Special issue on neuron–glia interactions

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1 Introduction

What is the physiological importance of bidirectional neuron–glia dynamic signaling in the brain? The amazing architecture of the brain consists of hundreds of billions of neurons, as well as trillions of supporting cells called glia which comprise approximately half the volume of the adult mammalian brain. Glial cells, divided into oligodendrocytes, microglia, and astrocytes, are organized into distinct non-overlapping domains whose boundaries are intimately in contact with synapses and cerebrovascular pathways. Since the first systematic studies of the central nervous system, the information communication and processing roles of neurons were clearly recognized, while the electrically non-excitable glial cells were investigated for their contribution to different physiological processes, such as differentiation, proliferation, and neurotrophic support. Astrocytes are now thought to go beyond these contributions, being involved in almost all aspects of the brain function. There is growing evidence that astrocytes are able to partition the extracellular space, altering and influencing the synaptic microenvironment, as well as neurons' growth. Astrocytes can alter the positioning and the diffusion of neuroactive substances, attracting cells able to repair neurons. Moreover, astrocytes synergistically regulate neuronal activities and blood circulation, thus influencing the neuronal metabolism. It is worth mentioning the relationship between astrocytes and several neurological disorders, i.e., epilepsy, stroke, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.

In the mid-1990s, evidence demonstrated how astrocytes show a different form of excitability, undergoing elevations in intracellular calcium concentration in response to the release of synaptic neurotransmitters rather than electrical changes in the membrane potential. Many cells employ a network of biochemical reactions for calcium signaling to carry information from the extracellular side to internal targets. But what underlying

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information do the glia acquire from the synapse? Democritus of Abdera would say: “we know nothing really; for truth lies at the bottom.” Thus, many efforts have been recently devoted to understanding the functional role of the calcium response in order to decipher how this complex dynamical response is regulated by the biochemical network of signal transduction pathways in the central nervous system. Several experiments indicated how calcium signals are generated in response to external stimuli encoding information via frequency, amplitude, or both modulations. Consequently, these observations were captured by several models consisting of dynamical variables and/or intracellular diffusion mechanisms exhibiting the above-mentioned modulations as well as different and more advanced encoding modes. This demonstrated how astrocytes are active participants in brain information processing and key elements in the physiology of the nervous system. Going further, some authors are fascinated by an “astrocentric hypothesis,” where astrocytes are being considered as the final stage of conscious processing.

Following these observations, some of the mechanisms underlying synaptic physiology are now becoming clearer. New reports are constantly enhancing our understanding of the bidirectional signaling between neurons and glia, opening fascinating new perspectives on their role. The underlying mechanisms and the crucial modulating role of glia are becoming clearer through the study of synaptic activities. Re-examinations and refinements of existing studies on the dynamics of neuron–glia interactions are under investigation with the aim to discover self-consistent models of the neuron–glia information processes able to capture the dynamical and computational properties of the synapse. All these efforts will have an impact both in brain neurophysiology and in network and nonlinear dynamics theory, defining a new path for neuroscience. The novel concept of the “tripartite synapse,” for the astrocyte processes’ close contact with the neuronal synapse, has been introduced. Astrocytes are considered to regulate the synaptic signaling currents between neurons, modulating the amount of neurotransmitters, including glutamate or adenosine–triphosphate, in the synaptic cleft through inter- and intracellular calcium dynamics.

The tripartite synapse involves a pre-synaptic neuron releasing neurotransmitters to activate or inhibit the activity of a post-synaptic neuron, the post-synaptic neuron, and the astrocyte that protects cells by taking up glutamate to prevent overexcitation and secretes growth factors. The astrocyte provides energy via glucose and modulates receptor function by locally released neurotransmitters. They are accurate sensors of neuronal activity and respond to the synaptic release of glutamate with oscillations in the intracellular calcium concentration. Glutamate elevations in the astrocyte domain trigger the internal release of inositol 1,4,5-trisphosphate, which stimulates intracellular calcium dynamics. The properties of intracellular calcium oscillations generated in astrocytes, including their amplitude, frequency, and propagation, are governed by the intrinsic properties of both neuronal inputs and astrocytes. Astrocytes discriminate neuronal inputs of different origins and can integrate concomitant inputs responding to calcium elevations. Calcium dynamics is controlled by the interplay of calcium-induced calcium release, a nonlinear amplification method dependent on the calcium-dependent opening of channels to calcium stores such as the endoplasmic reticulum, and the action of active transporters that enable a reverse flux. The level of inositol 1,4,5-trisphosphate is directly controlled by signals impinging on the cell from its external environment. The elevation of the intracellular calcium level in astrocytes, promoted by the extracellular glutamate, triggers the release of glutamate from the astrocyte, modulating the pre-synaptic and post-synaptic neural activities by promoting a depolarizing current in neurons.

As a reflection of the growing importance of neuron–glia investigations, the focus of this Special Issue of the *Journal of Biological Physics* is to publish outstanding recent results, challenging mathematical efforts, biophysically consistent models and in-depth analysis, as well as new perspectives, on neuron–glia interactions, roles, and signaling. This issue contains papers discussing a part of the brain that is largely unexplored and facing controversial neurophysiological processes. I definitely hope that this special issue will benefit, encourage, and inspire researchers looking beyond neurons, opening new exciting perspectives both in biological physics and in brain neurophysiology.

2 Guide to the special issue

The first paper of the Special Issue, by Ricci et al., presents a review of astrocyte–neuron interactions in neurological disorders. Ricci et al. discuss astrocyte functions, focusing specifically on their main functions in the regulation of cerebral blood flow, in brain metabolism, in synaptic regulation, and in inflammatory response. They report the emerging evidence of astrocyte dysfunction in the pathophysiology of neurological disorders, including neurodegenerative disease, stroke, epilepsy, migraine, and neuroinflammatory diseases, pointing out how glial cell dysfunction may promote development or progression of such diseases.

The paper by Staats and Van Den Bosch explores the recent evidence, which suggests a relevant role of astrocytes in the initiation and progression of amyotrophic lateral sclerosis. They discuss the recent research reporting how non-neuronal cells disturb the crosstalk between astrocytes and motor neurons, and as a consequence, motor neuron death in amyotrophic lateral sclerosis is accelerated. Emerging therapeutic approaches aimed to slow this fatal neurodegenerative disease are also reported, identifying the replacement of the bad environment of the motor neurons by transplanting healthy astrocytes as the newest and most promising approach.

Nobili describes in his paper novel perspectives and fascinating hypotheses in brain information processing. The author tries to explain how and why electroencephalographic signals can be generated even in the absence of neuronal spiking, discussing the relevance of synchronization and desynchronization mechanisms in the brain, as well as the requirement of universality and massive parallelism and the possible role played by the astrocytes. Modeling the effects of intrinsic subthreshold voltage oscillations and arguing how the dispersion of time relations among synaptic inputs would make it impossible to preserve the temporal ordering of information flows during recursive procedures, the author paves the way to discover neurodynamic mechanisms yet far from being totally explored.

The paper by Di Garbo presents a biophysical neural network model consisting of a pyramidal neuron, an interneuron, and an astrocyte able to describe the reciprocal intercommunication effects on the neural dynamics. Di Garbo demonstrates through a numerical simulation, in agreement with the experimental results, that the increase of the calcium concentration in the astrocyte determines a decrease of the oscillation period of the neural network, identifying the parameters that strongly influence the calcium dynamics. Such results are interpreted by the author from a biological point of view, suggesting the hypothesis that astrocytes could be implicated in the generation of epileptic phenomena and discussing interesting generalizations of his model.

The paper by De Pittà et al. investigates the modulation of intracellular calcium dynamics in astrocytes in response to synaptic activity, deriving a mathematical model for glutamate-induced astrocytic intracellular calcium dynamics. In the model, the essential biochemical features of the regulatory pathway of inositol 1,4,5-trisphosphate are identified. In agreement with available experimental data, De Pittà et al. describe self-sustained inositol 1,4,5-trisphosphate oscillations in terms of the coupling of inositol 1,4,5-trisphosphate metabolism with calcium dynamics, suggesting how glia-based self-consistent oscillators could be generated and modeling phase-locked calcium oscillations under conditions of intense stimulation. Phase-locked calcium oscillations could also be interpreted as a fingerprint of pathological conditions, such as in the case of epileptic patients with Ammon's Horn sclerosis. Furthermore, the authors demonstrate how inositol 1,4,5-trisphosphate dynamics are encoded by an amplitude and frequency modulation, while calcium oscillations are inherently frequency modulated.

Allegrini et al. provide a network model of mutual neuron–astrocyte interactions, investigating the possible roles of astrocytes in neuronal network dynamics. The authors studied the information entropy of neuronal firing, discussing the influence of neuron–glia interactions. The network model consists of computationally efficient models for neurons, astrocytes, and their communications. The authors observe how the entropy of the distribution increases in the presence of neuron–astrocyte interactions, increasing the computational complexity of the neural code. Their model shows how deficits in astrocytes could shut down neuron–astrocyte communications, giving rise to global synchronization events akin to pathological conditions such as epileptic shocks.

The paper by Postnov et al. describes a functional model of a neuron–astrocyte network that can reproduce typical local and global dynamical patterns observed in biological experiments. The authors spatially extend the concept of the tripartite synapse, mimicking the geometry of a two-dimensional biological astrocytic network, even if the reported qualitative and non-dimensional models remain reasonably simple for theoretical and numerical analysis. The model is capable of reproducing the main general responses and of explaining the underlying nonlinear mechanisms predicting dynamical patterns and structures that have not yet been experimentally observed. The authors address the problem of their model validation and generalization of the results.

Billeci et al. investigate how astrocytes influence the synaptic microenvironment and neuronal morphology using an image and data processing framework designed for the extraction and analysis of relevant dynamic morphological features of neurons *in vitro*. The authors describe their technique and the dedicated algorithms adopted to extract relevant features, such as morphometric variables, fractal dimension, and directionality, and they discuss the correlation and classification of cells according to their morphology and the effect of glia. The systematic and automated method by Billeci et al. represents an important step for the assessment of quantitative differences in dynamic neuron–glia morphology in a variety of experimental conditions.

Pereira and Furlan explore in their paper the exciting hypothesis that astrocytes could be involved with the formation of a multimodal “conscious scene” to be used for the coordination of adaptive behavior and as the final stage of conscious processing. They propose that the role of global neural synchrony in perceptual conscious processing could induce exchange of information patterns between embodied local field potentials and astrocytic calcium waves. Calcium waves are here considered as responsible for the “binding” of spatially distributed patterns into unitary conscious episodes. Pereira and Furlan suggest that the patterns embodied in calcium waves are generated by glutamatergic

excitation from neurons to astrocyte membrane receptors, arguing for a threshold for the activation of coherent calcium dynamics and a set of biophysical conditions that enter the conscious spotlight.

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