Neurocomputing 151 (2015) 34–48

Contents lists available at ScienceDirect

Neurocomputing

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

Thalamic inputs modulate cortical activity: Possibility to control the generation and the termination of seizure-like behaviour

Fabio Vallone [a,b,c], Andrea Cintio [a], Santi Chillemi [a], Angelo Di Garbo [a,*]

[a] Institute of Biophysics, CNR-National Research Council, 56124 Pisa, Italy
[b] The BioRobotics Institute, Scuola Superiore S.Anna, 56026 Pisa, Italy
[c] Neuroscience Institute, CNR-National Research Council, 56124 Pisa, Italy

ARTICLE INFO

Article history:
Received 31 January 2014
Received in revised form
11 September 2014
Accepted 18 September 2014
Available online 15 October 2014

Keywords:
Neurons
Interneurons
Synapses
Thalamus
Network dynamics
Seizure

ABSTRACT

Because of a dense loop pattern the thalamus receives and sends connections to cortical areas. In a recent experimental study it has been shown that injuries to the cerebral cortex can cause changes to the excitability of a set of neurons which reside in the thalamus. In this paper, using a computational approach, it is investigated how the interaction between thalamus and cortex compartments is involved in seizure expression. The numerical simulations of a realistic model of cortico–thalamo–cortical network show that seizure-like behaviour is an emergent property of the whole network. It is shown that pathological network states, as seizure-like dynamics, can be controlled by manipulating different model parameters determining the coupling between the thalamus components and the cortex. To be more specific it is established that a (partial or complete) reduction in the cortical seizure activity can be brought about silencing the neuron spiking activity in the thalamo-cortical module by adjusting (i) amplitudes and (ii) decay time constants of synaptic currents. These numerical results could be of interest for epilepsy treatment, since they allow to shed light on the mechanisms involved in generation and control of this pathological condition.

1. Introduction

About 50 million people worldwide have epilepsy, and they are usually controlled, but not cured, with medication. The most important mechanisms, relevant for a deep understanding of the seizure dynamics, are those driving the generation and termination of the ictal events. Although many studies have been carried out on seizures, the mechanisms of generation and termination still remain poorly understood (see for a complete review [1,2]). Recently a new vision of the epileptic seizures has been suggested [3]. Contrary to the traditional view, suggesting hypersynchronous neuronal activity during the ictal activity, a highly heterogeneous neuronal spiking activity has been observed. In particular, seizure termination can be described as a quasi-homogenous phenomenon leading to an almost complete cessation of the spiking activity [3]. In addition it has been found that the spike waveforms does not change at the seizure termination, an indication that depolarisation block is not the principal factor responsible for the cessation of the spiking activity [3]. In a recent computational study it has been shown that the dynamics of (intra-extra) cellular ionic concentrations could be the primary factor for the seizure termination [4], but this result does not seem to be in agreement with the experimental data of Truccolo et al. [3]. Therefore, among the possible mechanisms of generation and termination of seizure, thalamic inputs might play an important role. In fact the cortex is intimately connected with thalamus, and the cortico-thalamo-cortical excitatory loop can mediate network oscillations underlying epilepsies [5]. In particular, experimental studies [6] have shown that thalamic injection of GABAb antagonist decreases the seizure in a dose-dependent manner. Based on these findings, Steriade [7] has hypothesised that decreasing or abolishing the inhibitory effects of reticular thalamic neurons upon thalamocortical cells would affect the seizure-like behaviour (Steriade's hypothesis). Moreover, a recent experimental work shows that thalamocortical neuronal activity is required for post-stroke epilepsy; in addition a reduction of the activity of thalamocortical cells is sufficient to stop seizures [8]. Concerning the problem of seizure termination, it is worth remarking that in [9] it was shown that a clear connection exists between extinction and spatial synchronisation of populations. In particular, this general result could be useful to justify the possibility that the termination of seizures can arise from an emergent property of the network itself. In this paper, motivated by the above discussion, the effects of the synaptic connectivity of the cortico-thalamo-cortical network

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

http://dx.doi.org/10.1016/j.neucom.2014.09.070
0925-2312/

on the dynamics of seizure generation and termination will be investigated computationally.

2. Methods

2.1. Model description

The artificial network is composed by N_{PY} pyramidal neurons, N_{FS} FS interneurons, N_{RE} reticular neurons and N_{TC} thalamocortical neurons. A schematic representation of the network connectivity is reported in Fig. 1. The pyramidal neuron models are coupled by excitatory synapses and receive inhibitory inputs from the network of FS interneurons. For either the pyramidal neuron or the interneuron, a single compartment biophysical model is employed to describe its spiking activity. In particular, the adopted pyramidal and interneuron biophysical models were those proposed in [10]. The mathematical model of the jth pyramidal neuron reads:

$$C\frac{dV_j^P}{dt} = I_{P,j} - I_{Na} - I_K - I_M - I_L + I_{PP,j} + I_{IP,j} + I_{TP,j} + \eta_P \xi_{P,j}(t). \quad (1)$$

The biophysical mathematical model of the jth FS interneuron reads:

$$C\frac{dV_j^F}{dt} = I_{F,j} - I_{Na} - I_K - I_L + I_{FF,j} + J_{FF,j} + I_{PF,j} + I_{TF,j} + \eta_F \xi_{F,j}(t). \quad (2)$$

The current $I_{PP,j}$ arises from the excitatory coupling of the jth pyramidal neuron with the other cells, $I_{IP,j}$ describes the inhibitory current due to the coupling with the network of interneurons and $I_{TP,j}$ represents the excitatory inputs from TC cells. 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; $I_{PF,j}$ describes the excitatory current due to the coupling with the network of pyramidal neurons, and $I_{TF,j}$ represents the excitatory current from the TC pool. These currents will be defined in the next section.

The single compartment models of RE and TC cells were adopted from [11]. The mathematical model of the jth reticular neuron reads:

$$C\frac{dV_j^R}{dt} = -I_{Ca-T} - I_{LR} - I_{AHP} + I_{RRA,j} + I_{RRB,j} + I_{TR,j} + I_{PR,j} + \eta_R \xi_{R,j}(t). \quad (3)$$

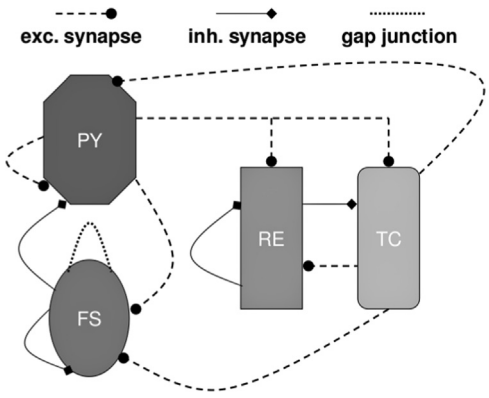

Fig. 1. Schematic representation of the neural networks connectivity. Pyramidal neurons (PY) receive excitatory inputs from thalamocortical cells (TC) and inhibitory inputs from FS interneurons. Thalamic reticular neurons (RE) receive excitatory inputs from pyramidal and TC neurons, and inhibit TC cells. FS interneurons are coupled by electrical synapses, inhibit PY neurons and receive excitatory inputs from PY on TC neurons.

The mathematical model of the jth thalamocortical neuron reads:

$$C\frac{dV_j^T}{dt} = -I_{Ca-T} - I_{LT} - I_{sag} + I_{RTA,j} + I_{RTB,j} + I_{PT,j} + \eta_T \xi_{T,j}(t). \quad (4)$$

The currents $I_{RRA,j}$, $I_{RRB,j}$ represent inhibitory coupling among RE cells, $I_{TR,j}$ and $I_{PR,j}$ describe respectively excitatory inputs from TC and pyramidal neurons. The currents $I_{RTA,j}$, $I_{RTB,j}$ represent inhibitory inputs due to the coupling with the network of RE neurons , $I_{PT,j}$ describes excitatory inputs from pyramidal neurons to TC cells.

The intrinsic ionic currents depend by activation and inactivation variables. These generic variables evolve in time according to the equations

$$\frac{dx_j}{dt} = \alpha_{x,j}(1 - x_j) - \beta_{x,j} x_j, \quad (5)$$

$$\frac{dy_j}{dt} = \frac{y_{j,\infty} - y_j}{\tau_{j,y}}, \quad (6)$$

The equations and the parameter of the model are given in Appendices A and B.

To reproduce the membrane potential fluctuations each jth cell type $c = (FS, PY, RE, TC)$ model is injected with the noisy current $\eta_c \xi_{c,j}(t)$, $\xi_{c,j}$ being an uncorrelated Gaussian random variable of zero mean and unit standard deviation $\langle \xi_{c,i}, \xi_{c,j} \rangle = \delta_{ij}, i \neq j = 1, 2, 3, , N_c$. The adopted value of the parameter η_c was chosen to get realistic amplitude of the fluctuations of membrane potential.

The reason of using a single compartment model of each cell is motivated by computational constraints. The simulation will be performed by using up to 180 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.

2.2. Synaptic coupling

The synaptic couplings among cells type $c, c' = FS, PY, RE, TC$ are assumed to be all-to-all.

The synaptic currents are of types $\alpha = (AMPA, GABAa, GABAb)$. A generic current I^α acting on the jth cell type c is defined by

$$I^\alpha_{cc',j} = -\frac{1}{N_c^\alpha} \sum_{k=1}^{N_c^\alpha} g^\alpha_{cc'} s_{cc',k}(t)(V_j - V_{cc'}) \quad (7)$$

where $g^\alpha_{cc'}$ represents the maximal amplitude of the coupling, the function $s_{cc',k}(t)$ describes the time evolution of the postsynaptic current, $V_{cc'}$ is the corresponding reversal potential and N_c^α is the normalisation factor determined by the number of neurons involved in the synaptic coupling of α-type. The generic time evolution of $s_{cc',k}(t)$ is described by

$$\frac{ds_{cc',k}(t)}{dt} = \gamma(1 - s_{cc',k}) - \delta s_{cc',k} \quad (8)$$

The equations and the parameter of the model are given in Appendix C.

'The electrical coupling among FS interneurons is all-to-all and the corresponding current on the jth cell is defined as

$$J_{FF,j} = \frac{1}{N_{FS} - 1} \sum_{k \neq j} g_{el}(V_j - V_k) \quad (9)$$

where g_{el} is the coupling amplitude. The parameters values for the coupling of FS neurons and PY interneurons are those adopted in [10] . The parameter values describing the amplitude of the synaptic current among neurons of the thalamus are those reported in [11].