Explaining burst profiles using models with realistic parameters and plastic synapses

T. Gritsun1*, J. Stegenga1, J. Le Feber1 and W.L.C.Rutten1

1 Biomedical Signal and Systems group, Department of Electrical Engineering, Mathematics and Computer Science, University of Twente, Enschede, the Netherlands
* Corresponding author. E-mail address: t.gritsun@utwente.nl

One of the most prominent features of the electrical activity of dissociated cultured neural networks is the phenomenon of network bursts. Profiles of the instantaneous firing rate during bursts vary in shape and intensity during neuronal culture development. To shed some light on burst profile variability we constructed “pacemaker-driven” random recurrent neural network models with both static and frequency dependent synapses. We show variation of burst features by changing the network parameters of the models. The best agreement was found by including synapses with short-term plasticity.

1 Introduction

We studied neural network collective behavior in terms of synchronized network bursts (NB): namely the formation and characteristics of bursts in cortical neurons cultured on multi electrode arrays (MEAs). A NB can be characterized by its profile, which is calculated as a (smoothed) estimation of the array-wide firing frequency [1, 2]. In this work we focused on three NB profile shape parameters: half-widths of rising phase (Rp), falling (Fp) phase and maximum firing rate (mFr). A batch simulation of the artificial network was used to generate bursts. We studied how profile parameters depended upon network parameters, such as average number of connections per neuron (connectivity, C), excitatory fraction ratio (R) and the time delay between pre-synaptic spike and post-synapse response (transmission delay, D). The simulations produced NB features in ranges similar to experimental data. These simulations help to understand the development of the network structure throughout culture life-time. Several mechanisms that modulate synaptic transmission are active during bursts. These may change the spatio-temporal structure of bursts on large timescales through spike-timing dependent plasticity (including LTP and LTD). On small timescales, short-term plasticity (STP) (e.g. facilitation and depression phenomena) may affect firing rates during bursts. To test its influence, we used synapse models with and without STP.

2 Methods

We used spontaneous recordings previously used in [1]. Shortly, we obtained neocortical neurons from 1-day old Wistar rats. Cultures of dissociated neurons were grown on MEAs and 2 hour long recordings were made daily starting around 7 days in vitro (DIV).

We analyzed Rp, Fp and mFr as defined by van Pelt et al. [2] from experimental spontaneous bursting activity over a period from 9 to 36 DIV. In order to mimic these features we constructed several spiking models of a recurrent neural network with random sparse connectivity maps. In brief, we used the quadratic integrate and fire neuronal model by Izhikevich [3], and static and frequency dependent synapse models by Tsodyks et al. [4]. We approximated the ranges of C during culture development from experimental counting of van Huizen’s et al. [5]. D was set in the range according to experimental findings of Muller et al. [6]. R was set in the range between 70% and 90% according to [7]. We ran batch simulation with normally distributed connectivity around C = {50, 100, ..., 550}, transmission delays around D = {5, 10, 15, 20} msec and excitatory fraction ratio R = {70, 80, 90}%. Synaptic strengths were normally distributed between 0 and 1 mV. We introduced inhomogeneous distribution of synaptic strength (up to 12 mV) and intrinsic activation in small neuronal subsets (i.e. ‘pacemakers’) into network models. The total number of neurons was 5000.

Network simulations were performed using both modified CSIM simulator [8] and C programming language (in MEX-file) in a Matlab environment (the MathWorks, Inc) on a PC compatible platform. We used Euler’s method to integrate neuronal and synaptic model equations with 1 ms simulation step.

The same NB parameters as in the experiments were calculated from the simulated spike trains and their sensitivity to variations of the network parameters C, R and D.

In this report we present several sensitivity plots of the mFr, Rp and Fp to variation of the connectivity C in order to compare simulated and experimental
data. The detailed results on the sensitivity analysis will be reported elsewhere.

3 Results

Figure 1 summarizes the development of three NB profile parameters acquired from 7 cortical cultures. In brief, mFr increases, Rp and Fp are more varied in first 3 weeks in vitro; mFr decreases, Rp and Fp are stabilized thereafter.

![Figure 1](image1)

**Fig. 1.** Dynamics of three NB features: maximum firing rate (A), half-width of rising phase (B) and falling phase (C). Mean and standard deviation (SD) values were averaged from burst profiles on each day of recording from 7 neural cultures. In general, mFr rises in the first and second week in vitro and decays in the third week. Cultures older than 3 weeks show more or less constant value with smaller SD.

Figures 2a and b show sensitivity curves for NB profile parameters to the connectivity C in the network simulations with static synapses. Network activity increases with higher C (see fig 2a) and decreases with longer D and lower R (not shown here). Activity developed into NBs in the simulations with C ≥ 250. Networks with high C and R, and short D produced activity explosions as shown in figure 2a at C = 450. Except for these explosions, simulated NB features resemble those of experimental data in the networks when D ranges from 5 to 20 msec, R from 70 to 90% and C between 350 and 550 (not shown here).

![Figure 2](image2)

**Fig. 2.** Sensitivity curves for the connectivity; their effect on the NB profile in NN models with static synapses. A: Mean curves and standard deviation are plotted for the maximum firing rate, B: half-width rising and half-width falling phase, summary curves.

In the next simulation batch static synapses were substituted for dynamic modelled by Tsodyks et al. [4], in order to see the effect of STP on profiles. Figures 3a and 3b show changes in dynamics of the NB parameters after introducing the adaptive synapses. Here burst were detected in networks with smaller C (around 150 - 200). STP rules allowed simulating networks with higher C without mFr explosions and less varied Rp and Fp. These simulations mimic experimental data better than previous, mainly for older cultures, where Rp and Fp are stabilized around 15 msec.

4 Discussions

The highly connected networks with static synapses produce NBs with higher firing rate and more varied Rp and Fp values than the networks with dynamic synapses.

Following high variation of Rp and Fp values at C ≥ 400, simulated NB profiles generated using static synapse model resemble profiles found in cultures younger than 3 weeks in vitro. This corresponds to elevated range of mFr values that can be found in experimental data. In older cultures mFr drops to the values that correspond to values produced by network models with smaller connectivity. Experimental data acquired from cultures three weeks old, and older, are reproduced by models with frequency dependent synapses. Indeed, these findings are in agreement with experimental data reported by Van Huizen et al. (1985) [5]. They showed that average number of synapses increases during development and reaches a maximum at 3 weeks in vitro, after which it stabilizes at a lower value.
We show the influence of STP on stability of the network activity through changes of network connectivity. First, STP prevented networks from activity explosions; next, it stabilizes Rp and Fp at shorter time values; and finally, it allows the networks to produce activity in smaller connectivity ranges. These shorter time ranges of Rp and Fp, which makes NB profiles narrower than profiles in the network models with static synapses, were caused by lower average firing rates.

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References