

Neuronal Spike Production の実モデル
と Spike Interval の確率分布について (補足講演)
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私は今回の研究会でプログラムにのせて講演を行う予定ではなかったが、先程の加納教授の Spike Interval の確率分布に関する講演内容と密接に関連する研究を私も過去に行なっており、その一部はたゞ今、皆様にお配りした論文 "Solutions for a Stochastic Model of Neuronal Spike Production" Math. Bioscience. Vol 8. 1970, pp. 323-341 に発表しているもので、暫く御時間をかり、その概要を紹介させて頂きたいと思ふ。

一言で云うならば、この研究は先程の加納教授の御講演の中の $a(t, y) = \text{const.}$ $b(t, y) = \sigma^2$ を変換した連続マルコフ過程に関する first passage problem を解くための通りの方法を提案し、かつ事例を示したものである。

即ち、モデルとしては1つの spike のあと一定の長さの絶対不応期を経過すると、連続マルコフ過程 y_t で表現される1個の着目している神経細胞の膜電位は

出発値 y_0 から出発し、平均速度 $a(t, y) = \lambda(\theta_r - y) + \sigma$ の
 分散速度 $b(t, y) = \sigma^2$ とした Kolmogoroff の forward
 equation に支配されて変化を続け、Threshold level
 θ_0 に始めて到達すると、その spike を発生するとす
 るのである。

このモデルには Resting potential level θ_r があって
 膜電位 y_t は常にこの θ_r level に向かって decay
 constant λ で exponential decay を行い、周囲
 の神経細胞から送って来る EPSP と IPSP の差額と
 しての upward surplus $\sigma > 0$ によって y_t が threshold
 level θ_0 に first passage を行い、このモデルになっ
 てお、もともと Aplysia Californica の visceral gan-
 glion の spike 発生に関する実験、観察にもついで
 Donald H. Perkel が 1964 年頃、提案したモデルを
 もとに、私が連鎖マルコフ過程のモデルとして modify し
 たものである。

さて、このマルコフ過程 y_t は Resting level θ_r に
 戻す力が弱いことからもすく想像
 されるように、数学的には Ornstein-Uhlenbeck process
 とよばれているものであり、わかめはそれに関する first
 passage problem を解かなくてはならないわけである。

さて、私の論文中には、→かのよ)なる通りの解法を提案した。

(その1) は Threshold level θ_0 がとくと、

$\theta_0 + \frac{d}{\lambda}$ という形で表わされるものとした場合の spike interval の確率分布を求め、結果として論文中の式 (19) の $p(t)$ のよ)る p.d.f. を完全に具体的な形で求めた。なお、この結果は M. I. T. の

Siebert 教授が全く別のアプローチで 1968年10月に M. I. T. の紀要に発表しており、私はこのことを 1969年8月、M. I. T. で行われた Biophysics の国際学会の量子部会で私が行った講演のあと Siebert 教授によつて知りました。

(その2) は再び一般の場合へ戻り、Darling-Siebert 流の工夫を用いて $p(t)$ のラプラス変換を求め、そのよ)る結果は論文 (44) 式のよ)る parabolic

cylindrical function を用いて具体的に表現する=と出来ます。しかし、この結果の stable な逆変換によつて

もとの $p(t)$ を求めるための数値解法にはそれ以上の苦勞を必要とする。これについては、ここでは話を省略す

る。(その3) はわかわけの Kolmogoroff の forward eq. を Crank-Nicholson のよ)る implicit method で

差分方程式に在りし、 θ_0 に相当する境界に、mass が各単位
 時間内に吸着されていく量を求めるヒストグラムをかく
 という方法を提案したものであり、加えてこれを極めと安定
 せる微分方程式として確率分布を求めることかまます。

しかも、このような方法を用いながらもモデルに含まれる
 いくつかのパラメータの最尤推定値を、たとえば人工ノイズ
 を加えた Kiefer-Wolfowitz process のよりの極限停留
 性で求めよう可能性もある。この first passage の
 微分方程式は実地応用上、有意義な方法ではあるか
 と考える次第である。

以下、Mathematical Bioscience Vol. 9, 1970 から
 前述の論文を転載する。

1975. 8. 14

吉沢新長宛へ。

拝読 貴誌 講義録 No. 181 (神経系と数論的
 解析) の配布を受けました。これを少しの遅れで
 いた所、pp. 165-183 にわたって、Mathematical
 Biosciences 所載の論文が くりくりと
 収録されています。おとよりを以て、この論文の
 著者(の中の一人)が、自分の講演題目の
 代りに 転載の旨を ことわって、おせておられた
 ものであります。ありがとうございます。

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この所載に 貴誌のせいで、研究所発行の刊行
 物として、配布するのは、不適当ではなから
 心配は有りませぬ。

今後このよきこと、幾ぶんおぼしめる方法を
 講じた方がよいのではなからと思ひます。と
 うごうご。このご書かちの、ないかば、せし
 りに 講義録 原稿を少しながらでも送るこ
 とより、意見でまゝです。

印刷所へ

中野尚男

Solutions for a Stochastic Model of Neuronal Spike Production

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ABSTRACT

Equations for a random-walk model describing the production of nerve impulses have been derived for the general case in which noisy depolarizations of the membrane potential are subject to a force that tends to restore the potential to an equilibrium, or "resting," value. This model, corresponding to the Ornstein-Uhlenbeck process, was developed previously to account for observed patterns of firing in neurons in which the membrane potential starting from a fixed value undergoes a one-dimensional random walk and triggers an impulse when its value reaches the critical "threshold value." Identifying neuron firing intervals with the first-passage time distribution for the associated random walk allows us to predict the interval statistics for a neuron from parameters associated with input to the neuron and certain parameters intrinsic to the neuron itself. The equations for the random-walk model have been solved by several techniques, permitting, for the first time, direct comparison between the output of the model and empirically observed interval distributions.

1. INTRODUCTION

The interspike interval histogram, which estimates the distribution of time intervals between successive discharges of a neuron, has become the most widely used and convenient statistical measure by which the

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neurophysiologist quantitatively summarizes the discharge characteristics and patterns of activity in single neurons [13, 15].

In the neurophysiological laboratory, the widespread availability of small general-purpose digital computers or special electronic devices has made such measures almost routine in the analysis of experimental data. This has been paralleled by an increased interest in these measures as the basis for comparing the output of models of neuronal networks, which can be simulated in a variety of ways, with empirically observed neuronal activity, in the hope that successful models can be used to make inferences concerning unobserved, or unobservable, processes taking place within the brain.

In general, the processes that produce the observed train of pulses emitted by a neuron under investigation are of two types. First, the output of a neuron depends on a complex spatiotemporal array of impulses that it receives from other neurons, each of which alters the probability of firing in the observed cell, typically by directly altering the electrical potential across the cell membrane. Second, the impulse-generating mechanism of the cell itself has certain complex features that determine the conditions under which it will fire. Thus the overall behavior of a neuron depends on extrinsic features related to its input and connectivity with respect to other cells, and on certain intrinsic properties that determine its firing times in relation to the input.

Ideally, we wish to determine or extract the parameters of the intrinsic processes of each neuron, and the parameters associated with its input from all other sources, by data-processing techniques applied to the empirically determined interval distribution or related measures. Such a hope for the solution of this inverse problem cannot be fulfilled even in principle, however, unless it is first shown how the interspike-interval distribution can be derived from a knowledge of intrinsic cell parameters and input distributions. At the present time the problem is usually attacked by computer modeling in which the assumed processes are simulated according to specific describing equations whose parameters are assigned physiologically reasonable values. Then, for any given set of assumptions, the behavior of the network and, specifically, the behavior of any neuron in the network can be described in terms of computed firing times, and from these an interval distribution can be tabulated for comparison with that derived from an observed spike train. For a review of this approach, see [13].

Alternatively, it would be desirable to derive the mathematical equations of the interval distribution directly from the mathematical assumptions of the model itself. But this is an extremely difficult problem and efforts to determine analytically neuron firing-interval distributions have

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been confined to rather simple cases. In general, these attempts fall into three major categories. The first type of approach ("quantal model") attempts to treat the case of a neuron with well-defined synaptic input from few channels (usually conforming to Poisson arrivals) with relatively large amplitude (so that intrinsic, continuous membrane noise can be neglected). In the simplest cases, the randomness of the output is derived from the randomness of the input and the calculated times to firing are based on counting statistics for the input [7, 9, 12, 16, 21]. More complex cases have also been treated by generalizations of the simpler model, which consider additive quantal step changes in potential or threshold whose duration is randomly distributed [6, 8, 19, 22].

A second approach to analytic formulation of the interval density generally assumes deterministic equations for the postimpulse time course of the state variables of the neuron—the membrane potential and threshold level—and calculates (under the assumption that no input is arriving at the neuron) the time when the membrane potential will cross the threshold for the first time. This is particularly applicable to receptor neurons under sustained stimulus input conditions, since the membrane potential crosses the threshold level at precise intervals and no additional discrete (quantal) changes in potential from other sources are present. Randomness in the output is achieved by assuming that Gaussian noise is added to the membrane potential or threshold level, or both [5, 11, 18, 24, 25].

A third approach has been to exploit the natural analogy between the drift of potential toward threshold following an impulse and the random-walk problem with an absorbing barrier [3, 4, 10, 17]. The interval distribution for neuron firings is then identified with the distribution of first-passage times for the random-walk process. In such a model the fluctuations in potential have generally been assumed to be small in comparison with the difference between the resting membrane potential and the threshold level, an assumption consistent with certain empirical observations of membrane "noise" [24] or with the assumption that synaptic input is arriving from multiple channels, each of which has small amplitude.

The Gerstein and Mandelbrot model [3] is a special case corresponding to a Wiener–Levy process; that is, there is no decay of the membrane potential toward a resting value in the absence of input. The models of Johannesma [10], Gluss [4], and Roy and Smith [17] all correspond to the Ornstein–Uhlenbeck process [2], in which there is a restoring force that causes an exponential decay of the membrane potential to a resting asymptotic value in the absence of the input. None of these authors, however, was able to solve the first-passage-time problem explicitly to obtain an interspike-interval distribution in closed form, although

Johannesma showed how to derive all the moments of the distribution. Siebert [20], also using the Ornstein-Uhlenbeck process, has obtained an explicit solution for a special choice of threshold function, using techniques different from those used here.

In this article we treat the problem of a neuron with decaying membrane potential and show various new approaches to obtaining solutions to the first-passage-time problem.

2. THE MATHEMATICAL MODEL FOR NEURONAL DYNAMICS

We approximate the natural behavior of the neuron with a model having two state variables, the membrane potential and the threshold potential (Fig. 1). The former is the difference between the potential inside

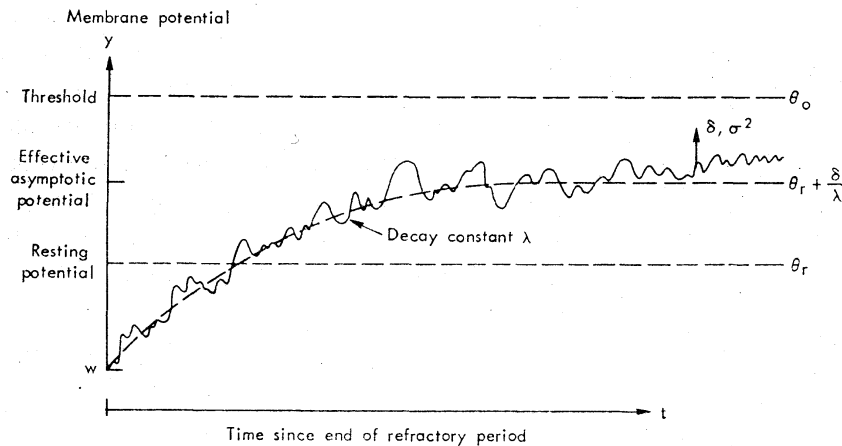


FIG. 1. Neuronal behavior model with two state variables.

of the cell and a reference potential (usually taken as zero) outside the cell, and this potential difference is a variable conventionally recorded by a microelectrode placed inside the cell. The second variable, the threshold potential, is taken here to be that value of the membrane potential which, when exceeded, leads inevitably to the production of an all-or-none event, the nerve impulse.

We also assume, on the basis of direct experimental observation, that following each impulse the membrane potential is restored to a so-called undershoot level w , following which there is an exponential decay of membrane potential toward an equilibrium level, or "resting potential," θ_r . For the purposes of the present model we assume that the threshold level is constant, although there is evidence that it has a more complex time-varying course after an impulse.

Finally, we make the rather general limiting assumption that input to

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the cell, developed at each synaptic contact made by incoming axons and generated upon the arrival of an impulse in any such axon, comes from a large number of axon sources. Each of these contributes only a small change in membrane potential, in either a positive or negative direction, whose amplitude is independent of the existing potential. Under these conditions we can assume that the net effect of the synaptic input is to add a noise signal to the exponential drift to the resting level and this random component may include a net drift toward the threshold corresponding to a surplus of excitatory input over inhibitory input.

We denote the transmembrane potential at time t by Y_t and let $f(t, y | 0, w)$ be the density function (pdf) of Y_t at time t given that the membrane potential is reset to w at time $t = 0$, corresponding to the time of the last firing of an impulse by the cell.

Under the assumptions already given, Y_t can be regarded as a continuous Markov diffusion process with drift velocity

$$a(t, y) = \lambda(\theta_r - y) + \delta \quad (1)$$

and velocity variance σ^2 , where λ is the decay constant of the membrane potential, δ is the net upward drift rate, and θ_r is the resting potential. It follows that $f(t, y | 0, w)$ is governed by the so-called forward diffusion equation or the Fokker-Planck equation

$$\begin{aligned} \frac{\partial f}{\partial t}(t, y | 0, w) \\ = \frac{\sigma^2}{2} \frac{\partial^2 f}{\partial y^2}(t, y | 0, w) - [\lambda(\theta_r - y) + \delta] \frac{\partial f}{\partial y}(t, y | 0, w) + \lambda f(t, y | 0, w). \end{aligned} \quad (2)$$

Making the substitution

$$x = \lambda(y - \theta_r) - \delta = -a(t, y) \quad (3)$$

and substituting into (2), we have

$$\frac{\partial f^*}{\partial t}(t, x) = \frac{\lambda^2 \sigma^2}{2} \frac{\partial^2 f^*}{\partial x^2}(t, x) + \frac{\lambda \partial(x f^*(t, x))}{\partial x} \quad (4)$$

where $f^*(t, x) = f(t, y)$.

Equation (4) is the forward equation of the Ornstein-Uhlenbeck process [2], which then is the formal mathematical equivalent of the physiological process by which the membrane potential drifts toward the threshold level under the influence of random synaptic input while subject to a force that tends to restore the potential to an equilibrium level. If there is a net surplus of excitatory input, this effectively raises the asymptotic membrane

potential by an amount equal to δ/λ . This model is then formally equivalent to the class of simulation models in which there is exponential decay of membrane potential toward a resting value, superimposed on which is a constant depolarizing force and added Gaussian noise of infinite band width.

In the sections that follow we will examine certain properties of the behavior of this model; in particular, we will derive (a) the first-passage-time distribution for a specific choice of threshold level, (b) the distribution of the membrane potential, (c) the first-passage-time distribution using Laplace transforms, and (d) the first-passage-time distribution using finite-difference equations.

3. THE SUBTHRESHOLD DISTRIBUTION OF MEMBRANE POTENTIAL OF THE NEURON MODEL

A problem of great importance in the application of mathematical models to neuronal processes is the determination of the interspike-interval distribution for each class of model for a given set of parameters. In subsequent sections we derive the interval density for our random-walk model of neuronal dynamics by solving the associated first-passage-time distribution (i.e., the distribution of times required to first reach threshold), starting from a neuronal firing. First we derive an expression for the membrane potential density $f(t, y | 0, w)$, that is, the distribution of potential values y at time t , starting at the postspike restoration value w at $t = 0$. The density obtained in this case is the solution to the so-called free-motional case of a random walk in which an absorbing barrier is never reached. Physiologically this is equivalent to determining the membrane potential distribution for purely subthreshold behavior, for example, when the threshold is a considerable distance from the effective asymptotic value of the membrane potential.

Starting with Eq. (2), the forward diffusion equation, we obtain a solution by making the change of variables

$$t' = e^{2\lambda t}, \quad (5)$$

$$y' = \left[y - \left(\theta_r + \frac{\delta}{\lambda} \right) \right] e^{\lambda t}. \quad (6)$$

Then

$$\begin{aligned} f(t, y) &= f'(t', y') \frac{\partial y'}{\partial y} \\ &= e^{\lambda t} f'(t', y') \\ &= (t')^{1/2} f'(t', y'), \end{aligned} \quad (7)$$

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and, calculating the several partial derivative terms corresponding to Eq. (2), it can be shown that $f'(t', y')$ satisfies the heat equation

$$\frac{\sigma^2}{4\lambda} \frac{\partial^2 f'(t', y')}{\partial y'^2} = \frac{\partial f'(t', y')}{\partial t'}. \quad (8)$$

The solution is known to be [14]

$$f'(t', y' | 0', w') = \left[\pi \frac{\sigma^2}{\lambda} (t' - 0') \right]^{-1/2} \exp \left[\frac{(y' - w')^2}{(\sigma^2/\lambda)(t' - 0')} \right]. \quad (9)$$

Returning to the original variables t, y , using (5) and (6), we have

$$f'(t', y' | 0', w') = \left\{ \frac{\pi\sigma^2}{\lambda} [\exp(2\lambda t) - 1] \right\}^{-1/2} \\ \times \exp \left[- \frac{(\{y - [\theta_r + (\delta/\lambda)]\} \exp(\lambda t) - \{w - [\theta_r + (\delta/\lambda)]\})^2}{(\sigma^2/\lambda)[\exp(2\lambda t) - 1]} \right] \quad (10)$$

and, using (7),

$$f(t, y | 0, w) = \frac{\exp(\lambda t)}{\{(\pi\sigma^2/\lambda)[\exp(2\lambda t) - 1]\}^{1/2}} \\ \times \exp \left[- \frac{(\{y - [\theta_r + (\delta/\lambda)]\} \exp(\lambda t) - \{w - [\theta_r + (\delta/\lambda)]\})^2}{(\sigma^2/\lambda)[\exp(2\lambda t) - 1]} \right] \\ = \left\{ \frac{\pi\sigma^2}{\lambda} [1 - \exp(-2\lambda t)] \right\}^{-1/2} \\ \times \exp \left[- \frac{(\{y - [\theta_r + (\delta/\lambda)]\} - \{w - [\theta_r + (\delta/\lambda)]\} \exp(-\lambda t))^2}{(\sigma^2/\lambda)[1 - \exp(-2\lambda t)]} \right]. \quad (11)$$

Thus the membrane potential has a time-varying normal distribution with mean

$$m(t) = \left(\theta_r + \frac{\delta}{\lambda} \right) + \left[w - \left(\theta_r + \frac{\delta}{\lambda} \right) \right] e^{-\lambda t}, \quad (12)$$

and variance

$$\sigma^2(t) = \frac{\sigma^2}{2\lambda} (1 - e^{-2\lambda t}). \quad (13)$$

4. FIRST-PASSAGE-TIME DISTRIBUTION OF THE RANDOM-WALK MODEL

A. Solution for a Specific Choice of Threshold

An analytic solution of the first-passage problem for a neuron whose potential is governed by (4) may be obtained if we assume, as before, that

the threshold is constant, and make the transformation (5), (6)

$$t' = e^{2\lambda t}, \quad y' = \left[y - \left(\theta_r + \frac{\delta}{\lambda} \right) \right] e^{\lambda t},$$

as discussed in Section 3. Then $f'(t', y')$ satisfies Eq. (8)

$$\frac{\partial f'}{\partial t'} = \frac{\sigma^2}{4\lambda} \frac{\partial^2 f'}{\partial y'^2}$$

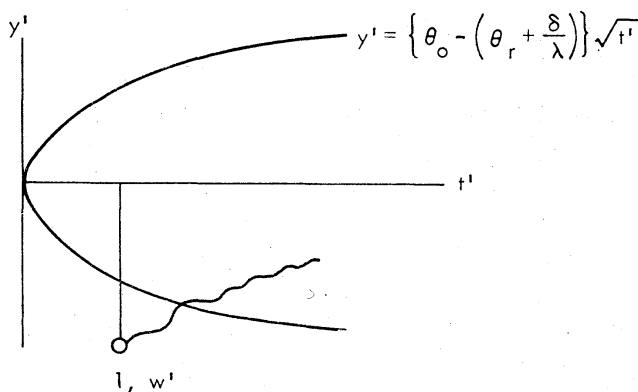


FIG. 2. Transformed random walk in t', y' space.

and the random walk (now governed by the heat equation (8)) in the t', y' space starts at $t' = 1$ and $y' = w - [\theta_r + (\delta/\lambda)] \equiv w' (< 0)$ corresponding to $t = 0, y = w$ (Fig. 2).

Setting $\sigma^2/2\lambda = \sigma^{*2}$ and $\tau = t' - 1$, we have

$$\frac{\partial f}{\partial \tau} = \frac{\sigma^{*2}}{2} \frac{\partial^2 f}{\partial y'^2}. \quad (14)$$

If we make the special choice of the t' axis as the absorbing barrier, we need only solve (14) for the condition $f' = 0$ at $y' = 0$. This means that we choose the threshold to be equal to the value $\theta_r + (\delta/\lambda)$, which, as pointed out earlier, is the effective asymptotic potential with drift δ or is the resting potential when $\delta = 0$. The solution of this boundary-value problem is obtained by the method of images [2] to be

$$f' = [(2\pi\tau)^{1/2}\sigma^*]^{-1} \left\{ \exp\left[-\frac{(y' - w')^2}{2\sigma^{*2}\tau}\right] - \exp\left[-\frac{(y' + w')^2}{2\sigma^{*2}\tau}\right] \right\}. \quad (15)$$

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The corresponding first-passage-time distribution is obtained as

$$\begin{aligned} p(\tau) &= -\frac{\sigma^{*2}}{2} \left(\frac{\partial f'}{\partial y'} \right)_{y'=0} \\ &= \frac{(-w')}{(2\pi\tau^3)\sigma^{*1/2}} \exp\left(-\frac{w'^2}{2\sigma^{*2}\tau}\right) \\ &= \frac{|w'|}{(2\pi\tau^3)^{1/2}[\sigma/(2\lambda)^{1/2}]} \exp\left[-\frac{w'^2}{(\sigma^2\tau/\lambda)}\right]. \end{aligned} \quad (16)$$

Thus,

$$p(t') = \frac{|w'| (2\lambda)^{1/2}}{(2\pi)^{1/2}\sigma} (t' - 1)^{-3/2} \exp\left[-\frac{w'^2}{(\sigma^2/\lambda)(t' - 1)}\right]. \quad (17)$$

Then, since

$$p(t) = p(t') \left| \frac{dt'}{dt} \right| = p(t') 2\lambda e^{2\lambda t}, \quad (18)$$

we have the result that for this threshold value

$$\begin{aligned} p(t) &= \frac{\{[\theta_r + (\delta/\lambda)] - w\} (2\lambda)^{3/2}}{(2\pi)^{1/2}\sigma} [\exp(2\lambda t) - 1]^{-3/2} \\ &\quad \times \exp(2\lambda t) \exp\left(-\frac{\{[\theta_r + (\delta/\lambda)] - w\}^2}{(\sigma^2/\lambda)[\exp(2\lambda t) - 1]}\right), \end{aligned} \quad (19)$$

a result that has also been obtained by Siebert [20], using a different approach. A typical interval distribution from Eq. (19) is shown in Fig. 3.

It can be shown that the mean firing time of the distribution is always finite; that is, that

$$E(t) = \int_0^{\infty} t p(t) dt < \infty \quad (20)$$

where $p(t)$ is given by Eq. (19). The proof is as follows. For sufficiently large t , say $t > M$, there exists a positive constant K such that

$$\exp\left\{-\frac{[\theta_r + (\delta/\lambda) - w]^2}{(\sigma^2/\lambda)[\exp(2\lambda t) - 1]}\right\} < K.$$

If we include the constant terms of (19) in the constant K , we have

$$E(t) < K \int_M^{\infty} t e^{2\lambda t} (e^{2\lambda t} - 1)^{-3/2} dt + \int_0^M t p(t) dt. \quad (21)$$

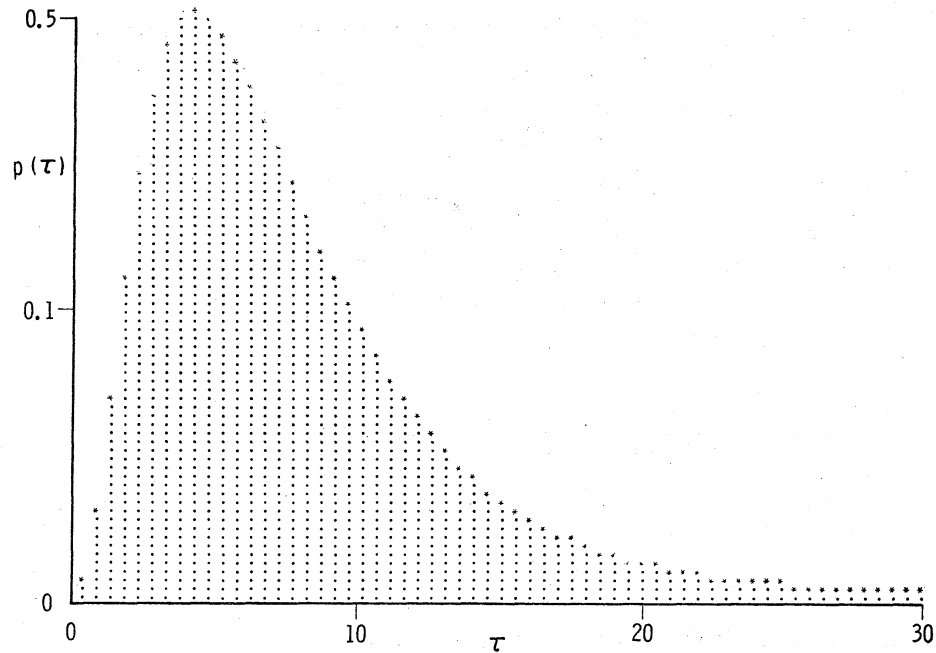


FIG. 3. Interval distribution calculated from Eq. (19) with parameter values $\lambda = 0.2$, $\theta_r = 4$, $w = 1$, $j = 5$, $\sigma = 7$.

To prove that $E(t)$ is finite we need only show that the first term on the right side of (21) is finite. But

$$\begin{aligned} te^{2\lambda t}(e^{2\lambda t} - 1)^{-3/2} &= te^{2\lambda t}e^{-3\lambda t}(1 - e^{-2\lambda t})^{-3/2} \\ &= te^{-\lambda t}(1 - e^{-2\lambda t})^{-3/2}. \end{aligned} \quad (22)$$

For $t > M$, $e^{2\lambda t} > e^{2\lambda M}$ and $e^{-2\lambda t} > e^{-2\lambda M}$, so $1 - e^{-2\lambda t} > 1 - e^{-2\lambda M}$, and therefore

$$(1 - e^{-2\lambda t})^{3/2} > (1 - e^{-2\lambda M})^{3/2},$$

so finally

$$(1 - e^{-2\lambda t})^{-3/2} < (1 - e^{-2\lambda M})^{-3/2}.$$

Using this and relation (22) we have, from (21)

$$\int_M^\infty te^{2\lambda t}(e^{2\lambda t} - 1)^{-3/2} dt < (1 - e^{-2\lambda M})^{-3/2} \int_M^\infty te^{-\lambda t} dt,$$

which is finite. Clearly, then, the mean firing time for this model of neuronal activity will always be finite for threshold values less than or equal to $\theta_r + (\delta/\lambda)$.

B. Laplace Transform Approach

In this section we derive the Laplace transform of the distribution, using an approach different from those previously employed by Gluss [4] and Roy and Smith [17].

If we let $p(\tau, \theta_0 | 0, w)$ be the probability density function of the first-passage times with respect to the threshold value θ_0 , then exploiting the Markovian property of the process and referring to the variables of Fig. 4,

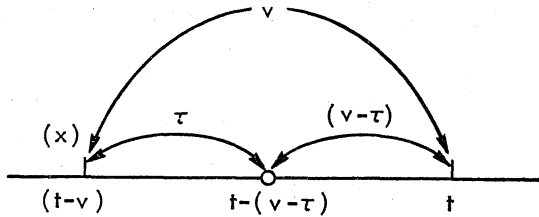


FIG. 4. Variable transformations for Eq. (23).

we have the following equation.

$$f(t, y | t - v, x) = \int_0^v p(\tau, \theta_0 | 0, x) f(t, y | t - (v - \tau), \theta_0) d\tau. \quad (23)$$

Then putting

$$f(t, y | t - v, x) \equiv g(t, y | v, x), \quad (24)$$

Eq. (23) becomes

$$g(t, y | v, x) = \int_0^v p(\tau, \theta_0 | 0, x) g(t, y | v + \tau, \theta_0) d\tau. \quad (25)$$

To obtain an expression for p in terms of g , we take Laplace transforms of both sides, which converts the convolution integral to the corresponding product of the two transformed functions of p and g ; that is,

$$\hat{g}(t, y | s, x) \equiv \hat{p}(s, \theta_0 | 0, x) \hat{g}(t, y | s, \theta_0) \quad (26)$$

where a circumflex signifies the Laplace transform of the respective functions. We then have

$$\hat{p}(s, \theta_0 | 0, x) = \frac{\hat{g}(t, y | s, x)}{\hat{g}(t, y | s, \theta_0)} \quad (27)$$

an expression for which can be derived as follows.

From the basic Markovian properties of the model, f is known to satisfy the backward equation

$$\frac{\sigma^2}{2} \frac{\partial^2 f}{\partial x^2}(t, y | t_0, x) + \{a(t, x)\} \frac{\partial f(t, y | t_0, x)}{\partial x} + \frac{\partial f(t, y | t_0, x)}{\partial t_0} = 0 \quad (28)$$

where $a(t, x)$ is the drift velocity $\lambda(\theta_r - x) + \delta$. Putting $t_0 = t - v$ and using the variable v , we have the following transformed equation.

$$\frac{\sigma^2}{2} \frac{\partial^2 f(t, y | t - v, x)}{\partial x^2} + \{a(t, x)\} \times \frac{\partial f(t, y | t - v, x)}{\partial x} - \frac{\partial f(t, y | t - v, x)}{\partial v} = 0. \quad (29)$$

From (24) it follows that the corresponding equation for g is

$$\frac{\sigma^2}{2} \frac{\partial^2 g(t, y | v, x)}{\partial x^2} + \{a(t, x)\} \frac{\partial g(t, y | v, x)}{\partial x} - \frac{\partial g(t, y | v, x)}{\partial v} = 0. \quad (30)$$

Taking Laplace transforms of both sides of this equation with respect to v , as before, we obtain

$$\frac{\sigma^2}{2} \frac{\partial^2 \hat{g}(t, y | s, x)}{\partial x^2} + \{a(t, x)\} \frac{\partial \hat{g}(t, y | s, x)}{\partial x} - \{s\hat{g}(t, y | s, x) - g(t, y | +0, x)\} = 0. \quad (31)$$

But since

$$g(t, y | +0, x) = f(t, y | t + 0, x) = f(t, y | t, x) = \delta(y - x) \quad (32)$$

where δ is the Dirac delta function, we have

$$\frac{\sigma^2}{2} \frac{\partial^2 \hat{g}(t, y | s, x)}{\partial x^2} + a(t, x) \frac{\partial \hat{g}(t, y | s, x)}{\partial x} - s\hat{g}(t, y | s, x) = 0. \quad (33)$$

From (26) it follows that $\hat{g}(t, y | s, x)$ can be factored into the product of a function of x only and a function of y only, namely,

$$\hat{g}(t, y | s, x) = u(x)\eta(y). \quad (34)$$

Similarly, it follows that

$$\hat{g}(t, y | s, \theta_0) = u(\theta_0)\eta(y), \quad (35)$$

and therefore, from (27),

$$\hat{p}(s, \theta_0 | 0, x) = \frac{\hat{g}(t, y | s, x)}{\hat{g}(t, y | s, \theta_0)} = \frac{u(x)\eta(y)}{u(\theta_0)\eta(y)} = \frac{u(x)}{u(\theta_0)}. \quad (36)$$

If we substitute the expression for $\hat{g}(t, y | s, x)$ in (26) into (33), we have

$$\frac{\sigma^2}{2} \frac{\partial^2 \hat{p}(s, \theta_0 | 0, x)}{\partial x^2} + a(t, x) \frac{\partial \hat{p}(s, \theta_0 | 0, x)}{\partial x} - s\hat{p}(s, \theta_0 | 0, x) = 0. \quad (37)$$

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Then substituting for \hat{p} the expression in (36), we get

$$\frac{\sigma^2}{2} \frac{d^2 u(x)}{dx^2} + a(t, x) \frac{du(x)}{dx} - su(x) = 0. \quad (38)$$

Letting $\xi = \lambda(\theta_r - x) + \delta$, $u(x)$ becomes

$$u(x) = u(\theta_r - (\xi - \delta)) = U(\xi), \quad (39)$$

and then we have

$$\frac{\sigma^2}{2} \frac{d^2 U(\xi)}{d\xi^2} + \xi \frac{dU(\xi)}{d\xi} - sU(\xi) = 0, \quad (40)$$

or

$$\frac{\lambda\sigma^2}{2} \frac{d^2 U(\xi)}{d\xi^2} - \xi \frac{dU(\xi)}{d\xi} - \frac{s}{\lambda} U(\xi) = 0. \quad (41)$$

But according to [27] Eq. (41) is satisfied by

$$U(\xi) = \exp\left(\frac{\xi^2}{2\lambda\sigma^2}\right) D_{-s/\lambda}\left[\frac{\xi}{(\lambda/2)^{1/2}\sigma}\right] \quad (42)$$

where $D_{-\nu}(a)$ is the parabolic cylindrical function (Weber function), given by the following integral representation.

$$D_{-\nu}(a) = \frac{\exp(-a^2/4)}{\Gamma(\nu)} \int_0^\infty \exp\left[\frac{-ax - x^2}{2}\right] x^{\nu-1} dx \quad (\nu > 0). \quad (43)$$

Thus from (36) and (42) we have our final result for the first-passage-time distribution in terms of its Laplace transform

$$\begin{aligned} \hat{p}(s, \theta_0 | 0, w) &= \frac{u(w)}{u(\theta_0)} \\ &= \frac{\exp\{[\lambda(\theta_r - w) + \delta]^2/2\lambda\sigma^2\} \cdot D_{-s/\lambda}\{[\lambda(\theta_r - w) + \delta]/[(\lambda/2)^{1/2}\sigma]\}}{\exp\{[\lambda(\theta_r - \theta_0) + \delta]^2/2\lambda\sigma^2\} \cdot D_{-s/\lambda}\{[\lambda(\theta_r - \theta_0) + \delta]/[(\lambda/2)^{1/2}\sigma]\}} \end{aligned} \quad (44)$$

This Laplace transform must be inverted to obtain the interval distribution as a function of time, but these results will be presented elsewhere.

It is interesting to note, however, that when we make the physiological assumption that there is no membrane potential decay, then in the absence of input, the neuronal dynamics are described by a simpler random-walk model where f is governed by the diffusion equation [3]; that is,

$$\frac{\partial f}{\partial t} = \frac{\sigma^2}{2} \frac{\partial^2 f}{\partial y^2} - \delta \frac{\partial f}{\partial y}. \quad (45)$$

Then the differential equation corresponding to (38) is simply

$$\frac{\sigma^2}{2} \frac{d^2 u(x)}{dx^2} + \delta \frac{du(x)}{dx} - su(x) = 0 \quad (46)$$

the solution of which is

$$u(x) = e^{\kappa x} \quad (47)$$

where

$$\kappa = \frac{-\delta}{\sigma^2} + \frac{1}{\sigma} \left[\left(\frac{\delta}{\sigma} \right)^2 + 2s \right]^{1/2}.$$

Then

$$\hat{p}(s) = \frac{u(w)}{u(\theta_0)} = \exp[\kappa(w - \theta_0)] \quad (48)$$

or

$$\begin{aligned} \hat{p}(s) &= \exp\left((\theta_0 - w) \left(\frac{\delta}{\sigma^2} - \frac{1}{\sigma} \left[\left(\frac{\delta}{\sigma} \right)^2 + 2s \right]^{1/2} \right)\right) \\ &= \exp[ab - a(b^2 + 2s)]^{1/2} \end{aligned} \quad (49)$$

where

$$a = \frac{\theta_0 - w}{\sigma} \quad \text{and} \quad b = \frac{\delta}{\sigma}.$$

Earlier, Gerstein and Mandelbrot had shown that the interspike-interval distribution for the diffusion-type random-walk model of the neuron was (in our notation)

$$\begin{aligned} p(t) &= \frac{\theta_0 - w}{(2\pi)^{1/2} \sigma t^{3/2}} \exp\left[-\frac{1}{2} \left(\frac{\theta_0 - w - \delta t}{\sigma t^{1/2}} \right)^2\right] \\ &= \frac{a}{(2\pi)^{1/2} t^{3/2}} \exp\left[-\frac{1}{2} (at^{-1/2} - bt^{1/2})^2\right]. \end{aligned} \quad (50)$$

The Laplace transform of (50) is the same as our expression (49). A typical distribution from (50) is plotted in Fig. 5 for this simpler model.

C. Finite-difference Equation Approach

In the continuous Markov model we have outlined here, the membrane potential distribution f satisfies the equation (2)

$$\frac{\partial f}{\partial t} = \frac{\sigma^2}{2} \frac{\partial^2 f}{\partial y^2} - [\lambda(\theta_r - y) + \delta] \frac{\partial f}{\partial y} + \lambda f,$$

with the initial condition

$$f(0, y | 0, w) = \delta(y - w)$$

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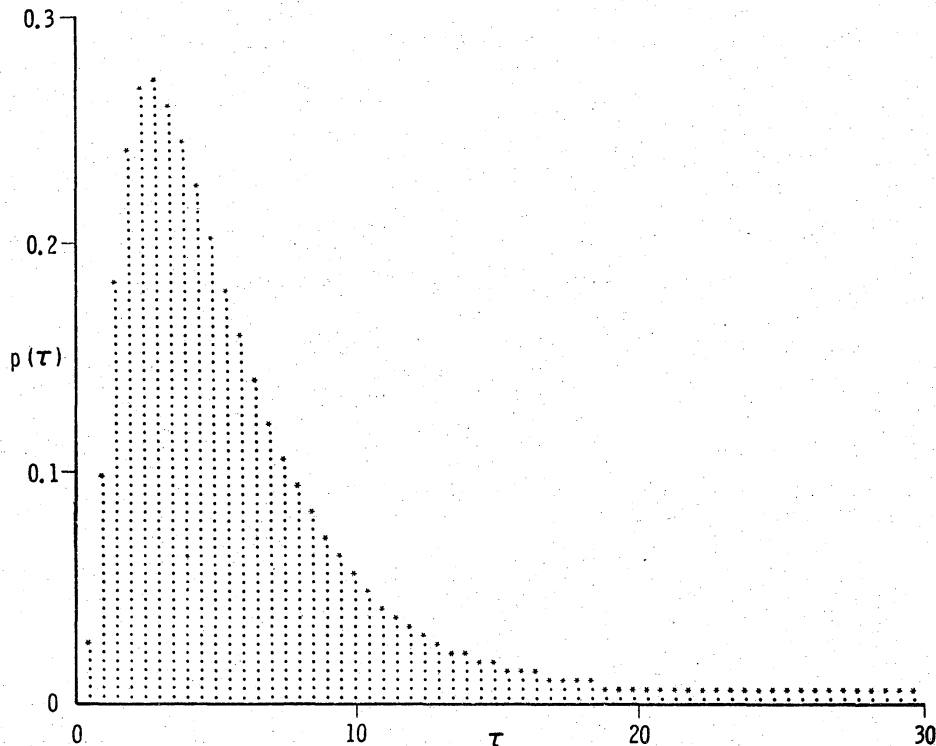


FIG. 5. Interval distribution calculated from Eq. (50) using parameter values $a = 4$, $b = 0.6$.

and the additional boundary condition

$$f(t, y | 0, w) = 0 \quad \text{at } y = \theta_0. \quad (51)$$

Our problem is to compute the spike-interval distribution

$$p(t, \theta_0 | 0, w) = \frac{\partial}{\partial t} \left[1 - \int_{-\infty}^{\theta_0} f(t, y | 0, w) dy \right] = - \frac{\partial}{\partial t} \int_{-\infty}^{\theta_0} f(t, y | 0, w) dy. \quad (52)$$

Analytic solutions for $p(t, y)$ for this problem have not been obtained except for special choices of the value of the threshold θ_0 (see Section 4, A). In this section, therefore, we show how this problem can be solved numerically using sets of finite-difference equations. Since the usual method by which the finite-difference equations corresponding to (2) are solved is quite unstable, we employ an implicit method, which uses a modification of the Crank–Nicholson type of implicit equations, as our technique [23].

As in Fig. 6, if h is the mesh size along the y axis and k is the mesh size

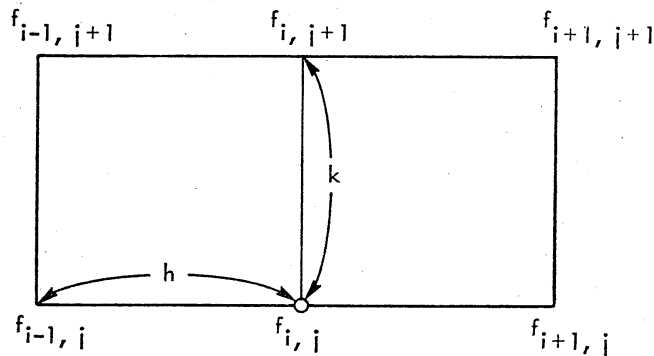


FIG. 6. Grid scheme for finite difference computation.

along the t axis, then we have the following finite-difference approximation.

$$\frac{\partial^2 f}{\partial y^2} \cong \frac{1}{2} \left(\frac{f_{i+1,j} + f_{i-1,j} - 2f_{i,j}}{h^2} + \frac{f_{i+1,j+1} + f_{i-1,j+1} - 2f_{i,j+1}}{h^2} \right); \quad (53)$$

and, letting $\sigma^2 = 2$, we have

$$\begin{aligned} \frac{f_{i,j+1} - f_{i,j}}{k} &= \frac{1}{2} \left(\frac{f_{i+1,j} + f_{i-1,j} - 2f_{i,j}}{h^2} + \frac{f_{i+1,j+1} + f_{i-1,j+1} - 2f_{i,j+1}}{h^2} \right) \\ &\quad - [\lambda(\theta_r - y_i + \delta)] \frac{1}{2} \left(\frac{f_{i+1,j} - f_{i-1,j}}{2h} + \frac{f_{i+1,j+1} - f_{i-1,j+1}}{2h} \right) - \lambda f_{i,j}. \end{aligned} \quad (54)$$

Then, putting $f = 0$ for $y = \theta_0$ and letting $r = k/h^2$, we have the following implicit equations corresponding to (2), for $i = 1, 2, 3 \dots m$ and $j = 0, 1, 2, \dots$

$$\begin{aligned} &\left\{ \frac{r}{2} + \frac{rh}{4} [\lambda(\theta_r - y_i) + \delta] \right\} f_{i-1,j+1} - (1+r)f_{i,j+1} \\ &\quad + \left\{ \frac{r}{2} - \frac{rh}{4} [\lambda(\theta_r - y_i) + \delta] \right\} f_{i+1,j+1} \\ &\quad = \frac{rh}{4} [\lambda(\theta_r - y_i) + \delta] (f_{i+1,j} - f_{i-1,j}) - \lambda k f_{i,j} - f_{i,j} \\ &\quad \quad - \frac{r}{2} (f_{i+1,j} + f_{i-1,j} - 2f_{i,j}). \end{aligned} \quad (55)$$

Then to obtain approximation of the first-passage distribution, we generate the sums

$$f_{1,j} + f_{2,j} + \dots + f_{m,j} = S_j,$$

and compute $\Delta j = S_j - S_{j+1}$ corresponding to Eq. (52). It is then only

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necessary to plot the values of Δj ($j = 0, 1, 2, \dots$) to obtain a curve that has the approximate shape of our interspike-interval distribution curve. In our trial cases, we used $h = 0.1$, $k = 0.01$ ($r = 1.0$); $\lambda = 0.1, 1, 10$; $\theta_r = 0.5$; $\delta = 0.1, 0.5, 1.0$; and $m = 6$.

Even with this larger mesh size, we obtain rather smooth interspike-interval curves, as shown in Fig. 7. It is simple to obtain finer and more

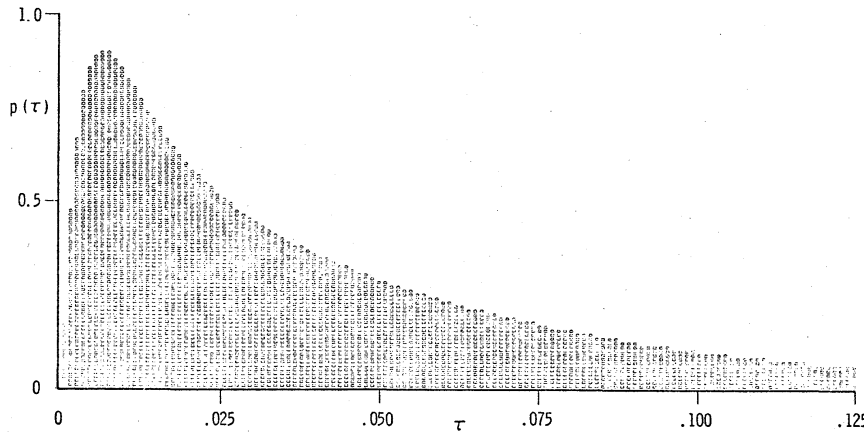


FIG. 7. Interval distribution calculated by finite-difference equation techniques. Parameter values: $x = 0.1$; $\theta_r = 0.5$; $j = 0.5$; $\sigma^2 = 2$. Mesh sizes: $h = 0.1$; $k = 0.001$.

precise estimates of the distribution curves. Indeed, this method for obtaining interval distributions is simpler and computationally shorter than the corresponding Monte Carlo simulations, which have been widely used.

SUMMARY

Despite the increasing reliance by neurophysiologists on the interspike-interval distribution as a quantitative measure of the behavior of single neurons, relatively little attention has been given to the theoretical problem of how, starting from elementary physiological considerations, such interval distributions could be predicted. Recently, efforts have been made to treat the neuronal firing problem as an example of a random-walk process to a boundary, treating the firing threshold as the boundary and the complex array of synaptic input and intrinsic cell noise as contributors to the random walk. The first-passage distribution then becomes identified with the interval distribution.

Several steps in the solution of this problem have been taken, starting with the approach of Gerstein and Mandelbrot [3], who treated the case in which no decay of membrane potential occurred in the absence of input.

Johannesma [10], Gluss [4], and Roy and Smith [17] generalized the process to include decay, but were unable to obtain solutions to the first-passage problem. Siebert [20] has recently derived a simple solution for the case of a particular choice of threshold function, which we have also derived here. In the present article we obtain closed-form solutions for the Laplace transform of the first-passage-time distribution and have obtained numerical results for these distributions, using sets of finite-difference equations. It is our hope that the properties of these solutions will be of value in interpreting neurophysiological data and will lead to new techniques for modeling and simulation of neuronal networks and processes.

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