A THEORETICAL ANALYSIS OF NEURONAL VARIABILITY

RICHARD B. STEIN
From the University Laboratory of Physiology, Oxford, England

ABSTRACT A simple neuronal model is assumed in which, after a refractory period, excitatory and inhibitory exponentially decaying inputs of constant size occur at random intervals and sum until a threshold is reached. The distribution of time intervals between successive neuronal firings (interresponse time histogram), the firing rate as a function of input frequency, the variability in the time course of depolarization from trial to trial, and the strength-duration curve are derived for this model. The predictions are compared with data from the literature and good qualitative agreement is found. All parameters are experimentally measurable and a direct test of the theory is possible with present techniques. The assumptions of the model are relaxed and the effects of such experimentally found phenomena as relative refractory and supernormal periods, adaptation, potentiation, and rhythmic slow potentials are discussed. Implications for gross behavior studies are considered briefly.

A. INTRODUCTION

During the past fifteen years considerable progress has been made in understanding the basis of the initiation and transmission of neuronal impulses in quantitative terms. The theories (Hodgkin and Huxley, 1952; Katz, 1950; Eccles, 1957) have been determinate; that is, a given applied voltage pattern or pattern of presynaptic neuronal firings is assumed to determine the subsequent behavior of the neuron exactly. Yet, one of the most striking observations in complex neuronal systems is the variability in firing intervals when external stimuli are held constant. Indeed, variable spontaneous activity often persists without any apparent external stimulus. It is generally assumed that this variability results from the fact that neurons possess large numbers of synapses and several types of inputs, so that excitatory impulses occur effectively at random. It has been shown experimentally at cholinergic (Del Castillo and Katz, 1954) and non-cholinergic neuromuscular junctions (Dudel and Kuffler, 1961) and at some cholinergic (Blackman *et al.*, 1963) and central nervous system synapses (Katz and Miledi, 1963) that, in the absence of neural inputs, excitatory quanta of transmitter are released at random and that the resulting depolarization decays roughly exponentially. Similarly, the random, quantal nature

of the photons falling on the retina has been found to account satisfactorily for the variability in vision at low light intensities (see Bouman, 1961, for a review of the evidence). Finally, excitatory and inhibitory presynaptic neuronal firings[1] have been shown to produce individual depolarizations which sum and decay roughly exponentially (Eccles, 1957). Whether the many inputs of the central neuron can be adequately described by assuming quantal effects at random intervals has not been clearly demonstrated. Where there are strong rhythmic slow potentials, for example, the assumption of random quantal excitation and inhibition is probably not valid.

The purpose of this paper is to consider what is known about the basis of neuronal activity and use this knowledge to derive certain quantitative, experimentally testable predictions about neuronal behavior under natural conditions. Initially, a simplified determinate model is assumed, together with the assumption that excitatory impulses of unit size do occur at random intervals. Several important properties of this model are derived. Similar calculations are then made for a more general model involving inhibitory as well as excitatory pulses. In the last section, the assumption of randomness will be relaxed and still more refined neuronal models will be considered. The reason for proceeding by stages is analytic. Even with the simpler model, the general form of such quantities as the interresponse time distribution is exceedingly complex. Special cases that yield exact quantitative predictions are therefore treated first, followed by a discussion of more general cases.

All parameters used are experimentally measurable quantities, and the predictions are thus directly testable. Despite the many interresponse time distributions in the recent literature, there are none known to the present author in which all the necessary parameters have been measured independently of the distribution and as a result, an exact experimental check cannot yet be made. The distributions considered are, however, compatible with the theoretical predictions. The complexity of the model necessary to fit any particular distribution must await better experimental data and will no doubt vary from case to case. The analysis should be of more general interest and where other specific assumptions are needed, methods similar to those used here can be applied.

One value of a deductive approach, such as outlined here, is that all constants are measurable quantities. The complexity of an adequate model for a neuron *in vivo* is thus open to direct verification in a particular situation. Conversely, an inductive method with sufficient free parameters is not open to experimental verification or rejection, since almost any curve can be fitted by variation of the parameters.

[1] In this paper "firing" refers to an all-or-none neuronal action potential. The terms excitatory (or inhibitory) impulses, and quantal excitation (or inhibition) refer to single intracellular responses to external stimuli which sum and decay with time until an action potential occurs. These terms are used in preference to the more common terms, excitatory postsynaptic potential (EPSP) and inhibitory postsynaptic potential (IPSP) which may indicate the summed response from many presynaptic neuronal firings and which do not generally refer to processes occurring in first order neurons or muscle end plates.

B. THEORY AND PREDICTIONS

The following model is assumed.

1. Excitatory impulses occur randomly with a frequency p_e/sec.

2. After each neuronal firing there is a refractory period of duration, t_o, during which the impulses have no effect and the membrane depolarization,[2] V_t, is reset to zero.

3. At times $t > t_o$, each impulse produces unit depolarization.

4. If the depolarization reaches a threshold of r units, the neuron fires.

5. For subthreshold levels, the depolarization decays exponentially between impulses with time constant τ.

There are several phenomena which are *not* taken into account by this model; such as the relative refractory period, the supernormal period, post-tetanic potentiation, pre- and postsynaptic inhibition, as well as the refinements of cable theory (Hodgkin and Rushton, 1946), and Hodgkin-Huxley theory. Each assumption will be considered later in the light of these phenomena and the effects of these refinements on the present calculations will be discussed.

(*a*) *The Distribution of Neuronal Firing Intervals.* A general expression for the expected interresponse time distribution for the model is not known, though a partial differential equation for the distribution will be derived later. The difficulty in calculating the distribution lies in assumption 5, that the depolarization decays exponentially between excitatory impulses. If the decay is negligible, the distribution can be derived exactly. The situation of negligible decay, where in our notation $p_e\tau \gg r$ will be treated as a first approximation. The limiting cases for the interresponse time distribution can then be derived immediately. If $r \leq 1$ each impulse causes a neuronal firing. The assumption of randomness implies that excitatory impulses and hence neuronal firings are exponentially distributed. For $r \gg 1$ the distribution approaches a normal distribution according to the central limit theorem of mathematics. For all r, the exact form is the well known gamma distribution[3] given in our notation by equation (1).[4]

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[2] Assumption 2 determines the zero point of V_t. Assumption 3 determines the unit of measuring V_t.

[3] The gamma distribution can be seen to be the product of two simpler factors as follows. If there are p_e impulses/sec., the probability that there will be an impulse in a short time, dt, is simply $p_e\,dt$. The probability of exactly $r - 1$ impulses in a time interval $t - t_o$ $(t \geq t_o)$ is given by the Poisson distribution with parameters p_e, $t - t_o$, and $r - 1$, namely $f(t) = [p_e(t - t_o)]^{r-1} \exp [-p_e(t - t_o)]/(r - 1)!$. The probability that the r^{th} impulse will occur between times t and $t + dt$, namely $f(t)\,dt$, is the product of these two and is seen to agree with equation (1) above. For further properties of the distribution, consult a probability text such as Fisz (1963).

[4] Strictly speaking the quantity $\bar{r}$ = integral part of $r + 1$ should be used in equation (1), if non-integral thresholds are allowed. If, for example, $r = 2.8$ units, at least $\bar{r} = 3$ impulses are required to surpass threshold.

$$f(t) = 0 \qquad , t \leq t_0$$

$$f(t) = \frac{p_e^r (t - t_0)^{r-1}}{(r-1)!} \exp\left[-p_e(t - t_0)\right] \qquad , t > t_0 \tag{1}$$

The cumulative gamma distribution $F(t) = \int_0^t f(t)\, dt$ has been tabled extensively by Pearson (1922).

For ease of visual inspection, interresponse time distributions in this article are plotted on cumulative probability paper. On this paper the two ends are spread out so that a cumulative normal curve plots as a straight line. Various gamma distributions are plotted in Fig. 1 in units of their standard deviations. Each is a smooth gentle curve on this paper and the amount of curvature is inversely related to the value of r. Plotted in this way, deviations are readily visible as "bends" or inflections in the graph.

For cases other than negligible decay, the distribution was derived by computer simulation.

The computation was done as follows. Random numbers over the interval $0 < x < 1$ were selected. The negative logarithm was then taken to produce a random exponential distribution of intervals. For each interval a unit depolarization was added after calculating the decay since the last impulse. The depolarization level was compared to threshold

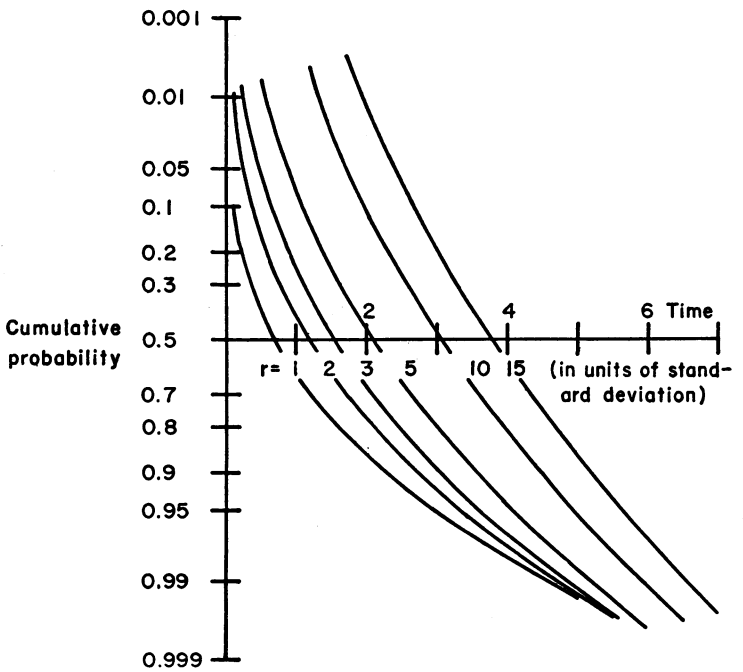

FIGURE 1 Gamma distributions. Distributions for various values of parameter r are plotted on cumulative probability paper for comparison with simulated distributions. A cumulative normal ($r \rightarrow \infty$) would give a straight line on this paper.

and the process continued until "firing." 500 firings were computed in this way for each value of p_e and r used. The mean, variance, and cumulative distribution were then printed out by the computer. Values of threshold (r) between 2 and 20 and values of impulse frequency (p_e) between 0.3 and 30 were used. The decay constant (τ) was set equal to 1 and the refractory period (t_e) equal to zero in the simulation.

For all values of parameters p_e and r, a gamma distribution such as that given in equation (1) could be used to fit the simulated distributions,[5] through with $p_e\tau \approx r$ systematic deviations were noted at early times when r was fairly large. Sample distributions are given in Fig. 2 together with a good fitting gamma distribution. The parameters which yielded the best fit, p', r', and t_o', were often quite different from the neuronal parameters p_e and r used, but varied in a systematic way as shown in Fig. 3. In this figure the standard deviations of some simulated distributions are plotted as a function of the mean. The slope gives an estimate of $(r')^{-1/2}$ since for gamma distributions with a given t_o', $r' = [(\mu_t - t_o')/\sigma_t]^2$.[6]

The reason for these results may be clarified by an example. Assume threshold is 2.8 units. If $p_e\tau \gg 2.8$, it will take just three excitatory impulses to surpass threshold and the distribution of times is given by a gamma distribution with parameters $r' = \bar{r} = 3$ and $p' = p_e$, as previously explained. As p_e decreases, decay enters in and sometimes 4 quanta are required or 5; then, the best fitting gamma curve has $r' > 3$. Eventually as many more quantal numbers enter in, the conditional probability of firing approaches a constant for all times after an initial period t_o' in which few firings occur, though the average depolarization increases. The distribution is then an exponential (a gamma distribution with $r' = 1$) beginning after t_o'. One would not expect t_o' to be sharply defined and hence an initial deviation would be predicted at very early times from responses occurring before t_o'.

These last conclusions can be derived more analytically. It will be shown later that in the absence of neuronal firings, the average time course of the depolarization level for this model denoted by μ_v is simply

$$\mu_v = (p_e\tau)(1 - e^{-t/\tau}) \tag{2}$$

The variance in level σ_v^2 is given by

$$\sigma_v^2 = (p_e\tau/2)(1 - e^{-2t/\tau}) \tag{3}$$

If $p_e\tau < r$ the average level is always less than threshold and approaches a constant, as does the variability. "Selecting out" those neurons that reach a level r in each interval will affect these equations, but, particularly where neuronal firings are

[5] It is important to note that many classes of curves can*not* be fitted by a gamma distribution. These include all negatively skewed curves, any reasonably flat curve (approaching a rectangular distribution), sharply peaked distributions (such as the Laplace distribution), or multipeaked distributions.

[6] The subscript t used with μ_t and σ_t^2 indicates that these are the mean and variance in time to neuronal firing.

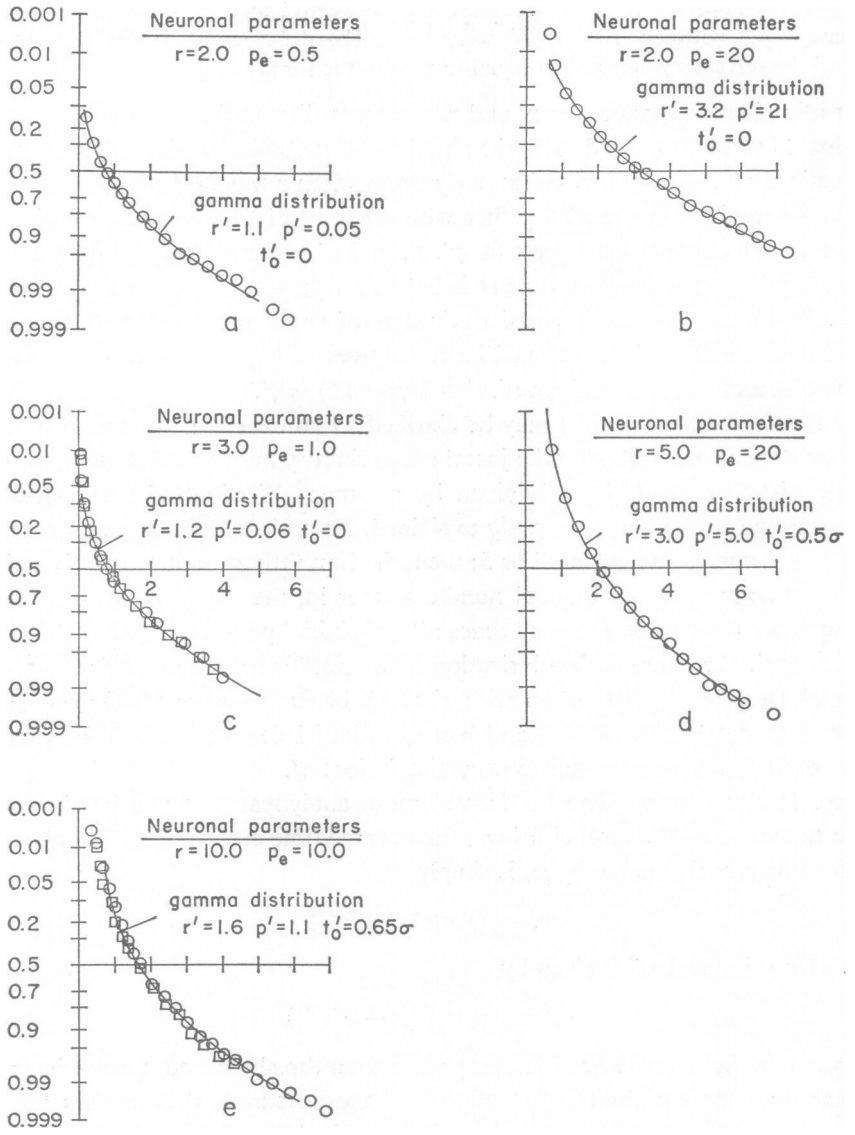

FIGURE 2 Computer simulated interresponse time distributions. The neuronal model is described in the test. Data are plotted on cumulative probability paper. Ordinate: cumulative probability of firing. Abscissa: time in units of the standard deviation. The solid line is a good fitting gamma distribution with the parameters p', r', and t_o' indicated near each curve. r and p_e refer to the neuronal parameters used in the simulation. A refractory period was not used ($t_o = 0$). ○ and □ refer to different simulations of 500 firings each.

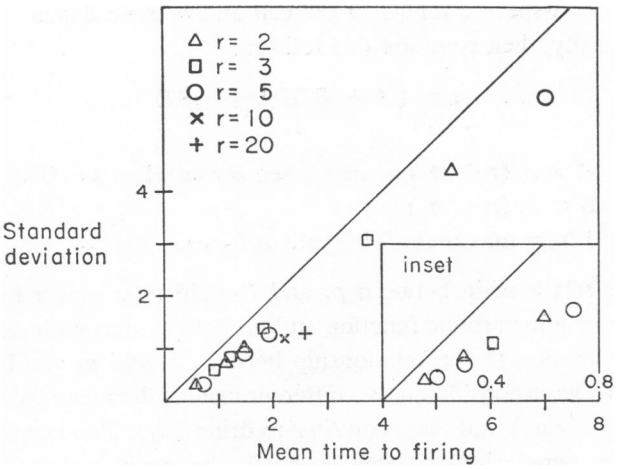

FIGURE 3 Standard deviation of simulated distributions as a function of the mean. Explanation in text. The solid lines in the main figure and in the inset are lines of unit slope passing through the origin. The inset at the lower right gives values for high firing rates (short mean times). Each point was calculated from a simulation of at least 500 firings. Time is measured in units of the time constant of depolarizing impulses (τ). Different symbols indicate different values of threshold (r) as given in the upper left-hand corner.

rare, the selections cannot reintroduce a time dependency. Thus, after a few time constants, the conditional probability of neuronal firing is constant and the distribution is exponential. Apparent refractory periods (t_o') obtained by finding the best fitting gamma distribution may exceed the neuronal refractory period by a couple of time constants (τ). The exact distribution can, of course, be predicted by computer simulation with the neuronal parameters r, $p_e\tau$, and t_o.

(*b*) *Neuronal Firing Rate as a Function of Stimulus Intensity.* In the limit of negligible decay where the gamma distribution with parameters p_e, r, and t_o provides a suitable fit, the neuronal firing rate as a function of the excitatory impulse rate (p_e) can be simply obtained. The mean, μ_t, and variance, σ_t^2, of the gamma distribution of equation (1) are known and are simply

$$\mu_t = r/p_e + t_o \qquad \sigma_t^2 = r/p_e^2 \tag{4}$$

The inverse of the mean gives the frequency of neuronal firings which will be denoted by α.

$$\alpha = 1/\mu_t = (p_e/r)/(1 + t_o p_e/r) \qquad \text{(assumes } p_e\tau \gg r\text{)} \tag{5}$$

This $x/1 + x$ form is known as a simple or rectangular hyperbolic function. It reduces to a straight line $\alpha = p_e/r$ for $p_e/r \ll 1/t_o$, that is, for most of the physiological range. In order to get α as a function of stimulus intensity, we must assume some relation between rate of excitatory impulses p_e and intensity I. If $p_e = a + bI$ where

a represents the non-specific inputs to the cell and b those depending (in this case linearly) on intensity, then equation (6) follows:

$$\alpha = (A + BI)/(1 + t_o BI) \tag{6}$$

where

$A = a/(r + at_o)$ = spontaneous rate when $I = 0$
$B = b/(r + at_o)$
$1/t_o$ = maximum firing rate as $I \to \infty$

However, the relationship between p_e and I could be a power function, a logarithmic relation, or a hyperbolic function and probably varies with sensory modality. A closer approximation to the relationship between α and p_e can be derived from equation (2). We have considered two different means, the mean *level* of depolarization at a given time (μ_v) and the mean *time* to firing (μ_t). However, if the fractional variability in the depolarization level is small, the mean time of neuronal firing should occur at the time (after the refractory period t_o) when the mean level reaches r. Thus,

$$r = (p_e\tau)[1 - \exp(-(\mu_t - t_o)/\tau)] \tag{7}$$

Rearranging and taking logarithms on both sides, we get

$$\mu_t = -(\tau)[\log(1 - r/p_e\tau)] + t_o \tag{8}$$

From equations (2), (3), and (7) it is seen that the fractional variability, $\sigma_t/(\mu_t - t_o)$, is proportional to $r^{-\frac{1}{2}}$ and thus decreases as r increases. In Fig. 4 the simulated means are plotted against the right-hand side of equation (8) (a refrac-

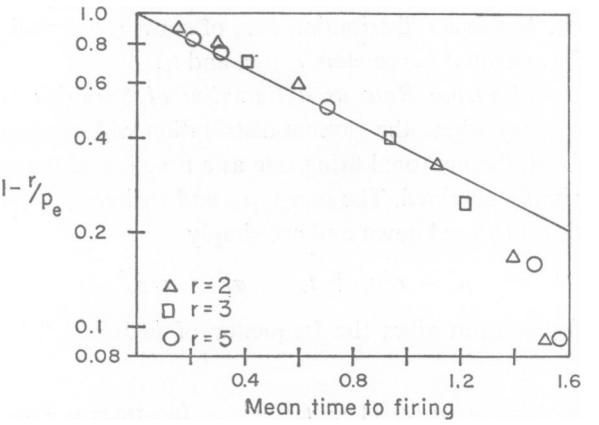

FIGURE 4 Mean times to firing for simulated distributions. The straight line (on a semilog plot) is the approximate result given by equation (8), $\mu = -\tau \log(1 - r/p_e\tau) + t_o$. In the simulated distributions $t_o = 0$ and $\tau = 1$. Different symbols indicate different values of threshold (r) as given in the lower left-hand corner. Note that as threshold increases the validity of the approximation improves.

tory period was not used in the simulation) and it is seen that the agreement is good down to $p_e \tau = 1.5r$, even for $r = 2$. The frequency of firing α is thus given by

$$\alpha = 1/\mu_t = \frac{1}{\tau \log [p_e\tau/(p_e\tau - r)] + t_o} \quad \text{(assumes } p_e\tau > 1.5r\text{)} \tag{9}$$

Again the relationship between p_e and I must be known to relate the frequency of firing to the stimulus intensity.

(*c*) *Strength-Duration Curves.* If a current is used to produce depolarization, the excitatory quantum may be as small as an ion. r would then be enormous and p_e proportional to the current i. Equation (7) would then hold exactly (if current is applied at discrete intervals to a resting neuron, there is no refractory period) and equation (10) for the time to firing results.

$$i_o/i = 1 - \exp(-t/\tau); \qquad i_o = kr/\tau; \qquad t = \mu_t - t_o \tag{10}$$

Equation (10) is the strength-duration curve already considered at the turn of the century by Lapicque (1907). Here it is seen as a special case derived from the more general equation (2).

(*d*) *Inhibitory Quanta.* Up to this point we have considered a purely excitatory model and one in which the size of the depolarizing impulse was independent of the depolarization level. However, for many neurons, inhibition plays a very important role. Furthermore, the size of the potential change resulting from an impulse is a function of the potential difference between the equilibrium potential for the impulse and the membrane potential, V_t. For excitatory impulses the equilibrium potential is typically five to ten times greater than the threshold depolarization so the assumption of constant-size impulses is a good one. However, for inhibitory impulses the equilibrium potential may be higher or lower than the resting potential and the size of an inhibitory impulse will not be constant. Finally, with an equilibrium potential above the resting potential, the excitation level (as measured by the number of excitatory quanta necessary for neuronal firing) may not be simply related to the depolarization, since inhibition in these cases results from very large permeability changes which tend to "clamp" the membrane at the equilibrium potential for inhibition (Eccles, 1964).

In the present paper we shall deal mainly with the special case of random inhibitory impulses of constant size, though the more general case with equilibrium potentials will be considered briefly. To include inhibition in the model we shall have to modify assumptions 1 and 3 specified on p. 175 to read:

(1′) Excitatory and inhibitory impulses occur randomly with a frequency p_e/sec. and p_i/sec. respectively.

(3′) At times $t > t_o$, an excitatory impulse produces unit depolarization while an inhibitory impulse produces u units repolarization.

We first examine the distribution of depolarization as a function of time, neglecting

neuronal firing ($r \to \infty$). Let V_t equal the depolarization at time t and let $F(v, t)$ equal the probability that $V_t \leq v$ at time t. From assumption 5 (exponential decay of depolarization for subthreshold values) we have immediately

$$dV_t/dt = -V_t/\tau \tag{11}$$

except for random points of discontinuity when impulses occur. Assumption (3′) above implies that for a short time interval δt, the probability of an excitatory impulse occurring is $p_e\,\delta t$ and the probability of an inhibitory impulse is $p_i\,\delta t$. The change of $F(v, t)$ with time is given by

$$F(v, t + \delta t) - F(v, t) = [1 - (p_e + p_i)\delta t][F(v + \delta v, t) - F(v, t)]$$
$$- p_e\delta t[F(v, t) - F(v - 1, t)] + p_i\delta t[F(v + u, t) - F(v, t)] \tag{12}$$

where from equation (11) $\delta v = (v/\tau)\,\delta t$.

The first term on the right accounts for the increase in $F(v, t)$ from the decay of the potential during the time δt in some trials from just greater than v to v or less, providing no impulse occurs. The second term accounts for the decrease in $F(v, t)$ from quantal excitation of units between $v - 1$ and v while the third term accounts for the increase in $F(v, t)$ from quantal inhibition of units between v and $v + u$.

Dividing equation (12) by δt and taking the limit as $\delta t \to 0$, we obtain[7]

$$\partial F(v, t)/\partial t = (v/\tau)\partial F(v, t)/\partial v - p_e[F(v, t) - F(v - 1, t)]$$
$$+ p_i[F(v + u, t) - F(v, t)] \tag{13}$$

This equation can be transformed to obtain the characteristic function of the distribution, defined by

$$C(s, t) \equiv \int_{-\infty}^{+\infty} \exp(ivs)\, dF(v, t) \tag{14}$$

where $i = (-1)^{\frac{1}{2}}$. From the properties of these transforms, it follows that

$$\partial C(s, t)/\partial t + (s/\tau)\partial C(s, t)/\partial s = -p_eC(s, t)[1 - e^{iu}] - p_iC(s, t)[1 - e^{-iu}]$$

This linear partial differential equation can be rewritten in terms of two ordinary linear differential equations (Piaggio, 1958, chapter 12) and solved by standard methods. Making use of the boundary condition $C(s, t_o) = 1$ we obtain the following:

[7] It is interesting to note that if we reintroduce a threshold r and assume that once V_t surpasses r, it remains at the value $r + dr$ for all subsequent time (in the terminology of Markov chains, $r + dr$ is an absorbing state) then $1-F(r, t)$ is the cumulative probability of neuronal firing up to time t. We then have an equation identical with equation (13) for $-\infty < v \leq r$ with the boundary condition $\partial F(r, t)/\partial t = p_e[F(r, t) - F(r - 1, t)]$. However, this equation cannot be transformed completely to obtain a solution by use of a transformation analogous to equation (14).

$$\log C(s, t) = \tau \int_{e^{-(t-t_0)/\tau}}^{\infty} [-p_e(1 - e^{ix})/x - p_i(1 - e^{-iux})/x]\, dx$$

Expanding the right-hand side in powers of x, integrating and evaluating at the limits, we get equation (15).

$$\log C(s, t) = \sum_{k=0}^{\infty} (is)^k(1 - \exp[(-k/\tau)(t - t_0)])(p_e\tau + p_i\tau(-u)^k) \qquad (15)$$

The n^{th} derivative of $\log C(s, t)$ with respect to (is) evaluated at $s = 0$ gives the n^{th} cumulant of the original distribution. The first two cumulants are simply the mean and the variance of the distribution of depolarizations as a function of time. Hence

$$\mu_v = \tau(p_e - up_i)[1 - \exp(-(t - t_0)/\tau)] \qquad (16)$$

$$\sigma_v^2 = (\tau/2)(p_e + u^2p_i)[1 - \exp(-2/\tau)(t - t_0)] \qquad (17)$$

For the case $p_i = 0$, these equations reduce to equations (2) and (3) which were previously discussed at some length. Three important facts follow from equations (15) through (17).

1. The mean level, the variance in level and the other moments approach a steady state in all cases.[8] Hence the distribution of depolarization levels becomes time-independent and for weak excitation (where the mean level is always below the firing level) or predominant inhibition ($up_i > p_e$) the conditional probability of neuronal firing is constant after several time constants (τ). Hence the tail of the interresponse time distribution will be an exponential.

2. Since the interresponse time distributions have an exponential tail at times greater than a few time constants, the mean (μ_t), variance (σ_t^2), and other moments of this distribution exist and are stable. Gerstein and Mandelbrot (1964) in a recent article claimed from calculations made using a random walk model that the interresponse time distribution might have no moments whatever. The discrepancy between these two predictions results from the fact that the random walk model they used neglected the decay of excitation or inhibition. It is precisely this decay that accounts for the stability at long times and the existence of moments which are particularly sensitive to responses occurring at long times.

3. From equations (16) and (17) it is seen that the variance in depolarization level increases with a time course twice as fast as that of the mean. (Higher moments increase still faster.) Hence with predominant inhibition, where the mean level decreases to a steady state less than zero, the variation about the mean increases more rapidly and the conditional probability of firing may increase to a fairly sub-

[8] Calculations have been made for the case in which inhibitory and excitatory potentials E_i and E_e are defined and the sizes of the excitatory and inhibitory impulses are assumed proportional to the difference between the membrane depolarization and the equilibrium potentials. Here a steady state also exists in which all moments are defined and calculable, though the approach to this steady state is no longer exponential.

stantial value before declining to a constant value. The resulting distribution has a sharp peak, followed initially by a period of faster than exponential decay which gradually becames more and more exponential at long times.

As our final example, we consider the limit of high firing rates where negligible decay of depolarization occurs before firing. We shall also assume that the effects of excitation and inhibition are equal and opposite. Then, the generating function and moments of the interresponse time distribution can be calculated by standard methods[9] (Bailey, 1964). The mean is given by:

$$\begin{aligned} \mu_t &= \frac{r-a}{p_e-p_i} + \frac{p_i}{(p_e-p_i)^2}\left[(p_i/p_e)^r - (p_i/p_e)^a\right] && p_i \neq p_e \\ &= \frac{r-a(r+a-1)}{2p_e} && p_i = p_e \end{aligned} \tag{18}$$

where a is the initial depolarization and the other symbols are as previously defined. (A refractory period t_0 could be added if required.) By inversion it is seen that the frequency of firing α is given by

$$\alpha = \frac{(p_e-p_i)^2}{(p_e-p_i)(r-a) + p_i\left[(p_i/p_e)^r - (p_i/p_e)^a\right]} \quad p_i \neq p_e \tag{19}$$

If excitation is predominant ($p_e \gg p_i$), then the firing rate is simply proportional to the difference $p_e - p_i$.

$$\alpha = (p_e - p_i)/(r-a) \tag{20}$$

With inhibition predominant ($p_i \gg p_e$) then the firing rate is a power function of p_e.

$$\alpha = p_i(p_e/p_i)^r \tag{21}$$

C. COMPARISON OF PREDICTIONS WITH THE LITERATURE

As was stated earlier, a proper experimental check is not yet possible since, in no case known to the author, have all the appropriate parameters been measured independently of the interresponse time distribution. In many, but not all of the preparations used, these measurements have not been technically possible. Nonetheless, the general nature of the results can be analysed. This will now be done in reverse order to that of the derivation of theoretical predictions.

(*a*) *Strength-Duration Curves.* Curves of the form of equation (10) have

[9] This particular model is known in other contexts as a birth and death process or a queueing theory model. The results are derived by setting up a differential equation and then using the technique of moment-generating functions. Gerstein and Mandelbrot (1964) have carried out extensive calculations on this approximation in terms of a random walk model. Unfortunately, they neglected to take into account the time distribution of each step. If the steps were assumed random, one of the defects of their model (that it could not account for an exponential distribution of interresponse times) would be eliminated.

been widely found experimentally in the literature (see Kandel and Spencer, 1961, for references to several recent studies with internal microelectrodes). There are, however, theoretical difficulties with the interpretation of this curve. From the cable theory of Hodgkin and Rushton (1946), a constant current applied at one point will cause the depolarization to increase faster than an exponential at the point of stimulation. (Several space constants away the depolarization increases more slowly than an exponential in such a way that the total capacity current flow is exponential.) From the theory of the active state developed by Hodgkin and Huxley (1952) two other effects occur:

1. As depolarization increases there is a transient increase in sodium ion permeability, the flow of sodium down its concentration gradient further increasing the rate of depolarization.

2. There is a delayed increase in potassium permeability and the flow of potassium down its concentration gradient will decrease the depolarization.

It is possible that these three effects cancel nearly enough to explain the fact that curves of the form of equation (10) have been widely found, though the best fitting parameters may be quite different from the resting membrane constants. Except in the case of very large neurons, voltage clamp experiments cannot yet be carried out. In the interest of keeping all the parameters experimentally measurable in ordinary preparations, this degree of approximation will be retained for the present.

(*b*) *Neuronal Firing as a Function of Stimulus Intensity.* In 1931 Matthews proposed a logarithmic relation between applied tension and firing rates in the muscle spindle. As more evidence has accumulated, even the proponents of this "log law" as a general neuronal relationship have admitted that considerable deviations are found both at high and at low intensities (Granit, 1955). Recently using a crustacean stretch receptor, an analogue of the mammalian spindle, Terzuelo and Washizu (1962) have shown that over the physiological range, firing rate is *directly proportional* to the generator potential and, in fact, to muscle length. It is only in the relationship between muscle length and tension that the logarithmic relation enters. Beidler (1961) has found a simple hyperbolic relation [similar to equation (5)] between intensity of stimulation and neuronal firing rate of chemoreceptors of the tongue, but has found a similar relation between stimulus intensity and generator potential, again indicating a linearity between firing rate and generator potential. For thalamic neurons of the somesthetic system which show considerable spontaneous activity, Mountcastle *et al.* (1963) recently found that a power law [similar to equation (21)] gave a better fit than a logarithmic relation, an exponential, or a simple hyperbolic function such as equation (5). Equations of the type of equation (6) or ones derived from equation (9) were not tested. Finally, Rushton (1961) has shown for the *Limulus* eye that, by using an extra parameter to take into account spontaneous activity, the logarithmic relation gave a good fit at low intensities as well as normal intensities.

It must be remembered that there are two parts to the problem under consideration. One is the relation between the external stimulus and the rate of depolarizing impulses (p_e) or the generator potential; the other part concerns the neuronal firing rate as a function of p_e. The relationship in the first part may well be modality-specific. In the two cases mentioned here, there was a linear relation between generator potential and length in the stretch receptor and a hyperbolic relationship in the chemoreceptor. Further data must be accumulated before generalizations can be drawn and in any case, this part of the problem is outside the predictions of the present paper.

On the second part of the problem, there seems to be general agreement from a number of experiments (see Granit *et al.*, 1963, for references). As first shown by Katz (1950), the firing rate is a linear function of the generator potential over a considerable range of normal physiological activity. In a number of cases the firing rate is also a linear function of applied current over much of the physiological range (Granit *et al.*, 1963; Terzuelo and Washizu, 1962; Rushton, 1961). Both these results follow from our calculations. From equations (2) or (16) depolarization level is seen to be proportional to p_e whether caused by synaptic activity or applied current. Equations (5), (9), and (19) for frequency of firing all reduce to a linearity in p_e over a considerable middle range. Thus we would predict frequency of firing to be proportional to depolarizing current or generator potential[10] over this range. The prediction of equation (20) that firing rate will also depend linearly upon the difference between excitation and inhibition strengths if an excess of excitation is retained, has also been strikingly confirmed (Granit and Renkin, 1961). Whether the "end effects" predicted by equations (9) and (19) are normally found, remains to be verified, but the effects noted by Granit *et al.* (1963) are in the right direction.

(*c*) *Interresponse Time Distributions.* In Figs. 5 and 6 are shown distributions from various sorts of neurons which have been adapted from the experimental literature and fitted with a gamma distribution where possible. Other distributions have been analysed with similar results by the author while still others in the literature (Kuffler, FitzHugh, and Barlow, 1957) were shown to fit a gamma curve and have not been reproduced here. The cumulative distributions (per cent of firings before a given time t) have been plotted on cumulative normal paper for ease of visual inspection as previously explained in connection with the simulated distributions. An excellent fit is obtained in most cases. Deviations are found at very early times for some neurons as expected from the discussions on p. 177. The

[10] The time course of the generator potential is often not a simple exponential as predicted by equation (2) but shows a peak shortly after the stimulus is first turned on, and then decays. However, where the exponential is not found, there is considerable evidence that the rate of intensity change is an important physiological stimulus in addition to the intensity level (see Matthews, 1963, for evidence concerning the muscle spindle). This, together with the normal adaptation found to a steady stimulus may well account for the initial peak.

apparent refractory period of some muscle spindle cells may, however, be higher than can be accounted for by that discussion. Certain neurons with large numbers of neuronal firings could not be adequately fitted by a gamma distribution [in particular, some of the thalamic neurons during spontaneous activity reported by Werner and Mountcastle (1963) (Fig. 6*d*), the slowly adapting touch receptors of Viernstein and Grossman (1961) (Fig. 6*c*), and some spontaneously firing cochlear neurons (Rodieck *et al.*, 1962; Fig. 5*b*)]. It is important to note, however, that each of these curves could not be fitted because it displayed a sharp peak followed by a long tail, as predicted for neurons with predominant inhibition. With differing levels of adaptation the distributions found by Viernstein and Grossman (Fig. 6*c*) all have roughly the same period of low slope (0 to 20 msec.), followed by a period of particularly high slope (20 to 30 msec.) as we would expect from this interpretation.[11] Furthermore, Mountcastle *et al.* (1963) found a power law relating stimulus strength and output frequencies over the physiological range as predicted for the case of predominant inhibition, though extreme caution must be used in interpreting this result since the transformations of stimulus strength taking place at more peripheral levels are far from fully understood. Most of the other quantitative findings of Werner and Mountcastle agree with predictions easily calculable for the case of pure excitation. (Preliminary calculations on the more difficult case including inhibition suggest that the results are also compatible with this case.) They found, for example, that for various degrees of stimulus intensity, the standard deviation of the distribution was a linear function of the mean. For a gamma distribution, we have $\mu_t = r/p_e + t_o$ and $\sigma_t^2 = r/p_e^2$. Solving for p_e and substituting, we obtain

$$\sigma_t = \mu_t r^{-\frac{1}{2}} + t_o r^{-\frac{1}{2}} \tag{22}$$

independent of the excitatory impulse frequency p_e. The samples of driven activity examined (Fig. 5*f* is an example) give negligible values of the refractory period ($<$ 1 msec.) which correlates with Werner and Mountcastle's finding that the intercept of the plot of σ_t *vs* μ_t was not significantly different from zero. The best fitting values of the apparent threshold r' agree well with the range found for the slope (0.47 to 0.84).

For spontaneous activity the ratio σ_t/μ_t was just under 1 (average 0.93) and increased as the mean increased, as we would predict if p_e were low and r' approaches 1. Since r' is again reasonably constant, we would again predict a linear relation between σ_t and μ_t, but this time with a substantial apparent refractory period (see Fig. 3 or the discussion on p. 179.) and hence a sizeable intercept. This agrees well with Werner and Mountcastle's results except that the regression coefficient for

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[11] An alternative explanation resulting from systematic threshold changes is discussed in the next section.

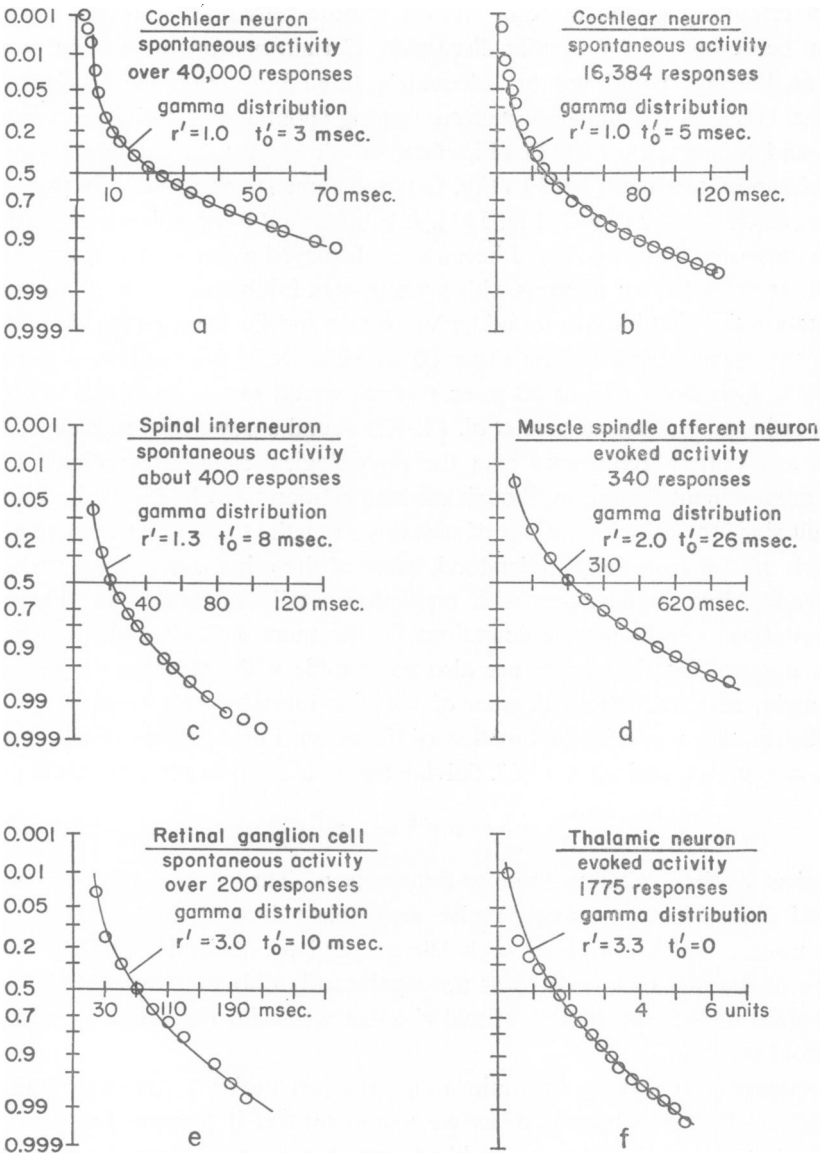

FIGURE 5

spontaneous activity is too large (1.2 to 1.8) to be simply accounted for by an analysis assuming a predominantly excitatory model.[12]

[12] Because of the differences between spontaneous and driven activity, Werner and Mountcastle concluded that there may be qualitatively different factors influencing the two modes of neuronal activity. The present analysis explains most of their findings, while assuming that exactly the same model operates in the two cases.

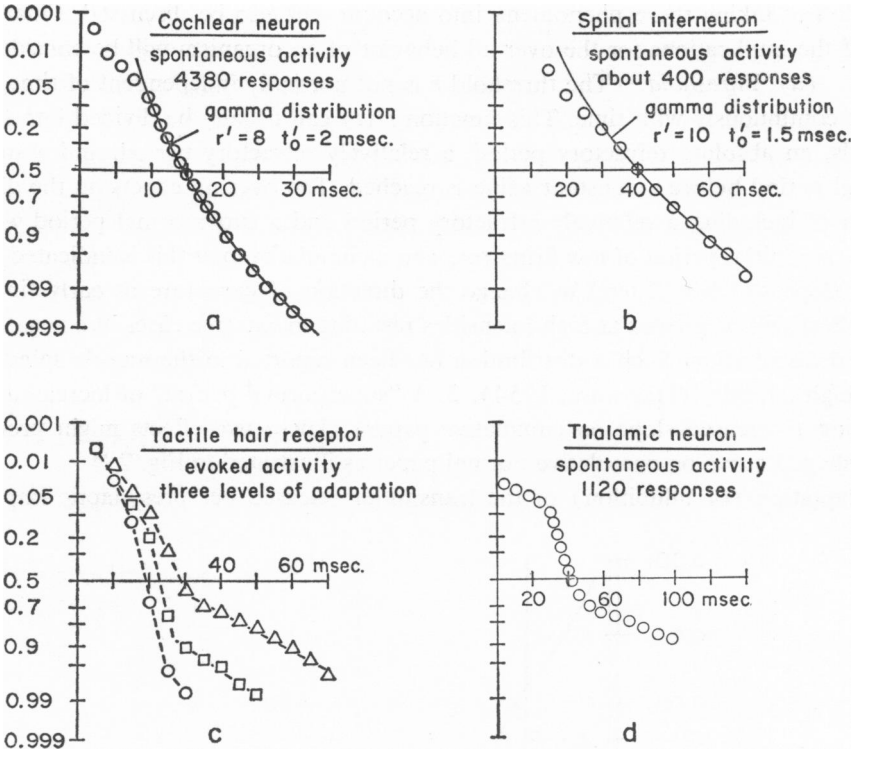

FIGURE 6

FIGURES 5 and 6 Experimental interresponse time histograms. Distributions were adapted from the literature and plotted on cumulative probability paper for comparison with predicted distributions. Ordinate: cumulative probability of firing. Abscissa: time in msec. or standard deviation units. Solid lines, where drawn, give gamma distributions with the apparent threshold (r') and apparent refractory period (t'_o) indicated. The references for the figures are as follows: Figs. 5*a*, 5*b*, and 6*a*, Rodieck *et al.* (1962); Figs. 5*c* and 6*b*, Hunt and Kuno (1959); Fig. 5*d*, Buller *et al.* (1953); Fig. 5*e*, Arden and Liu (1960); Figs. 5*f* and 6*d*, Mountcastle *et al.* (1963); Fig. 6*c*, Viernstein and Grossman (1961).

It should be stressed once again that careful measurements of r, p_e, p_i, t_o, and τ independently of the distribution should allow quantitative checks without any free parameters. The present discussion has, however, shown that the existing data agree quite well with the predictions of this analysis. Generalizations of the model to further increase its applicability are considered in the next section.

D. MORE GENERAL MODELS

In this section the assumptions of the model given in Section B will be discussed separately in the light of known physiological phenomena. The effects on the dis-

tribution of taking these phenomena into account will also be discussed. Finally, a few of the implications for the over-all behavior of an organism will be considered.

(*a*) *Threshold.* The threshold r is not normally independent of time, but varies continuously with time. This function r (t) can usually be divided into three periods, an absolute refractory period, a relatively refractory period, and a supernormal period before a constant value is reached. The over-all effects on the distribution of including a relatively refractory period and a supernormal period would be: 1. An initial period of low firing rate (on a cumulative plot this is indicated by a small slope which will tend to change the direction of curvature at early times). The effect will be greater at high intensities resulting in extreme cases in a negatively skewed distribution. Such a distribution has been reported in the muscle spindle at very high intensity (Hagiwara, 1954). 2. A "supernormal period" of increased rate of firing (increased slope on cumulative paper). These two effects might produce an S-shaped curve on cumulative normal paper as illustrated in Fig. 7.[18]

Adaptation (or inhibition) of the transmitter released per presynaptic impulse,

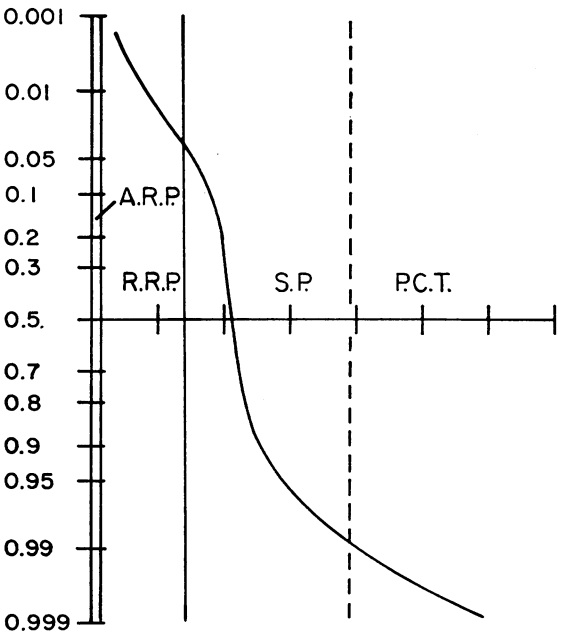

FIGURE 7 Effects of a time-varying threshold. Schematic representation of the effects on the interresponse time distribution of an absolute refractory period (A.R.P.), a relative refractory period (R.R.P.), and a supernormal period (S.P.) which gradually fades into a period of constant threshold (P.C.T.). Ordinate: cumulative probability Abscissa: time.

[18] This offers another explanation for the sharply peaked distributions discussed in the last section.

post-tetanic potentiation, or resistance changes that facilitate (or inhibit) the effectiveness of a given quantity of transmitter in depolarizing the membrane, all change the average quantal size and hence the effective threshold. Finally, a dendritic potential or generator potential that is maintained after firing may prevent the depolarization from returning to zero (the resting potential) and so change the effective threshold at high intensities. The ultimate effect, when either the depolarization is maintained above threshold or the Na-carrying system is inactivated, is complete blockage of firing. Effects of this sort are known with electrical stimulation (cathode block) and with natural stimulation (see Matthews, 1963, or Fuortes and Mantegazzini, 1962).

(*b*) *Quantal Size.* In different experimental preparations the unit of depolarization might be one of several disparate quantities, a single ion crossing the membrane, decomposition of a molecule of rhodopsin, a single packet of ACh or the transmitter released by a single presynaptic neuronal pulse. The last is most important if we are considering a general synaptic process, yet here unit size will not be constant. Computer simulation for the case of pure excitation using a rectangular distribution of quantal sizes has been carried out. As might be expected, the additional source of variability caused σ_t to increase faster than μ_t (or to decrease more slowly as the case might be). The effects were marked only at the two extremes of frequency.

Considering our example with $r = 2.8$ may clarify the nature of the results. With a variable quantal size, no matter how high the frequency of p_e, one never reaches the point where 3 impulses and only 3 are sufficient to fire. Therefore, one must always deal with apparent parameters r', p', and t_e'. On the other hand, when p_e is low, ($p_e\,\tau < r$), it has been shown that the average depolarization level is below threshold for all values of time. Firing occurs from the variability around this average. The provision of different size pulses increases the variability and hence the probability of firing. For example with $r = 3$, $p_e\,\tau = 1$, the mean time to firing was decreased from 20.2 to 13.3 with the introduction of variable quantal size.

(*c*) *Impulse Frequency.* There are several effects that cause variation in p_e. Slow adaptation or inhibition of presynaptic firing rates over an extended period will simply cause systematic changes in p_e. If such changes are rapid, occurring over a single interval, a function $p_e\,(T)$ must be used in which T is the time from the onset of stimulation. In this case, a curve more skewed than an exponential can result.

Commonly rhythmic potentials are measured in the nervous system and the inputs to cells in the vicinity are no doubt non-random. Some sense organs such as the ear are also subject to rhythmic stimuli such as pure tones. In extreme cases one would expect multipeaked distributions, the frequency of peaks determined by the input frequency. Multipeaked distributions have been found experimentally (Levick, 1963; Rodieck, Kiang, and Gerstein, 1962). A cyclic form for the function $p_e\,(T)$

can be used in these cases to simulate the expected distribution. McGill (1963) has recently considered the distribution for a neuronal model with a particular type of periodicity in some detail. Analysis of the distribution with any input, if the distribution is known for one, may be carried out by using the transfer function concept common in electrical engineering (Chapman and Smith, 1963).

All of these effects may have to be taken into account to quantitatively understand different neurons, while none of these refinements may be required to explain the distribution of others. When required, all the effects are experimentally measurable and can be used to simulate a distribution for comparison with that experimentally found. Cases may also arise when all of these refinements are not sufficient to explain the experimental results. However, far from negating the value of this analysis, such a case proves the merit of a deductive approach for it will then be clear that unknown and previously unsuspected factors must be present which play an important part in neuronal behavior.

(*d*) *Gross Response Times.* So far we have only considered the time distributions of single neurons. Yet the simple model discussed here has important implications for aspects of discrimination, learning, and performance where the over-all timing of an organism is involved. Consider a chain of n neurons. If each neuron has frequency of depolarizing impulses p_e/sec., thresholds r_j and $p_e\tau \gg r_j$

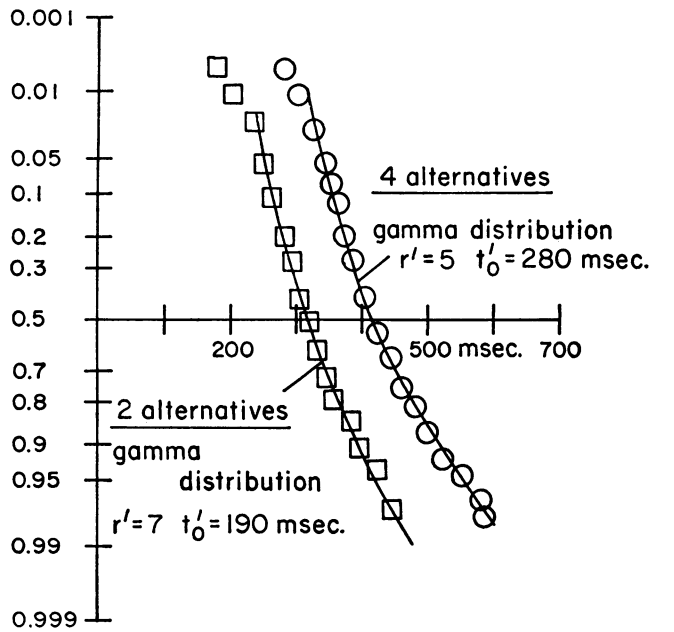

FIGURE 8 Gross response time distributions. Human reaction times to a visual discrimination with two or four alternatives. Each distribution consists of about 200 responses. The two distributions are from different highly practised subjects.

and $p_e \gg p_i$, then the over-all time distribution is a gamma distribution with p_e and $R = \Sigma_{j=1}^{n} r_j$. There will also be a constant time t_o to account for neuronal conduction time. If frequencies are not the same, the variance will in large part depend on the stage of *lowest* p_e and highest r_j. Others will simply add to t_o, since for a gamma distribution $\sigma^2 = r/p_e^2$ and the present model depends even more critically on p_e. Many neurons in parallel feeding into a common output stage is analogous to many presynaptic neurons in connection with a single postsynaptic neuron and all the previous discussion holds.

These considerations suggest that the three parameter gamma model should be capable of fitting many gross reaction time distributions and it has been found sufficient to fit most of the experimental distributions investigated. Others show the sharp peak and exponential tail characteristic of predominant inhibition (Bush and Mosteller, 1955; Kennedy and Travis, 1948; Stein, unpublished experiments, 1962—see for example Fig. 8). This may explain the apparent similarity in complexity between these curves and neuronal interresponse time curves (McGill, 1963). However, with gross response times it should not be possible in general to relate r' and p' to the r_j and p_e values of individual neurons.

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