Neural Modeling of Synchronized Bursting Events

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Abstract

In vitro neuronal networks are known to exhibit synchronized bursting events (SBE), during which most of the neurons in the system spike within a time window of approximately 100msec. Such phenomena can be obtained in model networks based on Markram-Tsodyks synaptic dynamics. We point out that in order to account correctly for the detailed behavior of SBEs several modifications have to be implemented in such models. Random input currents have to be introduced to account for the rising profile of SBEs. Introducing inhomogeneity in the distribution of neuronal thresholds and resistances we find that we are able to describe the profile of activity within the SBE and the heavy-tailed distribution of ISI and IEI. Thus we can account for the interesting appearance of Levy distributions in the data.

Key words: Synchronized bursts; Dynamic Synapses; ISI; IEI; Levy distribution.

1 Introduction

Synchronized activity of groups of neurons has been a subject of various theoretical and experimental studies. Recently, Segev *et al.* (7; 5; 6) performed long-term measurements of spontaneous activity of *in vitro* neuronal networks demonstrating a new form of synchronized activity. The experimental system is a 60 multi-electrode two-dimensional (2D) array on which the biological system is grown. Different morphological structures and sizes of networks were explored. The raster plot of a typical network reveals the appearance of Synchronized Bursting Events (SBEs), as in Fig. 1.

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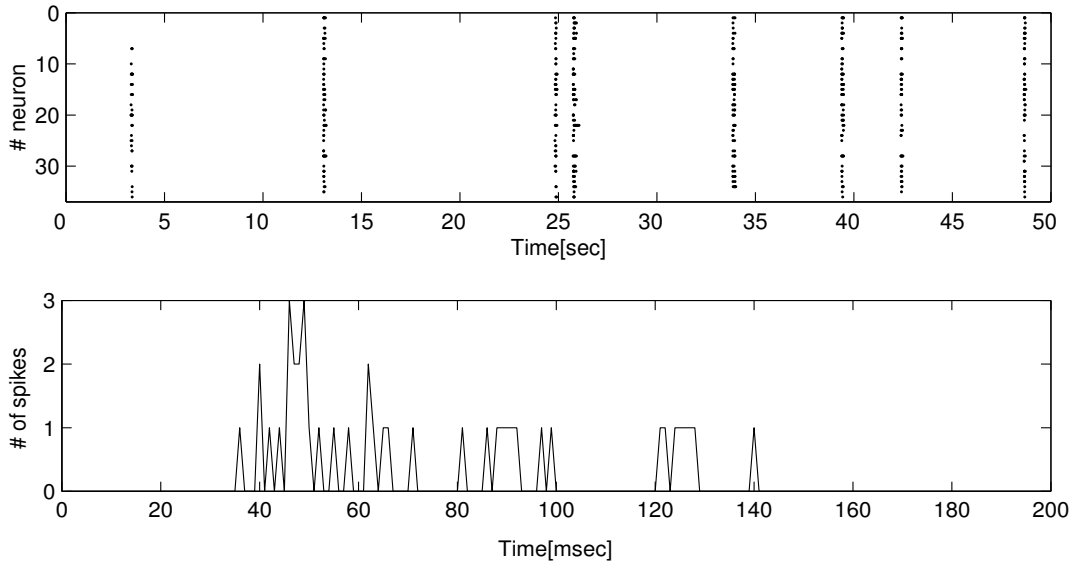

Fig. 1: Typical activity of the experimental network. upper frame: The raster plot reveals SBEs. lower frame: Detailed structure of an SBE.

The SBE involves rapid spiking of almost all the neurons in the network. It starts sharply and decays during a 100msec period. The SBEs are separated by long quiescence periods (1-10sec) during which there is almost no activity except for few sporadic spikes. The mean rate of SBEs is 0.2Hz (up to factor of 2). The distribution of the neurons and network activity were explored by (5; 6). The inter-spike interval (ISI) and inter-event interval (IEI) distribution reveal heavy tails. To study the latter, the distribution of the ISI and IEI increments (ΔISI and ΔIEI), were investigated. They have zero mean and are symmetric. The ΔISI distribution was well-fitted with Levy distribution up to 100msec, while the ΔIEI was well-fitted over another 3 decades. These observations imply that there is no characteristic time scale in the system.

Neural networks composed of integrate and fire (IF) neurons are able to generate bursting activity, as shown by Tsodyks *et al.* (4) in a model based on frequency-dependent synapses (2; 3). Using numerical simulations, we investigate what parameters of this model affect the dynamics of *in vitro* neural networks, and how they should be modified to account for the detailed spatiotemporal structures and neuronal activity observed experimentally.

2 The Model

Our model is based on Integrate and Fire (IF) neurons with frequency dependent dynamic synapses (4). The IF neuron is described by

$$\tau_{mem} \cdot \frac{dv}{dt} = -v + R_{mem} \cdot (I_{syn} + I_{ext}) \qquad (1)$$

where v, τ_{mem} and R_{mem} are the voltage, time constant and resistance of the cell membrane, respectively. Once v reaches a threshold the neuron fires and v is reset to v_{res}.

These point-like neurons are endowed with dynamic synapses that are responsible for the appearance of activity bursts. The strength of a synapse is described(2) by a parameter A_{ij}, representing the efficacy of a synapse connecting a pre-synaptic neuron (j) to a post-synaptic neuron (i). Biologically, the efficacy depends on the total number of ionic channels in the synaptic terminal, the capacity to produce neurotransmitter vesicles and more. The dynamics of the synapse is described by the following system of differential equations:

$$\frac{dx}{dt} = \frac{z}{\tau_{rec}} - u \cdot x \cdot \delta(t - t_{sp}) \tag{2}$$

$$\frac{dy}{dt} = -\frac{y}{\tau_{ina}} + u \cdot x \cdot \delta(t - t_{sp}) \tag{3}$$

$$\frac{dz}{dt} = \frac{y}{\tau_{ina}} - \frac{z}{\tau_{rec}} \tag{4}$$

where x, y, z are state variables representing the fraction of ionic channels in the synapse in the recover, active and inactive states, respectively, so $x + y + z = 1$. u represents the fraction of utilization of the recover state by each pre-synaptic spike. Once a spike from a pre-synaptic neuron arrives at the synaptic terminal at time t_{sp}, a fraction u of the recover state is transferred to the active state, which presents the fraction of open ionic channels through which the neurotransmitters can flow. The synaptic current from all pre-synaptic neurons to the post-synaptic neuron is therefore: $I^i_{syn} = \sum_{j=1}^{n} A_{ij} \cdot y_{ij}$ After a short time τ_{ina} the ionic channels transfer to the inactive state. From the inactive state there is a slow process of recovery $\tau_{rec} >> \tau_{ina}$ back to the recover state, completing a cycle of the synapse dynamics. The above description (with a constant variable u) captures well the dynamics of a depressing synapse. The variable u describes the effective use of synaptic resources and could be assigned to the probability of release of neurotransmitters or the concentration of Ca^{2+} ions in the synaptic terminal. In facilitating synapses each pre-synaptic spike increases the probability to excrete neurotransmitters to the synaptic cleft. In order to also capture the dynamics of facilitating synapses, another equation was added to the model:

$$\frac{du}{dt} = -\frac{u}{\tau_{fac}} + U \cdot (1 - u) \cdot \delta(t - t_{sp}) \tag{5}$$

where the constant parameter U determines the increase in the value of u each time pre-synaptic spike arrives. The initial condition is that $U = u$. Note that

when τ_{fac} approaches zero facilitation is not exhibited. When a pre-synaptic spike arrives, u is updated first, and then all other parameters *(x, y, z)*.

Tsodyks *et al.* (4) have demonstrated that a network of IF neurons with dynamic synapses of the type described above generates synchronized bursts. Their network was composed of 400 excitatory neurons and 100 inhibitory neurons with probability of 0.1 for connection between two neurons. The network was fed a fixed external input current I_{ext} which was generated by a random flat distribution centered at firing threshold (with a range of 5% of the threshold). The rate of SBEs obtained with this description is approximately 1Hz. After an SBE occurs it fades away rapidly since the fast firing neurons with depressing connections cause a sharp decline of recovering synapses. Between SBEs there is a low-rate activity driven mainly by I_{ext}. After recovery of synapses I_{syn} builds up and leads to a new burst.

Trying this approach for our system we find that it needs modifications. It is difficult to find parameters that will fit both the rate of SBEs and the low firing rate of neurons in between SBEs. Moreover, the profile of the experimental SBE, i.e. the activity of neurons within this event, rises sharply and decays exponentially, while the model as described so far leads to a Gaussian profile. The modifications that we propose are discussed in the next section.

3 Importance of Noise, Inhomogeneity and Dynamic Thresholds

We investigate three modifications of the model described above. One relates to the input current and the two others to removal of homogeneity in the structure of the network. The simulations reported below were performed on a network of 27 excitatory and 3 inhibitory neurons with 25% connectivity. For simplicity we chose V_{th} and V_{res} to be 1 and 0 respectively. Since τ_{ina} determines the decay of synaptic currents which dominate during the SBE, we increase τ_{ina} to 10msec, which leads to wide bursts (of order 100msec).

We introduce Gaussian external noise with expectation value of $\mu = 0.86$mv and standard deviation of $\sigma = 0.15$mv. Each 10 time steps (of 0.1msec each) a different value of external current is used. This leads to both quiescence between successive SBEs, and to a sharp increase in neuronal activity once an SBE happens. Since μ is below threshold, the neurons' firing rate is very low, which enables the synapses to recover quickly and almost completely. At the point where the synapses are recovered, a single spike from one of the neurons in the network generates a large I_{syn} to its targets, thus increasing the probability of an SBE. When the SBE fades away the synapses are in the inactive state, hence the only activity is the one driven by the noisy external currents. The expectation value and variance of the noise control the mean

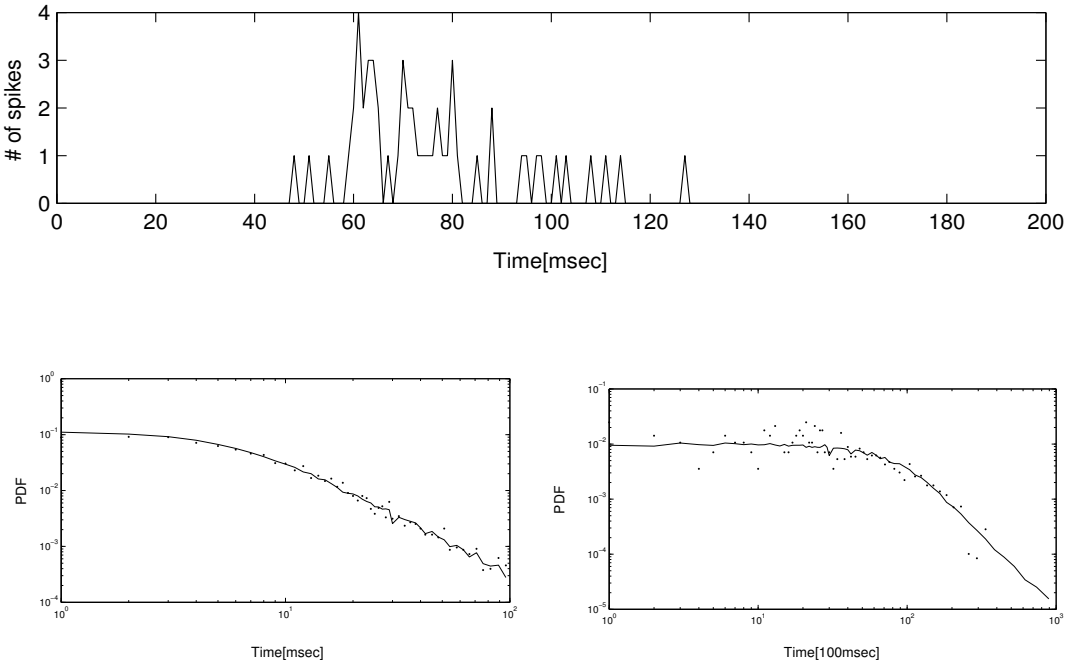

Fig. 2: Effect of dynamic threshold and inhomogeneous resistances. Upper frame: The SBE profile is the same as the experimental one. Lower frames: Simulated neurons fit the Levy distribution both in ΔISI(left) and ΔIEI(right).

rate of SBEs, that can be adjusted to fit the experimental values. However the profile of the SBE is still problematic, it builds up too fast. Moreover, the SBE sequence is nearly periodic. To cure these problems we introduce two sources of inhomogeneity into the system, in the values of resistances and of neuronal thresholds. Resistances are randomly selected from a flat distribution over the interval [0.2,0.7]. This allows to modify each neuronal I_{syn}, so the SBE builds up slower. Adaptation and regulation are well-known characteristics of neuronal activity. These effects can be modeled by dynamic thresholds, which change as function of the neuronal firing rate. We implemented this effect by the following equation.

$$\frac{d\theta_i}{dt} = -\frac{\theta_i - \theta_i(t=0)}{\tau_{th}} + S_i \cdot (\delta(t - t_{sp})) \tag{6}$$

where S_i is some stationary random function with flat distribution over the interval [-0.06,+0.04], and τ_{th} equals the SBE time width (100msec). Note that the threshold can be higher or lower than its initial value during the SBE, after which it recovers back to the initial value. This mechanism allows some neurons to increase or decrease their activity when they spike, which results in a good match (over five decades) to the probability distribution function of ΔISI and ΔIEI, and in perfect match to the experimental SBE spatio-temporal structure, as demonstrated in Fig. 2.

4 Summary

We have accounted for experimentally observed features of SBEs using, as the underlying model, the one by (4), based on IF neurons and dynamic synapses. We had, however, to introduce several modifications. They included noisy inputs, inhomogeneities in the parameters of the neurons (resistances and thresholds) and activity dependent dynamics of the thresholds. The inhomogeneities allowed us to capture the correct profile of the SBE. The dynamic thresholds gave us the possibility to account for Levy distributions of ΔISI and ΔIEI.

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