Astrocyte–neuron communication as cascade of equivalent circuits

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**Abstract**

The propagation of the neural information in the cerebral cortex relies on the transfer of electrochemical impulses and diffusion of neurotransmitter molecules between neuron cells connected in a network through synaptic junctions. In this scenario, increasing interest is growing on the critical role of gliacells, in particular astrocytes, in supporting the neuronal communication. Neuroglias communicate to each other through calcium signaling and are able to sense the activity of adjacent neurons and release gliotransmitter molecules such as glutamate and D-serine, which bind on receptors located on the synaptic terminal of neurons. In other terms, astrocytes can potentially modulate the neuronal activity of adjacent neurons as well as distant neurons through calcium signaling. In this paper, we describe the neuron–astrocyte communication paradigm, first identifying the molecular processes constituting the communication and then representing each process with equivalent electronic circuits, characterized by frequency response. The aim of this work is to propose an alternative tool for the stimulus–response analysis of the astrocyte–neuron system, in particular to quantify the impact of astrocytic stimulation on the natural activity of spiking neurons. The frequency response of the equivalent circuits shows that certain stimulation patterns evoked through the astrocytes are more effective than others and have the potential of significantly alter the neuronal activity.

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**1. Introduction**

Astrocytes are a particular star-shaped type of neuroglias, non-excitable cells which fill the spaces between neurons and support brain functions and intercellular coordination. For large part of the 20th century, the role of glias has been relegated to passive neuronal support in regulating the extracellular potassium \((K^+))\) level \([1]\) (potentially toxic) and in maintaining the ionic balance and for the absorption of exceeding neurotransmitter molecules in the synaptic environment \([2]\). Through the last decades, an increasing number of advanced experiments have shown that gliacells also have a critical impact in actively promoting and modulating the neuronal communication as well as in the neural information transfer \([3–6]\). As with neurons, astrocytes are also connected to each other through gap junctions, forming a large network of cells where the
intracellular communication is mainly performed with the propagation of cytosolic calcium ions concentration, \([Ca^{2+}]_c\), from one cell to another distant cell. This unique communication process is denoted as calcium signaling [7], where the propagation of \([Ca^{2+}]_c\) level is also called calcium wave [8,9]. The primal consequence of the increased intracellular \([Ca^{2+}]_c\) is the release of neurotransmitter molecules from the astrocyte (the term gliotransmitters is more precise when dealing with neuroglia). Main gliotransmitters are glutamate, ATP, D-serine and adenosine [3] which have direct impact on adjacent neurons equipped with compatible receptors located on the cell membrane. Particularly, glutamate is one of the most important and abundant neurotransmitter in the brain and neurons have several types of glutamate-sensitive receptors, such as AMPAR and NMDAR, ionotropic (direct, through ion channels) glutamatergic receptor, and mGluR, metabotropic (indirect, through a messenger) glutamate receptors (refer to Table 1 for a list of the acronyms used in the text).

An important component of the neuronal circuits is the synapse, where a transmitting pre-synaptic neuron releases neurotransmitter molecules which bind on receptors located on the membrane of the receiving post-synaptic neuron. When the astrocyte cell is in the vicinity of the synapse, the concept of tripartite synapse is introduced to underline the presence of the astrocytic terminal in the vicinity of two neurons. The mechanisms behind calcium signaling and release of gliotransmitters are complex and take into account several physiological processes. Alike neurons, astrocytes have on their membrane glutamate-sensitive receptors that once activated by nearby glutamate, trigger intracellular release of \(Ca^{2+}\) from internal stores. This process is carried out through chemical processes involving the presence of inositol 1,4,5-triphosphate (IP3), a secondary messenger molecule with pivotal role in mobilizing calcium ions into the cytosol. The initial elevation of internal \([Ca^{2+}]_c\) evokes further release of calcium ions from stores through the \(Ca^{2+}\)-induced \(Ca^{2+}\) release process (CICR) which enriches the calcium dynamics. In this regard, the dynamics of intracellular \([Ca^{2+}]_c\) can show, under particular conditions, oscillatory behavior with varying amplitude and frequency, also modulated by the level of IP3 [10,4]. All these processes taking place in the astrocyte cell, IP3 production, calcium signaling and intracellular \(Ca^{2+}\) dynamics, are critical in the regulations of astrocytic glutamate release. On one hand, IP3 is allowed to move to adjacent astrocytes through permeable gap junctions, propagating the calcium signaling to distant cells. On the other hand, the elevation of intracellular calcium which follows the IP3 production, triggers the release of astrocytic gliotransmitter molecules that diffuse in the synaptic cleft and finally bind to neuronal receptors. A potential impact of astrocytes is expected on the regulation of brain processes such as plasticity, learning and memory, where gluta
dependent NMDA receptors located on post-synaptic terminals have a leading role. Although the mechanisms concerning \(Ca^{2+}\) dynamics have been described with high accuracy in the literature, the impact of calcium signaling on these processes still remains unveiled and uncertain.

In this paper, we propose an alternative description of the astrocyte–neuron communication systems which encompasses the mechanisms introduced above. In the literature, a limited number of efforts have been dedicated to propose a communication engineering description of the neuronal system. In [11], the authors described the communication between neurons in terms of input/output blocks, with the purpose of nanomachine–neuron communications. A more theoretical analysis of multiple-input single output synaptic communications has been described in [12], whereas a block description of the neuronal process accounting for the stochastic release of neurotransmitters has been proposed in [13], with an extension to the tripartite synapse proposed in [14]. Successful attempts in using intercellular calcium signaling to establish a communication channel for neuronal applications have been reported by Nakano et al. in [15,16]. To our knowledge, no other existing investigations in the engineering of neuronal communication systems have considered the active presence of the astrocyte. We follow an engineering approach where the chemical and ionic quantities are represented with signals, whereas the biological mechanisms are modeled as input–output systems characterized by a frequency response, similarly to electronic communication systems. The equivalent transfer function of each process allows us to exploit the relations between different quantities involved in the coupled astrocyte–neuron entity. From the engineering point of view, the stimulus–response analysis through our proposed approach could contribute in understanding the impact of an artificial stimulation applied to the astrocyte in order to induce a certain response to the neuron. Moreover, our approach can provide further tools for design and implementation of biomimetic devices mimicking the behavior of neurons and astrocytes at micro and nano scale as well as for the implementation of innovative biomedical tools for the stimulation of neurons at nanoscale, as envisioned in [17,18].

The paper is organized as follows. In Section 2, a brief introduction to the tripartite synapse is given along with the description of the intracellular dynamics of molecules and calcium ions in the astrocyte–neuron system. In Section 3, we propose the representation of the tripartite

### Table 1
Acronyms used in the text and input/output signals.

<table>
<thead>
<tr>
<th>Block</th>
<th>Cell</th>
<th>Input</th>
<th>Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>Astrocyte</td>
<td>(V_m)</td>
<td>[IP3]</td>
</tr>
<tr>
<td>(2)</td>
<td>Astrocyte</td>
<td>[IP3]</td>
<td>([Ca^{2+}]_c)</td>
</tr>
<tr>
<td>(3)</td>
<td>Astrocyte/Neuron</td>
<td>([Ca^{2+}]_c)</td>
<td>([Ca^{2+}]_{mGluR})</td>
</tr>
<tr>
<td>(A)</td>
<td>Neuron</td>
<td>(V_r)</td>
<td>([Ca^{2+}]_{mGluR})</td>
</tr>
</tbody>
</table>

1. The cytosol is the inner part of the cell, within the cellular membrane.
2. Neurotransmitters are specific molecules stochastically released by neurons into the synaptic cleft when an action potential reaches the pre-synaptic terminal. Molecules diffuse through the cleft and bind on compatible receptors on receiving neurons, affecting their membrane potential.

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Fig. 1. Schematic diagram of the tripartite synapse. Astrocyte: calcium ions flow into the cytosol from internal IP$_3$/calcium sensitive store (activated by the presence of IP$_3$ and Ca$^{2+}$). Synapse: glutamate is released through exocytosis (membrane fusion) by vesicles located in pre-synaptic and astrocytic terminals and binds to mGluR and AMPAR/NMDAR.

synapse as a signal processing unit, describing the circuital representation of the biological processes in the astrocyte and their effects on pre-synaptic neurons. In Section 4, numerical simulations and results are discussed, while in Section 5 we draw the conclusions with some observations for future works and prospective.

2. Neuron–astrocyte communication

2.1. The tripartite synapse

The tripartite synapse, depicted in Fig. 1, refers to the synaptic area where astrocytes are located in the vicinity of neuronal terminals. Meta-botropic glutamate receptors (mGluR), located on the astrocyte, gather neurotransmitter molecules released by adjacent pre-synaptic neurons consequently to an action potential (spike) generated by soma (the core of neurons) and propagating through the axon (the neuronal communication channel). Alike neurons, astrocytes can release glutamate into the cleft in response to an increased activity of adjacent neurons, acting as feedback units to the neuron, or in response to calcium signaling from other astrocytes. Indeed, astrocytes also communicate to each other through gap junctions, specialized proteins permeable to molecules and ions moving between adjacent cells. Therefore, the astrocytic network provides additional connectivity for the coordination of glias, operating in parallel to the neuronal network. In our scenarios, neurons are described with the two-compartments Pinsky–Rinzel model [19,20], chosen for the accuracy in describing the physiological ionic mechanisms of CA3 neurons.

2.2. The internal dynamics of the astrocyte

The intracellular astrocytic calcium is essentially regulated by the presence of IP$_3$ molecules which trigger the internal release of Ca$^{2+}$ and, in turn, the release/diffusion

3 CA3 stands for Cornu Ammonis 3, a subregion of the hippocampus in the brain.
of glutamate in the tripartite synapse. The production of IP$_3$ is evoked by external events such as mechanical stimulation of the astrocytic membrane [21] or by the presence of glutamate (i.e., from adjacent neurons) binding on astrocytic mGluR [3]. Another source of IP$_3$ is also provided directly from other astrocytes through permeable gap junctions, where IP$_3$ moves from cell to cell. From the astrocytic side, we are interested in describing the dynamics of IP$_3$ concentration, denoted as [IP$_3$], for a given input applied to the cell, observing the response in terms of intracellular Ca$^{2+}$ concentration, denoted as [Ca$^{2+}$]. For the sake of simplifying the notation, the symbols without a specific subscript refer to molecular or ionic concentration in the astrocyte (refer to Table 1).

### 2.2.1. IP$_3$ production in the astrocyte

At molecular scale, what happens in the cerebral cortex is that the production of [IP$_3$] in the astrocyte is triggered by the presence of glutamate (Glu) molecules gathered by groups I and II metabotropic Glu receptors (mGluR) on the membrane surface. In [20,22], according to findings on IP$_3$ lifetime, reported in [23], the IP$_3$ synthesis has been described in a simple manner under the hypothesis that a quantized amount of IP$_3$ molecules are released after the increase of glutamate due to pre-synaptic spiking activity. Thus, the lifetime process of IP$_3$ leads to the following equation:

\[
\frac{d[IP_3]}{dt} = \frac{1}{\tau_{IP_3}} ([IP_3]^* - [IP_3])
\]

\[+ r_{IP_3} \Theta(V_{in} - 35 \text{ mV}) \cdot \text{production} \tag{1}\]

The first term on the right side refers to the IP$_3$ degradation, where [IP$_3]^*$ is the concentration at equilibrium (160 nM from experiments) and $\tau_{IP_3}$ is the degradation time constant (1.0/0.00014 ms). The second term refers to the production of IP$_3$, where $r_{IP_3}$ is the production rate in nM/s, with typical values in the range 0.1–1.5 µM/s to fit a given scenario. Coefficients shown in Eq. (1) have been measured through experiments conducted in [23]. The IP$_3$ production is enabled when the pre-synaptic potential $V_{in}$ is above a given threshold of 35 mV (\( \Theta \) is the Heaviside function). This is clearly an approximation of what actually happens at molecular level, which allows us to relate the production of IP$_3$ with the presence of glutamate in the synapse. However, in our scenario, we are interested in controlling the production process with a given stimulation pattern, in order to analyze the astrocyte as a neuron-independent unit, and observe its stimulus–response characteristic. To this end, we consider a generic signal $V_{in}$ that mimics the neuronal membrane potential and the release of glutamate. The threshold value is not critical and could be assumed equal to zero, though we keep the same 35 mV threshold to encompass the realistic scenario where IP$_3$ production is evoked by pre-synaptic spiking.

#### 2.2.2. The intracellular [Ca$^{2+}$] dynamics

The release of intracellular calcium ions in the astrocyte as well as in other non-excitable cells, is modulated by a number of mechanisms occurring in the cell. Among others, the IP$_3$-dependent release of Ca$^{2+}$ from internal calcium stored is considered the most effective. Once produced in-situ or received from other cells through gap junction, IP$_3$ molecules bind to receptors located on the surface of intracellular calcium stores, namely the sarcoplasmic and endoplasmic reticula (SR, ER), enabling the release of Ca$^{2+}$. Since internal stores are also sensitive to calcium ions, the rise of calcium concentration mobilizes further release of Ca$^{2+}$. This latter process is called Calcium-Induced Calcium Release (CICR). Additional calcium flow occurs spontaneously from ER into the cytosol (leakage flow) while Ca$^{2+}$ dependent ATPase pumps (SERCA) operate in the opposite direction to uptake Ca$^{2+}$ back into the stores for future use (pump flow). During rest conditions, [Ca$^{2+}$] is regulated by the balance between passive leakage from ER and SERCA uptake. When the IP$_3$ production is sustained for a sufficient time, the CICR combined with the SERCA process can lead to oscillations of [Ca$^{2+}$] [10,4]. The dynamics of [Ca$^{2+}$] and the release/uptake processes triggered by IP$_3$ has been described analytically by Sneyd in [21] and Li and Rinzel in [24], proposing a reduction of the De Young model [25] for single pool release of IP$_3$ (assuming the presence of only one internal store). Another model accounting for bidimensional diffusion has been presented in [26]. In our work, we use the Li–Rinzel model, for comparison with the astrocyte–neuron analysis presented in [20,22]. For the sake of simplifying our presentation, we omit further details on the model, already available in the literature (a short description can be found in [22]). However, we can summarize the dynamics of intracellular [Ca$^{2+}$] as follows:

\[
\frac{d[Ca^{2+}]}{dt} = J_{\text{leak}}([Ca^{2+}], [IP_3])
\]

\[+ J_{\text{leak}}([Ca^{2+}]^*) - J_{\text{pump}}([Ca^{2+}]^*) \tag{2}\]

where the three fundamental mechanisms, CICR, SERCA and leaking, correspond to $J_{\text{leak}}$, $J_{\text{pump}}$ and $J_{\text{leak}}$ respectively. For each term, the dependency on either Ca$^{2+}$ or IP$_3$ is emphasized. Since the dynamics of [Ca$^{2+}$] regulates the release of glutamate molecules from the astrocytic terminal, the coupled system IP$_3$–Ca$^{2+}$ impacts on post-synaptic neurons, where glutamate receptors, such as AMPAR and NMDAR, are also located. From the neuroscientific point of view, this effect is of fundamental importance for learning and plasticity processes, however its investigation is out of the scope of this paper.

### 2.3. The coupled [Ca$^{2+}$]–[IP$_3$] dynamics: AM/FM behavior

The joint dynamics of [IP$_3$] and [Ca$^{2+}$] is complex and assumes a wide range of behaviors according to stimulation and cell characteristics. Interestingly, under specific conditions, oscillations in intracellular [Ca$^{2+}$] can arise with variable amplitude and period. Therefore, from a communication perspective, the astrocytic calcium signaling has the ability of encoding information through amplitude and frequency modulation of intracellular
[Ca^{2+}], identified with AM and FM respectively [10,4]. In this respect, the analysis of IP3 production and Ca^{2+} dynamics as described in Eqs. (1)–(2), can reveal the required level of IP3 to evoke AM and FM behaviors in [Ca^{2+}]. A widely used tool to exploit the joint relation of two quantities is the bifurcation diagram, which in our scenario depicts the behavior of [Ca^{2+}] as a function of [IP3] at steady state. If [Ca^{2+}] oscillates, the diagram shows the maximum and minimum values of the wave. An example of AM bifurcation is provided in the left plot of Fig. 2, where the amplitude of [Ca^{2+}] is clearly modulated by the concentration of IP3. On the other hand, the AM period, depicted in the right plot of Fig. 2 for both AM and FM, is less sensitive to [IP3], when compared to FM.4 Hence, two different zones are identified in both cases: (1) non-oscillatory zone, where [Ca^{2+}] can be approximated as a linear or exponential function of [IP3]; (2) oscillatory zone (refer to Fig. 2). The analysis of [Ca^{2+}] oscillations allows us to discriminate between these operating zones and simplify the modeling when Ca^{2+} is approximately linearly or exponentially dependent on IP3.

To provide a visual comparison, the temporal behavior of [Ca^{2+}] for some sample scenarios is depicted in Fig. 3. As we can notice, in AM mode, the oscillation period for different [IP3] is approximately the same, while the amplitude is IP3-dependent. On the contrary, in FM mode we observe a frequency shift depending on the IP3 level, while the amplitude is not affected by [IP3], as expected. For what concerns our work, the bifurcation analysis is a powerful tool to estimate the operative point of the coupled system IP3–Ca^{2+} in the astrocyte, allowing us to simplify the modeling of Ca^{2+} dynamics when possible (e.g., constant oscillation frequency or fixed value for a given IP3). For the interested reader, a detailed description of the biological mechanisms responsible for calcium oscillations is provided in [4].

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4 The FM bifurcation diagram can be obtained using a different set of physiological parameters [4], obtaining a plot similar to AM but with wider aperture.
Fig. 4. Schematic representation of the processes along the communication pathway between astrocyte and pre-synaptic neuron. A stimulation applied to the astrocyte evokes the production of IP$_3$ (block 1). Internal Ca$^{2+}$ is released from internal stores (ER) (block 2), enabling the release of astrocytic glutamate in the cleft, which binds to pre-synaptic mGluRs. In the pre-synaptic side, two additive calcium contributions are identified, one is due to the opening of mGluR receptors (block 3) and one resulting from the spiking activity of the neuron itself through voltage-gated calcium channels (block A).

2.4. The impact of astrocytic Ca$^{2+}$ on the pre-synaptic neuron

In previous sections, we have illustrated the molecular processes that lead to the release of intracellular calcium ions in the astrocytic cytosol resulting from the production of IP$_3$, after stimulation of the cell. At this stage, two distinctive effects can be observed. On one hand, IP$_3$ molecules move to adjacent astrocytes through permeable gap junctions, giving rise to analogous calcium release in other cells, the basis of astrocytic calcium signaling. On the other hand, the increase of internal calcium leads to the release of astrocytic glutamate molecules which bind to receptors on pre-synaptic and post-synaptic neurons located in the tripartite synapse. The main objective of this paper is to describe the mechanisms involved in the communication directed from the astrocyte to adjacent neurons, in particular to pre-synaptic neurons, where neuroglias act as dynamic regulatory unit mediated by IP$_3$ and Ca$^{2+}$. For this reason, we focus our investigation on the impact of the astrocytic activity on the pre-synaptic terminal. In the proposed scenario, we assume that the pre-synaptic spiking neuron generates, independently, a sequence of action potentials which lead to the increase of Ca$^{2+}$ level at the pre-synaptic terminal. The adjacent astrocyte located in the tripartite synapse operates, as described in the previous sections, under the hypothesis that a given stimulation is applied to the cell in order to promote the release of glutamate through IP$_3$ production. Since glutamate-sensitive receptors, i.e., mGluRs, are located on the neuronal surface, the pre-synaptic spiking activity is modulated by the astrocyte. This communication chain between astrocyte and pre-synaptic neuron is depicted in Fig. 4, where each block represents a biological process. With this description, we easily identify the astrocytic processes described in Section 2.2 (blocks 1 and 2) and the neuronal processes (blocks 3 and A). In the latter, the contribution of calcium due to astrocytic glutamate release, denoted with [Ca$^{2+}$]$_{mGluR}$, is described with block (3). Block (A) accounts for the calcium influx into the pre-synaptic terminal when the spiking neuron emits an action potential, referred to as [Ca$^{2+}$]$_{AP}$. A more detailed description of neuronal blocks 3 and A is provided in the following section.

3. The astrocyte as signal processing unit

In Section 2, we have illustrated the basic elements which constitute the communication in the tripartite synapse, proposing a schematic description of the main biological processes and their mutual relations. We focused in particular on the astrocyte, which represents the central component of our analysis. In what follows, we propose a description of the neuron–astrocyte system by means of circuital representations of the biological processes described so far. Taking Fig. 4 as a reference, we define the input/output circuit for each block, (1, 2) and (3, A), identifying and discussing the input and output quantities and their equivalent representation as signals. The benefit of using a circuital representation resides in the possibility of carrying out a stimulus–response analysis for each process through the corresponding frequency response. In these terms, we can observe to what extent an input (e.g. a molecular/ionic concentration) impacts on the output of a given process. For example, an interesting application would be to investigate the sensitivity of mGluR-dependent calcium in the pre-synaptic terminal to variations of IP$_3$ level in the astrocyte. In what follows, we define the circuital description for each block depicted in Fig. 4. The equivalent circuital representation of the whole system is depicted in Fig. 5.

3.1. IP$_3$ production process

Recalling Eq. (1), the production process of IP$_3$ is regulated by two distinct phases: (1) production and rise of [IP$_3$]; (2) degradation and decay of [IP$_3$]. This dynamics is similar to the charge/discharge process found in a parallel RC circuit, where the behavior of the capacitor voltage resembles the dynamics of [IP$_3$]. Resorting to the works reported in [27, 13], we obtain the equivalent circuit depicted in Fig. 5, block (1). However, it is important to notice that the flow of neutral IP$_3$ molecules does not generate an electric current as the flow of polarized ions does. Therefore, the currents flowing in the IP$_3$ circuit should be considered as equivalent molecular currents which enable us to define a circuit representation of the IP$_3$
production process. Rearranging Eq. (1) we obtain the total equivalent current at the input of the circuit, identified as $i_{\text{IP}3}$, and representing the stimulation that induce the production of $\text{IP}_3$:

$$i_{\text{IP}3} = k_i \left( \frac{d[\text{IP}_3]}{dt} + \frac{1}{\tau_{\text{IP}3}}[\text{IP}_3] \right) - \frac{k_i}{\tau_{\text{IP}3}}[\text{IP}_3]^* = \text{input}_{\text{stim}}$$

(3)

where $k_i$ is a coefficient for the conversion from a concentration in Moles ($[\text{IP}_3]$) to a charge in Coulombs ($i_{\text{IP}3}$). The constant term on the right of Eq. (3) depends on the equilibrium concentration of $\text{IP}_3$, as defined in Section 2.2. Now, we compare the expression in Eq. (3) with the total current circulating in a parallel RC circuit, given by the sum of currents flowing through capacitor and resistor:

$$i_m = C \frac{dV}{dt} + \frac{V}{R} = i_{\text{IP}3}$$

(4)

where $i_m$ is the input current applied to the RC circuit, as shown in Fig. 4. Rearranging Eq. (3) to the formula shown in Eq. (4) and converting the voltage $V$ expressed in Volts to the molecular concentration $[\text{IP}_3]$ expressed in Moles, we obtain the equivalent capacitor and resistor for a RC circuit driven by the astrocytic $[\text{IP}_3]$:

$$C_{\text{IP}3} = \frac{k_i}{h_i}; \quad R_{\text{IP}3} = \frac{\tau_{\text{IP}3} h_i}{k_i}; \quad \tau_{\text{IP}3} C_{\text{IP}3} = \tau_{\text{IP}3}$$

(5)

where $h_i$ and $k_i$ are coefficients for the conversion from Moles to Volts and Moles to Coulombs, respectively. To simplify the reasoning, we can assume both coefficients equal to 1. Therefore, the total $\text{IP}_3$ current is given by the sum of the currents flowing through capacitor, $i_{\text{IP}3}$, and resistor, $i_{\text{IP}3}$.

The frequency response of astrocytic $\text{IP}_3$ production module stems from the parallel RC circuit shown in Fig. 5, block (1):

$$H_1(f) = \frac{1 + j2\pi f R_{\text{IP}3} C_{\text{IP}3}}{1}.$$

(6)

The normalized gain $I_{H_1}(f)$ is

$$I_{H_1}(f) = \frac{|H_1(f)|}{\max(|H_1(f)|)}.$$  

(7)

The group delay $\tau_{H_1}(f)$ is

$$\tau_{H_1}(f) = -\frac{d\phi_{H_1}(f)}{df},$$

(8)

where $\phi_{H_1}(f)$ denotes the phase, defined as

$$\phi_{H_1}(f) = \tan^{-1} \left( \frac{\Im(H_1(f))}{\Re(H_1(f))} \right).$$

(9)

3.2. Cytosolic $[\text{Ca}^{2+}]$ release process

In Section 2.2.2, we have introduced the dynamics of the astrocytic intracellular $[\text{Ca}^{2+}]$ regulated by $[\text{IP}_3]$, where the AM/FM behavior of calcium has been discussed. Recalling the model in Eq. (2), an equivalent circuit representation is not straightforward because of the presence of two different calcium behaviors, constant and oscillatory (as depicted in Figs. 2 and 3). For the sake of simplifying the system, we analyze separately the two phases of the release process. In the non-oscillatory zones, the intracellular $[\text{Ca}^{2+}]$ at steady state can be approximated by a linear or exponential function of $[\text{IP}_3]$. In this case, the $\text{Ca}^{2+}$ release process can be described through a proportionality constant which relates the input $[\text{IP}_3]$ to the output $[\text{Ca}^{2+}]$ (refer to Fig. 4):

$$[\text{Ca}^{2+}] = K_{\text{Ca-IP}_3} [\text{IP}_3] + [\text{Ca}^{2+}]_{\text{eq}}$$

(10)

where $K_{\text{Ca-IP}_3}$ is the proportionality constant retrieved from the non-oscillatory zones (Fig. 2 for the AM scenario). The term $[\text{Ca}^{2+}]_{\text{eq}}$ takes into account the initial condition of the astrocytic intracellular $[\text{Ca}^{2+}]$ at equilibrium (typically in the range $0.1 \div 0.3 \mu\text{M}$).

For what concerns the oscillatory phase, $[\text{Ca}^{2+}]$ shows oscillations when $[\text{IP}_3]$ is in a range of values which
depends on the physiological parameters of the cell. As an example we refer to Fig. 2, where the bifurcation diagram for the AM mode is depicted. The AM scenario is particularly interesting because the frequency in less sensitive to the variations of IP$_3$ level, allowing a more stable modeling at a given oscillation frequency, assumed constant for the observation interval. In this case, oscillations are observed in the range [IP$_3$] $\in [400-600]$ nM where the amplitude of [Ca$^{2+}$] is modulated by the increasing [IP$_3$]. The frequency is less sensitive to the level of IP$_3$ (refer to Fig. 2) and can be considered stable. Under these conditions, the release process in the oscillatory zone can be represented as an oscillator which resonates at the oscillation frequency, followed by a gain circuit that shapes the amplitude as needed. It is worth noticing that the resonating frequency assumes very low values, below 1 Hz, since calcium release is a much slower process (seconds) compared to the neuronal spiking (in the range of milliseconds).

To represent the oscillatory scenario in Fig. 2 we consider a simple Wien bridge oscillator which provides an oscillating output signal (a sine-wave). The equivalent circuit of block (2) is depicted in Fig. 5-(2). Note that [IP$_3$] ranging from 400 nM to 600 nM is here identified as a power supply voltage driven by the output signal from block (1). In terms of technical details concerning the electronic configuration of the circuit depicted in Fig. 5-(2), note that $R_0 = R_1/2$, while $R_{r,cy}$ and $C_{sw}$ are selected in accordance to the oscillating frequency, i.e.:

$$f_0 = \frac{1}{2\pi R_{sw} C_{sw}}.$$ \hspace{1cm} (11)

An equivalent circuit representation of cytosolic [Ca$^{2+}$] production depends on the operating phase, constant or oscillatory. When modeling the non-oscillatory phase, [Ca$^{2+}$] can be approximated by a linear function, so the frequency response is also constant, i.e.,

$$H_2^{(0)}(jf) = \text{constant} = K_{Ca-IP_3} \hspace{1cm} (12)$$

where $K_{Ca-IP_3}$ has been defined in Eq. (10). At oscillatory phase, however, the frequency response stems from the Wien bridge oscillator which resonates at a given frequency ($f_0 = 1/(2\pi R_{sw} C_{sw})$):

$$H_2^{(0)}(jf) = \frac{j2\pi f R_{sw} C_{sw}}{1 - (2\pi f R_{sw} C_{sw})^2} + j6\pi f R_{sw} C_{sw}.$$ \hspace{1cm} (13)

3.3. Glutamate binding on pre-synaptic mGluR

A primary consequence of the augmented concentration of glutamate in the synapse is the impact on the neural activity of nearby neurons, where glutamate-sensitive receptors are located, i.e., mGluR (pre-synaptic neuron), AMPAR and NMDAR (post-synaptic neurons). Since NMDAR are the primal source of Ca$^{2+}$ in post-synaptic neurons and critical for plasticity processes such as long-term depression (LTD) and long-term potentiation (LTP), the astrocytic feedback is expected to have a significant impact on post-synaptic neurons. However, we focus on the pre-synaptic side and although we do not describe in detail the glutamate release process, we illustrate the basic mechanism that relates the astrocytic [Ca$^{2+}$] with glutamate binding on pre-synaptic mGluRs. In this case, the rise of calcium level in the pre-synaptic terminal due to mGluR activation can be determined mathematically from available data [28]. In particular, from [22] we obtain:

$$\frac{d[Ca^{2+}]_{mGluR}}{dt} = -\gamma_1[Ca^{2+}]_{mGluR} + \alpha_1[Ca^{2+}]_{mGluR}[\Theta([Ca^{2+}] - 196.4 \text{ nM}) \hspace{1cm} (14)$$

where [Ca$^{2+}]_{mGluR}$ is the calcium increase due to mGluR activation, whereas [Ca$^{2+}$] is the cytosolic calcium level in the astrocyte as determined in Eq. (2) (we remind the reader that for astrocytic molecular and ionic concentrations we omit the subscript). The constants $\alpha_1$ and $\gamma_1$ refer to the production and decay rate of Ca$^{2+}$, respectively, where the production rate is assumed linearly dependent on [Ca$^{2+}$] and triggered when the astrocytic [Ca$^{2+}$] exceeds a given threshold, obtained from the same data [28]. Similarly to the IP$_3$ production/degradation process, we can represent the mGluR-dependent calcium process with an equivalent RC circuit with charge/discharge determined by the decay/production dynamics of [Ca$^{2+}]_{mGluR}$. Resorting to Eqs. (4) and (14), we obtain the equivalent capacitor and resistor for the mGluR calcium contribution:

$$C_{mGluR} = \frac{k_m}{h_m} \hspace{1cm} R_{mGluR} = \frac{h_m}{k_m} \gamma_1.$$ \hspace{1cm} (15)

where coefficients $h_m$ and $k_m$ convert from Moles to Volts and from Moles to Coulombs, respectively, to ensure that the quantities are consistent with voltage and current in the RC circuit. The equivalent circuit is depicted in Fig. 5-(3). Analogous to the IP$_3$ production/degradation process, the frequency response of the block describing the calcium increase in the pre-synaptic neuron due to the activation of mGluRs stems from the parallel RC circuit:

$$H_3(jf) = (1 + j2\pi f R_{mGluR} C_{mGluR})^{-1}.$$ \hspace{1cm} (16)

3.4. Total pre-synaptic [Ca$^{2+}$]

In the pre-synaptic terminal, we can identify two primal contributions to the concentration of calcium ions. The first one, identified with [Ca$^{2+}]_{AP}$, is due to the action potentials arriving at the pre-synaptic terminal and enabling the release of calcium ions through voltage-gated calcium channels. The other calcium source, denoted as [Ca$^{2+}]_{mGluR}$, is given by the augmented astrocytic activity in terms of glutamate release activating the pre-synaptic mGluRs (Section 3.3). Then, the total pre-synaptic level of calcium ions, [Ca$^{2+}]_{pre}$ can be approximated as follows [22]:

$$[Ca^{2+}]_{pre} = [Ca^{2+}]_{AP} + [Ca^{2+}]_{mGluR}.$$ \hspace{1cm} (17)

The dynamics of [Ca$^{2+}]_{AP}$ is based on the same concept we used for [IP$_3$] and [Ca$^{2+}]_{mGluR}$, where the increase in concentration is triggered when the pre-synaptic membrane potential exceeds a given threshold:

$$\frac{d[Ca^{2+}]_{AP}}{dt} = -\gamma_2[Ca^{2+}]_{AP} + \alpha_2[\Theta(V_m(t) - 35 \text{ mV}) \hspace{1cm} (18)$$

The terms $\alpha_2$ and $\gamma_2$ denote the production and decay rate respectively, similarly to Eq. (14) ($\alpha_2 = 4.27 \times 10^5$).
Fig. 6. The electronic circuit of block (2) mimics the oscillatory behavior of \([\text{Ca}^{2+}]\) observed when a constant stimulation is applied to the astrocyte for 80 s. The measured oscillation frequency is 0.0875 Hz, driven by the level of IP_3 obtained from block (1). Phase shift and gain have been added to the output of block (2) to match the actual amplitude of the calcium wave signal (values are chosen empirically according to the given scenario). The output of block (1) is also shown for comparison. We notice the close similarity between the electronic output and the observed calcium wave.

10^6 \text{nM ms}^{-1} and \(\gamma_2 = 10 \text{ ms}^{-1} \) [22]), which make the charge–discharge of \([\text{Ca}^{2+}]_{\text{AP}}\) phase very fast in order to follow the rapid discharge pattern of the action potential train (\(V_s\)). However, we can still represent \([\text{Ca}^{2+}]_{\text{AP}}\) with an equivalent RC circuit, where the equivalent capacitor and resistance are defined as:

\[
C_A = \frac{k_a}{h_a} \quad R_A = \frac{h_a}{k_a} \gamma_2 \quad R_A C_A = \gamma_2.
\] (19)

The coefficients \(h_a\) and \(k_a\) take into account the unit conversion as discussed previously in Sections 3.1–3.3. The equivalent circuit is depicted in Fig. 5-(A) and denoted as block-(A). The frequency response of block (A) is regulated by the same dynamics of block (1) and (3):

\[
H_A(jf) = (1 + j2\pi f R_A C_A)^{-1}.
\] (20)

4. Numerical results

In this section we show the behaviors of the biological processes described in Section 3 through mathematical models and their equivalent circuital representation. First, we discuss the time behavior of the quantities involved in the astrocyte–neuron system, from the initial stimulation applied to the astrocyte at the input of block (1), to the final calcium elevation observed in the pre-synaptic terminal at the output of block (3) and (A). Finally, we present the frequency response of each biological process through the electronic representation proposed in this paper. The aim is to compare the time behavior with the frequency response of the circuital representation, discussing the relations between different blocks.

4.1. Time behavior of the input/output signals

Starting from the leftmost side of the block description in Fig. 4 and the circuital representation in Fig. 5, we show the charge–discharge behavior of astrocytic \([\text{IP}_3]\) and \([\text{Ca}^{2+}]\) observing the input/output quantities driving blocks (1) and (2). To this end, we propose a scenario where a constant stimulation (input) is applied at the input of block (1) for 80 s in order to trigger the production of IP_3 molecules. As discussed before, in a realistic system the production of IP_3 is originated through mechanical stimulation, injection or after the glutamate release of the adjacent pre-synaptic neuron [22,21]. However, we model this mechanisms with a constant input to simulate the raising of \([\text{IP}_3]\) in the cell. The time behaviors of \([\text{IP}_3]\) and \([\text{Ca}^{2+}]\) are depicted in Fig. 6. As we can notice, when the stimulation is interrupted at \(t = 80\) s, the level of IP_3 decreases following the discharge constant \(\tau_{\text{IP}_3}\). For comparison, the output of the RC circuit in block (1) is also shown with circles, observing that the dynamics of the voltage across the capacitor, Eq. (4), is the same observed for \([\text{IP}_3]\), Eq. (1). In this particular scenario, the elevation of astrocytic \([\text{IP}_3]\) induces an oscillatory behavior of \([\text{Ca}^{2+}]\), with measured frequency equal to 0.875 Hz. As shown in Fig. 6, the calcium oscillation is characterized by a regular sinusoidal behavior which can be synthesized by the Wien-bridge circuit in Fig. 5-(2).

In what follows, we illustrate two sample scenarios to show the impact of the astrocytic activity on the pre-synaptic terminal, in particular concerning the \(\text{Ca}^{2+}\) elevation due to astrocytic glutamate release (refer to Fig. 5-(3)). In the first scenario, we assume that a stimulation is applied periodically at the input of block (1) for 60 s, represented in our description with a square wave signal. In Fig. 7, the quantities are represented as signals and depicted in a single plot for the sake of comparison. First, we notice that the production of IP_3 is triggered by the given stimulation pattern (block 1). Then, the intracellular release of \(\text{Ca}^{2+}\) is enabled by the rise of IP_3 which evokes the CICR process (block 2). We note in passing the visible calcium oscillations as observed in the
previous scenario reported in Fig. 6. Finally, the increased Ca$^{2+}$ level promotes the release of astrocytic glutamate molecules which bind on pre-synaptic mGluRs, enabling the increase of Ca$^{2+}$ in the neuron (block 3). Parameters in Eq. (1) have been chosen to simulate a maximum level of IP$_3$ production around the value of 0.45 μM. However, this parameter can be selected accordingly to fit the level of stimulation.

In the second scenario, the stimulation patterns is active for shorter time, 10 s, whereas the inactive phase is longer, 20 s. Then, the stimulation is represented with a square wave with duty cycle equal to 30%. The quantities observed in the astrocyte are depicted in Fig. 8, where we observe the regular influx of Ca$^{2+}$ into the neuron through mGlu receptors. As we notice, the behavior of [IP$_3$] and [Ca$^{2+}$] is affected by the stimulation pattern. When compared to the previous scenario with longer stimulation, the level of Ca$^{2+}$ has no oscillatory behavior and shows an higher average level, promoting glutamate release for a longer interval.

Upon the considerations discussed so far, we finally show the impact of the astrocytic activity on the total Ca$^{2+}$ level in the pre-synaptic terminal, under the hypothesis that the pre-synaptic neuron has a constant spiking activity. We consider two different stimulation scenarios,
proposing a comparison between the intracellular Ca\(^{2+}\) level in the pre-synaptic neuron without and with astrocytic activation. First, we simulate an active CA3 neuron characterized by a spiking frequency of 30 Hz (30 action potentials emitted per second). The neuronal dynamics follow the physiological Pinsky–Rinzel model \[19\]. Then, we compute the contribution of Ca\(^{2+}\) due to the spiking activity, that is \([\text{Ca}^{2+}]_{\text{AP}}\), as described before and represented by block-(A). In addition to the normal neuronal activity, we consider an active astrocyte located in the tripartite synapse, allowed to release glutamate in the vicinity of the pre-synaptic CA3 spiking neuron. The astrocyte is activated according to a given stimulation pattern with the aim to induce the production of IP\(_3\) and trigger the internal CICR process and the consequent astrocytic glutamate release. This event, as described in Sections 2.4 and 3.3, evokes a significant rise of calcium concentration in the adjacent neuron, quantified with \([\text{Ca}^{2+}]_{\text{mGluR}}\), represented by block-(3). The calcium contribution \([\text{Ca}^{2+}]_{\text{mGluR}}\) adds to the level of calcium observed in the neuron under spiking conditions, i.e., \([\text{Ca}^{2+}]_{\text{AP}}\).

As reference, we consider the same scenarios depicted in Figs. 7 and 8. In the first scenario, depicted in Fig. 9, we applied the same stimulation pattern of Fig. 7, where a constant astrocytic activation is sustained for 60 s and repeated at \(t = 120\) s. In the upper plot, we notice the impulsive calcium level due to voltage gated channels opened after an action potential is emitted. In the lower plot, the contribution \([\text{Ca}^{2+}]_{\text{mGluR}}\) (bottom-right plot of Fig. 8) is summed to \([\text{Ca}^{2+}]_{\text{AP}}\) to obtain the total calcium level in the pre-synaptic terminal. In correspondence of an increase of astrocytic calcium and the consequent glutamate release, the level of \([\text{Ca}^{2+}]_{\text{mGluR}}\) increases with a much slower dynamics (seconds) when compared to the voltage-gated calcium level \([\text{Ca}^{2+}]_{\text{AP}}\) (milliseconds). The same reasoning applies to the second scenario, depicted in Fig. 10 and based on the stimulation pattern shown in Fig. 8, where a shorter astrocytic activation is considered (each activation pulse lasts 10 s).

4.2. The frequency response of equivalent circuits

The alternative representation of the astrocytic feedback processes including the cytosolic IP\(_3\) production, cytosolic calcium release, glutamate release and glutamate binding to pre-synaptic mGluR, has been described in Section 3 through adequate electronic circuits shown in Fig. 5. As an effective tool for giving an insight into the performance of glia–neuron communication, we inspect the frequency response (in terms of normalized gain and group delay) of each individual circuit.

The normalized gain of IP\(_3\) production block \((1)\) is computed from Eq. \((7)\) for a frequency range from 0 Hz to 10 Hz and degradation time constant \(R_{\text{IP}_3}C_{\text{IP}_3} = \tau_{\text{IP}_3} = 1/0.00014\) ms \([22]\). The normalized gain is shown in Fig. 11 demonstrating the filtering role of the production block. Hence, the production block generates \([\text{IP}_3]\) with a slow dynamics. The gain of the succeeding block \((2)\) operating in the non-oscillatory phase is constant. In the oscillatory phase, however, the gain is computed from Eq. \((7)\) inserting \(H_2^o(\omega)\) instead of \(H_1^o(\omega)\). Since the calcium dynamics should be modeled as a slow process, the resonating frequency assumes very low values. For illustrative purposes, we plot the normalized gain of Wien bridge oscillator for two different scenarios. In the first one, the oscillator has been configured to generate an oscillatory signal with frequency \(f_0 = 0.1\) Hz to emulate \([\text{Ca}^{2+}]\) oscillations in AM mode when \([\text{IP}_3]\) = 650 nM (refer to Fig. 2). The second scenario considers an oscillatory signal

\[\text{Fig. 9.} \quad \text{Scenario 1: the astrocyte is activated for 60 s with a square wave signal, as illustrated in Fig. 7. Upper plot: every time an action potential reaches the pre-synaptic terminal, a rapid increase of calcium level is observed in the terminal (values are normalized to the maximum). Lower plot: in correspondence of astrocytic glutamate release, further calcium ions flow into the terminal, increasing the ionic concentration.}\]
Fig. 10. Scenario 2: the astrocytic activation is sustained for a shorter period of time, 10 s, as illustrated in Fig. 7.

Fig. 11. Frequency response of the three equivalent blocks. Block 2 operates in two resonant frequencies: 0.1 Hz (oscillation period = 10 s) and 0.04 Hz (period = 25 s) (refer to Fig. 5).

with $f_0 = 0.04$ Hz = 1/25 s to represent FM oscillations when $[I_{P2}] = 650$ nM (Fig. 2). Eventually, the normalized gain of the equivalent block representing the rise of $[Ca^{2+}]_{mGluR}$ in the pre-synaptic terminal is computed from Eq. (7) inserting $H_3(jf)$ instead of $H_1(jf)$ for $K_{mGluR}C_{mGluR} = \tau_{mGluR}/\gamma_1 = 48$ s [22]. The normalized gain is shown in Fig. 11. The block also acts as a low-pass filter. Although $[Ca^{2+}]$ from the oscillator usually has a very low frequency, $[Ca^{2+}]_{mGluR}$ seems to have even slower dynamics.

The group delays of individual blocks are computed from Eq. (8) inserting the corresponding phases. Individual delay functions are depicted in Fig. 12. At very low frequencies up to 0.1 Hz, the delay incurred by each individual block is non-linear and calcium signaling is distorted. For frequencies larger than 0.1 Hz, the astrocyte modulation of the neuronal activity does not incur the distortion and the process of astrocyte modulation can be observed as instantaneous.

Block A, depicted in Figs. 4 and 5, represents the calcium release process through voltage-gated calcium channel subsequent to the arrival of the action potentials to the pre-synaptic terminal. Since we thoroughly discussed this process in [14], we omit detailed discussion in this paper.

Fig. 12. The group delay of the three equivalent blocks is depicted for the same scenario in Fig. 11.
and only show the corresponding normalized gain and group delay functions (Fig. 13) to encompass the overall process of astrocytic modulation of neuronal activity. The block A acts as a low-pass filter but with larger cut-off frequency compared to the previously described blocks. The system frequency here refers to the temporal changes of the spiking rate function. In a bandwidth of interest, the block incurs a constant delay of \( 6 \mu s \).

### 4.3. Time-frequency analysis

In the last part of the discussion, we interpret the frequency response of the electronic circuits in Fig. 5. As an example, we take into account the response of block (1) corresponding to the production of IP\(_3\) molecules, which also represents the first step of the communication chain astrocyte–neuron (pre-synaptic). Let us consider the gain of the response concerning block (1) depicted in Fig. 11 (black line). As we notice, the frequency components higher than 0.1 Hz are strongly attenuated similarly to a low-pass filter centered in 0.01 Hz. The filtering effect of the circuit matches the physiological behavior of the IP\(_3\) production process, where the slow dynamics of the process is not sensitive to fast variations of the input stimulation. To graphically show the filtering effect, we applied a sine wave signal as a direct input to block (1) to drive the IP\(_3\) production process. Four different input frequency values have been used, \( f_{in} = [0.01, 0.1, 1, 10] \) Hz, whereas the filtered signals are depicted in Fig. 14. The first observation concerns the output level with respect to the basal IP\(_3\) level at rest, 0.160 \( \mu \text{M} \). When the frequency is relatively low, compared to the center value of 0.01 Hz, the input signal is slow enough to drive the production of IP\(_3\) up to values higher than two times the rest level (red dashed lines). On the contrary, for higher frequency, e.g. 1 Hz and 10 Hz, the input signal is too rapid, not allowing the slower production process to follow fast variations of the input. In fact, the corresponding IP\(_3\) level remains in the vicinity of the basal level.

A second observation concerns the effect on the subsequent blocks of the chain. When the IP\(_3\) production process is not able to follow the variations of the input stimulation, the rise of IP\(_3\) is limited and not adequate to promote the release of cytosolic Ca\(^{2+}\) from internal calcium stores. This effect can be observed in Fig. 15, where the behavior of block (1) and block (2) are depicted for two input frequency values, \( f_{in} = [0.01, 1] \) Hz. As we notice, when the input frequency is higher, the low IP\(_3\) level produced by block (1) is not sufficient to induce the release of Ca\(^{2+}\) in the astrocytic cytosol.

From the engineering point of view, the frequency stimulus–response analysis allows us to avoid stimulations
Fig. 15. The output of blocks (1) and (2) for two different frequency values of the signal at the input of block (1). Red lines represent the basal level of IP$_3$ and Ca$^{2+}$ at rest, used as reference for comparison purpose.

that are not suitable to trigger the astrocytic action. The proposed analysis and reasoning can be applied for a wide range of scenarios and for each biological process described in Fig. 5.

5. Observations and conclusions

Upon the considerations discussed in the paper, it has been shown that the intracellular calcium dynamics of astrocytes is a critical process with significant impact on the regulation of the neuronal activity. In a tripartite synapse, the astrocyte cell actively interacts with the neuronal response of adjacent pre-synaptic neurons, providing a feedback which is believed to regulate several brain processes. We investigated this special link between neuron and glia cells from the mathematic and electronic point of view, providing an alternative representation of the glia–neuron system. Electronic circuits able to mimic the intracellular processes and to emulate the dynamics of intracellular calcium ions, such as calcium oscillations and IP$_3$-dependent Ca$^{2+}$ release, have been introduced. The behavior of each process has been analyzed in terms of frequency response and gain, offering results which matches the expected behavior of the related chemical processes. In particular, the stimulus–response analysis has been provided for different stimulation patterns applied to the astrocyte, observing the consequent variation of Ca$^{2+}$ level in the pre-synaptic spiking neuron. In this respect, the potential applications of the proposed approach are manifold. On one hand, the astrocyte can be used to stimulate indirectly adjacent neurons. To this end, understanding the relations between astrocytic stimulation and neuronal response, as described in our work, is critical. Each electrochemical process involved in the communication operates as a filter, preventing the propagation of rapid variations of the molecular concentrations in the astrocyte. In a scenario where the astrocyte is externally stimulated, understanding this filtering behavior can give us useful insight in defining the most suitable stimulation pattern to obtain a certain effect on adjacent pre-synaptic neurons. On the other hand, the description of the astrocyte–neuron system with an engineering approach is of interest in the design of bio-inspired circuits and techniques attempting to mimic the neuronal processes, including the astrocytic network. Possible neuromorphic devices can also be benefited from the modeling of the neuronal and astrocytic processes through elementary input/output circuits.

References


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