Thalamo-Cortical Network and Seizure Dynamics: A Computational Study

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Abstract. Experimental data indicate that thalamic inputs are important factors for the generation and termination of seizures. In this paper a minimal biophysical model of cortico-thalamo-cortical network is investigated by a computational approach. The results show that a change in the amplitude of synaptic currents between thalamic and cortical neurons promotes seizure like dynamics. Moreover, the increase of the level of inhibition between neurons of the thalamic network is sufficient for seizure termination.

1 Introduction

About 50 million people worldwide have epilepsy, and they are usually controlled, but not cured, with medication. Although many studies have been made 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 discovered[3]. Contrary to the traditional view, suggesting hypersynchronous neuronal activity during the ictal activity, an highly heterogeneous neuronal spiking activity was observed. In particular, seizure termination is described by a quasi-homogenous phenomenon leading to an almost complete cessation of spiking activity[3]. In addition it was found that the spike waveforms does not change at seizure termination, an indication that depolarization block is not the principal factor responsible for the cessation of spiking activity [3]. Obviously, the most important mechanisms, relevant for a deep understanding of seizure dynamics, are those driving the generation and termination of the ictal events. Among the possible mechanisms of generation and termination of seizure, thalamic inputs can 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 [4]. Moreover, in a recent experimental work it was shown 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 [5]. Concerning the problem of seizure termination in [6] it was shown that a clear connection exists between extinction and spatial synchronization of populations. This general results could

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be useful to justify the possibility that the termination of seizures can arise from an emergent property of the network itself. Moreover, in a recent computational study it was shown that a depolarization block could be the primary factor for the seizure termination [7], but this result does not seem to be in agreement with the experimental data of Truccolo et al. [3]. Therefore, motivated by the above discussion the effects, of the synaptic connectivity of the cortico-thalamo-cortical network, 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 if reported in figure 1. The pyramidal neuron models are coupled by excitatory synapses and receive inhibitory inputs from the network of FS interneuron. 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 [8]. The mathematical model of the $j-th$ pyramidal neuron reads:

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

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

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

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

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

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: $\alpha_{m,j}(V_j) =$

$0.32(V_j+54)/[1-exp((V_j+54)/4)]$,$\beta_{m,j}(V_j) = 0.28(V_j+27)/[exp((V_j+27)/5)-1]$, $\alpha_{h,j}(V_j) = 0.128exp(-(V_j + 50)/18)$, $\beta_{h,j}(V_j) = 4/[1 + exp(-(V_j + 27)/5)]$, $\alpha_{n,j}(V_j) = 0.032(V_j + 52)/[1 - exp(-(V_j + 52)/5)]$, $\beta_{n,j}(V_j) = 0.5exp(-(V_j + 57)/40)$, $w_{j,\infty} = 1/[1+exp(-(V_j+35)/10)]$, $\tau_{j,w} = 400/[3.3exp((V_j+35)/20)+exp(-(V_j+35)/20)]$. 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 ($\nu \cong 5Hz$).

The current $I_{PP,j}$ arises from the excitatory coupling of the $j-th$ 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. These currents will be defined in the next section.

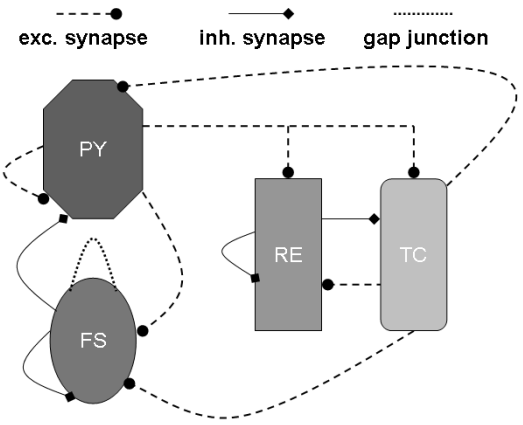

Fig. 1. Schematic representation of the neural networks connectivity. Pyramidal neurons (PY) receive excitatory inputs from thalamocortical cells (TC) and inhibitory inputs from FS interneurons. Thalamic reticular neurons (RE) receive excitatory inputs from pyramidal and TC neurons, and inhibit TC cells.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

To reproduce the membrane potential fluctuations each $j-th$ 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 $<\xi_{P,i},\xi_{P,j}>=\delta_{ij}, i \neq j = 1,2,3,,N_{PY}$. The adopted value of the parameter η_P was chosen to get realistic amplitude of the fluctuations of membrane potential.

The biophysical mathematical model of the $j-th$ FS interneuron reads:

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

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

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

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

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 ($\nu \cong 2Hz$).

The current $I_{FF,j}$ arises from the inhibitory coupling of the $j-th$ 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. To reproduce the membrane potential fluctuations each $j-th$ 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 $< \xi_{F,i}, \xi_{F,j} >= \delta_{ij}, i \neq j = 1, 2, 3, , N_{FS}$ and $< \xi_{P,i}, \xi_{F,j} >= 0$. The value of the η_F was chosen to get realistic amplitude of the fluctuation of membrane potential. The single compartment models of RE and TC cells were adopted from [9]. The mathematical model of the $j-th$ reticular neuron reads:

$$C\frac{dV_j}{dt} = -g_{Ca-R} m^2_{R,\infty}(V_j) h_{R,j}(V_j - V_{Ca}) - g_{LR}(V_i - V_{LR})$$
$$-g_{AHP} m_{j,AHP}(V_j - V_K) + I_{RRA,j} + I_{RRB,j} + I_{TR,j} + I_{PR,j} + \eta_R \xi_{R,j}(t) \tag{10}$$

$$\frac{dh_{R,j}}{dt} = 4.2(h_\infty(V_j) - h_{R,j})/\tau_{R,h}(V_j) \tag{11}$$

$$\frac{dm_{j,AHP}}{dt} = 0.02[Ca]_j(1 - m_{j,AHP}) - 0.025 m_{j,AHP} \tag{12}$$

$$\frac{d[Ca]_j}{dt} = -0.01 g_{Ca-R} m^2_\infty(V_j) h_{R,j}(V_j - V_{Ca}) - 0.08[Ca]_j \tag{13}$$

The maximal specific conductances and the reversal potentials are respectively: $C = 1\ \mu F/cm^2$, g_{Ca-R} =2 mS/cm^2, $V_{Ca} = 120\ mV$, $g_{LR} = 0.06\ mS/cm^2$, V_{LR} = -60 mV, $g_{AHP} = 0.3\ mS/cm^2$, V_K = -90 mV. The rate variables describing the currents are defined by: $m_{R,\infty}(V_j) = [1 + exp(-(V_j + 52)/7.4)]^{-1}$, $h_{R,\infty}(V_j) = [1 + exp((V_j + 78)/5)]^{-1}$, $\tau_{R,h}(V_j) = 100 + 500[1 + exp((V_j + 78)/3)]^{-1}$. 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. To reproduce the membrane potential fluctuations each $j-th$ cell model is injected with the noisy current $\eta_R \xi_{R,j}(t)$, $\xi_{R,j}$ being an uncorrelated Gaussian random variable of zero mean and unit standard deviation $< \xi_{R,i}, \xi_{R,j} >= \delta_{ij}, i \neq j = 1, 2, 3, , N_{RE}$. The adopted value of the parameter η_R was chosen to get realistic amplitude of the fluctuations of membrane potential.

The mathematical model of the $j-th$ thalamocortical neuron reads:

$$C\frac{dV_j}{dt} = -g_{Ca-T} m^2_{T,\infty}(V_j) h_{T,j}(V_j - V_{Ca}) - g_{LT}(V_j - V_{LT}) - g_{sag} r_j (V_j - V_{sag}) + I_{RTA,j} + I_{RTB,j} + I_{PT,j} + \eta_T \xi_{T,j}(t) \quad (14)$$

$$\frac{dh_{T,j}}{dt} = 4.2(h_{T,\infty}(V_j) - h_{T,j})/\tau_{T,h}(V_j) \quad (15)$$

$$\frac{dr_j}{dt} = (r_\infty(V_j) - r_j)/\tau_{sag}(V_j) \quad (16)$$

The maximal specific conductances and the reversal potentials are respectively: $C = 1\ \mu F/cm^2$, g_{Ca-T} =2.5 mS/cm^2, $V_{Ca} = 120\ mV$, $g_{LT} = 0.025\ mS/cm^2$, V_{LR} = -75 mV, $g_{sag} = 0.04\ mS/cm^2$, V_{sag} = -40 mV. The rate variables describing the currents are defined by: $m_{T,\infty}(V_j) = [1 + exp(-(V_j + 59)/6.2)]^{-1}$, $h_{T,\infty}(V_j) = [1+exp((V_j+81)/4.4)]^{-1}$, $\tau_h(V_j) = 30+220[1+exp((V_j+78)/3)]^{-1}$, $r_\infty(V_j) = [1+exp((V_j+75)/5.5)]^{-1}$, $\tau_{sag}(V_j) = 20+1000[exp((V_j+71.5)/14.2)+ exp(-(V_j + 89)/11.6)]^{-1}$. 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. To reproduce the membrane potential fluctuations each $j-th$ cell model is injected with the noisy current $\eta_T \xi_{T,j}(t)$, $\xi_{T,j}$ being an uncorrelated Gaussian random variable of zero mean and unit standard deviation $< \xi_{T,i}, \xi_{T,j} >= \delta_{ij}, i \neq j = 1, 2, 3, , N_{TC}$. The adopted value of the parameter η_T 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 excitatory synaptic coupling among pyramidal cells is assumed to be all-to-all. The excitatory synaptic current acting on the $j-th$ pyramidal cell is defined by

$$I_{PP,j} = -\frac{1}{N_{PY}-1}\sum_{k\neq j} g_e s_{PP,k}(t)(V_j - V_{PP}) \tag{17}$$

where $g_e = 0.5mS/cm^2$ 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 [8] the time evolution of $s_{PP,k}(t)$ is described by

$$\frac{ds_{PP,k}(t)}{dt} = T(V_k)(1 - s_{PP,k}) - s_{PP,k}/\tau_e \tag{18}$$

where $T(V_k) = 5(1 + tanh(V_k/4)$ and $\tau_e = 2ms$ 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 $j-th$ interneuron reads

$$I_{FF,j} = -\frac{1}{N_{FS}-1}\sum_{k\neq j} g_i s_{FF,k}(t)(V_j - V_{FF}) \tag{19}$$

where $g_i = 0.25mS/cm^2$ represents the maximal amplitude of the inhibitory coupling and V_{FF} is the corresponding reversal potential. The time evolution of $s_{FF,k}(t)$ is described by

$$\frac{ds_{FF,k}(t)}{dt} = T(V_k)(1 - s_{FF,k}) - s_{FF,k}/\tau_i \tag{20}$$

where $T(V_k) = 2(1 + tanh(V_k/4)$ and $\tau_1 = 10ms$ is the decay time constant.

The pyramidal cells excite the network of FS cells and the corresponding excitatory current acting on the $j-th$ interneuron is defined as

$$I_{PF,j} = -\frac{1}{N_{PY}-1}\sum_{k\neq j} g_{PF} s_{PF,k}(t)(V_j - V_{PF}) \tag{21}$$

where g_{PF} represents the maximal amplitude of the excitatory coupling and $V_{PF} = V_{PP}$ is the corresponding reversal potential. The time evolution of $s_{PF,k}(t)$ is driven by

$$\frac{ds_{PF,k}(t)}{dt} = T(V_k)(1 - s_{PF,k}) - s_{PF,k}/\tau_e \tag{22}$$

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

The network of FS interneurons feedback inhibition to the pyramidal neurons and the inhibitory current of the $j-th$ cell is given by

$$I_{FP,j} = -\frac{1}{N_{FS}-1}\sum_{k\neq j} g_{FP} s_{FP,k}(t)(V_j - V_{FP}) \tag{23}$$

where g_{FP} represents the maximal amplitude of the inhibitory coupling and $V_{FP} = V_{FF}$ is the corresponding reversal potential. The time evolution of $s_{FP,k}(t)$ is determined by

$$\frac{ds_{FP,k}(t)}{dt} = T(V_k)(1 - s_{FP,k}) - s_{FP,k}/\tau_i \tag{24}$$

where $T(V_k) = 2(1 + tanh(V_k/4)$ and $\tau_i = 10ms$ is the decay time constant.

The electrical coupling among FS interneurons is all-to-all and the corresponding current on the $j - th$ cell is defined as

$$J_{FF,j} = \frac{1}{N_{FS} - 1} \sum_{k \neq j} g_{el}(V_j - V_k) \tag{25}$$

where g_{el} is the coupling amplitude. The parameters values g_i, g_e, g_{PF}, g_{FP} are those adopted in [8] .

The excitatory coupling due to TC network on FS neurons is described by an AMPA current

$$I_{TF,j} = -\frac{1}{N_{TC}} \sum_k g_{AMPA(T-F)} s_{TF,k}(t)(V_j - V_{AMPA}) \tag{26}$$

where $g_{AMPA(T-F)}$ represents the maximal amplitude of the excitatory coupling and $V_{AMPA} = 0\ mV$ is the corresponding reversal potential.The time evolution of the synaptic variable $s_{TF,k}(t)$ is described by

$$\frac{ds_{TF,k}(t)}{dt} = s_\infty(V_k)(1 - s_{TF,k}) - s_{TF,k}/\tau_T \tag{27}$$

where $s_\infty(V_k) = 2[1 + exp(-(V_k + 45)/2)]^{-1}$, $\tau_T = 10\ ms$.

The excitatory coupling due to TC network on PY neurons is described by an AMPA current

$$I_{TP,j} = -\frac{1}{N_{TC}} \sum_k g_{AMPA(T-P)} s_{TP,k}(t)(V_j - V_{AMPA}) \tag{28}$$

where $g_{AMPA(T-P)}$ represents the maximal amplitude of the excitatory coupling and $V_{AMPA} = 0\ mV$ is the corresponding reversal potential.The time evolution of the synaptic variable $s_{TP,k}(t)$ is described by

$$\frac{ds_{TP,k}(t)}{dt} = s_\infty(V_k)(1 - s_{TP,k}) - s_{TP,k}/\tau_T \tag{29}$$

where $s_\infty(V_k) = 2[1 + exp(-(V_k + 45)/2)]^{-1}$, $\tau_T = 10\ ms$.

The inhibitory coupling among RE neurons are characterized by GABA-A and GABA-B synapses, defined by the following equations

$$I_{RRA,j} = -\frac{1}{N_{RE}} \sum_k g_{GABA-A} s_{RA,k}(t)(V_j - V_{GABA-A}) \tag{30}$$

where $g_{GABA-A} = 0.5\ mS/cm^2$ represents the maximal amplitude of the inhibitory coupling and V_{GABA-A} = -75 mV is the corresponding reversal potential.The time evolution of the synaptic variable $s_{RA,k}(t)$ is described by

$$\frac{ds_{RA,k}(t)}{dt} = x_\infty(V_k)(1 - s_{RA,k}) - s_{RA,k}/\tau_A \tag{31}$$

where $x_\infty(V_k) = 2[1 + exp(-(V_j + 45)/2)]^{-1}$ and $\tau_A = 12.5\ ms$

$$I_{RRB,j} = -\frac{1}{N_{RE}} \sum_k g_{GABA-B} s_{RB,k}(t)(V_j - V_{GABA-B}) \tag{32}$$

where $g_{GABA-B} = 0.1\ mS/cm^2$ represents the maximal amplitude of the inhibitory coupling and V_{GABA-B} = -90 mV is the corresponding reversal potential.The time evolution of the synaptic variable $s_{RB,k}(t)$ is described by

$$\frac{ds_{RB,k}(t)}{dt} = s_\infty(x_{RB,k})(1 - s_{RB,k}) - s_{RB,k}/\tau_B \tag{33}$$

$$\frac{dx_{RB,k}(t)}{dt} = x_\infty(V_k)(1 - x_{RB,k}) - x_{RB,k}/\tau_{x,B} \tag{34}$$

where $s_\infty(x_{RB,k}) = 0.01[1+exp(-(x_{RB,k}-1/e)/0.02)]^{-1}$, $\tau_B = 200\,ms\ x_\infty(V_k) = 5[1 + exp(-(V_j + 45)/2)]^{-1}$ and $\tau_{x,B} = 100\ ms$,

The excitatory coupling due to TC network on RE neurons is described by an AMPA current

$$I_{TR,j} = -\frac{1}{N_{TC}} \sum_k g_{AMPA(T-R)} s_{TR,k}(t)(V_j - V_{AMPA}) \tag{35}$$

where $g_{AMPA(T-R)} = 0.02\ mS/cm^2$ represents the maximal amplitude of the excitatory coupling and $V_{AMPA} = 0\ mV$ is the corresponding reversal potential.The time evolution of the synaptic variable $s_{TR,k}(t)$ is described by

$$\frac{ds_{TR,k}(t)}{dt} = s_\infty(V_k)(1 - s_{TR,k}) - s_{TR,k}/\tau_T \tag{36}$$

where $s_\infty(V_k) = 2[1 + exp(-(V_k + 45)/2)]^{-1}$, $\tau_T = 10\ ms$

The excitatory coupling due to PY network on RE neurons is described by an AMPA current

$$I_{PR,j} = -\frac{1}{N_{PY}} \sum_k g_{AMPA(P-R)} s_{PR,k}(t)(V_j - V_{AMPA}) \tag{37}$$

where $g_{AMPA(P-R)}$ represents the maximal amplitude of the excitatory coupling and $V_{AMPA} = 0\ mV$ is the corresponding reversal potential.The time evolution of the synaptic variable $s_{PR,k}(t)$ is described by

$$\frac{ds_{PR,k}(t)}{dt} = T(V_k)(1 - s_{PR,k}) - s_{PR,k}/\tau_e \tag{38}$$

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

The inhibitory coupling due to RE neurons on TC neuron are characterized by GABA-A and GABA-B synapses, defined by the following equations

$$I_{RTA,j} = -\frac{1}{N_{RE}} \sum_k g^{RT}_{GABA-A} s_{RA,k}(t)(V_j - V_{GABA-A}) \tag{39}$$

where g^{RT}_{GABA-A} represents the maximal amplitude of the inhibitory coupling and V_{GABA-A} = -75 mV is the corresponding reversal potential.The time evolution of the synaptic variable $s_{RA,k}(t)$ is described by

$$\frac{ds_{RA,k}(t)}{dt} = x_\infty(V_k)(1 - s_{RA,k}) - s_{RA,k}/\tau_A \tag{40}$$

where $x_\infty(V_k) = 2[1 + exp(-(V_j + 45)/2)]^{-1}$ and $\tau_A = 12.5\ ms$

$$I_{RTB,j} = -\frac{1}{N_{RE}} \sum_k g^{RT}_{GABA-B} s_{RB,k}(t)(V_j - V_{GABA-B}) \tag{41}$$

where g^{RT}_{GABA-B} represents the maximal amplitude of the inhibitory coupling and V_{GABA-B} = -90 mV is the corresponding reversal potential.The time evolution of the synaptic variable $s_{RB,k}(t)$ is described by

$$\frac{ds_{RB,k}(t)}{dt} = s_\infty(x_{RB,k})(1 - s_{RB,k}) - s_{RB,k}/\tau_B \tag{42}$$

$$\frac{dx_{RB,k}(t)}{dt} = x_\infty(V_k)(1 - x_{RB,k}) - x_{RB,k}/\tau_{x,B} \tag{43}$$

where $s_\infty(x_{RB,k}) = 0.01[1+exp(-(x_{RB,k}-1/e)/0.02)]^{-1}$, $\tau_B = 200\,ms$ $x_\infty(V_k) = 5[1 + exp(-(V_j + 45)/2)]^{-1}$ and $\tau_{x,B} = 100\ ms$,

The excitatory coupling due to PY network on TC neurons is described by an AMPA current

$$I_{PT,j} = -\frac{1}{N_{PY}} \sum_k g_{AMPA(P-T)} s_{PT,k}(t)(V_j - V_{AMPA}) \tag{44}$$

where $g_{AMPA(P-T)}$ represents the maximal amplitude of the excitatory coupling and $V_{AMPA} = 0\ mV$ is the corresponding reversal potential.The time evolution of the synaptic variable $s_{PR,k}(t)$ is described by

$$\frac{ds_{PT,k}(t)}{dt} = T(V_k)(1 - s_{PT,k}) - s_{PT,k}/\tau_e \tag{45}$$

where $T(V_k) = 5(1 + tanh(V_k/4)$ and $\tau_e = 2ms$ is the decay time constant. The parameter values describing the amplitude of the synaptic current among neurons of the thalamus were those reported in [9]. The remaining values describing the synaptic currents from cortical and thalamic cells were chosen to get realistic amplitude of the postsynaptic potentials.

3 Results

Let us start first by investigating how the the whole cortico-thalamo-cortical network behave in absence of coupling between cortical and thalamic compartments. The corresponding results are reported in the left panel of figure 2.

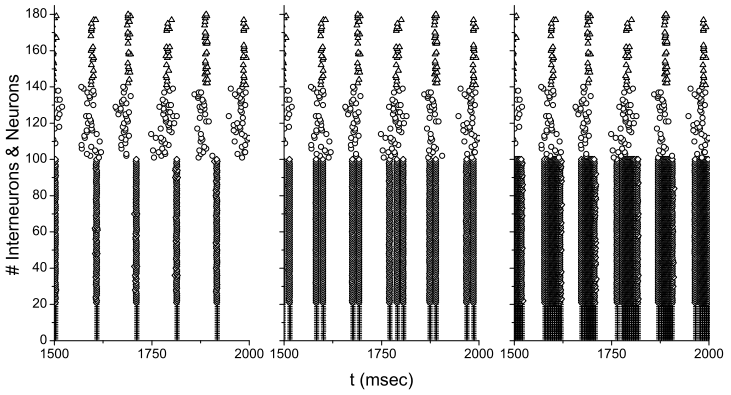

Fig. 2. Effects of coupling betweeen thalamic neuron and pyramidal neurons on the networks dynamics. Left panel: $g_{AMPA(T-P)} = 0$, $g_{AMPA(T-F)} = 0$, $g_{AMPA(P-T)} = 0$, $g_{AMPA(P-R)} = 0$,. Middle panel: $g_{AMPA(T-P)} = 0.2mS/cm^2$, $g_{AMPA(T-F)} = 0$, $g_{AMPA(P-T)} = 0$, $g_{AMPA(P-R)} = 0$. Right panel: $g_{AMPA(T-P)} = 0.8mS/cm^2$, $g_{AMPA(T-F)} = 0$, $g_{AMPA(P-T)} = 0$, $g_{AMPA(P-R)} = 0$. For all panels it is: $g_e = 0.5mS/cm^2$, $g_i = 0.25mS/cm^2$, $g_{el} = 0$, $I_P = 3.5\mu A/cm^2$, $I_F = 0.5\mu A/cm^2$, $g^{RT}_{GABA-A} = 0.15mS/cm^2$, $g^{RT}_{GABA-B} = 0.05mS/cm^2$, $N_{PY} = 80$, $N_{FS} = 20$, $N_{TC} = 40$, $N_{RE} = 40$. For all panels the plus symbols represent the FS interneurons, the diamonds represent the pyramidal cells, the open circles represent the TC neurons and the open triangles the RE neurons.

FS and pyramidal neurons fire in close synchrony and a qualitatively similar behaviour is exhibited by RE and TC cells (in this last case the level of network synchrony is smaller than that for the cortical compartment). In the middle panel are reported the results obtained in the case in which the pyramidal cell receive the excitatory synaptic inputs from TC cells ($g_{AMPA(T-P)} = 0.2mS/cm^2$). In this case there is an increment of the spiking activity of pyramidal neurons. The increase of the amplitude of the synaptic input from TC cells to pyramidal neurons promotes the generation of seizure-like dynamics (right panel of figure 2). This behaviour is in agreement with the experimental results described in [5]. An important point concerns the impact of the FS cells on the network dynamics when the synaptic input from TC to FS cells is set on. The results for the case $g_{AMPA(T-F)} = 0.5mS/cm^2$ are reported in the left panel of figure 3. Comparing these results with those reported in the right panel of figure 2 it follows that the main effect of this additional coupling is to enlarge the time window where the bursting of FS cells occur.

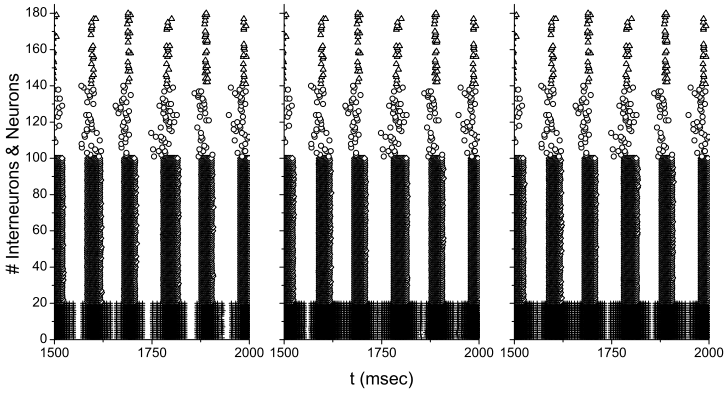

Fig. 3. Effects of coupling betweeen thalamic neuron and pyramidal neurons on the networks dynamics. Left panel: $g_{AMPA(T-P)} = 0.8mS/cm^2$, $g_{AMPA(T-F)} = 0.5mS/cm^2$, $g_{AMPA(P-T)} = 0$, $g_{AMPA(P-R)} = 0$, $g_{el} = 0$. Middle panel: $g_{AMPA(T-P)} = 0.8mS/cm^2$, $g_{AMPA(T-F)} = 1.2mS/cm^2$, $g_{AMPA(P-T)} = 0$, $g_{AMPA(P-R)} = 0$, $g_{el} = 0$. Right panel: $g_{AMPA(T-P)} = 0.8mS/cm^2$, $g_{AMPA(T-F)} = 1.2mS/cm^2$, $g_{AMPA(P-T)} = 0$, $g_{AMPA(P-R)} = 0$, $g_{el} = 0.15mS/cm^2$. For all panels it is: $g_e = 0.5mS/cm^2$, $g_i = 0.25mS/cm^2$, $I_P = 3.5\mu A/cm^2$,$g^{RT}_{GABA-A} = 0.15mS/cm^2$, $g^{RT}_{GABA-B} = 0.05mS/cm^2$, $I_F = 0.5\mu A/cm^2$, $N_{PY} = 80$, $N_{FS} = 20$, $N_{TC} = 40$, $N_{RE} = 40$. For all panels the plus symbols represent the FS interneurons, the diamonds represent the pyramidal cells, the open circles represent the TC neurons and the open triangles the RE neurons.

However, as expected, the increase of the inhibitory inputs determines a reduction of the time window where the bursting of the pyramidal cells occurs. Increasing more the coupling amplitude ($g_{AMPA(T-F)} = 1.2mS/cm^2$) promotes the increase of the firing activity of the FS cells (see middle panel of figure 3), but the activity of the pyramidal cell is practically unaffected. Similar results were found when the electrical coupling among FS cells was set on (see right panel of figure 3). Let us now study how the presence of the excitatory synaptic inputs from pyramidal cells to RE and TC neurons affects the network dynamics. The corresponding data reported in figure 4 show that both RE and TC cells now fire more synchronoulsly; moreover a reduction of the firing activity of the FS cells also occur (see for comparison the data in the middle panel of figure 3). Also in this situation the pyramidal cells exhibit seizure like behaviour. The increase of the amplitude of the synaptic inputs between RE and TC cells has a dramatic effect on the network dynamics. The corresponding results are reported in the right panel of figure 4 and clearly show that the seizure like behavior is terminated.

In addition the data show a complete cessation of spiking activity of the thalamic cells. Why this occurs? To respond to this question it is important to know how RE and TC cell models behave when receive excitatory (or inhibitory inputs). To this aim let us consider a single RE (or TC) cell injected with a

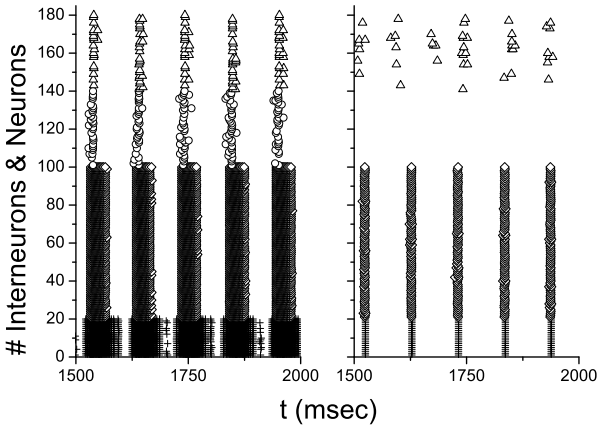

Fig. 4. Effects of coupling betweeen thalamic neuron and pyramidal neurons on the networks dynamics. Left panel: $g_{AMPA(T-P)} = 0.8mS/cm^2$, $g_{AMPA(T-F)} = 0.5mS/cm^2$, $g_{AMPA(P-T)} = 0.05mS/cm^2$, $g_{AMPA(P-R)} = 0.02mS/cm^2$, $g^{RT}_{GABA-A} = 0.15mS/cm^2$, $g^{RT}_{GABA-B} = 0.05mS/cm^2$. Right panel: $g_{AMPA(T-P)} = 0.8mS/cm^2$, $g_{AMPA(T-F)} = 1.2mS/cm^2$, $g_{AMPA(P-T)} = 0.05mS/cm^2$, $g_{AMPA(P-R)} = 0.02mS/cm^2$, $g^{RT}_{GABA-A} = 1.1mS/cm^2$, $g^{RT}_{GABA-B} = 0.9mS/cm^2$. For all panels it is: $g_e = 0.5mS/cm^2$, $g_i = 0.25mS/cm^2$, $g_{el} = 0$, $I_P = 3.5\mu A/cm^2$, $I_F = 0.5\mu A/cm^2$, $N_{PY} = 80$, $N_{FS} = 20$, $N_{TC} = 40$, $N_{RE} = 40$. For all panels the plus symbols represent the FS interneurons, the diamonds represent the pyramidal cells, the open circles represent the TC neurons and the open triangles the RE neurons.

depolarizing (hyperpolarizing) current. Let us first consider the RE cell that, for the adopted parameter values, generates action potential spontaneously at a frequency of about 8 Hz. When this cell is injected with a depolarizing current the amplitude of the action potential decreses as the amplitude current grows (the corresponding frequency exhibit small changes). When the current amplitude is greater than 1.1 mA/cm^2, the firing disappears. Therefore, for the RE cell model a depolarizing input depress the firing activity. If the RE cell model is injected with an hyperpolarizing current, the amplitude of the action potential increases. However, for amplitudes of the injected current smaller than -1 mA/cm^2 the firing ceases (data not shown). Let us now consider the TC cell model. In this case, for the adopted parameter value, the value of the membrane potential of a single TC cell is at resting (about $-55mV$). If the cell is injected with a depolarizing current the values of the membrane potential increases but no firing occurs. If the TC cell is injected with an hyperpolarizing current of amplitude -0.7 mA/cm^2 then a firing activity starts (with a frequency of about $2.5Hz$). As the current gets smaller values both the amplitude of the action potential and the firing frequency decrease; the firing disappears for current amplitude smaller than -1.4 mA/cm^2 (data not shown). The single pyramidal neuron (or the FS interneuron) model when injected with a constant current behaves more regularly than RE or TC cells [8,10]. Then, it can be shown qualitatively that the seizure

termination (see figure 4) is a direct consequence of the response properties of the single RE and TC neuron models to depolarizing (hyperpolarizing) inputs discussed before.

Taken together these results are qualitatively in keeping with those described in [5]. In particular in this experimental work it was shown that the inhibition of thalamocortical neurons interrupted seizures, and this indicates that a suitable modulation of the activity of the cortico-thalamo-cortical network could be used to control seizures generation and termination.

4 Conclusions

The main goal of this paper was the understanding of some possible mechanisms controlling epileptic seizures dynamics. Recently, experimental results pointed out that thalamic inputs modulate seizure dynamics: i.e. they can promote generation and termination of ictal activity [5]. Motivated by these experimental data, we studied the dynamical behaviour of a biophysical inspired network of four coupled populations of cells: the first population is composed by coupled FS interneurons (coupled by inhibitory and electrical synapses), the second one is constituted by coupled pyramidal cells (coupled by excitatory synapses), the third is composed by thalamic reticular neurons RE (coupled by inhibitory synapses), while the last pool is composed by thalamocortical cells TC. In particular, our attention was focused to study how alteration of the coupling among thalamic and cortical neurons affects the whole network firing activity. The numerical simulations have shown that the increase of the amplitude of the excitatory coupling from TC neurons to pyramidal cells promotes the generation of seizure-like behaviour (see figure 2). Furthermore, the addition of the excitatory coupling from TC neurons to FS interneurons enlarges the time window where the bursting of FS cells occurs. As a consequence, the fast bursting regime of the pyramidal cells is reduced. The presence of excitatory synaptic inputs from pyramidal neurons to RE and TC neurons produce a synchronization of the firing activity of both RE and TC cells. A remarkable result is obtained when the inhibitory coupling on TC cells from the RE pool is increased. Indeed the spiking activity of the TC neurons is absent and we observed a complete cessation of the bursting regime of pyramidal neurons (see figure 4). In conclusion this computational study have clearly shown that the cortico-thalamo-cortical network is capable of promoting (or inhibiting) cortical ictal activity. These findings are in agreement with the experimental results described in [5].

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