

Analysis of Bursting in Stein's Model with Realistic Synapses

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Abstract. By introducing realistic synaptic potentials to the Stein's stochastic model of neuron we obtain a new model able to produce bursting activity. The mechanism of burst initiation is described and basic characteristics, such as period of bursting, period of quiescence and frequency of spikes are calculated from model parameters.

Key words: Bursting activity — Synapse — Stochastic neuronal model

Bursts are series of action potentials on neuronal membrane alternating with relatively long quiescent periods. Bursting activity is a very characteristic neuronal behavior and it can often be found in the recorded action potential trains of some neurons. In literature we can find two main groups of mathematical models of bursting neurons: a) conductance models based on Hodgkin and Huxley equations with certain dependency between ionic currents (Av-Ron et al. 1993), or, b) models of simple neural networks with a certain kind of connectivity. Outputs of stochastic models, like the Stein's model, usually are of Markovian character and they therefore cannot generate spike patterns such as bursts. This article describes a new stochastic model based on Stein's neuronal model, with synapses corresponding to the conductance models. This model is able, under certain conditions, to produce bursting activity.

Stein's neuronal model (Tuckwell 1979; Lánský 1983), is very often used by neurobiologists for its efficiency and relative simplicity. Stochastic inputs to the neuronal cell are modelled by step functions that increase or decrease the membrane potential at random time points, the differences of which have an exponential distribution. Contributions of many synaptic inputs (point processes) converge to Poisson process (consequence of Palm-Khintchine theorem). Therefore, synaptic activation is described by two independent Poisson processes (one for excitation, one for inhibition), that increase or decrease the trajectory of the stochastic process by a and i , respectively. During intervals between the excitatory or the inhibitory

synaptic activation the membrane potential drops to zero with the relaxation time constant τ_a . When for the first time potential $X(t)$ exceeds the threshold level S , we suppose that the neuron produces spike. Then $X(t)$ is reset and starts again from the value $X(0)$. Therefore, we describe neural firing as the first passage time of the stochastic process $X(t)$. The interspike interval (ISI) is a random variable T given by relationship:

$$T = \inf \{t \geq 0, X(t) > S\} \quad (1)$$

where the stochastic process $X(t)$ is determined by equation:

$$dX(t) = -\frac{1}{\tau_a} X(t)dt + a dN^+(t) + i dN^-(t) \quad (2)$$

where the initial value $X(0) < S$, and $\tau_a > 0$ is the membrane time constant, $a > 0$, $i < 0$ are the magnitudes of the synaptic activation steps, $N^+(t)$, $N^-(t)$ are two independent homogeneous Poisson processes with initial values $N^+(0) = N^-(0) = 0$ and with intensities λ and ω .

A simple and physiologically reasonable model of time dependent potential of a single synapse is the alpha function (Bernard et al. 1994):

$$h(t) = \frac{t}{\tau^2} \exp\left(-\frac{t}{\tau}\right) \quad (3)$$

where τ is the synaptic time constant. In case of synaptic activation at different time points the total synaptic potential corresponding to one mediator is

$$h_s(t) = \sum_i h(t - t_i) \text{Heaviside}(t_i) \quad (4)$$

where t_i are time points of synaptic activation. In case of more synaptic mediators we sum potentials $h_s(t)$ with different weights a and synaptic time constants τ , as will be shown later.

In the original Stein's model the synaptic activations $dN^+(t)/dt$ and $dN^-(t)/dt$ are summations of delta functions (Dirac distributions). Let us replace each delta function by alpha function (3) and use different time constants for excitatory and inhibitory activation. Then, activations $dN^+(t)/dt$ and $dN^-(t)/dt$ are replaced by functions $h_s^+(t)$ and $h_s^-(t)$ in the form of Equation (4) (Fig. 1). Functions $h_s^+(t)$ and $h_s^-(t)$ are not reset after spike. The model is first passage time of the stochastic process $X(t)$ described by equation:

$$dX(t) = -\frac{1}{\tau_a} X(t)dt + a h_s^+(t)dt + i h_s^-(t)dt \quad (5)$$

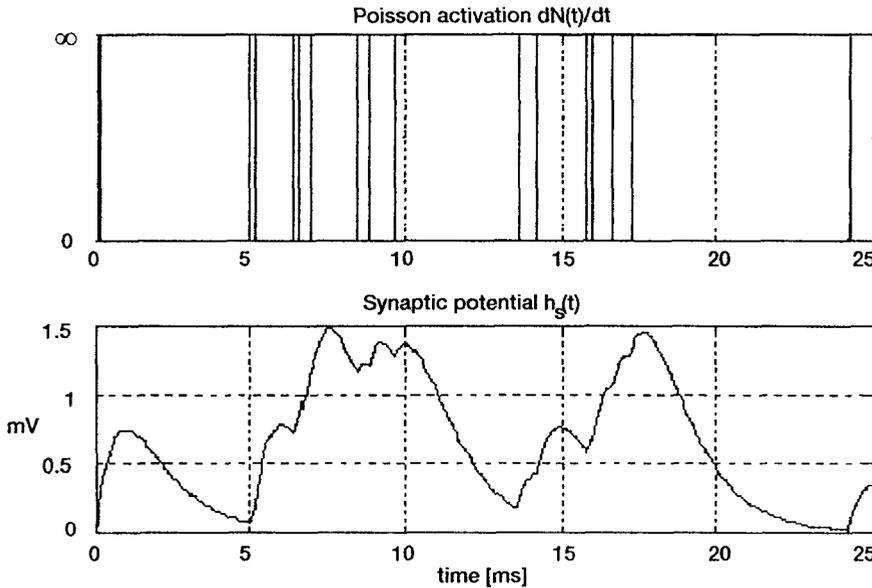


Figure 1. Poisson activation (delta functions) and the corresponding realistic synaptic potential $h_s(t)$. Parameters: Poisson intensity $\lambda = 1$, synaptic time constant $\tau = 1$.

with initial condition $X(0) = 0$, where a and ι are weights of synaptic excitation and inhibition. τ_a is the relaxation constant of axon membrane, and functions $h_s^+(t)$ and $h_s^-(t)$ are given by (4) with activation time instants t_i^+ and t_i^- determined by Poisson processes $N^+(t)$ and $N^-(t)$, and with time constants τ^+ and τ^- , resp. Equation (5) describes a model of neuron with many synapses corresponding to one excitatory and one inhibitory mediator. This model will be generalised later.

Under certain conditions, we can observe bursting activity of the modified Stein's neuronal model. The bursting mechanism can be explained in the following way (Fig. 2): a realistic synapse is a time invariant dynamic system that works as low-pass filter. High frequencies at the output are suppressed to such an extent that the period of changes of the synaptic potential is longer than the mean interspike interval. Then, if the potential on synapses is higher than a certain activation level, the neuron can fire several times, which can be considered a burst. If the synaptic potential is less than the activation level, the neuron does not fire: this is the quiescent period between bursts. Intuitive conditions of bursting are: (i) the mean value of the total synaptic potential should be close to the activation threshold, (ii) at least one synaptic mediator has to have time constant greater than the relaxation time constant of the axonal membrane, and (iii) variance of

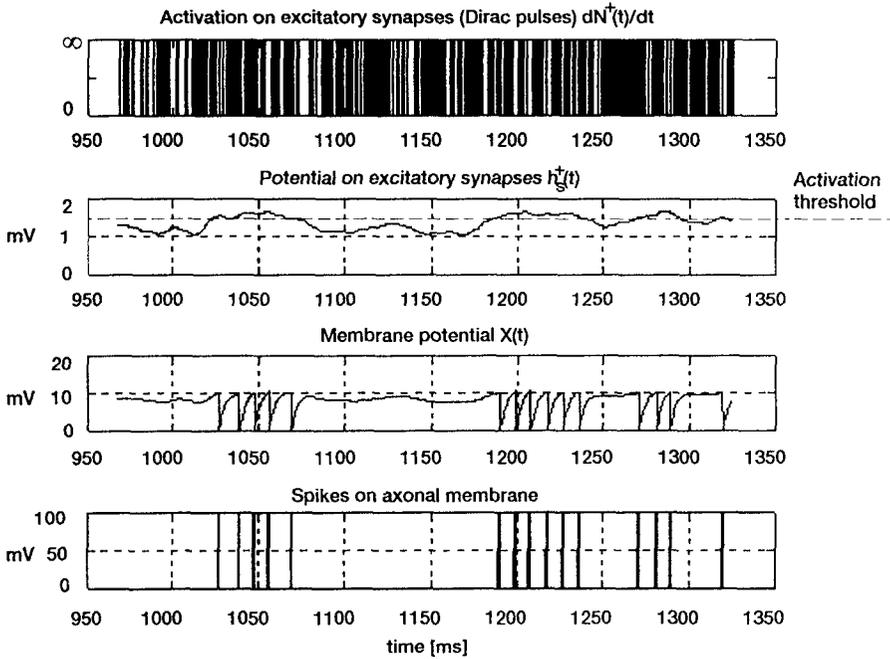


Figure 2. Schematic representation of burst initiation caused by realistic synapses. Parameters: Stein's model without inhibition, Poisson intensity $\lambda = 1.38$, membrane relaxation time constant $\tau_a = 5.8$ ms, synaptic time constant $\tau = 30$ ms, threshold $S = 10$ mV. Spikes on the axonal membrane were added artificially to show the time points when the membrane potential reaches the threshold.

quick synapses should be less than variance of slow synapses. Fig. 2 shows the mechanism of bursting activity of the Stein's model with realistic synapses.

A signal with bursts is described by three parameters: mean period of bursting, T_B , mean period of quiescence between bursts, T_Q , and mean frequency of spikes in bursting period, f_b . Other characteristics often used in neurobiology, such as long tail of ISI histogram or line-like pattern on scatter plot of i -th and $(i + 1)$ -th spike time differences, are not very convenient for analytical purposes.

First, we find the analytical solution for the simplified model with a large number of synapses, corresponding to one excitatory mediator, and then we will generalize it for more synaptic mediators. The scheme of the simplified model, with the parameters used in the analysis, is in the Fig. 3.

This model is described by differential equation:

$$dX(t) = -\frac{1}{\tau_a} X(t) dt + h_s(t) dt \quad (6)$$

with initial condition $X(0) = 0$, and $h_s(t)$ is given by (4) with activation time points

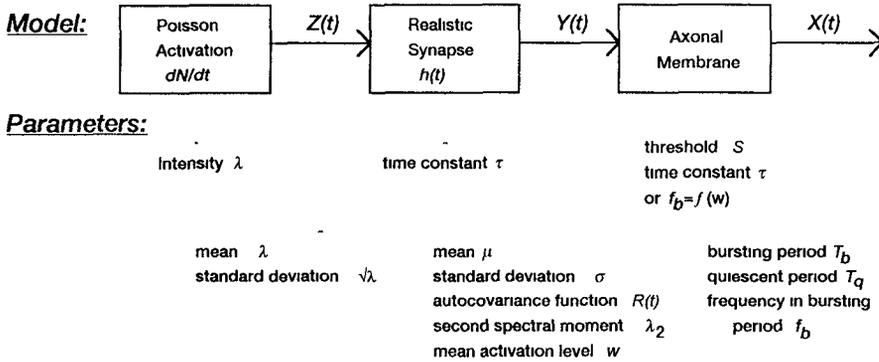


Figure 3. Schematic representation of Stem's model with realistic excitatory synapses. signals and parameters used in the analysis. Signal $Z(t)$ is an approximation of dN^+/dt , signal $Y(t)$ is an approximation of $h(t)$

t_i determined by the Poisson process $N^+(t)$. Following for example the procedure of Lánský (1983) we approximate the Poisson process $N^+(t)$ by the Wiener process with drift $V(t) = \lambda t + \sqrt{\lambda}dW(t)$, where $W(t)$ is standard Wiener process. The signal $dN^+(t)/dt$ can be approximated as $Z(t) = dV(t)/dt = \lambda + \sqrt{\lambda}dW(t)/dt$, which is white noise with a normal distribution, mean λ , and standard deviation $\sqrt{\lambda}$. Signal $Z(t)$ passes through the time invariant linear system of a realistic synapse with the impulse transfer function $h(t)$, which has Laplace transform $H(s) = 1/(1 + \tau s)^2$. The signal $Y(t)$ at the synaptic output has the autocovariance function $R(t) = (\lambda/4) (|t|/\tau^2 + 1/\tau) \exp(-|t|/\tau)$, mean $\mu = \lambda$ and standard deviation $\sigma = (1/2)\sqrt{\lambda/\tau}$. From Rice's formula (Leadbetter et al 1983) we get the mean number of upcrossings of the level x per unit time interval of the process $Y(t)$:

$$N_U = \frac{\sqrt{\lambda_2}}{2\pi\sigma} \exp\left(-\frac{(x - \lambda)^2}{2\sigma^2}\right) \tag{7}$$

where $\lambda_2 < \infty$ is the second spectral moment, which can be obtained as $\lambda_2 = -R''(0) = \lambda/(4\tau^3)$. After some algebra using Rice's formula (7) for process $Y(t)$ we get the period of bursting, T_B , as the average length of the interval between upcrossing and downcrossing of the level x , and the period of quiescence, T_Q , as the average length of the interval between downcrossing and upcrossing:

$$T_B = \frac{\Phi(-u)}{N_U} = \frac{2\pi\sigma\Phi\left(-\frac{(x - \mu)}{\sigma}\right)}{\sqrt{\lambda_2} \exp\left(-\frac{(x - \mu)^2}{2\sigma^2}\right)} \quad T_Q = \frac{\Phi(u)}{N_U} = \frac{2\pi\sigma\Phi\left(\frac{(x - \mu)}{\sigma}\right)}{\sqrt{\lambda_2} \exp\left(-\frac{(x - \mu)^2}{2\sigma^2}\right)} \tag{8}$$

where $\Phi(u)$ is the normal distribution function, and $x = S/\tau_a$ is the activation threshold for Stein's model. Mean bursting frequency f_b is obtained from Equation (6) for $h_s(t) = \text{const} = w$ as

$$f_b = -\frac{1}{\tau_a \ln\left(\frac{w\tau_a - S}{W\tau_a}\right)} = -\frac{1}{\tau_a (\ln(\tau_a w - S) - \ln(\tau_a) - \ln(w))} \quad (9)$$

where w is the mean level of the synaptic potential $Y(t)$ above the activation threshold $x = S/\tau_a$:

$$w = \mu + \sigma \frac{\exp\left(\frac{(x - \mu)^2}{2\sigma^2}\right)}{\sqrt{2\pi}\Phi\left(-\frac{(x - \mu)}{\sigma}\right)} \quad (10)$$

The model with several excitatory and inhibitory mediators is obtained from model (6) in Fig. 3 by replacing signal $Y(t)$ by weighted sum of signals $Y_k(t)$ corresponding to the different mediators. The model is described by differential equation:

$$dX(t) = -\frac{1}{t_a}X(t)dt + \sum_k a_k h_s^{(k)}(t)dt \quad (11)$$

where $k = 1, 2, \dots$ denotes the synaptic mediator, functions $h_s^{(k)}(t)$ are given by (4) with time constants $\tau^{(k)}$, and weights a_k and activation time instants $t_i^{(k)}$ determined by independent Poisson processes $N^{(k)}(t)$. Summation of non-correlated normal processes $N(\mu, \sigma)$ with weights a_k is also a normal process with a mean $\mu = \sum(a_k \mu_k) = \sum(a_k \lambda_k)$, variance $\delta^2 = \sum(a_k^2 \sigma_k^2) = 1/4 \sum(a_k^2 \lambda_k \tau_k)$ and a second spectral moment $\lambda_2 = 1/4 \sum(a_k^2 \lambda_k / \tau_k^3)$. Spike frequency in burst periods, the period of bursting and the period of quiescence are obtained by substitutions to (8), (9) and (10).

The following Table compares simulation results of about 1200 spikes in each file, with calculated parameters. Values show good correspondence. The differences can be explained by approximation of signal $dN^+(t)/dt$ by white noise, and by the fact that to evaluate a signal obtained by simulation, the minimum length of the quiescent period had to be set to distinguish and to separate bursting periods. In signals where bursts are not very clear this value cannot be determined exactly. Programs for simulations were written in Matlab and run on a PC 486 and a HP 9000 (Hrubý 1994). Due to an enhanced computation speed we used the differential equations method for the problem of summation of synaptic potentials (Bernard et al. 1994).

In all models described in this article the action potential does not reset synaptic potentials, as it is in the original Stein's model, i.e. after each spike some level of

Table 1. Computer simulation results and calculated parameters.

Model parameters					Calculation and simulation results						
Solution	λ	τ	τ_a	S	μ	σ	$1/N_U$	T_B	T_Q	w	f_b
Simulation	2	10	0.5	1.1	2.041	2.269	95.77	18.60	92.76	2.3266	0.680
Calculation	2	10	0.5	1.1	2.000	2.236	93.73	17.39	76.34	2.3222	0.680
Simulation	1.7	30	5.8	10	1.7002	0.115	192.65	79.87	109.53	1.817	0.0557
Calculation	1.7	30	5.8	10	1.7000	0.119	192.41	80.744	111.66	1.810	0.0567

potential can remain on synapses. The fact makes our model similar to the double compartment model of Rospars and Lánský (1993). In our opinion, this arrangement better describes the real situation on the cell membrane and this feature is also essential for generating bursts. A more exact model is obtained by introducing reversal potentials to the Stein's model with realistic synapses, because slow synaptic currents, e.g. associated with GABA B, or NMDA receptors, are voltage dependent and they are open only at a relatively high level of stimulation. These modifications will be referred to a separate article.

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