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Synchronization in neuronal cultures

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Abstract. We have developed a model able to describe the experimentally observed activity behavior of 2D neuronal cultures as the coupling between neurons varies. As $[Ca^{2+}]$ in the medium increases, a gradual transition occurs from an asynchronous state in which neurons behave as independent oscillators, to a synchronous state where bursts of collective activity appear.

1 Introduction

Synchronization bifurcation in living neuronal networks arises from the collective dynamics [1, 2] of individual nonlinear oscillators and underlies a fundamental macroscopic hallmark of neural activity. Despite the stochastic nature of neurotransmitter release in synapses, noise at the single neuron level and variability in the network connectivity, coherent activity patterns spontaneously emerge through coupling and lead to dynamical regimes that cannot be reduced to microscopic behavior. The three-dimensional structure of the brain gives rise to a highly complex information propagation, meaning that neurons or neurons assemblies can rarely be studied in isolation, as they are generally subjected to a very large number of stimuli originating from a wide range of distances. Although investigation of cerebral activity in vivo by means of electroencephalography (EEG), magnetoencephalography and functional Nuclear Magnetic Resonance (fNMR) has significantly enhanced our understanding of brain function mechanisms, in vitro reconstruction of neuronal networks has turned out to be a crucial tool in investigating fundamental questions about biological computation, mechanisms of information spread and neurodegenerative disorders [3]. Experimentally, such a reconstruction can be carried out by seeding dissociated neurons extracted from hippocampal cells of rat or mouse embryos on a suitable substrate; axons and dendrites grow in such a way that neurons self-organize after a few days into a quasi two-dimensional network [4]. The change in scale required by in vitro studies is irreplaceable, firstly because it allows to control the experimental physico-chemical environment (for instance by the addition of drugs or salts), secondly because it enables to record by means of fluorescent calcium imaging [5], [6] or multi-electrode array devices [4] data unreachable in vivo. We focus on the theoretical interpretation of experiments devoted to the study of the spontaneous activity of in vitro populations of neurons. The main observation of these experiments is the occurrence of bursts of global activity as the calcium concentration $[Ca^{2+}]$ gradually increases [7, 8]. Such a result can be interpreted as a collective continuous synchronisation phenomena in the framework of dynamical systems, or as a percolation transition [1, 9]. We aim at modeling such a transition from a synchronous to an asynchronous state that occurs in these 2D

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neuronal cultures when the calcium concentration is increased.

2 Modeling methods

This modelisation work is conducted in collaboration with the Weizmann Institute, where the experiments were performed in the team of Elisha Moses. We aim at building a model that would be as close as possible to experimental results. In vitro cultures were obtained by seeding primary neuronal cells extracted from mice embryos on a 2D plate where they form a networks after some days. The electrical activity of the network was recorded by patching cells with Multi-Electrode Arrays (MEA). The MEA recorded on a single neuron appear as a series of spikes and burst spikes associated with neuronal activity. The information we need is encoded in a spike raster; hence we disregard the spike profile. So, a single neuron activity is considered from a binary point of view: a neuron is either active ot inactive.
Let us firstly begin by recalling some basic features of neuronal morphology. Communication between neurons involves not only propagation of action potentials in a single direction along dentrites and axons, but also physico-chemical processes associated with the release of neurotransmitters through the synaptic cleft [4]; the latter process is driven by calcium concentration and involves exocytosis. The neuronal population we deal with is heterogeneous, which means that zero calcium neuron oscillation periods span over one decade of seconds. It should be noticed that short frequency neuron are more numerous that long period ones as can be seen from the histogram in figure 2.

2.1 Dynamical model

The main experimental result on which we focus is the following: by increasing calcium concentration in the medium, a transition gradually appears form an asynchronous behavior where neurons behave as independant self-sustaining oscillators to a synchronous state where bursts of a collective behavior occur.
Let us now describe the modeling of a single neuron. We implemented the adaptive integrate and fire model suggested by R. Brette and W. Gerstner [10]. A neuronal membrane is modeled by a capacitor whose behavior is driven by four terms:
a) A leaky term.
b) An exponential term associated with a spike emission as soon as the potential reaches a threshold value.
c) An adaptation current w.
d) A term accounting for ionic currents I_e and $I_s$that flow through the membrane.

A wide range of possible dynamics is enabled by the presence of two caracteristic time scales associated with such a dynamical system, one for the membrane ($\tau_m = C_m/g_L$), the other one τ_w for the adaptation current, where $\tau_w >> \tau_m$

$$\text{if} \qquad V \leq V_{peak} \begin{cases} C_m \frac{dV}{dt} = -g_L(V - E_L) + \\ g_L \Delta_T \exp\left(\frac{V-V_{th}}{\Delta_T}\right) - w + \\ I_e + I_s \\ \\ \tau_w \frac{dw}{dt} = a(V - E_L) - w \end{cases} \tag{1}$$

$$\text{else} \quad \text{if } V > V_{peak} \begin{cases} V \text{ is set to } V_r \\ w \text{ is incremented by } b \end{cases} \tag{2}$$

C_m is the membrane capacitance, E_L is the resting potential, g_L is the leak conductance, Δ_T is the slope of the spike upstroke, V_{th} is the spiking threshold, τ_w is the adaptation current time scale, and a is the adaptation conductance; I_e is the external input current and I_s accounts for the sum of the synaptic currents sent by the neighbors of the neuron; the neuron spikes when the membrane potential exceeds the spiking threshold value V_{th}. V quickly reaches its maximum value V_{peak}, and V is prevented from diverging by resetting it to a value V_r while the adaptation current is incremented by the spike triggered adaptation current b.

2.2 Bifurcation analysis and single neuron activity

We deal with intrinsically bursting neurons. A simulated evolution of the membrane potential together with the adaptation current as a function of time is shown in figure 1 and reported in figure 3.

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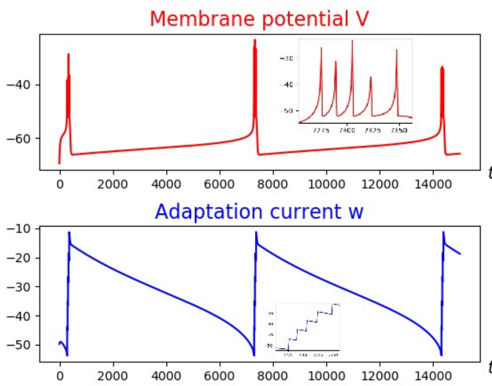

Figure 1. Behavior of the membrane potential V and the adaptation current w as a function of time for bursting neurons

The analysis of the dynamical (V, w) system is based on the nullclines, respectively defined by $\frac{dV}{dt} = 0$ and $\frac{dw}{dt} = 0$. These curves are plotted in figure 2 and 3.Such a system system undergoes a bifurcation, which occurs in the following way: if a is less than some critical value a_c, the slope a of the $V - w$ nullcline, there are two fixed points (one stable, the other one unstable) and oscillations are not possible. Hence a must be lower than a_C to ensure the absence of fixed points as shown on figure 3.

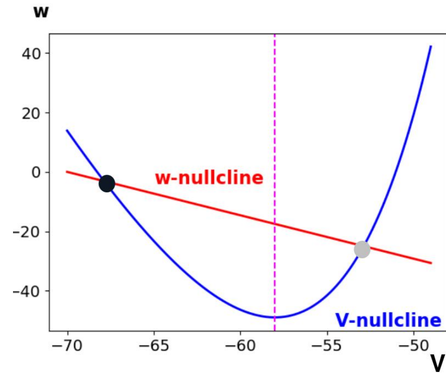

Figure 2. Nullclines of the dynamical system for the w-nullcline slope $a = -4.58 > a_c$ and neuronal intrinsic parameters listed in the ANNEX (the critical value is $a_c = -4, 96$). Two intersection points occur, preventing from an oscillatory regime

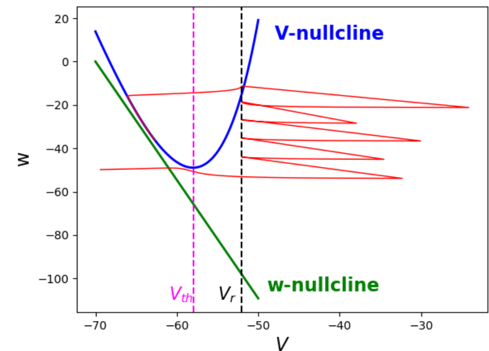

Figure 3. Phase space diagram of the dynamical system for $a = -5, 46 < a_c$ and the same neuronal intrinsic parameters as on figure 3; The critical value is $a_c = -4, 96$. Red lines show a bursting cycle with five spikes whose temporal evolution is depicted on figure 1

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2.3 Connection between neurons

The connection between two neurons A and B, with a spike arriving at time t is modeled by an alpha-shaped post-synaptic current.

$$I_s(t) = s_{AB}.I_0 \frac{t - \tau}{\tau_s} e^{(\tau - t)/\tau_S} \quad (3)$$

2.4 Parametrisation of a single neuron and a neuronal population activity

As can be seen from equations (1) and (2), the parametrization of a single isolated neuron requires 11 physical quantities; nine among them, deduced from experimenta data or from the literature, are listed in the annex (I_s is not a parameter). The remaining ones are determined by relying on the bursting times and the firing rates extracted from experimental data [2]. The parametrization of an uncoupled neurons population is obtained by a random trial according to the frequency distribution shown on figure 4 in an area delimited by $V_r \in [-52mV, -48mV]$ and τ_w lying in $[100ms, 1000ms]$.

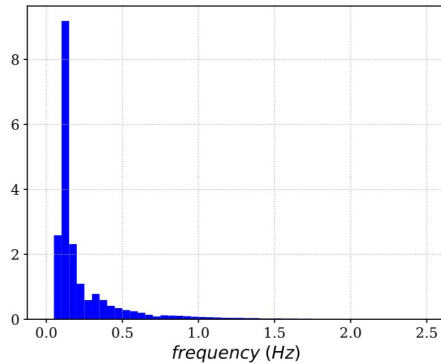


Figure 4. Frequency Histogram of the disconnected neurons

2.5 construction of the neuronal network

The network is constructed by randomly distributing points with a fixed density over a disk and then connecting them according to an Exponential Distance Rule with a probability caracterised by a lenght scale λ (see figure 5). The number of connections in the network is normalized according to to a given value $\bar{k}$ of the mean incoming links of neurons. For a given value of the mean connectivity $\bar{k}$, the width of the k distribution decreases when λ increases. Hence, connectivity randomness is more important in the short range regime.

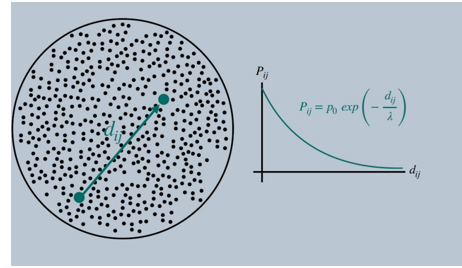


Figure 5. Construction of a network: distance-dependent probability of connection between two neurons (λ is the range scale).

3 Calcium dependent phase transition of synchronization dynamics

Increasing calcium concentration within the culture medium produces three main effects. The synaptic current, the synaptic noise and the coupling increase with $[Ca^{2+}]$, while the neuronal excitability decreases with $[Ca^{2+}]$. In the framework of a linear model, these effects are assumed to be proportional to $[Ca^{2+}]$. Therefore, the physical hypotheses considered here are as follows:

i) The normalized calcium factor c is defined as $c = [Ca^{2+}]/1mM$.

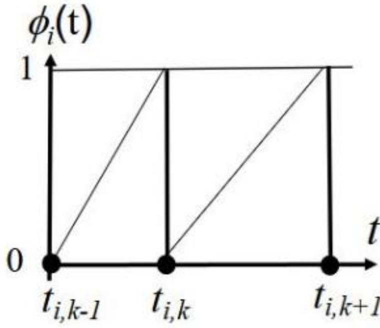
ii) The synaptic coupling is proportional to the calcium concentration : $s = cs_{max}$.

iii) The spike triggered adaptation is a linear fonction of the concentration : $b = b_{min} + c(b_{max} - b_{min})$.

iv) The synaptic noise is modeled by a poissonian noise of 15 Hz with a peak current $I_{noise}^{max} = (1 + c)$.

The phase of a single neuron is caracterised by a piecewise function defined on the basis of successive events at different times as shown on figure 6. The collective behavior of the network is defined as the total phase $\phi(t)$ of the neuronal population.

$$\phi(t) = \frac{1}{N} \sum_{i=1}^{i=N} \phi_i(t) \tag{4}$$



$$\phi_i(t) = \frac{t - t_{i,k}}{t_{i,k+1} - t_{i,k}}, t \in [t_{i,k}, t_{i,k+1}]$$

$$t \in [t_{i,k}, t_{i,k+1}]$$

Figure 6. Phase of a discrete series of individual events

Figure 7 and 8 show raster plots of two simulations results, the first one at $[Ca^{2+}] = 0$, where neurons are disconnected, the second one at $[Ca^{2+}] = 0.5$ where the synchonisation of the neuronal population can clearly be seen. The total phase of the neuronal population is shown by black lines.In the first case, the network phase behaves randomly, while the phase displays a periodic dynamical regime of the network in the synchronous regime. Moreover it clearly appears that the variance of the total network phase [11] is a convenient variable to describe the synchronisation process.

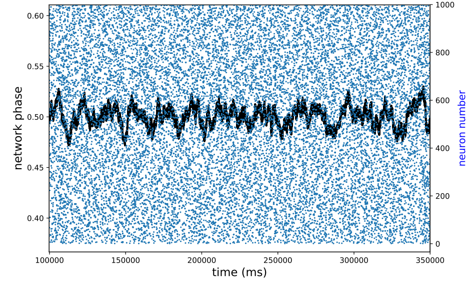


Figure 7. Raster plot of a thousand neurons population at zero calcium as a function of time; the total phase of the neuronal population is shown by black lines

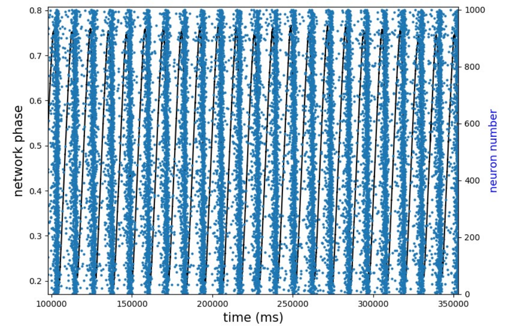


Figure 8. Raster plot of a thousand neurons population at $[Ca^{2+}] = 0.5mM$ as a function of time; the total phase of the neuronal population is shown by black lines. The mean number of incoming links per neuron is $\bar{k}$

4 Conclusion

We developed a model that incorporates a broad range of biologically relevant mechanisms and is able to qualitatively predict the behavior of neuronal cultures as a function of the concentration $[Ca^{2+}]$. Larger-scale simulations should make it possible to provide quantitative predictions and offer a robust tool for predicting neuronal network dynamics and guiding future experimental

investigations.

ANNEX

Numerical values of a single neuron parameters

$$\begin{cases} C_m = 100\ pF \\ E_L = -70\ mV \\ g_L = 10.2\ nS \\ \Delta_T = 7.2\ mV \\ V_{th} = -58.0\ mV \\ \tau_w \in [100.0\ ms, 1000\ ms] \\ a = -5.46\ nS \\ I_e = 0.0\ mA \\ V_{peak} = 20.0\ mV \\ V_r \in [-52.0\ mV, -48\ mV] \\ b = 10.0\ pA \end{cases} \tag{5}$$

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