INTERSPIKE INTERVAL FLUCTUATIONS IN THE CRAYFISH STRETCH RECEPTOR

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ABSTRACT Trains of nerve impulses from the crayfish stretch receptor under steady conditions are found to be extremely regular with a standard deviation of $S = 0.7 \times 10^{-2}\tau$ when τ, the mean interval, is in the 15 to 80 msec range. Such a small fluctuation increases the problems of film recording, accurate measurement of intervals, and especially, drifts. Experimental and mathematical techniques are described to obviate these problems. Evidence is found for a serial correlation coefficient of about -0.2 in the range, $\tau = 35$ msec to $\tau = 70$ msec. Shot noise and Johnson noise in a long axon are evaluated in detail and are shown to be comparable in size. It is also shown that neither shot noise nor Johnson noise is large enough to explain simply the observed interval fluctuations. Other types of membrane noise are discussed.

INTRODUCTION

Primary and higher order sensory neurons often give rise to regular trains of impulses, and a coefficient of variation (standard deviation/mean interval) as small as a few per cent has been found (Buller, et al., 1953; Hagiwara, 1954; Goldberg, et al., 1964).

The patterns of impulses are of interest for two reasons: first, for any meaningful information they carry and second, as a reflection of cell noise and molecular processes in the membrane (Verveen and Derksen, 1965). In principle, the noise limits the amount of information the sequence can carry. Thus a study of noise or randomness in a sequence of impulses can help in understanding both sensory coding and the cell membrane.

This paper describes work on the slowly adapting crayfish abdominal stretch receptor (Florey and Florey, 1955), in which the noise is much less than has so far been found in other neurons. The coefficient of variation in this neuron falls below 0.8% for intervals less than 80 msec. A preliminary report of this work has already been presented (Firth, 1965).

The size of the fluctuation in this simple system, with no synaptic input, is of interest in complex systems, e.g. motoneurons, where the fluctuation in interval is due both to the membrane noise and to more or less random synaptic bombardment. One must be able either to substract or to ignore noise not due to such bombardment.

From the crayfish's point of view it may be helpful to have such a noiseless receptor, for it has only a pair of such receptors for each segment whereas a mammalian muscle group has 10 to 100 times as many stretch receptors (muscle spindles) whose outputs are likely pooled to increase the accuracy.

These variations are difficult to measure for two reasons: first, fluctuations in interval of 0.8% are so small that the standard methods of measurement and recording are inadequate. Second, drifts due to adaptation and other causes far outweigh and tend to mask the variation of interest.

METHODS

Preparation. The receptor muscle of the crayfish was left intact while overlying ventral muscles were removed (Florey and Florey, 1955). The nerve trunk was cut about 10 mm from the receptor and drawn by suction into a glass capillary (50 to 100 μ in diameter). A stainless steel needle (no. 10) surrounding the capillary acted as a shield and also formed the indifferent electrode; a finer needle (no. 27) sealed inside the capillary acted as the other electrode and also served to apply suction inside the capillary.

The preparation was bathed in oxygenated Van Harreveld's solution which could be warmed or cooled. The temperature 2 mm from the receptor was monitored with a thermistor (1 mm in diameter).

The receptor was stimulated simply by flexing the tail. Inadvertent mechanical stimuli were guarded against by using data only from periods when the bathing solution was at rest and by mounting the whole experiment on a heavy steel plate sitting on a bicycle inner tube.

Recording. The size and shape of the recorded action potentials are of no interest here providing they are constant enough from impulse to impulse. Thus, conventional recording on moving film was not necessary since the small fluctuation of the intervals would have made such methods tedious and uneconomical (owing to the high film speed needed). The very constancy of the intervals allows one to "subtract" a constant major part and to "expand" the remainder; this was done electronically, as follows: the amplified nerve impulse triggered a pulse generator. The resulting 0.5 msec pulse in turn triggered a variable delay. The end of the delay triggered an oscilloscope sweep generator but the beam intensity was turned down so that no spot was visible until the arrival of the next standard pulse which intensified the spot to make a blip of constant length (as well as triggering the variable delay again). The film moved at right angles to the sweep. Film speed can be quite slow (1 cm/sec for 40 msec intervals) and the time delay and sweep speed are adjusted so that the random pattern of blips covers the width of the film.

This vivid visual display helped to show that data must not be used from periods when fluid flowed over the receptor.

Measurement of Intervals. After this work was under way a LINC computer became available, but in view of the preliminary nature of the study the film display was still needed. The information on film was transferred into the computer by altering a simple film viewer which had a mirror to project the image onto a screen. The mirror mounting was modified to allow rotation about an axis in its plane and parallel to the length of the film. A lever, worked by hand, rotated the mirror and varied a linear potentiometer at the same time. This gave a voltage proportional to the position of a blip on the film. (In effect the system was a time-to-amplitude converter.) The position was represented in digital form (8 bits) and stored on tape at the press of a button. Up to two intervals were read every second with this device and it may be useful in other situations.

ANALYSIS OF INTERSPIKE INTERVALS IN PRESENCE OF DRIFT

It was clear from the records (see Fig. 1) that methods used by other workers (Hagiwara, 1954; Buller, et al., 1953) to compensate for a drifting mean would not work as well here. They felt sure that within a group of 20 to 50 intervals the mean did not change significantly. Two facts led to the use of a different analysis: (*a*) The variance of the difference of two independent random variables is the sum of the variances of each variable. (*b*) The finite differences of successively higher order of a smooth function get progressively smaller. This may readily be seen, for example, from a table of sines, on taking differences (Hartree, 1952).

Let the r^{th} interspike interval be $\tau_r = \tau_0 + y_r$ where τ_0 is the constant time delay "subtracted" and y_r is the additional time necessary to complete the interval (represented by the height of a blip on the film). The mean interval is $\tau = \langle\tau_r\rangle = \tau_0 + \langle y_r\rangle$ and the standard deviation S_0 is given by $S_0^2 = \langle y_r^2\rangle - \langle y_r\rangle^2$. (A factor $n/n - 1$ is omitted here for clarity and mean values are represented by brackets $\langle \quad \rangle$.)

The observed value y_r is regarded as the sum of two parts, a drift of arbitrary form $a(r)$ and a random variable v_r with zero mean. In this paper v_r is of interest, whereas the drift or adaptation, $a(r)$, is unwanted.

Thus $y_r = a(r) + v_r$ and $S_0^2 = \langle v_r^2\rangle + \langle a^2(r)\rangle - \langle a(r)\rangle^2$. For short v^2 will be written for $\langle v_r^2\rangle$ and $a(r)$ can always be adjusted to make $\langle a(r)\rangle = 0$.

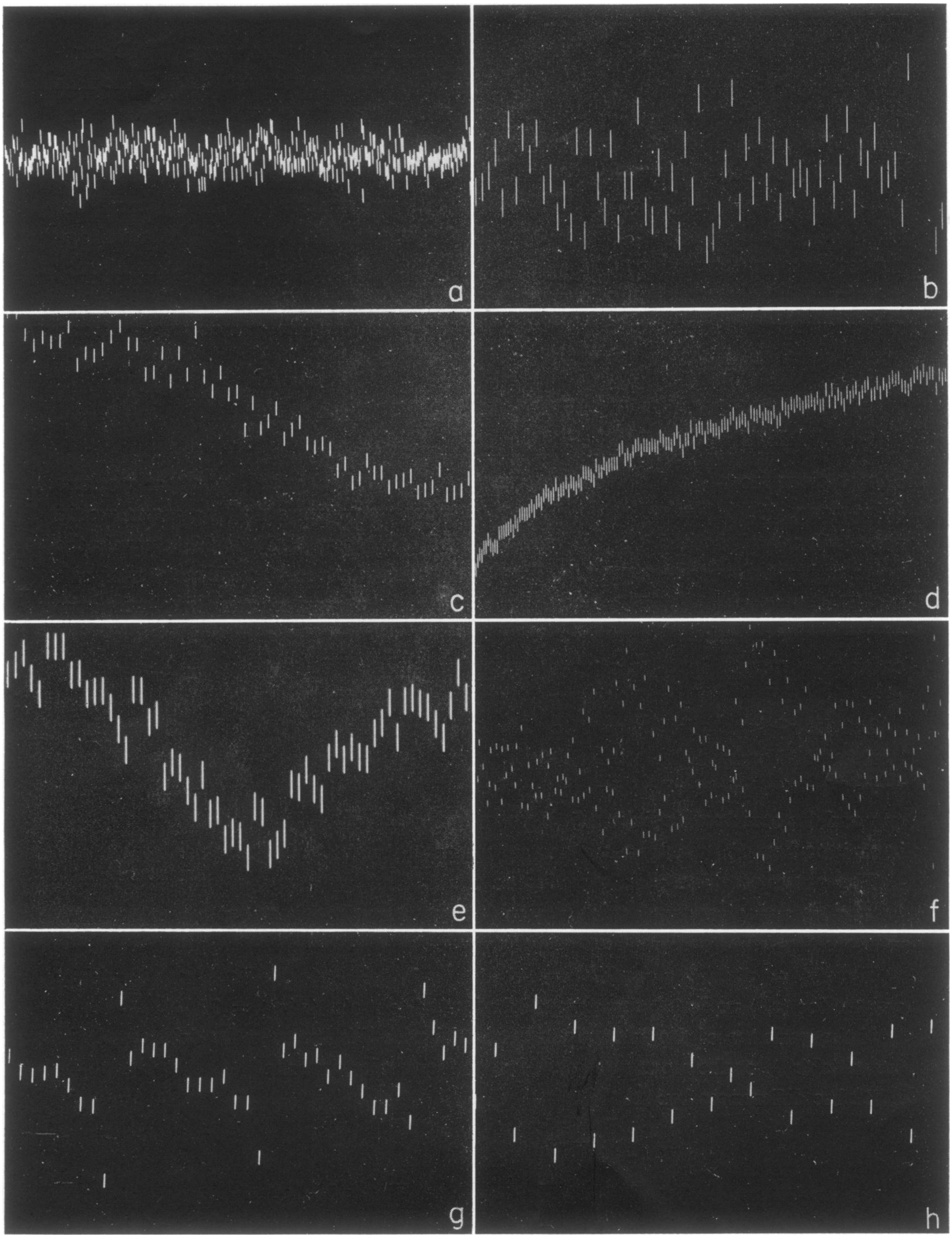
If the variance of the intervals is estimated with this formula the drift causes an error, $\langle a^2(r)\rangle$, or the mean square drift over the whole sequence.

Define differences by:

$$_1\Delta_r = y_r - y_{r+1}$$

$$_2\Delta_r = {_1\Delta_{r-1}} - {_1\Delta_r} = y_{r-1} - 2y_r + y_{r+1}$$

$$_3\Delta_r = {_2\Delta_{r-1}} - {_2\Delta_r}$$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If there is no drift ($a(r) = 0$) and no correlation between successive variables v_r, one finds:

$$\langle {}_1\Delta_r^2 \rangle = 2v^2, \qquad \langle {}_2\Delta_r^2 \rangle = 6v^2, \qquad \langle {}_3\Delta_r^2 \rangle = 20v^2$$

so estimates (S_1, S_2, S_3) of the standard deviation are defined by $S_1^2 = \langle {}_1\Delta_r^2 \rangle/2$, $S_2^2 = \langle {}_2\Delta_r^2 \rangle/6$, $S_3^2 = \langle {}_3\Delta_r^2 \rangle/20$.

When drift is included $\langle {}_1\Delta_r^2 \rangle = 2v^2 + \langle a(r) - a(r+1) \rangle^2$, etc., but for a fairly smooth drift $a(r+1) - a(r) \simeq da(r)/dr = d(r)$ etc.

Hence:

$$S_1^2 = v^2 + \langle a'^2 \rangle/2;$$
$$S_2^2 = v^2 + \langle a''^2 \rangle/6;$$
$$S_3^2 = v^2 + \langle a'''^2 \rangle/20.$$

To see the error introduced into S_0^2, S_1^2, S_2^2 by several kinds of drift, take the following examples: linear drift $a(r) = A \times (r - n)$ for $2n$ intervals; sinusoidal drift $a(r) = A \sin \omega r$ for n intervals; level shift $a(r) = A \tan^{-1} \omega r$ for $2n$ intervals; adaptation $a(r) = A/(1 + \omega r)$. A represents the amplitude of the drift, and $1/\omega$ is the number of intervals occuring during the characteristic drift time.

The errors introduced into the estimate of v^2 by using S_0^2, S_1^2, S_2^2 are shown in Table I. In line 3, $\tan \theta = \omega n$. If ωn is several times greater than unity, $\theta \simeq \pi/2$ which provides the simplification in lines 4 and 6.

As a numerical example, consider a sinusoidal drift with 20 impulses in one complete drift cycle ($\omega = 2\pi/20$). If drift and fluctuation are comparable, $v^2 = A^2$, the error introduced by the drift is 50% in S_0^2, 2.5% in S_1^2, and 0.1% in S_2^2. An advantage of this way of measuring variance is that no particular curve need be fitted to the points in order to provide a moving mean. (It is worth noting, though, that ${}_2\Delta_r = y_{r-1} - 2y_r + y_{r+1} = -2[y_r - (y_{r-1} + y_{r+1})/2]$ which is the local deviation from a moving mean.) The main disadvantage arises from the assumption that successive intervals are uncorrelated (apart from drifts). This problem is discussed below.

The analysis acts as a high pass filter since any "genuine" fluctuation which might be present for several intervals is rejected along with the drift. Therefore slower fluctuations which may be of interest are not so well treated by these methods.

FIGURE 1 Samples of interval sequences recorded on film as described in text. (*a*) Pip height = 0.5 msec, τ = 40 msec, no drift, horizontal time scale compressed; (*b*) Pip height = 1 msec, τ = 45 msec, no drift, typical display; (*c*) Pip height = 1 msec, τ = 50 msec, shift to a new level; (*d*) adaptation; (*e*) Pip height = 0.5 msec, τ = 53 msec, drifting mean; (*f*) Pip height = 0.2 msec, τ = 20 msec, smooth fluid flow over receptor; (*g*) Pip height = 2 msec, τ = 85 msec, dripping flow over receptor; (*h*) Pip height = 1 msec, τ = 30 msec, deteriorating cell, alternating large and small intervals.

TABLE I

	Error		
Drift	in S_0^2	in S_1^2	in S_2^2
1. $A \times (r - n)$	$\simeq n^2/3$	$1/2$	0
2. $A \sin \omega r$	$1/2$	$\omega^2/4$	$\omega^4/12$
3. $A \tan^{-1} \omega r$	$\simeq (\pi/2)^2$	$\frac{\omega^2}{4} \cdot \left(\frac{\vartheta + \frac{1}{2} \sin 2\vartheta}{\tan \vartheta} \right)$	$\frac{\omega^4}{12} \left(\frac{\vartheta - \frac{1}{4} \sin 4\vartheta + \frac{1}{3} \sin^2 2\vartheta}{\tan \vartheta} \right)$
4. $A \tan^{-1} \omega r$	$\simeq (\pi/2)^2$	$\simeq \frac{\omega^2}{4} \frac{\pi}{2} \frac{1}{\omega n}$	$\simeq \frac{\omega^4}{12} \cdot \frac{\pi}{2} \cdot \frac{1}{\omega n}$
5. $A/(1 + \omega r)$	$\frac{1}{1 + \omega n} - \left[\frac{\log (1 + \omega n)}{\omega n} \right]^2$	$\frac{\omega^2}{6} \frac{1}{\omega n}$	$\omega^4 \cdot \frac{2}{21} \cdot \frac{1}{\omega n}$
6. $A/(1 + \omega r)$	$\simeq \frac{1}{\omega n}$		

A factor, A^2, has been omitted from the last three columns.

RESULTS

$S - \tau$ Curve. Out of nine crayfish whose receptors appeared to behave similarly records from two crayfish (No. 7 and No. 9) were analyzed in detail. The values of S_0 and S_2 for experiment No. 9 are plotted against mean interval τ in Figs. 2 and 3.

Experiment No. 7 was based on 6400 interspike intervals and experiment No. 9 on 14,300, so that each point in No. 7 and No. 9 is calculated from about 264 and 204 intervals, respectively.

A comparison of $S_0 - \tau$ and $S_2 - \tau$ plots shows clearly the usefulness of using mean square differences as a measure of variance.

In Fig. 3 the band fitting the points was drawn by eye and in Fig. 4 this band and the best parabola fitted to experiment No. 7 are superposed. There is good agreement in the slope at the origin and at higher values of τ, ($dS_2/d\tau = 0.7 \times 10^{-2}$, up to $\tau = 80$ msec).

There appears to be a break in the $S_2 - \tau$ curve at about 100 msec in experiment No. 9. A similar break in experiment No. 7 cannot be ruled out, as the parabola was fitted merely for convenience and there were no observations between 50 and 80 msec. The contribution to S_2 from noise in the electronic equipment and error in the measuring system was only 5% of S_2 for the very shortest intervals, which represent the worst case.

Correlations between Intervals. So far in this paper the fluctuation v_r has been treated as uncorrelated (i.e. $\langle v_r v_{r+s} \rangle = 0$ for $s > 0$). A comparison of S_1^2,

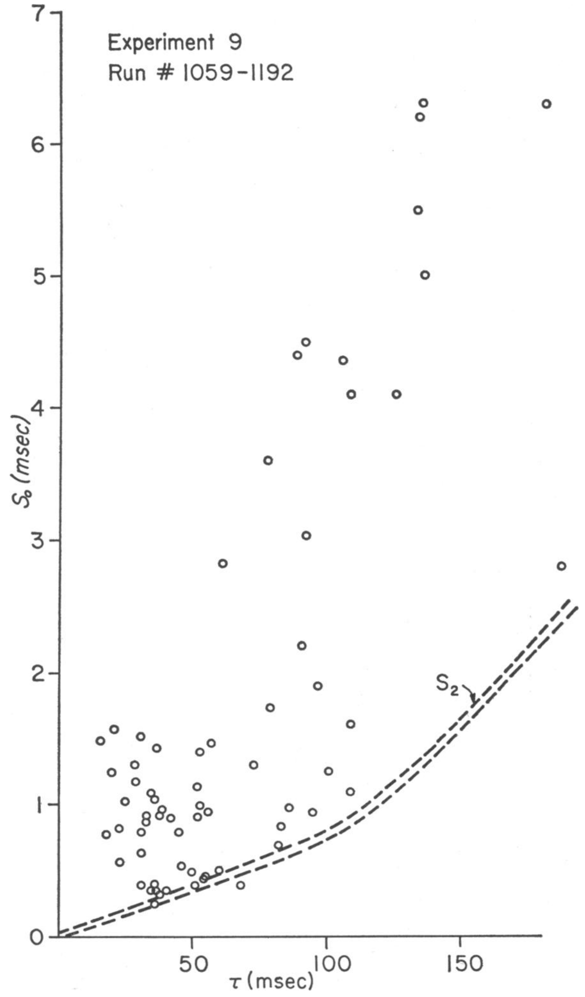


Figure 2 Standard deviation S_0 of intervals (calculated in the usual manner, $S_0^2 = \langle \tau_r^2 \rangle - \langle \tau_r \rangle^2$) as a function of mean interval. Compare Figs. 2 and 3.

S_2^2, S_3^2 allows correlations to be estimated. If one assumes that $\langle v_r v_{r+1} \rangle$ is the most significant correlation, it can be shown that $S_3^2 - S_2^2 \simeq -\langle a''^2 \rangle/6 - \langle v_r v_{r+1} \rangle/6$, and $(S_2^2 - S_1^2) - 2(S_3^2 - S_2^2) \simeq -\langle a'^2 \rangle/2$, neglecting $\langle a'''^2 \rangle$ compared with $\langle a''^2 \rangle$ and $\langle a''^2 \rangle$ compared with $\langle a'^2 \rangle$.

In Fig. 5, $(S_3^2 - S_2^2)/S_2^2$ is plotted against τ and there is some indication, at least in experiment No. 9, that $(S_3^2 - S_2^2)$ is positive between 35 msec and 70 msec indicating a serial correlation coefficient $\langle v_r v_{r+1} \rangle / v^2 \simeq -0.2$. This deviation from zero cannot be blamed on drift, for $\langle a''^2 \rangle$ must be positive and, therefore, if acting alone would appear to give a negative value of $(S_3^2 - S_2^2)$.

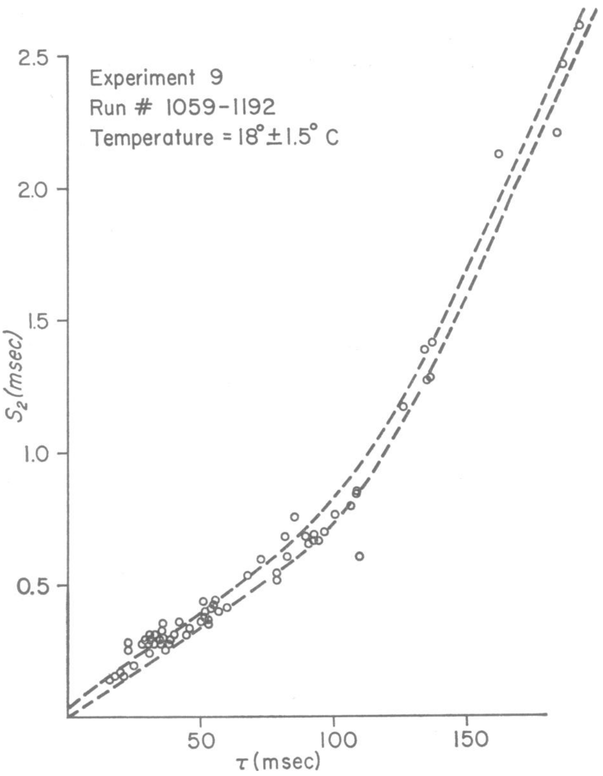


FIGURE 3 Standard deviations S_2 of intervals (calculated from second differences of intervals) as a function of mean interval.

At about 25 msec, $(S_3^2 - S_2^2)$ is negative but it is not known if this is caused by a significant contribution from $\langle a''^2 \rangle$ or whether $\langle v_r v_{r+1} \rangle$ becomes positive. Fig. 1h shows part of a record from a receptor known to be moribund and a definite alternation of long and short intervals is observed giving a negative $\langle v_r v_{r+1} \rangle$.

Fig. 6 shows a plot of $(S_2^2 - S_1^2)/S_2^2$ versus $(S_3^2 - S_2^2)/S_2^2$. If there were no drift and no correlations higher than the first the points should lie on the line $y = 2x$ whatever the value of $\langle v_r v_{r+1} \rangle$. The tendency of the points about this line suggests that the difference between S_1^2, S_2^2, and S_3^2 is due to a significant value of $\langle v_r v_{r+1} \rangle$ rather than to drifts.

THEORY OF NOISE AND COMPARISON WITH RESULTS

The main result of this work is the smallness of the interspike interval fluctuation $(S/\tau = 0.7\%)$ and the linear nature of the $S - \tau$ curve up to 80 msec. For comparison, some interval fluctuations for other receptors and higher order neurons are given below:

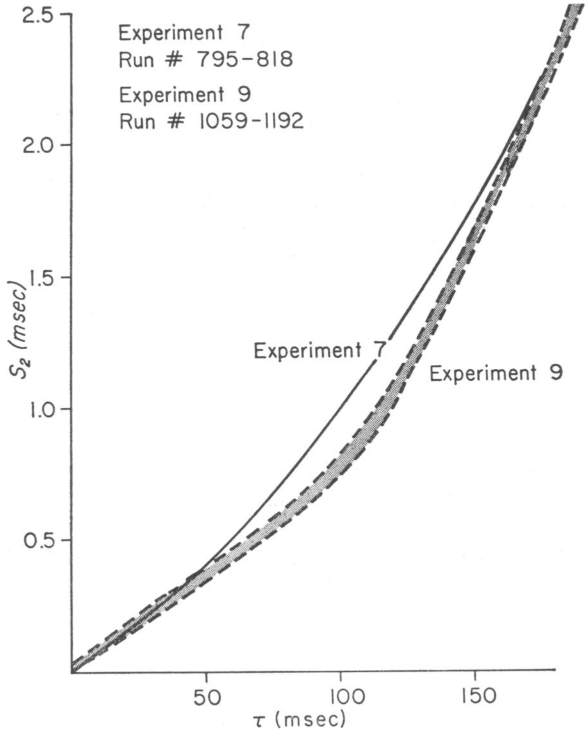


FIGURE 4 Comparison of S_2-τ curves from experiments 7 and 9. (The band between the dotted lines represents the region of confidence for experiment 9; a lower value of S_2 is given more weight than a higher one because drift can only increase the apparent value of S_2.)

Touch capsule in skin of cat (Werner and Mountcastle, 1965) $S/\tau = 3\%$.

Muscle spindle of frog (Buller, et al., 1953; Hagiwara, 1954) $S/\tau = 2.7\%$, ($\tau = 10$ msec), $S/\tau = 31\%$, ($\tau = 100$ msec).

Low discharge rate units in superior olivary complex (Goldberg, et al., 1964) $S/\tau = 6\%$.

Thalamic lemniscus neuron (Poggio and Viernstein, 1964) $S/\tau = 42\%$.

For a crayfish axon stimulated electrically, Verveen and Derksen (1965) found a relative spread of 1.2% in the stimulus required.

The irregularity in the output of a primary sensory neuron is probably an accidental and undesirable feature (Werner and Mountcastle, 1965), but in higher order neurons the irregularity (as measured by the standard deviation) may be part of the signal, not the noise. Thus, more subtle analyses have revealed interesting regularities (Poggio and Viernstein, 1964; Goldberg et al., 1964; Rodieck et al., 1962). In primary sensory neurons the irregularity is small and, despite evidence for correlations in the present work, it seems unlikely to be a carrier of informa-

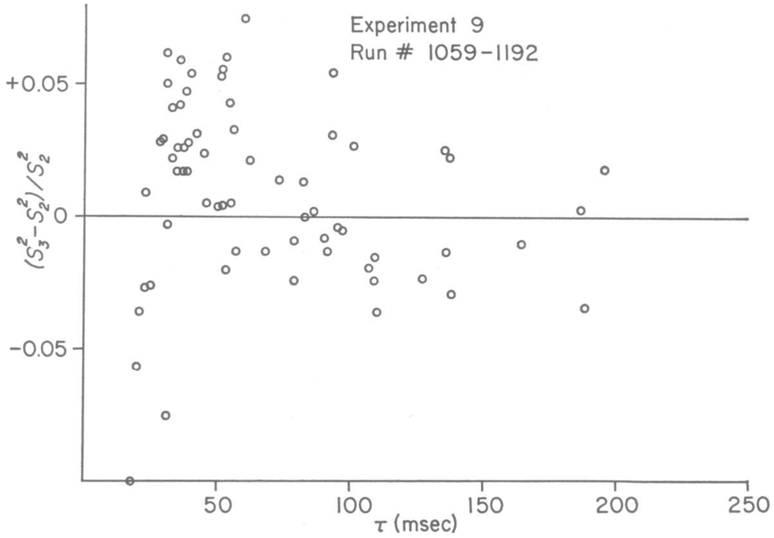


Figure 5 Serial correlation between adjacent intervals. If the drift is fairly small ($\langle a''^2 \rangle$ small), the serial correlation coefficient $\langle v_r v_{r+1} \rangle / v^2$ is approximately $-6(S_3^2 - S_2^2)/S_2^2$.

tion. The mean interval characterizes the sequence almost completely in the steady state and hence must be the only significant quantity.

Interval fluctuation may have several causes and intracellular recording is necessary to separate them. For example, some kinds of noise cause fluctuations in the rising intracellular potential (called ramp potential here), others in the firing level; intracellular recording can clearly separate these two effects.

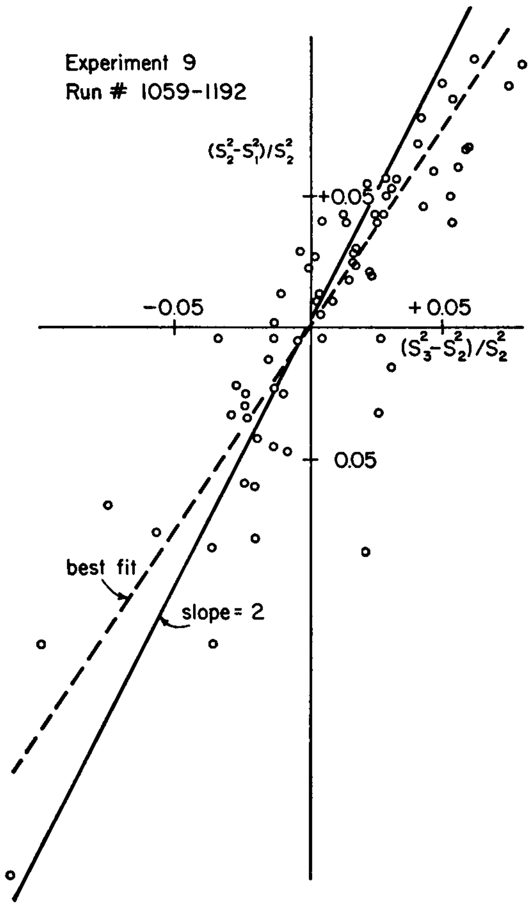
It has been helpful to make a tentative classification of noise as follows: (*a*) electrical or chemical (Bartholomay (1958) discusses fluctuations in small chemical systems); (*b*) thermal or shot; (*c*) bounded or unbounded [illustrated below in example (*a*)].

Category (*a*) refers to the primary cause of the noise (e.g., voltage or threshold fluctuation).

In category (*b*), thermal fluctuations depend primarily on kT (k = Boltzmann's constant, T = absolute temperature) whereas shot noise depends on the size of random small shots and their mean rate of occurrence.

Examples.

(*a*) *Resistor or Johnson noise:* This is caused by thermal fluctuations; it acts by way of fluctuations in potential across the membrane; it is bound in the sense that there is a mean square voltage which does not increase with time (classification: electrical, thermal, bounded). However, if the fluctuating variable of main interest were the net charge through the resistor, then, since the mean square net charge increases linearly with time, the fluctuation would be unbounded



FIGURES 6 Differences between S_1^2, S_2^2, S_3^2 due to serial correlation. If the difference between S_1^2, S_2^2, and S_3^2 is due mainly to a first correlation $\langle v_r\ v_{r+1}\rangle$ then $(S_2^2 - S_1^2)/S_2^2$ versus $(S_3^2 - S_2^2)/S_2^2$ should have a slope of 2, as shown.

and analogous to the drunkard's walk (MacDonald, 1962; Gerstein and Mandelbrot, 1964).

(*b*) *Electrical shot noise:* This is present if the membrane current (in or out) is carried by ions or groups of ions which cross the membrane in a statistically independent way. This noise is electrical, shot, and bounded (if current is the variable of interest). If the shot forming device were a fluctuating pore or other conducting mechanism, the cause might be seen as chemical, not electrical.

(*c*) *Synaptic noise:* As Fatt and Katz (1952) showed for the muscle end plate, small packets of transmitter (inhibitory in the crayfish stretch receptor) may be spontaneously and randomly released, thereby causing shot noise with shots large compared with a single ion. Inquiry as to the cause of the "spontaneous" release of a packet takes us back to thermal fluctuations in a membrane. A chain of triggering might allow a random small cause to produce a random larger effect, but with the larger variability typical of the smaller system.

(*d*) The Hodgkin-Huxley (1952) model does not explicitly use stochastic processes, but some constants in the equations vary rapidly with temperature, showing that thermal fluctuations may directly affect the basic mechanism of the conductance changes (Fitzhugh, 1955).

From various assumptions and known data, the interval fluctuations due to resistor noise and simple shot noise in a long axon may be estimated. When a ramp potential rises linearly from a fixed origin to a constant firing level (V_0), a membrane fluctuation ΔV produces a relative interval fluctuation $S/\tau \simeq \Delta V/V_0$ when $\Delta V/V_0$ is small.

Intracellular experiments show $V_0 \sim 10$ to 15 mv (Eyzaguirre and Kuffler, 1955) and the present work finds $S/\tau \sim 0.7\%$.

For Johnson noise from membrane and axoplasmic resistance

$$\langle \Delta V^2 \rangle \simeq \frac{2kT}{\pi^2 C_m (2a)^{3/2}} \left(\frac{R_i}{R_m}\right)^{1/2} \beta_{\max}{}^{1/2}$$

and for shot noise from ions crossing the membrane singly

$$\langle \Delta V^2 \rangle \simeq \frac{e\mathcal{E}_m}{2\pi^2 C_m (2a)^{3/2}} \left(\frac{R_i}{R_m}\right)^{1/2} \pi\sqrt{2}.$$

R_i and R_m are the axoplasmic and membrane specific resistances and C_m is the membrane specific capacitance. $2a$ = diameter of axon, $\mathcal{E}_m$ = equilibrium membrane potential. $\beta_{\max} = R_m C_m \times f_{\max}/2\pi$ where $f_{\max}$ is a cutoff frequency for membrane response to stimulation. (See Appendix for details of the calculations.)

Taking $C_m = 1\ \mu\text{f/cm}^2$, $R_m = 10^3\ \Omega\ \text{cm}^2$, $R_i = 10^2\ \Omega\ \text{cm}$, $2a = 10\ \mu$, $f_{\max} = 10\ kc/s$ we find $\beta_{\max} \simeq 63$.

Then $\langle \Delta v^2 \rangle^{1/2} \simeq 8\ \mu\text{v}$ for Johnson noise so that we expect $S/\tau \simeq 0.07\%$. Because of the slow dependence of $\langle \Delta v^2 \rangle^{1/2}$ on the membrane constants and on $\beta_{\max}$, there is little chance of adjusting these parameters to produce the observed value of S/τ ($=0.7\%$). Thus another model or effect is needed.

The ratio

$$\langle \Delta V^2 \rangle_{\text{shot}} / \langle \Delta V^2 \rangle_{\text{Johnson}} \simeq \frac{e\mathcal{E}_m}{kT} \times 0.07,$$

and the membrane potential

$$\mathcal{E}_m \simeq \frac{kT}{e} \log\left([K^+]_i/[K^+]_o\right)$$

hence

$$S_{\text{shot}} \simeq S_{\text{Johnson}} \times 0.26(\log [K^+]_i/[K^+]_o)^{1/2}.$$

Thus the interval fluctuations due to shot noise and Johnson noise are comparable and are inadequate to explain the observed value.

If the ions cross the membrane in groups the charge, in effect, will be larger resulting in more shot noise. Synaptic noise, pore or membrane gate fluctuations, or possible cooperative phenomena would all have larger shot values.

Fluctuations which are not primarily electrical are not shorted out by the cable action of the nerve and therefore may be quite large locally.

Shape of Curve. Although the size of the interval fluctuation is not explained by simple shot noise or resistor noise, the shape of the $S - \tau$ curve (in particular, the upward curvature) may be accounted for by the shape of the ramp potential under different degrees of stretch (Verveen, 1965). The fluctuation Δt in interval τ is given by $\Delta t = \Delta V_{\text{noise}}/$(slope of ramp potential at firing level). Also $\tau =$ firing level/(average slope over interval) so that $S/\tau = \Delta t/\tau =$ (ΔV noise/firing level) (average slope over interval/slope at firing level).

The intracellular work of Eyzaguirre and Kuffler (1955) shows that the last factor increases at larger τ; thus this formula predicts a rise in S/τ for larger τ.

Correlations. The use of mean square differences to estimate S^2 tends to discard correlations over several interspike intervals and thus to subtract the effect of low frequency cell noise on S^2. If there really are correlations the low frequency part of the noise spectrum becomes important and one cannot assume that the state of the cell is reset to zero after every action potential. Such low frequency noise observed over one interspike interval will look like unbounded noise. Again, work with intracellular electrodes will help to solve this problem.

APPENDIX

CALCULATION OF MEMBRANE NOISE

Johnson Noise.

The fluctuation in membrane potential at any point may be calculated by adding up contributions from every point, suitably attenuated and phase-shifted. However, for a simpler linear cable it is easiest to find the input resistance at the point of interest.

From the cable equation,

$$V + \frac{1}{\omega_0}\frac{\partial V}{\partial t} = \lambda^2 \frac{\partial^2 V}{\partial x^2}$$

(where $\lambda^2 = r_m/r$ and $\omega_0 = 1/r_m c_m$), taking the Fourier transform gives

$$(1 + i\omega/\omega_0)v(\omega) = \lambda^2 \frac{\partial^2 v(\omega)}{\partial x^2}.$$

For a semi-infinite cable fed with current at the end, $x = 0$, the solution is $v(\omega) =$

$\exp -[(1 + i\omega/\omega_0)^{1/2}\, x/\lambda]$ and the input impedance for a cable extending in both directions is

$$v/2I = \frac{rv}{2}\frac{\partial v}{\partial x} = \frac{r\lambda}{2(1 + i\omega/\omega_0)^{1/2}}.$$

Writing $\omega/\omega_0 = \beta$ for simplicity, one finds the resistive part of the input impedance to be

$$\frac{r\lambda}{2}\left(\frac{1}{1+\beta^2} + \frac{1}{(1+\beta^2)^{1/2}}\right)^{1/2}$$

(Fatt and Katz, 1952).

For Johnson resistor noise $\langle V^2 \rangle = 4kT \times$ resistance $\times$ band width. Therefore

$$\langle V^2 \rangle = 4kTr\lambda \frac{\omega_0}{4\pi} \int \left(\frac{1}{1+\beta^2} + \frac{1}{(1+\beta^2)^{1/2}}\right)^{1/2} d\beta$$

$$= 4kTr\lambda \frac{\omega_0}{4\pi} [(1 + \beta_{\max}{}^2)^{1/2} - 1]^{1/2}$$

In terms of specific membrane parameters,

$$r = R_i/\pi a^2, \qquad \lambda^2 = aR_m/2R_i, \qquad \omega_0 = 1/R_mC_m$$

$$\therefore \langle V^2 \rangle \simeq \frac{2kT}{\pi^2 C_m (2a)^{3/2}} \left(\frac{R_i}{R_m}\right)^{1/2} \beta_{\max}{}^{1/2} \qquad \text{when} \quad \beta_{\max} \gg 1$$

The frequency response of the triggering mechanism is not known, but such concepts are very likely inapplicable, so a simple cutoff frequency, $\beta_{\max}$, has been used. (This integral diverges without a cutoff.)

Fatt and Katz (1952) chose $f_{\max} = 10\ kc/s$ which gives $\beta_{\max} \simeq 63$ for the membrane parameters used in the discussion (see also Fitzhugh, 1955). The cutoff $f_{\max}$ affects S according to $S \propto f_{\max}{}^{1/4}$ and is therefore not very critical.

Shot Noise. If a stream of independent particles has a mean rate, N/sec, then in an interval, t, the number, n, crossing a surface in the stream will fluctuate about the mean $\langle n \rangle = Nt$ with variance $\langle \delta n^2 \rangle = \langle n^2 \rangle - \langle n \rangle^2 = Nt$. For a stream of charges, e, one finds charge fluctuations $\langle \delta_q{}^2 \rangle = eIt$ where I is the mean current, and the voltage fluctuations due to these charge fluctuations across a series resistor (noiseless) are $\langle \delta v^2 \rangle = eIR^2 \times$ band width of detector. To apply this idea to the membrane one assumes the ions cross independently. Net flow in fact may be zero, but the active and passive transports are independent so their shot effects will add together.

For a long, discrete cable composed of series resistors, r_i, leakage resistors, r_m, capacitors, C_m, and fluctuating emf V_m in series with the resistors r_m, the author has shown that

$$\langle V^2(\omega) \rangle = \frac{|V_m(\omega)|^2}{1 + \omega^2 C_m{}^2 r_m{}^2} \cdot \frac{\tanh l \tanh l^*}{\tanh (l + l^*)}$$

where $\sinh l = [(1 + i\omega C_m r_m) r_i/4r_m]^{1/2}$

If the fluctuating emf, V_m, is due to shot noise from current driven through the membrane resistance by the steady membrane potential $\mathcal{E}_m$, going from a discrete to a continuous cable gives

$$\langle V^2(\omega)\rangle = \frac{e\,\mathcal{E}_m}{\pi(2a)^{3/2}}\,(R_m R_i)^{1/2}\,\frac{1}{(1+\beta^2)^{1/2}}\,\frac{1}{(1+i\beta)^{1/2}+(1-i\beta)^{1/2}}.$$

To find the mean square voltage fluctuation integrate over the appropriate frequency range, remembering $f = \omega/2\pi = \omega_o\beta/2\pi$

$$\langle V^2\rangle = \frac{e\,\mathcal{E}_m}{2\pi^2 C_m(2a)^{3/2}}\left(\frac{R_i}{R_m}\right)^{1/2}\left[\frac{4}{\sqrt{2}}\tan^{-1}\left(\beta+(1+\beta^2)^{1/2}\right)^{1/2}\right]_{\beta_{\mathrm{min}}}^{\beta_{\mathrm{max}}}$$

When $\beta_{\mathrm{max}} \gg 1$ and $\beta_{\mathrm{min}} \simeq 0$, the term in square brackets becomes $\pi\sqrt{2}$. Thus the integrated shot noise converges, in contrast to the integrated resistor noise whose divergence results from the axoplasmic and external resistance, not from the membrane resistance.

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