Neurocomputing 114 (2013) 15–23

Contents lists available at SciVerse ScienceDirect

Neurocomputing

journal homepage: www.elsevier.com/locate/neucom

The role of glutamatercic and GABAergic synapses on the dynamics of neural networks: How they impact the transition to seizure?

Angelo Di Garbo*, Michele Barbi, Santi Chillemi

Istituto di Biofisica CNR, Sezione di Pisa, via G. Moruzzi 1, 56124 Pisa, Italy

ARTICLE INFO

Available online 26 October 2012

Keywords:
Neurons
Interneurons
Synapses
Network dynamics
Seizure

ABSTRACT

The balance between inhibition and excitation is at the basis of the maintenance of stable and normal brain electrical activity. Experimental results revealed that inhibitory synapses can become depolarizing as the intracellular concentration of Cl^{-1} of the postsynaptic cells increases. In this work the dynamical behaviour of a network of pyramidal cells coupled to inhibitory fast-spiking interneurons was studied by simulations. In particular, in agreement to the experimental data, it was found that the biophysical properties of the inhibitory/excitatory synapses strongly impact the network dynamics and the transition to seizure.

1. Introduction

The brain is populated by excitatory neurons and inhibitory interneurons. Among interneurons the most prominent class is that of fast-spiking (FS) cells: they are coupled by inhibitory and electrical synapses and are capable of generating synchronous oscillations [1,2]. These cells exert a powerful control of the firing activity of pyramidal neurons by means of somatic and perisomatic synaptic GABAergic contacts [3]. Interneurons receive excitatory inputs from pyramidal cells and then feedback inhibition to them by modulating their firing activities [4]. This mechanism is at the core of the existence of an excitatory–inhibitory feedback loop between pyramidal cells and interneurons [1–3,5]. When the cellular mechanisms regulating these processes are compromised (like in epilepsy) the dynamics of this network becomes more complex and not well known. For instance recently it was shown that FS interneurons are the drivers of seizure like phenomena by activating directly pyramidal cells through excitatory GABAergic transmission [6,7]. It was shown that in particular conditions (for instance when an accumulation of Cl^{-} occurs) inhibitory GABAergic synapses can be converted to excitatory. However, at present it is still unresolved whether interneurons are actively capable of promoting seizure like activity by means of this mechanisms. On the other side, it was suggested recently that the exhaustion of GABAergic release and an increase of the excitatory synaptic activity could be an important mechanisms underlying the transition to seizure [8]. Motivated by the previous remarks in the present paper we studied the synchronization phenomena occurring in a network of interconnected FS interneurons and pyramidal neurons. To gain realistic results the cells and their synaptic connections were described by biophysical inspired models. In particular, we investigated the conditions driving the synchronization phenomena and the transition to seizure like dynamics in this complex network.

2. Methods

2.1. Model description

The artificial network is composed by N_{PY} pyramidal neurons and N_{FS} FS interneurons. The pyramidal neuron models are coupled by excitatory synapses and receive inhibitory inputs from the network of FS interneuron. The FS interneurona are coupled by electrical and inhibitory synapses and receive excitatory inputs from pyramidal cells. A schematic representation of the network connectivity is reported in Fig. 1.

For either the pyramidal neuron or the interneuron, a single compartment biophysical model is employed to describe its spiking activity. In particular, we adopt the pyramidal and interneuron biophysical models proposed in [9]. The mathematical model of the jth pyramidal neuron reads

$$C\frac{dV_j}{dt} = I_{P,j} - g_{Na}m_j^3 h_j(V_j - V_{Na}) - g_K n_j^4(V_j - V_K) - g_M w_j((V_j - V_M)) - g_L(V_j - V_L) + I_{PP,j} + I_{IP,j} + \eta_P \xi_{P,j}(t), \quad (1)$$

$$\frac{dm_j}{dt} = \alpha_{m,j}(1 - m_j) - \beta_{m,j} m_j, \quad (2)$$

* Corresponding author.
E-mail address: angelo.digarbo@pi.ibf.cnr.it (A. Di Garbo).
URL: http://www.pi.ibf.cnr.it (A. Di Garbo).

0925-2312/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.neucom.2012.08.045

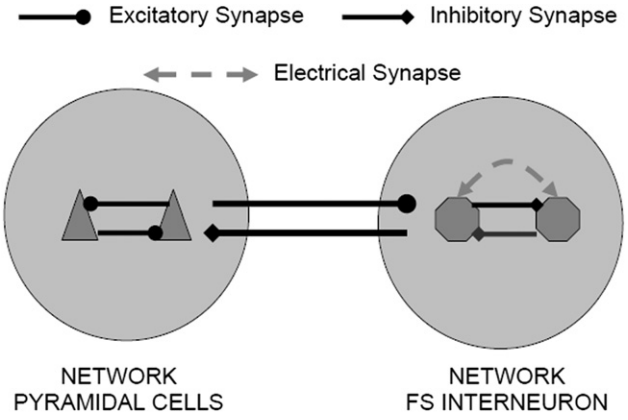

Fig. 1. Schematic representation of the neural networks connectivity.

$$\frac{dh_j}{dt} = \alpha_{h,j}(1-h_j) - \beta_{h,j}h_j, \tag{3}$$

$$\frac{dn_j}{dt} = \alpha_{n,j}(1-n_j) - \beta_{n,j}n_j, \tag{4}$$

$$\frac{dw_j}{dt} = \frac{w_{j,\infty}-w_j}{\tau_{j,w}}, \tag{5}$$

where $C = 1\ \mu F/cm^2$, $I_{P,j} = I_P$ $(j = 1,2,..N)$ is the external stimulation t. The maximal specific conductances and the reversal potentials are respectively: $g_{Na} = 100\ mS/cm^2$, $g_K = 80\ mS/cm^2$, $g_M = 1\ mS/cm^2$, $g_L = 0.15\ mS/cm^2$ and $V_{Na} = 50\ mV$, $V_K = -100\ mV$, $V_M = -100\ mV$, $V_L = -72\ mV$. The rate variables describing the currents are defined by: $\alpha_{m,j}(V_j) = 0.32(V_j+54)/[1-\exp((V_j+54)/4)]$, $\beta_{m,j}(V_j) = 0.28(V_j+27)/[\exp((V_j+27)/5)-1]$, $\alpha_{h,j}(V_j) = 0.128\exp(-(V_j+50)/18)$, $\beta_{h,j}(V_j) = 4/[1+\exp(-(V_j+27)/5)]$, $\alpha_{n,j}(V_j) = 0.032(V_j+52)/[1-\exp(-(V_j+52)/5)]$, $\beta_{n,j}(V_j) = 0.5\exp(-(V_j+57)/40)$, $w_{j,\infty} = 1/[1+\exp(-(V_j+35)/10)]$, $\tau_{j,w} = 400/[3.3\exp((V_j+35)/20)+\exp(-(V_j+35)/20)]$. In this model the onset of periodic firing occurs through an Hopf bifurcation for $I_P \cong 3.25\ \mu A/cm^2$ with a well defined frequency ($\nu \cong 5$ Hz).

The current $I_{PP,j}$ arises from the excitatory coupling of the jth pyramidal neuron with the other cells, while $I_{IP,j}$ describes the inhibitory current due to the coupling with the network of interneurons (see Fig. 1). These currents will be defined in the next section.

To reproduce the membrane potential fluctuations each jth cell model is injected with the noisy current $\eta_P\xi_{P,j}(t)$, $\xi_{P,j}$ being an uncorrelated Gaussian random variable of zero mean and unit standard deviation $\langle \xi_{P,i},\xi_{P,j}\rangle = \delta_{ij}$, $i \neq j = 1,2,3,N_{PY}$). The adopted value of the parameter η_P was chosen to have a realistic amplitude of the fluctuations of membrane potential.

The biophysical mathematical model of the jth FS interneuron reads

$$C\frac{dV_j}{dt} = I_{F,j} - g_{Na}m_j^3h_j(V_j-V_{Na}) - g_Kn_j^4(V_j-V_K) - g_L(V_j-V_L) + I_{FF,j} + J_{FF,j} + I_{PF,j} + \eta_F\xi_{F,j}(t), \tag{6}$$

$$\frac{dm_j}{dt} = \alpha_{m,j}(1-m_j) - \beta_{m,j}m_j, \tag{7}$$

$$\frac{dh_j}{dt} = \alpha_{h,j}(1-h_j) - \beta_{h,j}h_j, \tag{8}$$

$$\frac{dn_j}{dt} = \alpha_{n,j}(1-n_j) - \beta_{n,j}n_j, \tag{9}$$

where $C = 1\ \mu F/cm^2$, $I_{F,j} = I_F$ $(j = 1,2,..,N)$ is the external stimulation current. The maximal specific conductances, the reversal potentials and the rate variables are equal to those adopted for the pyramidal cell model. In this model the onset of periodic firing occurs through an Hopf bifurcation for $I_F \cong 1.04\ \mu A/cm^2$ with a well-defined frequency ($\nu \cong 2$ Hz).

The current $I_{FF,j}$ arises from the inhibitory coupling of the jth FS interneuron with the other cells, while $J_{FF,j}$ describes the current due to the electrical coupling (gap-junction) among interneurons; lastly $I_{PF,j}$ describes the excitatory current due to the coupling with the network of pyramidal neurons. These currents will be defined in the next section. To reproduce the membrane potential fluctuations each jth cell model is injected with the noisy current $\eta_F\xi_{F,j}(t)$, $\xi_{F,j}$ being an uncorrelated Gaussian random variable of zero mean and unit standard deviation $\langle \xi_{F,i},\xi_{F,j}\rangle = \delta_{ij}$, $i \neq j = 1,2,3,N_{FS}$) and $\langle \xi_{P,i},\xi_{F,j}\rangle = 0$. The value of the η_F was chosen in order to get realistic amplitude of the fluctuation of membrane potential.

The reason for using a single compartment model of each cell is motivated by computational constraints. The simulation will be performed by using up to 100 coupled neuron models, and this requires a high computational cost. Therefore, for the aim of the present work, the choice of using a single compartment biophysical model of each cell is a good compromise between two requirements: computational advantages and realistic network of coupled neurons. An additional justification of using a single compartment modeling comes from the neurophysiological information on the properties of inhibitory synapses between FS and pyramidal cells. In fact it is well known that these interneurons make mainly somatic contacts with the pyramidal cells and for this reason they exert a powerful control of the firing activity of them [10]. Because the results that will presented here are intended as a preliminary study of this complex network, then that is why a single compartment modeling is adopted. The introduction of a multi-compartment modeling is very interesting because several other relevant network dynamical properties could be investigated. However, this is out of the scopes of the present paper and it will be addressed in a future work.

2.2. Synaptic coupling

The excitatory synaptic coupling among pyramidal cells is assumed to be all-to-all. The excitatory synaptic current acting on the jth pyramidal cell is defined by

$$I_{PP,j} = -\frac{1}{N_{PY}-1}\sum_{k\neq j} g_e s_{PP,k}(t)(V_j - V_{PP}), \tag{10}$$

where $g_e = 0.5\ mS/cm^2$ represents the maximal amplitude of the excitatory coupling, the function $s_{PP,k}(t)$ describes the time evolution of the postsynaptic current and V_{PP} is the corresponding reversal potential. According to [9] the time evolution of $s_{PP,k}(t)$ is described by

$$\frac{ds_{PP,k}(t)}{dt} = T(V_k)(1-s_{PP,k}) - s_{PP,k}/\tau_e, \tag{11}$$

where $T(V_k) = 5(1+\tanh(V_k/4))$ and $\tau_e = 2$ ms is the decay time constant.

Similarly the inhibitory synaptic coupling among FS interneurons is assumed to be all-to-all and the synaptic current on the jth interneuron reads

$$I_{FF,j} = -\frac{1}{N_{FS}-1}\sum_{k\neq j} g_i s_{FF,k}(t)(V_j - V_{FF}), \tag{12}$$