

Neuronal Interspike Time Distributions and the Estimation of Neurophysiological and Neuroanatomical Parameters

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The first three moments of the interspike interval are determined for Poisson excitation of a neuron with exponentially decaying membrane potential and a fixed threshold for action potentials. Analytic calculations are presented for the first and second moments for small threshold to EPSP ratios and a wide range of input frequencies. The coefficient of variation plotted against mean interval reveals maxima and minima which had not been apparent from computer simulations. Numerical methods are employed for higher thresholds and for the third moment. The dependence of mean and standard deviation on threshold is approximately exponential at a given input frequency. From experimentally determined histograms of interspike intervals for two spontaneously active *cat* cochlear nucleus neurons, estimates are made of their membrane time constants, input rates of excitation and threshold to EPSP ratios. The number of connections from cochlear nerve fibers to these neurons is hence deduced.

1. Introduction

Histograms of interspike times have been obtained experimentally for many different neurons in studies which have been quite differently motivated. The underlying principle is that the histogram characterizes a neuron's spontaneous activity (a neuronal "signature" or "finger-print") and that significant changes in the state of the connections or inputs will cause a significant change in the histogram. Pfeiffer & Kiang (1965) found that discharge patterns varied systematically with anatomical location in the cochlear nucleus and a correlation has been found between the shapes of histograms and the location of neurons in the various layers of primate somato-sensory cortex (Whitsel, Roppolo & Werner, 1972). Other studies have focussed on the bursting behavior of epileptic neurons (Wyler & Fetz,

1974), changes during classical conditioning (O'Brien, Packham & Brunnhoelzi, 1973), differences between sleep and wakefulness (Benoit & Chataignier, 1973) and characterization of fast and slow pyramidal tract neurons (Koike, Mano, Okada & Oshima, 1970).

On the theoretical side there have been advanced many models of nerve membrane potential in the presence of random synaptic activation. Reviews can be found in Moore, Perkel & Segundo (1966), Fienberg (1974) and Holden (1976). One avenue of attack has been through computer simulation, e.g. Segundo *et al.* (1968), which provides a useful first step in the light of the analytic difficulties encountered in solving any realistic model. Diffusion approximations in which membrane depolarization is an Ornstein-Uhlenbeck process have been studied analytically and the moments of the interspike time obtained from the Laplace transform of the first passage density. Other models have employed step changes in membrane potential with exponentially distributed life times, e.g. Goel, Richter-Dyn & Clay (1972).

It has been well established for many CNS neurons that somatic membrane potential responds to synaptic activation, whether the invaded boutons are electrotonically close or remote, with a depolarization (EPSP) or hyperpolarization (IPSP) which has a fairly short rise time followed by an exponential-like decay. The latter clearly cannot be ignored and seems to have first been included in stochastic modelling of nerve firing by Stein (1965). To illustrate, consider a neuron whose threshold depolarization is four times the EPSP amplitude and which receives EPSP's at a rate of 400 s^{-1} . In the absence of decay the firing rate would be about 100 s^{-1} . If decay is included with a time constant of 5 ms (*cat* spinal motoneuron) one calculates the firing rate to be only about 14 s^{-1} (Tuckwell, 1976a).

Our aims in this paper are to find analytic expressions for the first and second moments of the interspike time for a Stein model neuron for threshold to EPSP ratios ≤ 2 ; to study the behavior of the coefficient of variation as a function of mean interval for a wide range of input frequencies; to determine the first three moments by numerical methods as functions of input rate, threshold to EPSP ratio and membrane time constant; and finally to estimate these three parameters for two *cat* cochlear nucleus neurons from the first three moments of their interspike time during spontaneous activity.

2. Stochastic Differential Equation and Moment Equations

In the generalized form of Stein's model (Stein, 1967; Tuckwell, 1977), the depolarization of the membrane from resting level is the solution $V(t)$ of the stochastic differential equation of a Markov process. Assuming the decay

rate is the same for all post-synaptic potentials we have:

$$dV(t) = -\sigma V(t) dt + \int_{(-\infty, \infty)} uv (dt \times du), \quad (1)$$

where σ is the reciprocal of the time constant of decay, τ , (assumed independent of V). This is an approximation because it is known (at least for *cat* spinal motoneurons) that this time constant depends on the location of the active synapses (Jack, Miller, Porter & Redman, 1971). It is pointed out that the time constant referred to is that of decay of a post-synaptic (PSP) potential *as seen at the soma* which is assumed to be near the region where the temporal summation of PSP's occurring at various synaptic locations determines how close the neuron is to the spike threshold.

In equation (1), the quantity $v(t, du)$ is the number of PSP amplitudes falling in the interval $[u, u+du]$ up to time t . This is assumed to be a temporally homogeneous Poisson process so that:

$$E[v(t, du)] = t\psi(du), \quad (2)$$

where E denotes expectation and ψ is the rate measure. The total mean rate of arrival of PSP's (of all amplitudes) is thus:

$$\Lambda = \int_{(-\infty, \infty)} \psi(du).$$

If the PSP distribution has a density, $\psi(du) = \phi(u) du$, then the conditional probability density of PSP's given that a PSP occurred is $\phi_p(u) = \phi(u)/\Lambda$. The case where ϕ_p is exponential has recently been treated by Losev (1975) and Tsurui & Osaki (1976).

Exact calculations of the moments other than the first have not appeared for Stein's model and we will determine these when there is a single excitatory input of rate parameter λ giving rise to EPSP's of amplitude ε . In this case $\phi_p(u) = \delta(u-\varepsilon)$ and the set $\{\varepsilon\}$ has a ψ -measure of λ . The integral in equation (1) can then be replaced by a single Poisson increment:

$$dV(t) = -\sigma V(t) dt + \varepsilon dN_\lambda(t), \quad (3)$$

where $N_\lambda(t)$ is a Poisson process of rate parameter λ . If an action potential is generated when $V(t)$ first reaches or exceeds the threshold θ , then the time of occurrence, T , of this event is the same as the time at which $X(t) = V(t)/\varepsilon$ first reaches or exceeds $\rho = \theta/\varepsilon$ (scale invariance). Thus we may study the simpler equation:

$$dX(t) = -\sigma X(t) dt + dN_\lambda(t). \quad (4)$$

Let $X(t)$ have initial value $x \in [0, \rho)$. The random variable T which is the time of first exit of $X(t)$ from $[0, \rho)$ has been shown (Tuckwell, 1976b) to have first, second and third moments, $F(x)$, $S(x)$ and $T(x)$, respectively,

which satisfy the following differential-difference equations:

$$-\sigma x \frac{dF}{dx} + \lambda[F(x+1) - F(x)] = -1, \quad (5)$$

$$-\sigma x \frac{dS}{dx} + \lambda[S(x+1) - S(x)] = -2F(x), \quad (6)$$

$$-\sigma x \frac{dT}{dx} + \lambda[T(x+1) - T(x)] = -3S(x), \quad (7)$$

with boundary conditions $F(x) = S(x) = T(x) = 0$ for $x \geq \rho$; $F(x)$, $S(x)$ and $T(x)$ have finite limits as x approaches zero, from above, and the constraint that $F(x)$, $S(x)$ and $T(x)$ are continuous on $[0, \rho)$. The quantities needed are $F(0)$, $S(0)$ and $T(0)$ for a neuron initially at resting level; that is, these quantities correspond (with allowance for the refractory period) to the moments μ'_1 , μ'_2 and μ'_3 of the interspike time.

3. Calculations and Results

(A) ANALYTIC EXPRESSIONS FOR $\rho \leq 2$

Let $\lambda = R\sigma$ where $R = n$ or $R = 1/n$, $n = 1, 2, 3 \dots$. Then, as outlined in the appendix, the first moment is:

$$\mu'_1 = \frac{2}{\lambda} + a_1, \quad (8)$$

where, with $\rho = 1 + \Delta$, $0 < \Delta \leq 1$,

$$a_1 = \frac{\Delta^R/\lambda}{1 - RI_1(\Delta)}, \quad (9)$$

$$I_1(\Delta) = \alpha^R \sum_{j=0}^{\infty} \frac{\alpha^j}{j+R}, \quad (10)$$

where we have set $\alpha = \Delta/(1 + \Delta)$. The second moment is:

$$\mu'_2 = \frac{2}{\lambda^2} + b_1 + \frac{2}{\lambda} \mu'_1, \quad (11)$$

where we have defined:

$$b_1 = \frac{4\Delta^R + (2Ra_1/\lambda)[RI_2(\Delta) - \log \Delta]}{1 - RI_1(\Delta)}, \quad (12)$$

with:

$$I_2(\Delta) = \log(1 + \Delta)I_1(\Delta) + \alpha^R \sum_{j=0}^{\infty} \frac{\alpha^j}{(j+R)^2}. \quad (13)$$

The moments μ'_1 and μ'_2 were computed for $n = 1, 2, \dots, 20$ (for both cases $R = n$ and $R = 1/n$) for $\rho = 1, 1.1, 1.2, \dots, 2.0$, as well as some particular values of ρ of interest. The results for μ'_1 and μ'_2 are shown only for $\rho = 1.5$ and 2.0 in Fig. 2. Here we focus attention on the coefficient of variation σ_T/μ'_1 , where σ_T is the standard deviation of the interspike time. This quantity is plotted against the mean interspike time in Fig. 1.

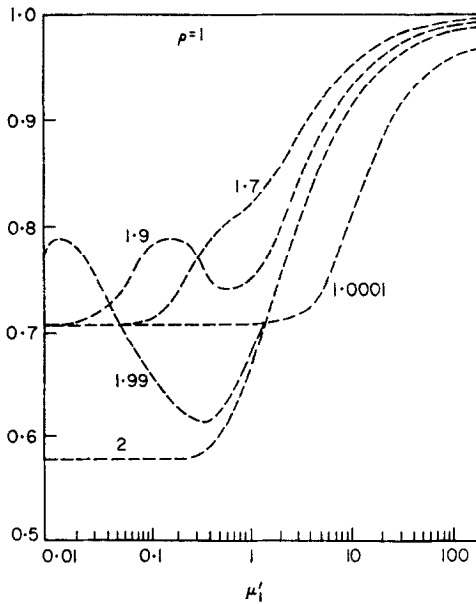


FIG. 1. Coefficient of variation of T vs. the logarithm of its mean, μ'_1 , in units of the time constant τ . The number on each curve is the ratio ρ of the threshold θ to EPSP amplitude ε .

As is well known, in the limit of large input frequencies the random variable T approaches a gamma variate. Thus if $1 < \rho < 2$, the first moment asymptotes to $2/\lambda$, the second moment to $6/\lambda^2$ and the coefficient of variation to $1/\sqrt{2}$. If $\rho = 2$, however, three EPSP's must occur before threshold is reached and the coefficient of variation asymptotes to $1/\sqrt{3}$. In general, if $[\rho]$ is the greatest integer contained in ρ then the coefficient of variation will tend to $(1 + [\rho])^{-\frac{1}{2}}$ in the limit of small mean intervals. In the limit of large mean intervals variability approaches the Poisson limit and the coefficient of variation approaches unity.

That these limiting behaviors existed is well known both for real neurons (see Enright, 1967, for a general discussion) and in computer simulation

studies of Stein's model (Stein, 1967). It has been thought previously, however, that for Stein's model the coefficient of variation is a monotonically increasing function of the mean interval for all values of the threshold to EPSP ratio. The results shown in Fig. 1 indicate otherwise. When ρ is exactly two or just greater than one, i.e. 1.0001, the coefficient of variation is apparently monotonic. The plot for $\rho = 1.7$ shows the appearance of a ripple which becomes a noticeable maximum and minimum for $\rho = 1.9$. The right hand part of the curve in this latter case tends to follow the curve for $\rho = 2.0$, which heads asymptotically towards $1/\sqrt{3}$ in a monotonic fashion. However, the curve for $\rho = 1.9$ must eventually reach $1/\sqrt{2}$ which forces it to turn upward, resulting in the observed minimum and maximum. The curve for $\rho = 1.99$ stays with that for $\rho = 2.0$ to even shorter mean intervals whereupon it commences on an even more pronounced minimum and maximum.

There are thus two main points of interest in the results obtained for the coefficient of variation. Firstly, a higher value of ρ does not imply a smaller coefficient of variation for a given mean interval. Secondly, for a given ρ , Stein's model with excitation only, does not yield a coefficient of variation which is necessarily an increasing function of the mean interval. Of course, one must take into account the absolute refractory period to compare these results with experiment and the conditions for Stein's model to be valid must be fulfilled (Tuckwell, 1976c).

(B) NUMERICAL CALCULATIONS

Analytic techniques become increasingly difficult as ρ increases or for the calculation of the third moment for Stein's model. The reason for this is that integrals of integrals must be found in order to solve the differential-difference equations (5)–(7). A numerical method has therefore been employed to find solutions of these equations with great accuracy. We illustrate the technique with equation (7) for $\rho = 2$. Define

$$\begin{aligned} T_1(x) &= T(x+1), & 0 < x \leq 1, \\ T_2(x) &= T(x), & 0 < x \leq 1, \end{aligned} \quad (14)$$

with a similar notation for $S(x)$ and $F(x)$. Then equation (7) can be written as a system of differential equations on $(0, 1]$:

$$-\sigma(x+1) \frac{dT_1}{dx} - \lambda T_1(x) = -3S_1(x), \quad (15)$$

$$-\sigma x \frac{dT_2}{dx} + \lambda [T_1(x) - T_2(x)] = -3S_2(x), \quad (16)$$

Continuity requires that:

$$T_1(0) = T_2(1), \tag{17}$$

and the finiteness of the derivative at $x = 0$ requires, from equation (7), that:

$$\lambda[T_1(0) - T_2(0)] = -3S_2(0), \tag{18}$$

[We assume in the calculation of $T(x)$ that $S(x)$ is already determined.] The iteration commences by making two estimates, t_1 and t_2 , for $T_1(0)$. The latter determines $T_2(0)$ so the "initial value problem" for equations (15) and (16) is established. This problem is solved twice numerically, once for each estimate of $T_1(0)$, employing a fourth order, variable step size Runge-Kutta method with error control. Let $L(t_i)$, $i = 1, 2, 3 \dots$, be the resulting values of $T_2(1) - T_1(0)$. Using the secant method we recursively obtain a sequence $\{t_i\}$ which converges to the value t such that $L(t) = 0$. For $\rho = 2$ it was found that $|t - t_4| < 0.00001$.

The main interest in the moments is their actual magnitudes as each one exhibits simply monotonic dependence on the parameters of the model. Figure 2 shows a plot of the first moment μ'_1 and the square root of the

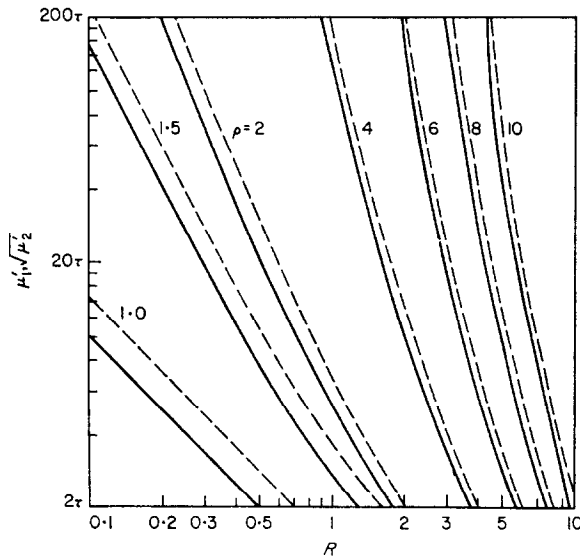


FIG. 2. Logarithmic plot of the first moment, μ'_1 , of T and the square root, $\sqrt{\mu'_2}$, of the second moment plotted against the input rate parameter $R = \lambda\tau$, λ being the actual input frequency. The heavy lines correspond to the first moment, the dashed lines to the square root of the second. The range of expected output intervals shown is between 2 and 200 time constants which represent moderate to slow frequencies of action potentials for many neurons.

second, $\sqrt{\mu'_2}$ for various values of ρ as functions of the input rate parameter R . The Poisson limit ($\rho = 1$) is also shown. The cases illustrated have mean interspike times between 2 and 200 time constants which cover the physiological range of values expected when Stein's model can be expected to perform reasonably well. The dependence of both μ'_1 and $\sqrt{\mu'_2}$ on input rate is extremely similar in this range. Noticeable, however, is that $d\mu'_1/dR$ becomes increasingly negative for larger ρ .

It is interesting that μ'_1 is approximately a linear function of $R = \lambda\tau$ over fairly wide frequency ranges. Thus we may set, for a given ρ ,

$$\mu'_1 \simeq k_1 - k_2\lambda \quad (19)$$

The expected interspike interval will be $\mu'_1 + T_R$ if T_R is the refractory period. Hence the approximate mean frequency of action potentials will be:

$$f \simeq (k_1 - k_2\lambda + T_R)^{-1}, \quad (20)$$

which, upon expansion gives approximately the linear relationship:

$$f = a + b\lambda, \quad (21)$$

when $k_2\lambda(k_1 + T_R) \ll 1$, which is in accordance with our previous results for DSCT neurons (Tuckwell, 1976c).

To illustrate the dependence of the firing rate on *threshold* for a given input frequency we show a plot of frequency of spikes (exact) f , versus ρ in Fig. 3 for $R = 1, 2, 3$. The frequencies were calculated for a neuron with $\tau = 5$ ms and the refractory period was ignored. As can be seen, the dependence of f on ρ is severe, being approximately like $e^{-\rho}$. Thus any condition which tends to increase the effective threshold (afterhyperpolarization,

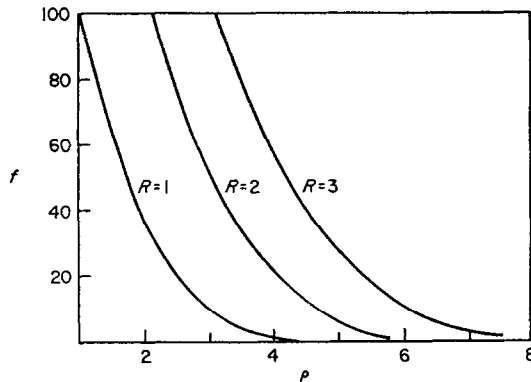


FIG. 3. Showing the strong dependence of output frequency f on the threshold to EPSP ratio ρ at three given input frequencies. Here the time constant was set at 5 ms and the values of f are in s^{-1} . No refractory period was assumed in computing f .

inhibition) will exert a powerful effect on the frequency of action potentials. We point out that including T_R in the calculation of f will lead to S-shaped curves rather than exponentially decreasing functions as shown.

Finally, to illustrate how variability of intervals depends on threshold at a given input frequency we have plotted, in Fig. 4, the standard deviation σ_T in units of τ against ρ for $R = 1, 2, 3$. Again we see a severe dependence, as σ_T goes approximately like e^ρ . The n th moment of the interspike time will behave approximately like $e^{n\rho}$ as ρ increases.

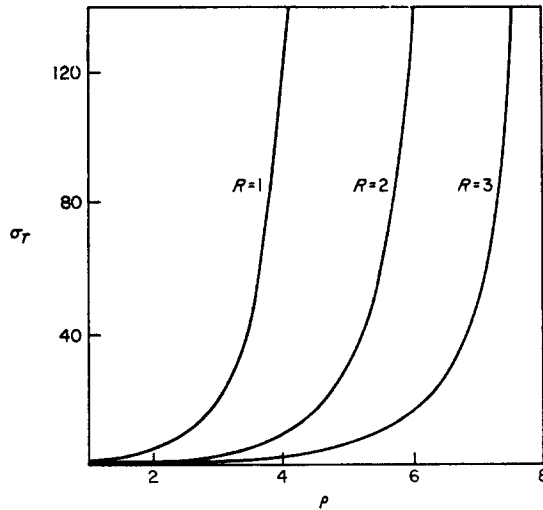


FIG. 4. Showing the strong dependence of variability, as measured by the standard deviation σ_T , on threshold at three given input frequencies. The unit of σ_T is the time constant τ .

4. Estimation of Time Constant, Input Rate and Threshold from Interval Histograms

In this section we focus on the so-called "inverse problem" (Gluss, 1967; Kryukov, 1976) which consists of the estimation of neuronal parameters from interspike time data. It is clear that for very high input rates of excitation, the moments of the interspike time in Stein's model will be close to those of a gamma variate. These moments are all determined by the values of ρ and λ . At lower input rates the interspike interval has moments which depend on three parameters, λ , ρ and τ . One would like to see whether these three quantities could be estimated from the first three moments of interspike time. There will be pitfalls in this endeavour due to uncertainties in the

physiological properties of the neuron under consideration but we proceed with this estimation procedure using Stein's model with excitation only. The histograms chosen for analysis here are those of two *cat* cochlear nucleus neurons undergoing spontaneous activity.

Many studies of distributions of interspike intervals of *cat* cochlear nucleus neurons have been reported (Gerstein & Kiang, 1960; Grossman & Viernstein, 1961; Pfeiffer & Kiang, 1965; Gerstein, Butler & Erulkar, 1968) for both spontaneous activity and response to tones of various frequencies and intensities. A theoretical investigation using a superposition of renewal processes for the input of AVCN (anterior ventral cochlear nucleus) and Stein's model for PVCN (posterior VCN) neurons was made by Molnar & Pfeiffer (1968). Figures 5 and 6 show the interval histograms for the spontaneous activity of two *cat* cochlear nucleus neurons, designated B92.12 and B81.20, obtained recently by Bourk (pers. comm.). The recording techniques are basically as outlined in Pfeiffer & Kiang (1965). The bin widths on which these histograms were originally based were 1 ms and 0.4 ms respectively. For B92.12 the total number of extracellularly recorded spikes was 8036 whereas for B81.20 the number was 17151. Both histograms are such that the underlying distributions are unimodal and resemble gamma densities of fairly low orders, suggesting that the thresholds of these neurons are not extremely large relative to the EPSP amplitudes. The time constants of decay of EPSP's for cochlear nucleus neurons have not been reported.

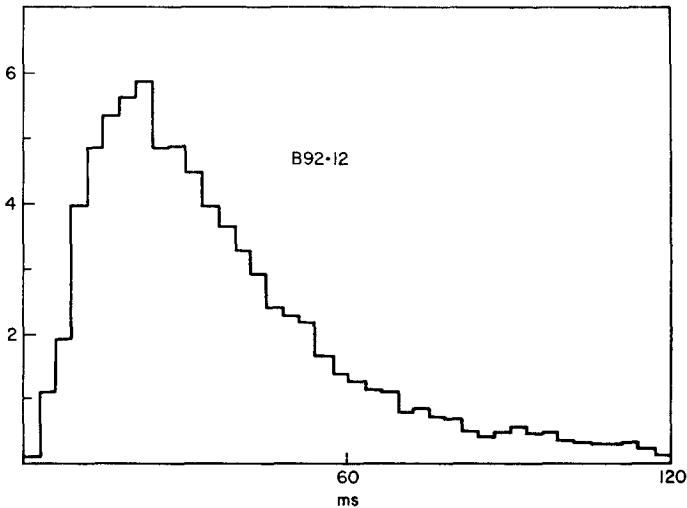


FIG. 5. Experimentally determined histogram of interspike intervals for unit B92.12 of *cat* cochlear nucleus during spontaneous activity. Some of the tail has been omitted.

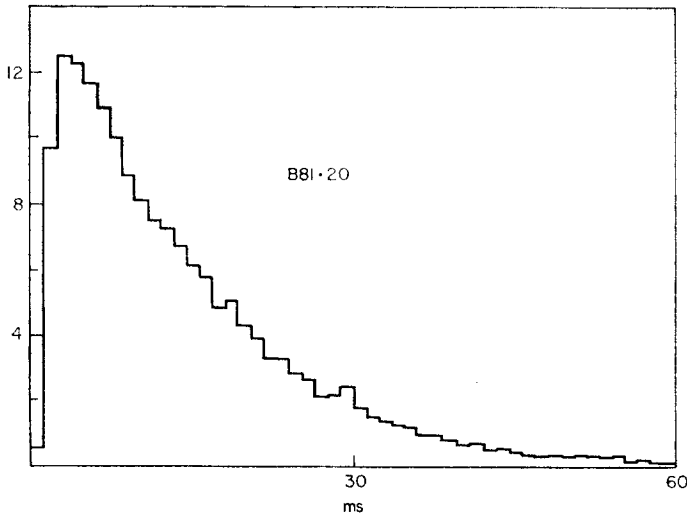


FIG. 6. Experimentally determined histogram for B81.20 of *cat* cochlear nucleus.

In order to obtain sample moments to compare with the model it is necessary to assume a value for the absolute refractory period. This was set at $T_R = 1$ ms. The method of estimation of parameters is as follows. Let m'_1 , m'_2 and m'_3 be the sample moments of $T - T_R$. The moments μ'_1 , μ'_2 and μ'_3 for the model are functions of λ , ρ and τ or R , ρ and τ .

$$\begin{aligned} \mathcal{D}_1(R, \rho, \tau) &= \mu'_1(R, \rho, \tau) - m'_1, \\ \mathcal{D}_2(R, \rho, \tau) &= \sqrt{\mu'_2(R, \rho, \tau)} - \sqrt{m'_2}, \\ \mathcal{D}_3(R, \rho, \tau) &= \sqrt[3]{\mu'_3(R, \rho, \tau)} - \sqrt[3]{m'_3} \end{aligned}$$

all of which have units ms. Choose a value of ρ and let R vary such that for each value of R chosen the value of τ is fixed by the condition $\mathcal{D}_1 = 0$. Compute \mathcal{D}_2 and \mathcal{D}_3 . As R varies \mathcal{D}_2 is found to pass through zero. At the value of R for which $\mathcal{D}_2 = 0$, compute D_3 , the corresponding value of \mathcal{D}_3 . The set of parameters which minimizes $|D_3|$ is taken as the set of estimates, which we will denote by $\hat{\lambda}$ (or \hat{R}), $\hat{\rho}$ and $\hat{\tau}$.

For neuron B92.12 we have $m'_1 = 36.87$, $\sqrt{m'_2} = 46.28$ and $\sqrt[3]{m'_3} = 56.23$ ms. A plot of D_3 , the value of \mathcal{D}_3 at which $\mathcal{D}_1 = \mathcal{D}_2 = 0$, against ρ is shown in Fig. 7. A smooth curve was drawn through several calculated points. The values are extremely small for the range of ρ values considered and D_3 actually passes from negative to positive values as ρ increases. The value of ρ at which $|D_3|$ is a minimum (zero in this case) is $\hat{\rho} = 4.5$. The corresponding value for $\hat{\tau}$ is 9.1 ms and that for $\hat{\lambda}$ is 352 s^{-1} .

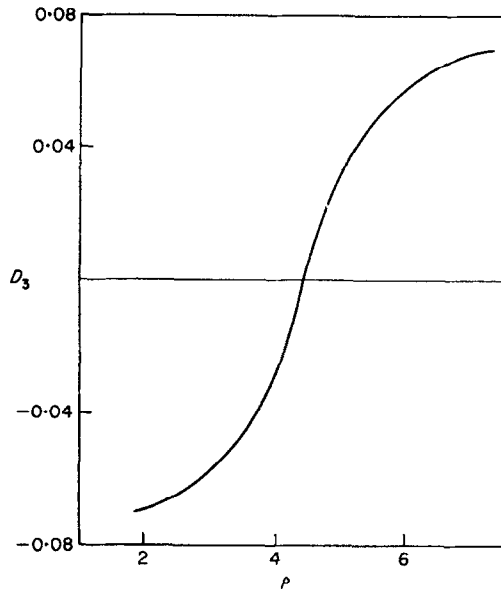


FIG. 7. D_3 , the value of \mathcal{D}_3 which occurred when \mathcal{D}_1 and \mathcal{D}_2 were both zero, plotted against ρ for neuron B92.12. For explanation see text.

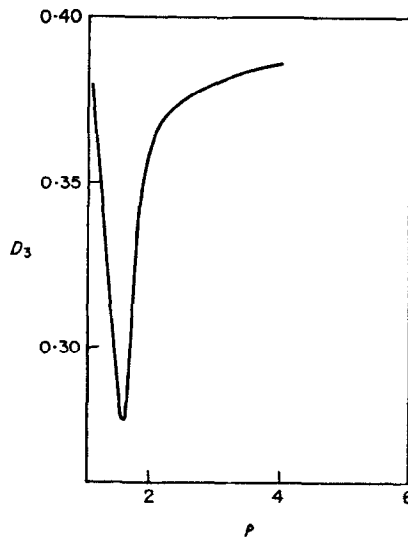


FIG. 8. D_3 , the value of \mathcal{D}_3 which occurred when \mathcal{D}_1 and \mathcal{D}_2 were both zero, plotted against ρ for neuron B81.20. For explanation see text.

For neuron B81.20 we have $m'_1 = 13.19$, $\sqrt{m'_2} = 17.59$, and $\sqrt[3]{m'_3} = 21.74$ ms. In this case the plot (Fig. 8) of D_3 against ρ reveals a sharp minimum. The estimate of ρ is $\hat{\rho} = 1.6$, the corresponding value for $\hat{\tau}$ is 5.3 ms and that for $\hat{\lambda}$ is 208 s^{-1} .

As pointed out previously (Tuckwell, 1976a), it is possible to obtain better estimates of the ratio of threshold to EPSP amplitude by making allowance for the finite rise time (α , say) of EPSP's. Let ε be the actual EPSP amplitude (i.e., peak value) and let θ be the actual threshold depolarization. The effective jump size is then $\varepsilon' = \varepsilon e^{\alpha/\tau}$ and the effective threshold is $\theta' = \theta + \varepsilon' - \varepsilon$. The estimate we have made should correspond to ρ' which is related to the actual value of ρ by:

$$\rho = e^{\alpha/\tau}(\rho' - 1) + 1.$$

Since details of EPSP's recorded intracellularly for *cat* cochlear nucleus neurons are not available we can only suppose that a typical value for α is about 1 ms, based on data for *cat* spinal motoneurons (Burke, 1967). This leads to the revised estimates $\hat{\rho} = 4.9$ for B92.12 and $\hat{\rho} = 1.7$ for B81.20.

It is natural to enquire whether these estimates are physiologically and anatomically reasonable. The mean firing rate of cochlear nerve fibers is about 40 s^{-1} based on the data in Molnar & Pfeiffer (1968). Assuming that in their spontaneously active states the neurons B92.12 and B81.20 are receiving excitation only from cochlear nerve fibres we deduce that the expected number of fibers (which may of course bifurcate) synapsing with B92.12 is nine whereas for B81.20 this number is 5.

There are many different cell types in the cochlear nucleus (Osen, 1969; McDonald & Rasmussen, 1971; Brawer, Morest & Kane, 1974). Osen classified nine cell types in AVCN, PVCN and the dorsal CN, and though there are recognizable subdivisions within the nucleus there is some overlap with "typical" cells tending to be at the centers of the subdivisions. Furthermore, inputs to most cochlear nucleus neurons arise in more than one cochlear nerve fiber with many cells in AVCN receiving inputs from only "three or so" cochlear nerve fibers (Molnar & Pfeiffer, 1968). Though there are many cell types in AVCN, the most frequent large neurons are of two chief kinds—bushy and stellate cells (Brawer *et al.*, 1974). These groups have either a few very large endings (Bulbs of Held) or a large number of boutons which occur mostly on the dendrites (spindle or stellate cells). It is suspected from our estimates, therefore, that B81.20 is one of the former category—a few connections from cochlear nerves which are strong due to their location on the cell body thus leading to a small ratio of threshold to EPSP amplitude. The unit B92.12, on the other hand, would seem to belong to the spindle cell

category with more but weaker connections from cochlear nerve afferents leading to a higher ratio of threshold to EPSP ratio.

The time constants estimates for these cells seem reasonable based on the range of membrane time constants obtained for cat spinal motoneurons (Eccles, 1964; Jack *et al.*, 1971). Furthermore, the fact that the time constant of decay for EPSP's estimated for B92.12 is longer than that for B81.20 is in accordance with the more electrotonically remote location of the excitatory synapses for the class of cell in which it is suspected that B92.12 belongs.

Finally, we summarize the chief possible sources of error in the procedures we have used.

(i) Uncertainty in the spike generating mechanisms—assumption of a trigger zone.

(ii) Neglect of afterhyperpolarization, time dependence of threshold recovery after a spike and assumption that $T_R = 1$ ms.

(iii) Inclusion of excitatory inputs only and the assumption that the EPSP amplitude is not a random variable.

(iv) Sampling error in the moments of the interspike time.

(v) The assumption that the input process is temporally homogeneous and Poisson.

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APPENDIX

To obtain the first and second moments of the time between action potentials we must obtain $F(0)$ and $S(0)$ where $F(x)$ and $S(x)$ satisfy equations (5) and (6) of the text. In the following we assume $\lambda = \sigma/n$. The results for $\lambda = n\sigma$ can be derived in closed form or by using the expressions for $\lambda = \sigma/n$ with n replaced by its reciprocal. We will solve equations (5) and (6) with $\Delta_1 < x < 1 + \Delta$ where $0 < \Delta \leq 1$, and $\Delta_1 < \Delta$ and impose the conditions that $F(\Delta_1)$ and $S(\Delta_1)$ both be zero. Then we let $\Delta_1 \rightarrow 0$ to obtain the required results.

We denote F and S by $F_1(x)$ and $S_1(x)$ for $\Delta \leq x < 1 + \Delta$ and $F_2(x)$ and $S_2(x)$ for $\Delta_1 < x < \Delta$. Utilizing the facts that $F(x)$ and $S(x)$ vanish for $x \geq 1 + \Delta$ we solve the simple first order equations:

$$-\sigma x \frac{dF_1}{dx} + \lambda F_1(x) = -1, \quad (\text{A1})$$

$$-\sigma x \frac{dS_1}{dx} + \lambda S_1(x) = -2F_1(x), \quad (\text{A2})$$

to obtain:

$$F_1(x) = \frac{1}{\lambda} + a_1 x^{-(1/n)}, \quad (\text{A3})$$

$$S_1(x) = \frac{2}{\lambda^2} + \frac{2a_1}{n\lambda} x^{-(1/n)} \log x + b_1 x^{-(1/n)}, \quad (\text{A4})$$

where a_1 and b_1 are integration constants. Utilizing these expressions in

equations (5) and (6) we can find $F_2(x)$ and $S_2(x)$ as:

$$F_2(x) = \frac{2}{\lambda} + a_2 x^{-(1/n)} + \frac{a_1}{n} x^{-(1/n)} I_1(x), \quad (\text{A5})$$

$$S_2(x) = x^{-(1/n)} \left[\frac{6x^{1/n}}{\lambda^2} + \frac{2a_2 \log x}{n\lambda} + \frac{2a_1}{n^2 \lambda} I_2(x) + \frac{b_1}{n} I_1(x) + b_2 \right], \quad (\text{A6})$$

where:

$$I_1(x) = \int \frac{y^{(1/n)-1}}{(y+1)^{1/n}} dy, \quad (\text{A7})$$

$$I_2(x) = \int \frac{x I_1(y)}{y} dy + \int \frac{x \log(y+1) y^{(1/n)-1}}{(y+1)^{1/n}} dy, \quad (\text{A8})$$

a_2 and b_2 being a further pair of integration constants.

The integral $I_1(x)$ can be obtained by change of variable:

$$\begin{aligned} I_1(x) &= n \int \frac{[x/(x+1)]^{1/n} dZ}{1-Z^n} \\ &= n \left(\frac{x}{x+1} \right)^{1/n} \sum_{j=0}^{\infty} \frac{[x/(x+1)]^j}{nj+1}. \end{aligned} \quad (\text{A9})$$

The integral $I_2(x)$ can be found by parts on the first integral in equation (A8) and then utilizing the same change of variable as before to yield:

$$I_2(x) = \log x I_1(x) - n^2 \int \frac{[x/(x+1)]^{1/n} \log Z}{1-Z^n} dZ, \quad (\text{A10})$$

which after some algebra becomes:

$$I_2(x) = \log(x+1) I_1(x) + n^2 \left(\frac{x}{x+1} \right)^{1/n} \sum_{j=0}^{\infty} \frac{[x/(x+1)]^j}{(nj+1)^2}. \quad (\text{A11})$$

We now impose the requirements that F and S be continuous at $x = \Delta$ and approach zero as $x \rightarrow \Delta_1$. This gives two equations for a_1 and a_2 and two equations for b_1 and b_2 . We will use vertical slash to indicate definite integration limits. We then obtain the following expressions:

$$a_1 = \frac{(\Delta^{1/n} - 2\Delta_1^{1/n})/\lambda}{1 - I_1(x)|_{\Delta_1}^{\Delta}}, \quad (\text{A12})$$

$$a_2 = \frac{-a_1 I_1(\Delta_1) - 2\Delta_1^{1/n}}{n - \lambda}, \quad (\text{A13})$$

$$b_1 = \frac{\frac{1}{\lambda^2} [4\Delta^{1/n} - 6\Delta_1^{1/n}] + \frac{2a_1}{n\lambda} \left[\frac{I_2(x)|_{\Delta_1}^{\Delta}}{n} - \log \Delta \right] + \frac{2a_2}{n\lambda} \log \left(\frac{\Delta}{\Delta_1} \right)}{\left(1 - \frac{I_1(x)|_{\Delta_1}^{\Delta}}{n} \right)} \quad (\text{A14})$$

In the case where $\Delta_1 \rightarrow 0$ we obtain, after careful examination of the limiting behaviour of various terms,

$$a_1 = \frac{\Delta^{1/n}}{\left(1 - \frac{I_1(\Delta)}{n}\right)}, \quad (\text{A15})$$

$$b_1 = \frac{\frac{4\Delta^{1/n}}{\lambda^2} + \frac{2a_1}{\lambda} I_2(\Delta)}{\left(1 - \frac{I_1(\Delta)}{n}\right)}. \quad (\text{A16})$$

Since dF/dx and dS/dx are required to be finite as $x \rightarrow 0$, we obtain the expressions for the first and second moments of the interspike time as given by equations (8) and (11) by inserting the value $x = 0$ in equations (5) and (6). The series expressions for I_1 and I_2 converge quite rapidly.