A CMOS Neuromorphic Approach to Emulate Neuro-Astrocyte Interactions

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Abstract—A CMOS neuromorphic circuit is proposed with two main features. First, we emulate the uptake of neurotransmitters by astrocytes, a type of glial cell, that plays an active role in the coordination of information between neurons. Second, we propose a synapse inactivation mechanism, which prevents the saturation of postsynaptic neurons in the absence of an astrocytic process. We show the influence of both mechanisms on the firing of a small network of neurons interacting with an astrocyte. We also incorporate the release of gliotransmitters by the astrocytic microdomain into this network according to the activities of neighbor synapses. This work contribute to better understanding the importance of astrocytes in neuro-glia interactions, and illustrates the active role astrocytes play.

I. INTRODUCTION

The role of glial cells, in particular astrocytes, in neuronal communication has been subject of debate during recent decades. While it still remains to be elucidated to what extent astrocytes may influence the flow of information in the brain, there is substantial evidence that shows astrocytes are not silent in this process [1], [2]. Meanwhile, studies have revealed their capability to modulate the excitability of neurons at least in two different ways.

First, by the uptake mechanism astrocytes maintain the balance of neurotransmitter concentration, i.e. glutamate, in the extracellular space [3]. Without this mechanism presynaptic neurons would disconnect their synapses from the postsynaptic neurons when a large amount of neurotransmitters is released into the synaptic cleft [4]. We refer to this process as “synaptic inactivation”, which results in decreasing the likelihood of a neuron to fire. Second, as an active element in the communication between neurons, astrocytes are endowed with the ability to also modulate synapses by the release of transmitters, so called gliotransmitters, influencing synaptic transmission [5], [6], [7], [8].

Our goal for the experiment described in this paper is to create neuromorphic circuits incorporating the influence of astrocytes as part of the BioRC Biomimetic Real-time Cortex project [9]. The aim is to demonstrate some gross first-order intercellular behavior of the astro-neuronal communication, focusing on synapse modulation by an astrocyte. Specifically, we propose CMOS circuits to emulate the astrocytic uptake and synaptic inactivation mechanisms. We also incorporate the astrocytic microdomain mechanism previously published by our group that demonstrated the communication between two neurons via an astrocyte, but did not reduce the synaptic concentration of neurotransmitters during astrocytic uptake, and did not inactivate synapses not connected to astrocytes [10].

To emulate the astrocytic uptake mechanism we designed a small circuit to limit the synaptic cleft voltage that represents neurotransmitter concentration in the cleft. To emulate the synaptic inactivation process, we designed a feedback stage that monitors the cleft voltage, so that pre- and postsynaptic circuits are disconnected in the case of a voltage (neurotransmitter concentration) above the threshold. Conversely, synapses surrounded by an astrocytic process are modulated by the uptake of neurotransmitters, maintaining the voltage cleft below the threshold that inhibits the inactivation stage.

The proposed circuit is a high frequency design, containing parasitic capacitances along with transistor channel and interconnection resistances. We utilize such nonlinearities to avoid using discrete elements such as resistors and capacitors. While our small example circuits are quite fast, the performance will be slowed significantly when the massive fan out and fan in proportional to biological neurons are implemented, due to capacitive loading and interconnect resistance. Thus the relative timing differences between our electronics and the biological waveforms will be significantly reduced.

To show the influence of astrocytic mechanisms on neuronal firing, we have designed and simulated a small network of neurons spanned by an astrocyte. The presynaptic neurons are excited with regular spike trains. The firing of neurons depend on the total excitatory postsynaptic potential (EPSP) that may vary according to the influence of astrocyte mechanisms and the number of synapse connections.

II. BIOLOGICAL BACKGROUND

Unlike neurons, astrocytes are not electrically excitable cells, i.e. their excitability is not based on the generation of action potentials. Instead, they posses a chemical and mechanical form of excitability that is manifested in their intracellular Ca$^{2+}$ waves. Recent publications have shown that astrocytes, like neurons, integrate, process information, and discriminate between synapses [11], [12]. Each astrocyte has hundred of long thin processes that contact thousands of neuronal synapses, and can span over a hundred neurons.
Astrocytes form “tripartite synapses” [11], i.e. at the synaptic level the pre- and post-synaptic elements are enwrapped by an astrocytic element. A variety of gliotransmitters is released from astrocytic compartments according to the neuronal activity across a microdomain, i.e. individual regions on an astrocytic process that may have different structures.

Their high resting potential, high conductance, low intracellular concentrations of glutamate, and excitatory amino acids such as EAAT1 and EAAT2 make astrocytes efficient in the uptake of glutamate [13]. It is this mechanism that allows astrocytes to limit the diffusion or “spillover” of glutamate, so that synapses at a particular location do not activate receptors on neighboring synapses [3]. Despite the fact that glutamate is the main excitatory neurotransmitter in the CNS system, an excessive release of glutamate without an astrocytic uptake mechanism can result in the saturation of synapses and the eventual loss of synapse connections [4], [14]. Undoubtedly, the astrocytic uptake mechanism is an important synapse regulator. Although neurons have their own uptake mechanism, their transporters face the opposition of a higher electrochemical gradient and constant variations in the membrane potential [15], [13], [16].

In addition to glutamate uptake, astrocytes influence neuronal behavior by the release of gliotransmitters, i.e. glutamate, D-serine, GABA, and ATP. When calcium waves are induced on astrocytes, a bidirectional form of communication with neurons at the “tripartite synapse” occurs [11]. These findings suggest that at a “tripartite synapse” the excitability of neurons is under the influence of astrocytic-neuronal interactions. Astrocytes are also endowed with the ability of conveying information between distant synapses within the same microdomain [17].

A number of experiments have investigated the potential role of astrocytes in synaptic plasticity [18]. Many studies on the excitatory Schaffer collateral synapse in the CA1 region of the hippocampus have suggested that astrocytes play a role in short-term depression and short-term potentiation, by their ability to strengthen and weaken synapses [11], [19]. It is known that long-term potentiation requires the activation of NMDA receptors. These receptors are activated by D-serine molecules. The source of D-serine in the brain is astrocytes, so it is suggested that for LTP to occur in the hippocampus and prefrontal cortices, astrocytes have to be part of the process [18].

III. BACKGROUND IN NEUROMORPHIC ENGINEERING

Recent advances in neuromorphic engineering have focused mainly on neural mechanisms such as spike timing dependent plasticity (STDP) [20], [21], synaptic rewiring [22], [23] and neural spiking [24], [25]. There has been a focus on emulating biological neural networks based on these mechanisms to demonstrate learning. An increasing interest in astrocytic-neuronal communication has paralleled our development of neuromorphic circuits incorporating astrocytes. To the best of our knowledge, our group provided one of the first contributions to the area with the detection of neural activity and emulation of the glutamate release by astrocytes upon calcium excitability [10]. Moreover, our designs include synapse circuits [26], [27] with focus on emulating biological features such as the neurotransmitter release, neurotransmitter concentration, neurotransmitter reuptake, and transmitter-receptor interaction.

The design of biomimetic circuits to be used in large scale networks is a major challenge due to the massive interconnections in the brain. The existence of synaptic divergence (fan out in engineering terms) and convergence (fan in), causes significant delays in electronic circuits. Thereafter, our small example circuits work at nanosecond (CMOS) speed. These circuits, when incorporated into large networks with thousands of synapses per neuron, will slow down significantly due to wiring interconnection capacitances [28].

The compartmentalized construction of our neuromorphic circuits and the ability to control neural parameters directly by means of specific control voltages allow us to insert additional mechanisms without extensive circuit redesign. In this paper we use this compartmentalized approach to insert the uptake of glutamate by astrocytes and the synapse inactivation mechanism, along with the astrocytic calcium $Ca^{2+}$ release causing glutamate release easily into the neurotransmitter section of our synapses, as described in the next section.

IV. CIRCUIT IMPLEMENTATION

The excitatory synapse along with the astrocytic and the synapse inactivation mechanisms are shown in Fig.1. Stages (2) and (4) shows the pre- and post-synaptic sections separated by the synaptic cleft. The astrocytic uptake mechanism is emulated in Stage (3), while the influence of the astrocytic release of gliotransmitters induced by the communication with neighbor synapses is performed in Stage (5). The synapse inactivation mechanism in Stage (6) feeds back the synaptic cleft activity into the presynaptic neuron by means of Stage (1).

The synapse circuit consists of two main parts: neurotransmitter (presynaptic) and receptor (postsynaptic) sections. The $Presynaptic\ Input$ normally receives a regular train of spikes from the $Input\ Spikes$ terminal. On the presynaptic side, the input pull-up transistors charge the $Synaptic\ cleft$ node during the spike time. The input $NT\ Conc.$ modulates the concentration of neurotransmitters. Within the time duration that no arrival of spikes occur the $Synaptic\ cleft$ node is discharged through the input pull down transistors. This mimics the drop of neurotransmitters in the synaptic cleft by the reuptake process which can be tuned by the input $Reuptake$. The charge in the $Synaptic\ cleft$ node mimics the concentration of neurotransmitters in the cleft over time. The $Synaptic\ cleft$ signal is characterized by a fast rise time and a slow fall time constant.
The presynaptic section is a modified version of the BioRC excitatory synapse circuit [10]. We have removed a pMOS transistor in the pull-up part that self-limited the cleft voltage (cleft neurotransmitter concentration) to increase the dynamic range in the Synaptic_cleft node. This further modification allows us to show the astro-neuron interaction between the uptake mechanism and the synapse. In order to compensate for the node capacitance removed and maintain existing circuit timing, an nMOS transistor has been inserted into the cleft. To incorporate the contribution of gliotransmitters into the synaptic cleft, an adder [29] was introduced into the cleft section in a previous publication [10].

The output of the postsynaptic stage is the excitatory postsynaptic potential (EPSP), which is roughly proportional to the neurotransmitter concentration in the synaptic cleft, modulated by receptor availability on the synaptic ion channels. The gliotransmitters released from Stage (5) adds to the neurotransmitters in the Synaptic_cleft to facilitate the firing of postsynaptic neurons. These gliotransmitters are released from one of the compartments of the astrocytic microdomain (a distributed resistive network), when the other compartments of the microdomain have been excited by neurotransmitters released from other synapses, as shown in Fig.2. In this process neighbor synapses mediated by the propagation of Ca^{2+} through the microdomain influence each other. The AstroCa^{2+} is the control signal that causes the synaptic cleft to be offset by a voltage Astro_glut_release. This models the amount of glutamate gliotransmitter that is injected into the cleft by the astrocyte.

While there are many control inputs in the neuromorphic circuits we produce, in actual implementations those control inputs would be common to many neurons or would be generated internally on chip, based on the state of the circuit as execution progressed. We show them as inputs to the circuit to illustrate the level of control the designer and user have over the behaviors of each circuit. Versions of our neuromorphic circuits have such inputs produced by additional circuits that would be found on the final chip. Routing is indeed a major challenge, but advances in 3-D connectivity are pushing the levels of integration possible using current CMOS technology. Nanotechnology will likely be required for brain-scale neural networks.

Figure 2 shows several compartments of an astrocyte circuit. It is a distributed resistive (pass transistor) network that takes inputs from the voltages representing synaptic cleft neurotransmitter concentrations of different synapse circuits. The neurotransmitter voltage from each synapse is fed into a non-inverting delay circuit whose output voltage representing released neurotransmitters is summed with delayed neurotransmitter voltages from other synapses. This emulates the
time taken by the astrocyte to take up neurotransmitters and generate $\text{Ca}^{2+}$. The rise in potential at the resistive network ($\text{AstroCa}^{2+}$) models the increase and spread of calcium across the astrocyte. The outputs of the astrocyte compartments control transistors in each synapse such that the synapse adds an offset voltage $\text{Astro\_glut\_release}$ to the synaptic neurotransmitter concentration voltage to emulate the increase in neurotransmitters in the synapse due to the astrocytic release of glutamate caused by the increase of intracellular calcium.

The neurotransmitter concentration in the cleft is also influenced by the astrocytic glutamate uptake mechanism in Stage (3). The nMOS transistor connected as a diode emulates the uptake of neurotransmitters. In biological neurons, the astrocytic uptake mechanism exert a control on the transmitters in the cleft, so that the postsynaptic neuron is not overwhelmed by the presynaptic neuron. To model this behavior, an upper bound limit is set by the $\text{Astro\_glut\_control}$ voltage. The mechanism is activated when the cleft node rises above $V_{th, h} + \text{Astro\_glut\_control}$ voltage, where $V_{th, h}$ is the threshold of the transistor. In the absence of the astrocytic uptake, a large enough rise in the cleft voltage triggers the circuit in Stage (6), whose threshold is set to be greater than the threshold for the astrocytic uptake, thus giving priority to the astrocytic mechanism when available at the synapse.

Stage (6) consists of a negative level-sensitive latch component, where the input $\overline{ck}$ is controlled by an inverting stage. The outputs ($Q$, $\overline{Q}$) determine the synapse state by means of selecting the input to the presynaptic stage in Stage (1). An excess of voltage in the cleft node above the threshold of Stage (6) causes the inverting stage to set $\overline{ck}$ to 0.0 V through the pull down transistor, so that the output $Q$ becomes $V_{dd}$. This forces 0.0 V into the presynaptic input, thus resulting in the synapse inactivation. The transistors connected to the input of the nMOS transistor in the inverting stage in Stage (6) provide a two-fold operation. They increase the activation threshold and also allow us to slow down the process of inactivation by increasing the path delay through the diffusion capacitances. An asynchronous reset signal ($\overline{Reset}$) is also available to reestablish the synapse function.

The latch component consists of one pMOS pass transistor that allows transferring the input $V_{dd}$ when $\overline{ck}$ is low, and a transmission gate that controls a feedback loop that saves the data into the latch when $\overline{ck}$ is high. The feedback loop consists of a NAND gate to introduce the reset signal, and an inverter.

V. SIMULATION RESULTS

The network shown in Fig.3 illustrates the configuration we used for this experiment. In a network of silicon neurons an astrocyte spans several synapses to create the neuro-astrocyte interactions. In our experiment, synapses S1–S4 are modulated by the two astrocytic mechanisms, i.e. glutamate uptake and the astrocytic microdomain (dashed cyan arrows). The presynaptic neurons N1–N3 fire regular train of spikes at the same rate. The firing of spikes by postsynaptic neurons N4–N6 is determined by the EPSP contributions of their respective synapses. We set the firing threshold so that these neurons fire when there is enough dendritic potential (about equal to the sum of the EPSPs of the three synapses). To show the influence of the astrocytic mechanisms on the firing of neurons, we run simulations of the circuit network for two different conditions: First in the absence of astrocytic mechanisms, and second in the presence of astrocytic mechanisms.

The $NT\_Conc.$ voltage in synapses S1–S3, S6 and S7 is set to 900 mV, while S4 and S5 are set to 2.0 V. For the ease of description let us refer to these two type of synapses as “normal” and “strong”. Notice that the contribution of one strong synapse to the total EPSP of a neuron is more than that of two normal synapses. So that a neuron with a strong synapse needs only the help of one additional normal synapse to generate action potentials. Nevertheless, the strong synapse cannot keep contributing to the total EPSP due to the triggering of its inactivation mechanism. Conversely, when the astrocytic uptake mechanism is available, the cleft voltage is bounded by the astrocytic uptake threshold that inhibits the inactivation mechanism and thus keeps the synapse contribution.

The simulation in Fig.4 shows the action potential of postsynaptic neurons along with their respective total EPSPs in the network without astrocytic mechanisms. Neuron N4 is connected only to two normal synapses S1 and S2, so it does not have sufficient EPSP to fire. While neuron N5 has the same number of synaptic connections to S3 and S4, it is able to fire due to the fact that S4 is a strong synapse and so provides N5 with enough EPSP to start firing. However, as shown in the middle panel, the total EPSP:N5 decays over time, so that after some spikes the neuron stops firing. This happens due to the triggering of the inactivation stage in synapse S4. Notice that this mechanism is triggered after a delay giving chance
to the synapse to stay connected by reducing the amount of neurotransmitters.

Neuron N6 has three synapse connections, where S5 has a similar condition to S4 and thus it cannot continue contributing to EPSP.N6. This eventually leaves the neuron with only two normal synapses S6 and S7 which are not enough to fire N6. Nevertheless, N6 fires one action potential more than N5. This is because the total EPSP.N6 is initially larger than that of N5, and so after triggering the inactivation mechanism the decaying process starts from a higher EPSP voltage.

In steady state, the total EPSP.N6 is larger than that of N5, but as the same as that of N4. This corresponds to the contribution of S6 and S7 to N6 which is the same contribution as S1 and S2 to N4, while N5 receives a contribution from only S3. Notice that in the absence of astrocytic uptake mechanism, synapses S4 and S5 are inactivated due to the increase of neurotransmitters in their clefts.

For this experiment we have set the Astroglut_control voltage in Stage (3) to 200 mV, so that the astrocytic uptake activation level for this experiment is 850 mV. The Astroglut_release voltage in Stage (5) is set to 200 mV, while the Reuptake, Spread, and Receptor voltages are set to 470 mV, 500 mV, and 800 mV respectively. The circuit simulations were conducted using TSMC 18 CMOS technology in SPECTRE using a power supply of 1.8 V.

The simulation results for the network interacting with the astrocytic mechanisms is illustrated in Fig.5. These results show that the astrocytic circuits influence the firing of neurons N4–N6 by the modulation of synapses S1–S4. Notice that without the help of astrocyte, neuron N4 cannot fire as illustrated in the previous simulation of Fig.4.

Now, in Fig.5(b), neuron N4 starts firing after elapsing a time delay, that is when sufficient gliotransmitters are added into the synapses. The sum of gliotransmitters to the cleft voltage strengthens the synapses S1 and S2, so that raising the EPSP.N4 above the firing threshold. These contributing signals are respectively illustrated by Cleft.Glio.S1 and Cleft.Glio.S2 in the bottom panel of Fig.5(a). The cleft voltage of S1 is shown by cleft.S1 signal in the top panel, where the normal synapses (S1–S3, S6 and S7) have similar cleft signals.

The AstroCa$^{2+}$ control signals are shown in the middle panel of Fig.5(a), which are the control of transistors in Stage (5) of synapses S1–S3. The major contribution of gliotransmitters from the microdomain is for synapse S3 as the AstroCa$^{2+}$ compartment is under the direct influence of synapse S4 which releases more neurotransmitters than other synapses within the astrocytic microdomain.

In Fig.5(b), the middle panel shows that neuron N5 continues firing a regular train of spikes. This is in contrast with the case of Fig.4, where neuron N5 stops firing after some time since synapse S4 is inactivated without the intervention of astrocyte. Now, synapse S4 is controlled by the astrocytic uptake mechanism which prevents the inactivation process by limiting the cleft voltage of S4 to 850 mV, i.e. the threshold of the uptake mechanism in Stage (3). Thus the glutamate uptake plays a fundamental role in the firing of neuron N5.

We also show the cleft signal of synapse S5, Cleft.S5, in Fig.5(a). This signal illustrates the time taken for the synapse to disconnect from the postsynaptic neuron N6. As we previously mentioned, this synapse has an excess of neuro-
Fig. 5: In Fig. 5(a) the top panel shows the cleft signals for synapses S1, S4 and S5. The middle panel shows the AstroCa$^{2+}$ control signals for synapses S1–S3, while the bottom panel shows the gliotransmitter release from the astrocytic microdomain. The synaptic cleft of S4 is controlled by the astrocytic glutamate uptake mechanism. Since synapse S5 lacks an astrocytic uptake, the Synapticclef t node rises above the S4 level. Synapse S5 is eventually disconnected from the presynaptic side after a delay. In Fig. 5(b), neuron N4 begins firing due to the contribution of astrocytic gliotransmitters, even though it has only two normal synapses. Neuron N5 continues firing by the virtue of the astrocytic glutamate uptake mechanism. Neuron N6 is not able to maintain regular firing because the astrocytic glutamate uptake mechanisms is not present on synapse S5, so it is eventually disabled.
transmitters and does not have an astrocytic uptake mechanism to regulate its behavior. As shown in Fig. 5(b), after some presynaptic action potentials the synapse will be inactivated and thus N6 cannot continue firing.

VI. CONCLUSION

We have used neuromorphic circuits to demonstrate a substantial feedback interaction between astrocytes and neurons. Although the role of glial cells in neural functioning is not completely understood, our circuits provide an experimental mechanism for researchers to investigate possible influences of glial cells. The small network we have designed shows the importance of astrocytic processes in the synapse. Astrocytes modulate synapses through the uptake of neurotransmitters or the release of gliotransmitters. While we have been able to demonstrate the modulation of synapses by astrocytic mechanisms, and the excitation of astrocytes by neurons it is only the first step in circuits to implement the complex interactions between neurons and astrocytes. The next step is Monte Carlo simulations to determine behaviors under process and environmental variations. Scaling to larger circuits is also planned.

REFERENCES