

Firing Rates of Motoneurons with Strong Random Synaptic Excitation

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Abstract. The expected time to firing of a nerve impulse when there is Poisson excitation is calculated exactly in Stein's model. This is done at various input frequencies and various ratios of threshold to epsp magnitude, extending some previous calculations. The appropriate conditions for the validity of the model are discussed. Details of a particular calculation are given which involves the solution of a differential-difference equation. The results are presented as variation of expected time to firing as a function of input frequency for a given threshold to epsp ratio. The experimental results of Redman et al. for Poisson monosynaptic excitation of cat spinal motoneurons lead to the estimation of the epsp size which was not measured. The magnitude of the epsps predicted is in good agreement with that expected under the given conditions of stimulation. The predicted variation of epsp magnitude with input frequency is in accordance with that obtained in other experiments. When the finite rise time of epsps is taken into account the predicted epsp sizes are in better agreement with their expected amplitudes.

1. Introduction

A nerve cell may be depolarized with respect to its resting condition either naturally by synaptic excitation (which may be artificially induced) or by intracellular injection of current. If sufficient depolarization occurs the threshold for instigation of an action potential (spike) is reached whereupon a sequence of time and voltage dependent conductance changes is commenced. These give rise to such post-spike potentials as the delayed-depolarization (missing or slight in some cells), after-hyperpolarization (AHP) and late after-depolarization. For an interesting set of articles which relate to these phenomena in connection with

the repetitive firing of cat spinal motoneurons in response to intra-cellular current injection the reader may see Kernell (1965a, b, c), Granit et al. (1966a, b), Schwindt and Calvin (1972, 1973a, b), Calvin and Schwindt (1972), Schwindt (1973), Calvin (1974), Kernell and Sjöholm (1972, 1973), and Gustafsson (1974).

It is of great interest to ascertain how a nerve cell responds to random synaptic inputs. The primary goal of studying this problem is the determination of the firing pattern for various input sequences and types (excitatory and/or inhibitory, somatic and/or dendritic). A secondary goal is to estimate various neuronal parameters (strength and rate of synaptic input, thresholds, time constants etc.) from the statistics of the firing pattern. Thus for some cells which are not amenable to intra-cellular recording one hopes to estimate neuronal properties from the statistics of the interspike interval. Such endeavours may be complicated by bursting or by unknown spontaneous or extraneous pace-maker properties.

Quite often, however, nerve cells do receive effectively random synaptic inputs when exhibiting "spontaneous" activity. Thus, for example, the output train from cat retinal ganglion cells is effectively Poisson as is indicated by the exponential distribution of waiting times for action potentials in some of the lateral geniculate neurons (Bishop et al., 1964). This means that target cells in the visual cortex will receive synaptic input from these LGN cells which is also Poisson (though other inputs may be present). Similar observations have been made on certain cat auditory neurons (Rodieck et al., 1962).

Another motivation for studying the response of neurons to random inputs is provided by the experimental approaches of certain laboratories whereby stimulation of a nerve cell according to a prescribed random sequence of pulses (Poisson, white noise) is achieved (Bryant et al., 1973; Brillinger et al., 1976;

Bryant and Segundo, 1976). Whereas those experiments have focussed on neurons of *Aplysia*, this report is mainly directed at cat spinal motoneurons receiving Poisson monosynaptic excitation as was achieved in the experiments of Redman and Lampard (1968) and Redman et al. (1968). Finally we note that the current problem is important to elucidate patterns of spontaneous activity of cortical cells whose input is effectively random. Approaches to that problem can be found in Roy and Smith (1969) and Holden (1976).

The model employed here was introduced by Stein (1965) in which the depolarization $X(t)$ in the absence of synaptic inputs decays according to

$$\frac{dX}{dt} = -\sigma X(t) \quad , \quad (1)$$

where σ is the reciprocal of the time constant τ of the membrane. If we add an excitatory synaptic input which is Poisson of rate λ and produces step-epsps of amplitude ε , we have for $X(t)$, now a Markov process,

$$dX(t) = -\sigma X(t)dt + \varepsilon d\Pi_\lambda(t), \quad (2)$$

where Π_λ is the Poisson process. This model can be generalized to handle an arbitrary number of excitatory and inhibitory synaptic potentials with prescribed probability densities for their amplitudes.

We now point out why and when this model should be reasonable one for the process under consideration, with particular reference to cat spinal motoneurons. Under strong synaptic activation many afferent fibers with terminals on the motoneuron surface are active and the subsequent epsp amplitudes may be as large as 5 to 7 mV. The average epsp size depends of course on the average number of active boutons and the source of the afferents. The intra-cellular records of such epsps show a resemblance to a step with a fairly short rise time and exponential decay (Brock et al., 1952; Eccles et al., 1957; Coombs et al., 1959; Curtis and Eccles, 1959, 1960; Burke, 1967). The threshold depolarization θ for these neurons is usually between 10 and 12 mV.

If the cell is spiking relatively slowly then the post-spike potentials will have subsided, on average, by the time the excitation starts to arrive, on average, or becomes significant. Since the AHP is the most significant after-potential, peaking at a few mV about 10 ms after the spike, then consideration of this after-potential should not be very important in Redman et al.'s experiment because the output frequency was never greater than 10 s^{-1} for Poisson stimulation. This type of firing is referred to as the "occasional spike mode" by Calvin (1974, 1975).

The remaining consideration is that Stein's model is a "point" model which takes a "lumped" capacitance and resistance in parallel to represent the neuronal

membrane. The existence of a "trigger zone" at the initial segment, which is (Conradi, 1969) devoid of synapses, for motoneurons of the cat spinal cord, is well documented (Calvin, 1975). This region has the lowest threshold on the soma-dendritic surface of the neuron for generation of an action potential. Consequently Stein's model should be a good representation for neurons which (a) undergo strong synaptic activation; that is, the post-synaptic potentials are a relatively large fraction of the threshold depolarization (b) spike fairly slowly (occasional spike mode) (c) have an effective trigger zone which is the site of effective temporal and spatial summation of post-synaptic potentials. These conditions seem to be adequately met in Redman et al.'s experiments.

Our aim here is to present a few details of calculations of the firing rates of cat spinal motoneurons undergoing strong Poisson synaptic excitation. The threshold depolarization and time constant for these neurons are well known. In Redman et al.'s experiments the epsp sizes were not measured as no intra-cellular recording was made. Though an estimate of the average epsp size in those experiments could be made using other sets of data (Burke, 1967; Blankenship and Kuno, 1968; Kuno and Miyahara, 1969a, b; Jack et al., 1971) we will use our calculations of the motoneuron firing rate to predict the average epsp amplitude, thus providing a consistency check on the model. We will assume that $\tau = 5.8 \text{ ms}$, this being the average value reported for Ia epsps by Jack et al. (1971). This value is, as expected, higher than that obtained from current injection (Nelson and Lux, 1970).

The methods to be employed have been described previously (Tuckwell, 1975, 1976a) and in the following section only one of a set of calculations will be given. A less mathematical report is being presented elsewhere (Tuckwell 1976b).

2. Calculations and Results

We suppose that the first epsp has arrived and taken the depolarization to ε . The expectation of the time to firing is obtained by solving the differential difference equation

$$-\sigma X \frac{dF}{dx} + \lambda F(x + \varepsilon) - \lambda F(x) = -1, \quad (3)$$

where $F(x)$ is the expected time to leave an interval I such that the initial value of $X(t)$ is $x \in I$.

Suppose that the Poisson rate is $\lambda = n\sigma$ and the ratio of threshold θ to ε is $2 + \Delta_2$, with $0 < \Delta_2 \leq 1$. (Note that the expected firing time depends only on θ/ε for given values of λ and σ . This is also true for the diffusion approximation.) We set $F = F_1$ for $x \in [1 + \Delta_2, 2 + \Delta_2)$, $F = F_2$ for $x \in [\Delta_2, 1 + \Delta_2)$, and $F = F_3$ for

$x \in (\Delta_1, \Delta_2)$, where $\Delta_1 < \Delta_2$. The idea is to eventually take the limit as $\Delta_1 \rightarrow 0$ to ensure that the depolarization escapes from $(\Delta_1, 2 + \Delta_2)$ through $2 + \Delta_2$.

From (3) we obtain the general recurrence relation

$$F_j(x) = x^{-n} \left[\frac{x^n}{\lambda} + n \int_x^{\infty} x^{n-1} F_{j-1}(x+1) dx + f_j \right], \quad (4)$$

where f_j , $j=1, 2, 3$, is the set of integration constants and we will have $F_0(x)=0$ for $x \geq 2 + \Delta_2$. (Note that we have set $\varepsilon=1$ because $2 + \Delta_2$ is the ratio θ/ε). Upon application of (4) we obtain the following results.

$$F_1(x) = x^{-n} \left[\frac{x^n}{\lambda} + f_1 \right], \quad (5)$$

$$F_2(x) = x^{-n} \left[\frac{2x^n}{\lambda} + n f_1 I_n(x) + f_2 \right], \quad (6)$$

$$F_3(x) = x^{-n} \left[\frac{3x^n}{\lambda} + n^2 f_1 J_n(x) + n f_2 I_n(x) + f_3 \right], \quad (7)$$

where we have defined the integrals

$$I_n(x) = \int_x^{\infty} \frac{x^{n-1}}{(x+1)^n} dx, \quad (8)$$

$$J_n(x) = \int_x^{\infty} \frac{x^{n-1} I_n(x+1)}{(x+1)^n} dx. \quad (9)$$

The first of these integrals can be evaluated explicitly without trouble. The second can be evaluated up to $n=3$, but the expressions are so lengthy that they will not be written down here.

We impose continuity requirements on $F(x)$ at $1 + \Delta_2, \Delta_2$, and require that $F(x)$ continuously approach zero at Δ_1 . This gives three equations for f_1, f_2 , and f_3 . Upon solving for the first constant we obtain

$$f_1 = \frac{\frac{\Delta_2^n}{\lambda} - \frac{3\Delta_1^n}{\lambda} + \frac{(1+\Delta_2)^n}{\lambda} [1 - n I_n|_{\Delta_1}^{\Delta_2}]}{1 - n^2 J_n|_{\Delta_1}^{\Delta_2} - n I_n|_{\Delta_1}^{1+\Delta_2} + n^2 I_n(1+\Delta_2) I_n|_{\Delta_1}^{\Delta_2}}, \quad (10)$$

where the vertical bars indicate limits of integration. One then finds f_2 which is needed because the first escape time of $X(t)$ commencing at 1 is

$$F(1) = \frac{2}{\lambda} + n f_1 I_n(1) + f_2. \quad (11)$$

Taking into account the time to the first jump which took $X(t)$ to 1 we obtain for the expectation of the time to firing

$$\bar{T} = \frac{3}{\lambda} - \frac{(1+\Delta_2)^n}{\lambda} + f_1 [1 - n I_n|_1^{1+\Delta_2}] + T_R, \quad (12)$$

where we have added a fixed absolute refractory period T_R which is quite small (about 1.5 ms for lumbosacral motoneurons).

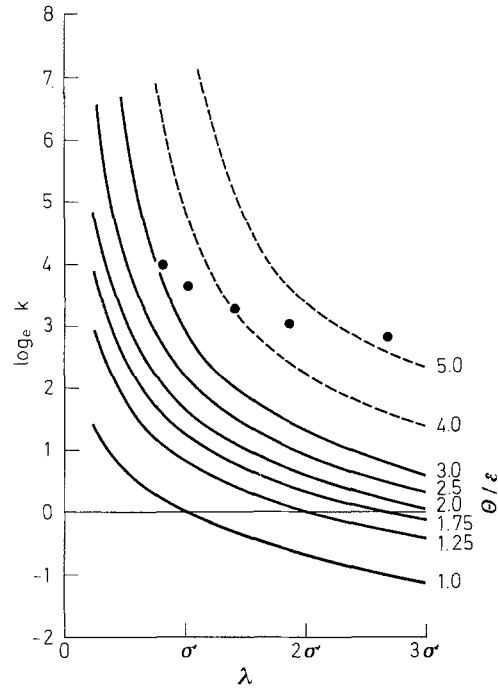


Fig. 1. The quantity $\log_e k$ plotted against mean rate of arrival of epsps, for various values of the ratio of threshold to epsp amplitude. The expected time between output pulses is $T_R + k\tau$ where τ is the membrane time constant and T_R is the absolute refractory period. The input rate, λ , is expressed in units of the reciprocal, σ , of the membrane time constant

Explicit calculations of the above type were done as follows. For $\lambda = \sigma/2, \sigma, 2\sigma$, and 3σ the values of θ/ε were 1.25, 1.5, 1.75, 2.0, 2.5, and 3.0. For $\lambda = \sigma/4$ the values 2.5 and 3.0 were not considered for θ/ε (these lead to extremely low firing rates).

It is convenient to present the expected time to firing in the form

$$\bar{T} = T_R + k\tau \quad (13)$$

which is possible because our calculations were done with $\lambda^{-1} = \tau/n$ and $\lambda^{-1} = n\tau$. In Figure 1 we show the variation of $\ln(k)$ as a function of input rate, expressed in terms of σ , for various values of θ/ε . These results enable the expected time to firing to be calculated with the aid of (13) for any neuron for which Stein's model is appropriate when the time constant and θ/ε are known. The most interesting feature of these plots of $\ln(k)$ versus input frequency is how closely they resemble the curve obtained for a neuron with $\theta/\varepsilon = 1$. The waiting time average is then just $1/\lambda$. The two dashed lines on the figure are approximate results for $\theta/\varepsilon = 4.0$ and 5.0 . These were obtained by plotting $\ln(k)$ versus θ/ε at various input frequencies and then extrapolating with smooth curves.

The Poisson rates used in Redman et al. (1968) were 25, 35, 44, 60, 80, and 115 per second on each of

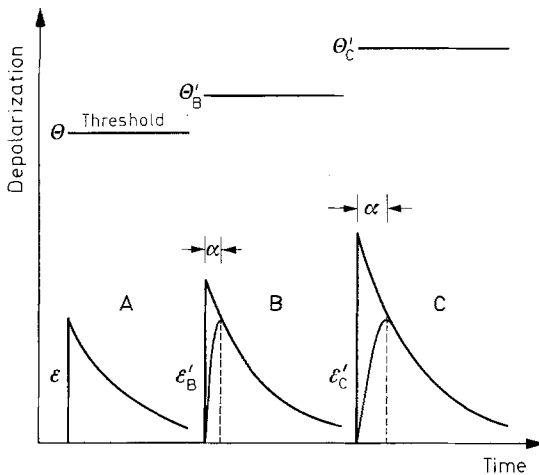


Fig. 2A—C. Showing how an epsp with a finite rise time can be replaced by a step change in depolarization. (A) The response to a delta-function current as used in Stein's model. (B) An epsp with a moderately small rise time is replaced by an effective jump of magnitude ϵ'_B . (C) An epsp with a longer rise time, as one might expect for activation of distal dendritic synapses, is replaced by a still larger effective jump. Note the increase in effective thresholds as the rise time increases

four independent stimulators each of which provided approximately the same strength excitation to the motoneuron under study. These input frequencies should thus be multiplied by 4 to obtain the correct value of λ . When the lowest input frequency was employed, no discharges were recorded, from which it is inferred that the waiting time to firing has an average value of the order of the period of recording (around 60 s). The mean output frequencies obtained by Redman et al. were converted to waiting times for spikes, the absolute refractory period was subtracted and the resulting time converted to units of τ , the time constant (5.8 ms). The corresponding values of $\ln(k)$ were obtained and the resulting points are indicated by filled circles in Figure 1. It can be seen that these experimental points traverse an increasing sequence of values of θ/ϵ .

Using interpolation the values of θ/ϵ are approximately 3.1, 3.4, 4.0, 4.5, and 5.2 for those input frequencies at which action potentials were obtained. Using the value $\theta = 12$ mV (Calvin and Schwandt, 1972, Figure 2) we thus obtain estimates of the corresponding epsp amplitudes of 3.9, 3.5, 3.0, 2.7, and 2.3 mV at the input frequencies 140, 176, 240, 230, and 460 s^{-1} .

These values for the epsp amplitudes are in good agreement with the expected amplitudes for excitation through bundles containing a few afferent fibers as was the case in Redman et al.'s experiment. The decline in epsp size with increasing frequency of stimulation is in agreement with that obtained for steady state repetitive

monosynaptic Ia excitation of spinal motoneurons (Curtis and Eccles, 1960). However, the agreement is good only if we take the frequency in the random case to be the total frequency with all four stimulators. If the decline in epsp size with increasing frequency is pre-synaptic (limited available total transmitter substance) as was suggested by Curtis and Eccles, then the decline in epsp size should be in accordance with the frequency of stimulation of each afferent bundle taken separately. There may, however, be post-synaptic interaction between the epsps from the different sources of stimulation so that this contributes to the unexpected rapid decline of epsp amplitude.

There are other factors which may account for some of this discrepancy. Firstly, Stein's model does not take into account the after-hyperpolarization which must always lead to a decrease in output frequency. This will effectively increase the threshold thus making the values of θ/ϵ less for Redman et al.'s experiments (corresponding to shifting the curves in Figure 1 upwards). Secondly, recurrent inhibition will also increase the effective threshold, probably by a few mV (Burke et al., 1971). Thirdly, the rise time for actual epsp's is finite. Suppose in fact that the rise time is α ms and that the amplitude of an epsp is ϵ when it arrives with the neuron at resting potential. Then one can get an improved model for the depolarization potential by making the jump in Stein's model into an effective jump of magnitude (see Fig. 2),

$$\epsilon' = e^{\alpha/\tau} \epsilon. \quad (14)$$

This makes the membrane potential trajectories agree after the rise time. There will of course be a dependence of ϵ' on the depolarization already present when the epsp arrives but one could take the average for the case of an epsp arriving at resting level and one arriving near threshold to get a better estimate. If this procedure is adopted then to make the model consistent one must add the difference between ϵ' and ϵ to the threshold. Suppose one takes the value 1.0 ms for the rise time (appropriate for Ia excitation of cat spinal motoneurons) and the values $\theta = 12$ mV, $\tau = 5.8$ ms, and $\epsilon = 5$ mV. Then Stein's model sets $\theta/\epsilon = 2.4$, whereas if we incorporate the effective epsp amplitude (14) we obtain the value 2.02 for this ratio. That is, there will be an increase in output frequency.

Noteworthy in this connection is that for a given set of input and neuronal parameters, an epsp with a longer rise time leads to a smaller effective ratio θ/ϵ (see Fig. 2). Since epsps which arrive from terminals on distal dendrites tend to have longer rise times than those arriving at proximal dendrites and the soma (Rall et al., 1967) then a random sequence of epsps of distal-dendritic origin will lead to a higher expected

output frequency than a corresponding sequence of epsps of the same amplitude arriving at the soma or proximal dendrites. There is an additional factor which makes the output frequency higher for activation of distal-dendritic synapses. This is that epsps of such an origin tend to decay with a longer time constant. A fuller analysis of the quantitative differences for these two types of input will be deferred to a future article.

We pursue the matter of finite rise times in relation to Redman et al.'s results. Using the average rise time of $\alpha = 1.38$ ms, obtained by Burke (1967) for Ia monosynaptic epsps in cat spinal motoneurons we find that the effective epp amplitude becomes $\varepsilon' = 1.27\varepsilon$. Let the effective value of θ be denoted θ' . The experimental firing rates should correspond more closely with the values of θ'/ε' . These should then be converted to the actual values of θ/ε according to the formula

$$\frac{\theta}{\varepsilon} = 1.27 \left(\frac{\theta'}{\varepsilon'} \right) - 0.27. \quad (15)$$

Using the values from the experimental points in Figure 1, we obtain our final estimates of threshold to epp ratio as 3.7, 4.0, 4.8, 5.4, and 6.3. These correspond ($\theta = 12$ mV) to epp sizes of 3.2, 3.0, 2.5, 2.2, and 1.9 mV respectively. These values, being somewhat smaller than those obtained without modifying Stein's model, are in closer agreement with the amplitudes one expects to find for the stimulus conditions in Redman et al.'s experiment.

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Note added in proof. The above calculations showed that there was an effective increase in θ/ε as the frequency of excitation and the output frequency of spikes increased. It was difficult to reconcile this with the results of Curtis and Eccles (1960). A recent calculation (Tuckwell and Walsh, 1976) showed that even though the steady state epsp amplitude decreases as input frequency of triangular current pulses (representing synaptic excitation) increases, this decrease cannot be attributed to transmitter depletion. In fact, for such current pulses the effective epsp amplitude (see Eq. (14)) is independent of the membrane potential when the current pulse arrives. Since it seems unlikely that the after-hyperpolarization would lead to the observed increases in the effective values of θ/ε seen at higher frequencies, it is more likely that recurrent inhibition mediated by Renshaw cells is the source of hyperpolarization in the experiment considered. The magnitude of this hyperpolarization will in fact increase as the motoneuron discharges more rapidly and lead to the observed changes in θ/ε .