Sources of periodical force in noisy integrate-and-fire models of neuronal dynamics

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A standard stochastic integrate-and-fire model used for a long time as the simplest realistic neuronal descriptor has been studied recently in the presence of deterministic time periodic driving force. The relevance of this modification for the description of biological systems is discussed. In this way two possible sources of periodic modulation are discovered. [S1063-651X(97)11602-6]

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Stochastic processes have frequently been employed in theoretical neurobiology in attempts to explain the mechanism of neuronal firing (see [1] for reviews). In most of these neuronal models, one-dimensional stochastic processes serve to describe the membrane depolarization whose development depends on the integrated activity of synaptic inputs. When the membrane potential of a model neuron exceeds a fixed threshold level for the first time, the neuron fires, i.e., produces an action potential. After each firing, the membrane depolarization is reset to an initial value and subsequent inputs lead to another discharge. Thus, the interspike interval corresponds to the first passage time for the stochastic process describing the membrane potential, and it is a random variable defined as the time interval from the moment of resetting to the moment of the first threshold crossing. The resetting of the membrane potential wipes out all the memory on the input that has been accumulated at the integrating device prior to the firing. This erasure of the memory has been criticized since the early days of the integrate-and-fire models [2]. Under the condition of time homogeneity of the underlying input stochastic processes, the resetting mechanism ensures that the interspike intervals are independent and identically distributed random variables and thus they form a renewal process. Unfortunately, the experimental data do not always show the renewal character. Despite the critique and partial discrepancy with the experimental data, integrate-and-fire models have been continuously developed and they play an indisputable role in theoretical studies on neuronal coding [1].

Recently, two papers [3,4] appeared aimed at an analysis of the integrate-and-fire models with time-variable input. In [3], the membrane potential is characterized by an Ornstein-Uhlenbeck (OU) stochastic process with a periodic driving force,

$$\frac{dX}{dt} = -X/\tau + \mu + F(t) + A\cos(\omega t), \quad X(0) = x_0, \quad (1)$$

where $X = \{X(t); t \geq 0\}$ represents the cell membrane voltage, μ being a drift parameter (in [3] it was required to be positive), $\tau > 0$ being a constant governing the decay of X to a resting level, and finally, A and ω are the constants characterizing the periodic driving force. For notational simplicity we set the resting level to zero, as was also done in [3]. The term $F(t)$ in Eq. (1) represents the noise term—Gaussian and δ correlated with zero mean and strength (or variance) $2D$. The membrane potential X given by Eq. (1) makes excursions to the firing threshold located at $S > x_0$. As soon as the threshold is reached, a firing event occurs and the membrane potential is reset deterministically and instantaneously to its starting point $X(0)$. The reset in model (1), as presented in [3], includes the restart of the periodic driving force which enables to apply the renewal theory abstraction again. Similarly to all one-dimensional integrate-and-fire models with time-homogeneous input, also in this model, the interspike intervals are identified with the first passage time of X across S and the properties of this random variable are thoroughly studied in [3]. This has to be stressed as the first-passage-time problem for the OU process itself [$A = 0$ in Eq. (1)] has been a challenging task for many decades and in [3] a very novel approach to this problem was introduced.

Model (1) without its random and periodic parts is the basic neuronal model,

$$\dot{x} = -x/\tau + \mu, \quad x(0) = x_0, \quad (2)$$

known also as the deterministic leaky-integrator or Lapicque model [5]. In generalizations of (2) $\mu = \mu(t)$ has been usually identified with the input signal and the simple assumption of a periodic rather than constant stimulation has been employed. The main characteristic of the deterministic leaky-integrator model with periodic force is that it is able to produce the phase locking effect. This means that the crossings of $x(t)$ through the threshold S may be phase locked with the period of a stimulus. Formally, we are interested in a distribution of time points $t_1 < t_2 < \cdots < t_k < \cdots$, such that at each of these time instants, the threshold is reached for the first time, $x(t_k^-) = S$, then the function $x(t)$ is reset to its initial value x_0 and for $t > t_k$

$$\dot{x} = -x/\tau + \mu + A\cos(\omega t), \quad x(t_k^+) = x_0. \quad (3)$$

Interspike intervals for model (3) are defined as $t_{k+1} - t_k$. Of course, restarting the periodic component of the model whenever the threshold is reached, only the interspike intervals of constant length are produced.

The main form in which the results for Eq. (3) as well as for the experiments with periodic stimulation have been pre-

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sented is a cycle histogram reflecting the spike synchronization to the phase of the driving force [6]. Using this method, the times of spike occurrences are converted mod$2\pi/\omega$ so that they fall within the interval of one period, $2\pi/\omega$. Model (3) has been mainly used for describing sensory neurons under external periodic stimulation [6]. However, one can imagine that also a periodic activity of higher-order neurons may lead to the use of this model. Actually, the experimental examples are not always taken from the first-order sensory neurons, which are in direct contact with the external world, but from higher-order centers, where the stimulation is probably reflected by a synchronized increase and decrease of postsynaptic activation coming from the neurons closer to the transduction of an external physical signal (light, chemical compound, sound) into an internal electrical representation. This effect can appear even without an apparent external stimulation being simply caused by any periodic synchronization of the input activity. Even a single pacemaker neuron acting upon the studied neuron and contributing substantially to its membrane potential can represent a periodic input [7].

Given model (3), it looks natural to study Eq. (1) as its stochastic counterpart. As mentioned before, model (3) was derived from Eq. (2) and the OU process is a stochastic counterpart to Eq. (2). However, the OU model has probably never been postulated as a randomization of Eq. (2) but it has always been derived as a diffusion approximation to a model with discontinuous trajectories [8]. In this way the model has kept the biological interpretation of its parameters and the significance of the underlying mechanisms has been transparent. Similarly, through a direct derivation of Eq. (1) from a biologically interpretable model some deeper insight can be gained. The aim of this note is to rederive model (1) and to show what this derivation implies for the results presented in [3,4]. The paper should contribute to a better understanding of the resetting after spike generation, and further, it should point out the future tasks to be solved.

The simplest, biologically acceptable and most common way to derive model (1) is to start from Stein's model [9] describing fluctuations of the membrane potential. In this manner also the OU model was formally derived [10,11] including the proof that the first passage time of Stein's model converges to the first passage time of OU process. Stein's model of the membrane potential is a one-dimensional stochastic process $X=\{X(t);t\geqslant 0\}$ which can be expressed in the form

$$dX(t)=-\frac{1}{\tau}X(t)dt+adP^{+}(t)+idP^{-}(t);\quad X(0)=0, \tag{4}$$

where $\tau>0$, $i<0<a$ are constants; $P^{+}(t)$, $P^{-}(t)$ are two independent homogeneous Poisson processes with the intensities λ and β, respectively. Following model (4) the values a and i represent the amplitudes of excitatory and inhibitory postsynaptic potentials, respectively. The membrane time constant τ reflects the exponential decay of X to the resting level which is again transformed to zero. The initial depolarization is put equal to the resting potential. Properties of the model (4) are as follows: synaptic activation of a neuron leads to a postsynaptic potential (PSP) which is characterized by a short rise time. Therefore, the corresponding membrane potential change is modeled by a step discontinuity. The stream of PSPs is considered Poissonian which appears an appropriate imitation mainly for spontaneous activity or for evoked activity due to a constant stimulus of long duration.

It is important to stress that in model (4) there is a clear distinction between intrinsic parameters (τ, i, a, S, and the reset value) and the input parameters (λ and β). The intrinsic parameters are characteristics of the neuron and can be measured directly. The input parameters characterize the activity of the network, the stimulus, or both and must be estimated from experimental data. In [12], the ranges of the parameters of Stein's model are given. A consequence of the diffusion approximation is that the clear distinction between these two types of parameters disappears [13]. This is the price paid for the simplification of mathematical problems related to the model.

Kallianpur [10] used the formulation of Ricciardi [14], where both excitatory and inhibitory inputs are numerous Poisson processes with different intensities as well as different jumps. Such a description is biologically more transparent (realistic) as each of the processes characterizes one synapse with its intensity of PSPs as well as its PSP amplitude, which may among other features reflect the distance from the trigger zone. However, their description is notationally complicated and for our purpose unnecessary. We will use the approach of [11] employing Eq. (4) where all the excitatory inputs are represented by one input stream and where the second stream represents the inhibitory inputs. The first and second infinitesimal moments of X defined by Eq. (4) are

$$M_1(x)=\lim_{\Delta\to 0}\frac{E(X(t+\Delta)-X(t)|X(t)=x)}{\Delta}$$

$$=-x/\tau+\lambda a+\beta i, \tag{5}$$

$$M_2(x)=\lim_{\Delta\to 0}\frac{E([X(t+\Delta)-X(t)]^2|X(t)=x)}{\Delta}=\lambda a^2+\beta i^2. \tag{6}$$

In diffusion models the membrane potential is described by a scalar diffusion process. Let us recall how the OU model can be obtained from Eq. (4). In general, a sequence of models $\{X_n\}$ given by Eq. (4) and characterized by a quadruplet $\{\lambda_n,\beta_n,a_n,i_n\}$ is needed such that for $n\to\infty$ it holds: $\lambda_n\to\infty$, $\beta_n\to\infty$, $a_n\to 0$, $i_n\to 0$, the quantities (5) and (6) converge to the drift and infinitesimal variance of the OU process, and the higher infinitesimal moments tend to zero. An example assuring the existence of the OU limit of Eq. (4) is given by

$$\lambda_n=n^2\sigma^2/2+n\mu,\quad \beta_n=n^2\sigma^2/2, \tag{7}$$

$$a_n=-i_n=1/n \tag{8}$$

inducing

$$M_1(x)_n\to -x/\tau+\mu,\quad M_2(x)_n\to\sigma^2. \tag{9}$$

We can see that even $\mu<0$ can be obtained since with negative μ in Eq. (7) the sequence of λ_n may start from a fixed value n_0 of the index n.

Now, we need to decide how to change Eqs. (7) and (8) to achieve Eq. (1). This can be done from a biological point of view in two different manners. The difference follows from the fact which of the involved parameters are considered as varying in time and which are kept time independent.

(A) *Endogenous periodicity*. This assumes that whereas the intensities of input processes are kept invariant in time, the amplitudes of PSPs are periodically changing. For example, we may consider

$$a_n=\frac{1}{n}\left(1+2\frac{A\ \cos(\omega t)}{n\sigma^2}\right),\quad i_n=-\frac{1}{n}, \tag{10}$$

while the intensities λ_n, β_n are defined by Eq. (7).

(B) *Exogenous periodicity*. It may be characterized by assuming time varying intensities, for example,

$$\lambda_n=n[\mu+A\ \cos(\omega t)]+n^2\sigma^2/2,\quad \beta_n=n^2\sigma^2/2, \tag{11}$$

and amplitudes of PSPs time invariant as defined by Eq. (8). Starting index in Eqs. (10) and (11) has to be selected in a way that assures $a_n>0$, respectively, $\lambda_n>0$, which is only a formal restriction, similar to the problem of negative μ, as we are interested in the limit, $n\to\infty$. In both of the above cases we obtain

$$M_1(x)_n\to -x/\tau+\mu+A\ \cos(\omega t) \tag{12}$$

and constant infinitesimal variance σ^2. Let us remember that a generalization based on periodically varying intensities was mentioned even in Stein's original paper [9], where it was written ''A cyclic form of the function $\lambda(t)$ can be used in the cases to simulate the expected (multipeaked) distributions.'' Nonhomogeneous Poisson processes have been successfully used in neuronal modeling as well as in the description of experimental data [15]. The above described procedure clearly illustrates the distinction between the intrinsic and the input parameters present in Stein's model and further blurred by the diffusion approximation.

Recently, in [7] a model similar to both Eqs. (1) and (4) was used. It is more convenient to write it in the integral form using as much as possible the notation of Eqs. (4),

$$X(t)=-\frac{1}{\tau}\int_0^t X(s)ds+aP^+(t)+a[t\omega/2\pi];\quad X(0)=0, \tag{13}$$

where [ ] stands for an integer part. This is also an integrate-and-fire model with a straightforward interpretation. There are two excitatory inputs to the neuron; the first one is a pacemaker neuron firing at constant intervals $2\pi/\omega$, the second one is a Poissonian neuron with firing intensity λ. The regular input corresponds to the cosine part in Eq. (1) and the Poissonian to the noise. In the above introduced classification this is an example of exogenous periodicity acting upon the neuron. The authors of [7] studied the model in a special parametric regime when two or more input pulses sufficiently close together can evoke a response—a coincidence detector. A symmetrical shape of the autocorrelation function in their Fig. 1 suggests that the regular (periodic) input was not restarted after the firing. Within a certain range of the parameter λ the neuron fires with higher probability at intervals close to the proximity of multiples of $2\pi/\omega$ creating the phase locking effect.

Longtin and his co-workers [16] simulated bistable neuronal model analogous to Eq. (1),

$$\frac{dX}{dt}=-dU(X)/dx+F(t)+A\ \cos(\omega t),\quad X(0)=x_0, \tag{14}$$

where U is a double-well potential. Model (14) permits us to discard the phenomenological assumption of the firing threshold S of the integrate-and-fire models as the interspike intervals, in this model, are identified with the transition (return) times between two states. Viewing the state variable as the soma potential, the model assumes a stochastic reset from an excited state (the right well) to the resting state (the left well). This model lacks a simple intuitive interpretation similar to that of Stein's model, however, the bistability of realistic (Hodgkin-Huxley-type) neuronal models may serve as a strong reasoning for them. The periodic component seems to be of exogenous nature in all the bistable models.

We have seen that model (1) can be derived using a realistic biological reasoning, at least at the level corresponding to the derivation of the OU process as a neuronal model. The problem that stands out is the reset after the spike generation, namely, the question of the periodic component restart. For constant input the reset implies, in physiological terms, that the nerve impulse initiation destroys all remaining PSPs or, in other words, that there is no transmitter persistence. This is a practically unavoidable feature of one-point models and can be only phenomenologically overcome by a random reset [17] or by taking into account, at least minimally, the spatial properties of the neuron [18,19]. For nonhomogeneous input the reset, in addition to the destroying the accumulated potential built up at the dendrite, may also reset the input signal. Now, we may compromise and accept the periodic force restart when it does not involve any external modulation, but we should not accept it when the external input signal is studied. The exogenous reasoning seems to be more physiologically plausible and it is clear that model (1) was originally proposed for this situation since in [3] the periodic part was called ''stimulus.''

Under the scenario of endogenous periodicity, the interspike intervals are always independent and identically distributed random variables forming a renewal process, not only in the case of Poissonian approximation as mentioned in [3]. The solution to the first passage time problem for model (1) is only the first step in the case of exogenous periodicity. What remains is to analyze the effect of not restarting the periodic driving force. The most interesting part of this investigation should not be based on interspike intervals, as these are correlated and thus their histogram has a limited information value, but on the cycle histogram. A study analogous to those on the deterministic leaky-integrator model (3) with periodic driving force should be performed. As predicted in [3], for the Poissonian limit of firing times and for the high driving frequency ω, with respect to the time to a crossing, there would be a negligible difference between the models with and without the driving force restart.

Bulsara *et al.* [3] present an extensive discussion of their results including the case when no periodical signal is applied, $A=0$ (see Figs. 4–6 of [3]). Furthermore, they compare their analytical results with the simulations (see Sec. IV of [3]). The coincidences between approximations and simulations are very impressive. Nevertheless, in all these cases the simulated densities are systematically shifted to the longer interspike intervals than those derived analytically. This effect may be caused by the overestimation of the first passage time by simulation [20]. Therefore, a better way to judge the efficiency of the method would be a comparison with existing tables [21] or with sophisticated numerical methods [22]. These comparisons would increase the reliability of the results when the periodic driving force is considered. In that case no other method beside simulation is available.

In [3], the model performance is divided with respect to the mutual position of the threshold S and $\mu\tau$ which is the asymptotic voltage of the model without modulation ($A=0$). This is obviously the most natural separation because when $S<\mu\tau$ the crossings of the threshold are present, even without any noise and vice versa. Nevertheless, a finer division, implicitly also present in [3], may lead to the separation of the model neuron activity into three regions [23,18]. For $\mu\tau \gg S$ we may expect that the role of the noise is relatively small; the probability density of the first passage time is narrow and symmetric—close to the the normal distribution. In the opposite case, when $\mu\tau \ll S$ and the initial voltage is not close to the threshold, the firings appear in accordance with a Poisson process (interspike intervals are exponentially distributed) and approximations for the intensity of this process are well known [24]. The most critical and therefore also the most interesting case is when $\mu\tau \approx S$, where the results are not so predictable. When periodic modulation is included, this separation can also be made but the amplitude of the periodic signal has to be considered.

In the noise-activated regime, $\mu\tau<S$, a new approximation method is devised in [3]. The firing time is viewed as arising from two distinct events; the passage from the initial depolarization to the asymptotic potential $\mu\tau$ and the passage from this value to the threshold. The first component has a known probability density function [1,3]. The second component is in [3], approximated by replacing the model by the Wiener process with a drift (perfect integrator model) confined between a lower reflecting $\mu\tau$ and an upper absorbing boundary S. The first-passage-time problem for the Wiener process confined between reflecting and absorbing boundary was solved recently in [25]. A detailed comparison of [3] and [25] seems to be worth the effort.

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[1] L. Ricciardi, *Diffusion Processes and Related Topics in Biology* (Springer, Berlin, 1977); H. Tuckwell, *Introduction to Theoretical Neurobiology* (Cambridge University Press, Cambridge, England, 1988).
[2] C. Stevens, Biophys. J. **4**, 417 (1964).
[3] A. Bulsara, T. Elston, C. Doering, S. Lowen, and K. Lindberg, Phys. Rev. E **53**, 3958 (1996).
[4] A. Bulsara, S. Lowen, and C. Rees, Phys. Rev. E **49**, 4989 (1994).
[5] B. Knight, J. Gen. Physiol. **59**, 734 (1972); J. Fohlmeister, Kybernetik **13**, 104 (1973).
[6] C. Ascoli, M. Barbi, S. Chillemi, and D. Petracchi, Biophys. J. **19**, 219 (1977); H. Scharstein, J. Math. Biol. **6**, 403 (1979); M. Barbi and E. Ferdeghini, Biol. Cybern. **39**, 45 (1980); J. Fohlmeister, F. Adelman, and R. Poppele, Biophys. J. **30**, 79 (1980); J. Fohlmeister, J. Theor. Neurobiol. **1**, 251 (1982); A. Palmer and I. Russell, Hearing Research **24**, 1 (1986); X. Yu and E. Lewis, IEEE Trans. Biomed. Engn. **36**, 36 (1989).
[7] F. Chapeau-Blondeau, X. Godivier, and N. Chambet, Phys. Rev. E **53**, 1273 (1996).
[8] B. Gluss, Bull. Math. Biophys. **29**, 233 (1967); B. Roy and D. Smith, Bull. Math. Biophys. **31**, 341 (1969); R. Capocelli and L. Ricciardi, Kybernetik **8**, 214 (1971); S. Sato, Math. Biosci. **39**, 53 (1978); L. Ricciardi and L. Sacerdote, Biol. Cybern. **35**, 1 (1979).
[9] R. Stein, Biophys. J. **5**, 173 (1965).
[10] G. Kallianpur, in *Contributions to Statistics*, edited by P. Sen (North-Holland, Amsterdam, 1983).
[11] P. Lánský, J. Theor. Biol. **107**, 631 (1984).
[12] H. Tuckwell and W. Richter, J. Theor. Biol. **71**, 167 (1978).
[13] J. Inoue, S. Sato, and L. Ricciardi, Biol. Cybern. **73**, 209 (1995).
[14] L. Ricciardi, Biol. Cybern. **24**, 237 (1976).
[15] D. Linebarger and D. Johnson, Hearing Res. **23**, 185 (1986); B. Edwards and G. Wakefield, J. Neurosci. Meth. **45**, 1 (1992); M. Miller and K. Mark, J. Acoust. Soc. Am. **92**, 202 (1992).
[16] A. Longtin, A. Bulsara, and F. Moss, Phys. Rev. Lett. **67**, 656 (1991); A. Longtin, J. Stat. Phys. **70**, 309 (1993), A. Longtin, A. Bulsara, D. Pierson, and F. Moss, Biol. Cybern. **70**, 569 (1994).
[17] P. Lánský and C. Smith, Math. Biosci. **93**, 191 (1989); P. Lánský and M. Musila, Biol. Cybern. **64**, 285 (1991).
[18] P. Lánský and J. Rospars, Biol. Cybern. **72**, 397 (1995).
[19] P. Bressloff, Physica D **80**, 399 (1995).
[20] P. Lánský and V. Lánská, Comput. Biol. Med. **24**, 91 (1994).
[21] J. Keilson and H. Ross, *Passage Time Distributions for Gaussian Markov (Ornstein-Uhlenbeck) Statistical Processes* (SIAM, Providence, 1975).
[22] L. Ricciardi and S. Sato, J. Appl. Prob. **25**, 43 (1988); L. Ricciardi and S. Sato, in *Lectures in Applied Mathematics and Informatics*, edited by L. Riciciardi (Manchester University Press, Manchester, 1990).
[23] C. Smith, in *Single Neuron Computation*, edited by T. McKenna, J. Davis, and S. Zornetzer (Academic, Boston, 1992).
[24] A. Nobile, L. Ricciardi, and L. Sacerdote, J. Appl. Prob. **22**, 611 (1985).
[25] W. Schwarz, J. Appl. Prob. **29**, 597 (1992).