

# External termination of recurrent bursting in a model of connected local neural sub-networks<sup>\*</sup>

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## Abstract

Epileptic seizures are characterized by repetitive synchronous neuronal bursting activity. To study external influences on this activity, a simple model of a chain loop of neuronal networks has been developed with the goal of understanding how external stimuli can contribute to reduction or cessation of such abnormal recurrent bursting activity. Using this simulated loop model, one can demonstrate that an external stimulus that normally can initiate repetitive activity can terminate the bursting activity when applied to a chain loop of sub-networks, which has actively propagating bursts. The ability of external currents to terminate activity is dependent upon loop length and the timing of the applied external stimulus. Termination of propagation in long loops (40–64 sub-networks in this model) requires application of multiple simultaneous stimuli to different sub-networks.

*Keywords:* Neural network; Epilepsy; Stimulation; Afterdischarges; Bursting

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## 1. Introduction

Recently there has been a growing interest in neural stimulation to reduce the frequency of seizures. The most developed technologies (e.g. vagal nerve stimulation) as well as investigational paradigms (thalamic stimulation) involve continuous intermittent repetitive stimulation [11, 9, 10]. New approaches involve more event-driven stimulation to terminate repetitive bursting. In humans short electrical stimulation that is applied for cortical mapping may produce repetitive or periodic excitatory discharges in cortex called afterdischarges (ADs) [3]. ADs induced by electrical stimulation during cortical mapping in patients with epilepsy may progress

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to produce of clinical seizures. A second electrical stimulation may stop ADs by disrupting them and in epileptic patients decreases the probability of occurrence of seizures [7, 4]. The fact that external electrical stimulation can terminate these discharges raises the possibility of new methods of seizure control. Designing such a device is made difficult because little is known about the mechanism of stopping ADs by electrical stimulation in cortex. Theoretical and model systems are needed to understand the mechanism of action of these techniques. In particular, neural network models are attractive systems to address the influences of these interventions. Here we propose a mechanism of cessation of synchronized bursting activities by external stimuli to a simulated multi-segmental neural network. This can serve as a model for further refinement of stimulus parameters of brain stimulation for reducing seizure generation and propagation in intact biological systems.

## 2. Methods

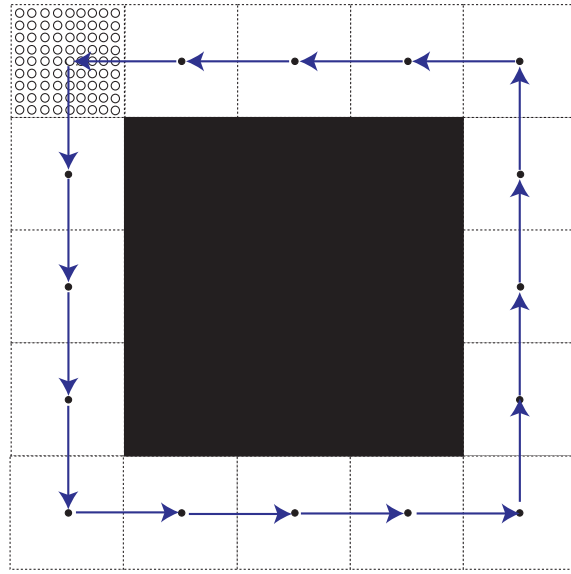
Epileptic seizures represent temporary episodic periods of increased network excitation. The model of synchronous bursting in a neural network employed here is based on the principles utilized in a previously described model [6, 5]. These studies were done in networks with exclusively excitatory connections. The principles of these networks incorporate active membrane properties for each neuron, defined numbers of synaptic connections for each neuron, and modifiable synaptic weights for excitatory and inhibitory connections respectively. The net properties of each neuron are modeled as single compartments. This results in considerable benefits in computational efficiency when dealing with networks of more than a few neurons. Neurons are modeled using a conductance-based model [8, 1] presented in Appendix A. These modeled neurons are synaptically connected and capable of generating action potentials. The neuron model incorporates two inward currents,  $I_{Na}$  and  $I_{Ca}$ , three outward potassium currents, the delayed rectifier  $I_K$ , the Ca-dependent  $I_{K(Ca)}$  and the transient  $I_A$  current, and a leak current  $I_L$ . The synaptic connection between cells is modeled by a synaptic current  $I_{syn}$ . The synaptic conductance is represented by a sum of two exponential functions (Appendix B). The overall strength of a connection is represented by a single synaptic weight parameter and a delay parameter represents all delays between cells. In these simulations we use a network of 81 excitatory neurons to simulate a small locally connected region of the modeled cortex. Each cell receives excitatory input from 2 cells. Presynaptic neurons are chosen randomly with the range of connections covering all neurons. A pseudo-random generator is used to choose connections for each cell. This produces a network with no predefined structure of circuits. The weight of synaptic connections is equal to 60. These values were chosen after multiple simulations with different relative synaptic weights, so that synchronized network bursting could be produced by excitatory input. The interneuronal latency is  $3.6 \pm 0.5$  ms.

While the neuronal substrate of epileptic seizures involves paroxysmal bursting of neurons in a local circuit, the clinical manifestations of seizures result mostly from spread of activity from these local circuits to involve adjacent and remote brain regions. We introduce the concept of multi-segmental neuronal networks, which allow for modeling of the spread of bursting activity. The simulated multi-segmental neuronal network comprises a group of serially connected local neural sub-networks, which form a chain loop (Fig. 1A). This chain loop can serve as generic model of a cortical circuit [2] or interconnected circuit of different brain structures. Each sub-network consists of 81 synaptically connected excitatory neurons<sup>1</sup> as described before. The chain loop of networks consists of a finite number of sub-networks (13–64). Sub-networks are not identical because for each network connections are created separately. To simulate the chain loop of networks the outputs of neurons of each preceding sub-network are connected to inputs of neurons of the subsequent sub-network. In these simulations each neuron in a sub-network receives input from one randomly selected neuron from the preceding sub-network. Repetitive activities in chain loops are initiated by the external depolarizing current ( $I_{ext} = 10\text{--}25 \mu\text{A}/\text{cm}^2$ ) applied to all neurons in a one selected sub-network at the beginning of the simulation

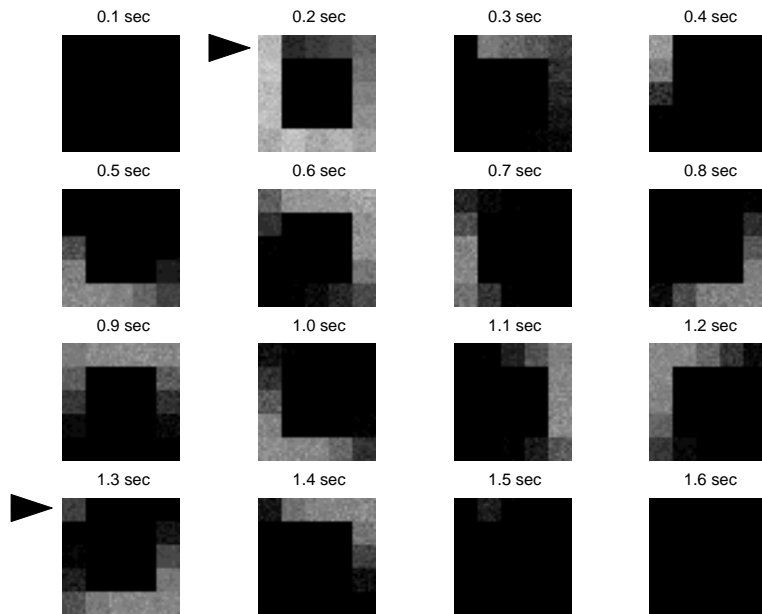
### 3. Results

The parameters of neuron and synaptic models were selected to be consistent with observations from in vitro and in vivo systems and to allow generation of bursts of action potentials in a small network. At the beginning of simulations all neurons are in the resting state (stable node point). Activation of the network by applying external excitatory input to neurons results in synchronized bursts of action potentials of all neurons in a sub-network. In a simulated chain loop of locally connected sub-networks, stimulation of any selected sub-network results in spreading of bursting activity to the adjacent sub-networks. The initial stimulus usually initiates recurrent activity in a loop. Fig. 1B shows how the 50 ms long external current locally delivered to the simulated chain loop (to all neurons of a selected sub-network) initiates repetitive activity in the loop of networks. The observed frequency of the triggered repetitive activity is dependent on the length of the loop and does not exceed 5 Hz. The minimal length of the loop in which self-sustained oscillation is observed is 13 (for the selected values of model parameters). In short loops consisting of 16 or less sub-networks, the repetitive activity is in the range of 2.5–3 Hz. In longer loops, lower frequencies of repetitive bursting are observed; different modes of oscillation also exist. For a loops consisting of 45 or more sub-networks, frequencies of oscillations below 1 Hz can be observed. External current delivered locally, when recurrent activity propagates through the chain loop, alters the propagation

<sup>1</sup> We exclude inhibitory connections; however, analogous simulations can be performed in the presence of inhibition.



(A)



(B)

Fig. 1. (A) Schematic diagram of a loop of 16 randomly connected local network. Each small square represents 81 locally connected neurons (shown only in one square and indicated by circles). Each neuron in a sub-network has two randomly assigned inputs from neurons inside the sub-network and one randomly assigned input from neuron in the preceding sub-network. Arrows show the pattern of connections between sub-networks. (B) Recurrent bursting in a loop shown in diagram A. The activity in the loop is evoked by applying external current to all neurons in one sub-network indicated by arrow. The time is shown at the top of each frame. The first stimulus which initiates activity is applied at 0.2 s. The second at 1.3 s ceases recurrent bursting. The gray scale indicates relative intensity of bursting in sub-networks, black is lack of bursts.

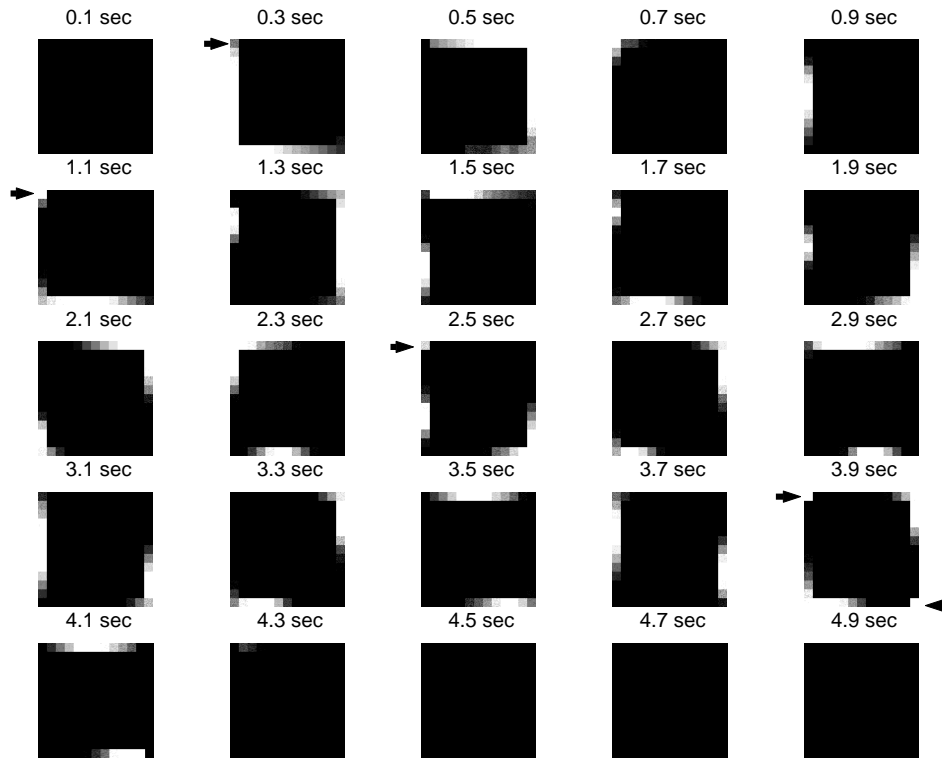


Fig. 2. Pattern of activity in a chain loop of 48 sub-networks. Activity in the loop is evoked by applying external current to all neurons in one sub-network indicated by the arrow in square at times 0.2 s and 1.1 s. Two evoked bursts propagate along the loop. Additional stimulation of at 2.5 s does not produced new activity. Application of two stimuli simultaneously to two different sub-networks at 3.9 s terminates both propagating bursts in loop. The gray scale indicates intensity of bursting in local sub-network, black is lack of bursts.

process and may result in cessation of that activity. In short loops consisting of 16 or less sub-networks, external current delivered to neurons in a sub-network shortly (150–200 ms) after occurrence of repetitive activity in that sub-network results in immediate cessation of repetitive activity in the loop. External current delivered to a single sub-network in longer loops (20–64 sub-networks) may result in increasing frequency of recurrent activity in the loop (Fig. 2). However, in such long loops the same external current delivered simultaneously to a few different sub-networks also results in cessation of recurrent activity in that loop (Fig. 2).

#### 4. Discussion

Neural network models provide major advantages in studying the various factors that influence the ability of external stimuli to terminate bursting behavior. In this study, we implement a particular model of stimulation, an external current applied simultaneously to all neurons in a particular network. This may not reflect the type of electric field modulation employed in the mentioned experimental studies. How-

ever, it may better relate to stimulation by implanted electrodes in specific brain structures. A mechanism by which recurrent synchronized activity stops in a chain loop of model can be explained based on intrinsic membrane properties of neurons and interactions of pools of locally connected neurons. The spike frequency adaptation in neurons (AHP process) plays an important role in the termination of this activity. When neurons in one sub-network are forced to fire bursts of action potentials by background noise activity or external current, the recurrent activity begins to propagate through the chain loop of networks by exciting neighboring sub-networks. The velocity of propagation of the activity in a chain loop is determined primarily by the number of connections between sub-networks (the connection density parameter) and by values of the synaptic weight and delay parameters. In our model, the activity propagates in a chain loop with a constant velocity and various sub-networks in the chain loop are activated at different times. The burst duration in a single neuron is determined by the AHP process. In each neuron the bursting activity period is followed by the AHP process e.g. a period of decreased excitability. Neurons in each sub-network fire bursts almost simultaneously and this results in the temporary inability of these neurons to continue firing and the cessation of bursts in a sub-network. The AHP process in neurons is slow in comparison to the process of spreading of recurrent activity in the loop through synaptic connections between (and within) subsequent sub-networks. If the loop is short enough, the external current delivered to sub-networks, even in situations when all neurons are recovered from the AHP process, does not initiate new activity in this loop because neurons in consecutive sub-networks have not yet recovered from the AHP and remain inactive. The existing moving activity continues its propagation in the loop until it meets the sub-network activated by external currents where neurons are not capable of maintaining it. In this model of a chain loop of sub-networks, the timing of the stimulus that will terminate bursting is determined for the given loop length. Once determined, the window of stimulation after an individual burst is very critical. Stimuli that are applied outside of a very narrow (50 ms duration) window fail to terminate bursting permanently. This is due to the underlying mechanisms of cessation of bursting in this model. The stimulation in one selected sub-network has to occur at the time before the arrival of circulating activity and when subsequent sub-networks are still in a relative refractory period, preventing them from fully responding to excitation from this particular sub-network. On the other hand, the refractory period in this selected sub-network induced by the stimulus must overlap with the time of arrival of the circulating activity from the previous bursts in the previous sub-networks. The exact timing is dependent on the chain loop length, frequency of oscillation in the loop and the length of the relative refractory period in the network, which in turn is dependent on both the intrinsic properties of the neurons ( $I_{K(Ca)}$  current) and network connections. In these simulations termination by an external stimulus was possible in loops consisting of 14–25 sub-networks and for frequencies of oscillations 2–5 Hz. For chain loops longer than 45 sub-networks multiple modes of oscillations exists. Termination by external stimuli is possible but requires application of two stimuli in two different sub-networks simultaneously.

## Appendix A. The neuron model equations

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

$$\frac{dW}{dt} = \frac{W_\infty(V) - W}{\tau_w(V)} \quad (A.2)$$

$$\frac{dX}{dt} = \frac{X_\infty(V) - X}{\tau_x} \quad (A.3)$$

$$\frac{dB}{dt} = \frac{B_\infty(V) - B}{\tau_b} \quad (A.4)$$

$$\frac{dC}{dt} = K_p(-I_{Ca}) - RC \quad (A.5)$$

where

$$I_{Na} = \bar{g}_{Na} m_\infty^3(V)(1 - W)(V - V_{Na}) \quad (A.6)$$

$$I_{Ca} = \bar{g}_{Ca} X^2 \frac{K_c}{K_c + C}(V - V_{Ca}) \quad (A.7)$$

$$I_K = \bar{g}_K W^4(V - V_K) \quad (A.8)$$

$$I_{K(Ca)} = \bar{g}_{K(Ca)} \frac{C}{K_d + C}(V - V_K) \quad (A.9)$$

$$I_A = \bar{g}_A A_\infty(V)B(V - V_K) \quad (A.10)$$

$$I_L = \bar{g}_L(V - V_L) \quad (A.11)$$

$$\tau_w(V) = \frac{1}{\lambda} \left( e^{a^{(w)}(V - V_{1/2}^{(w)})} + e^{-a^{(w)}(V - V_{1/2}^{(w)})} \right)^{-1} \quad (A.12)$$

$$P_\infty(V) = \left( 1 + e^{-2a^{(P)}(V - V_{1/2}^{(P)})} \right)^{-1}, \text{ for } P = W, m, X, A, B \quad (A.13)$$

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 (13), 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  $R = 0.006$  is the removal rate constant of the intracellular calcium concentration.  $C_m = 1 \mu\text{F}/\text{cm}^2$  is the membrane capacitance.  $\tau_w$  is the relaxation time function, and  $\tau_x = 25$  ms and  $\tau_b = 10$  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  $\bar{g}_i$ , the activation and inactivation variable or function, and the driving force  $(V - V_i)$ , where:  $\bar{g}_{Na} = 120$  mS/cm<sup>2</sup>,  $\bar{g}_{Ca} = 1.0$  mS/cm<sup>2</sup>,  $\bar{g}_K = 15$  mS/cm<sup>2</sup>,  $\bar{g}_A = 12.5$  mS/cm<sup>2</sup>,  $\bar{g}_L = 0.3$  mS/cm<sup>2</sup>,  $\bar{g}_{K(Ca)}$  in the range 0.5 - 3.5 mS/cm<sup>2</sup> 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.

## Appendix B. Synaptic model equations

$$I_{syn} = \sum_{j=1}^{N_{syn}} w_j g_j(t) (V - E_{syn}) \quad (\text{B.1})$$

$$g(t) = \bar{g}_{syn} \sum_{i=1}^N \left( e^{-\frac{\Delta t_i}{\tau_d}} - e^{-\frac{\Delta t_i}{\tau_o}} \right) \quad (\text{B.2})$$

where  $i$  denotes summation over past action potentials and  $j$  over the number of input synapses.  $\bar{g}_{syn} = 0.0112 \text{ mS/cm}^2$ ,  $E_{syn} = -10 \text{ mV}$ ,  $\tau_d = 3 \text{ ms}$ ,  $\tau_o = 0.5 \text{ ms}$ ,  $w_j$  in range 30–60,  $\Delta t_i$  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  $N_{syn} = 2$ .

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