Proceedings of the National Academy of Sciences*, *119*(43), e2207912119,

De Pittà, M., Brunel, N., Volterra, A. (2016). Astrocytes: Orchestrating synaptic plasticity? *Neuroscience*, *323*, 43–61,

De Pittà, M., Goldberg, M., Volman, V., Berry, H., Ben-Jacob, E. (2009). Glutamate regulation of calcium and ip 3 oscillating and pulsating dynamics in astrocytes. *Journal of biological physics*, *35*, 383–411,

De Pittà, M., Volman, V., Berry, H., Parpura, V., Volterra, A., Ben-Jacob, E. (2012). Computational quest for understanding the role of astrocyte signaling in synaptic transmission and plasticity. *Frontiers in computational neuroscience*, *6*, 98,

Gerstner, W., Kistler, W.M., Naud, R., Paninski, L. (2014). *Neuronal dynamics: From single neurons to networks and models of cognition.* Cambridge University Press.

Goenaga, J., Araque, A., Kofuji, P., Herrera Moro Chao, D. (2023). Calcium signaling in astrocytes and gliotransmitter release. *Frontiers in Synaptic Neuroscience*, *15*, 1138577,

Guimarães, K., Madureira, D.Q., Madureira, A.L. (2018). Interactions between astrocytes and the reward-attention circuit: A model for attention focusing in the presence of nicotine. *Cognitive Systems Research*, *50*, 15–28,

Halassa, M.M., Fellin, T., Takano, H., Dong, J.-H., Haydon, P.G. (2007). Synaptic islands defined by the territory of a single astrocyte. *Journal of Neuroscience*, *27*(24), 6473–6477,

Han, R.T., Kim, R.D., Molofsky, A.V., Liddelow, S.A. (2021). Astrocyte-immune cell interactions in physiology and pathology. *Immunity*, *54*(2), 211–224,

Hwang, S.-N., Lee, J.S., Seo, K., Lee, H. (2021). Astrocytic regulation of neural circuits underlying behaviors. *Cells*, *10*(2), 296,

Joshi, S.N., Joshi, A.N., Joshi, N.D. (2023). Interplay between biochemical processes and network properties generates neuronal up and down states at the tripartite synapse. *Physical Review E*, *107*(2), 024415,

Kastanenka, K.V., Moreno-Bote, R., De Pittà, M., Perea, G., Eraso-Pichot, A., Masgrau, R., ... Galea, E. (2020). A roadmap to integrate astrocytes into systems neuroscience. *Glia*, *68*(1), 5–26,

Kater, M.S., Badia-Soteras, A., van Weering, J.R., Smit, A.B., Verheijen, M.H. (2023). Electron microscopy analysis of astrocyte-synapse interactions shows altered dynamics in an alzheimer's disease mouse model. *Frontiers in Cellular Neuroscience*, ,

Koch, C., & Poggio, T. (1999). Predicting the visual world: silence is golden. *nature neuroscience*, *2*(1), 9–10,

Lorenzo, J., Binczak, S., Jacquir, S. (2022). Synaptic communication in diverse astrocytic connectivity: A computational model. *2022 44th annual international conference of the ieee engineering in medicine & biology society (embc)* (pp. 158–161).

Lorenzo, J., Vuillaume, R., Binczak, S., Jacquir, S. (2020). Spatiotemporal model of tripartite synapse with perinodal astrocytic process. *Journal of computational neuroscience*, *48*, 1–20,

Naud, R., Marcille, N., Clopath, C., Gerstner, W. (2008). Firing patterns in the adaptive exponential integrate-and-fire model. *Biological cybernetics*, *99*, 335–347,

Oschmann, F., Berry, H., Obermayer, K., Lenk, K. (2018). From in silico astrocyte cell models to neuron-astrocyte network models: A review. *Brain research bulletin*, *136*, 76–84,

Ozer, M., Perc, M., Uzuntarla, M. (2009). Controlling the spontaneous spiking regularity via channel blocking on newman-watts networks of hodgkin-huxley neurons. *Europhysics Letters*, *86*(4), 40008,

Palabas, T., Longtin, A., Ghosh, D., Uzuntarla, M. (2022). Controlling the spontaneous firing behavior of a neuron with astrocyte. *Chaos: An Interdisciplinary Journal of Nonlinear Science*, *32*(5), ,

Perea, G., & Araque, A. (2009). Synaptic information processing by astrocytes. *Astrocytes in (patho) physiology of the Nervous System*, 287–300,

Perea, G., Navarrete, M., Araque, A. (2009). Tripartite synapses: astrocytes process and control synaptic information. *Trends in neurosciences*, *32*(8), 421–431,

Postnov, D., Koreshkov, R., Brazhe, N.A., Brazhe, A.R., Sosnovtseva, O.V. (2009). Dynamical patterns of calcium signaling in a functional model of neuron–astrocyte networks. *Journal of biological physics*, *35*, 425–445,

Postnov, D., Ryazanova, L., Sosnovtseva, O. (2007). Functional modeling of neural–glial interaction. *Biosystems*, *89*(1), 84-91, https://doi.org/https://doi.org/10.1016/j.biosystems.2006.04.012 Retrieved from https://www.sciencedirect.com/science/article/pii/S030326 (Selected Papers presented at the 6th

International Workshop on Neural Coding)

Preman, P., Alfonso-Triguero, M., Alberdi, E., Verkhratsky, A., Arranz, A.M. (2021). Astrocytes in alzheimer's disease: pathological significance and molecular pathways. *Cells*, *10*(3), 540,

Rao, R.P., & Ballard, D.H. (1999). Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects. *Nature neuroscience*, *2*(1), 79–87,

Savtchouk, I., & Volterra, A. (2018). Gliotransmission: beyond black-and-white. *Journal of Neuroscience*, *38*(1), 14–25,

Schmid, G., Goychuk, I., Hänggi, P. (2001). Stochastic resonance as a collective property of ion channel assemblies. *Europhysics Letters*, *56*(1), 22,

Shadlen, M.N., & Newsome, W.T. (1998). The variable discharge of cortical neurons: implications for connectivity, computation, and information coding. *Journal of neuroscience*, *18*(10), 3870–3896,

Spratling, M.W. (2017). A review of predictive coding algorithms. *Brain and cognition*, *112*, 92–97,

Stimberg, M., Goodman, D.F., Brette, R., De Pittà, M. (2019). Modeling neuron–glia interactions with the brian 2 simulator. *Computational glioscience*, 471–505,

Tesler, F., Linne, M.-L., Destexhe, A. (2023). Modeling the relationship between neuronal activity and the bold signal: contributions from astrocyte calcium dynamics. *Scientific Reports*, *13*(1), 6451,

Tewari, S.G., & Majumdar, K.K. (2012). A mathematical model of the tripartite synapse: astrocyte-induced synaptic plasticity. *Journal of biological physics*, *38*, 465–496,

Theodosis, D.T., Poulain, D.A., Oliet, S.H. (2008). Activity-dependent structural and functional plasticity of astrocyte-neuron interactions. *Physiological reviews*, *88*(3), 983–1008,

Vuillaume, R., Lorenzo, J., Binczak, S., Jacquir, S. (2021). A computational study on synaptic plasticity regulation and information processing in neuron-astrocyte networks. *Neural Computation*, *33*(7), 1970–1992,

Wang, J., Tu, J., Cao, B., Mu, L., Yang, X., Cong, M., ... Li, Y. (2017). Astrocytic l-lactate signaling facilitates amygdala-anterior cingulate cortex synchrony and decision making in rats. *Cell reports*, *21*(9), 2407–2418,

Zierenberg, J., Wilting, J., Priesemann, V. (2018). Homeostatic plasticity and external input shape neural network dynamics. *Physical Review X*, *8*(3), 031018,

Zorec, R., Horvat, A., Vardjan, N., Verkhratsky, A. (2015). Memory formation shaped by astroglia. *Frontiers in integrative neuroscience*, *9*, 56,