

Network bursts in cortical neuronal cultures

‘Noise- versus pacemaker’- driven neural network simulations.

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Abstract— Dissociated neuronal cultures provide a useful platform to study behavior and development of biological neural networks. Isolated from external inputs neural cultures generate electrical activity of their own, showing several features. The most striking feature is the phenomenon of, more or less regular, network bursts, i.e. simultaneous firing of many neurons in a relatively short time window. In this paper we address the issue of spontaneous bursting activity in cortical neuronal cultures and explain what might cause this collective behavior using computer simulations of two different neural network models. While the common approach to activate a passive network is done by introducing synaptic noise, we show that a small subset of pacemaker neurons can trigger network bursts which better resemble experimental bursts.

Keywords-random recurrent neuronal network; network burst; synaptic connectivity

I. INTRODUCTION

Spontaneous activity in neuronal cultures usually appears as a synchronous firing of many neurons, recorded via micro-electrode arrays (MEAs). This so-called network burst (NB) represents collective behavior of the neural network (NN) and has become subject of many recent experimental [1, 2, 3, 4] and modeling studies [5, 6, 7]. These studies usually present the statistical analysis of the NN activity only. Modeling is aiming to understand the mechanisms underlying it. Mostly, researches introduce noise in order to evoke activity in NN's and explain short onset and relatively long offset of NB profiles using noise parameters, adaptive synapses [7] and neuronal intrinsic bursting features [6]. However, several studies suggest that intrinsically active neurons, referred to as pacemakers, drive network activity [8, 9].

We study NB profile features in computer simulated models using both ‘noise-driven’ and ‘pacemaker-driven’ approaches. Throughout the paper a comparison is made with experimentally recorded network activity of neuronal cultures.

II. METHODS

A. Experimental setup

We used cortical neurons obtained from either newborn or E18 Wistar rats. The cells were plated on 60 electrode MEAs using procedures described in [3]. In total 7 cultures were recorded for several weeks in vitro and analyzed statistically. Over these daily recordings three intra-burst parameters, namely maximum firing rate (mFr), half-width of the rising slope (Rs), half-width of the falling slope (Fs) (see fig. 1), were calculated as follows: mFr is taken at burst peak, Rs and Fs are the intervals (in ms) between burst peak and 50% of burst height, of rising and falling slopes respectively [2].

B. Simulation models

The model was based on recurrent NNs with random sparse connectivity maps. Two methods were used to ignite activity in the network models: noise injection and introduction of intrinsically driven ‘pacemaker - neurons’. In the noise model, in order to mimic synaptic or membrane noise [10], each neuron received a Poissonian spike train with 330 Hz mean firing rate. The second model uses the idea of the presence of endogenously active cells, which fire regularly on their own as described by Latham et al. [8] and ‘privileged’ neurons [9].

The models contained a neuronal and a network part. For the neuron part, we used the Izhikevich neuronal model [11] to reproduce the whole range of physiological variability of basic cortical neuronal spiking forms [12].

For the network part we performed simulations with the following ranges of the network parameters:

- Connectivity (K_{\max}) was set as the upper boundary of normally distributed number of connections per neuron and ranged from 100 to 1100 in steps of 100. (i.e. neurons had random number of connections, normally distributed between 0 and K_{\max} .)
- Transmission delays ranged between 1 and 20 ms with normal distributions.
- Excitatory fraction ratio (R) was set to 70%.

- Synaptic weights were normally distributed between 0 and 1mV.

The total number of neurons was 5000 and in the pacemaker-driven simulations around 16% percent of neurons were intrinsically active neurons. Similarly, mFr, Rs and Fs were calculated from simulated NBs.

III. RESULTS

Figure 1 shows the mean and standard deviation (SD) values of three NB parameters, namely mFr, Rs and Fs, acquired from neural cultures of different age. In general we observed an increase of the firing rate during the 2nd and 3rd week in vitro (fig. 1a), which correlates with increasing number of synapses observed by Ichikawa et al. in similar experiments [13]. Further mFr decline is assumed to be the result of cell death. Figure 1b shows the natural range of Rs being faster than Fs, except for values on DIVs 20 and 22.

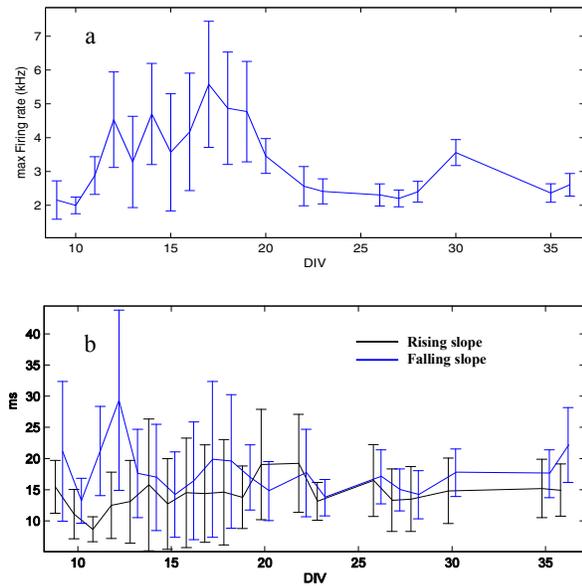


Figure 1: Experimental dynamics of three network burst features: maximum firing rate (a), rising and falling slope widths (b) of the NB profile. Mean and standard deviation values were obtained from burst profiles on each day of recording from 7 neuronal cultures.

In simulations with step-wise growing connectivity NBs appeared at $K_{max} = \{700, 500\}$ for noise and pacemaker driven NNs respectively, and then mFr increased with increasing connectivity (fig. 2a). Rising and falling slopes of network bursts are shown in fig. 2b. Comparison of the figures 1 to 2 indicates the right ranges of the network parameters in simulations compared to experimental NB profiles. However, in these simulations most of the Rs values were higher than those in the experimental data. We found that 'noise-driven' NN required an elevated and maintained network firing rate (not shown here). While developing into the main phase, this elevated onset increased Rs values, making it unnaturally longer than Fs. In figure 2b we see that Rs is slower than Fs, which contradicts experiment (see mean curves).

In the second simulation experiment, a small subset of 'pacemaker-neurons' was added, which were modeled as excitatory neurons with intrinsic activation features. We ran these models without any noise injection. We observed (in the simulations; results not shown) that pacemakers synchronized first to each other and then, together, they provided input to the network strong enough to generate NBs that show striking resemblance to NB profiles acquired from experimental recordings. These NN models produced NB profiles with several realistic features: short NB onset, symmetric and left-shifted main phases in most cases, and occasionally even rare features like a flanking phase on the slope of the main phase. Figure 3c shows that on average Fs is slightly bigger than Rs and both curves simulated for $K_{max} = 500$ (and higher) are in the range of the experimental data. Here, NBs become wider as the result of elevated firing rate.

In case of the noise drive, the neuronal network (NN) received Poissonian spike train with constant mean firing rate and rose total network-wide activity in an exponential manner. In case of the pacemaker drive, the NN receives input built by synchronized pacemakers, which is strong enough to recruit the rest of the network, and to do that also faster than in the previous case.

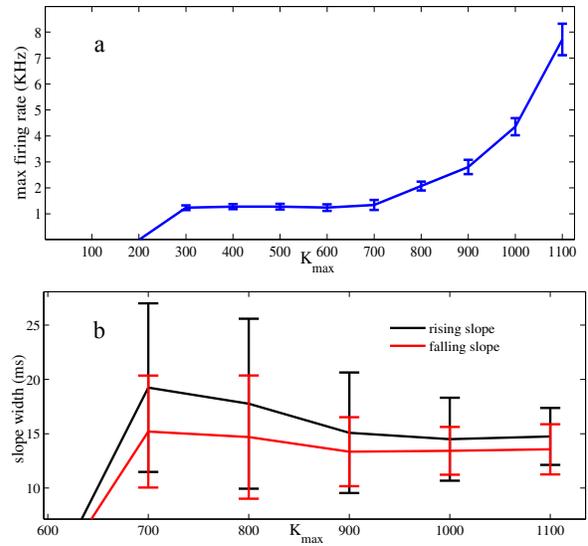


Figure 2: Sensitivity curves for the NB features to changing network connectivity in the 'noise - driven' NN simulations. Mean curves and standard deviation bars are plotted for the maximum firing rate (a) and rising and falling slope widths (b), in NN simulations with different K_{max} .

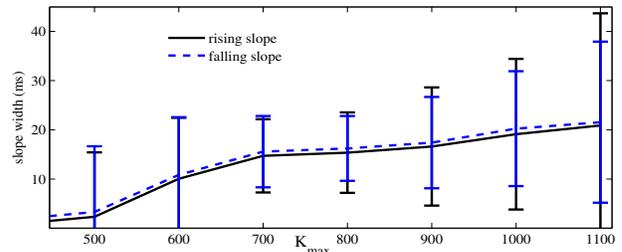


Figure 3: Sensitivity curves for the rising and falling slope widths in 'pacemaker - driven' NN simulations with increasing connectivity K_{max} .

IV. DISCUSSION

Spontaneous bursting behavior in cortical neuronal cultures has been a central issue in many recent experimental and modeling studies. In spite of the big repertoire of bursting patterns, there were several attempts to characterize NBs according to their profile features; see for example [2 - 4]. Features become clear after statistical analysis of the experimental recordings; they may be explained via NN modeling and statistical comparison with experimental data. In this work we mainly focused on the main phase of NB profiles, which represents the activation of most neurons in the network. Using simple statistical analysis of both experimental and simulated data we addressed issue of possible mechanisms of NB phenomena and sensitivity of its parameters to changing connectivity.

Our results suggest that bursting behavior requires high connectivity. Figure 2a indicates that NBs appear when connectivity is higher than about 700. Then mFr increases with higher connectivity, which is in agreement with increasing firing rate and number of synapses in neuronal cultures during 2nd and 3rd weeks in vitro. So far we have analyzed global NB features, including maximum firing rate, rising and falling slopes; and compared 'noise-driven' versus 'pacemaker-driven' NN. There are enough supporting evidences for both methods [8, 9, 10]. However, we show that 'pacemakers' play the key role in formation of NB profiles by a shift towards shortened rising slopes. We can explain the network-wide burst onset as a response to synchronization of 'pacemakers' that ignite the rest of the network. Thereby, our simulations helped to find a remarkable relationship between several experimental findings, namely: NB profile shapes and existence of 'privileged' neurons [9] and their role in collective activity.

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REFERENCES

- [1] Y. Jimbo, A. Kawana, P. Parodi and V. Torre, "The dynamics of a neuronal culture of dissociated cortical neurons of neonatal rats," *Biol. Cybern.* 83 1-20, 2000
- [2] J. van Pelt, M.A. Corner, P.S. Wolters, W.L.C. Rutten and G.J. Ramakers, "Longterm stability and developmental changes in spontaneous network burst firing patterns in dissociated rat cerebral cortex cell cultures on multielectrode arrays," *Neurosci. Lett.* 361 86-9, 2004
- [3] J. Stegenga, J. le Feber, E. Marani and W.L.C. Rutten, "Analysis of cultured neuronal networks using intra-burst firing characteristics," *IEEE Trans. Biomed. Eng.* 55(4):1382-90 2008
- [4] D.A. Wagenaar, J. Pine and S.M. Potter, "An extremely rich repertoire of bursting patterns during the development of cortical cultures," *BMC Neurosci.* 7, 2006
- [5] C. Mehring, U. Hehl, M. Kubo, M. Diesmann, A. Aertsen, "Activity dynamics and propagation of synchronous spiking in locally connected random networks," *Biol. Cybern.* 88: 395-408, 2003
- [6] D. A. French and E.I. Gruenstein, "An integrate-and-fire model for synchronized bursting in a network of cultured cortical neurons," *J. Comp. Neurosci.* 21:227-241, 2006
- [7] E. Persi, D. Horn, V. Volman, R. Segev and E. Ben-Jacob, "Modeling of synchronized bursting events: the importance on inhomogeneity," *Neural Comput.* 16(12), 2577-2595, 2004
- [8] P.E. Latham, B.J. Richmond, S. Nirenberg and P.G. Nelson, "Intrinsic dynamics in neuronal networks. I. theory," *J. Neurophysiol.*, vol. 83, pp. 808-827, 2000
- [9] D. Eytan, S. Marom, "Dynamics and effective topology underlying synchronization in networks of cortical neurons," *J Neurosci* 26:8465-8476, 2006
- [10] A. Destexhe, M. Badoual, Z. Piwkowska, T. Bal, and M. Rudolph, "A novel method for characterizing synaptic noise in cortical neurons," *Neurocomputing* 58-60:191-196, 2004
- [11] E. M. Izhikevich, "Simple model of spiking neurons," *IEEE Trans. Neural Networks*, vol. 14, pp. 1569-1572, Nov., 2003
- [12] M. Toledo-Rodriguez, A. Gupta, Y. Wang, Cai Zhi Wu and H. Markram, "Neocortex: basic neuron types," in: M.A. Arbib, Editor, *The Handbook of Brain Theory and Neural Networks* (2nd edn ed.), MIT Press (2002) pp. 719-725
- [13] Ichikawa M, Muramoto K, Kobayashi K, Kawahara M, Kuroda Y, Formation and maturation of synapses in primary cultures of rat cerebral cortical cells: An electron microscopic study. *Neurosci Res* 16:95-103,1993