PROBABILISTIC FIRING OF NEURONS CONSIDERED AS A FIRST PASSAGE PROBLEM

M. TEN HOOPEN

From the Institute of Medical Physics TNO, Utrecht, The Netherlands

ABSTRACT A formalized neuron receiving unitary excitatory impulses at random is considered. Each impulse provokes an effect of equal magnitude and of a duration not constant for each impulse, but which varies according to an exponential distribution. The effects sum until a threshold is reached when a response occurs. The distribution of intervals between successive responses is computed and compared with those obtained from a model in which the effects decay exponentially with time. Upon introducing inhibitory impulses also, the theory is applied to data on discharge characteristics of driven and spontaneously active thalamic neurons reported in the literature.

INTRODUCTION

To account for variability in neuronal unitary activity, models have been proposed which were based on the summation of effects brought about by impulses patterned in some way and a response occurring as soon as a minimum amount of summated effect was present. Rapoport (1950) considered a Poisson arrival of impulses, each having the same unit effect and lasting a constant period of time after arrival. Barlow (1963), in a comment on the information capacity of nervous transmission, poses that it is questionable whether the response of a nerve cell depends on the number of impulses that have arrived in a strictly delimited interval. He suggests that one had probably better use an exponential weighting function rather than a rectangular window. In Gerstein and Mandelbrot's (1964) random walk model for spike activity, the membrane potential moves at regular intervals, either one small step away from or toward the firing level. Otherwise formulated, the thus stepwise change in potential can be considered to be the result of equally spaced impulses, which each have an effect of the same absolute value and which endure up to the moment of firing, but which can be either of positive sign (depolarizing effect) or of negative sign (hyper- or repolarizing effect). As pointed out by Stevens (1964), the persistence of an effect by each impulse remaining essentially unchanged for the entire interspike interval would imply a membrane time con-

stant of several hundreds of milliseconds. Time constants of this magnitude have not been encountered, at least not in the vertebrate nervous system (Eccles, 1964). This peculiarity stands out the more so as it was assumed, on the other hand, that the neuron's membrane potential is reset following each spike, which implies that the response destroys all remaining postsynaptic potentials, or, that there is no persistence of transmitter substance.

The criticism of Gerstein and Mandelbrot's model as to a sometimes very long lasting effect and of Rapoport's as to an abruptly ceasing effect does not hold good for a model proposed by Stein (1965) and Fetz and Gerstein (1963), and which was based on the following assumptions: (*a*) excitatory impulses occur at random with a mean frequency f_e; (*b*) after each firing there is a refractory period of duration t_0; (*c*) at times $t > t_0$ each impulse produces unit depolarization; (*d*) if the depolarization level reaches a threshold of r units, the neuron fires; (*e*) for subthreshold levels, the depolarization decays exponentially with a time constant τ. It is in principle possible to compute the interval distribution $p(t)$ numerically, its main characteristics, the mean interval duration between successive firings μ, and the standard deviation σ, but this procedure is a laborious one and the said authors had to rely mainly on results of Monte Carlo simulations. To illustrate this, we note that Stein's theoretical part was restricted to the limiting cases with either τ or r approaching infinity. In the first case, the problem degenerates to a trivial model with $p(t)$ approaching the gamma distribution. The second case is, properly speaking, irrelevant as it means no firing at all. In fact, the only expressions simultaneously containing the parameters r and τ are his formulas (7) and (8) for the mean firing interval, which were found approximately valid for $f_e \cdot \tau > 1.5\ r$.

In view of this it may be expedient to draw attention to a model resembling the former very closely, permitting an exact solution for the interval distribution, and presenting fewer difficulties in computation, particularly with regard to the σ versus μ relationship, which is often used in analyzing neurophysiological data. The model to be discussed is identical with the one just described, except that at subthreshold levels the unit depolarization of an incoming impulse does not decay exponentially,[1] but remains constant during a time interval that is exponentially distributed with a mean τ. Again, if the total depolarization reaches the threshold, firing occurs. Even with this sole divergent point, there are similarities, as we shall see.

It is believed that this model forms a compromise between the models based on more or less realistic concepts and those accessible to analytical approach but with artifical assumptions. The main part of this note deals with an attempt to organize the simulation results of the model with exponential decay of depolarization with the help of the theory of the model with exponentially distributed decay. In a later

[1] Regarding assumption (*e*), we note that exponential decay of the total summed depolarization is identical with the assumption that the effect of each individual impulse decays exponentially.

section inhibitory influences will be included and the theory will be applied both to model studies and to activity patterns of thalamic neurons under different states of sensory stimulation, reported in the literature.

EXCITATION

In this section we denote by an impulse, an excitatory impulse that increases the depolarization level by one unit. The interval distribution $p(t)$ will be derived for $t_0 = 0$. If the $t_0 \neq 0$ the interval distribution equals $p(t - t_0)$ for $t > t_0$ and zero for $0 < t < t_0$. We define $P_k(t) \cdot dt$ as the probability of a neuron storing $k(<r)$ units of depolarization at time t after the last response has occurred at $t = 0$. $P_k(t + dt)$ can then be expressed in terms of $P_k(t)$, $P_{k-1}(t)$, and $P_{k+1}(t)$, and in terms of the probability of increase or decrease of the level by one unit in a time interval $(t, t + dt)$. The arrival of impulses being Poisson distributed with mean frequency f_e, the probability of increase of the depolarization level by one unit in $(t, t + dt)$ is equal to $[f_e \cdot dt]$. The probability of arrival of two or more impulses in $(t, t + dt)$ and therefore the probability of increase of the level by two or more units in $(t, t + dt)$, is of second or higher order in dt and thus vanishes. The probability of no level increase in $(t, t + dt)$ is then equal to $[1 - f_e \cdot dt]$. The assumption of an exponentially distributed decay with mean τ enables us to write for the probability of decrease of the level by one unit in $(t, t + dt)$, when k units are stored at time t, as being equal to $[k \cdot dt/\tau]$. Again the probability of decrease of the level by two or more units in $(t, t + dt)$ is of second or higher order in dt and thus vanishes. Likewise, the probability of the level not decreasing in $(t, t + dt)$ is given by $[1 - k \cdot dt/\tau]$

We have for $k = 0, 1, \ldots, (r - 1)$:

$$\left.\begin{aligned} P_k(t + dt) = {} & P_{k+1}(t) \times [1 - f_e \cdot dt] \times [(k + 1)\, dt/\tau] \\ & + P_k(t) \times [f_e \cdot dt] \times [k \cdot dt/\tau] \\ & + P_k(t) \times [1 - f_e \cdot dt] \times [1 - k \cdot dt/\tau] \\ & + P_{k-1}(t) \times [f_e \cdot dt] \times [1 - (k - 1)\, dt/\tau]. \end{aligned}\right\} \quad (1)$$

with the annotation that for $k = r - 1$ the term with $P_{k+1}(t)$ and for $k = 0$ the term with $P_{k-1}(t)$ vanishes. When $dt \to 0$, one obtains a set of first order differential equations that can be solved by conventional methods (see Appendix). Further, $p(t) \cdot dt = P_{r-1}(t) \times$ [probability of increase in level by one unit in $(t, t + dt)$] $\times$ [probability of no decrease in level by one unit in $(t, t + dt)$]. For $dt \to 0$ it follows $p(t) = f_e \cdot P_{r-1}(t)$.

For a precise comparison between the two models we shall have to restrict ourselves to the limiting cases where either r or τ becomes infinite, as for these situations exact solutions are only known for the model with exponential decay. With τ large in comparison with r/f_e, $p(t)$ approaches the gamma distribution for both models.

In the absence of firing, or with r becoming infinite, the average time course of the depolarization level, after the stimulation having started at $t = 0$, proves to be in both cases:

$$\mu_*(t) = f_*\tau\{1 - \exp(-t/\tau)\} \tag{2}$$

Therefore, on an average, the total amount of summed depolarization, or the total amount of effective transmitter substance, $\int_0^t \mu_*(\bar{t})\cdot d\bar{t}$, is also the same. Equally, after cessation of stimulation the mean average time course of the depolarization is the same for both models and exponentially shaped. The main difference between the models is constituted by the time course of the variance in level which equals

$$\sigma_*^2(t) = f_*\tau\{1 - \exp(-2t/\tau)\}/2 \tag{3a}$$

for the model with exponential decay.

In case of exponentially distributed decay one finds (see Appendix)

$$\sigma_*^2(t) = \alpha(t) \times f_*\tau\{1 - \exp(-2t/\tau)\}/2 \tag{3b}$$

with $\alpha(t) = 2\{1 - \exp(-t/\tau)\}/\{1 - \exp(-2t/\tau)\}$. As $1 \leq \alpha(t) \leq 2$ for all t, the variance is at most twice as large in the latter case. This in turn means, that if a threshold is present, the shortest interval time and the mean interval duration are at most a few times shorter; this difference becoming smaller as $r/f_*\tau$ decreases. Alternatively f_* must be taken smaller in order to obtain the same mean interval duration.

This heuristic reasoning is supplemented quantitatively by comparison with some of the simulation results of Stein (1965). The parameter values r, f_*, and t_0 of his Figs. 2*a*, *c*, and *e* are listed in columns *a*, *b*, and *c* of Table I in row 1. The results, as far as characterized by μ and σ, are given in row 3. These could be obtained indirectly as explained in the next paragraph. The model with exponentially distributed decay gives values for μ and σ enumerated in row 4, if the same values of the parameters r, f_*, and t_0 are used. Comparing rows 3 and 4 one observes that for $r/f_*\tau = 4$ or 3, μ is two to three times smaller, for $r/f_*\tau = 1$ the difference is 15%.

Stein has compared for r up to ten the interval distributions from the simulation with the gamma distribution. This approach offers the advantage that this distribution possesses a simple expression for μ and σ, whereas σ/μ is independent of f_*. The latter property especially is an aid to curve fitting by nomographic methods. All interval distributions could be fitted well by this distribution, but the parameters that yielded best fit: r', f_*', and t_0' and given in row 2 were often quite different from the neuronal parameters: r, f_*, and t_0 (= 0) used in the simulation. It was further reported that these varied in a systematic way, although we were not able to observe this very closely, at least not in a quantitative way, nor could we extrapolate the mapping of these sets of parameters; e.g., to higher values of r. Meanwhile it enabled us to compute μ and σ of the distributions in an easy way from $\mu = r'/f_*'$ and $\sigma = \sqrt{r'}/f_*'$ (row 3). Alternatively one may compare the simulation data by the model with

TABLE I

		a	*b*	*c*	Row
Parameter values used in simulation of model with exponential decay	r	2	3	10	1
	f_e	0.5	1	10	
	t_0	0	0	0	
	$r/(f_e\tau)$	4	3	1	
Parameter values of best fitting gamma distribution	r'	1.1	1.2	1.6	2
	f'_e	0.05	0.06	1.1	
	t'_0	0	0	0.73	
Results from simulation 1, as computed from best fitting gamma distribution, 2	μ	22.0	20.0	2.19	3
	σ	21.0	18.3	1.15	
Results from model with exponentially distributed decay for parameter values as in 1	μ	8.8	8.0	1.91	4
	σ	7.5	7.2	1.07	
Same if input frequency is taken equal to f''_e such that μ equals the value obtained in 3	f''_e/f_e	0.52	0.63	0.94	5
	μ	22.0	20.0	2.19	
	σ	21.8	19.2	1.27	

exponentially distributed decay after adjusting of parameters. If the mean frequency f_e is changed into f''_e, such that μ equals the values found from the simulation model (row 3), the other two parameters r and t_0 being unchanged, one has values of f''_e as given in row 5.

Whereas fitting with the gamma distribution is reported to require three parameter values to be changed: f'_e, r', and t'_0, sometimes by as much as a factor ten (compare rows 1 and 2), for the model with exponentially distributed decay a modification of f_e with a factor of two or less seems to suffice in order to give a reasonably good agreement. This can be judged by inspection of σ in rows 3 and 5. In addition we refer to Fig. 1, where cumulative interval distributions $\int_0^t p(\bar{t})\cdot d\bar{t}$ are plotted with t in units of the respective standard deviations ($= \sqrt{r'}/f'_e$). Circles ($\circ$) are for r', f'_e, and t'_0, circles ($\cdot$) for r, f''_e, and t_0. As the former set of parameter values were reported to give the best fit to the curves obtained from the simulation, we have not thought it necessary to redraw these; this procedure would have been less accurate.

In Figs. 2*a* and *b* data from Stein's simulation studies with $\tau = 1$ are denoted by marks for different values of r; these were recomputed from his Figs. 4 and 3 respectively. Fig. 2*a* gives $1/f_e$ vs. μ for $r = 1$ (45° line) and for $r = 2, 3, 5, 10$, and 20 in increasing order of magnitude as dotted curves for the model with exponentially distributed decay and with f_e uncorrected. For $1/f_e$ small, we have for both models the limiting relation $\mu \approx r/f_e$ as illustrated by the dashed line valid for $r = 2$.

For $1/f_e$ large, the model under discussion behaves asymptotically as

$$(r - 1)!/f_e(f_e\tau)^{(r-1)}.$$

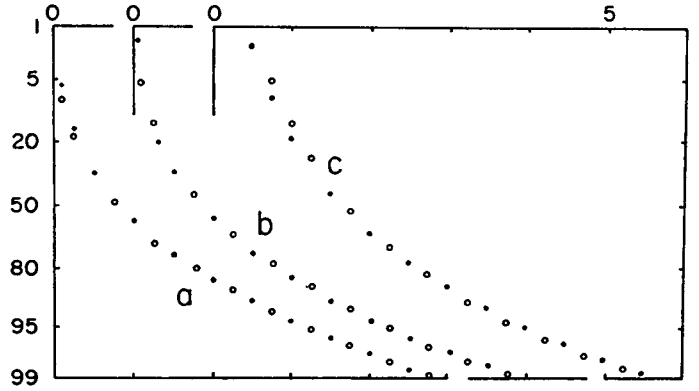

FIGURE 1 Cumulative interval distributions $\int_0^t p(\tilde{t}) \cdot d\tilde{t} \cdot (\circ)$ from simulations of model with exponential decay; $(\cdot)$ for model with exponentially distributed decay. For details see text and Table I.

In the range of f_e used, the differences are most pronounced for $r = 2$. For a given value of f_e the value for μ is at most twice as small as for the model from the simulation as anticipated earlier. For larger values of r, the differences become smaller. Unfortunately, no data for r larger than five were given.

Fig. 2*b* gives σ vs. μ for $r = 1$ (45° line) and for $r = 2, 3, 5, 10$, and 20 in decreasing order of magnitude as dotted curves.

For μ small, we have in both cases $\mu = \sigma\sqrt{r}$ as indicated by the dashed line valid for $r = 20$. For μ large, both models give $\mu = \sigma$. For the ranges of μ investigated, the deviations between the two models are most marked for small values of r. For $r = 10$ and $r = 20$ there seems to be good agreement.

INHIBITION

Fetz and Gerstein (1963) and Stein (1965) have introduced inhibition in the following way. All assumptions remained unchanged except that, in addition to excitatory impulses, there are also inhibitory impulses, Poisson distributed with a mean frequency f_i and which have a hyper- or repolarizing effect. The effects are of equal magnitude and the time constants are also the same. The direct analogy for the model under discussion would be a model in which the excitatory and inhibitory impulses have a unit effect of opposite sign, the duration of which is in both cases exponentially distributed with a mean τ. Ths concept leads formally to the theory of bivariate birth and death processes; in the presence of a threshold this is difficult to evaluate. We consider a slightly different version of the interaction between excitation and inhibition, which should not differ much from the previous one in its outcome and which can be solved in the same way as in the case of pure excitation. The following definitions are used (cf. Fig. 3).

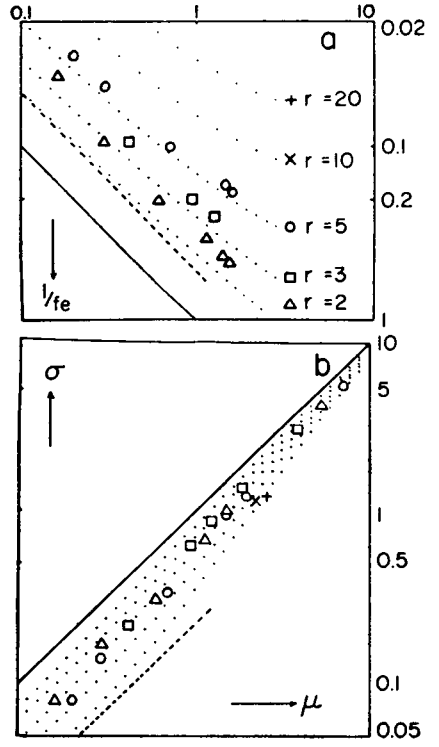

FIGURE 2 Mean input interval, $1/f_e$ versus mean output interval, μ versus standard deviation σ. Marks from simulation of model with exponential decay for values of r as indicated; adopted from Stein (1965). All coordinates in units of τ. Dotted curves for model with exponentially distributed decay; dashed lines are asymptotes.

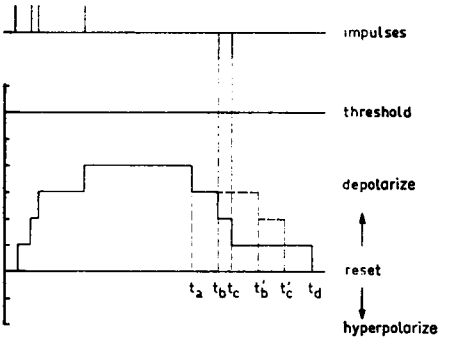

FIGURE 3 Sketch of the mode of inhibition. At $t = 0$, when a response has occurred, the membrane potential equals the reset value. After arrival of four excitatory impulses, the potential depolarizes with four units. In the absence of further stimulation, this level might return to the original one at times t_a, t_b', t_c', t_d. If two inhibitory impulses arrive, the potential may change at t_a, t_b, t_c, t_d.

If the level is depolarized relative to the value without any stimulation and smaller than the threshold value, an excitatory impulse continues to depolarize the level and is said to increase the level. An inhibitory impulse decreases the level by one unit, but it has no further lasting effect. Increasing the level by one unit can therefore be brought about by the arrival of an excitatory impulse only and the probability of this occurring in a time interval $(t, t + dt)$ after the last response at $t = 0$ equals

again $[f_e \cdot dt]$. A decrease of level is provoked by the arrival of an inhibitory impulse or if the effect of a previously arrived excitatory impulse ceases to exist.

As in the previous section, it follows that the probability of decreasing the level by one unit in $(t, t + dt)$, when k excitatory effects are stored, is given by $[f_i + k/\tau] \cdot dt$.

If the level is hyperpolarized relative to the reset level at $t = 0$, an inhibitory impulse hyperpolarizes the level further, or decreases the level, by one unit, which effect is exponentially distributed in time with a mean duration τ. The probability of decrease of the level by one unit in $(t, t + dt)$ equals $[f_i \cdot dt]$. An increase of the level towards the threshold occurs if an excitatory impulse arrives or if the effect of a previously arrived inhibitory impulse becomes extinct. The probability of increasing the level by one unit in $(t, t + dt)$ is thus given, when k inhibitory effects are present, by $[f_i - k/\tau]$. dt where k is a negative number.

For $1 \leq k \leq r - 1$ we may write:

$$\left.\begin{aligned} P_k(t + dt) = {} & P_{k+1}(t) \times [1 - f_e \cdot dt] \times [f_i + (k + 1)/\tau]\, dt \\ & + P_k(t) \times [f_e \cdot dt] \times [f_i + k/\tau]\, dt \\ & + P_k(t) \times [1 - f_e \cdot dt] \times [1 - f_i\, dt - k/\tau\, dt] \\ & + P_{k-1}(t) \times [f_e \cdot dt] \times [1 - f_i \cdot dt - (k - 1)/\tau\, dt] \end{aligned}\right\} \quad (4a)$$

with the annotation that for $k = r - 1$, the term with $P_{k+1}(t)$ vanishes.

For $-\infty < k < 0$

$$\left.\begin{aligned} P_k(t + dt) = {} & P_{k+1}(t) \times [f_i \cdot dt] \times [1 - f_e \cdot dt - (-k - 1)/\tau\, dt] \\ & + P_k(t) \times [f_i \cdot dt] \times [f_e - k/\tau]\, dt \\ & + P_k(t) \times [1 - f_i \cdot dt] \times [1 - f_e\, dt - (-k/\tau)\, dt] \\ & + P_{k-1}(t) \times [1 - f_i\, dt] \times [f_e - (k - 1)/\tau]\, dt. \end{aligned}\right\} \quad (4b)$$

For $k = 0$

$$\left.\begin{aligned} P_0(t + dt) = {} & P_1 \times [1 - f_e \cdot dt] \times [f_i + 1/\tau]\, dt \\ & + P_0 \times [1 - f_e \cdot dt] \times [1 - f_i \cdot dt] \\ & + P_0 \times [f_i \cdot dt] \times [f_e \cdot dt] \\ & + P_{-1} \times [1 - f_i\, dt] \times [f_e + 1/\tau]\, dt. \end{aligned}\right\} \quad (4c)$$

For $dt \to 0$ one obtains first order differential equations, from which follows $P_{r-1}(t)$. Again, $p(t) = f_e \cdot P_{r-1}(t)$.

In order to compare the two models, we must, for the same reasons as before, restrict ourselves to the cases r infinite or τ infinite. For r large, the average time course of the depolarization level is found to be the same in both cases and the variance in level is again larger for the model with exponentially distributed decay.

As in the previous section, we can infer that the mean interval duration between responses is a few times smaller in case of exponentially distributed decay. For τ very large, both models are identical. One has for $f_e > f_i$ (cf. Appendix).

$$p(t) = r(f_e/f_i)^{r/2} t^{-1} e^{-(f_e+f_i)t} I_r(2t\sqrt{f_e f_i}) \tag{5}$$

I_r denotes the modified Bessel function of order r

$$\mu = r/(f_e - f_i) \tag{6}$$

$$\sigma^2 = r(f_e + f_i)/(f_e - f_i)^3 \tag{7}$$

Skewness $\lambda = \int_0^\infty (t - \mu)^3 p(t)\, dt/\sigma^3$ is given by

$$\lambda = 2r(f_e^2 + 4f_e f_i + f_i^2)/\{(f_e - f_i)^5 \sigma^3\} \tag{8}$$

Kurtosis $\kappa = \int_0^\infty (t - \mu)^4 p(t)\, dt/\sigma^4$ is given by

$$\kappa = 3 + 6\{f_e^3 + 9f_e^2 f_i + 9f_e f_i^2 + f_i^3\}/\{r(f_e - f_i)(f_e + f_i)^2\} \tag{9}$$

For $f_i \geq f_e$, μ becomes infinite, contrary to Stein (1965) who claims a finite firing rate that equals $1/\mu = f_i\ (f_e/f_i)^r$ for $f_i \gg f_e$. We cannot follow fully his deduction, but it is compatible with a model that has an additional assumption: if, and as long as, the depolarization is equal to the reset value, inhibitory impulses have no effect, or otherwise stated, no hyperpolarization is possible.

The theory has been compared with simulation studies made by Fetz and Gerstein (1963). As an example, we shall take the distribution in their Fig. 4, obtained for $f_e = 2/3$ msec^{-1} and $\tau = 180$ msec, redrawn in our Fig. 4 (+). After inspection from a photographic enlargement we found $\mu = 14.8$ msec, $\sigma = 4.7$ msec and a total number of counted intervals of 4076. Unfortunately, these authors did not mention the value of r. But if the two models are to give similar results, it should be possible to determine the value of this parameter by trial and error. A value of $r = 10$ is seen to give a good agreement: Fig. 4 (curve). In this particular case,

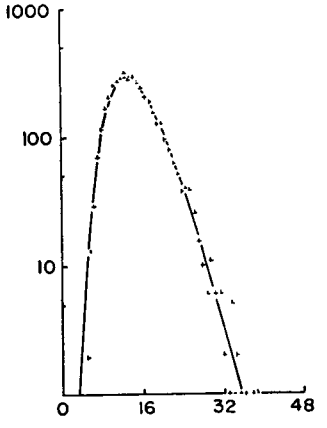

FIGURE 4 Interval distributions (+) from simulation of model with exponential decay for $f_e = 2/3$ msec^{-1} and $\tau = 180$ msec; redrawn from Fetz and Gerstein (1963). Curve for model with exponentially distributed decay. Abscissa in milliseconds; ordinate in counts per 0.8 msec.

$\tau \gg 1/f_e$ and if so wished, one may use the gamma distribution without much error.

By making use of the known values for μ and σ, the value of r can be evaluated in a more elegant way. In Fig. 5, curve a relates μ and σ for different values of r according to the formulas derived in the Appendix. The experimental coordinates 14.8/4.7 are close to the theoretical ones for $r = 10$: 15.6/5.1. The gamma distribution approximation in this picture is situated at: 15.0/4.7.

Another result with excitatory impulses was given in their Fig. 9 and is redrawn in Fig. 6 (+). We found $\mu = 15.1$ msec and $\sigma = 4.8$ msec, denoted by point A in Fig. 5, and a total number of 3937 intervals counted. No parameters at all were listed, but finding the mean interval duration and the standard deviation to be nearly the same as in the preceding example, we have deliberately taken the same parameter values for curve A in Fig. 6, which gives a good fit. In addition skewness and kurtosis were checked; the difference was less than 5%.

The other interval distribution of their Fig. 9 is redrawn in Fig. 6(·). We found $\mu = 27.6$ msec and $\sigma = 14.5$ msec from a total of 3938 intervals. It is characterized in Fig. 5 by point B. The distribution was obtained upon introducing inhibitory impulses with a mean frequency f_i that is unknown to us. This offers us another checking possibility as to the compatibility of the two models. Starting from the case of pure excitation, we can proceed to trace the μ versus σ relationship, most conveniently with the help of formulas (6) and (7), because $\tau \gg 1/(f_e - f_i)$ as will be shown. If desired, this may be done in a more refined way by direct computation from the interval distributions at different values of f_i. Increasing f_i, all other parameters kept constant, corresponds to an emigration along curve b in Fig. 5, starting at a point on curve a. The point on curve b nearest to the coordinates of B, 27.6/14.5, is found to be 27.7/14.3 for $f_i = 0.305$ msec^{-1}. This value, therefore, must reflect the

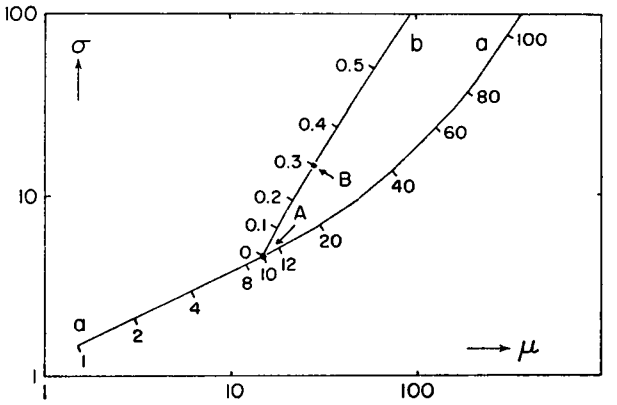

FIGURE 5 Mean interval μ versus standard deviation σ for model with exponentially distributed decay for $f_e = 2/3$ msec^{-1} and $\tau = 180$ msec. Curve a for $f_i = 0$ and values of r as indicated along the curve. Curve b for $r = 10$ and values of f_i in msec as indicated along the curve. Points A and B from simulation of model with exponential decay from interval distributions given in Fig. 6.

rate of inhibition which has been used. The interval distribution appertaining to it is given as curve *B* in Fig. 6. From this we can confirm now that $\tau \gg 1/(f_e - f_i)$.

As a final example, interval distributions recorded by Werner and Mountcastle (1963) during different states of a neuron will be analyzed. They found for the relative spread, RS = σ/μ, of distributions for driven and spontaneously active thalamic neurons values with mean 0.52 and 0.93. There was a linear regression between σ and μ of distributions of consecutive sampling periods for both states of the neuron. The slope, the regression coefficient RC, differed considerably and ranged from 0.47 to 0.84 (mean 0.63) for driven and from 1.2 to 1.8 (mean 1.52) for spontaneous activity.

From this they concluded that qualitatively different factors influencing the two modes of activity are likely to exist. Stein (1965) has been in doubt about this; he found a satisfactory relation between RS and RC in case of the driven state, but failed to do so for the spontaneous activity. We agree with this author that in the latter case the RC is too large to be simply accounted for by an analysis assuming a purely excitatory model. Upon introducing inhibitory effects, an agreement can be obtained. To link the different states of a neuron, we assume that these are caused by external factors, cf. f_e and/or f_i, and not by a change in the neuronal parameters τ, t_0, and r. Otherwise these parameters would have to vary by several factors in magnitude. There is evidence that this is not the case. The threshold r, *inter alia* may, under physiological circumstances, change only a few per cent (ten Hoopen and Verveen, 1963).

To simplify a survey and to avoid tedious computations, we further take $t_0 = 0$ and τ infinite, so that formulas (6) and (7) apply. It is emphasized that these quantities may be introduced, if desired. Although the investigation of Werner and Mountcastle was extended over tens of cells for only one, neuron 17-2, the mean interval duration and its standard deviation for both driven and spontaneous activity was explicitly given, to mention: μ = 12.5 msec, σ = 6.9 msec,

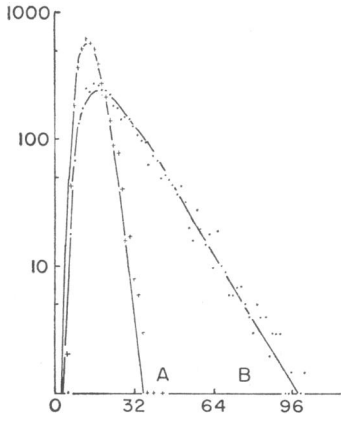

FIGURE 6 Interval distributions from simulation of model with exponential decay; (+) for excitatory impulses only; (·) for excitatory and inhibitory impulses; redrawn from Fetz and Gerstein (1963). Curves from model with exponentially distributed decay for $f_e = 2/3$ msec^{-1} and $r = 10$, *A* for $f_i = 0$ and *B* for $f_i = 0.305$ msec^{-1}. Abscissa in milliseconds; ordinate in counts per 1.6 msec.

and RS = 0.55; and, μ = 68.5 msec, σ = 66.1 msec, and RS = 0.97. These values are characterized by points *A* and *B* in Fig. 7. RC can be roughly estimated from the summarized results in their Fig. 3 and were measured as 0.6 and 1.4. If we take f_e as the independent variable, one finds for $f_i = 0.199$ msec^{-1} and $r = 6$ a curve relating σ and μ which nearly covers the points *A* and *B* for $f_e = 0.679$ msec^{-1} and $f_e = 0.287$ msec^{-1} respectively. It turns out that if only f_i were variable, no fitting is possible, but a combination of both excitatory and inhibitory factors is conceivable.

The regre: sion coefficient may be taken to be equal to the slope of the σ vs. μ curve at points *A* and *B*, which is

$$[\partial\sigma/\partial f_e]/[\partial\mu/\partial f_e] = (f_e + 2f_i)r^{-0.5}(f_e^2 - f_i^2)^{-0.5}$$

One finds 0.68 for driven and 1.32 for spontaneous activity; these values are in good agreement with those estimated above. As to this example, there is no discrepancy between RS anud RC of the cell under different circumstances. It would be of interest to repeat the computations for other neurons, but unfortunately the data for different strengths of sensory stimulation have been lumped together and the relation between μ, σ, and RC during driven and spontaneous activity is lost in their over-all figure, Fig. 3.

As yet, our theory interferes with the opinion of Werner and Mountcastle in that there is no gradual transition between different modes of activity. Also the data of Poggio and Viernstein (1964) on the same class of neurons (39-2 and 36-7) situated in our Fig. 7 as (+) and (·) show the same trend, although these interval distributions are anything but symmetrical and require, in addition to μ and σ, other specifications as skewness and kurtosis (formulas 8 and 9).

Werner and Mountcastle's Fig. 2 is reproduced in Fig. 8. The points relate σ and μ for 308 sampling periods and for 18 degrees of stimulation. The total mean values are μ = 28.526 msec and σ = 15.490 msec. Although a highly significant linear

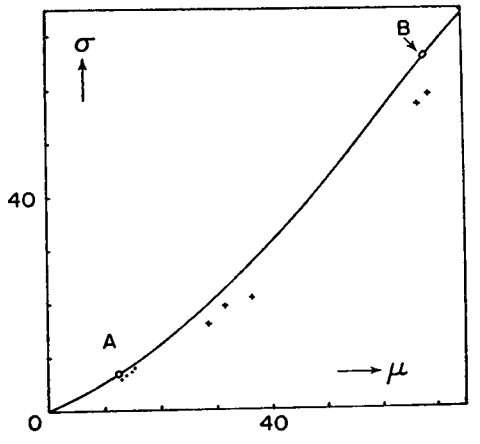

FIGURE 7 Mean interval μ versus standard deviation σ. Marks for three thalamic neurons during different modes of activity; adopted from Werner and Mountcastle (1963) and Poggio and Viernstein (1964). Curve for model with f_e as independent variable. Abscissa and ordinate in milliseconds.

regression was found (RC = 0.721), the over-all course of the points seems slightly concave relative to the abscissa. The curve, from the theory for changing f_e, f_i = 0.199 msec^{-1}, and $r = 8$, gives a good fit, but we have not looked systematically for an optimum solution. For $f_e = 0.481$ msec^{-1} one finds $\mu = 28.5$ msec and $\sigma = 15.7$ msec. If the slope of the curve in this point may again be identified with RC, one finds RC = 0.711, which is very near the experimentally found value.

The question arises whether the means and the standard deviations for samples recorded during one mode of activity (spontaneous or during one constant stimulus intensity) also show a linear regression, and, if so, what slope is present. As the over-all activity is governed by f_e, at least in these examples which would seem to be representative of the entire population judging the RS and RC, it seems most likely that the slope for each set of samples would also be given by $[\partial\sigma/\partial f_e]/[\partial\mu/\partial f_e]$.

This would then provide another check on the model, but variations due to the finite sample length may obscure such a relation. As the points for each state (on the average a number of 308/18 points) have not been given separately, no pronouncement concerning this problem can be made.

As within one mode of activity small variations are probably involved, the alternatives: variations in f_i, as well as in the neuronal parameters r, t_0, and τ or even combinations thereof, cannot be excluded beforehand. If solely f_i fluctuates one would find:

$$\mathrm{RC} = [\partial\sigma/\partial f_i]/[\partial\mu/\partial f_i] = (2f_e + f_i)r^{-0.5}(f_e^2 - f_i^2)^{-0.5}$$

and if r fluctuates:

$$\mathrm{RC} = [\partial\sigma/\partial r]/[\partial\mu/\partial r] = \sigma/2\mu.$$

DISCUSSION

A comparison is made between a neuronal model in which inputs, occurring randomly and with an exponentially distributed duration of effects, sum until

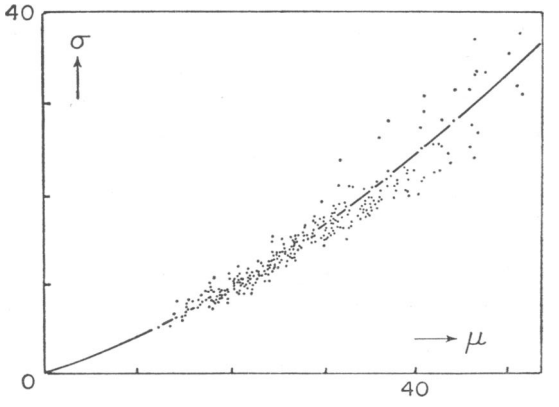

FIGURE 8 Mean interval μ versus standard deviation σ. Points for thalamic neuron during different states of activity; redrawn from Werner and Mountcastle (1963). Curve for model with f_e as independent variable. Abscissa and ordinate in milliseconds.

a threshold is reached, and a model in which the effect of an impulse decays exponentially with time. There can be little doubt about the latter being more realistic than the former, in which, during stimulation, the persistence of effects is often very short and sometimes rather long. Yet, the assumption of a Poisson arrival of impulses is an approximation of the same order and seems to have become common law in neuromime studies. The advantage of the assumption of exponentially distributed decay durations is that it permits an analytical approach.

Comparison between the two models has revealed the differences between the interval distributions to be small if the input frequency is corrected by a factor. The minimum value used for this factor was 0.52; for $r = 10$ and $f_e \cdot \tau = 10$ it amounted to 0.94. It will very probably converge towards 1 for large values of r and smaller values of $f_e \cdot \tau$, but further investigation is needed to determine this with certainty. In the interim, the model presented may be useful as a compromise between a handy theoretical framework on the one hand and, via the model with exponential decay, a proper reflection of the biological situation on the other hand.

Apart from the quality of being merely a reference, the model has also merits of its own, and against the negatively tinged arguments mentioned we can place a more positive one. For, although all nerve fiber impulses impinging upon a neuron are believed to have the same shape and intensity for a given fiber, the net effect of an incoming impulse as to excitation or inhibition may be different, depending on the transmission properties of a particular synapse and/or on the distance between the site of arrival on the soma or dendrites, relative to the axon hillock, the point of response ignition. Together with possibly decremental conduction in these structures, these spatio-temporal phenomena may very well be associated with effect durations which are not identical for each impulse. A way to account for this is to assume the durations of effects to be exponentially distributed.

Another advantage of the model is that nonlinear summation can be introduced without difficulty; by this is meant a persistence of effects dependent on the momentary value of the subthreshold depolarization level. We refer to an interpretation of repetitive firing of nerve cells given by Fuortes and Mantegazzini (1962).

They pointed out that in many nervous structures upon stimulation in the form of an electrical current step, the membrane potential develops in the beginning essentially along an exponential curve, as does the mean time course of the depolarization level in the two models discussed. If the membrane potential is depolarized to a certain level, a graded or local response may develop which increases the depolarization and may bring it to the proper threshold level when all or nonfiring occurs. This behavior can be incorporated into the model with exponentially distributed decay by taking the probability of extinction in an interval $(t, t + dt)$ not being equal to $k \cdot dt/\tau$. To simplify matters, we consider excitatory impulses only, although this property seems to be most pronounced for inhibitory influences, but according to some other function of k or by letting τ be dependent on the value of

the depolarization level. For example one might insert for the probability of extinction in $(t, t + dt)$ a quantity $k \cdot dt/\tau(k)$ as soon as k reaches a certain value such that for higher larger values of the depolarization level this probability is enhanced and the probability of reaching the threshold is increased.

Other extensions, such as dependence of the parameters on time, present themselves but they are beyond the scope of this essay.

All models discussed and referred to in this paper have at least one serious drawback in common: it is assumed that, after a response, the depolarization level starts each time from the same reset level and no persistence of transmitter effect is taken into account. An opposite case, complete persistence of transmitter substance, can be dealt with analytically for the model with an exponentially distributed decay time but numerical evaluation is tedious (ten Hoopen and Reuver, 1966). To be precise, one may assume the depolarization level not to be affected at all by a response but to continue its course, as in the case without threshold, with a mean value equal to $(f_e - f_i)\tau$, and a response occurring as soon as and as long as the level is equal to or larger than the threshold value r. The minimum time intervals are then determined by the refractory period. Also a refractory period whose duration is not constant, but varying stochastically, can be inserted.

Reset of the depolarization level also implies that the durations of successive intervals are completely independent of each other. But, from inspection of serial and autocorrelation coefficients, as far as studied, it has become apparent that in most instances there exists a deviation from randomness in the time sequence of nerve impulses.

Especially the study of Poggio and Viernstein (1964) has shown that there is often some degree of organization in the time series of neural events. If these sequential effects are not taken into account and the interval distribution is accepted as the only substrate of unitary neuronal activity, models are often nonunique and model building is not very fruitful, as has been discussed thoroughly by Moore et al. (1965). To illustrate this, it is remarked that the interval distributions treated may very well be accounted for by the large class of models that have the concept of a fluctuating threshold and with an appropriate time course of recovery after firing. In short, the main conclusion must be that the interval distributions alone simply do not give enough information for unravelling adequately the underlying mechanism responsible for variability in neural activity.

APPENDIX

IN COLLABORATION WITH H. A. REUVER

From the difference equations (1) one obtains for $dt \to 0$ and after rearranging of terms a set of r first order differential equations:

$$P'_{r-1}(t) = -[f_e + (r - 1)/\tau]P_{r-1}(t) + f_e P_{r-2}(t).$$

$$P_k'(t) = [(k+1)/\tau]P_{k+1}(t) - [f_e + k/\tau]P_k(t) + f_e P_{k-1}(t) \quad \text{for} \quad 0 < k < r-1$$

$$P_0'(t) = [1/\tau]P_1(t) - f_e P_0(t)$$

with initial conditions $P_0(0) = 1$ and $P_k(0) = 0$ for $1 \leq k \leq r-1$.

For r infinite the average time course of the depolarization level is, by definition, given by:

$$\mu_v(t) = \sum_{k=0}^{\infty} kP_k(t).$$

As $\mu_v'(t) = \sum_{k=0}^{\infty} kP_k'(t) = f_e \sum_{k=0}^{\infty} P_k(t) - 1/\tau \sum_{k=0}^{\infty} kP_k(t)$

$= f_e - \mu_v(t)/\tau$ and $\mu_v(0) = 0$, one has $\mu_v(t) = f_e\tau\{1 - \exp(-t/\tau)\}$ (2)

The variance in level is defined as:

$$\sigma_v^2(t) = \sum_{k=0}^{\infty} k^2 P_k(t) - \mu_v^2(t).$$

$$\frac{d}{dt}\sigma_v^2(t) = \sum_{k=0}^{\infty} k^2 P_k'(t) - 2\mu_v(t)\cdot\mu_v'(t) = -2\sigma_v^2(t)/\tau + \mu_v(t)/\tau + f_e \quad \text{with} \quad \mu_v(0) = 0.$$

One finds: $\sigma_v^2(t) = \mu_v(t)$, from which formula (3*b*) follows.

$p(t)$ can be written in a compact form if expressed in the Laplace transform notation:

$$p(s) = \int_0^{\infty} \exp(-st)\cdot p(t)\, dt = L[p(t)].$$

Likewise $P_k(s) = L[P_k(t)]$.

Then $p(s) = f_e P_{r-1}(s)$

$P_{r-1}(s)$ equals the quotient of the determinants $A(s)$ and $B(s)$.

$A(s)$ has as elements $a_{i,j}$ with

$$\begin{aligned}
a_{k,k} &= -\{s + f_e + (r-k)/\tau\} && k = 1, 2, 3 \cdots r. \\
a_{k,k-1} &= (r-k+1)/\tau && k = 2, 3, \cdots r. \\
a_{k-1,k} &= f_e && k = 2, 3, \cdots r. \\
a_{i,j} &= 0 && \text{otherwise.}
\end{aligned}$$

$B(s)$ equals $A(s)$ except that the elements $a_{k,1}$ are replaced by zero for $k = 1, 2, 3 \ldots (r-1)$, and by -1 for $k = r$.

Further

$$\mu = -p'(s)|_{s=0} \quad \text{and} \quad \sigma^2 = p''(s)|_{s=0} - \mu^2$$

One finds:

$$\left.\begin{aligned} f_e\cdot\mu &= 2 + 1/(f_e\tau) \\ (f_e\cdot\sigma)^2 &= 2 + 4/(f_e\tau) + 1/(f_e\tau)^2 \end{aligned}\right\} \quad \text{for} \quad r = 2$$

$$\left.\begin{aligned} f_e\cdot\mu &= 3 + 3/(f_e\tau) + 2/(f_e\tau)^2 \\ (f_e\cdot\sigma)^2 &= 3 + 12/(f_e\tau) + 21/(f_e\tau)^2 + 12/(f_e\tau)^3 + 4/(f_e\tau)^4 \end{aligned}\right\} \quad \text{for} \quad r = 3.$$

For $r \geq 4$

$$f_e \cdot \mu = r + (r-1)r/(2f_e\tau) + \sum_{k=2}^{r-1} k!/(f_e\tau)^k \sum_{0}^{k-2} (f_e\tau)^m/m!$$

$$(f_e \cdot \sigma)^2 = (f_e \cdot \mu)^2 - 2\, d_r/(-f_e)^{r-2}$$

with

$$d_r = -\{f_e + (r-1)/\tau\}\, d_{r-1} - f_e(r-1)/\tau \cdot d_{r-2} - (-1)^{r-1} f_e^{r-2} - (-1)^{r-1} f_e^{r-2} \sum_{k=1}^{r-2} k!/(f_e\tau)^k \sum_{0}^{k} (f_e\tau)^m/m!$$

and $d_3/f_e = -3 - 3/(f_e\,\tau)$ and $d_2 = 1$.

From the difference equations (4) one obtains from $dt \to 0$ an infinite set of first order differential equations with initial conditions $P_0(0) = 1$ and $P_k(0) = 0$ for all other k (ranging from $r-1$ through $-\infty$). $P_k(t)$ and $p(t) = f_e \cdot P_{r-1}(t)$ can be approximated as closely as desired by solving a finite section of equations, analogously as in the case with pure excitation, of the infinite set.

For r infinite the average time course of the depolarization level is derived from:

$$\mu_e(t) = \sum_{k=-\infty}^{\infty} kP_k(t) \quad \text{with} \quad \mu_e(0) = 0.$$

One finds:

$$\mu_e(t) = \tau(f_e - f_i)\{1 - \exp(-t/\tau)\}.$$

This expression is identical with the one derived by Stein (1965) for the model with exponential decay.

We were not able to derive μ and σ in closed form and these were computed from $p(t)$.

For τ infinite and $f_e > f_i$ the equations can be solved by the method of generating functions (cf. Bailey, 1964, who gives formulas (5), (6), and (7) explicitly).

Received for publication 3 November 1965.

REFERENCES

BAILEY, N. T. J., 1964, Stochastic Processes, New York, John Wiley and Sons, Inc.

BARLOW, H. B., 1963, *Kybernetik*, **2**, 1.

ECCLES, J. C., 1964, The Physiology of Synapses, Berlin, Springer Verlag.

FETZ, E. E., and GERSTEIN, G. L., 1963, *Quart. Progr. Report, M.I.T.*, **71**, 249.

FUORTES, M. G. F., and MANTEGAZZINI, F., 1962, *J. Gen. Physiol.*, **45**, 1163.

GERSTEIN, G. L., and MANDELBROT, B., 1964, *Biophysic. J.*, **4**, 41.

MOORE, G. P., PERKEL, D. H., and SEGUNDO, J. P., 1966, *Ann. Rev. Physiol.*, **28**, 493.

POGGIO, G. F., and VIERNSTEIN, L. J., 1964, *J. Neurophysiol.*, **27**, 517.

RAPOPORT, A., 1950, *Bull. Math. Biophysics*, **12**, 187.

STEIN, R. B., 1965, *Biophysic. J.*, **5**, 173.

STEVENS, C. F., 1964, *Biophysic. J.*, **4**, 417.

TEN HOOPEN, M., and REUVER, H. A., 1966, Utrecht, The Netherlands, Institute of Medical Physics TNO report.

TEN HOOPEN, M., and VERVEEN, A. A., 1963, *in* Nerve, Brain and Memory Models, (N. Wiener and J. P. Schadé, editors), Amsterdam, Elsevier Publishing Co.

WERNER, G., and MOUNTCASTLE, V. B., 1963, *J. Neurophysiol.*, **26**, 958.