

# Role of Astrocyte in Desynchronization Analogue Neural Network

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**Abstract:** Neural synchronization is considered as a key role in several neurological diseases, such as Parkinson's and Epilepsy's disease. During these diseases, there is increased synchronization of massive numbers of neurons. In addition, evidences show that astrocytes modulate the synaptic interactions of the neuronal population. The Astrocyte is an important part of a neural network that can be involved in the desynchronization of the neuronal population. In this paper, we design a new analog neuromorphic circuit to implement the effect of astrocyte in the desynchronization of neural networks. The simulation results demonstrate that the astrocyte circuit as a feedback path can be desynchronized to a synchronized neural population. In this circuit, as a first step, the population of twenty neurons is synchronized with the same input currents. Next, by involving an astrocyte feedback circuit, the synchronization of the neural network is disturbed. Then, the neuronal population will be desynchronized. The proposed circuit is designed and simulated using HSPICE simulator in 0.35  $\mu\text{m}$  standard CMOS technology.

**Keywords:** Synchronization, Astrocyte, Neural Network, Analog Circuit.

## 1 Introduction

**S**YNCHRONIZATION process plays an important role in brain function [1, 2]. Synchronization between neuronal populations causes diseases like epilepsy and Parkinson's [3, 4]. Improper functioning of the glial cells causes Parkinson's disease, which is a common problem in adults [5]. Symptoms such as unusual tremors and muscle stiffness are seen in many patients [6]. Epilepsy has affected the brain function of more than 50 million people worldwide. The sudden propagation of synchronous firing in a great ensemble of neurons causes seizures in epilepsy [5, 7]. The researchers' findings give us a good understanding of epilepsy disease [8]. Evidence shows that the

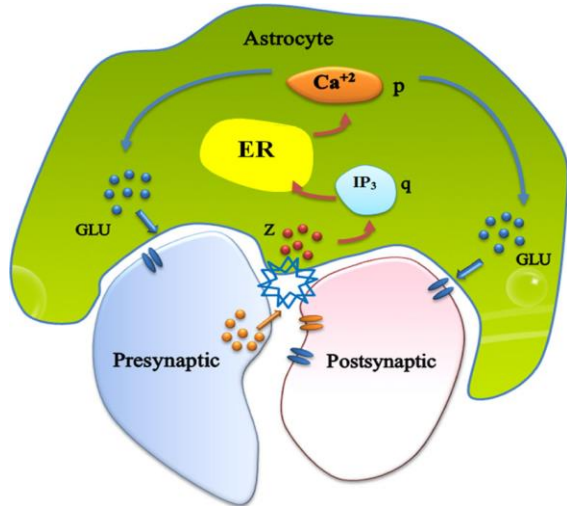
interactions between neurons and astrocytes should be studied to understand epilepsy [9, 10]. Astrocytes are star-shaped cells and they are the most numerous types of glial cells that form half the volume of brain tissue [11, 12]. Scientists thought that astrocytes were only trophic support for neuronal cells in the nervous system, but research in recent years has shown that they have a key role in brain activity like synaptic activities, neurotransmission, and neuronal signaling [9]. They are also excitable cells that have essential tasks in synaptic transmission in the nervous system [13]. Nowadays, researchers conclude that astrocyte interactions go beyond neurotrophic support. Recent evidence show that astrocytes are involved in the development of diseases such as Parkinson's, migraine, and epilepsy [9]. Astrocytes do not have the action potentials, but they react to neural activity by increasing intracellular calcium levels. They can understand neurotransmission and increase their calcium that leads to the release of glutamate transporters like glutamate or ATP, which can modulate the synaptic power of neighboring neurons [14, 15]. Therefore, they take part in synaptic transmission and complete the interactions of the neural population. In this way, the term "tripartite synapse" (Fig. 1) can be expressed, which refers to a set of presynaptic neurons, postsynaptic neurons, and

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**Fig. 1** Tripartite synapse which is consisted of the presynaptic neuron, postsynaptic neuron, and astrocyte.

astrocytes [15-17]. In this way, astrocytes “listen and respond” to the synapse [18]. And also, Amiri and *et al.* in [19] show that astrocytes can asynchronize the synchrony between two coupled neurons through changing the synaptic strengths.

Based on this finding, astrocytes are a good option as a stimulator for hyper-synchronous oscillations [20]. In this paper, we have implemented a functional approach to show the effect of astrocyte in desynchronization of neural population, that we use the Izhikevich neuron model which is developed by Wijekoon and Dudek. For stimulator, we used the astrocyte Circuit, which recently has been designed by Ranjbar and colleagues. The whole simulations are implementation in Hspice software. The parts of the paper are organized as follows. In Section 2 the dynamic model of the used astrocyte, the biological description of the neuron model (Izhikevich model), and their interaction in the presence of neurons are presented. The neuromorphic circuit consisting of neuron circuit, astrocyte circuit, and astrocyte-neuron interaction circuit is explained in Section 3. Section 4 presented the results of simulations and finally, Section 5 concludes the article.

## 2 Dynamic Models of Network

In this section, we present used different parts of the neural network. First, we describe the Izhikevich neuron model, and then we present an astrocyte model and its mathematical description.

### 2.1 Neuron Mathematical Model

We use the Izhikevich neuron mathematical model [21]. This simple model has the ability to generate bursting and spiking activities. This is a simple model that produces the dynamical behavior of biological neurons including bursting and spiking activities. The neuron model is described as follows [21]:

**Table 1** Parameter values of neuron and astrocyte models.

Neuron parameter	Value
$a$	0.02
$b$	0.2
$c$	-65
$d$	6
$v$ -th	30
Astrocyte parameter	Value
$K_1, K_4$	1
$K_2, K_3$	2
$K_5$	0.05
$K_6$	1.5

$$\dot{v} = 0.04v^2 + 5v + 140 - u + I \quad (1)$$

$$\dot{u} = a(bv - u) \quad (2)$$

with the auxiliary after-spike resetting:

$$\text{If } v \geq 30\text{mV} \begin{cases} v \leftarrow c \\ u \leftarrow u + d \end{cases} \quad (3)$$

$v$  and  $u$  are membrane potential and membrane recovery variables, respectively.  $a$ ,  $b$ ,  $c$ , and  $d$  are neuron parameters.  $I$  is the input current. Table 1 list the values of the parameters.  $u$  accounts for the activation of  $K^+$  ionic currents and inactivation of  $Na^+$  ionic currents. When  $V$  reaches +30mV,  $V$  and  $U$  are reset according to (3).

### 2.2 Astrocyte Mathematical Model

Numerous studies emphasize that glial cells have an important role in synaptic information processing [17]. If the calcium concentration levels increase, it releases ATP, glutamate, and other neurotransmitters into the synaptic space, which regulates the synapse activity of nearby neurons by feedback mechanism [18]. The dynamics of the biophysical astrocyte model are modeled by Montaseri simplified astrocyte model [22]. This mathematical model will be useful to study the behavior of astrocyte in a small neuron-astrocyte network. In a simplified model, despite some simplifications, the essential features of the biophysical astrocyte model are maintained [22]. This astrocyte model is described by the following equations:

$$\begin{cases} \dot{q} = (1 + \tanh[k_1(Z - k_2)])(1 - q) - k_3q \\ \dot{p} = -k_4p + k_5 + k_6q \end{cases} \quad (4)$$

where  $q$  is the astrocyte internal state,  $k_i$ ,  $i = 1, 2, \dots, 6$ , are constants listed in Table 1,  $Z$  and  $p$  are the input and output of the model, respectively. Synaptic activity between astrocyte and neuron is shown by the parameter  $Z$  (astrocyte input).

The neural interaction stimulates the generation of the second messenger, inositol (1, 4, 5)-trisphosphate (IP3) that is modeled by the internal variable  $q$  which finally leads to the growth of intracellular calcium level. In this

way, the astrocyte mediator ( $p$ ) is released and can control nearby neurons.

### 2.3 Neuron-Astrocyte Interaction Model

A method for studying physiologically network and effect astrocyte in the regulation of synaptic activities is that the network of neurons is formed and astrocyte cell is placed into the network. To have synaptic transmission between neuron and astrocyte and information processing, communication between neuron and astrocyte is necessary [23, 24]. Astrocytes participate in synaptic transmissions through a mechanism of the physiological feedback [25]. Glutamate release from astrocytes is necessary for activates glutamate receptors located presynaptically or postsynaptically. Therefore, a slow transient current is created by the activation of postsynaptic NMDA receptors. That may contribute to synchronization in a network while activation of presynaptic NMDA receptors helps latter glutamate release [17]. To form a network, a feedback path between astrocyte and neurons is modeled. The general schematic of the circuit is illustrated in Fig. 2. The output of the astrocyte is defined as:

$$i_{ast} = \gamma \cdot p \tag{5}$$

The feedback strength from astrocyte to neurons is represented by  $\gamma$ . with considering the effect of astrocyte feedback (Fig. 2), the input complete current equation into the neuron is defined as follows:

$$i(t) = i_{const}(t) + i_{ast}(t) \tag{6}$$

where  $i_{ast}(t)$  is the feedback current from astrocyte and  $i_{const}(t)$  is synaptic input current of the neuron.

## 3 Neuron-Astrocyte Interaction Circuits

### 3.1 The Izhikevich Neuron Circuit

The neuron circuit is used in this paper proposed by [26]. It is based on the Izhikevich neuron model [21] (Fig. 3, neuron circuit) that implements a biologically neuron using only 14 MOSFETs and it has two state variables: membrane recovery ( $U$ ) and membrane potential ( $V$ ), which are illustrated by voltages across

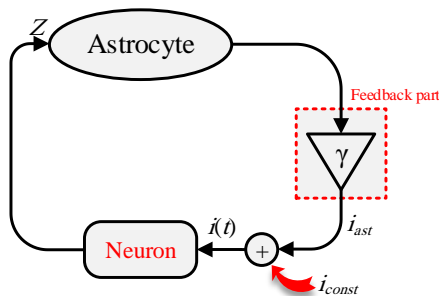


Fig. 2 The general schematic of the relationship between neuron and astrocyte.

capacitors  $C_u$  and  $C_v$  respectively [26, 27]. This circuit can easily be tunable to a desired cortical neuron type [27].

The circuit dynamics can be approximated by the following equations:

$$\frac{dV}{dt} = \begin{cases} a_1V^2 - a_2V - a_3U^2 + a_4U + a_5 + i_1, & V > U - V_T \\ a_6V^2 - a_7V - a_8UV + i_2, & \text{otherwise} \end{cases} \tag{7}$$

$$\frac{dU}{dt} = a_9V^2 - a_{10}V - a_{11}U^2 + a_{12}U + a_{13} \tag{8}$$

with a reset after spike:

$$V > V_{th} \text{ then } \begin{cases} V \leftarrow c \\ U \leftarrow U + d \end{cases} \tag{9}$$

where,  $a_i$ ,  $V_T$ ,  $V_{th}$ ,  $i_i$ ,  $c$ , and  $d$  are constants depending on the neuron circuit parameters and the process parameters of the CMOS technology. The elements of the circuit are chosen so that the variable  $u$  changes slowly relative to variable  $v$  [19].

By changing  $V_c$  and  $V_d$ , spike different shapes are produced, which are similar to the biological state [26]. Their parameter values are listed in Table 2. The power consumption of this model is in the range of 9 pJ per spike [26].

### 3.2 The Astrocyte Circuit

The astrocyte circuit is used in this paper designed by [28]. This circuit is a simple CMOS circuit that implements the astrocyte model (as described in Section 2.2). It can show good behavior of the biological astrocyte model. The operation of the circuit is based on the differential pair circuit from underlying nonlinear characteristics of MOS transistors (in the analog domain, above threshold) [28]. This circuit is presented in Fig. 4, which consisted of two parts that generate “ $p$ ” and “ $q$ ” dynamics. Voltages across capacitors  $C_p$  and  $C_q$  ( $V_p$  and  $V_q$  respectively) show two state variables ( $p$ ,  $q$ ). The creation “ $q$ ” and “ $p$ ” states of the astrocyte model are based on the charging and discharging of  $C_q$  and  $C_p$  Capacitors. The state variable “ $q$ ” is generated by the  $q$ -part circuit that inputs of this

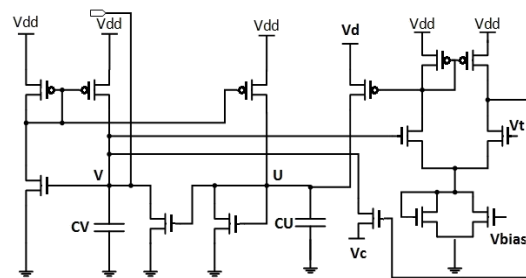


Fig. 3 The neuron circuit which was heretofore designed by Wijekoon and Dudek that  $U$  and  $V$  are state variables.

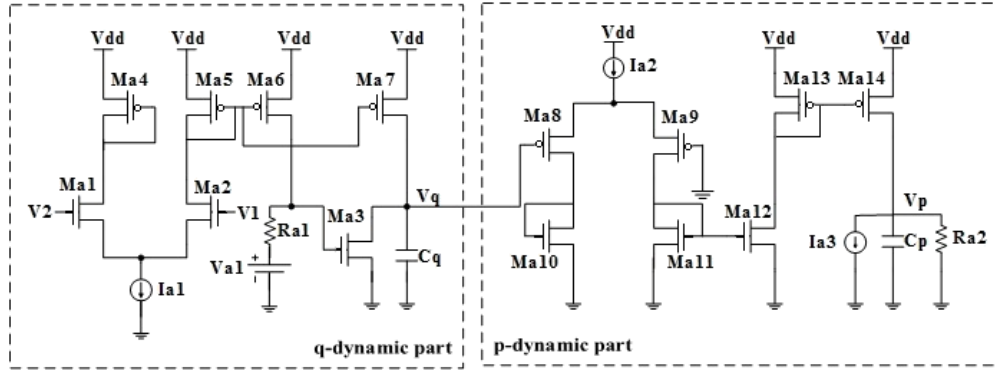


Fig. 4 The astrocyte circuit,  $V_q$  and  $V_p$  illustrate  $q$  and  $p$  state variables.

part are  $V_1$  and  $V_2$ , and its output is  $V_q$  ( $V_q$  is the input for the  $p$ -part circuit).

The final output of the astrocyte circuit is the output voltage of the  $p$ -part circuit ( $V_p$ ). Substituting the parameters of Table 1 into (4), we have:

$$\begin{cases} \dot{q} = (1 + \tanh[(Z - 2)])(1 - q) - 2q \\ \dot{p} = -p + 0.05 + 1.5q \end{cases} \quad (10)$$

and each part of (10), constructs as follow:

$$\dot{q} = \underbrace{(1 + \tanh[Z - 2])}_{I_{k1}} - \underbrace{[(1 + \tanh[Z - 2])q + 2q]}_{I_{k2}} \quad (11)$$

$$\dot{p} = - \underbrace{p}_{I_{k3}} + \underbrace{(0.05 + 1.5q)}_{I_{k4}} \quad (12)$$

Here,  $I_{k1}$  and  $I_{k2}$  are the main terms to construct the nonlinear term “ $1 + \tanh(Z-2)$ ” which is used in the differential pair circuit. Considering Fig. 4 and according to [28], we have:

$$I_{k1} = 1 + \tanh[Z - 2] = \frac{I_{a1}}{2C_q} \left( 1 + \tanh \left[ \frac{2(V_1 - V_2)}{v_{ov2}} \right] \right) \quad (13)$$

$$\begin{aligned} I_{k2} &= 1 + \tanh[Z - 2]q + 2q \\ &= \frac{I_{a1} k_{Ma3} R_{a1}}{2C_q} \left( 1 + \tanh \left[ \frac{2(V_1 - V_2)}{v_{ov2}} \right] \right) V_q \\ &\quad + \frac{k_{Ma3}}{C_q} (V_{a1} - V_{thn}) V_q \end{aligned} \quad (14)$$

$$v_{ov2}^2 = \frac{2I_{a1} L_{Ma2}}{k_{Ma2} W_{Ma2}}, \quad k' = c_{ox} \mu_n, \quad V_{thn} \text{ is threshold voltages,}$$

$k_{Ma3} = c_{ox} \mu_n (W/L)_{Ma3}$  and  $I_{a1}$  is the current source as shown in Fig. 4.

It is used in the same way to produce  $p$  state.  $p$  and  $q$  are dependent linearly, thus is used the linear region of the differential pair circuit.

$$I_{k3} = p = \frac{1}{C_p R_{a2}} V_p \quad (15)$$

$$I_{k4} = 0.05 + 1.5q = \frac{1}{C_p} \left( \frac{I_{a2}}{2} - I_{a3} \right) + \left( \frac{I_{a2}}{\sqrt{2} C_p v_{ov9}} \right) V_q \quad (16)$$

In this way, the two main parts of the circuit are designed ( $p$  and  $q$  dynamics model). The values of parameters of the circuit are listed in Table 2.

### 3.3 The Feedback Path Circuit

Astrocyte circuit can desynchronize a coupled neural population. First, astrocyte output should be converted to the current and then applied to the neuron circuit.

We use the neuron-astrocyte interaction circuit proposed by [28] that is shown in Fig. 5. For analyzing feedback circuit, according to (5) and Fig. 5, and using the linear region of the differential pair circuit, we have:

$$I_{Mf5} = \gamma \cdot p = I_{Mf1} - I_{f2} = \frac{I_{f1}}{2} + \left( \frac{I_{f1}}{\sqrt{2} v_{ovf1}} \right) (V_f) - I_{f2} \quad (17)$$

due to the  $I_{f2} = \frac{I_{f1}}{2}$ ,  $(W/L)_{Mf3} = (W/L)_{Mf5} = (W/L)_{Mf6}$ ,

and  $(W/L)_{Mf7} = (W/L)_{Mf8}$  we have:

$$i_{ast} = I_{out} = \gamma \cdot p = \left( \frac{I_{f1}}{\sqrt{2} v_{ovf1}} \right) (V_f) \quad (18)$$

Table 2 Parameter values used in the simulations of the neuron and Astrocyte circuit.

Neuron	Value	Astrocyte	Value
$V_c$	0.1 V	$V_{a1}$	0.1 V
$V_d$	1.9 V	$I_{a2}$	9.8 $\mu$ A
$V_t$	1.55 V	$R_{a1}$	6 k $\Omega$
$(W/L)_{Mn1,2,3}$	2.3/1	$I_{a1,2}$	20 $\mu$ A
$(W/L)_{Mn5}$	5.3/1	$C_{p,q}$	1 pF
$(W/L)_{Mn7}$	11.3/14	$R_{a2}$	115 k $\Omega$
$(W/L)_{Mn9,10,11,12}$	1/4	$(W/L)_{Ma1,2}$	0.9/5
$(W/L)_{Mn4}$	1.3/22	$(W/L)_{Ma4,5,6,7}$	10/1
$(W/L)_{Mn6}$	0.65/18	$(W/L)_{Ma11,12}$	10/1
$(W/L)_{Mn8}$	1.3/1	$(W/L)_{Ma3}$	1/5
$(W/L)_{Mn13,14}$	4/8	$(W/L)_{Ma8,9,10}$	10/1
$i_{const}$	0.1 $\mu$ A	$(W/L)_{Ma13,14}$	9.2/1
$V_{bias}$	0.6 V		
$C_u$	1 pF		
$C_v$	0.1 pF		

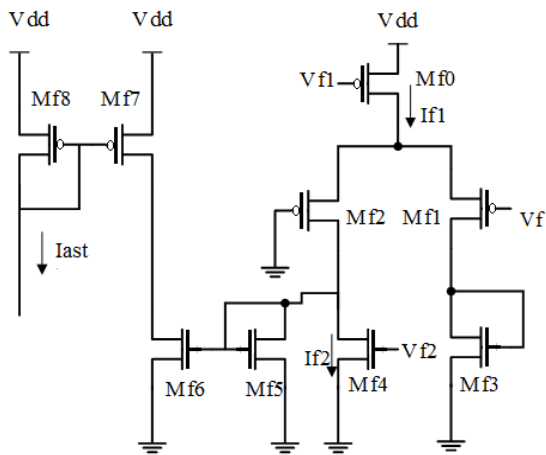


Fig. 5 Feedback circuit from astrocyte to neuron.

Table 3 Parameter values of the feedback circuit.

Feedback parameter	Value
$V_{f1}$	0.1 V
$(W/L)_{Mf0}$	9.5/1
$(W/L)_{Mf1,2}$	1/5
$I_{f2}$	20 $\mu$ A
$(W/L)_{Mf3,4}$	5/1
$(W/L)_{Mf5,6}$	5/1

here  $v_{ovf1}^2 = \frac{2I_{f1}L_{Mf1}}{k_{Mf1}W_{Mf1}}$ ,  $k' = C_{ox}\mu_p$ ,  $I_{f1}$ , and  $I_{f2}$  are the

currents of  $M_{f0}$  and  $M_{f4}$ , respectively. Parameters of feedback circuit are listed in Table 3.

#### 4 Simulation Results

In this part, different experiments to show the effect of the astrocyte in desynchronization are performed. The results of several simulations are presented and discussed.

All circuits have been simulated by HSPICE software with 0.35  $\mu$ m technology and power supply  $V_{dd} = 3.3$  V. As the first simulation, to show the output behavior of the astrocyte circuit, different inputs with various frequencies are applied. Fig. 6 shows the simulation results.

Sinusoidal input voltage “ $V_1$ ” (see Fig. 4) is applied to astrocyte with  $V_{Amp} = 1.5$  V and (a)  $f = 10$  kHz, (b)  $f = 100$  kHz, (c)  $f = 1$  MHz, and (d)  $f = 10$  MHz. According to the results, with increasing input frequency, astrocyte output ( $v_p$ ) changes and discharging time of astrocyte output is decreasing compare with input frequency, and also increasing input voltage is caused the output voltage of astrocyte to increase.

Therefore, according to this feature, astrocyte can be detected the distance of received spikes. This astrocyte performance helps to detect the synchronization firing of the neural network. We will use from astrocyte as the detector of synchronization and destroy the synchronization by designed a feedback current circuit. In the next experiment, according to Fig. 7, a population

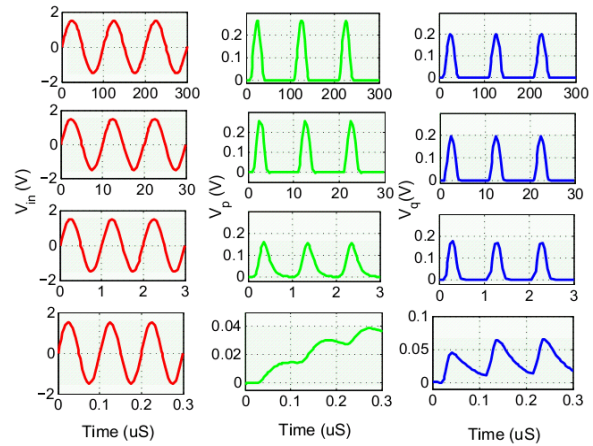


Fig. 6 Time responses of astrocyte analog circuit for sinusoidal input with  $V_{Amp} = 1.5$  V and (a)  $f = 10$  kHz, (b)  $f = 100$  kHz, (c)  $f = 1$  MHz, and (d)  $f = 10$  MHz. (red color): input signal, (green color):  $V_p$ , (blue color):  $V_q$ .

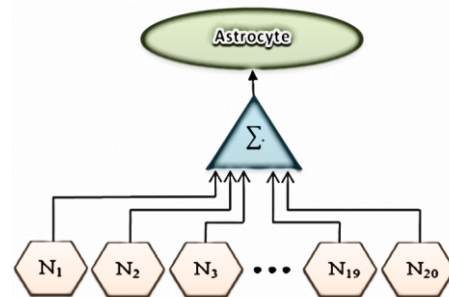


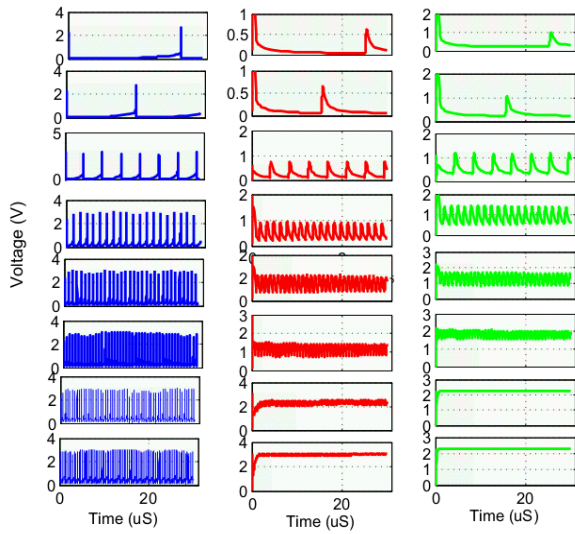
Fig. 7 Diagram of twenty coupled neurons and astrocyte.

of twenty neurons is synchronized with the same input currents, and then the output voltage of neurons combined together and applied to the astrocyte as input.

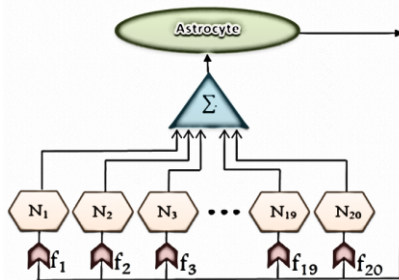
The results demonstrated in Fig. 8 show output of neurons and the astrocyte output ( $V_p$ ) for different input currents of neurons. Same input current is applied to all neurons with values (a)  $I = 0.001$   $\mu$ A, (b)  $I = 0.01$   $\mu$ A, (c)  $I = 0.1$   $\mu$ A, (d)  $I = 0.5$   $\mu$ A, (e)  $I = 1$   $\mu$ A, (f)  $I = 1.5$   $\mu$ A, (g)  $I = 2$   $\mu$ A, (h)  $I = 3$   $\mu$ A. It can be observed, all of the neurons are fire at the same time, and a complete synchronization is happening.

It can be concluded from the results with different currents that: the output astrocyte for nearby spikes of the neuron (more input) will be increased. If the distance between the spikes is higher the power of the input voltage of the astrocytes decreases and therefore the output of the astrocyte decreases.

So, this feature can be used to destroy the synchronization of neurons in a network and desynchronize them. Next, we show how the analog astrocyte circuit can desynchronize a synchronized neural population. As said in the previous part, at first, we coupled twenty neurons. Astrocyte circuit can desynchronize a synchronized neural population. So, we use astrocyte in order to control synchronization. Therefore, we combine the output voltages of the neurons together and applied to the astrocyte input. The



**Fig. 8** Time responses of astrocyte output and neuron output when the output of the neurons is combined and applied to the astrocyte input for different neuron input currents with (a)  $I = 0.001 \mu\text{A}$ , (b)  $I = 0.01 \mu\text{A}$ , (c)  $I = 0.1 \mu\text{A}$ , (d)  $I = 0.5 \mu\text{A}$ , (e)  $I = 1 \mu\text{A}$ , (f)  $I = 1.5 \mu\text{A}$ , (g)  $I = 2 \mu\text{A}$ , and (h)  $I = 3 \mu\text{A}$ . (From up to bottom). Output of all neuron (blue color),  $V_q$  (red color),  $V_p$  (astrocyte output) (green color).



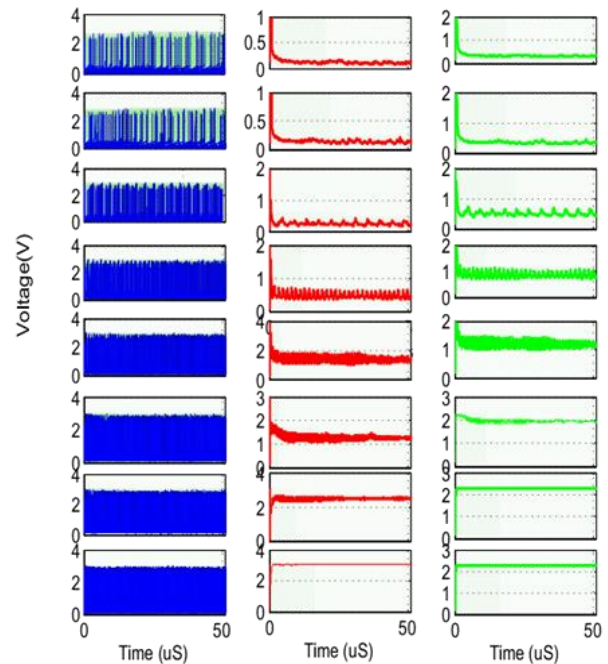
**Fig. 9** Diagram for the effect of astrocyte in desynchronization twenty coupled neurons with feedback path.

output voltage of astrocyte should be converting to the current by feedback circuit then applied to all neurons. The general schematic demonstrates in Fig. 9. In this way, we were able to desynchronize, the neural population. The simulation results are illustrated in Fig. 10. This figure shows the effect of astrocyte in desynchronizing a population for different currents of neuron input with (a)  $I = 0.001 \mu\text{A}$ , (b)  $I = 0.01 \mu\text{A}$ , (c)  $I = 0.1 \mu\text{A}$ , (d)  $I = 1 \mu\text{A}$ , (e)  $I = 1.5 \mu\text{A}$ , and (f)  $I = 2 \mu\text{A}$ . As can be observed neural populations become desynchronized.

The maximum power consumption of the total circuit is about 20 mW, while the number of the used transistors is 474. The supply voltage is 3.3 V.

### 5 Conclusion

The Synchronization phenomenon plays an important role in brain activities such as information processing and neural signaling. But hyper-synchrony processes can cause disorders in brain activity. For example,



**Fig. 10** Effect of astrocyte in desynchronization twenty coupled neurons with feedback circuit for different neuron input currents with (a)  $I = 0.001 \mu\text{A}$ , (b)  $I = 0.01 \mu\text{A}$ , (c)  $I = 0.1 \mu\text{A}$ , (d)  $I = 0.5 \mu\text{A}$ , (e)  $I = 1 \mu\text{A}$ , (f)  $I = 1.5 \mu\text{A}$ , (g)  $I = 2 \mu\text{A}$ , and (h)  $I = 3 \mu\text{A}$ . (From up to bottom). (blue color): the neurons output membrane potential, (red color):  $V_q$ , (green color):  $V_p$  (astrocyte output).

resting tremor in Parkinson’s disease (PD) is caused by a synchronized population of neurons. For this reason, various methods have been proposed to stimulate neurons. An effective way to desynchronize the neuronal population is to use astrocyte as stimulation. A novel, effectively desynchronizing stimulation technique is presented: stimulation with the astrocyte is a good method to desynchronize neuronal populations. In this paper, we design an analog neural population consists of 20 neurons and 1 astrocyte and feedback circuits. We show that the output astrocyte can be detected spiking synchronization of nearby neurons. When the nearby neurons fire at the same time, the output of the astrocyte circuit is increased. By this future of astrocyte, the feedback current can be disturbing the synchronization of the neural population. Simulation results indicate that our stimulation technique has a good effect on desynchronization in the population. All circuits are designed at  $0.35 \mu\text{m}$  CMOS technology in Hspice software.

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