Neuron-glia interactions and brain circuits

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Abstract: Recent evidence suggests that glial cells take an active role in a number of brain functions that were previously attributed solely to neurons. For example, astrocytes, one type of glial cells, have been shown to promote coordinated activation of neuronal networks, modulate sensory-evoked neuronal network activity, and influence brain state transitions during development. This reinforces the idea that astrocytes not only provide the "housekeeping" for the neurons, but that they also play a vital role in supporting and expanding the functions of brain circuits and networks. Despite this accumulated knowledge, the field of computational neuroscience has mostly focused on modeling neuronal functions, ignoring the glial cells and the interactions they have with the neurons. In this chapter, we introduce the biology of neuron-glia interactions, summarize the existing computational models and tools, and emphasize the glial properties that may be important in modeling brain functions in the future.

Keywords: Neuron-glia interaction, Brain circuit, Neuronal network, Neuronal excitability, Synaptic transmission and plasticity, Computational modeling, Brain simulation science

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1.1. Introduction

Glial cells are non-neuronal cells in the central and peripheral nervous system that are not able to fire action potentials. Glia was first discovered in 1856 by Rudolf Virchow, and later divided into oligodendrocytes, astrocytes, ependymal cells, and microglia in the central nervous system and Schwann cells and satellite cells in the peripheral nervous system. The morphology and physiology of glia as well as the ratio of neuron-to-glia vary between different brain areas. The common belief is that glial cells are not like neurons – they maintain homeostasis, form myelin, and provide support and protection for neurons. In the neuron-centric view, changes in neuronal activity depend solely on the intrinsic properties of neurons and the information transmitted. Over the past ten years, this assumption has been questioned more frequently as new evidence about the multiple roles of glial cells in the brain has emerged. Recent work has shown that glia may have more active roles in the brain functions than has been previously thought, not only in developing but also in mature circuits.

Astrocytes are star-shaped cells representing the largest group of glial cells in our brain. There are two types of astrocytes, protoplasmic astrocytes in the grey matter and fibrous astrocytes in the white matter. Astrocytes are the most diverse glial cell type in the central nervous system. In different brain regions they differ in morphology, physiology, and expression of genes encoding the most fundamental proteins responsible for astroglial function. In general, astrocytes have a soma as well as perisynaptic and perivascular processes. Perisynaptic processes surround neuronal synapses and enclose part of extracellular space (sometimes also called perisynaptic, extrasynaptic, or periastrocytic space in the literature). Perivascular processes connect the astrocyte with blood vessels and enclose some extracellular space called the perivascular space. Below we present a generic view of some of the most important biophysical and cellular mechanisms that are shown to underlie important astrocytic functions (for more information, see for example Kettenmann and Ransom 2013; Verkhratsky and Butt 2013).

One of the most important functions of astrocytes is to clear excess extracellular potassium and other ions from the brain extracellular space, the narrow microenvironment that surrounds every cell of the central nervous system (Orkand et al. 1966). This prevents the over-excitement of neuronal networks. Equally important is their role in regulating glutamatergic synaptic transmission by taking up excessive glutamate (Danbolt 2001), transforming it into glutamine, and then releasing glutamine into the extracellular space for presynaptic terminal to metabolize

it back to glutamate. Astrocytes also promote formation of excitatory synapses and establishment of synaptic connectivity in the developing central nervous system (Allen and Eroglu 2017). In addition, astrocytes have recently been shown to contribute to the information processing capabilities of brain circuits and affect animal behavior (see, e.g., Pannasch and Rouach 2013; Oliveira et al. 2015; Poskanzer and Yuste 2016; Chever et al. 2016; Lines et al. 2020). Recent experimental glioscience research can thus revolutionize our understanding of rodent and human brain function (see also Volterra et al. 2014; Bazargani and Attwell 2016). Theoretical and computational neuroscience modeling methods as well as brain simulation science tools (Einevoll et al. 2019), combined with tools developed for computational glioscience (Savtchenko et al. 2018), can offer ways to greatly facilitate the understanding of glial contributions to overall brain functions.

Nearly three decades of research has provided us with substantial knowledge of neuron-glia interactions. As described by Bazargani and Attwell (2016), there has been three waves of research when different types of hypotheses have prevailed. In the remaining sections, we present state of the art in astrocyte biology, emphasizing some key properties that may be important in modeling neural and brain functions in the future. We also summarize the existing methods and tools targeted to modeling of glial functions as well as give examples of computational models developed in the field.

1.2. Neuron-astrocyte interactions and altered neuronal and circuit excitability

Astrocytes are specialized glial cells that are positioned in a close vicinity of neurons and can interact with neurons to alter neuron's intrinsic excitability as well as the excitability of brain circuits. The study of astrocytic cell membrane and intracellular mechanisms is not straightforward. Astrocytes do not express all-or-none phenomenon like action potential firing but instead use calcium ions as a signaling mechanism. Experimental manipulation of astrocytic calcium concentration is not an easy task and can produce different results depending on the approach and context (for a more detailed discussion, see, e.g., Agulhon et al. 2010; Fujita et al. 2014; Sloan and Barres 2014). Additional tools, both experimental and computational, are required to understand the vast complexity of astrocytic calcium signaling and its decoding to advance functional consequences in the brain. Until 2010, most of the studies were performed using *in vitro* cell cultures and slice preparations, and only recently studies addressing astrocyte roles in brain functions *in vivo* have accumulated. The goal of

future research is to better understand the integrated operation of various calcium-mediated astrocytic regulatory mechanisms in neuronal excitability and information processing in the brain.

Astrocytes display complex biochemical and biophysical mechanisms, which are known to be involved in many physiological phenomena in the brain. These mechanisms can be divided into several categories according to the molecule(s) involved. The most relevant are **(i)** membrane transport proteins involved in movement of ions, small molecules, and macromolecules across the biological membrane (summarized in Kettenmann and Ransom 2013), **(ii)** membrane receptor proteins, the activation of which can trigger an increase in the astrocytic calcium concentration *in vitro* (Backus et al. 1989; Kimelberg 1995; Jalonen et al. 1997) and *in vivo* (Beltrán-Castillo et al. 2017), **(iii)** calcium-dependent signaling pathways or other mechanisms that are activated by cell membrane mechanisms and govern the production and release of different molecular mediators from astrocytes (summarized in Kettenmann and Ransom 2013), and **(iv)** astrocyte-released substances that target the neuronal and vascular systems as well as other glial cells (see, e.g., Perea and Araque 2007; Jourdain et al. 2007). The above-mentioned astrocytic mechanisms have been shown to depend on the developmental stage. Additionally, these mechanisms operate at different temporal and spatial scales. Computational techniques may help to clarify their contributions in brain circuits and tissue, both in healthy and impaired conditions. Some of the above-mentioned mechanisms have already been considered in computational glial and astrocyte models to understand the role of neuron-astrocyte interactions in the intrinsic excitability of neurons and in neuronal network functions (Manninen et al. 2018b).

In addition to a rich repertoire of cell membrane and intracellular mechanisms directly controlling and indirectly influencing neuronal excitability, astrocytes can be coupled via gap junction channels (Orkand et al. 1966) to form a sort of cellular network called the "astrocytic syncytium" (Giaume et al. 2010). Intercellular calcium signaling (Cornell-Bell et al. 1990) through gap junctions has been extensively demonstrated, particularly in *in vitro* preparations. Astrocytic gap junctions have been shown to play a crucial role in the control of extracellular Na^+, K^+, Ca^{2+}, and Cl^- homeostasis *in vitro* (Rose and Ransom 1997) and *in vivo* (Ma et al. 2016). The study of astrocytic gap junctions in neuronal depolarization, excitability, synchronization, and brain circuit function has gained more and more interest over the past decade. Gap junction-coupled astrocyte networks have been shown to modulate synaptic strength and plasticity through facilitation of glutamate and K^+ removal during synaptic activity

(Pannasch et al. 2011). Furthermore, electrophysiological and Ca^{2+} imaging experiments in neocortical slices have shown that electrical stimulation of a single astrocyte activates other astrocytes of the surrounding local network and can trigger synchronization of neighboring neurons (Poskanzer and Yuste 2011). Computational models for gap junction-coupled astrocytes have been developed to better understand intercellular Ca^{2+} signaling and Ca^{2+} waves in astrocyte networks resembling *in vitro* cell culture conditions (Lallouette et al. 2014). However, more studies are clearly needed to better understand the developmental expression of gap junction channels and their functional consequences *in vivo*.

Recently, astrocytes have been reported to play a role in neuronal activity and network oscillations (see, e.g., Carmignoto and Fellin 2006; Poskanzer and Yuste 2016). In the study of Poskanzer and Yuste (2016), astrocytic Ca^{2+} activity has been shown to precede circuit shifts that dominate the slow-oscillation state. In addition, alterations in normal astrocytic physiology have been associated with several neuropsychiatric and neurodegenerative diseases. In order to computationally link all relevant intra- and intercellular mechanisms of astrocytes with neuronal intrinsic and circuit excitability calls for better understanding of the astrocytic mechanisms *in vivo* and, consequently, for more biologically realistic models of astrocytes. To this purpose, new experimental techniques and protocols are being developed to further clarify the existence and roles of gap junctions in the astrocyte syncytium in different brain areas and developmental phases *in vivo*.

1.3. Neuron-astrocyte interactions, synaptic transmission and synaptic plasticity

Astrocytes are anatomically organized into three-dimensional, non-overlapping spatial territories, or domains, *in vivo*. This process of anatomical segregation is called astrocyte tiling. It means that the processes of astrocytes rarely overlap the domains of other astrocytes. *In vivo* reconstructions of astrocytes show complex morphological structures with more branched and dense processes compared to neurons (Bushong et al. 2002; Oberheim et al. 2009; Vasile et al. 2017; Calì et al. 2019). Within an anatomical domain a single astrocyte can send its fine processes to reach a nearby neuron. A single cortical astrocyte is estimated to contact altogether 20,000 to 120,000 synapses in rodents and up to 2,000,000 synapses in humans (Oberheim et al. 2009). Astrocytes also send their endfoot processes to envelop vascular smooth muscle cells and control brain blood flow (Attwell et al. 2010). The complex morphology and anatomical organization of astrocytes calls for new computational methods to better understand the spatial

compartmentalization of astrocytes and the roles of astrocyte processes in synaptic transmission and plasticity.

Astrocytes have been shown to be important regulators of neural development and maturation (Allen 2013), including the control of the number of synapses (Ullian et al. 2001) and synaptic connectivity (Eroglu and Barres 2010). Synaptic plasticity, defined as the activity-dependent change in the strength or efficacy of the synaptic connection between a pre- and postsynaptic neuron, is expressed in the brain in diverse forms across multiple timescales. Accumulating experimental evidence indicates that glial cells, including astroglia, modulate synaptic transmission and plasticity during postnatal development and maturation of cortical circuits. Evidence for such a modulation has been found at least in the following brain areas: somatosensory/barrel cortex (Takata et al. 2011; Min and Nevian 2012), hippocampus (Yang et al. 2003; Perea and Araque 2007; Navarrete et al. 2012; Sibille et al. 2014; Letellier et al. 2016; Sherwood et al. 2017), and prefrontal cortex (Petrelli et al. 2018). These studies also suggest that the biophysical and biochemical mechanisms modulating synaptic transmission and plasticity may be diverse and depend on the brain area and the type of a synapse.

Like all living cells, astrocytes are capable of exocytotic release of molecules. Over the past two decades, the concept that astrocytes can release neuroactive molecules, gliotransmitters, which in turn modulate neuronal excitability and synaptic transmission, has radically changed our understanding of brain physiology. This concept states that astrocytes, together with pre- and postsynaptic neuronal components, make up a functional tripartite synapse (Araque et al. 1999). Astrocytic release of gliotransmitters (e.g., glutamate, d-serine, and adenosine triphosphate) is generally accepted to be a Ca^{2+}-dependent process although studies exist that did not find the link between astrocytic Ca^{2+} and release of gliotransmitters (Agulhon et al. 2010). Recent imaging studies and morphology reconstructions (Calì et al. 2019) give additional evidence for the concept of the tripartite synapse. In these reconstruction studies, some of the astrocyte processes are shown to be very close to synapses, so that three elements are grouped together: the pre- and postsynaptic processes and one astrocytic process. The short physical distance in the triad could thus allow direct communication between neurons and astrocytes.

The exocytotic release of substances from astrocytes can provide one way to modulate synapses and synaptic activity, along with other mechanisms that were presented in the previous section. In our previous study, using a detailed model of a synapse, we have shown that astrocyte processes can take part in synapse computation (Manninen et al. 2020). In this *in silico* study,

we show how complex biochemical and biophysical mechanisms at the pre- and postsynaptic neurons and in the astrocytic process modulate long-term depression in spike-timing-dependent plasticity in somatosensory cortex during postnatal development (Min and Nevian 2012). The interplay between neurons and glia in synapse development and plasticity *in vivo* is under intense research (Stogsdill and Eroglu 2017). Combination of wet-lab and computational techniques will be crucial in the future to better understand the complex nature of neuron-astrocyte interactions and the remaining controversies in the field. This integration of wet-lab and computational studies is crucial for better understanding of disease mechanisms. As an example, a hallmark of many neurodevelopmental disorders is abnormal synapse formation and function. Since glial cells have been shown to play a role in synapse development and maturation, it is possible that atypical functioning of glial cells underly many developmental brain disorders.

1.4. Computational modeling and simulation

A few hundreds of computational models for astrocytes and neuron-astrocyte interactions have been developed so far. These include biophysically detailed models of the above-mentioned key astrocytic mechanisms, such as the mechanisms related to K^+ buffering and Ca^{2+} dynamics, for various neural phenomena as well as phenomenological models lacking mechanistic details and described by relatively simple equations. However, multi-compartmental models of astrocytes considering all-important biophysical details do not exist. For a comparison, almost all different neuron types of a rodent brain have at least one representative multi-compartmental model fitted against electrophysiological and other data. Moreover, there is no well-established way of modeling neuron-astrocyte interactions at the network level although many models exist; methodologies and approaches are under development.

In this review, we are mainly interested in the models and approaches that incorporate astrocytic Ca^{2+} dynamics. In Figure 1.1. we present the number of Ca^{2+} dynamic models published for astrocytes per year (Manninen et al. 2018b, 2019). We can conclude that the computational glioscience field kicked off around the year 2000. For a comparison, tens of multi-compartmental whole-cell models exist just for cortical pyramidal cells (see e.g. Huhtala et al. 2020). These neuron models were implemented using e.g. NEURON simulator (Carnevale and Hines 2006) and are available in ModelDB (McDougal et al. 2017).

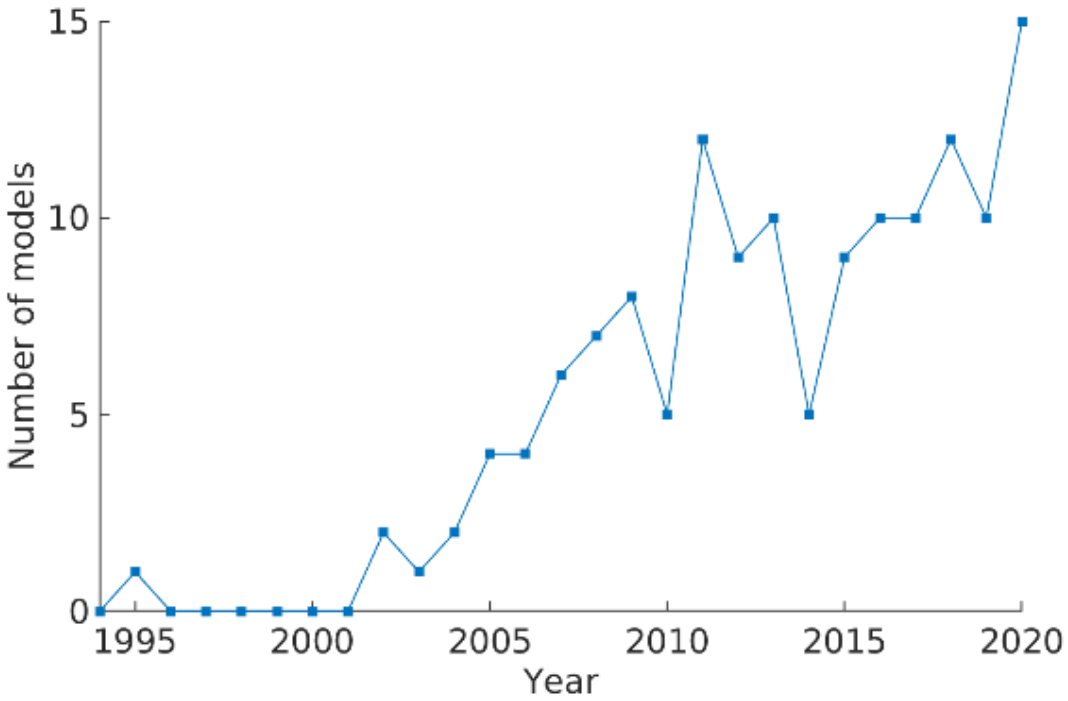

Figure 1.1. *Number of published models per year for astrocytes involving Ca^{2+} dynamics. In all these models, the Ca^{2+} dynamics is derived from a few published models originally not developed for astrocytes. None of the plotted astrocyte models are multi-compartmental models with all cell membrane phenomena described, but instead they mainly model Ca^{2+} dynamics. For a comparison, tens of multi-compartmental whole-cell models exist just for cortical pyramidal cells implemented using e.g. NEURON simulator (see e.g. Huhtala et al. 2020). Data modified from Manninen et al. (2018b, 2019).*

1.4.1. The scope and complexity of glial computational models

We can choose between biophysical mechanistic and phenomenological modeling or combining them when modeling the dynamical behavior of neurons and astrocytes. Among neuron models, Hodgkin and Huxley (1952) model, Traub et al. (1991) model or its derivative Pinsky and Rinzel (1994) model are examples of biophysical models, while FitzHugh-Nagumo model (FitzHugh 1961), Morris and Lecar (1981) model, integrate-and-fire (IF) type models like adaptive exponential integrate-and-fire model (Brette and Gerstner 2005), and Izhikevich (2007) model are examples of phenomenological models. The above-mentioned neuron models can be incremented with more detailed ion channel and receptor models or intracellular signaling pathways related to, for example, Ca^{2+} dynamics, different protein kinases and phosphatases. For the synapse, the models range from the biophysically detailed vesicular

release models (e.g., Bollmann et al. 2000) to the reduced and computationally efficient models (e.g., Tsodyks and Markram, 1997; Tsodyks et al., 1998).

Some key astrocytic mechanisms have been modeled and characterized in several studies (see, e.g., Linne and Jalonen 2014; Manninen et al. 2018b, 2019). Of these, our recent study (Manninen et al. 2018b) is the most detailed analysis of the astrocyte models. The features of more than hundred models with detailed enough astrocytic Ca^{2+} dynamics were compared to show the similarities and differences between the models (Manninen et al. 2018b). Even though some of these models are relatively simple in terms of equations, we can mostly consider them biophysical because they model some key biophysical mechanisms of astrocytes.

Most of the astrocyte models consider the dynamics of inositol trisphosphate receptors (IP_3Rs), sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA pump), and leak flux from the endoplasmic reticulum to the cytosol, and they can also incorporate other mechanisms, such as plasma membrane Ca^{2+}-ATPase (PMCA pump), Na^+/Ca^{2+} exchanger (NCX), and K^+ channels. Most of the models utilized the Ca^{2+} dynamics models by De Young and Keizer (1992), Li and Rinzel (1994), and Höfer et al. (2002) with small modifications (for details of these models, see Manninen et al. 2018b). More phenomenological models are represented by, for example, Postnov et al. (2007). Many different types of models have been used to describe astrocytes' effect on neurons (e.g., Tsodyks and Markram 1997; Tsodyks et al. 1998; Nadkarni and Jung 2003; Postnov et al. 2007; Volman et al. 2007), but also detailed astrocytic vesicle release models have been used (e.g., Bertram et al. 1996). Gap junctions have as well been modeled between astrocytes (e.g., Höfer et al. 2002; Lallouette et al. 2014). In addition to models considering astrocytic Ca^{2+} dynamics, there are hundreds of different types of astrocyte models considering mechanisms to other ions than Ca^{2+} but these models are not discussed here. To get an idea about modeling of these other mechanisms, see, for example, the books by Keener and Sneyd (2009) and Dupont et al. (2016).

1.4.2. Simulation tools

Because of the complexity of astrocyte morphologies and the fact that astrocytes possess Ca^{2+} (instead of Na^+) excitability, new tools are clearly needed to advance the field of glioscience modeling. A few simulation tools already exist for modeling astrocyte functions and dynamics on various levels (Table 1.1.). Two of the available simulation tools, ASTRO (Savtchenko et al. 2018) and STEPS (Hepburn et al. 2012), are built for morphologically detailed multi-

compartmental cell models which are needed in the computational neuroscience field. STEPS was developed first for neuronal models and just recently extended to astrocytes (Denizot et al. 2019), while ASTRO was developed directly to model astrocytes. ASTRO tool was built on top of NEURON simulator (Carnevale and Hines 2006). Both ASTRO and STEPS can be used to study reaction-diffusion systems with electrophysiology, and STEPS specializes in stochastic simulation. The rest of the tools listed in Table 1.1. were built for neural network simulations. Brian 2 (Goodman and Brette 2008) and NEST (Gewaltig and Diesmann 2007) were originally built for spiking neural network models, but recently Brian 2 was extended to also include glial cell modeling making possible to construct neuronal-glial network models (Stimberg et al. 2019) and NEST version of astrocyte extension is in preparation. ARACHNE (Aleksin et al. 2017), on the other hand, was developed directly for modeling neuron-glia interactions in large networks. Examples of models that have been developed using these tools can be found in Table 1.1. and in ModelDB (McDougal et al. 2017).

Table 1.1. *Simulation tools for modeling astrocyte functions, neuron-astrocyte interactions and astrocyte modulation of neuronal networks.*

Name	**ARACHNE**	**ASTRO**	**Brian 2**	**NEST**	**STEPS**
Reference	Aleksin et al. 2017	Savtchenko et al. 2018	Goodman and Brette 2008	Gewaltig and Diesmann 2007	Hepburn et al. 2012
Web address	https://github.com/LeonidSavtchenko/Arachne	https://github.com/LeonidSavtchenko/Astro	https://briansimulator.org/	https://www.nest-simulator.org/	http://steps.sourceforge.net/STEPS/default.php
Applicability	Neuronal-glial networks	Morphologically detailed multi-compartmental cell and synapse models	Spiking neural networks	Spiking neural networks	Morphologically detailed multi-compartmental cell and synapse models
Programming language	C++, MATLAB	NEURON-based tool, C++, hoc, MATLAB	Python	Python, C/C++	Python, C/C++
Example model	Model by Aleksin et al. 2017 can be found in https://github.com/LeonidSavtchenko/Arachne/tree/master/ExamplePLOS	Model by Savtchenko et al. 2018 can be found in ModelDB (accession number 243508)	Model by Stimberg et al. 2019 can be found in https://github.com/mdepitta/comp-glia-book/tree/master/Ch18.Stimberg	In preparation	Model by Denizot et al. 2019 can be found in ModelDB (accession number 247694)

1.5. Computational models

Computational models of astrocytes and neuron-astrocyte interactions can be divided into four broad groups: **(i)** models describing one or more properties of single astrocytes, **(ii)** models connecting several astrocytes together, **(iii)** models describing neuron-astrocyte interactions in a single synapse, and **(iv)** models describing neuron-astrocyte interactions in brain circuits and networks (see also, Manninen et al. 2018b). Here, we focus on the models of neuron-astrocyte interaction, so in what follows we will only briefly present the single astrocyte and astrocyte network models. Instead, readers are encouraged to take a look at the previous work (Manninen et al. 2017, 2018a,b, 2019) and recently published models (e.g., Savtchenko et al. 2018; Denizot et al. 2019). In the following sections, we will present examples of models in the last two categories (**iii)** and **(iv).** The examples of models in **(iii)** include models where a single, either an excitatory or an inhibitory, synapse exists between two neurons and a nearby astrocyte, or a single neuron has a bidirectional connection with a single astrocyte. The examples of models in **(iv)** include models with more than one synapse, and some of the example network models have a few hundred or even thousands of cells.

1.5.1. Models of single astrocytes and astrocyte networks

Unlike the detailed multi-compartmental neuron models available for different brain areas, the models including the whole astrocyte morphology, the ion channel descriptions, and other relevant mechanisms do not exist. One of the most detailed models thus far for single astrocytes was developed by Savtchenko et al. (2018), and for the fine astrocyte process by Denizot et al. (2019). Most of the single astrocyte and astrocyte network models were developed to study Ca^{2+} dynamics often in single compartments, for example, in the soma, but some exist to study vascular events and homeostasis. Half of the single astrocyte and astrocyte network models were not developed for certain brain area but were generic (Manninen et al. 2018b, 2019). About 20 % of the single astrocyte models and 50 % of the astrocyte network models considered intracellular or extracellular diffusion of molecules and ions, while the single astrocyte models included more molecules and ions as variables than the astrocyte network models. The astrocyte network models either included diffusion in the extracellular space or gap junctions between the astrocytes, or both. The larger number of astrocytes were modeled in the astrocyte network models; the fewer number of variables were usually modeled per astrocyte (Manninen et al. 2018b). These earlier models serve as a starting point to construct

biophysically more detailed, morphologically realistic models of astrocytes in the future. The simulation tools presented in Table 1.1. will make it possible to incorporate more details in different compartments of astrocytes (soma, large processes, fine processes) provided that new data will become available (imaging, electrophysiology, etc.).

1.5.2. Models for neuron-astrocyte interactions in synapses

The neuron-astrocyte synapse models have been developed to study different phenomena, such as Ca^{2+} dynamics, synaptic plasticity, and hyperexcitability. Theoretical concepts like information transfer and synchronization of activity have also been addressed using these models. In addition, some of the models consider the regulation of vascular blood flow. Half of the single neuron-astrocyte synapse models were generic and thus not developed for a certain brain area (Manninen et al. 2018b, 2019). Half of the models used more complex biophysical details, while the other half used simpler phenomenological neuron models. Diffusion of molecules and ions have been rarely modeled, only one single synapse model out of 35 models published before 2018 took diffusion into account (Manninen et al. 2018b). Of the published single neuron-astrocyte synapse models, we will discuss about the models by Volman et al. 2007, Nadkarni et al. (2008), Tewari and Majumdar (2012), De Pittà and Brunel (2016), and the recently published model by Manninen et al. (2020) (See Table 1.2.).

Of these models, Manninen et al. (2020) and Tewari and Majumdar (2012) used a biophysically detailed neuron models and Nadkarni et al. (2008) used a relatively simple neuron model without considering the membrane potential. Volman et al. (2007) modeled only one neuron, the rest of the models incorporated both the pre- and postsynaptic neurons. All the models integrated several previously published model components for astrocytic mechanisms, of which Nadkarni et al. (2008), Tewari and Majumdar (2012), and De Pittà and Brunel (2016) used a more biologically realistic equation for the concentration of IP_3 than Volman et al. (2007) and Manninen et al. (2020). Nadkarni et al. (2008) used a detailed presynaptic vesicular release model and a relatively simple astrocytic glutamate release model. On the other hand, Tewari and Majumdar (2012) used biophysically detailed presynaptic and astrocytic vesicle release models, while the other models (Volman et al. 2007; De Pittà and Brunel 2016; Manninen et al. 2020) used biophysically simpler models.

Table 1.2. *Examples of neuron-glia interaction models combined with models of single synapses. In short, these models include two neurons (ie. pre- and postsynaptic compartments of neurons), a synapse between them, and an astrocyte (typically one compartment only). In principle, these are single synapse models where astrocytic modulation of a synapse is taken into account. Under 'Synapse model', we include the references of both the neurotransmitter and gliotransmitter release models.*

MODEL	NEURON MODEL	ASTROCYTE MODEL	SYNAPSE MODEL	BRAIN AREA / EVENT
Manninen et al. 2020 (ModelDB, accession number 266819)	PRE Hodgkin and Huxley type model (Fiala et al. 1996; Erreger et al. 2005; Clarke and Johnson 2008; Safiulina et al. 2010; Lavzin et al. 2012) POST Hodgkin and Huxley type model (De Young and Keizer 1992; Reuveni et al. 1993; Li and Rinzel 1994; Pinsky and Rinzel 1994; Avery and Johnson 1996; Destexhe et al. 1998; Blackwell 2002; Sarid et al. 2007; Kim et al. 2013; Zachariou et al. 2013; Markram et al. 2015)	De Young and Keizer 1992; Li and Rinzel 1994; Nadkarni and Jung 2003; Wade et al. 2012	Tsodyks et al. 1998; Lee et al. 2009; De Pittà et al. 2011; De Pittà and Brunel 2016	Somatosensory cortex / Synaptic plasticity
De Pittà and Brunel 2016	PRE (Graupner and Brunel 2012) POST (Gerstner and Kistler 2002; Graupner and Brunel 2012)	De Young and Keizer 1992; Li and Rinzel 1994; Höfer et al. 2002; De Pittà et al. 2009; Goldberg et al. 2010; Lallouette et al. 2014; Wallach et al. 2014	Tsodyks et al. 1998	Hippocampus / Synaptic plasticity
Tewari and Majumdar 2012	PRE Hodgkin and Huxley type model (De Young and Keizer 1992; Li and Rinzel 1994; Erler et al. 2004; Blackwell 2005; Nadkarni and Jung 2003; Keener and Sneyd 2009) POST IF model (Tsodyks and Markram 1997; Destexhe et al. 1998; Lisman and Zhabotinsky 2001)	De Young and Keizer 1992; Li and Rinzel 1994; Höfer et al. 2002; Shuai and Jung 2002; Nadkarni and Jung 2003, 2007; De Pittà et al. 2009	Bertram et al. 1996; Tsodyks and Markram 1997; Bollmann et al. 2000; Nadkarni et al. 2008	Hippocampus / Synaptic plasticity
Nadkarni et al. 2008	PRE (Nadkarni and Jung 2007) POST exponential current	De Young and Keizer 1992; Li and Rinzel 1994; Shuai and Jung 2002; Nadkarni and Jung 2003, 2007	Bertram et al. 1996; Tsodyks and Markram 1997; Nadkarni and Jung 2007	Hippocampus / Synaptic transmission
Volman et al. 2007	PRE Morris and Lecar (1981) model	De Young and Keizer 1992; Li and Rinzel 1994; Nadkarni and Jung 2003	Tsodyks et al. 1998	Cortex / Synaptic transmission

1.5.2. Models for neuron-astrocyte interactions in brain circuits and networks

Half of the neuron-astrocyte network models were generic and developed to study many different biophysical events, such as Ca^{2+} dynamics, synchronization, information transfer, synaptic plasticity, and hyperexcitability (Manninen et al. 2018b, 2019). Most of these models utilized simple phenomenological neuron models and modeled gap junctions between astrocytes. About 30 % of the models included intracellular or extracellular diffusion of molecules and ions. Most of these models had maximum of four variables per astrocyte, meaning the astrocytes were often modeled in simpler way than in the other model groups. Of the published neuron-astrocyte network models, we will discuss about the models by Postnov et al. (2009), Aleksin et al. (2017), Gordleeva et al. (2019), Stimberg et al. (2019), and Li et al. (2020) (See Table 1.3.).

Of these models, Aleksin et al. (2017) and Gordleeva et al. (2019) presented the most detailed ones. As with the neuron-astrocyte synapse models, also here the models integrated several previously published model components for astrocytic mechanisms, of which Aleksin et al. (2017) used the lowest number of variables (i.e., differential equations), Postnov et al. (2009) used the simplest equations, and the rest modeled many mechanisms. Especially, Gordleeva et al. (2019) and Stimberg et al. (2019) used a bit more complex equation for the concentration of IP_3 than the rest of the models. The simpler models gave the possibility to model more cells compared to the more detailed models. None of the network models used a detailed presynaptic vesicular release model or detailed gliotransmitter release model. However, Aleksin et al. (2017) and Gordleeva et al. (2019) used Tsodyks et al. (1998) model for their neurotransmitter or gliotransmitter equation and Stimberg et al. (2019) and Li et al. (2020) used the whole Tsodyks et al. (1998) synapse model for both the presynaptic and astrocytic terminals.

Table 1.3. *Examples of neuron-glia interaction models in the context of networks. Under 'Neuron model', we provide the number of modeled excitatory (E) and inhibitory (I) neurons or the number of pyramidal cells (PY) and interneurons (IN) used to build the model. Under 'Astrocyte model', we provide the number of astrocytes used to build the model. Under 'Synapse model', we have included both the neurotransmitter and gliotransmitter release models as well as the gap junction models between astrocytes and other models describing the synapse models.*

MODEL	NEURON MODEL	ASTROCYTE MODEL	SYNAPSE MODEL	BRAIN AREA / EVENT
Li et al. 2020	400 E, 100 I LIF model (Jahr and Stevens 1990; Destexhe et al. 1994; Gerstner and Kistler 2002; Silchenko and Tass 2008)	400 (De Young and Keizer 1992; Li and Rinzel 1994; Nadkarni and Jung 2003, 2007; Ullah et al. 2006; Li et al. 2017)	Destexhe et al. 1994, 1998; Tsodyks et al. 1998; Nadkarni and Jung 2007; Goldberg et al. 2010; De Pittà and Brunel 2016	Cortex / Excitatory-inhibitory balance
Stimberg et al. 2019 (https://github.com/mdepitta/comp-glia-book/tree/master/Ch18.Stimberg)	3200 E, 800 I IF model	3200 (De Young and Keizer 1992; Li and Rinzel 1994; Höfer et al. 2002; Shuai and Jung 2002; De Pittà et al. 2009; Goldberg et al. 2010; Wallach et al. 2014)	Tsodyks et al. 1998; De Pittà et al. 2009, 2011; Lallouette et al. 2014; De Pittà and Brunel 2016	Neocortex / Synchronization
Gordleeva et al. 2019	2–100 E Hodgkin and Huxley type model (Esir et al. 2018)	1–2 (De Young and Keizer 1992; Li and Rinzel 1994; De Pittà et al. 2009; Gordleeva et al. 2018)	Tsodyks et al. 1998; Ullah et al. 2006; De Pittà et al. 2009; Kazantsev 2009; Gordleeva et al. 2012, 2018; Li et al. 2016	Hippocampal CA1-CA3 / Synaptic transmission
Aleksin et al. 2017 (https://github.com/LeonidSavtchenko/Arachne/tree/master/ExamplePLOS)	100 PY, 100 IN Hodgkin and Huxley type model (Kopell et al. 2010)	100 (De Young and Keizer 1992; Li and Rinzel 1994; Nadkarni and Jung 2003; Volman et al. 2007)	Tsodyks et al. 1998; Olufsen et al. 2003; Volman et al. 2007	Hippocampal CA1 / Synchronization and plasticity
Postnov et al. 2009	2–3 FitzHugh-Nagumo model (FitzHugh 1961)	1–10 (Dupont and Goldbeter 1993; Sneyd et al. 1994; Kopell et al. 2000; Postnov et al. 2007)	Kopell et al. 2000; Ullah et al. 2006; Postnov et al. 2007	Generic / Ca^{2+} dynamics

Finally, we would like to conclude that most of the computational models for astrocytes are not available in model repositories which makes it challenging to study and further develop the models (for more discussion, see Manninen et al. 2018b, 2019, and for available models, see ModelDB (McDougal et al. 2017)). Therefore, the field of computational glioscience should strive for the principles of reproducible science (Cannon et al. 2007; Nordlie et al. 2009; Crook et al. 2013; McDougal et al. 2016; Manninen et al. 2017, 2018a,b, 2019; Rougier et al. 2017).

1.6. Conclusions

In this chapter we have summarized the most significant experimental findings of neuron-astrocyte interactions and how they influence brain circuits. In particular, we have discussed the role of astrocytes in cellular excitability, synaptic transmission, and synaptic plasticity. The findings presented here clearly indicate that astrocytes can no longer be neglected when studying brain circuits and their functions. We have also examined the state of the art in computational modeling of neuron-astrocyte interactions, particularly in excitability, synaptic transmission and plasticity. We conclude that computational modeling studies are increasingly presented to provide further evidence that astrocytes are an integral part of brain circuit functions. There is, however, a lot to gain from creating improved, data-based astrocyte models. For example, the complex astrocyte morphology as well as the astrocytic cell membrane biophysics should be represented more realistically compared to existing astrocyte models.

Most of the knowledge on astrocytes is collected using *in vitro* cell culture and slice preparations. To further our understanding there is a need for *in vivo* studies of astrocytes' biology and function. New wet-lab measurement techniques and selective pharmacology tailored specifically for astrocytes, will be necessary to develop new *in silico* models of astrocytes, particularly to understand human brain disorders and diseases. Dysfunction in neuron-glia interactions may contribute to the pathogenesis of neurodevelopmental and neurodegenerative disorders. A neuron–glia crosstalk that governs the maturation and remodeling of synapses will be one important future research area where integration of morphological, biophysical, and biochemical wet-lab data and *in silico* modeling may provide to be fruitful to understand progression of brain disorders.

Acknowledgements

This research has received funding from the European Union's Horizon 2020 Framework Programme for Research and Innovation under the Specific Grant Agreement Nos. 720270 (Human Brain Project SGA1), 785907 (Human Brain Project SGA2), and 945539 (Human Brain Project SGA3), and the Academy of Finland (decision Nos. 297893, 318879, 326494, 326495, 345280).

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