2015 International Symposium on Nonlinear Theory and its Applications
NOLTA2015, Kowloon, Hong Kong, China, December 1-4, 2015

Synaptic Mechanism of Synchronized Bursting Events in Neuronal Cultures

Yu-Ting Huang†, Yu-Lin Cheung‡, Chun-Chung Chen‡, Pik-Yin Lai† and C. K. Chan‡

†Dept. of Physics and Center for Complex Systems, National Central University,
Chungli, Taiwan 320, ROC
‡Institute of Physics, Academia Sinica, Nankang, Taipei, Taiwan 115, ROC

Abstract—Synchronized bursting event (SBE) is a generic feature of neuronal cultures in which most of neurons in the network are bursting synchronously. Although the origin of SBE is still unclear, they are believed to be the result of the self-organized dynamics of a random network and it has been proposed that one can make use of these SBEs for information encoding. Here we investigate properties of the SBE in a growing neuronal culture as a function of network properties which can be modified by drugs or the age of the cultures. We find that most of the observed properties of the SBEs can be accounted for in a model of short term synaptic plasticity (STSP). Our results suggest that networks exhibiting SBEs are in an oscillatory state due to the STSP and strong recurrent connections. For these networks, information can only be stored in between the SBEs and they are probably not good candidates for information encoding.

1. Introduction

Neuronal cultures grown on top of multi-electrode array (MEA) systems have become a standard experimental platform for the study of computational capabilities of living random neural networks in the last two decades [1]. The ultimate goal of these studies is to create networks with useful functions [2]. These kind of studies are not just guided by the faith that these cultures should retain some properties of their original tissue; namely the brain. It has been shown numerically that useful functions such as working memory [3] can be implemented in a random network endowed with short term synaptic plasticity (STSP) [4], a form of memory in the molecular levels observed in biological synapses. Although cultured networks have been studied extensively for the understanding and construction of such functional networks in the past decade, very little success has been achieved towards this goal.

One of the main obstacles in the understanding of these cultured networks is that it is still not clear how information is being coded into the firings of the neurons in these networks. For example, the ubiquitously observed spontaneous network activities in these cultures, known as synchronized bursting events (SBE) [5], discovered more than 30 years ago [6], is still poorly understood. During a SBE, most of the neurons in the network are firing in bursts more or less simultaneously for a duration of the order of a second. The origin these SBEs are still largely unknown. It has been proposed that these SBE are related to information coding and storage [7] in the networks and there have been many attempts [8, 9] to make use of these SBE (either trained or spontaneous) to produce useful functions. Intuitively, these SBEs should be the result of the synaptic interaction between neurons in the cultures. In fact, it has been shown that the spatial temporal structures of these SBEs are a function of the connectivities of the cultures [10] and related to the excitatory/inhibitory interactions of the system [11]. A detailed understanding of these spontaneous SBEs in terms of synaptic plasticity should be the first step towards the goal of the construction of functional networks. It is natural to ask whether these SBEs can be understood in terms of STSP, an essential component for a functional network and what kind of information is being coded into the SBEs.

Here we investigate properties of the SBE in a growing neuronal culture as a function of network properties which can be modified by the age of the cultures and use a mean-field model to understand our results.

2. Materials and Method

In this study, we have performed experiments and developed a mean-field model to understand experimental results. The mean-field model is an extension of of a model of short term synaptic plasticity.

2.1. Experiments with neuronal cultures

Neuronal cultures grown on top of multi-electrode arrays (MEA) are used in our experiments. For cultures preparation[10], cortex tissues from are extracted from embryonic day 18 Wistar rat embryos. The cortices are dissociated by 0.125% trypsin and gently triturated. A small drop (5uL) of cell solution are added to each multi-electrode array (MEA60-200-ITO, Qwane Biosciences SA, Switzerland) that has been pre-treated with 0.1% Polyethylenimine resulting in an approximate density of 3000-5000 cells/mm^2. The MEAs are filled with culture medium (DMEM with 5% FBS, 5% HS and 1% penicillin/streptomycin) 30 min after seeding. Samples are incubated at 37^{o}C with 5% CO_2 and half of medium is changed twice a week. The advantage of using MEAs is that we will be able to record neuronal activities at multiple sites simultaneously. Extracellular activities from 60

electrodes (ITO transparent electrodes with 40 μm diameter and 200 μm spacing, arrangement of 8×8 grids without 4 corners) are recorded by using a MEA 1060-Inv-BC (Multi Channel systems) with 1100X amplified at a sample rate of 20K Hz. Data are recorded for a duration of 10 minutes at 33 ^{o}C with 5% CO_2 by using MC_RACK software (Multi Channel Systems).

2.2. Mean-Field Model

One of the interesting aspect of the SBEs is that during SBE, almost all the neurons in the network are firing more or less synchronously and therefore the dynamics of the whole network can be treated as if it is the dynamics of a single cell in a mean field manner. Of course, the input to the mean field "cell" is the total effective output from the recurrent connections of the network. In this manner, the network is getting input its own output as shown in Figure 1. With such a picture, the dynamics of the whole network can be studied through the modeling of the mean firing rate $E(t)$ in Figure 1. In particular, the $E(t)$ can be compared to the firing rate time histograms (FRTH) measured in experiments.

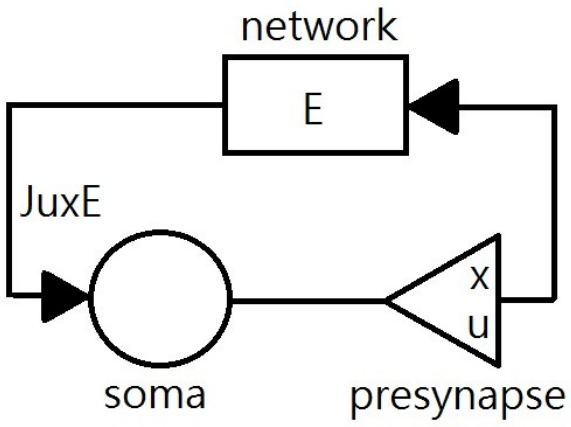

Figure 1: Schematic diagram showing the mean field model for the recurrent network with synaptic interaction. Note that the role of the network in the model is just to produce an amplification of J times.

There are two components in the mean field description of the system during SBE; namely the recurrent connection and the synaptic mechanism. In the following, the recurrent connection is simply modeled by a strength J while we will make use of a synatpic model by Tsodysk and Markram [12] for the synaptic interaction. It is known that this TM model for STSP is capable of producing various kind of dynamics [13].

In the TM model, the mean firing rate E of the network, with a recurrent connection strength J receiving a global inhibition I_0, is governed by:

$$\frac{dE}{dt} = \frac{1}{\tau}\left[-E + \alpha \ln(1 + e^{\frac{JuxE+I_0}{\alpha}})\right] \quad (1)$$

where α is the threshold of the gain function for the recurrent excitation. The synaptic mechanism is implemented as the dynamics of the available neurotransmitter fraction x [14] with its releasing probability u as a function of E, and are governed by the following equations:

$$\frac{dx}{dt} = \frac{\mathcal{X}_o - x}{\tau_D} - uxE \quad (2)$$

$$\frac{du}{dt} = \frac{U - u}{\tau_F} + U(1 - u)E. \quad (3)$$

where $\mathcal{X}_o \leq 1$ and U are the baseline level of x and u respectively. The time scales are: $\tau \sim 10$, $\tau_D \sim 100$ and $\tau_F \sim 1000$ ms.

With suitable choice of parameters, the TM model can produce oscillations[13] similar to the times scales of the sub-bursts observed in experiments. However, these oscillations will persist in the TM model. In order to model the finite duration of SBEs as observed in our experiment, an extension to the TM model known as TMX model [15] is used to provide this dynamics as:

$$\frac{d\mathcal{X}_o}{dt} = \frac{X_0 - \mathcal{X}_o}{\tau_X} - \beta E \quad (4)$$

where time dependent $\mathcal{X}_o$ is introduced to model the fatigue of the maximal fraction of available neurotransmitter fraction for some baseline constant X_0, time constant $\tau_X (>> \tau_D)$ and fatigue rate constant β.

3. Results

3.1. Experimental Results

Figure 2 (upper panel) shows a typical raster plot of a SBE from a culture grown on top of the MEA. It can be seen that there seems to be sub-bursts within the SBE. In the FRTH, in which the spikes for all the channels are added within a 5 ms window, these sub-bursts can be seen more clearly (Figure 2, lower panel)

One interesting characteristic of these measured FRTH is that their shapes can strongly depend on the state of the cultures. For example, Figure 3 shows the changes in the shape of the FRTH as the culture matures. Presumably, the structure of the FRTH is controlled both by the network connections and the synaptic interactions between the neurons in the network. As the culture matures, it is clear that both the network connections and the synaptic interaction in the network increase. From the complexities of these FRTH, it seems that the SBE can be used for information encoding and processing.

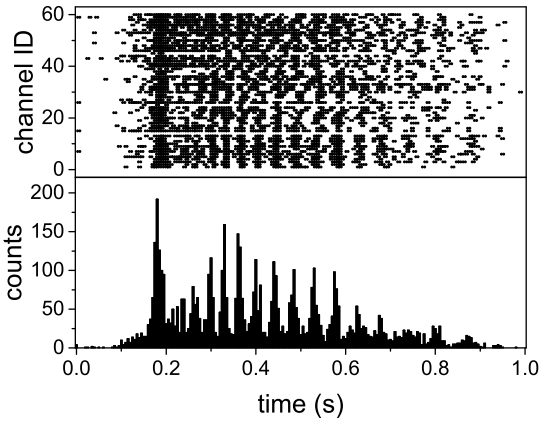

Figure 2: Raster plot of the firing activities in all the 60 channels of the MEA (upper panel) and the corresponding FRTH (see text for definition) during a SBE (lower panel)

3.2. Simulation Results

With the TMX model, it can be shown that the system can be turned into an oscillatory state with $E(t)$ looks very similar to those shown in Figure 3. For example, Figure 4 shows the simulation results of the TMX with various parameters. It can be seen that with proper choice of simulation parameters, the essential features of the measured FRTHs from SBEs can be reproduced. These oscillation states of $E(t)$ are the results of too strong a positive feedback [15] in the system. In fact, in this TMX model, the sub-busrts seen in the FRTHs are the results with large enough U and J. That is: when there is strong enough recurrent connections and synaptic interactions.

In Ref[15], it is shown that there are two states of the system; one with a low firing rate $E(t)$ and the other one having the structure of $E(t)$ similar to those shown in experiments. The main factors which govern the state of the cultures are the X_0 and J_0. That is: the structure of the network and the synaptic interaction. With this picture, the number of sub-bursts in a SBE depends on how much X_o is available in the beginning of the SBE. When the frequency of the occurrence of the SBE is high as at late DIVs, there is not enough time between SBE for the X_o to recover to a high value. Therefore, the number of sub-bursts decreases as the frequency of occurrence of SBE increases at late DIVs. This last finding is the consistent with our experimental observations.

4. Discussions

From the discussions above, it is clear that the TMX model can generate the complex SBEs patterns observed in the cultures. However, since the oscillatory structures of the FRTHs from the experiments are the results a positive

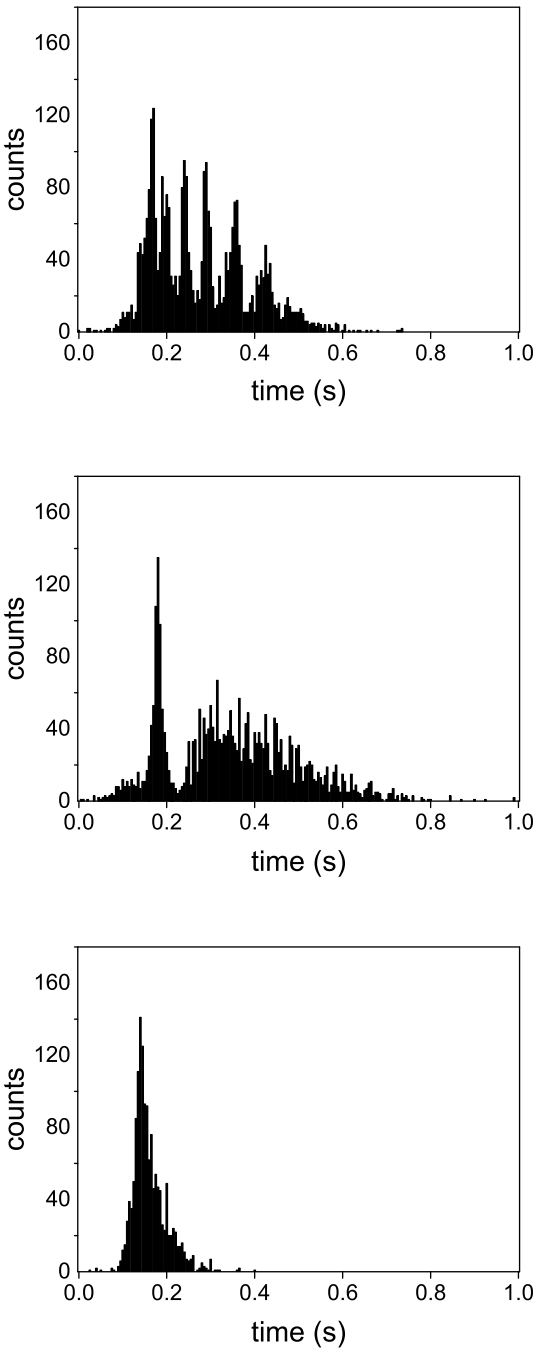

Figure 3: Measured FRTHs from cultures at various DIV. From top to bottom: 9 DIV, 18 DIV and 22 DIV respectively. Note that although the number of the spikes within each SBE decreases as DIV increases, the overall activities of the cultures increase with DIV because the frequency the occurrence of SBE increases with DIV.

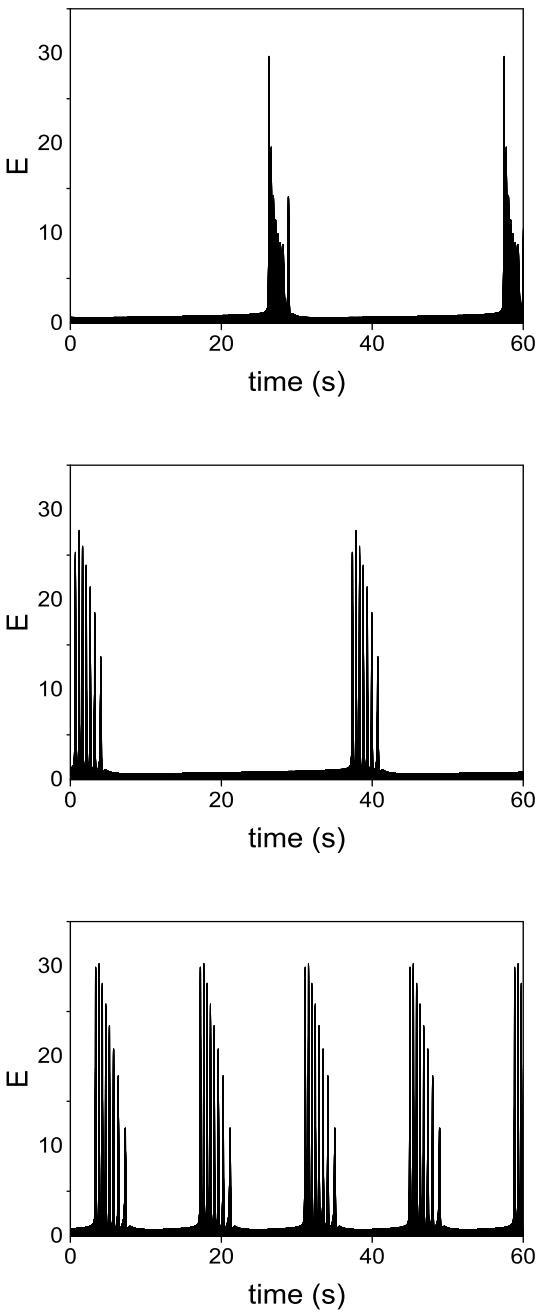

Figure 4: Simulation results with the TMX model with different values of τ_D and J Top: τ_D= 0.15 and J=4.5; Middle: τ_D= 0.2 and J=4.5. Bottom: τ_D= 0.2 and J=6. The other values of the parameters in the model are X_0=0.95; U_0=0.30; ; I_0=-1.3; a = 1.25; τ = 0.013; ;τ_F=1.5; τ_x=20; β=0.01

feedback oscillation loop, it is difficult for the system to use SBEs to encode any information. Information written to the network will be washed out by these self-substaining oscillations. As these oscillations are caused by too much positive feedback in the system, the observation of SBEs in cultures suggests that there are too many connections in the system. Perhaps, this is one of the main reasons why it is difficult to make use of these systems for useful functions.

Acknowledgments

This work has been supported by the Ministry of Technology of Taiwan.

References

[1] Taketani M., Baudry M. "Advances in network electrophysiology: Using multi-electrode arrays." New York: Springer (2006)

[2] Ito S, Yeh et al., PLoS ONE 9(8): e105324 (2014)

[3] Jonides J1 et al., Annu Rev Psychol. 59: 193224 (2008)

[4] Markram et al., Nature. 382(6594): 807-810 (1996)

[5] Maeda E., Robinson H. P. C.and Kawana A., Journal of Neuroscience. 15(10): 6834-6845 (1995)

[6] Gutnick MJ, Connors SW, Prince DA, J Neurophysiol 48: 1321-1335 (1982)

[7] John M. Beggs and Dietmar Plenz, The Journal of Neuroscience, 2 June 2004, 24(22): 5216-5229 (2012)

[8] Wagenaar DA et al, JOURNAL OF NEUROSCIENCE 25(3) 680-688 (2005)

[9] Pimashkin A et al, Front. Neural Circuits 7:87 (2013)

[10] L.-C. Jia, M. Sano, P.Y. Lai and C. K. Chan, Phys. Rev. Lett 93, 088101 (2004)

[11] Xin Chen and Rhonda Dzakpasu, Phys. Rev. E 82, 031907 (2010)

[12] Mongillo, G.O.Barak, M. Tsodyks, Science 319, 1543-1546 (2008)

[13] J. M. Cortes et. al, PNAS 110(41) 16610 (2013).

[14] Tsodyks, M. V. and H. Markram PNAS, 94(2): 719-723 (1997)

[15] Yu-Ting Huang, et al. "Positive Feedback and Synchronized Bursts in Neuronal Cultures", preprint, (2015).