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SIMULATION OF HIPPOCAMPAL NEURAL NETWORKS UNDER BICUCULLINE, WITH NOISE AND SYNAPTIC DELAYS

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ABSTRACT
A synchronous activity of neural networks is observed after introduction of bicuculline, an antagonist of inhibitory connections, into the nutritive solution of in vitro preparations containing neural networks of hippocampal neurons. The signals measured by microelectrode arrays show trains of bursts of activity. This study aims to reproduce this behavior in a mathematical model. The approach is twofold: firstly, we develop a simple biophysical model coupled with a measurement model to validate the sensing of the real net, and secondly, we use both models to understand the mechanism of the real net. Since the network is not connected to other areas, we use synaptic noise on an excitatory neural network to reproduce the bursting activity. Furthermore, delays are introduced that allow the emergence of different patterns of bursting.

KEY WORDS
Microelectrode arrays, neuron-electrode coupling, stochastic resonance, Izhikevich model, hippocampus, delayed neural networks.

1 Introduction

When studying the activity of neurons using microelectrode arrays (MEA), it is important to understand the measurement process to obtain a correct explanation of the measured signals [1, 2]. We are currently developing an experiment to monitor ordered living neural networks using MEA [3]. To evaluate our experimental setup and understand all the steps of the measurement process, we are also developing a mathematical modeling approach that allows us to describe the neural networks, the electrical coupling between the network and the electrodes as well as the electronic devices in terms of adequate physical and biophysical models.

In this study, we measure the neural activity of an organotypic slice of rat hippocampus (Synapcell, Grenoble, France) in the CA3 region. Bicuculline is added to the preparation to block the inhibitory connections. The measured signals then display a periodic bursting activity (see Figure 2(a) and 2(d)). To reproduce this behavior, we create a neural network governed by an Izhikevitch model [4, 5], in which all the connections are excitatory. In this model, random inputs representing the influence of other areas are usually taken into account to generate an activity. However, with in vitro preparations, this model is inappropriate since there are no inputs from other areas. To induce a spontaneous activity as observed in vitro, we introduce a random activity on the synapses [6]. Furthermore, we add delays to take into account of the durations of propagation as well as transmission. The measurement process is simulated via a linear model, as proposed by Martinoia [7]. Some of the results have been initiated in previous studies in [8, 9].

Before reproducing the real behavior, we study the influence of different parameters (noise, delays, transmission duration) on the behavior of the model. This study allows us to reproduce partially the measurements made in the CA3 region under bicuculline. The paper is structured as follows. Firstly we describe the biophysical model of the neural network along with an analysis of the effect of noise on a single neuron and on two coupled neurons. Then, we present the physical model that takes into account the coupling between the neurons and the electrodes. Finally, we examine the effects of delays and transmission durations.

2 Presentation of the neural network

2.1 Description of the model

For numerical simulations, $n_{neurons}$ neurons are computed using an Izhikevich model [4, 5]. In this model, each neuron is characterized by its membrane potential v, and a variable u which is necessary in the spiking mechanism of the neuron. The neuron is modeled as a quadratic integrate-and-fire neuron, while a threshold rule is used to simplify the fast reset dynamics. Each neuron i is thus governed by:

$$\frac{dv_i(t)}{dt} = 0.04 \cdot v_i^2(t) + e \cdot v_i(t) + f - u_i(t) + I_i(t) \quad (1)$$

$$\frac{du_i(t)}{dt} = a \cdot (b \cdot v_i(t) - u_i(t)) \quad (2)$$

$$\text{if } v_i(t) \geq v_{thresh}, \quad \text{then} \begin{cases} v_i(t) \leftarrow c \\ u_i(t) \leftarrow u_i(t) + d \end{cases} \quad (3)$$

The initial parameter values of the neurons in the CA3 region of the hippocampus acting as integrator neurons are taken from [10] and set to $a = 0.02$, $b = -0.1$, $c = -55$, $d = 6$, $e = 4.1$, $f = 108$, $v_{thresh} = 30$. For numerical integration and stability, we use two successive Euler approximations by dividing the time step by two and blocking $v_i(t)$ to v_{thresh} when spikes occur. An input current is considered at each neuron soma using

$I_i(t) = I_{i,syn}(t) + I_{i,noise}(t)$. $I_{i,syn}(t)$ is the synaptic current source given in our model by $I_{i,syn}(t) = g \cdot S_{i.} \cdot \sigma(t)$. $S_{i.}$ is the ith row of the connectivity matrix S representing all the afference of neuron i, where element $S_{i,j}$ is 1 if neurons i and j are connected and zero otherwise. Note that we set $S_{i,i} = 0$ to avoid self connection (autapse). $\sigma(t)$ is a vector of $\{0,1\}^{n_{neurons}}$ indicating firing neurons. g is the synaptic conductance, which is assumed to be the same for all neurons. $I_{i,noise}(t)$ is an additive noise corresponding to fluctuations on the synaptic ionic channels: $I_{i,noise}(t) = g_{noise} \cdot U_{i.}(t) \cdot \bar{\sigma}(t)$. This noise models the fluctuations of the ionic channels and synaptic bombardments from neurons outside the network. A random uniform noise $U_{ij}(t)$ between 0 and 1 is introduced on each connection to simulate stochastic behavior of synapses. g_{noise} controls the level of noise. $\bar{\sigma}(t)$ is the logical not of σ indicating that noise is active only when no spikes occur.

2.2 Influence of g and g_{noise}

Simulations with a duration of $10\,s$ and a sampling rate of $10\,kHz$ are carried out to study the influence of the model parameters. An external current step I_{ext} is incorporated into the model to stimulate the neuron in the interval $[0.5\,s, 9.5\,s]$. An estimation of the firing rate f_i for neuron i is obtained by counting the number of spikes and then dividing this number by the duration of the current step ($9\,s$). By varying I_{ext}, we can study the deterministic behavior of one neuron. The resulting f-I curve [11] is plotted in Figure 1(a), where we see that the rheobase (minimum I_{ext} for spiking) is given by 2.25.

We use a neural network of two neurons with a single connection from neuron one to neuron two to study the deterministic coupling between two neurons. $I_{ext} = 10$ is applied to neuron one to obtain a firing rate $f_1 = 28.33\,Hz$. The effect of variations of g on the f_2/f_1 ratio is shown in Figure 1(b). Below the threshold $g = 165$, the coupling is too weak, and the neurons act as if they were uncoupled. Above $g = 165$, the coupling is effective, as shown by the variation of f_2/f_1 which follows a Devil's staircase function, a well known effect in the coupling of nonlinear dynamical systems [12].

The stochastic behavior of one neuron can be studied by varying the amount of noise with g_{noise}. Results are illustrated in Figure 1(c) and 1(d). For $g_{noise} > 4.4$, the rheobase vanishes and the neurons are spontaneously spiking. This behavior is similar to the noisy f-I curves described in [11] for the Hodgkin and Huxley model. The effect of noise on the transmission between two neurons is obtained with a neural network of two neurons with only one connection between them. As described previously, a current step of $I_{ext} = 10$ is introduced on neuron one to generate a spiking rate of $28.33\,Hz$. g and g_{noise} are assumed to be equal and are varied to generate the f_2/f_1 ratio given in Figure 1(c). The noise destroys the Devil's staircase. The value of g necessary to initiate a coupling between the neurons is lower than previously observed under the same conditions but without noise (4.4 against 145). For the present model, this means that noise facilitates the transmission between neurons by reducing the value of g required to induce spikes on efferent neurons.

3 Signal with neuron-electrode coupling

3.1 Description of the model

A linear filter made up of resistances and capacitances is used to generate signals such as those recorded by a MEA using Martinoia's model [7]. The filtering can be written:

$$x_i(t) = h(t) * v_i(t) \tag{4}$$

where x_i is the measurement of neuron i according to an electrode. As an electrode j on a MEA senses the extracellular behavior of several neurons, we use a mixture of $n_{rec,j}$ signals with random weights. Thus, the potential measured by electrode j can be written as:

$$V_{rec,j}(t) = \sum_{i=1}^{n_{rec,j}} w_i x_i(t) + V_{rec,noise}(t) \tag{5}$$

where w_i is a random weight simulating the attenuation due to distance. The w_i values are independent and uniformly distributed over $[0,1]$. $V_{rec,noise}$ represents additional noise due to current fluctuations on the electrode. It is obtained by convolution of the transfer function of the electrode h_{elec} and a Gaussian white noise $I_{elec,noise}$ (whose power is tuned to match the recorded noise power):

$$V_{rec,noise}(t) = h_{elec}(t) * I_{elec,noise}(t) \tag{6}$$

The simulations of the recorded signals on the electrodes can now be compared to the experimental recordings.

3.2 Experimental settings and simulation results

A rat hippocampus slice is placed onto a MEA. We then add bicuculline to the solution, and after 10 minutes, record the activity of neurons in the CA3 region. A typical measurement is illustrated in Figure 2(a). In this signal, we observe periodic bursts of activity. In the example given here, there are 11 bursts in $5\,s$ leading to a bursting rate of $f_{burst} = 2.2\,Hz$.

Random networks with $n_{neurons} = 500$ are simulated to match the in vitro conditions. In the simulation, we assume that each neuron has $10\,\%$ of excitatory connections (the connectivity matrix S contains $10\,\%$ of 1, each neuron being connected to approximately 50 neurons) according to [10]. We generate simulations lasting $5\,s$ at a sampling rate of $10\,kHz$ to study the influence of g and g_{noise}. When noise is introduced into the model, we observe a spontaneous bursting activity, as shown in Figure 2(b). Table 1 reports the time-evolution of the bursting

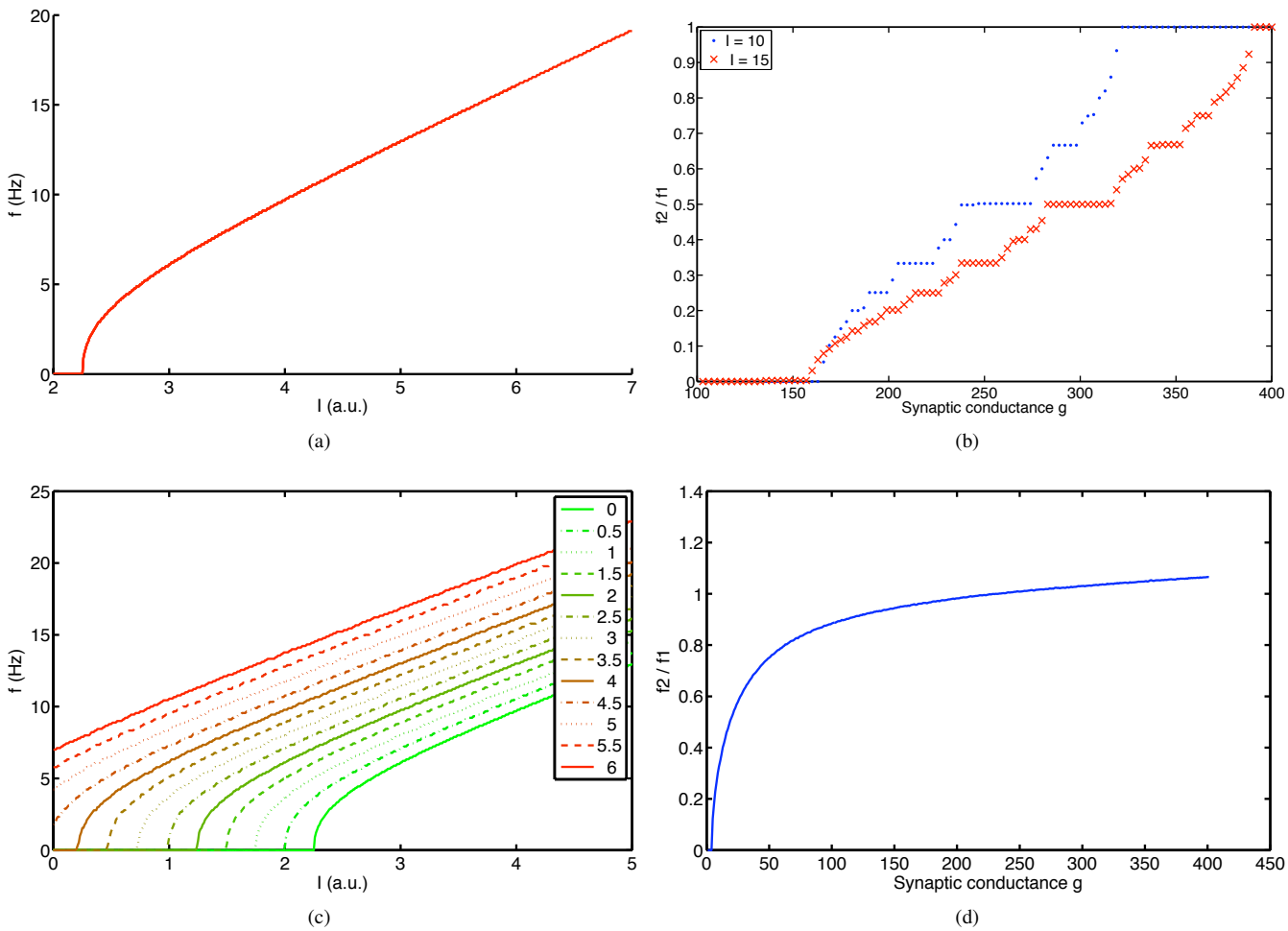


Figure 1. Estimations of: a) firing rate f as function of the input current I_{ext} (f-I curve); b) f_2/f_1 ratio between two neurons as function of the synaptic coefficient g with $I_{ext} = 10$; c) f-I curve for different value of g_{noise} given in legend; d) influence of varying $g = g_{noise}$ on the f_2/f_1 coupling. The introduction of noise enhances transmission between neurons.

effect (measured by the frequency of bursting) for different values of g and g_{noise}. When g is constant, an increase of g_{noise} increases the frequency of synchronous bursts (f_{burst}). As shown previously, synchronous bursting is initiated above a threshold value of g_{noise} ($g_{noise,0} = 4.4$, see also Figure 1(d)). As described in section 2.2, neurons exhibit a spontaneous spike rate when $g_{noise} \geq 4.4$, we observe a synchronization of the activity of neurons due to excitatory connections. When noise is increased, the bursting frequency is increased. On the contrary, when the value of g is increased, the bursting frequency is reduced. This can be explained by the fact that more current is supplied to each neuron, pushing the state variables u and v more rapidly to a recovery state at which no spikes occur. When g is too strong, the neurons saturate.

Table 1. Bursting frequency f_{burst}

$f_{burst}\,(Hz)$	g	1	5	10	50
g_{noise}					
1		0	0	0	0
5		3.6	3	2	sat.
10		8.8	5.4	3	sat.
50		31	10	5.4	sat.

$n_{neurons} = 500$, $t_1 = 0\,ms$, $\Delta_t = 0.1\,ms$.
sat. is an abbreviation for the saturation of neurons.

4 Influence of delays

In the model, we consider two different delays to take into account the time taken for the presynaptic potential of an afferent neuron to initiate a postsynaptic potential on the efferent neuron. The first delay is used to model the propagation of spikes in the axon of the afferent neuron as well as the neurotransmitter release ($0.1\,ms$ to $44\,ms$ [13] or 2–3 ms [7]). The second delay models the duration of the synaptic transmission ($0.5\,ms$ to $4\,ms$ in [11]). For the sake of simplicity, these two delays are taken into account in the conductance profile via the function $G(t) =$

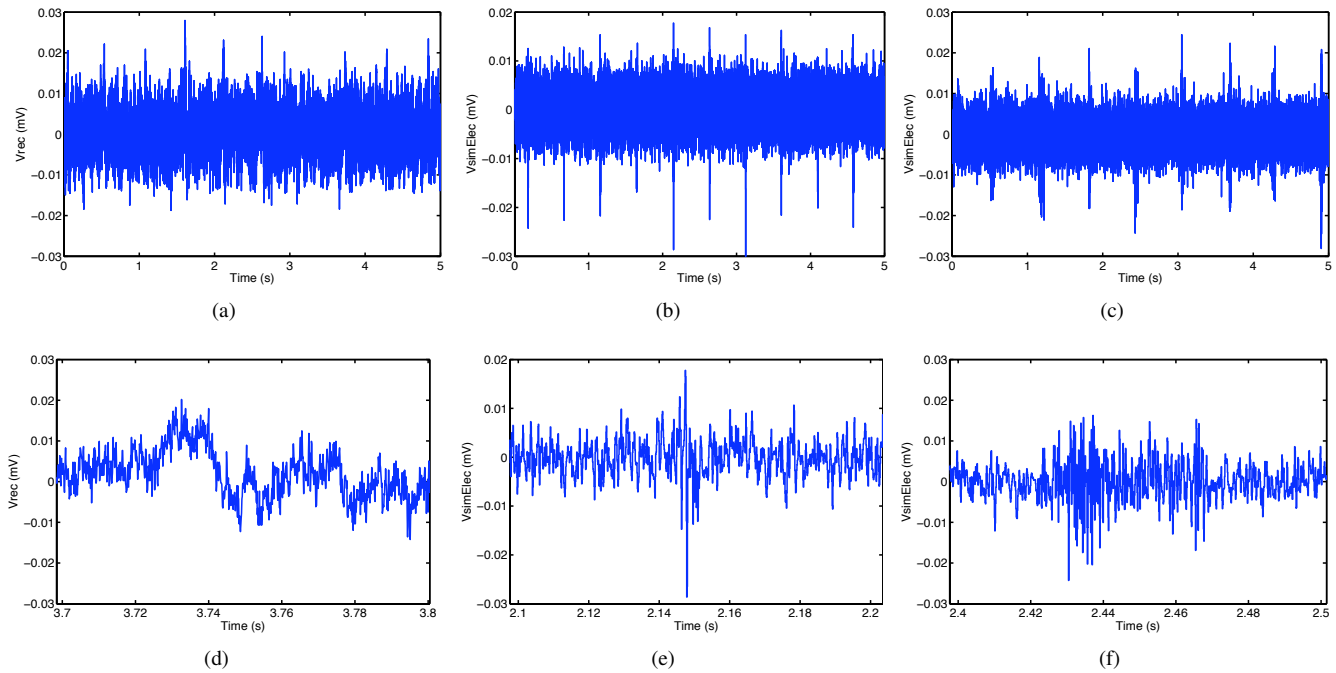


Figure 2. a) Recording of a hippocampus slice under bicuculline. Periodic bursts of activity are observed. b) Simulation with $g = 1$, $g_{noise} = 4.5$. c) Simulation with $g = 1$, $g_{noise} = 4.5$, transmission of synaptic current lasting $3\,ms$ with a $0.5\,ms$ delay. d) Detailed view of a). e) Detailed view of b). f) Detailed view of c), with burst duration of the order of d).

$g\Pi_{\Delta t}(t - t_1)$ where $\Pi_{\Delta t}(t) = \begin{cases} 1 & \text{if } t \in [0, \Delta t] \\ 0 & \text{otherwise} \end{cases}$.

The influence of t_1 is given in Table 2 with $\Delta t = 0.1\,ms$, $g = 1$, $g_{noise} = 4.5$. While there is only a small effect on the observed patterns, we note an increase in the duration of the burst Dt_{burst}.

Table 2. Influence of t_1

t_1 (ms)	Mode	Frequency f_{burst} (Hz)	Duration of burst Dt_{burst} (ms)
0.1	sync.	2	10
0.5	sync.	2	20
1	sync.	2.2	25
5	sync.	2.2	40

$g = 1$, $g_{noise} = 4.5$, $\Delta t = 0.1\,ms$.
sync. stands for synchronized and refers to synchronization of neurons

The influence of Δt is given in Table 3 with $t_1 = 0.5\,ms$, $g = 1$, $g_{noise} = 4.5$. An increase in Δt dramatically increases the burst duration while producing a small decrease in the bursting frequency. This effect is presented in Figure 2(c) and 2(f). A chaotic behavior of bursting dynamics is observed with increasing duration of the synaptic delay. Figure 3(a) presents an example of such a signal obtained for $Dt = 8\,ms$. Further studies are required to explain this phenomenon in more detail.

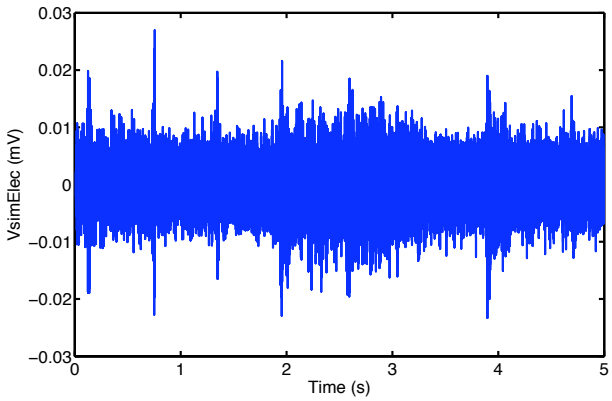
Table 3. Influence of Δt

Δt (ms)	Mode	Frequency f_{burst} (Hz)	Duration of burst Dt_{burst} (ms)
0.5	sync.	1.8	8
1	sync.	1.8	20
5	sync. + chaos.	1.6	30 to 200
10	sync. + chaos.	-	-

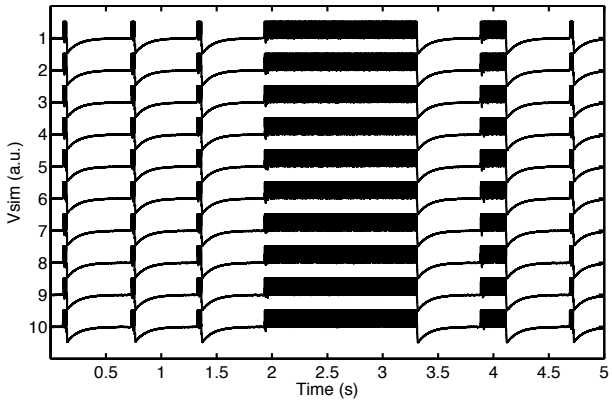
$t_1 = 0.5\,ms$, $g = 1$, $g_{noise} = 4.5$.
sync. stands for synchronized and refers to synchronization of neurons.
chaos. refers to chaotic behavior of the bursting duration and frequency.

5 Discussion and conclusion

In this study, we analyze the influence of different parameters on the generation of signals such as those observed with a microelectrode array. Bursting activity occurs in the simulated neural network, when driven by synaptic noise, thus mimicking the activity measured in a slice of rat hippocampus. We can simulate burst durations similar to those observed with experimental in vitro preparations adding a delay and a duration in the modeling of the synaptic transmission. The bursting pattern produced by the model is problematic, since we obtain signals with higher frequencies than those observed in vitro. We consider that the neuron-coupling model is not optimal so we will need to change the values in the model to match the experimental settings. Variations of parameters a, b and d could also lead to variations of pattern as described in [8] and thus require further investigation. We believe that the simple model presented here is of interest for studying the influence of noise on neural dynamics and computation.



(a)



(b)

Figure 3. a) Simulation with $g = 1$, $g_{noise} = 4.5$, transmission of synaptic current lasting $8\,ms$ with a $0.5\,ms$ delay, note presence of chaotic bursting. b) Intracellular potentials of 10 neurons of the network.

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