# Intrinsic bursting properties and pattern of activity in spatially distributed networks [1]

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**Abstract**

This paper addresses the hypothesis that during seizures, changes in the dynamics of $[Ca^{2+}]_i$ transients caused by saturation of intracellular calcium removal or buffering systems can result in observed alterations of seizure dynamics. Using large neural network models of single compartment neurons, we show how changing $[Ca^{2+}]_i$ and effects on calcium-mediated afterhyperpolarization may influence the spatiotemporal characteristics of seizure patterns. Such changes in $[Ca^{2+}]_i$ may also be important contributions to seizure termination. These studies can provide insights into the understanding of mechanisms of the dynamic changes seen in seizures in humans.

*Key words:* neural network, epilepsy, afterhyperpolarization, intracellular calcium, seizure dynamics

## Introduction

Temporal lobe epilepsy is a disorder in which seizures often begin as paroxysmal electrical discharges in the mesial temporal regions and then propagate regionally through the temporal lobe. It is not fully understood how this recruitment takes place and why this process undergoes dynamical changes. Changes in neuronal and cerebral synchrony can be studied by examining the changes in the macroscopic EEG. Time frequency analyses applied to intracranial EEG recordings from mesial temporal lobe onset seizures reveal interesting seizure evolution, showing that this is typically a dynamic process with signal composed of multiple frequencies [1,2]. Based on the time evolution of the

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EEG, several periods can be identified including seizure initiation, transitional rhythmic activity, organized rhythmic activity, and intermittent bursting activity [3]. The seizure onset and the following period of transitional rhythmic activity (when seizures propagate regionally) are by themselves evolving and dynamic processes. Close examination shows that the subsequent ictal periods also undergo dynamical changes. The organized rhythmic period is typically a dynamic process characterized by maximum predominant frequency of 5 - 8 Hz with a monotonic decline in frequency over a period of less that 60 seconds.

Although much work has been done on epileptic foci, the cellular and circuit properties in cortex that underlay temporal lobe seizures dynamics are not well understood. Calcium and calcium-dependent systems in neurons have for a long time been implicated as mechanisms that may be important in epilepsy [4,5]. It has been shown in a slice model of biculline-induced spontaneous epileptiform activity that changes in $[Ca^{2+}]_i$ concentration in neurons correlate with epileptiform field potentials and intracellular depolarizing shifts in these neurons [6]. $Ca^{2+}$ influx into neuron may be associated with short-term enhancement of synaptic and possibly neuronal activity [7,8]. The other consequence of calcium entry is the activation of $Ca^{2+}$ dependent potassium channels, which leads to membrane hyperpolarization (AHP) [9]. This mechanism is functionally inhibitory and has been identified as important in suppresion of epileptiform activity in many experimental models of epilepsy [10–13]. This evidence suggests that calcium and its effects on calcium-mediated after-hyperpolarization may influence the characteristics of seizure dynamics.

In this paper we address whether changes in the dynamics of $[Ca^{2+}]_i$ transients in neurons caused by saturation of intracellular calcium removal systems can result in alterations of seizure dynamics. To test this hypothesis we begin with a model of a spatially distributed array of interconnected subnetworks capable of reproducing synchronized bursting activity. We then use simulation to review how this array responds to external periodic stimulation and demonstarate how changes in the removal rate of $[Ca^{2+}]_i$ can result in alteration of frequency of burst activity in this network. We demonstrate that slow decreasing of ability to remove $Ca^{2+}$ by calcium buffering and removal systems in neurons can produce the phenomenon of decrease in time of the frequency of bursts in neurons.

## Methods

A network is composed of an array of 28 by 28 sub-networks where each subnet consists of 81 excitatory and 9 inhibitory interneurons. Neurons are modeled as single-compartment units using the conductance-based model with a reduced number of variables (see Appendix). The excitatory cells fire repetitive bursts in response to constant current or synaptic input with a frequency depen-

dent on the calcium elimination rate. The inhibitory interneurons respond to excitatory input with high-frequency nonadapting spike trains. Within a sub-network of 90 neurons connectivity is random all-to-all (any neuron can potentially synapse with any other neuron) with a connection probability less than 5% for e-e and e-i, and 45% for i-e and i-i connections. Each neuron has as inputs two excitatory and two inhibitory synapses. The synaptic delays have a mean value of 3.6 ms and a standard deviation of 0.5 ms. Randomly selected excitatory neurons in neighboring sub-networks are connected. Each sub-network is synaptically connected with 16 randomly selected sub-networks and the range of these connections covers 100 neighboring sub-networks (8100 excitatory neurons). There are only excitatory connections between sub-networks and the total number of connections between two sub-networks does not exceed four. Repetitive bursting activity in the network array is triggered by a periodic stimulation of excitatory neurons in four sub-networks in the center of the array. During simulations the calcium removal rate constant $R$ is decreased exponentially with $\tau_{_R} = 20$ s (Eq. 4).

## Results

*Dependence of burst frequency in network on driving current*

A brief pulse of excitatory current injected into excitatory neurons in one sub-network in the center of an network array drives all neurons in the network to fire bursts of action potentials synchronously. In this network array of 28 by 28 sub-networks, the bursting activity occurs in the remote sub-networks within less than 30 ms after the onset of stimulation (Fig. 1). Brief pulses of current injected periodically (7-50 Hz) induce periodic synchronous bursting activity in the network array. The frequency of induced synchronous bursting activity in the network (excluding neurons located in the stimulated sub-networks) is determined by the calcium influx rate, the volume of $I_{K(Ca)}$ and the recovery time from afterhyperpolarization, not by the frequency of stimulation. The characteristic frequency observed in the network is 7 Hz and it corresponds to the intracellular calcium removal rate $R = 0.023$. However, brief current pulses injected with a frequency less than 7 Hz can force neurons in the network to synchronize their activity at a frequency the same as the frequency of injected current pulses. As the strength of inhibitory synapses increase, the number of neurons in the subnet firing bursts synchronously decreases. Strong inhibition leads to self-sustained patterns of activity.

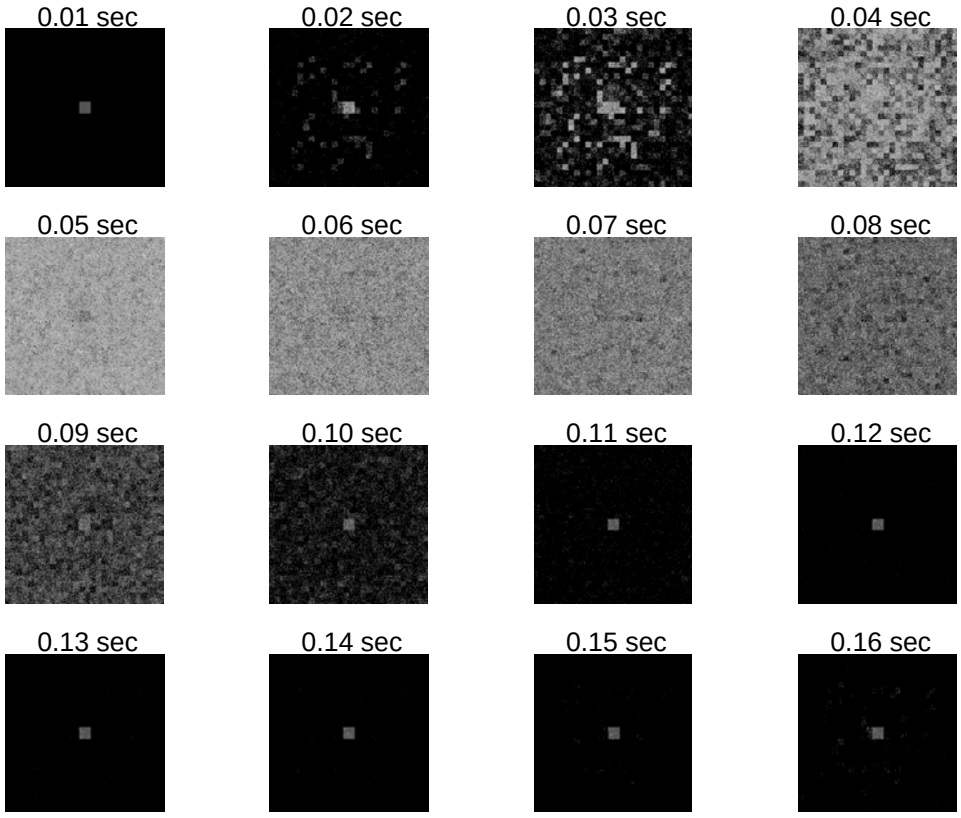


Fig. 1. The pattern of activity in a network array of 28 by 28 sub-networks where each sub-network consists of 81 excitatory and 9 inhibitory neurons. Only the pattern of activity in excitatory neurons in the array is shown (252 x 252 neurons). The brightness of each pixel is proportional to the number of action potentials fired by respective neurons in 10 ms interval ending at the given time indicated at the top (black is 0, white is $\sim 3$ action potentials). Bursting activity in the network array is triggered by injecting periodic pulse of depolarizing current (50 Hz amplitude 25 $p$A) to excitatory neurons in four sub-networks in the center of the array. At the time 0.05 s (40 ms after the begining of stimulation at 0.01 s) the whole network is active.

*Dependence of burst frequency in network on recovery time from afterhyperpolarization*

Our results show that changes in the intracellular calcium removal rate in neurons in simulated networks produce changes in the frequency of synchronous bursting activity that are observed in this network. A network array of 28 by 28 sub-networks was activated by periodic excitatory input with a frequency of 7 Hz applied to neurons in four sub-networks in the center of the array. During the 45 seconds of simulation, the intracellular calcium removal rate constant $R$ was decreased exponentially from 0.017 to 0.003. Without changing the frequency of stimulation we observed decline in the frequency of bursts activities in neurons remote from the site of stimulation from 6.5 to 1.5 Hz

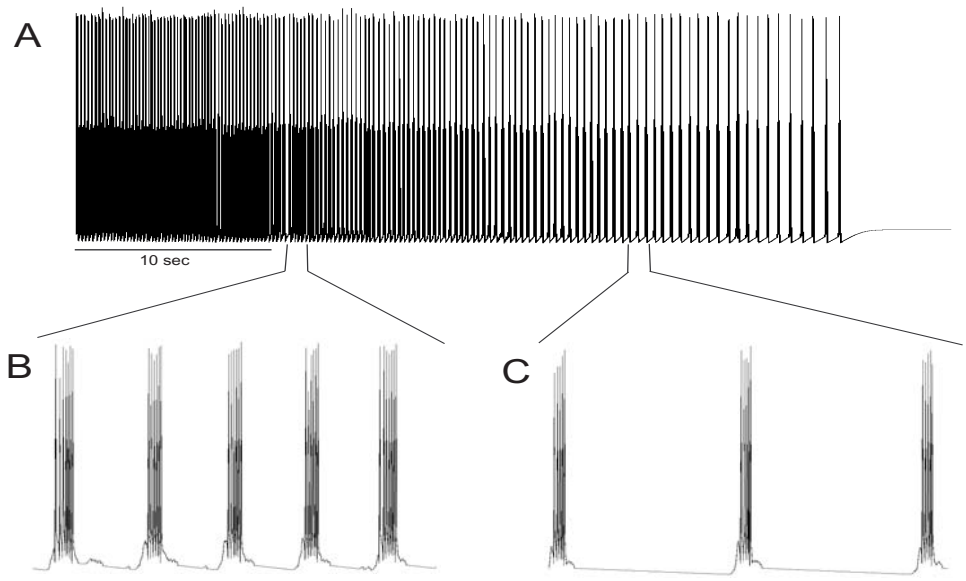


Fig. 2. Illustration of qualitative change in neuronal bursting pattern. Trace A shows membrane potential of one neuron located near the border of the network array in Fig. 1 (remote from the site of stimulation). Total time shown on A is 45 seconds. Trace B and C show an expanded view of several bursts in 1 second period from trace A in 10 s and 30 s of simulation. Calium removal rate $R$ decreased expotentialy from 0.017 ($t$=0 s) to 0.003 ($t$=45 s)

(Fig. 2). This decline in frequency was correlated with the decrease of the value of removal rate of $[Ca^{2+}]_i$ in excitatory neurons ($R$ in a range 0.017 - 0.003) (Fig. 3).

## Discussion

A primary purpose of these studies was to describe a possible mechanism involved in the evolution and dynamics of the predominant rhythm, which is observed in EEGs of temporal lobe seizures in humans. Intracranial EEG recordings indicates that temporal lobe seizures are dynamic proceses and may sequentially include periodic spike activity (single spikes repeated in regular intervals), organized rhythmic activity (the large amplitude predominantly monotonic rhythmic activity) and intermittent bursting (periods of polyspike activity alternating with periods of diminished activity) [3]. A neural network model reported here can reproduce characteristics of repetitive synchronous neuronal bursting that resembles patterns observed during periods of organized rhythmic activity in the temporal lobe. Our particular goal here was to model changes in the dynamics of rhythmic neuronal activity during this period. These types of seizures are triggered by epileptic foci located in the mesial temporal structures. Thus in this study we do not model epileptic foci in detail but rather concentrate on modeling the response of the network to variety of

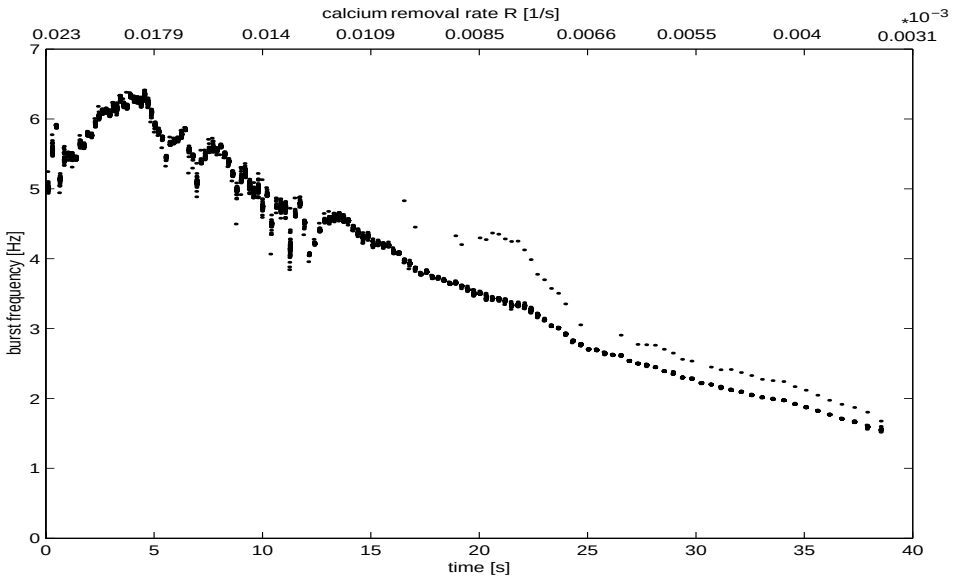


Fig. 3. Decreasing the calcium removal rate during simulation decreases the frequency of bursts in neurons in the sub-networks. Frequency of bursts is measured in all excitatory neurons in one sub-networks remote from the site of stimulation. The vertical axis represents the frequency of bursts. The bottom horizontal axis represents time and the top axis represents the calcium removal rate $R$. Decreasing $R$ produces changes in the frequency of bursts similar to changes in the frequency of the predominant periodic rhythm observed in experimental and clinical epilepsy.

periodic external excitatory inputs. The periodically injected current pulses we use to activate the network represent the input from the epileptic focus. To allow generation of synchronous bursts in this network, parameters in models of neurons and synapses were selected to reproduce the pattern of frequency change consistent with observations from intracranial EEG recordings during temporal lobe seizures. The presented model of a spatially distributed network can represent a section of cortex without long-range connections. The number of neurons in our model is sufficient to reproduce electrical activity that could be detectable by a macroscopic electrode. Although we do not model EEG explicitly in our simulation, the frequency of synchronous bursts in our network model can reflect the frequency that is observed in EEG recorded during organized rhythmic seizure activity. In the icatl EEG the most orderly synchronous neuronal activity is represented by periodic signals of low complexity. Intentionally in this paper our efforts concentrate on modeling a period of organized rhythmic activity in seizure that is characterized by one predominant rhythm.

The frequency of bursts observed in neurons is not primarily determined by the frequency of stimulation. This means that the observed frequency of bursts in the network does not depend entirely on the characteristics of external input (which represent input from the focus). Neurons will fire synchronous bursts with the frequency that is determined by the $[Ca^{2+}]_i$ removal parameters $R$ in the presence of any excitatory external input. However, it is possible

to achieve low frequency of bursts in the model if the frequency of injected external current pulses is below the frequency determined by the $[Ca^{2+}]_i$ removal rate $R$.

Altered level of somatic $[Ca^{2+}]_i$ and the time of decay of $Ca^{2+}$ transients produces changes in the frequency of bursts. Changes in the intracellular calcium removal rate in neurons in the simulated network produce changes in the frequency of bursts in neurons. In particular, decreasing the calcium removal rate during simulation produces a decline in the frequency of bursts, similar to the decline observed in the frequency of the predominant periodic rhythm in clinical temporal lobe epilepsy.

The mechanism of synchronization of neuronal activity in the network relies on excitatory inter-connections between sub-networks, which cause firing of excitatory neurons in the network together. Not every excitatory neuron in every sub-network fires on every cycle. Bursts in neurons are then synchronously terminated by afterhyperpolarization in neurons ($I_{K(Ca)}$ current). Hence periods of synchronous bursts in neurons alternate with refractory periods caused by afterhyperpolarization. Thus the frequency of bursts in the network is regulated by the recovery time from afterhyperpolarization, which depends on the rate of the intracellular calcium removal. Normally neurons may utilize several calcium buffering components to regulate $[Ca^{2+}]_i$. These include (but are not restricted to) binding to calcium buffers. Each time after a short-term neuronal excitation the surplus of $[Ca^{2+}]_i$ is quickly removed from the cytoplasm in order to avoid prolonged exposure to cytotoxic levels [14]. Seizures however, are abnormally long-term periods of increased neuronal synchrony. The prolonged $Ca^{2+}$ influx into neurons during a seizure may lead to alteration in the regulation of $[Ca^{2+}]_i$ due to saturation of removal or buffering systems. Such alterations in the calcium homeostatic mechanisms were observed in pilocarpine models of epilepsy in hippocampal neuronal culture following the induction of epileptogenesis [15,16]. Elevated level of $[Ca^{2+}]_i$ in neurons may lead to potentiation of $I_{K(Ca)}$ current [17] and to spontaneous termination of seizure.

In conclusion, changes in the dynamics of epileptic seizures observed in ictal EEG recordings may reflect processes on the cellular and network-circuit level. Alteration in $[Ca^{2+}]_i$ and calcium removal mechanisms have profound effects on bursting network behavior.

## Appendix

### (A) The neuron model equations

$$C_m \frac{dV}{dt} = I_{syn} - I_{Na} - I_{Ca} - I_K - I_{K(Ca)} - I_A - I_L \qquad (1)$$

$$\frac{dY}{dt} = \frac{Y_\infty(V) - Y}{\tau_{_Y}} \; for \; Y = \{W, X, B\} \tag{2}$$

$$\frac{dC}{dt} = K_p(-I_{Ca}) - RC \tag{3}$$

$$\frac{dR}{dt} = -\frac{1}{\tau_{_R}}R \tag{4}$$

$$\tau_{_W}(V) = \frac{1}{\lambda}\left(e^{a^{(W)}(V - V_{1/2}^{(W)})} + e^{-a^{(W)}(V - V_{1/2}^{(W)})}\right)^{-1} \tag{5}$$

$$P_\infty(V) = \left(1 + e^{-2a^{(P)}(V - V_{1/2}^{(P)})}\right)^{-1} \; for \; P = \{W, m, X, A, B\} \tag{6}$$

$$where: \tag{7}$$

$$I_{Na} = \overline{g}_{Na} m_\infty^3(V)(1 - W)(V - V_{Na}) \tag{8}$$

$$I_{Ca} = \overline{g}_{Ca} X^2 \frac{K_c}{K_c + C}(V - V_{Ca}) \tag{9}$$

$$I_K = \overline{g}_K W^4 (V - V_K) \tag{10}$$

$$I_{K(Ca)} = \overline{g}_{K(Ca)} \frac{C}{K_d + C}(V - V_K) \tag{11}$$

$$I_A = \overline{g}_A A_\infty(V) B (V - V_K) \tag{12}$$

$$I_L = \overline{g}_L (V - V_L) \tag{13}$$

$$\tag{14}$$

Description and values of parameters used in model computations: $V$ is the membrane potential, $W$ is the recovery variable, $C$ is the intracellular calcium concentration, $X$ and $B$ are respectively the calcium channel activation variable and transient potassium channel inactivation variable. The steady-state functions $m_\infty$, $A_\infty$, $W_\infty$, $X_\infty$, and $B_\infty$ are modeled as sigmoidal curves (Eq. 6), determined by two parameters: the half maximum voltage $V_{1/2}$(values are -31, -20, -35, -45 and -70 mV respectively) and a slope $a$ of the curve at this point (values are 0.065, 0.02, 0.055, 2.0, and -0.095 respectively). $K_p = 0.0002$ is the conversion factor from calcium current to concentration and $R$ is the removal rate variable of the intracellular calcium concentration, $\tau_{_R} = 20$ s is decay time of $R$. $C_m = 1\ \mu\mathrm{F/cm}^2$ is the membrane capacitance. $\tau_{_W}$ is the relaxation time function, and $\tau_{_X} = 3\ ms$ and $\tau_{_B} = 1\ ms$ are relaxation time constants for recovery $W$, calcium activation $X$, and potassium transients inactivation $B$ variables. Ion currents $I_i$ are described by the product of three terms: the maximal conductance $\overline{g}_i$, the activation and inactivation variable or function, and the driving force $(V - V_i)$. where: $\bar{g}_{Na} = 120\ \mathrm{mS/cm}^2$, $\bar{g}_{Ca} = 1.0\ \mathrm{mS/cm}^2$, $\bar{g}_K = 15\ \mathrm{mS/cm}^2$, $\bar{g}_A = 12.5\ \mathrm{mS/cm}^2$, $\bar{g}_L = 0.3\ \mathrm{mS/cm}^2$, $\bar{g}_{K(Ca)} = 3.5\ \mathrm{mS/cm}^2$ for excitatory and $0.5\ \mathrm{mS/cm}^2$ for inhibitory neurons are maximum conductances for the respective channels and $V_{Na} = -50$ mV, $V_{Ca} = 124$ mV, $V_K = -72$ mV, and $V_L = -50$ mV are values of the reversal potentials for the respective ions and leak current. $K_d = 0.5$ and $K_C = 2$ are the calcium concentration functions constants.

**(B) Synaptic model equations**

$$I_{syn} = \sum_{j=1}^{N_{syn}} w_j g_j(t)(V - E_{syn}) \tag{15}$$

$$g(t) = \overline{g}_{syn} \sum_{i=1}^{N} \left( e^{\frac{-\Delta t_i}{\tau_d}} - e^{\frac{-\Delta t_i}{\tau_o}} \right) \tag{16}$$

where $i$ denotes summation over past action potentials and $j$ over the number of input synapses. $\overline{g}_{syn} = 0.0112$ mS/cm$^2$, $E_{syn} = -10$ mV,$\tau_d = 3$ ms, $\tau_o = 0.5$ ms, $w_j$ is 60 for excitatory and 10 for inhibitory synapses, $\Delta t_i$ denotes time elapsed since $i$-th action potential arrival on synapse, $N$ is the number of past action potentials with significant contribution to the sum and $N_{syn}$ is the number of synaptic inputs, in these simulations $N_{syn} \geq 4$ (2 excitatory and 2 inhibitory inputs).

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