Astrocytes in modulating subcellular, cellular and intercellular molecular neuronal communication

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ABSTRACT

Astrocytes are one of the most abundant cell types in our brain. They modulate the brain homeostasis and play a role in the synaptic signalling and thus the molecular propagation inside the brain. Moreover, they form communication networks that co-localise with the neuronal networks with comparable topological complexity. There is an increasing piece of evidence that astrocytes are important in plasticity and learning from the level of the single synapse to the entire network. Moreover, several diseases are molecular communications on different scales from the synaptic to network level.

CCS CONCEPTS

• **Applied computing** → **Life and medical sciences**; *Telecommunications*; *Computational biology*; *Systems biology*.

KEYWORDS

Astrocytes, Neurons, Networks, Molecular communications, Modulation

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1 INTRODUCTION

Recent evidence has strengthened the concept of the multilevel interplay between neurons and astrocytes. Astrocytes play a wide role on neuronal homeostasis and are capable of modulating the neuronal plasticity and learning. However, there is uncertainty on the molecular signalling mechanisms and their importance on neuronal functions. Understanding the underlying mechanisms is crucially needed as astrocytes are emerging as a culprit to several neuronal diseases from Alzheimer's to epilepsy.

Astrocytes are glial cells responsible for various tasks, including ion buffering, neurotransmitter and energy homeostasis in the brain. Astrocytes communicate with neurons by taking up and releasing excitatory and inhibitory molecules to regulate synaptic functions [11, 34]. This regulation occurs at the so-called tripartite synapse, where an astrocyte process engulfs the neuronal synapse [1] (Fig 1A). The astrocytic gliotransmission - that refers to the modulation of synaptic signalling by astrocytic calcium-mediated messengers like glutamate - in neuronal communication has evoked increasing interest in neuroscience. However, the role of gliotransmission is still controversial as some works discuss in favour or against it [11, 34].

There are several molecular communication pathways between neurons and astrocytes (Fig. 1A-B), on the intracellular level within astrocytes (Fig. 1C), and between the astrocytes through the gap junctions (Fig. 1D). Thus, further studies in molecular communication systems are crucial to characterise the information flow using molecules between astrocytes and astrocytes-neurons in various temporal and spatial levels. One astrocyte can connect to up to 2 million neuronal synapses [31] – and each astrocyte connects to several other astrocytes (Fig. 2), creating a large network that allows the flow of information carrying molecules. Astrocyte use Ca^{2+} as mediator for the regulation and release of various other molecules, including ions, which influence synaptic neurotransmitter release. Most of the Ca^{2+} activity happens in the astrocyte cytosol with the diffusion and reaction among ion channels and various organelles. The Ca^{2+} activity can extend to the branches, to the entire astrocyte or even into the astrocyte network (Fig. 1C-D).

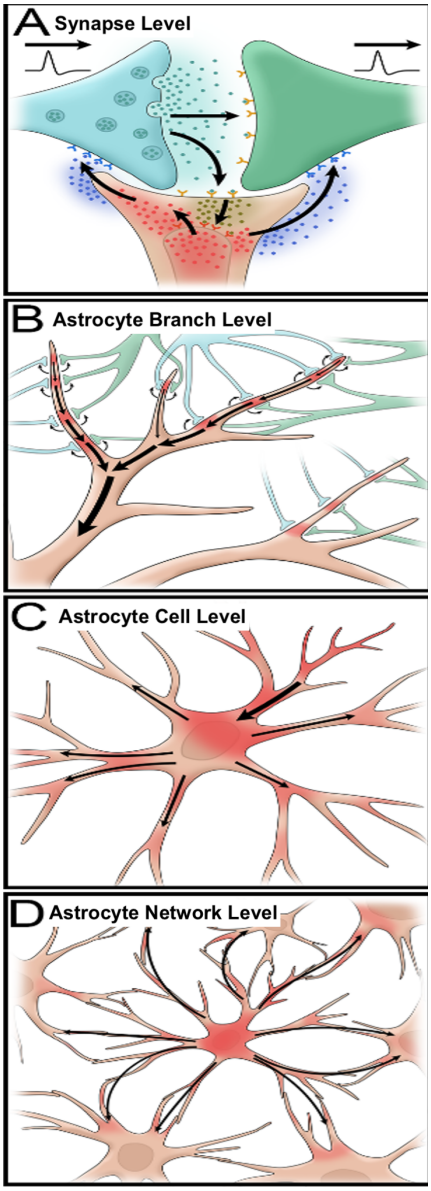

Figure 1: Molecular communication scales in neuron-astrocyte communications. A) Synapse level: the presynaptic neuron (in cyan) and the post-synaptic neuron (in green) are encapsulated by the astrocyte (in orange). The presynaptic neuron releases neurotransmitters (cyan dots), which bind the receptors on the post-synaptic and astrocytic membranes. In response to the binding, a cascade of chemical reactions (in green) lead to the elevation of intracellular Ca^{2+} levels (in red). The Ca^{2+} concentration rise triggers the release of gliotransmitters and ions (in blue), which in turn bind to the neuronal membranes modulating the neuronal activity. B) Astrocyte branch level: The local intracellular Ca^{2+} concentration rises in the astrocyte branch, as well as other ionic transients, can accumulate and lead to the propagation of Ca^{2+} transients. C) Astrocyte cell level: Ionic transients and small molecules can diffuse in the whole astrocyte. D) Astrocyte network level: The molecules can also diffuse in the whole astrocyte network through the gap junctions.

The composition of the macroscale spaces in the brain depends on the ratio between neurons and astrocytes, since they communicate in different ways that ultimately lead to different communication profiles when looking at the network level. The astrocyte-neuron ratio in rodents is 1:2 and can peak to 1.4:1 in the human cortex [27]. Moreover, human astrocytes are far more complex and more abundant in our brain than the astrocytes in other animals [29, 38]. Thus, astrocytes can heavily contribute to the modulation of neuronal activity and complex brain functions in four different levels that comprise different molecular communication channels (Fig. 1). This modulation can be mediated through the direct release of gliotransmitters in synapses, which will affect the plasticity of neuronal connections. In addition, this release can be dependent on the computational behaviour of the Ca^{2+} signalling channels in neurons [17, 31], which results in the concept of brain metaplasticity [14, 25].

Molecular communications is used as a tool to analyse biological intercellular communication as a communication system, which helps to characterise the causal relationship between a transmitter cell, a biological channel and a receiver cell. Approaches from the field of molecular communications can bring light to the modulatory role of a transmitter astrocytes in neural communications, which may provide interesting methodology tools to acquire the analysis on the various non-linearities within this system, such as the Ca^{2+} and glutamate release. The exact characterisation of these non-linearities is an open question where many different astrocytes pathways and mechanisms cannot be fully investigated in-vitro or in-vivo. Computational modelling thus becomes a central method to assess, quantify and analyse astrocyte-neuron communication. In this paper, we explore the various critical physiological characteristics in different levels of astrocyte molecular signalling, including the synapse level, the astrocyte branch level, the astrocyte cell level, as well as the astrocyte network level. We further analyse these scenarios by investigating what type of modelling methodologies are proposed in the literature, what type of modulation is used, and the future research directions in this area.

2 COMPUTATIONAL METHODS ASSESSING ASTROCYTE MOLECULAR SIGNALLING

The roles of astrocytes are assessed using in-vivo, in-vitro and in-silico approaches. In-vivo animal studies can reveal the actual mature neuronal system function. However, assessing the molecular communication level is extremely difficult. In in-vitro assays, the interplay of astrocytes and neurons in various levels are easier to assess. In-vitro cell cultures and modern organ-on-chip technologies provide the best control and observation. These technologies include, e.g., microfluidics [24], neuronal and astrocyte patterning, electric, light and chemical stimulation and sensing, including Ca^{2+} imaging [28]. These tools assess molecular communications in larger branches. However, assessing the signalling in small branches of astrocytes and their interaction with the synapses is well warranted. Generally, the computational simulations and in-silico models – including our previous work [5, 21] - are concentrating on some specific scales and lack either biophysical or geometrical details in models and/or miss a detailed description of the ionic

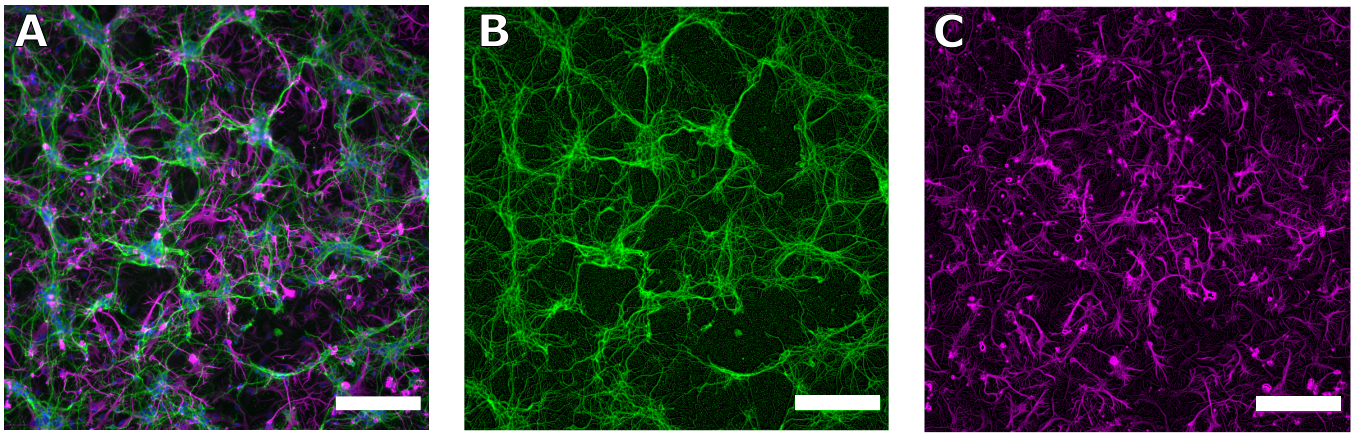

Figure 2: In-vitro neuron-astrocyte network. A) Immunocytochemistry image of a neuron-astrocyte network. Neurons are stained with MAP2 (Microtubule Associated Protein 2) in green, and astrocytes are stained with GFAP (Glial Fibrillary Acidic Protei) in magenta. Cell nuclei are stained with DAPI (4,6-diamidino-2-phenylindole) in blue. B) shows the neuronal network and c) the astrocyte network highlighting the almost equally complex cellular morphology and network topology. The image processing code for MATLAB was adapted from [26]. The scale bar (200 μm) of the images are marked in white.

communication and homeostatic pathways important in the function of astrocytes and the neuronal communication.

2.1 Synapse Level

Together with a pre- and postsynaptic neuron, an astrocyte forms the tripartite synapse, controlled through transmitter molecules and astrocytic local calcium signaling [1] (Fig. 1A). Several biophysical computational models on tripartite synapses exist [23, 30]. In addition to gliotransmission, astrocytes play a role on ion buffering and homeostasis and have been shown to contribute to the formation and pruning of synapses [7]. As some of the volumes, e.g. perisynaptic astrocytic processes, and molecular concentrations, e.g. Ca^{2+}, are very small, an important molecular communication level to consider is the role of diffusion and availability of molecules as shown in in-silico by Denizot et al. [10].

2.2 Astrocyte branch level

One astrocyte can interact with a large group of synapses locally - from several hundred thousand to millions of synapses per astrocyte in the human brain [29]. The combined synaptic trafficking leads to a local astrocyte Ca^{2+} rise that can also spread in the astrocyte processes, as shown in in-vitro and in-vivo recordings [35]. However, the mechanisms, and the effects of branch geometry and formation, are elusive [6] and corresponding biophysical models are now emerging. Emerging biophysical finite element model (FEM) with simple 2D geometry of the branches has been presented by e.g., [18] suggesting that branch morphology plays a crucial role as a channel for molecular communication modulator. Fig 2 shows the various morphological complexity for astrocytes and neurons, as the neurons would have different branches size as opposed to astrocytes, which would have a "star" like shape. However, the astrocytic morphology shapes the way molecules are propagated within and outwards the cell.

2.3 Astrocyte cell level

The individual synaptic-induced Ca^{2+} rises can accumulate in the astrocyte and diffuse throughout the cell [37]. In-vitro recordings demonstrate that stimulated astrocyte calcium dynamics can induce gliotransmission [20]. The astrocyte activation can trigger gliotransmitter release in the stimulated synapses as well as in a distal area. Many compartmental-type biophysical models of astrocyte Ca^{2+} have been presented [9, 16]. However, the morphology has been only considered in a few models [13, 18, 33]. On a single astrocyte level, we have developed a finite element model of the calcium and IP_3 signalling in the complex astrocyte geometry driven by the neurotransmitter input from the synapses. Our results on the single-cell level highlight the role of astrocyte morphology on the astrocyte molecular communications [18]. Savtchenko et al. [33] tool ASTRO combines the characteristic astrocytic morphological features with the functional features at different scales, from the branch level to the whole-cell level. ASTRO is a multi-compartmental model that reproduces the complex tree-like astrocyte morphology and incorporates ionic currents and molecular fluxes. With this model, it is possible to study the different ionic intracellular dynamics and the different Ca^{2+} signals in the branches and in the soma and how those diffuse through the cell. Further results have shown ways to calculate the limits of operation of the Ca^{2+} and IP_3 signalling cascade with or without control of incoming IP_3 [3].

2.4 Astrocyte network level

Astrocytes are connected into networks modulated by the intracellular and intercellular molecule trafficking, mediated by gap junctions [12]. Fig. 2 shows the spatial connective properties of astrocytes in in-vitro co-cultures. This has also been shown with in-silico models by Lallouette et al. [19]. Barros et al. have taken a similar approach to study the effect of Alzheimer's disease in

astrocyte networks [5]. However, the role of astrocyte network-level signalling on neuronal network plasticity and learning is not well-established [8], and the first models of the biophysical signalling driven integrated neuronal, and astrocyte networks are just emerging, e.g., by Lenk et al. [21, 22]. On the network level, the astrocyte Ca^{2+}-driven activity can modulate the neuronal network through the interconnections in the tripartite synapses. Our results on network-level demonstrate the role of astrocytes as regulators of network signalling [5, 22]. Another aspect of network-level astrocyte Ca^{2+} is the interaction with pericytes and downstream with the endothelia of the blood-brain barrier contributing to control the energy and nutrient balance in the brain [15].

2.5 Analysis

All these levels highlight the role of astrocyte in neuronal molecular communications and adaptation, and call for assessing their role in neuronal communication with limited literature available. Valenza et al. [36] used an artificial spiking neuronal network communication model with tripartite synapses modelled as a non-linear transistor-like model. Their results showed that astrocytes created subgroups of neurons with a polychronic activity that can be considered a basis for the network memory. Barros et al. [2] studied the molecular communication through Ca^{2+} signalling through GJs using also astrocyte type cells showing the importance of the cellular interplay (i.e., GJ coupling) in the communication performance between the different modelled cells. In a follow-up work, Barros et al show that this communication mechanism can be used for computation [4]. Moreover, the role of astrocytes in learning has been proposed and demonstrated in artificial neuronal networks and classification tasks [32]. Astrocyte present ways to regulate the plasticity of neuronal connections, increasing their reliability at good functioning states. Work such as [23, 30] provides insight into all the levels described in this paper, as those reviews explore more the biophysical properties of astrocytes as opposed to signal modulation.

Table 1 shows a comparison of modulation and existing modelling tools in the multiple astrocyte molecular signalling levels presented in this paper. We also explore the pros and cons existing in each level, identifying future research questions. Most of the modelling methodologies available come from simple diffusion equations to more complex non-linear ODEs, to stochastic reaction-diffusion equations. Those methods apply to all levels given appropriate modifications in certain relationships (e.g. Ca^{2+} versus glutamate release, morphology versus Ca^{2+} diffusion) as well as model parameters (initial states of Ca^{2+}, K, *Na et cetera*).

3 DISCUSSION AND CONCLUSIONS

The role of astrocytes in learning and information processing in normal and pathological functions in the brain are still elusive. In general, astrocytic functions include modulation and control of neural communication and, further, energy homeostasis in the brain. All these are coupled with astrocytic Ca^{2+} activity and various other molecular communications. However, much of the mechanisms and their role in neuronal functions are yet to be assessed. Integration of different methods - in-vivo, in-vitro, and in-silico - are crucially needed for better understanding the role of astrocytes in controlling the neuronal homeostasis and processes, and above all, the information processing. This complex interplay of astrocytes and neuronal functions calls for further studies, including using molecular communication paradigms. More studies are needed to clarify these complex and multiscale system interactions and their molecular information transfer. This can have the potential to facilitate studies on associated pathological conditions, also enabling personalised medicine developments, including better in-vitro organ-on-chip systems and more realistic biophysical models of astrocyte-neuronal systems.

For lower levels, including the astrocyte cell level, astrocyte branch and synapse levels, the study of mechanical propagation properties of molecules is possible. Therefore, we can use molecular kinetic or finite element models (FEM). For higher levels, such as the astrocyte network level, graph theory or mass models were explored previously and serve as a reasonable model for predictable membrane activity relationships in the population of cells. The modeling, in all levels, is a continuous effort in the computational biology domain, and molecular communications can help contribute in quantify the astrocyte-neuronal channel in a descriptive manner. We also can see that in different levels, the provided references have pointed to different modulation methods. These modulation methods are basically types of processes that trigger further modulation in neighbouring cells or populations. In order to keep the analysis accessible to readers, we do not further explore sequential modulation effects. For the synapse level, glio- or neurotransmitters that propagate in the synaptic cleft are the modulation method that induces further activity in post-synaptic neurons and sequential neural networks. Gliotransmitters, both excitatory and inhibitory, can be released by astrocytes and bind the pre-and post-synaptic neuron, modulating the neuronal membrane depolarization. Ca^{2+} signals are, instead, the main modulators of the communication. However, co-dependent signalling molecules, e.g., IP_3, sodium or potassium, also influence organelles activity at the cellular level, as well as neighbouring astrocytes at the network level. Gap junctions between astrocytes allow the propagation of the molecules, such as small ions and IP_3, which can induce Ca^{2+} elevations in distal astrocytes in the network, thus making the intercellular communications also a means of modulatory phenomena. Many future research directions can emerge from modulation effects, especially in computational modelling of propagation of modulatory signals in networks of astrocytes and neurons. Since there are biological implications risen from modulatory effects (including changes in population-level normal activity), robust computational models can support activity prediction tools in various levels, which is a valuable contribution to the understanding of these systems.

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Table 1: Comparison of the modulation of multiple astrocyte modeling levels with pros and cons.

Level	Modeling Methodology	Pros	Cons	Modulation Method	Reference
Synapse level	Diffusion Equations, Non-linear ODE, Molecular Kinetics	• Closed-form solutions are possible • Capture the essence of the interface between astrocytes and neurons • Suitable to applications in artificial intelligence • Applicable to the understanding of microscopic molecular interactions and propagation	• Large number of non-linearities • Hard to validate existing models • Lack of imaging and quantification tools • Rely on other methods for validation, including mRNA analysis • Hard to integrate with higher level models	Glio- or neuronal transmitter- and ion-based	[1, 7, 10, 23, 30]
Astrocyte branch level	Non-linear ODE, FEM, Diffusion Equations	• Visualization of localized micro-scale subcellular diffusion • Improved characterization of 3D enviroments • Lower complexity modeling,	• Perisynaptic astrocyte processes are the hardest to validate • Lack of functional studies that show wide importance of branches in the modulation of higher levels, e.g., network	Calcium concentration-based	[6, 18, 23, 29, 30, 35]
Astrocyte cell level	FEM, Stochastic Reaction Diffusion Networks, Non-linear ODEs	• Capture of biological non-linearities • Modular models with reasonable integration capabilities • Possible to analyze the role of organelles and reaction pathways in the signals produced	• Large number of non-linearities • Closed-form solutions are not always possible • Computationally expensive	Calcium concentration-based	[3, 15, 18, 20, 23, 30, 33]
Astrocyte network level	Graph Theory, Stochastic Reaction Diffusion Networks, Non-linear Dynamics, Mass Models	• Coverage of large area of a tissue population • Effects of spatial signal propagation captured • Less complex models	• Loss of biological physiological effects in models • Specialised and non-general models under non-verifiable assumptions	Calcium concentration-based	[2, 4, 5, 8, 19, 21–23, 30, 32, 36]

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