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Recording and simulation of hippocampal neural networks with bicuculline

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Abstract

In this study we compare the neural activity of a population of neurons recorded with a MEA to simulations of equivalent networks obtained on a computer when bicuculline, an antagonist of inhibitory connections, is introduced into the nutritive solution. The aim of this study is to obtain a model producing extra-cellular data that match the synchronicity of two different real networks: cell culture and hippocampus slice. One compartment model of neuron and neuron-electrode model are used to simulate experiments. Parameters of the models are fitted to match in vivo data. It is shown that the variation of the noise level at the synaptic level induce a variation in the period of the bursting effect of bicuculline and produce variation in amplitude of the recorded signal.

Background/Aims

In this study we compare the neural activity of a population of neurons recorded with a MEA to simulations of equivalent networks obtained on a computer when bicuculline, an antagonist of inhibitory connections, is introduced into the nutritive solution. It is known that this drug enhances the network activity and synchronization of the neural activity is observed. The aim of this study is to obtain a model producing extra-cellular data that match the synchronicity of two different real networks: cell culture and hippocampus slice. This is a step to validate these models and switch to the design of more complicated networks containing both inhibitory and excitatory connections.

Methods

For the organotypic hippocampus slice of E17 rat (H1: 18 days in vitro (DIV18), CA1 region; Origin: SynapCell, Grenoble France) laid on a MEA, a preparation of bicuculline $10^{-2}M$ is added to the nutritive solution. For the DIV26 mice culture of hippocampal neurons on MEA (C20), bicuculline $10^{-4}M$ is added. In both cases, the activity is observed after $10\,min$. Circular electrodes have a diameter of $35\,\mu m$ and are separated by a distance of $100\,\mu m$. Signals are enhanced by a x 100 amplification.

For numerical simulations, n_{neuron} integrator neurons are computed using an Izhikevich model [Izhikevich, 2003, Izhikevich, 2004]. The evolution of the intracellular membrane potential v and of a recovery variable u for each neuron i is described by a generalized integrate-and-fire model using a set of non linear differential equations and a spiking rule:

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

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

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

The initial parameter values of the neuron in the CA3 region of the hippocampus as integrator neurons are taken from [Hocking and Levy, 2006] 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 occurred.

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 source of current 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 indicating all the afference of neuron i, which 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 $\{0, 1\}$ indicating firing neurons. g is the synaptic conductance, the same for all neurons. Random networks with 70 % of connections (S contains 70 % of 1) are generated (21 connections for C20 simulation and 350 connections for H1 simulation). This value is taken for a ratio of 0.7 between excitatory and inhibitory neurons for a fully connected network. The use of this model for $i_{syn}(t)$ does not enable to take into account the biologic delays observed during synaptic transmission and the specific transfer function for dendrites.

$I_{i,noise}(t)$ is an additive noise corresponding to

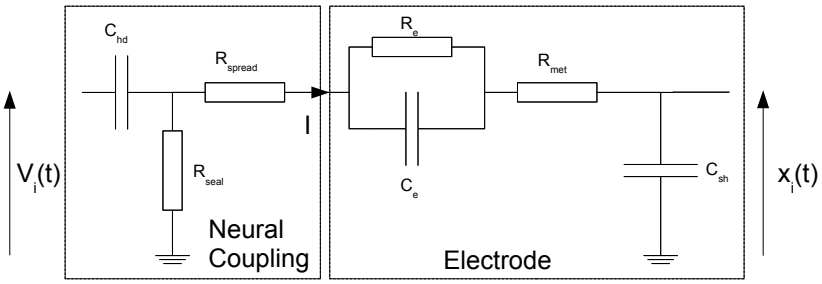

Figure 1: Martinoia's model of neuron-electrode coupling [Martinoia et al., 2004].

fluctuations on the synaptic ionic channels. A random uniform noise $U_{ij}(t)$ between 0 and 1 was introduced on each connection for stochastic behavior of synapses. $I_{i,noise}(t) = g_{noise} \cdot U_{i.}(t) \cdot \bar{\sigma}(t)$ with $\bar{\sigma}(t)$ logical not of σ. g_{noise} is the parameter that control the level of noise.

A filtering model using resistances and capacitances to design the neuron-electrode coupling is used to generate signals as those recorded by a MEA using the Martinoia's model [Martinoia et al., 2004]. The electric equivalent scheme is presented in Fig. 1.

The filtering introduces by such a model can be written:

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

The Laplace transform H of the transfer function h is given by:

$$H(p) = \frac{p_3(p+p_2)p}{(p_2p_3 + (p_2+p_3+p_4)p + p^2)(p+p_1)} \tag{5}$$

with $p_1 = 1/(R_{seal}C_{hd})$, $p_2 = 1/(R_eC_e)$, $p_3 = 1/(R_1C_{sh})$, $p_4 = 1/(R_1C_e)$ and $R_1 = R_{spread} + R_{met}$. R_{spread} is an ohmic drop between the cell and the electrode. R_{met} is the metallic resistance of the electrode. R_{seal} is the sealing resistance between the cell and the electrode and corresponds to the leak of current to the electrolyte bath. C_{hd} is a capacitive component due to a polarization layer between the cell and the electrode. C_{sh} is the shunt capacitance between metallic electrode and ground. R_e and C_e are respectively the resistive and capacitive components at the electrolyte-electrode interface using a basic electrode model [Robinson, 1968]. We used the values given in [Martinoia et al., 2004]: $R_{spread} = 11.7\,k\Omega$, $R_{met} = 1.5\,\Omega$, $R_{seal} = 5\,M\Omega$, $C_{hd} = 17.45\,pF$, $C_{sh} = 5\,pF$, $R_e = 140\,k\Omega$, $C_e = 1.14\,nF$.

As an electrode j on a MEA senses the extracellular behavior of several neurons, we use a mixture of signals with random weight simulating the attenuation due to distance to the electrode for each sensed neuron in a set of $n_{rec,j}$ neurons. This corresponds to the equation:

$$V_{rec,j}(t) = \sum_{i=1}^{n_{rec,j}} w_i x_i(t) + V_{rec,noise}(t) \tag{6}$$

with w_i a random uniform weight simulating the attenuation due to distance, x_i the extracellular measures of neuron i concerned by electrode j, $n_{rec,j}$ number of neurons concerned by electrode j and $V_{rec,j}$ the recorded potential on electrode j. $V_{rec,noise}$ is and additional noise due to current fluctuations on the electrode. It was obtained by convolution of the transfer function of the electrode h_{elec} with scheme given in Fig.1 and a gaussian white noise of current $I_{elec,noise}$ with a standard deviation of $500\,pA$ for H1 and $50\,pA$ for C20, manually set to match recorded noise level:

$$V_{rec,noise}(t) = h_{elec}(t) * I_{elec,noise}(t) \tag{7}$$

$$H_{elec}(p) = \frac{R_e}{1 + p/p_2} \tag{8}$$

The simulation frequency was set to $10\,kHz$ as the sampling frequency of recorded signals in both conditions.

Results

The parameters driving the neurons firing rate and the collective behavior of the network are fitted to match biological observations considering only excitatory connections due to the blockade of inhibitory connections by bicuculline. Examples of recorded signals are given in Fig. 2(a) and 3(b). We tuned the parameters to obtain a simulated networks of $n_{neuron} = 500$ neurons for H1 and $n_{neuron} = 30$ neurons for C20. These values corresponds to the number of neurons observed in the structure and neurons recorded near an electrode in the different culture and corresponds to densities of our experiments of approximately $5 \cdot 10^4\,cells \cdot mm^{-2}$ for H1 and $3 \cdot 10^3\,cells \cdot mm^{-2}$ for C20 (in the order of those reported in [Wang and Buzsáki, 1996, Wheeler and Novak, 1986] for example). These values are also taken according to the constructive

Table 1: Parameters values

a	b	d	n_{neuron}	g	g_{noise}	n_{rec}
0.005	-0.1	5	30	20	25	10
0.004	-0.02	1	500	1	1	100

signals recorded on electrode when synchrony is present that leads to peak to peak amplitude of about $0.150\,mV$ for H1 and $0.015\,mV$ for C30. This ratio, of about 10 between the two conditions, is in accordance with the cultures densities ratio and the number of recorded neurons (the same ratio is observed for noise current). Parameters values for neurons are given in Tab. 1.

Results of simulated signals are presented in Fig. 2(c) and 3(d). In our experiments, the period of bursting can be driven by different parameters including noisy inputs weights. The effect on the different parameters are as following: a is the time scale of the recovery variable, the slower value, the slower recovery (a low induces a low bursting rate, a high, high bursting rate); b is the sensitivity of the recovery variable u, the slower value, the slower is the sensitivity to the fluctuation of v (b high induces high bursting rate, b low, low bursting rate); d is the after spike reset of u, it controls, in part, the interspike rate of the model (d high induces low interspike rate, d low, high interspike rate). The synaptic noise introduces phase shifts between neurons that modify synchronism and amplitude in the recorded signal. Differences in patterns generated by synchronized bursts of firing neurons from in vitro measurements are possibly due to our model that does not take into consideration synaptic delays. We observed a modulation of the frequency due to the addition of noise, that can be explained by the fluctuations around the resting state: increasing nose can initiate more easily new spikes. Synchronization is driven by g and the level of noise g_{noise}, that potentially trigger spikes. A better study of the parameters initiated in this phenomenon must be done to be quantified and identified with experimental data and tested with other experimental conditions as those described in [Canepari et al., 1997] for example.

Conclusion/Summary

Results indicate that the presence of noise on synaptic inputs, in addition to the blockade of inhibitory connections, is required to produce synchronous bursts with a given period. The tuning of the noise level gives then a good concordance with real signals.

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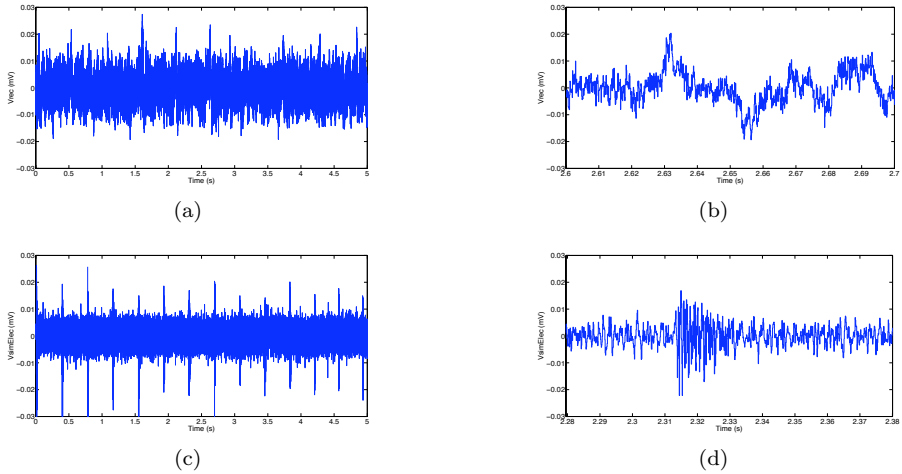

Figure 2: Comparison of 5 s of signal for a) recorded neurons on a slice of hippocampus H1, c) simulated recording of 100 neurons (out of 500) using an Izhikevich model with no synaptic delays. Zooms of a burst of synchronized neurons is given for (b) recorded neurons and d) simulated neurons

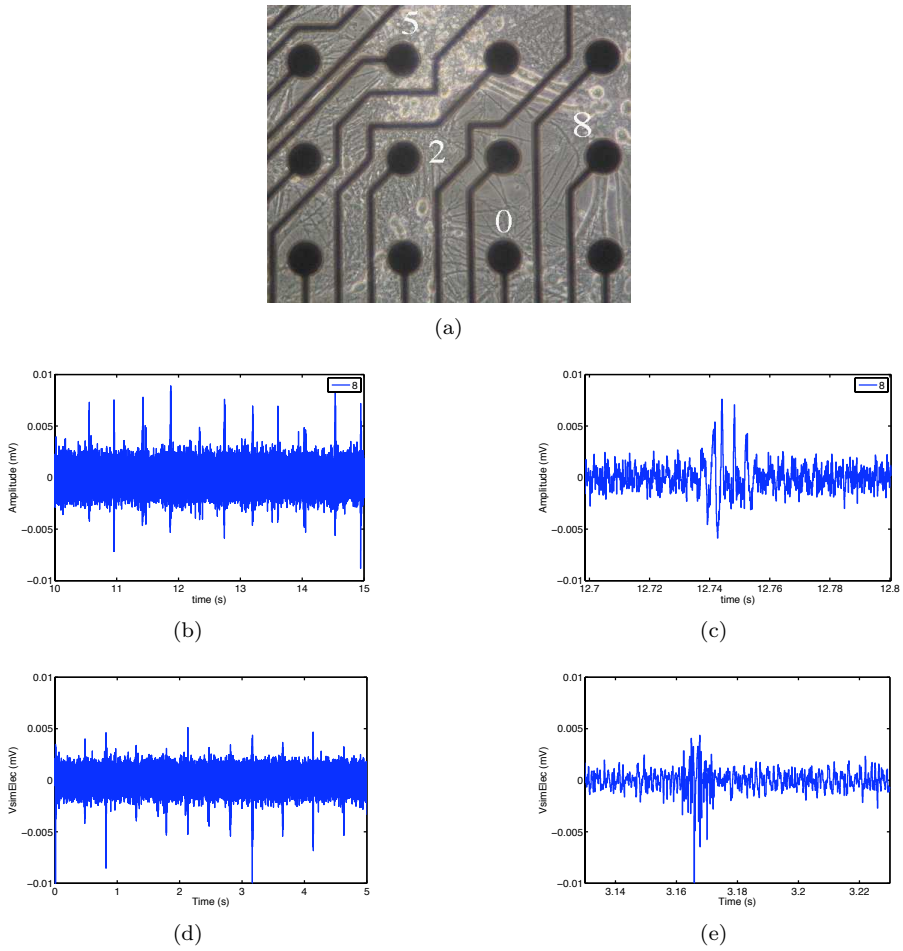

Figure 3: Comparison of 5 s of signal for a) recorded neurons from hippocampus grown in vitro C20, c) simulated recording of 10 neurons (out of a network of 30 neurons) using an Izhikevich model with no synaptic delays. Zooms of a burst of synchronized neurons is given for (b) recorded neurons and d) simulated neurons