Modeling of spontaneous synchronized periodic activity observed in *in vitro* networks

Maria Marinaro and Silvia Scarpetta

Dipartimento di Fisica"E. R. Caianiello", Salerno University, Baronissi (SA) IT

INFM Sezione di Salerno (SA) IT, and IIASS Vietri sul mare (SA) Italy

Abstract

Recently Segev et al. [1,2] have done long-term measurements of spontaneous activity of cortical cell neural networks placed on multi-electrode arrays. Their observations differ from predictions of current neural network models in many features. The aim of this paper is to show that the same EI network model introduced in a previous paper [3] by one of us Z.Li and J. Hertz, to model driven activity and spike-timing-dependent-plasticity in cortical areas, is able to reproduce the experimental results of spontaneous activity of [1,2] (and the observed Power Spectrum Density (PSD) features), when we consider the model in isolation with intrinsic noise terms. Using preliminary analytical results as a guide line, we perform numerical simulations of the stochastic equations for the instantaneous firing rates. In one regime of parameters the network shows spontaneous synchronous periodic activity, and the PSD shows two peaks at the first and second harmonics, and a broad band at low frequency (indicating positive long range time correlations), in agreement with experiments. The two high peak in the PSD fades away when we increase the level of noise.

Preprint submitted to Elsevier Science *29 May 2002*

1 Introduction and motivations

To reveal the rules which govern network spontaneous activity, i.e. without any stimulation from the external world, is a preliminary requirement for the understanding of the network activity inside animal brain, when subject to continuous stimulation from other part of the brain. Spontaneous (and stimulation-driven) synchronized periodic activity has been observed in many in vivo and in vitro experiments. The understanding of the specific mechanisms underlying these spontaneous spatio-temporal pattern of activity is important for the comprehension of many aspects of brain activity, like central pattern generator activity, epilepsy, etc. Much efforts has been devoted recently to study in-vitro neural networks, in which various numbers of neurons are grown and recorded on a multi electrode arrays, which enables the study of isolated network. Recently Segev et al. [1,2] have done accurate long-term measurements of the spontaneous activity of two-dimensional cortical cell neural networks placed on multi-electrode arrays. They observed, for a critical range of Ca concentration, periodic synchronized bursting activity, that fades away after about ~ 20 min. Periodic synchronized bursting is observed at $1mM$ Ca concentration and not at higher (2 mM) and lower (0.5 mM) concentrations. Their observation differ from prediction of current neural network models in many features. They try to model the phenomena performing numerical simulations of an integrate-and-fire network model with random connections. Adding (1) dynamic threshold and (2) activity-dependent synaptic connections, they reproduce much of the observed network activity, but do not obtain a complete explanation of the experimental results. For example, their numerical simulations capture the two different activity patterns observed experimentally and the transition between aperiodic synchronized bursting versus periodic synchronized bursting when Ca concentration (and therefore model connection strengths) was increased, but they do not reproduce the transition from periodic synchronized bursting versus aperiodic activity observed experimentally when Ca concentration was increased over the critical interval. The Power Spectral Density (PSD) at the beginning shows two high peaks at first and second harmonic of the periodic network activity, which become lower and lower with time, and after ~ 20 min the PSD is almost flat. Moreover they observe that energy distribution over low frequencies has a broad band with power low decay that indicates the existence of positive long range time correlations in the sequences. These PSD features, and in particular the changes that happen in time scale of several minutes and the behavior at low frequency, have not been explained by the model of Segev et al [1,2], and as far as we know, until now the explanation is lacking. We shows that some insights and a good agreement with experiments of Segev et al. can be obtained with a simple spiking-rate Excitatory-Inhibitory (EI) network model with noise, as that one introduced in a previous paper [3] by one of us Z.Li and J. Hertz to study non-spontaneous driven activity and spike-timing-dependent-plasticity in cortical areas. The spatio-temporal patterns of spontaneous activity in our model is consequence of the simple dynamics of the interacting excitatory and inhibitory units, and depends critically from the synaptic organization of the EI network. In section 2 the model is described and in sec 3 the numerical results are reported together with comments and conclusions.

2 The model

Our starting point are the instantaneous-firing-rate equations [4,3] governing the instantaneous-firing-rates $g_u(\mathbf{u})$ and $g_v(\mathbf{v})$. The state variables $\mathbf{u}, \mathbf{v}$ describe respectively the excitatory and inhibitory units; g_u, g_v are sigmoidal activation functions. The state variables u_i, v_i of the many interacting excitatory and inhibitory neurons evolve throw time, following the equations of motion:

$$\dot{u}_i = -\alpha u_i - \sum_j H_{ij} g_v(v_j) + \sum_j J_{ij} g_u(u_j) + \bar{F}_i(t), \tag{1}$$

$$\dot{v}_i = -\alpha v_i + \sum_j W_{ij} g_u(u_j) + F_i(t). \tag{2}$$

where α^{-1} is a time constant (about few milliseconds, for simplicity assumed the same for excitatory and inhibitory units), and J_{ij}, W_{ij} and H_{ij} are the synaptic strengths All these parameters are non-negative; the inhibitory character of the inhibitory units v_i is expressed by the minus sign preceding H_{ij} on the right-hand side of Eqn. (1). $\bar{F}_i(t)$ and $F_i(t)$ are stochastic variables that describe intrinsic noise, respectively on the excitatory and inhibitory units, not included in the statistical definition of u, v. In (cultured) interacting neurons systems noise can be due to several reasons, like thermal fluctuation, ion channel stochastic activities, and many others. We take the intrinsic noise $\bar{F}_i(t), F_i(t)$ to be uncorrelated white noise, such that $< F_i(t) >=< \bar{F}_i(t) >= 0$ and $< F_i(t)F_j(t') >=< \bar{F}_i(t)\bar{F}_j(t') >= \Gamma\delta_{ij}\delta_{t-t'}$. Apart from small fluctuations, that we neglect, the matrices $\mathbf{J}, \mathbf{H}, \mathbf{W}$ can be taken symmetric, indeed there is no reasons for the isolated spontaneously grown system to break this symmetry, nevertheless the connections between excitatory and inhibitory neurons are still asymmetric in this scenario, and the complete connection matrix $\begin{pmatrix} \mathbf{J} & -\mathbf{H} \\ \mathbf{W} & 0 \end{pmatrix}$ is asymmetric too. A periodic synchronous bursting event with frequency ω_0, like that observed by Segev et al. [1,2] , will correspond in our model to a firing rate $g(u_i)$ (and state variable u_i) such that the local Power Spectrum Density of unit i, PSD_i, and the global power spectrum $PSD = \sum_i PSD_i/N$ has a peak in ω_0. A state vector $\mathbf{u}(t) = \boldsymbol{\xi} cos(\omega_0 t) = \boldsymbol{\xi} e^{i\omega_0 t} + \text{c.c.}$, where the ξ_i are real positive-or-null numbers, represent a synchronous periodic activity of all excitatory units, at frequency ω_0, ξ_i describes the amplitudes of the bursting on the different excitatory units. The spiking-rate of the neurons $g(\mathbf{u}(t))$ is a periodic function with period $T = 2\pi/\omega$, it reaches the highest value at time t where $cos(\omega_0 t) = 1$. When the bursting is periodic but not synchronous, i.e. there is a phase lock between the neurons involved in the bursting, it correspond to $u_i(t) \propto |\xi_i| \cos(\omega_0 t - \phi_i)$. We can describe both synchronous and phase-locked periodic activities by writing $u_i(t) = \xi_i e^{-i\omega_0 t} + \text{c.c.}$ and taking the ξ_i real in the first case and complex ($\xi_i = |\xi_i| e^{i\phi_i}$) in the second. A preliminary analytical solution of the noisy model in isolation (that will be reported in a paper currently in preparation) has put in evidence that the model exhibit different spontaneous regimes, which correspond to different values of the real and imaginary parts of eigenvalues of the connection matrix. In particular, when we use in the model long-range $J_{ij} = j_0/N + \epsilon\,\eta_{ij}$ and $W_{ij} = W_0/N + \epsilon\,\eta_{ij}$, and short-range $H_{ij} = h_0\delta_{ij} + \epsilon\,\eta_{ij}$, (where $\epsilon << 1$, and η_{ij} are quenched random values with zero mean), three different regimes can be distinguished, depending from the values of j_0, W_0, h_0, α:

A) the damped fixed-point regime, where there's no spontaneous oscillatory activity

B) the damped sub-oscillatory regime, where there's spontaneous synchronous oscillatory activity only if driven by noise (or by external periodic input)

C) the spontaneously periodic oscillatory regime, where spontaneous activity is oscillatory, periodic and synchronous, even without noise; in this regime the activity exhibit diverging oscillations in the linearized system which become stable when nonlinear terms are considered.

Model activity in regime C mimic the spontaneous synchronous periodic activity observed in cultured experiments at 1mM Ca concentration [2].

3 Numerical Results

We use sigmoidal nonlinearity of excitatory neurons activation function $g_u(\mathbf{u})$, while we take for simplicity g_v as linear near the fixed point (this choice is supported by physiology). We focus on the case when g_u deviates from linearity near the fixed point $\bar{\mathbf{u}}$ due to saturation. Fig.1.A show the function that we have used in our numerical nonlinear simulations for excitatory units. The nonlinear stochastic differential equations of the isolated network, with $N = 10$ excitatory and $N = 10$ inhibitory units, was numerically integrated using the Runge-Kutta method, and we calculate the PSD of excitatory activity given by $< \sum_i |\tilde{u}_i(\omega)|^2 > /N$, using Bartlett windowing.

In order to investigate the regime B, we use the following parameters $\alpha = 50 sec^{-1}$, $J_{ij} = \frac{j_0}{N} = \frac{2(\alpha-0.1)}{N}$, $W_{ij} = W_0/N, H_{ij} = h_0\delta(i-j)$, and $W_0 = h_0 = \sqrt{0.25 j_0^2 + 0.25}$. Parameters are such that in the linear approximation the characteristic frequency (of the damped solution) is $\omega_0 = \sqrt{-j_0^2/4 + h_0 W_0} = 0.5 rad/sec$. Without noise, the numerical simulations shows that, after a short transient, the activity of the network is stacked on the fixed point, and $u = 0, v = 0$. Interestingly, numerical simulations of the system with noise $\Gamma \neq 0$, shows synchronous collective oscillatory behavior in the neurons activity, both in the nonlinear system and in the linearized one (see Fig.1.BC). In the regime B, noise induces synchronous oscillatory activity, where amplitude and the interval between subsequent maxima (IEI) are not constant (see Fig. Fig.1.C). This synchronous collective oscillatory behavior correspond to a broad peak in the PSD of the neurons activity at the characteristic frequency ω_0 of the system. This noise-induced collective activity (which is highly spatially correlated but decorrelates in time quite fast) mimics the aperiodic synchronous activity observed at 0.5 mM Ca and 2.0 mM Ca concentration in [2].

In order to investigate the regime C, we use the following parameters $\alpha = 50 sec^{-1}$, $J_{ij} = \frac{j_0}{N} = \frac{2(\alpha+0.07)}{N}$, $W_{ij} = W_0/N, H_{ij} = h_0\delta(i-j)$, and $W_0 = h_0 = \sqrt{0.25 j_0^2 + 0.25}$. Parameters are such that in the linear approximation the characteristic frequency (of diverging solution) is $\omega_0 = 0.5$ rad/sec. Introducing the nonlinearity through the function $g_u(u_i) \sim u_i - a u_i^3$, $a > 0$, make the system reach the saturation and shift the frequency to the value $\omega_0 = \sqrt{\frac{2 h_0 W_0 \alpha}{j_0} - \alpha^2} = 1.9$ rad/sec. As shown in Fig. 2 the noiseless nonlinear numerical simulations shows stable synchronous bursting periodic activity $\mathbf{u}$, with frequency about 1.9 rad/sec. This behavior holds only in regime C, i.e. for a particular range of parameters; we check numerically for example that we are out of the regime using both lower ($j_0 = 99.86$) or higher ($j_0 = 103$) values of excitatory-excitatory connections (instead of $j_0 = 100.14$), leaving all the other parameters invariate. As shown in Fig.2, the Power Spectral Density have two high peaks at first and second harmonic of the periodic network activity, resembling the experimental results of [2]. Fig. 3.BC shows the PSD calculated numerically for different level of the noise. The two peaks at first and second harmonic in the PSD become lower and lower with noise level Γ. Fig. 3.C shows clearly that the power spectrum has a broad band distribution at low frequency, very similar to the experimental results of Fig. 3 in [1]. It means that both the experimental time sequence [1] and our simulated model has positive long-range time-correlations.

Numerical results also show that noise changes the frequency of the periodic activity, albeit very slightly. This change in frequency cannot be seen from the experimental PSD, perhaps because it is covered by statistical errors of the measurement. A possible explanation of the fading of periodicity observed in time scale of several minutes in the experimental PSD may be found in the noise effects shown here. Other explanation can be found in this framework for this phenomena, for example , in addition to the noise effect, if there is plasticity of synapses driven by the spontaneous periodic activity itself, then the changes in connections parameters can change the frequency value and also make the network migrates from regime C to B and A regimes. This hypothesis is currently being investigated analytically.

References

[1] R. Segev, M. Benveniste, E. Hulata, N. Cihen, A. Palevski, E. Kapon, Y. Shapira. Phys. Rev. Lett. 2002 (in press).

[2] R. Segev, Y. Shapira, M. Benveniste, E. Ben-Jacob. Phys. Rev. E **64** 011920, 2001.

[3] S. Scarpetta, Z. Li, J. Hertz. NIPS 2000. Vol 13. T. Leen, T. Dietterich, V. Tresp (eds), MIT Press (2001).

[4] P. Dayan, L.F. Abbott, Theoretical Neuroscience, (MIT Press, Cambridge, 2001).

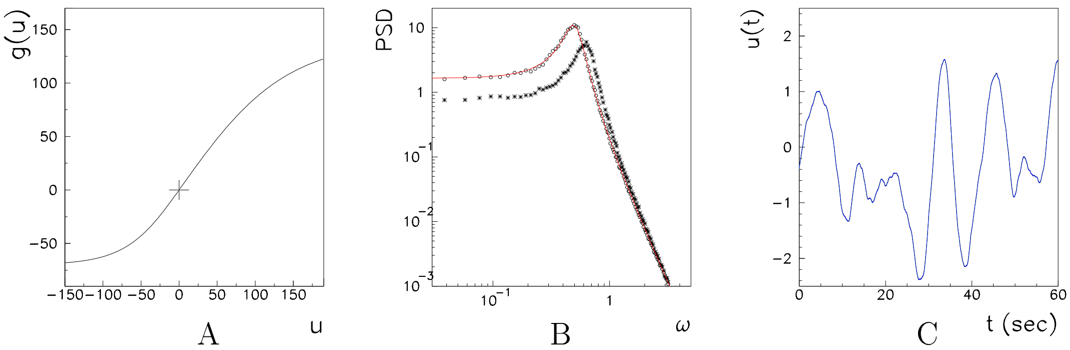


Fig. 1. A. Activation function used in simulations for excitatory units u_i. B. Power Spectrum Density of excitatory units, in the regime B, with $\Gamma = 0.0004$. Stars shows results of numerical simulations using the activation function shown in A, circles shows simulation results for the linearized system, while red solid line is theoretical prediction in linear approximation. A broad peak at $\omega \neq 0$ in the PSD is induced by noise. B. The time behavior of the state variable $u_i(t), i = 1, \ldots, N$ in the linear numerical simulation in the regime B, with $\Gamma = 0.004$. All units $u_i(t)$ shows synchronous (aperiodic) oscillatory activity. Differences in the time behavior between variables $u_i(t)$ are so small that all the lines $u_i(t)$ overlaps each other.

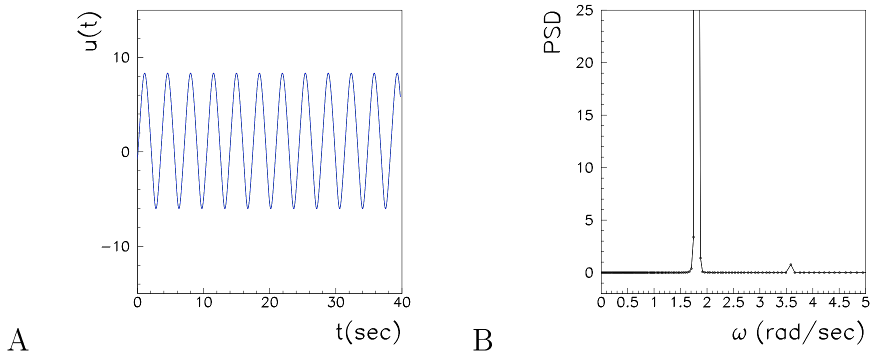
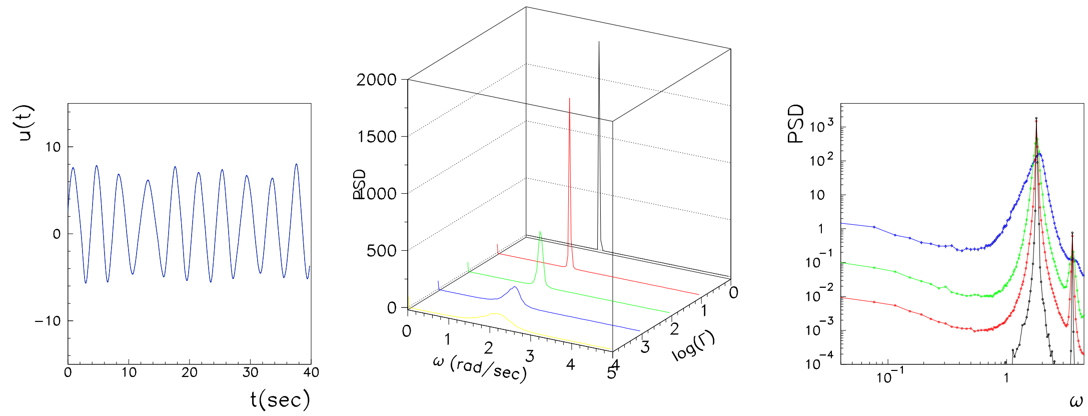


Fig. 2. A. Time behavior of the state variables $u_i(t)$ in the noiseless nonlinear numerical simulation of the isolate EI network in the regime C, using the activation function of Fig. 1.A. All the state variables $u_i(t)$ follow the same time evolution, showing clearly stable periodic synchronous activity. B. Power Spectrum Density of the excitatory unit activity shown in A. The peaks in the first and second harmonic mark clearly the collective synchronous periodic activity.



A B C

Fig. 3. A. The time behavior of the state variable $u_i(t), i = 1, \ldots, N$ in the nonlinear numerical simulation of the noisy network consisting of $N = 10$ excitatory and $N = 10$ inhibitory cells, in the regime C, with $\Gamma = 0.01$. Differences in the time behavior of the state variables $u_i(t)$ are so little that all the ten lines $u_i(t), i = 1, \ldots, 10$ overlaps each other. The activity is almost periodic, but noise decorrelates the signal over long time scales. B. Power Spectrum Density of the excitatory units activity of the noisy nonlinear networks in regime C, plotted versus the noise level $log_{10}\Gamma$. Black line: no-noise $\Gamma = 0.0$, red line: $\Gamma = 0.0001$, green line: $\Gamma = 0.001$, Blu line: $\Gamma = 0.01$, Yellow line: $\Gamma = 0.1$. Noise make the high periodic activity fades away. C. Log-log plot of the Power Spectrum Density shown in fig. B. The two high peaks in the PSD correspond to the first and second harmonics of the activity period. The low frequency power spectrum distribution shows a broad peak in $\omega = 0$.