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Vesicular mechanisms and estimates of firing probability in a network of spiking neurons

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Abstract

A neural network with mutual excitatory connections and external stimulation is investigated. The units of the network are Morris–Lecar neurons. The synaptic transmission is described at the vesicular level. Random number of activated vesicles at synaptic contacts and random quanta of released transmitter are considered. These fluctuations are applied in a form of inhomogeneous Poisson processes, at the time scale of the spike duration. The parameters of these processes depend on the presynaptic spiking activity and on the strength of afferent connections. It is shown how synchronization of the activity in the network appears. A statistical analysis of spiking times is performed, showing smooth mean behavior of response frequencies. A diffusion approximation of the network Poissonian process is derived from which an analytical formula for firing probability is calculated.

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Keywords: Conductance-based neuronal model; Vesicle; Network; Diffusion approximation; Inhomogeneous Poisson process

1. Introduction

Neuronal processes, at both the single level and the level of network, are rather naturally endowed with a stochastic character. Fluctuations of membrane potential depend on the unpredictable occurrences of presynaptic activity and the random release of quanta of neurotransmitter in synaptic transmission mechanism [1–5]. An additional aspect, which has to be considered for realistic modeling of a neuron, is the highly nonlinear dynamics of its membrane potential. Usually, the leaky integrate-and-fire model is favored for its simplicity in its single [6,7], or multi-compartment formulation [8–10]. It is almost always used as a test case for the theoretical studies, however, its lack of biological realism is simultaneously criticized. On the other hand, the increasing availability of efficient computational facilities enables assessment of the fully realistic concept of Hodgkin and Huxley models (HH) [11],

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which include the active ionic channels of numerous types. Nevertheless, many simplified models inspired by the HH system have been devoted to analysis of the spiking behavior in both the deterministic [12–14] and the stochastic case [15]. The FitzHugh–Nagumo system with a polynomial interaction [16,17], is one example of compromise between realism and tractability. Here, another similar method, inspired by the work of Lecar and Nossal [18], is employed.

Time spans of the models of synaptic transmission are usually restricted to the time intervals during which presynaptic events act on the postsynaptic membrane and thus, the time scales are of the order of interspike intervals. Here, we propose a formalization of the synaptic transmission, at a time scale of the order of spike duration, which is based on the theory of compound Poisson processes. In this approach, the number of activated vesicles at a given chemical synapse is modeled as a random number whose statistical properties depend on the presynaptic spiking activity and on the strength of interneuronal connection. Further, it is assumed that random quanta of neurotransmitter are released by each vesicle.

Three different levels of neuronal activity—synaptic transmission, membrane dynamics and network dynamics—are simultaneously investigated in this paper. It enables us to predict firing events for spiking neurons of the HH type in a network. In this way we extend some previous work [19] (see also [20]) to neuronal models of the HH type.

2. The model of membrane excitability

Before considering the structure of synaptic interactions among cells, we introduce the dynamical properties of each neuronal unit. Let us recall that for HH neurons, various ionic currents through channels may be considered with the introduction of numerous activation and inactivation variables. Technical difficulties related to nonlinearities associated with the high number of variables have implied the development of low-dimensional approximations [12].

The reduction approach of Morris and Lecar [13,14] is used here. Two kinds of channels, voltage gated Ca^{++} channels, and voltage gated delayed rectifier K^+ channels, are present in their model. The calcium current plays the role of Na^+ current in the original HH system. Thus, the membrane potential equation, under the action of an external input $I^{\text{ext}}(t)$, has the following form:

$$C\frac{dV}{dt} = f(V, X) + I^{\text{ext}}(t), \tag{2.1}$$

$$\frac{dX}{dt} = k_X(V)(\bar{X}(V) - X), \tag{2.2}$$

where

$$f(V, X) = \overline{g_{\text{Ca}}}\,\bar{m}(V)(V_{\text{Ca}} - V) + \overline{g_{\text{K}}}X(V_{\text{K}} - V) + \overline{g_{\text{L}}}(V_{\text{L}} - V). \tag{2.3}$$

The functions $\bar{m}(V)$, $\bar{X}(V)$ and $k_X(V)$ are of the form

$$\bar{m}(V) = \frac{1}{2}\left(1 + \tanh\left(\frac{V - V_1}{V_2}\right)\right), \tag{2.4}$$

$$\bar{X}(V) = \frac{1}{2}\left(1 + \tanh\left(\frac{V - V_3}{V_4}\right)\right), \tag{2.5}$$

$$k_X(V) = \varphi \cosh\left(\frac{V - V_3}{2V_4}\right). \tag{2.6}$$

In these equations, X has the meaning of the fraction of open K^+ channels, $\bar{m}(V)$ acts as an instantaneous activation of Ca^{++} channels, $k_X(V)$ is a relaxation constant for each given value of membrane potential V, C is the membrane

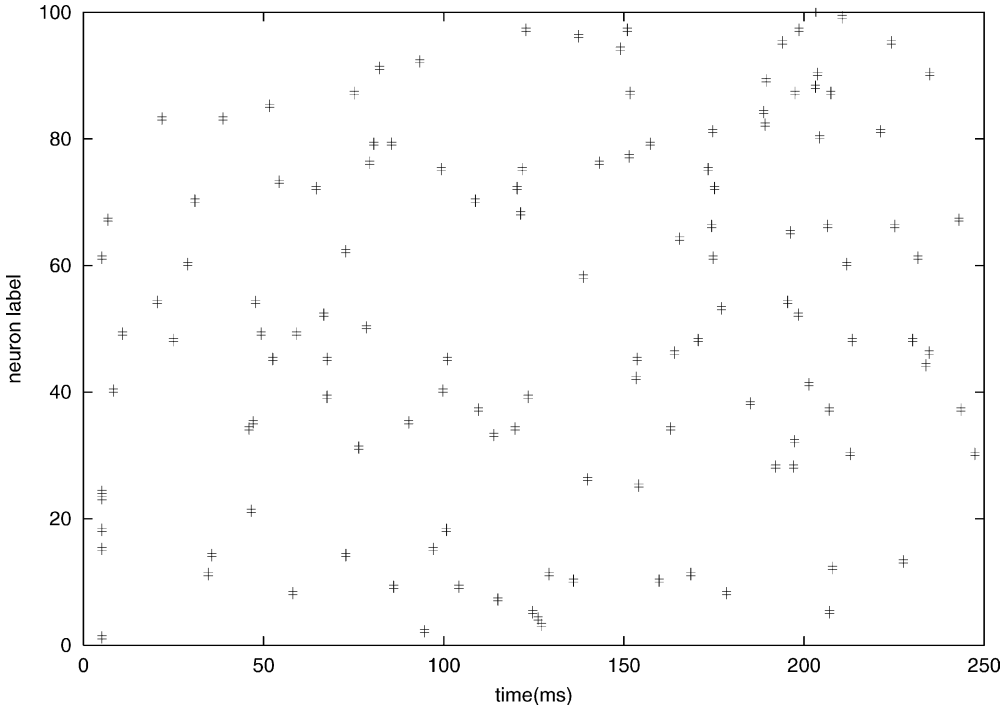

Fig. 1. The spatiotemporal structure of external stimulations acting on the neurons in the network. For each neuron, a sequence of randomly distributed stimulation instants is generated such that intervals between these instants are independent and exponentially distributed random variables. The distributions have the same parameter for all cells. The stimulations have the form of a squared pulse which is not apparent from the figure. Mean interval between pulses: 200 ms, width and amplitude of pulses: 1 ms, 3 nA.

capacitance, $\overline{g_{\mathrm{Ca}}}$, $\overline{g_{\mathrm{K}}}$ and $\overline{g_{\mathrm{L}}}$ are constants with conductance dimension, V_{Ca}, V_{K} and V_{L} are the resting potentials for the two different kinds of ions and for the leakage current, V_1, V_2, V_3, V_4 and φ are constants.

The system described by Eqs. (2.1)–(2.6) was found to be a sufficiently exact model for biologically plausible spiking activity of neurons. In particular, it is able to reproduce quite correctly the all-or-none signal emission, the emergence of oscillations associated with Hopf bifurcations leading to spike trains, bistability when a stable steady-state and a stable oscillation coexist and the burst generation with slowly varying injected current. In what follows, for a collection of N such model neurons, each neuron is submitted to stimulation of the form of train of squared pulses (representing incoming action potentials), such that the time intervals between pulses are independent and exponentially distributed random variables with a constant parameter. This represents an external input to the network (see Fig. 1) with the intrinsic properties described below.

3. Synaptic inputs as inhomogeneous compound Poisson processes

In this section, we introduce a model of synaptic transmission between cells of a network of N neurons described in Section 2. We consider chemical excitatory synapses $\{j \to i\}$, between neurons i and j, which act mainly as current sources modulated by neurotransmitters on postsynaptic receptors. The selfinteractions $\{i \to i\}$ are excluded.

For a $\{j \to i\}$ synapse, the number of activated vesicles on postsynaptic neuron i is taken as an inhomogeneous Poisson process $N_j(t)$, with time dependent parameter $\lambda_j(t)$, while the synaptic current $I_i^{\mathrm{syn}}(t)$ is given by the

(formal) derivative

$$I_i^{\mathrm{syn}}(t) = \frac{\mathrm{d}\xi_i(t)}{\mathrm{d}t} \tag{3.1}$$

of the following stochastic process:

$$\xi_i(t) = \sum_{\{j\to i\}} J_{ij} \sum_{k=1}^{N_j(t)} \alpha_k, \quad i = 1, 2, \ldots, N, \tag{3.2}$$

where J_{ij} is the synaptic efficacy of the $\{j \to i\}$ synapse that will be specified later. The $\{\alpha_k\}$, $k = 1, 2, \ldots$, are independent identically distributed random variables, with some probability density $f(\alpha)$, identical for all neurons. Taking into account the excitatory character of the synaptic junction, the support of $f(\alpha)$ is R_+ and its mean $\bar{\alpha}$ is positive. The variables $\{\alpha_k\}$ mimic the (random) quanta of neurotransmitter which are released by the activated vesicles. The processes $\{N_j(t)\}$, $j = 1, \ldots, N$, are supposed to be mutually independent and independent of the variables $\{\alpha_k\}$. It is assumed that the parameter $\lambda_j(t)$ of the Poisson process $N_j(t)$ depends on the mean presynaptic activity of the $\{j \to i\}$ synapse. It is taken as $\lambda_j(t) = \eta\Theta(\overline{V_j}(t) - \beta)$, where $\overline{V_j}(t)$ is the mean of the presynaptic membrane potential and β is a threshold value for spiking behavior. Here Θ is a step function, such that $\Theta(u(t)) = 1$ if $0 < u(t) < u_1$ and $\mathrm{d}u/\mathrm{d}t \geq 0$, u_1 being some constant, and $\Theta(u(t)) = 0$ if these conditions are not satisfied. Thus, Θ is similar to Heaviside function, with an additional condition on $u(t)$. In this way, if the presynaptic neuron j is not spiking at a time t, the parameters $\lambda_j(t)$ are equal to zero and no vesicles are activated (with no synaptic current). Otherwise, if the presynaptic neuron j is spiking at time t, the process $N_j(t)$ contributes to the generation of current on postsynaptic neuron i. The parameters $\lambda_j(t)$ then take the value η in a time interval whose length Δ is smaller than the duration of the action potential of presynaptic neuron, and are zero outside. Thus, the synaptic current $I_i^{\mathrm{syn}}(t)$ on postsynaptic neuron i is essentially composed of impulses occurring over intervals of time whose length is smaller than the time support of the presynaptic action potentials. In Fig. 2, the typical excitatory postsynaptic potentials are shown in a subthreshold or suprathreshold regime.

4. The network dynamics

The model of membrane depolarization of an individual neuron under external input, and a stochastic model of synaptic interactions between neurons connected in a network, were proposed in the preceding sections. The complete dynamical system describing the behavior of this network is the extended version of Eqs. (2.1) and (2.2), given by the following system of stochastic differential equations:

$$C\,\mathrm{d}V_i(t) = (f(V_i, X_i) + I_i^{\mathrm{ext}}(t))\,\mathrm{d}t + \mathrm{d}\xi_i(t), \tag{4.1}$$

$$\mathrm{d}X_i(t) = k_X(V_i)(\bar{X}(V_i) - X_i)\,\mathrm{d}t, \quad i = 1, 2, \ldots, N \tag{4.2}$$

where ξ_i is given by Eq. (3.2).

The network is formally based on the assumption that each neuron is connected to the remaining $N - 1$ units, however, the effect of the connection strongly depends on the values of synaptic weights J_{ij} that were chosen to obey a Gaussian function:

$$J_{ij} = \frac{J_{\max}}{N} \exp(-\gamma(i - j)^2), \quad i, j = 1, \ldots, N, \tag{4.3}$$

where the parameter γ controls the range of interactions between cells and $J_{\max}$ an amplitude factor measuring the efficiency of the synaptic contact, with respect to the size of the network.

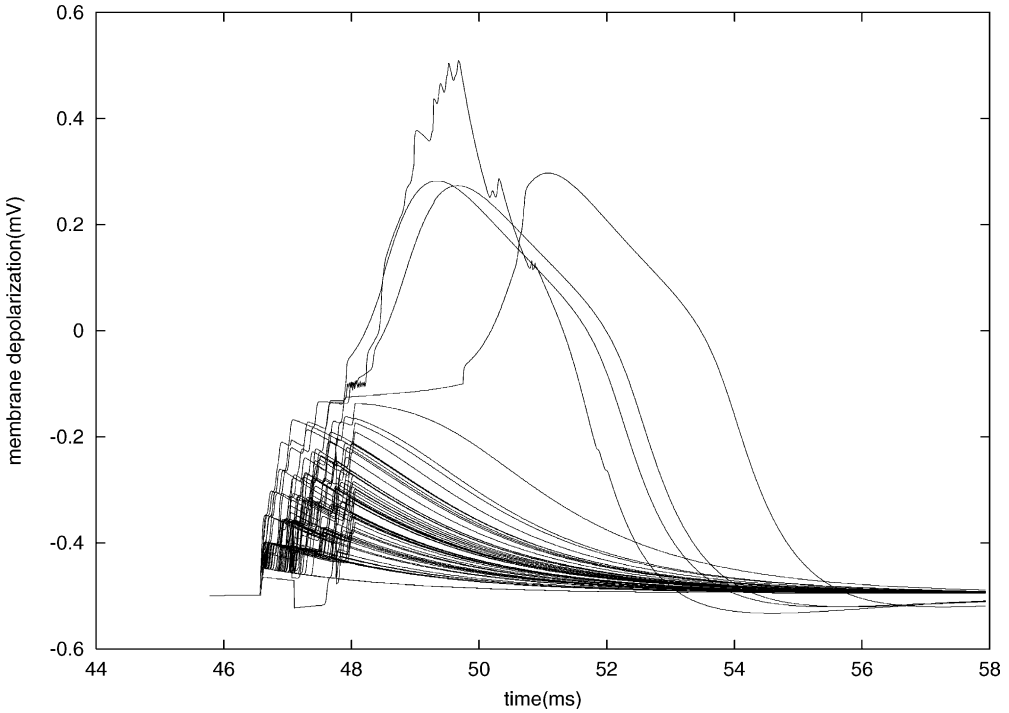

Fig. 2. The superimposed plots of the membrane depolarization in a network of 100 Morris–Lecar neuron models during synaptic current exchange. Random numbers of activated vesicles are driven by inhomogeneous Poisson processes. Subthreshold and suprathreshold behavior can be distinguished. An action potential is generated in the output of the neuron in four cases only. Neuronal parameters: $\overline{g_{\mathrm{Ca}}} = 1\,\Omega^{-1}\,\mathrm{m}^{-2}$, $V_{\mathrm{Ca}} = 1\,\mathrm{mV}$, $V_{\mathrm{K}} = -0.7\,\mathrm{mV}$, $\overline{g_{\mathrm{K}}} = 2\,\Omega^{-1}\,\mathrm{m}^{-2}$, $\overline{g_{\mathrm{L}}} = 0.5\,\Omega^{-1}\,\mathrm{m}^{-2}$, $V_{\mathrm{L}} = -0.5\,\mathrm{mV}$, $V_1 = -0.01\,\mathrm{mV}$, $V_2 = 0.15\,\mathrm{mV}$, $V_3 = 0.1\,\mathrm{mV}$, $V_4 = 0.145\,\mathrm{mV}$, $\varphi = 0.2\,\mathrm{ms}^{-1}$. Synaptic current parameters: $\bar{\alpha} = 0.04\,\mathrm{nA\,ms}$, $\overline{\alpha^2} - (\bar{\alpha})^2 = 0.001\,\mathrm{nA}^2\,\mathrm{ms}^2$, $\beta = -0.1\,\mathrm{mV}$, $\eta = 0.4\,\mathrm{ms}$. Network parameters: $N = 100$, $J_{\max} = 250$, $\gamma = 0.1$. The same parameters are used in Figs. 3–7.

The external inputs $I_i^{\mathrm{ext}}(t)$, $i = 1, \ldots, N$, appearing in Eq. (4.1), are produced by the generation of sequences of Poissonian squared pulses. Each neuron is submitted to a train of pulses which are different realizations of the same Poisson process. When a neuron receives such a pulse, it always fires because the amplitude of the pulse was chosen to be sufficiently high. In addition, a neuron may also fire due to the excitatory connections with all other neurons in the network.

In this section, numerical results analyzing this Poissonian neural network system will be presented. The synchronization of firing in the network is documented. A diffusion approximation of the stochastic system is built in the next section. The diffusion approximation method permits to obtain analytical results which are not available for the original system.

4.1. The numerical scheme

When the jth neuron fires, a sequence of instants $\{t_k^j\}$, $k = 1, 2, \ldots$, is generated, such that the time intervals are randomly distributed according to an exponential distribution with parameter $\lambda_j(t)$ (see Section 3 for the definition of this parameter). The sum $\xi_i(t) = \sum_{\{j \to i\}} J_{ij} \sum_k \alpha_k \theta(t - t_k^j)$, $i = 1, 2, \ldots, N$, is constructed with $\{\alpha_k\}$, $k = 1, 2, \ldots$, a random Gaussian sequence of numbers (as models of quanta of neurotransmitter), with parameters preventing to take negative values, and $\theta(\cdot)$ being the Heaviside function. See Fig. 3 for a representation of the current $\xi_i(t)$ in a form of a train of pulses occurring during the time duration of a presynaptic spike.

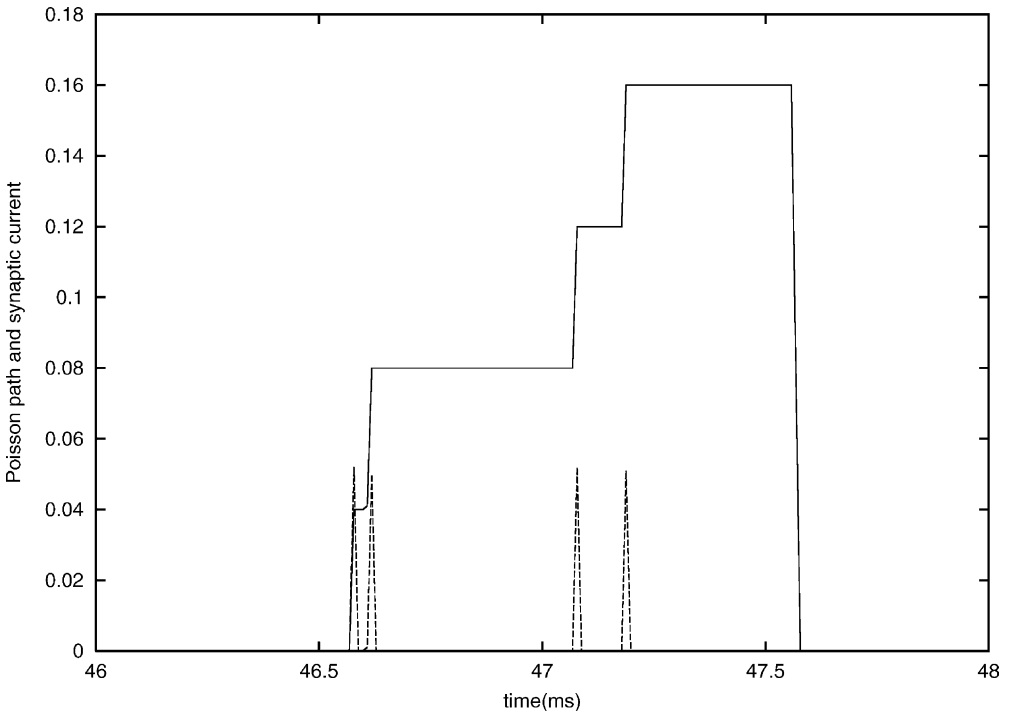

Fig. 3. An example of the postsynaptic current generated by incoming stimulation. A new vesicle is activated at each time the step function changes its value in accordance with a Poisson process. Four vesicles are activated here. Resulting synaptic currents are shown as pulses. The mechanism takes place over the time period of duration of a presynaptic spike.

The simulation time is divided into subintervals which are denoted $\{\Delta_m\}$, $m = 1, 2, \ldots$, according to the spatiotemporal structure of external stimulation and which are called time windows (see Fig. 4 for illustration). The first instant of external stimulation τ_1 is selected. It is the left-hand border (l.h.b.) of the first window Δ_1. Then, the l.h.b. τ_2 of the second window Δ_2 is chosen as the nearest instant of external stimulation over all neurons which

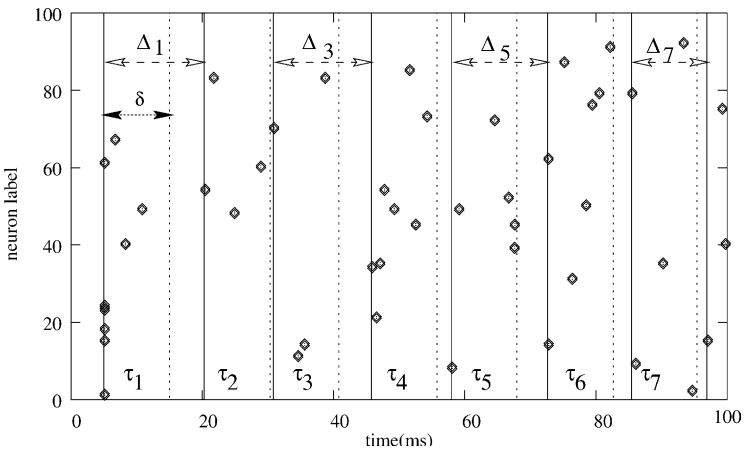

Fig. 4. The time windows for the mean response frequency analysis of the Morris–Lecar network. Windows Δ_1, Δ_3, Δ_5, Δ_7 and l.h.b. $\tau_1, \ldots, \tau_7$ of windows $\Delta_1, \ldots, \Delta_7$ are shown when $\delta = 10$ ms.

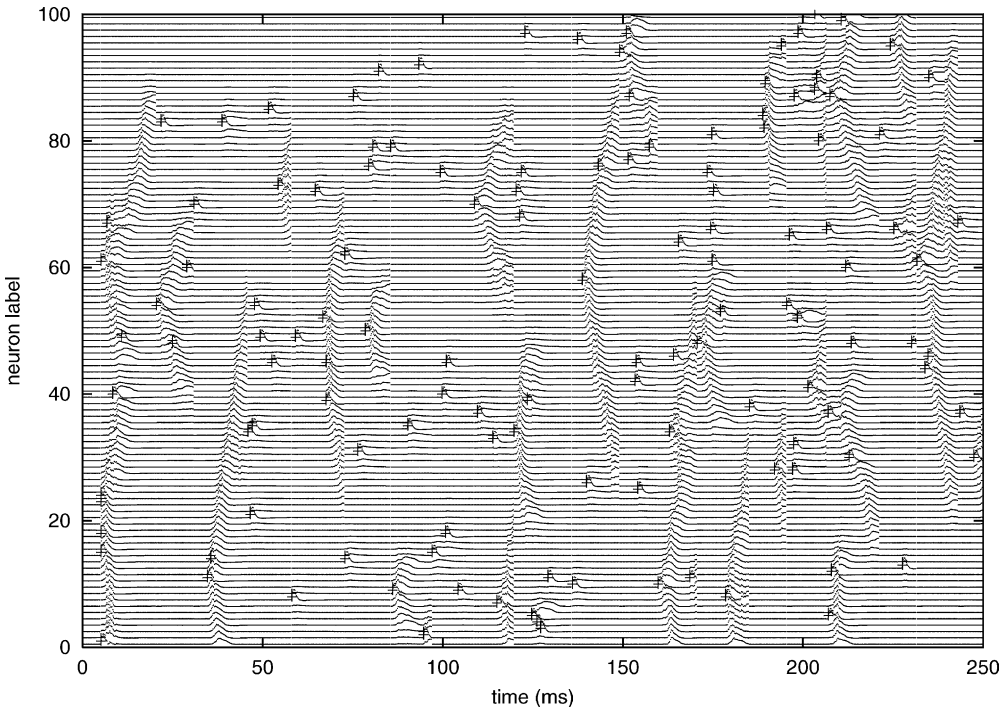

Fig. 5. The membrane depolarization of each neuron in the network (lines) with the instants of external stimulations (crosses). The external stimulation is identical with that in Fig. 1. Some of the external signals evoke a spatial wave of action potentials, whereas others only a single spike.

occurs at a time $\tau_2 > \tau_1 + \delta$, where δ is kept fixed for all windows ($\delta = 10$ ms). The procedure continues recursively. The division of time permits to study the evolution of spiking activity in the network when the fixed stimulation but variable synaptic transfer is employed.

The integration of the systems (4.1) and (4.2) was performed for sufficiently many trials, with fixed (arbitrary) choice of the external stimulations. At each time the jth neuron is spiking in a window Δ_m, with l.h.b. τ_m, the instant of firing, with τ_m taken as origin, is stored as T_j^m. T_j^m is time to the generation of the first spike produced by neuron j in the window Δ_m. It is a random variable and is called response time. In parallel with the rate coding concept [6], we calculate the inverse of the response times and call them response frequencies. A mean of response frequencies was evaluated for all neurons and for each window, under the condition of one realization of external stimulation but random variation of the synaptic mechanism.

4.2. Synchronization and mean response frequency

How the neuronal activity can be synchronized within the network if $J_{\max}$ is sufficiently high is illustrated in Fig. 5 (the number of cells is $N = 100$ and $J_{\max} = 250$). The time variation of the membrane depolarization of each cell in the network is presented with the spatiotemporal structure of external stimulations. It can be seen that external stimuli acting on some neurons induce no effect on the neighboring cells. This is due to the random nature of the synaptic contacts, for which insufficiently many vesicles are released. On the other hand, some externally induced spikes spread and create waves of action potentials across the network.

Another way to analyze the synchronization process is to present raster plots in such a way that only the spike instants of each firing neuron are indicated. The random nature of synaptic contacts is illustrated in Fig. 6a and b, where the parameters are the same as in Fig. 5, with different realization of the sequences $\{t_j^k\}$, $j = 1, \ldots, N$. Due to this variability, which may be an obstacle for a sufficiently accurate control of the dynamical behavior of the network, it is necessary to go along a multi-sample analysis. In order to achieve this goal, it will be convenient, in what follows, to characterize the firing processes of neurons in the network in the time windows $\{\Delta_m\}$, $m = 1, 2, \ldots$.

The mean response frequencies reported on the l.h.b. of each window are shown in Fig. 7 together with the spatiotemporal structure of the external inputs. It can be observed that the maximal values of the means are obtained on the l.h.b. of each window, where an external stimulation occurs. At this time, a wave may spread away from the neuron which is under this external stimulation.

5. A white noise approach

5.1. The diffusion approximation

In the previous section, a dynamical system for the network of conductance-based neural models was analyzed with numerical integration techniques. In this section, we propose an approach suitable for analytical analysis. We replace the initial dynamical systems (4.1) and (4.2), for which the synaptic interaction terms were built in terms of inhomogeneous Poisson processes by a new system based on interactions of the diffusive type, including white noise processes. Actually, due to the small contribution of quantas in small numbers of activated vesicles in the synaptic contacts, one can replace the processes $\xi_i(t)$ in (4.1) by their diffusion approximations [21,22]. These processes, which are described in terms of Brownian motion $W(t)$, are built in such a way that the first and the second differential moments of the original and the approximated process coincide. In our case, the diffusion approximation $Y_i(t)$ of $\xi_i(t)$ has a differential given by

$$\mathrm{d}Y_i(t) = \bar{\alpha} \sum_{\{j \to i\}} J_{ij} \lambda_j(t)\, \mathrm{d}t + \left(\overline{\alpha^2} \sum_{\{j \to i\}} J_{ij}^2 \lambda_j(t) \right)^{1/2} \mathrm{d}W_i(t), \quad i = 1, 2, \ldots, N, \tag{5.1}$$

where $\overline{\alpha^2}$ is the second moment of the probability density $f(\cdot)$ of the (random) quanta of neurotransmitters, $\overline{\alpha^2} = \int_{R_+} \alpha^2 f(\alpha)\, \mathrm{d}\alpha$.

Thus, Eq. (4.1) for the stochastic system of membrane potentials and activation–inactivation variables of all neurons in the network, under the action of synaptic inputs and external inputs $I_i^{\mathrm{ext}}(t)$ is replaced by the equation:

$$C\, \mathrm{d}V_i(t) = (f(V_i, X_i) + \mu_i(t) + I_i^{\mathrm{ext}}(t))\, \mathrm{d}t + \sigma_i(t)\, \mathrm{d}W_i(t), \quad i = 1, 2, \ldots, N, \tag{5.2}$$

where the drift term $\mu_i(t)$ is given by

$$\mu_i(t) = \bar{\alpha} \sum_{\{j \to i\}} J_{ij} \lambda_j(t), \tag{5.3}$$

and the diffusion coefficient $\sigma_i(t)$ is such that

$$\sigma_i(t) = \left(\overline{\alpha^2} \sum_{\{j \to i\}} J_{ij}^2 \lambda_j(t) \right)^{1/2}. \tag{5.4}$$

Eq. (4.2), of course, remains the same.

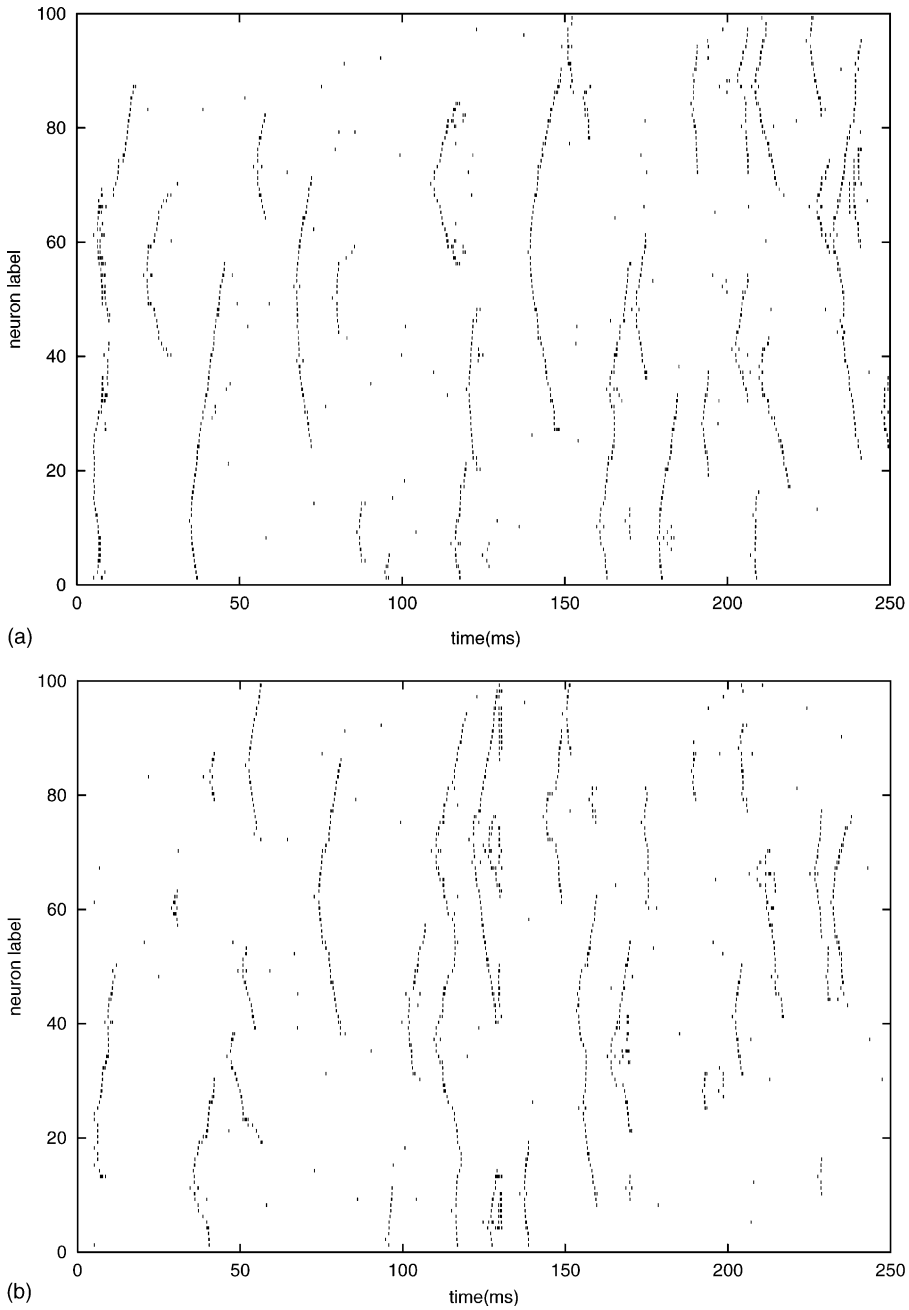

Fig. 6. The raster patterns corresponding to the depolarizations shown in Fig. 5. The firing instants of each neuron are shown as small straight lines. This presentation clearly shows two types of events, either single spikes or their waves. (a) and (b) correspond to different realizations of synaptic currents and same realization of the external input. The figures illustrate how different network outputs can be generated.

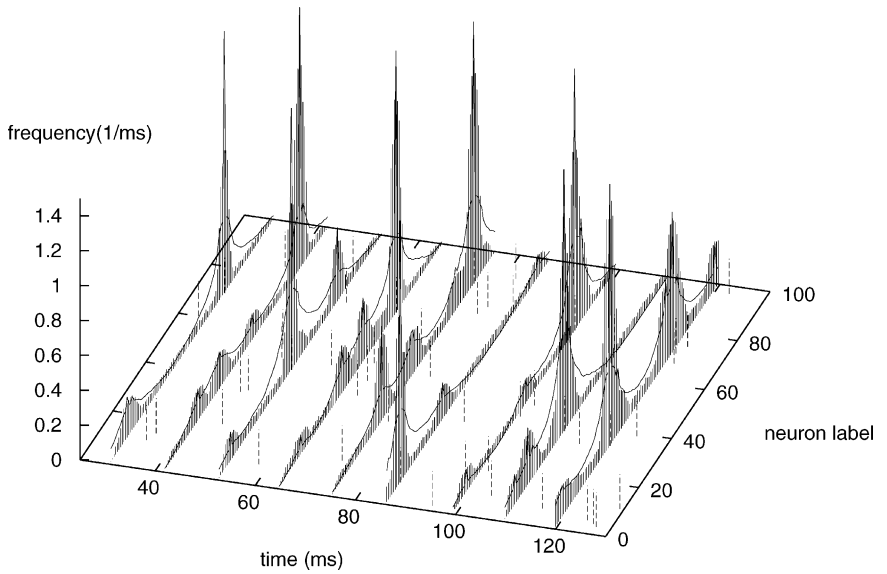

Fig. 7. Comparison of mean response frequency obtained directly from the Poissonian model and from its diffusion approximation. Nine time windows are shown. In each window, for each cell, the mean response frequency is evaluated by taking as time origin the l.h.b. of the window. Mean values are estimated from a sufficiently high number of trials and are plotted as vertical bars for each neuron at this border time. Continuous lines show mean response frequency for the diffusion approximation of the inhomogeneous Poisson vesicular processes. The spatiotemporal structure of external stimulations appears here as vertical lines (broken lines).

5.2. *The mean response frequency for the diffusion model*

The diffusion model of the network given by Eqs. (4.2) and (5.2) was integrated in the various windows $\{\Delta_m\}$, $m = 1, 2, \ldots$, which were described in Section 4.1. When one considers a given window Δ_m, it can be observed that the neurons are divided in two groups.

The first subset, denoted Σ_1, is composed of cells which are firing in this window even if they are isolated. These neurons continue to fire when connected in the network, due to the excitatory character of the interactions. The second subset, denoted Σ_2, is composed of cells which are silent during the period Δ_m when they are isolated. Then, these neurons may become active in this window when the network is interconnected. Their behavior depends on the values of efficacies J_{ij}, on the characteristics of synaptic transmission and on the network size N. For parameters used in our simulations, the ratio between number of neurons in Σ_2 and Σ_1 is approximately 5–10%. Let a cell, belonging to Σ_2, be indexed by l. In Eq. (5.3), the drift $\mu_l(t)$ contains the following two terms:

$$\mu_{l,1}(t) = \bar{\alpha} \sum_{\{j \to l\}}^{j \in \Sigma_1} J_{lj} \lambda_j(t), \qquad \mu_{l,2}(t) = \bar{\alpha} \sum_{\{j \to l\}}^{j \in \Sigma_2} J_{lj} \lambda_j(t). \tag{5.5}$$

The drift value $\mu_{l,1}(t)$ can be evaluated with better accuracy than $\mu_{l,2}(t)$ because neurons in Σ_1 were already active prior the interconnection in the network. Actually, one has

$$\mu_{l,1}(t) = \bar{\alpha} \sum_{\{j \to l\}}^{j \in \Sigma_1} J_{lj} \Theta(\overline{V_j}(t) - \beta). \tag{5.6}$$

The terms in the sum (5.6) are impulse functions, which may overlap, with time support that can be identified exactly for all presynaptic cells $j \in \Sigma_1$. The time variations of $\mu_{l,1}(t)$, being considered in the rather short time interval Δ_m are small. Thus, this term is further approximated by a constant term $\overline{\mu_{l,1}}$ defined as the temporal mean of $\mu_{l,1}(t)$ on the interval Δ_m. Concerning the drift term $\mu_{l,2}(t)$, we note that it has been evaluated in terms of presynaptic activity of cells j in Σ_2 that, if isolated, are not spiking, but that may fire when they are connected. We approximate $\mu_{l,2}(t)$ by

$$\overline{\mu_{l,2}} = \frac{\bar{\alpha}}{2} \sum_{\{j \to l\}}^{j \in \Sigma_2} J_{lj}. \tag{5.7}$$

Finally, one has

$$\mu_l(t) \simeq \overline{\mu_l} = (\overline{\mu_{l,1}} + \overline{\mu_{l,2}}), \quad t \in \Delta_m, \ \ l \in \Sigma_2. \tag{5.8}$$

In the same way as we determined the drift term, we assign the values $\overline{\sigma_{l,1}}$ to the temporal mean of $\sigma_{l,1}(t) = \left(\overline{\alpha^2} \sum_{\{j \to l\}}^{j \in \Sigma_1} J_{lj}^2 \lambda_j(t)\right)^{1/2}$ on the interval Δ_m. Let $\overline{\sigma_{l,2}} = \left((\alpha^2/2) \sum_{\{j \to l\}}^{j \in \Sigma_2} J_{lj}^2\right)^{1/2}$, so that the diffusion coefficient $\sigma_i(t)$ in Eq. (5.2), for $t \in \Delta_m$, acquires the following approximated value:

$$\sigma_l(t) \simeq \overline{\sigma_l} = (\overline{\sigma_{l,1}} + \overline{\sigma_{l,2}}), \quad t \in \Delta_m, \ \ l \in \Sigma_2. \tag{5.9}$$

Therefore, for a neuron from Σ_2, when connected into the network, stochastic equation (5.2) is replaced, for a given $t \in \Delta_m$, by the equation

$$C\,\mathrm{d}V_l(t) = (f(V_l, X_l) + \overline{\mu_l} + I_i^{\mathrm{ext}}(t))\,\mathrm{d}t + \overline{\sigma_l}\,\mathrm{d}W_l(t), \quad l \in \Sigma_2. \tag{5.10}$$

The mean response frequency analysis was performed for the diffusion approximation along the same lines as for the initial system, built in terms of Poisson processes (Sections 4.1 and 4.2). If $\widetilde{T}_j^{\,m}$ is the response time for the system (5.10) (and (4.2)), for the jth neuron in the mth window, the means of $\{(\widetilde{T}_j^{\,m})^{-1}\}$ for all neurons $j = 1, \ldots, N$ in the network, and all windows $m = 1, 2, \ldots$, were evaluated for sufficiently many trials. In Fig. 7, the graphs of these means are shown where j varies from 1 to 100, in each window Δ_m, $m = 1, \ldots, 9$. The obtained curves show a reasonable agreement with the mean response frequency obtained from the simulation with Poisson processes.

5.3. The tangent mapping of the deterministic part

In order to get more information about the nonlinear stochastic process (5.10) (and (4.2)) in the time window Δ_m, we look for its dynamics in the vicinity of well identified singular points, in the absence of noise ($\sigma_i(t) = 0$), and of external stimulation ($I_i^{\mathrm{ext}}(t) = 0$). There are at most three such singular points, for all possible realistic values of the parameters V_1, V_2, V_3, V_4, φ, V_{Ca}, V_{K}, $\overline{g_{\mathrm{Ca}}}$, $\overline{g_{\mathrm{K}}}$, $\overline{g_{\mathrm{L}}}$ and C. Thus, for each $l \in \Sigma_2$, let us denote (V_l^S, X_l^S) the components of a singular point S, which satisfy the equations:

$$f(V_l^S, X_l^S) + \overline{\mu_l} = 0, \tag{5.11}$$

$$X_l^S = \overline{X_l}(V_l^S), \quad l \in \Sigma_2. \tag{5.12}$$

This point is a resting state of the system. The structure of the isoclines for such a system is of N shaped and parabolic type [14] in the two-dimensional phase space (V_l, X_l) for each l. Let us now expand the deterministic part around S. The tangent mapping A_l around such a point S has the following components of a 2×2 matrix:

$$A_{l,11} = -\overline{g_{\mathrm{Ca}}}\left(\frac{\mathrm{d}\bar{m}}{\mathrm{d}V_l}(V_l^S, X_l^S)(V_l^S - V_{\mathrm{Ca}}) - \bar{m}(V_l^S, X_l^S)\right) - \overline{g_{\mathrm{K}}} X_l^S - \overline{g_{\mathrm{L}}}, \tag{5.13}$$

$$A_{l,12} = -\overline{g_K}(V_l^S - V_K), \tag{5.14}$$

$$A_{l,21} = -\frac{dk_X}{dV_l}(V_l^S, X_l^S)(\bar{X}(V_l^S) - X_l^S) + k_X(V_l^S)\frac{d\bar{X}}{dV_l}(V_l^S, X_l^S), \tag{5.15}$$

$$A_{l,22} = -k_X(V_l^S). \tag{5.16}$$

Thus, denoting $v_l = (V_l - V_l^S, X_l - X_l^S)$, $(-\eta_{lj})_{j=1,2}$ the eigenvalues of A_l and U_l the transformation which diagonalizes A_l (which can be characterized), in the basis of eigenvectors of A_l, one obtains the following system of stochastic equations describing the dynamics around S:

$$d\chi_l(t) = L_l\chi_l(t)\,dt + K_l\,dz_l(t), \quad l \in \Sigma_2, \quad t \in \Delta_m, \tag{5.17}$$

where $\chi_l = U_l v_l$, L_l the diagonal matrix, $(L_l)_{j,k=1,2} = -\eta_{lj}\delta_{j,k}$, $\delta_{j,k}$ the Kronecker symbol, K_l the vector with components $U_{l,11}$ and $U_{l,12}$, and $z_l(t) = \overline{\sigma_l}W_l(t)$. Using Eq. (5.17), firing probability at time t can be calculated.

5.4. Separatrix condition and estimate of firing probability

Let us assume that parameters of individual cells are such that η_{l1} and η_{l2} are positive (condition (a)). This condition is naturally fulfilled by choosing parameters of the Morris–Lecar system such that the neuron model can fire. Thus Eq. (5.17) describes two independent Ornstein–Uhlenbeck processes with drifts η_{l1} and η_{l2} and diffusion coefficients $D_{l,1m} = (U_{l,1m})^2(\sigma_l)^2$, $m = 1, 2$, $l \in \Sigma_2$. The transition probability density function for these processes, for $t \in \Delta_m$ and τ the l.h.b. of Δ_m, is given by

$$\rho(\chi_{l1}, \chi_{l2}, t|\omega_{l1}, \omega_{l2}, \tau) = \prod_{m=1,2}\left\{\sqrt{\frac{\eta_{lm}}{\pi\mu_{lm}(t-\tau)}}\exp\left\{\frac{-\eta_{lm}(\chi_{lm} - \omega_{lm}\exp(-\eta_{lm}(t-\tau))^2}{\mu_{lm}(t-\tau)}\right\}\right\}, \quad l \in \Sigma_2, \tag{5.18}$$

with $\mu_{lm}(t) = D_{l,1m}(1 - \exp(-2\eta_{lm}t))$ and ω_{l1}, ω_{l2} are values of the stochastic process at time τ which depend on the external stimulations acting as brief current pulses.

Now, the behavior of the neuron with index $l \in \Sigma_2$, under stochastic synaptic inputs crucially depends on the nature of its resting state S, as it was derived in Eqs. (5.11) and (5.12). Two generic cases can occur: the first corresponds to S as a unique stable resting state. The second is associated to the existence of three singular points with one as a saddle point. When there exists a saddle point's stable manifold, namely when the threshold is strict and corresponds to a separatrix, the cell has two distinct behaviors: spike emission or silence according to the position of initial conditions with respect to the separatrix. We assume (condition (b)) that the parameters of individual cells are such that this is the case and we follow the method which was used in [18] (for different neural models and different inputs) to estimate the firing probabilities. Thus, the question whether a neuron fires or remains silent is related to the crossing of the separatrix. If η_{l1} denotes the eigenvalue of the tangent mapping for the unstable manifold around the saddle point S, the process crosses the separatrix if the first component χ_{l1} of χ_l is positive. Thus, in our case (conditions (a) and (b)), the probability of firing at time t is given by

$$\begin{aligned} P_t(\text{firing}) &= \text{Prob}(\chi_{l1}(t) > 0|\chi_{l1}(\tau) = \omega_{l1}) \\ &= \frac{1}{2}\left\{1 + \text{erf}\left(\sqrt{\frac{\eta_{l1}}{D_{l11}(1 - \exp(-2\eta_{l1}(t-\tau)))}}\omega_{l1}\exp(-\eta_{l1}(t-\tau))\right)\right\}, \quad l \in \Sigma_2, \end{aligned} \tag{5.19}$$

where erf is the error function. Here, the terms η_{l1} and $D_{l,11}$ depend on the state of all neurons of the network and on the values of synaptic efficacies J_{ij} through the drift terms $\overline{\mu_l}$ and the diffusion coefficients $\overline{\sigma_l}$ as they appear in

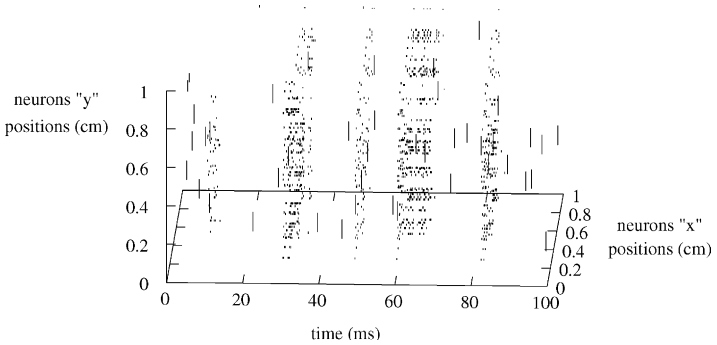

Fig. 8. The raster patterns for neurons in a two-dimensional bounded domain. Neurons are uniformly distributed in $[0, 1] * [0, 1]$. The spatiotemporal structure of their spiking activity is shown (points). External stimulations are of the same type as for the one-dimensional network (segments). Values of the parameters are the same as used in Fig. 2, $\chi = 20\,\mathrm{cm}^{-2}$.

Eqs. (5.8) and (5.9). These diffusion parameters themselves depend on the statistical characteristics $\bar{\alpha}$ and $\overline{\alpha^2}$ of the vesicular variables occurring at the synaptic contacts.

6. Conclusions

We have investigated an integrated model of a neural network which includes three levels of description of biophysical reality that are usually studied separately. In this situation, of course, many features of real systems were not taken into account. Among most important of these is the absence of inhibitory connections in the network. The other simplification we used is that the neurons interact with each other without time delay. It means that every neuron obtains synaptic current almost immediately, delayed only by the onset of the synaptic transmission, after the input neuron fires. If this assumption is removed, the observed spatiotemporal patterns of firing would have more variable forms. Another simplification employed is that the network is practically linear. This is caused by one-dimensional Gaussian distribution describing the synaptic weights. If a two-dimensional distribution is used, then a three-dimensional representation of the spiking activity in the network shows a cluster organization of cells (see Fig. 8, where the network is composed of cells which are randomly distributed in the bounded domain $[0, 1] * [0, 1]$ of R^2 with a uniform distribution and the connection matrix is such that $J_{ij} = (J_{\max}/N) \exp(-\chi \| \overrightarrow{U_i} - \overrightarrow{U_j} \|^2)$, $i, j = 1, \ldots, N$, where $\overrightarrow{U_i} \in R^2$, $i = 1, 2, \ldots, N$ are the locations of the cells, $\| \overrightarrow{U_i} - \overrightarrow{U_j} \|$ is the distance between cells i and j, and χ is a parameter).

The studied model shows that in response to external stimulation a synchronized firing of the network arises. Despite the fact that this synchronization is random, mean response frequencies exhibit smooth behavior which is obtained from the numerical simulation of the discrete stochastic process as well as its diffusion approximation. Finally, the evolution of the deterministic part of the model is given in the vicinity of the singular points and an analytical formula for the probability of a firing at a given time is calculated.

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References

[1] M.R. Bennett, J.L. Kearns, Statistics of transmitter release at nerve terminals, Prog. Neurobiol. 60 (2000) 545.
[2] P. Faure, D. Kaplan, H. Korn, Synaptic efficacy and the transmission of complex firing patterns between neurons, J. Neurophysiol. 84 (2000) 3010.
[3] C. Auger, A. Marty, Quantal currents at single-site central synapses, J. Physiol. (London) 526 (2000) 3.
[4] F. Ventriglia, V. Di Maio, A Brownian simulation model of glutamate synaptic diffusion in the femtosecond time scale, Biol. Cybern. 83 (2000) 93.
[5] V. Matveev, X. Wang, Implications of all-or-none synaptic transmission and short-term depression beyond vesicle depletion: a computational study, J. Neurosci. 20 (2000) 1575.
[6] W. Gerstner, W.M. Kistler, Spiking Neuron Models, Cambridge University Press, Cambridge, 2002.
[7] T. Shimokawa, K. Pakdaman, T. Takahata, S. Tanabe, S. Sato, A first passage-time analysis of the periodically forced noisy leaky integrate-anf-fire model, Biol. Cybern. 83 (2000) 327.
[8] P.C. Bressloff, Dynamics of compartmental model integrate-and-fire neuron with somatic potential reset, Physica D 80 (1995) 399.
[9] P. Lansky, R. Rodriguez, Two-compartment stochastic model of a neuron, Physica D 132 (1999) 267.
[10] R. Rodriguez, P. Lansky, A simple stochastic model of spatially complex neurons, Biosystems 58 (2000) 49.
[11] A.L. Hodgkin, A.F. Huxley, A quantitative description of membrane current and its application to conduction and excitation in nerve, J. Physiol. (London) 117 (1952) 500.
[12] T.B. Kepler, L.F. Abbott, E. Marder, Reduction of conductance-based neuron models, Biol. Cybern. 66 (1992) 381.
[13] C. Morris, H. Lecar, Voltage oscillations in the barnacle giant muscle fiber, Biophys. J. 35 (1981) 195.
[14] J. Rinzel, G.B. Ermentrout, Analysis of neural excitability and oscillations, in: C. Koch, I. Segev (Eds.), Methods of Neural Neuronal Modelling: From Synapses to Networks, MIT Press, Cambridge, MA, 1989 (revised 1998).
[15] H.C. Tuckwell, Introduction to Theoretical Neurobiology, Cambridge University Press, Cambridge, 1988.
[16] H. Tuckwell, R. Rodriguez, Analytical and simulation results for stochastic Fitzhugh–Nagumo neurons and neural networks, J. Comput. Neurosci. 5 (1998) 91.
[17] B. Lindner, L. Schimansky-Geier, Analytical approach to the stochastic FitzHugh–Nagumo system and coherence resonance, Phys. Rev. E 60 (1999) 7270.
[18] H. Lecar, R. Nossal, Theory of threshold fluctuations in nerves I, II, Biophys. J. 11 (1971) 1048.
[19] P. Blanchard, P. Combe, H. Nencka, R. Rodriguez, Stochastic dynamical aspect of neuronal activity, J. Math. Biol. 31 (1993) 189.
[20] L. Ingber, Statistical mechanics of neocortical interactions, Physica D 5 (1982) 83.
[21] P. Lansky, On approximations of Stein's neuronal model, J. Theoret. Biol. 107 (1984) 631.
[22] L. Ricciardi, Diffusion Processes and Related Topics in Biology, Springer, Berlin, 1977.