THEORY OF THRESHOLD FLUCTUATIONS IN NERVES

II. ANALYSIS OF VARIOUS SOURCES OF MEMBRANE NOISE

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ABSTRACT Threshold fluctuations in axon firing can arise as a result of electrical noise in the excitable membrane. A general theoretical expression for the fluctuations is applied to the analysis of three sources of membrane noise: Johnson noise, excess $1/f$ noise, and sodium conductance fluctuations. Analytical expressions for the width of the firing probability curve are derived for each of these noise sources. Specific calculations are performed for the node of Ranvier of the frog, and attention is given to the manner in which threshold fluctuations are affected by variations of temperature, ion concentrations, and the application of various drugs. Comparison with existing data suggests that threshold fluctuations can best be explained by sodium conductance fluctuations. Additional experiments directed at distinguishing among the various noise sources are proposed.

I. INTRODUCTION

In the preceding paper (Lecar and Nossal, 1971, henceforth referred to as paper I), we developed general formulas relating the firing probabilities of axons to physical noise sources associated with the processes underlying excitation. We now derive explicit expressions for three major sources of neural noise and examine how associated threshold fluctuations vary with changes in experimental parameters such as temperature, divalent ion concentration, and the application of various drugs. The object of these calculations is to analyze available experimental findings on threshold fluctuations in terms of hypothetical membrane noise sources.

Representative noise sources are Johnson noise, $1/f$ (excess) noise, and channel noise (Na^+ conductance fluctuations). Johnson noise arises from the thermal motion of charged particles and is the fundamental noise which must be considered in any conductor (Kittel, 1958). Our concern with $1/f$ noise is prompted by reports of its presence in the frog node of Ranvier (Derksen and Verveen, 1966) and the lobster giant axon (Poussart, 1969, 1971). Similarly, we consider the conductance fluctuations which would accompany the random opening and closing of microscopic channels because a number of kinetic models of the voltage-dependent ionic conductances in nerve presume the existence of such channels (Hille, 1970 *a*).

We focus upon the probability of firing as a function of stimulus strength for pulses of constant duration. We have shown that this quantity obeys the relation (from paper I, equation 35)

$$P(\text{fire} \mid I) = \tfrac{1}{2}\left[1 + \operatorname{erf}\left(\frac{I - I_\theta}{RI_\theta}\right)\right],$$

where I is the stimulating current, I_θ is the threshold value of current, and R is the relative spread of the distribution. The distribution curve was shown in Fig. 6 of paper I; R is the width of the transition region where the probability of firing rises from 0 to 1.

In paper I (equation 26) we derived a general expression for R in terms of membrane electrical parameters,

$$R = (\sqrt{2}\, D^{1/2} V_1)/(Z_{11} V_\theta^*). \tag{1}$$

Here V_1 is the Na equilibrium potential, V_θ^* is the threshold depolarization measured from rest, and Z_{11} is a factor which arises from the geometry of the $V\sigma$ phase plane and is a function of various membrane variables (see paper I, equation 18). The parameter D depends upon the nature of the noise source, and is defined in paper I (equation 24) as:

$$D = \int_0^\infty \int_0^\infty e^{-p_1(\xi+\eta)} \langle X(\xi) X(\eta) \rangle \, d\xi \, d\eta \,. \tag{2}$$

In equation 2, the quantity $X(t)$ is related to the random Langevin noise forces which appear in a modified Hodgkin-Huxley (HH) description of the ionic conductances of the axon membrane (cf. equations 19 and 13 of paper I). The rate constant p_1 is a complicated function of several of the membrane rate constants (equation 17, paper I). In effect, p_1 represents a rate of passage through the threshold region, so that its magnitude (and its variation with experimental parameters) governs the relative effectiveness of all noise sources. (More precisely, p_1 is the rate constant associated with motion of the axon state variable in a direction away from the threshold separatrix.)

In the following sections (II–IV) we derive analytic expressions for the relative spread pertaining to each of the above-mentioned noise sources. These theoretical results are then compared with experimental data in section V, in order to identify the source of the observed threshold fluctuations.

II. JOHNSON NOISE

At first glance it seems inappropriate to apply the usual Nyquist theorem for Johnson noise to a nonlinear system such as the nerve membrane (van Kampen, 1965). As was shown in paper I, however, the voltage noise need only be evaluated in the neighborhood of the threshold singular point of the $V\sigma$ equations. In this region the Na conductance is only 5% of the total conductance and the equivalent circuit for the axon can be divided into a large linear dissipative element and a parallel, high-impedance, nonlinear term. In other words, for times sufficiently short that the Na current has not fully developed, we can regard the thermal noise source as a Johnson source appropriate to a linear resistance composed of the parallel leak and resting potassium resistances (see Fig. 1).

The Johnson noise source generates a random voltage $\tilde{V}(t)$ in series with g_0. By the Nyquist theorem (Kittel, 1958), the mean square value of this random function is

$$\langle \tilde{V}^2 \rangle = 4kTG^{-1}\Delta f,$$

where k is Boltzmann's constant, T is the absolute temperature, G is the conductance, and Δf is the bandwidth of the detector. Since the noise spectrum is constant, the Wiener-Khintchine theorem (see Equation 10 below; also, Kittel, 1958) immediately gives the autocorrelation function,

$$\langle \tilde{V}(t)\tilde{V}(t+\tau) \rangle = 2kTG^{-1}\delta(\tau), \tag{3}$$

where τ is an arbitrary time delay and $\delta(\tau)$ is the Dirac delta function. In our particular application, G is the resting membrane conductance, $G \equiv C(\gamma_0 + \sigma_B\gamma_1) \approx C\gamma_0$, where γ_0, γ_1, and σ_B have been defined in equations 4 and 6 of paper I.

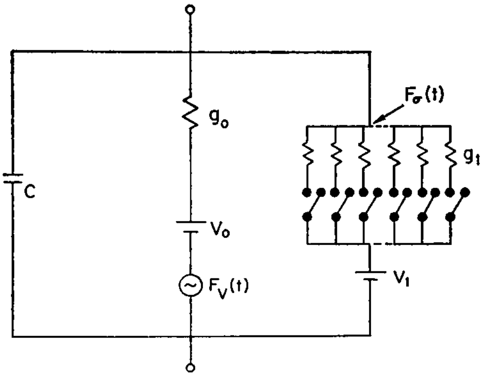

FIGURE 1 The $V\sigma$ equivalent circuit in the presence of noise. One circuit path is composed of parallel leakage and potassium conductivities g_0 in series with an effective ionic battery V_0 and a noise voltage source $F_V(t)$. The latter is composed of Johnson noise and excess $1/f$ noise. The other branch of the circuit contains a sodium driving force in series with a group of conducting channels which randomly open and close.

Referring to Fig. 1, we see that the random force in equation 10, paper I, is given by

$$F_V(t) = C^{-1}G\tilde{V}(t). \tag{4}$$

It now follows from equation 4 that the autocorrelation function of the Langevin force is given as

$$\langle F_V(t)F_V(t+\tau)\rangle = 2kTC^{-2}G\delta(\tau). \tag{5}$$

In order to obtain the random force $X(t)$ appearing in equation 2, we must perform the transformation given by equation 19, paper I. For the case of voltage fluctuations, the projected Langevin force is given as $X(t) = Z_{11}F_\epsilon(t) = Z_{11}V_1^{-1}F_V(t)$. Substituting this term into equation 2 yields the following expression for D_{Johnson},

$$\begin{aligned} D_{\text{Johnson}} &= (Z_{11}/V_1)^2 \int_0^\infty \int_0^\infty \langle F_V(\xi)F_V(\eta)\rangle e^{-p_1(\xi+\eta)}\,\mathrm{d}\xi\,\mathrm{d}\eta\,, \\ &= 2(Z_{11}/V_1)^2 \int_0^\infty \int_0^\eta \langle F_V(0)F_V(\eta-\xi)\rangle e^{-p_1(\xi+\eta)}\,\mathrm{d}\xi\,\mathrm{d}\eta\,. \end{aligned} \tag{6}$$

The integral in equation 6 may be evaluated by performing the coordinate transformation $z = \xi + \eta$, $w = \xi - \eta$. The integral then becomes

$$D_{\text{Johnson}} = 2(Z_{11}/V_{11})^2 \int_0^\infty e^{-2p_1z} \int_0^z \langle F_V(0)F_V(w)\rangle e^{p_1w}\,\mathrm{d}w\,\mathrm{d}z.$$

Recalling from equation 5 that the second integrand is a delta function, we immediately obtain

$$D_{\text{Johnson}} = (Z_{11}^2kTG)/(V_1^2C^2p_1). \tag{7}$$

Finally, the relative spread associated with a Johnson noise source is found by substituting equation 7 into equation 1,

$$R_{\text{Johnson}} = \left(\frac{2kTG}{p_1C^2V_\theta^{*2}}\right)^{1/2}. \tag{8}$$

III. EXCESS NOISE CONTRIBUTION

We now consider a source of nonequilibrium, or "excess" noise. Nerve membranes show considerable low-frequency excess noise with a characteristic $1/f$ frequency spectrum (Derksen and Verveen, 1966; Poussart, 1969, 1971). The physical origin of this noise is poorly understood, but it is believed to be generated in the K^+ transport system. Because the K^+ conductance does not change within the time range under consideration, we can regard the $1/f$ noise source as localized in the linear part of the circuit. With this assumption, the derivation of a Langevin force from the noise power spectrum is analogous to the preceding derivation. Although written as a voltage, in the present case, the effective noise source really represents the fluctuations in the K^+ conductance.

From the work of Verveen and Derksen (Derksen, 1965; Derksen and Verveen, 1966) and Poussart (1969, 1971), the excess noise in the resting nerve membrane can be described by the power spectrum

$$S(\omega) = \lambda^{-1}E^2/(1 + \omega/\lambda). \tag{9}$$

The parameters E and λ are empirical; λ is the inverse of a relaxation time and E^2 is the noise intensity. Although little is known about the variation of E^2 and λ when experimental parameters of the axon are changed, the current dependence of the amplitude E^2 has been studied. To a good approximation E is proportional to $(V - V_K)^\gamma$, where $(V - V_K)$ is the departure of the membrane potential from the potassium equilibrium potential. The constant γ appears to be close to 1 (Derksen and Verveen, 1966; Poussart, 1968), but may in fact have the value 0.75 (Poussart, 1971).

Using the Wiener-Khintchine theorem (Kittel, 1958), which relates the time behavior of the autocorrelation of a random function $C(t)$ to its power spectrum $S(\omega)$, we can now find the autocorrelation function for the noise source of equation 9. The theorem states

$$C(t) = (1/2\pi) \int_0^\infty S(\omega) \cos \omega t \, d\omega \, . \tag{10}$$

Substituting for $S(\omega)$ from equation 9 and rewriting equation 10 in terms of the dimensionless parameter $X = \omega t$, we obtain

$$f(t) = (E^2/2\pi) \int_0^\infty \frac{\cos X}{X + \lambda t} \, dX \tag{11}$$

$$= (E^2/2\pi) \, \mathcal{G} \, (\lambda t) \, ,$$

where $\mathcal{G}(X)$ is defined by

$$\mathcal{G}(X) = -Ci(X) \cos X - si(X) \sin X. \tag{11a}$$

The "trigonometric integrals" $Ci(X)$ and $si(X)$ are transcendental functions whose properties are tabulated (Abramowitz and Stegun, 1964).

As in the previous section, we can write a Langevin force with a known autocorrelation function,

$$F_V(t) = (G/C)\tilde{E}\,(t), \tag{12}$$

where the quantity $\tilde{E}\,(t)$ is defined by

$$\langle \tilde{E}\,(D)\tilde{E}\,(t)\rangle = (E^2/2\pi)\mathcal{G}(\lambda t). \tag{13}$$

Using equation 12 and 13 to define the Langevin force for $1/f$ noise, we substitute into equation 2 to obtain

$$\begin{aligned} D_{1/f} &= (1/2\pi)\left(\frac{Z_{11}GE}{CV_1}\right)^2 \int_0^\infty \int_0^\infty \mathcal{G}(\lambda \mid \xi - \eta \mid) e^{-p_1(\xi+\eta)}\, d\xi\, d\eta\,, \\ &= (1/\pi)\left(\frac{Z_{11}GE}{CV_1}\right)^2 \int_0^\infty \int_0^\xi \mathcal{G}(\lambda\xi - \lambda\eta)\, e^{-p_1(\xi+\eta)}\, d\xi\, d\eta\,. \end{aligned} \tag{14}$$

If we define a new variable χ as $\chi \equiv \xi - \eta$, it is evident that equation 14 may be rewritten as

$$D_{1/f} = (1/\pi)\left(\frac{Z_{11}GE}{CV_1}\right)^2 \int_0^\infty e^{-2p_1\xi} \int_0^\xi e^{p_1\chi}\mathcal{G}(\lambda\chi)\, d\chi\, d\xi, \tag{15}$$

so that an integration by parts yields

$$D_{1/f} = (1/2\pi)\left(\frac{Z_{11}GE}{CV_1}\right)^2 p_1^{-1} \int_0^\infty e^{-p_1\xi}\mathcal{G}(\lambda\xi)\, d\xi\,. \tag{16}$$

We note that the integral appearing in equation 16 is the Laplace transform of $\mathcal{G}(\lambda\xi)$ and may be evaluated as (Abramowitz and Stegun, 1964)

$$\int_0^\infty e^{-p_1\xi}\mathcal{G}(\lambda\xi)\, d\xi = \lambda^{-1}\left[\frac{(p_1/\lambda)\ln(p_1/\lambda) + \pi/2}{(p_1/\lambda)^2 + 1}\right]. \tag{17}$$

Equation 17 can be simplified by noting that p_1 is of the order of 10^4 sec^{-1} (see Table I) and λ is of the order of 1 (Derksen, 1965), so that $p_1/\lambda \sim 10^4$ and $(p_1/\lambda)^2 + 1 \cong (p_1/\lambda)^2$. Consequently, it is appropriate to keep only the first term on the right-hand side of equation 17 and simplify the denominator. With these modifications, equations 16 and 17 provide the following expression

$$D_{1/f} = (1/2\pi)\left(\frac{Z_{11}GE}{p_1CV_1}\right)^2 \ln(p_1/\lambda)\,. \tag{18}$$

Concomitantly, from equation 1 the relative spread for $1/f$ noise is found to be

$$R_{1/f} = (1/\sqrt{\pi})\,\frac{GE}{p_1CV_\theta^*}\,[\ln(p_1/\lambda)]^{1/2}\,. \tag{19}$$

IV. CONDUCTANCE FLUCTUATIONS AND THE POSSIBILITY OF DISCRETE CONDUCTING CHANNELS

So far we have treated noise sources which can be represented as belonging to a passive path in parallel with the excitable element. From the point of view of understanding membrane processes, a more interesting noise source is the fluctuation in the voltage-dependent Na conductance. We now analyze the contribution of such conductance noise to the threshold fluctuations. Specifically, we shall be concerned with a model in which conductance noise is caused by the opening and closing of unitary conducting channels.

Arguments for the existence of channel mechanisms of conduction in nerves are reviewed by Hille (1970 *a*). Two kinds of evidence which suggest a quantal conduction mechanism for the early Na current are the discrete subthreshold responses observed by del Castillo and Suckling (1957), Lüttgau (1958), and Hille (1970 *b*), and the hyperpolarizing Na jumps seen by Verveen and Derksen (1968). Also, certain synthetic "excitable" bilayer membranes have been shown to operate by the opening and closing of microscopic channels (Ehrenstein et al., 1970).

In this section we consider a model in which the voltage-dependent conductance is the sum of N identical microscopic conducting units, each of which is switched on and off at random (see Fig. 1). The variable σ, which represents the normalized conductance (cf. equation 6, paper I), is equal to the fraction of channels open at any instant. In steady state the conductance is a function of voltage alone $\sigma_\infty(V)$, and the approach to steady state is given by equation 9, paper I.

We now derive a Langevin force associated with thermal fluctuations of the number of open channels. The equilibrium properties of the channel fluctuations can be obtained in a general way by a straightforward statistical argument. Let us represent the normalized conductance of the ith channel by a variable s_i, such that $s_i = 1$ when the ith channel is open and $s_i = 0$ when the ith channel is closed. The average value of s_i is equal to the probability that the ith channel is open. Since all the channels are identical and independent, the probability that any channel is open is in turn given by the expectation value of σ, the normalized membrane conductance. Thus we write

$$\langle\sigma\rangle = N^{-1}\sum_{i=1}^{N}\langle s_i\rangle = \langle s_i\rangle. \tag{20}$$

Similarly, the expectation value of σ^2 can be evaluated as

$$\langle\sigma^2\rangle = \left\langle\left(N^{-1}\sum_{i=1}^{N} s_i\right)^2\right\rangle = N^{-2}\sum_{i=1}^{N}\sum_{j=1}^{N}\langle s_i s_j\rangle\,; \tag{21}$$

however the independence of the channels implies

$$\langle s_i s_j\rangle = \langle s_i\rangle, \qquad i = j;$$
$$\langle s_i s_j\rangle = \langle s_i\rangle^2, \qquad i \neq j,$$

so that equation 21 becomes

$$\langle\sigma^2\rangle = N^{-2}[N(N-1)\langle\sigma\rangle^2 + N\langle\sigma\rangle]. \tag{21 a}$$

The instantaneous fluctuation of σ from its mean value is given by the relation

$$\langle\tilde{\sigma}^2\rangle = \langle\sigma^2\rangle - \langle\sigma\rangle^2. \tag{22}$$

Thus the relation for the mean square conductance fluctuation as a function of the mean conductance follows by substitution of equations 20 and 21 *a* into equation 22

$$\langle\tilde{\sigma}^2\rangle = \langle\sigma\rangle(1 - \langle\sigma\rangle)N^{-1}. \tag{23}$$

In order to complete the derivation of a Langevin force we now determine the manner in which the fluctuations decay. The method we adopt is to use equation 23 to specify the intensity of the coupling between the system and the heat bath, even when the system is not in equilibrium. In this way, the amplitude of the Langevin force is fixed as a function of voltage alone. Our analysis uses the macroscopic kinetic equations to describe the regression of the fluctuations. This procedure would seem to be valid for the relaxation process described here, provided that the fluctuations are not excessively large (Onsager, 1931 *a* and *b*; Zwanzig, 1961).

To determine the properties of the Langevin force we rewrite the phenomenological equation for the relaxation of the voltage-dependent conductance (equations 8 and 9, paper I) to include the (as yet undetermined) Langevin force,

$$\frac{d\sigma}{dt} = 3\lambda(V)\sigma^{2/3}[\sigma_\infty(V)^{1/3} - \sigma^{1/3}] + F_\sigma(t)\,. \tag{24}$$

If the conductance fluctuations are small compared with the mean conductance, $|\tilde{\sigma}| \ll \langle\sigma\rangle$, we can simplify equation 24 by writing σ as $\langle\sigma\rangle + \tilde{\sigma}$ and expanding equation 24 in powers of $\tilde{\sigma}$. We may then subtract terms related to motion in the absence of fluctuations, obtaining

$$\frac{d\tilde{\sigma}}{dt} \cong 3\lambda(V)\left\{\tfrac{2}{3}\left[\frac{\sigma_\infty(V)}{\langle\sigma\rangle}\right]^{1/3} - 1\right\}\tilde{\sigma} + F_\sigma(t)\,. \tag{25}$$

Equation 25 has presupposed an artificial situation in which there are no autonomous voltage fluctuations; however, once the form of the Langevin function has been determined, we can treat cases in which both voltage and conductance fluctuations coexist. In the neighborhood of the threshold singular point $[\langle\sigma\rangle \cong \sigma_\infty(V_B)]$ equation 25 can be simplified to

$$\frac{d\tilde{\sigma}}{dt} \approx -\lambda(V)\tilde{\sigma} + F_\sigma(t)\,. \tag{26}$$

The amplitude of the correlation function for F_σ may now be obtained from equations 23 and 26. Assuming that on an observable time scale (Chandrasekhar, 1943)

$$\langle F_\sigma(t)F_\sigma(t+\tau)\rangle = A\delta(\tau), \tag{27}$$

we can solve equation 26 and take the expectation value of the square of the solution. We substitute from equation 27 in the resulting integrals to obtain

$$\langle\tilde{\sigma}(t)^2\rangle = \langle\tilde{\sigma}(0)^2\rangle e^{-2\lambda t} + (A/2\lambda)(1 - e^{-2\lambda t}). \tag{28}$$

As t approaches infinity in equation 28 we find

$$\langle\tilde{\sigma}^2\rangle_{\text{steady state}} = (A/2\lambda);$$

however, we know from equation 23 that, for steady state at a given voltage,

$$\lim_{t\to\infty}\langle\tilde{\sigma}(t)^2\rangle = \sigma_\infty(V)[1 - \sigma_\infty(V)]N^{-1}. \tag{29}$$

Consequently, comparing equation 28 with equation 29, we can solve for A and substitute into equation 27 to obtain

$$\langle F_\sigma(t)F_\sigma(t+\tau)\rangle \cong 2\lambda(V)N^{-1}\delta(\tau)\sigma_\infty(V)[1 - \sigma_\infty(V)]. \tag{30}$$

Having obtained a Langevin force which represents the conductance fluctuations, we now substitute equation 30 into equation 2 to obtain

$$D_\sigma = 2N^{-1}Z_{12}^2\int_0^\infty\int_0^\infty e^{-p_1(\xi+\eta)}\lambda[V(\xi)]\sigma_\infty[V(\xi)]\{1 - \sigma_\infty[V(\xi)]\}\delta(\xi-\eta)\,\mathrm{d}\xi\,\mathrm{d}\eta\,. \tag{31}$$

Here the factor Z_{12} arises from the definition of $X(t)$ (equation 19, paper I) and is explicitly defined in equation 18, paper I. During motion along the separatrix the voltage V is approximately equal to the voltage at the singular point V_B, and equation 31 simplifies to

$$D_\sigma \cong 2N^{-1}Z_{12}^2 p_1^{-1}\lambda(V_B)\sigma_\infty(V_B)[1 - \sigma_\infty(V_B)]. \tag{32}$$

Substituting equation 32 into equation 1, we now obtain an expression for the relative spread caused by conductance fluctuations as

$$R_\sigma = N^{-1/2}(Z_{12}/Z_{11})(2V_1^2/p_1V_\theta^{*2})^{1/2}\{\lambda(V_B)\sigma_\infty(V_B)[1 - \sigma_\infty(V_B)]\}^{1/2}. \tag{33}$$

From simple statistical reasoning, one might have expected R_σ to be equal to the reciprocal square root of the number of channels open at threshold. Since about 65 sodium channels are required to be open at threshold (Hille, 1970 *a*), the relative spread would then be $\sqrt{65} \sim 12\,\%$, a number much larger than the usual observed value. The absence of such large threshold fluctuations led Bass and Moore (1968) to doubt the notion of conducting channels; however, threshold fluctuations are random motions in the y_1-direction and the σ random force is more nearly parallel to the y_2-direction (see section III of paper I). The term Z_{12}/Z_{11} appearing in equation 33 is just the inverse slope of the separatrix line in the linearized ($V\sigma$) model (cf. equation 18, paper I), and represents the effect of the geometry of the phase plane. Using experimental values of the various membrane parameters (see Table I and equation 18, paper I) we find $Z_{12}/Z_{11} \sim 0.3$, yielding a value for R_σ of $\sim$4%.

V. DISCUSSION AND COMPARISON WITH EXPERIMENT

The main results of our calculations are the formulas giving the relative spread in terms of measurable circuit parameters. For the purpose of discussion, we rewrite the formulas of equations 8, 19, and 33 in the following manner:

$$\begin{aligned} R_{\text{Johnson}} &= (p_1^{-1/2}/V_\theta^*)(2kTG/C^2)^{1/2}, \\ R_{1/f} &= (p^{-1/2}/V_\theta^*)\left(\frac{GE}{\sqrt{\pi}C}\right)[p_1^{-1} \ln (p_1/\lambda)]^{1/2}, \qquad (34) \\ R_\sigma &= (p_1^{-1/2}/V_\theta^*)N^{-1/2}(Z_{12}/Z_{11})\{2V_1^2\lambda(V_B)\sigma_\infty(V_B)[1 - \sigma_\infty(V_B)]\}^{1/2}. \end{aligned}$$

All the membrane parameters appearing in equation 34 have been determined experimentally. Using the values from Table I, we find the following for the contributions of each of the noise sources:

$$R_{\text{Johnson}} \sim 0.002,$$

$$R_{1/f} \sim 0.003,$$

$$R_\sigma \sim 0.04.$$

The value of R_σ was computed for $N = 7500$, the number of channels estimated for a single node of Ranvier (Hille, 1970 *a*).

Thus, if the Na activation really operates by the opening of $\sim 10^4$ unitary channels, the conductance noise will be the dominant contributor to the threshold fluctuations. Additional information relating the proposed noise sources to the threshold fluctuations can be obtained by analyzing the manner in which threshold fluctuations vary with experimental conditions. Some experimental variables for which the HH circuit parameters have been extensively studied are temperature, external calcium concentration, external sodium concentration, and concentrations of various drugs. We shall next consider the variation of relative spread as a function of these parameters. Experimental coefficients used in the following computations are for the node of Ranvier of frog sciatic nerve, and are summarized in Table I.

TABLE I

PARAMETERS USED IN COMPUTATIONS[*]

(*a*) Standard Node Parameters

Parameter	Value	Temperature coefficient Q_{10}
Resting potential, $V_0 \cong V_K \cong V_L$, *mv*	-75	
Reversal potential, $V_1 = V_{Na}$, *mv*	$+48$	
Membrane capacitance *C*, *pF*	1.5	
Resting conductance, $g_0 = g_K n_\infty^4(V_0) + g_L$, *μmho*	0.048	1.2[‡]
Maximum Na conductance, $g_1 = g_{Na} h_\infty(V_0)$, *μmho*	0.63	1.3[‡]
Coordinates of threshold singular point	$V_B = -53.5$ mv $\sigma_B = 0.00926$	
Na$^+$ time constants τ_m, τ_h		1.8, 3.0[‡]
Positive eigenvalue p_1 of principal axis transformation (calculated according to equation 17, paper I), sec^{-1}	1.10×10^4	-0.3 (see Fig. 2)

(*b*) Noise Parameters

Parameter	Value
Number of Na channels[§]	$N = 7500$
$1/f$ noise parameters[‖]	
Spectral amplitude, *mv*	$E = 0.04$
Cutoff frequency, sec^{-1}	$\lambda = 1$

[*] Parameters for frog node of Ranvier at $T = 22°C$ (Hille, 1968) unless otherwise noted.

[‡] Dodge and Frankenheuser, 1959.

[§] Hille, 1970 *a*.

[‖] Derksen and Verveen, 1966.

Temperature

Experimentally, there is a marked decrease in relative spread when the temperature is raised (Erlanger et al., 1941). This observation is particularly intriguing since random motion usually increases with temperature. The theoretical behavior of R as a function of temperature, predicted from equation 34, is shown in Fig. 2. The figure also shows the factor $p_1^{-1/2}$, which is common to all the expressions appearing in equation 34. We see that the temperature dependence of p_1 is the dominant quantity in determining the manner in which the relative spread changes, for all of the noise sources.

As can be seen from equations 17 and 14 of paper I, the temperature dependence of p_1 is primarily determined by the temperature dependence of $\tau_m(V)$. As $\tau_m(V)$ decreases, the system moves through the threshold region more rapidly and hence has less opportunity to diffuse away from its unperturbed trajectory. Thus, even though the fluctuations from the physical noise sources increase with increasing

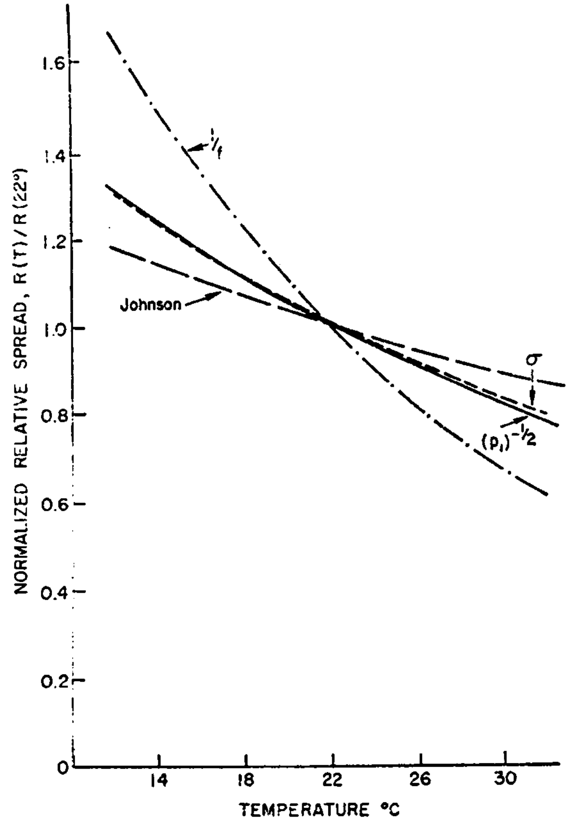

FIGURE 2 The relative spread for variations in temperature, normalized to the values at T = 22°C. All noise sources are seen to give rise to decreasing relative spread with increasing temperature. The normalized factor $(p_1)^{-1/2}$ (see text) is also shown, indicating that most of the temperature behavior is due to the variation of the gross excitation kinetics of the axon rather than the temperature variation of the noise source.

temperature, the temperature dependence of the relative spread is governed more strongly by the change in the deterministic motion along the separatrix than by the increased noise.

External Calcium

Next we predict the effect of varying external calcium concentration. Although no data currently exist on the effect of Ca upon threshold fluctuations, it is interesting to see whether such experiments could differentiate between noise sources. The principal effect of varying external calcium concentration is to shift some of the excitability parameters along the voltage axis. The quantities, $m_\infty(V)$, $\tau_m(V)$, $h_\infty(V)$, and $\tau_h(V)$ are known to shift 5–8 mv/e-fold change in calcium concentration (Frankenhaeuser and Hodgkin, 1957; Hille, 1968). These shifts cause a concomitant change in the position of the threshold singular point (V_B, σ_B), in turn determining a

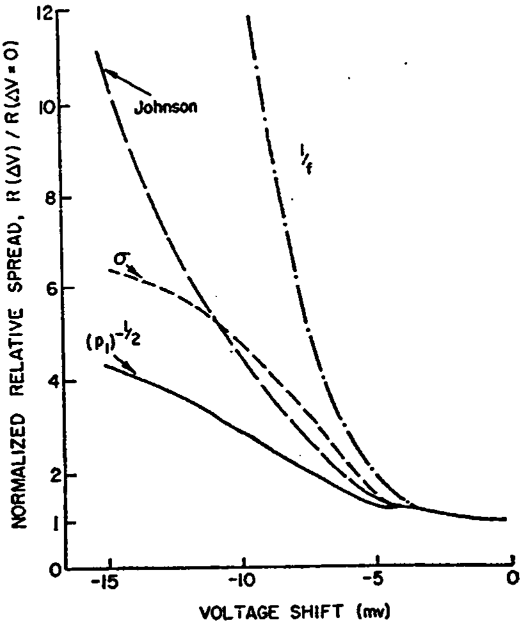

FIGURE 3 The effects of removal of Ca^{++} from the bathing solution; normalized relative spread, as a function of the shift of $m_\infty(V)$ along the voltage axis. An e-fold decrease of calcium leads to a 5-8 mv negative displacement of the m_∞ curve. The relative spreads R associated with the various noise sources all increase with decreasing Ca^{++}.

new set of elements in equation 14, paper I. The main parameters which are significantly altered are the eigenvalues p_1 and p_2, and the geometric factors of the Z matrix.

Fig. 3 shows the relative spread plotted as a function of the shift in $m_\infty(V)$ and $h_\infty(V)$. For all noise sources, an increase in fluctuations with decreasing calcium is predicted. In terms of the parameters of equation 34, the dominant effect of the shifting singular point is the variation in p_1 for shifts up to approximately -10 mv. For larger shifts, the term V_0^* which appears in equation 34 is also important since the distance between the resting and threshold singular points decreases markedly when most of the calcium is removed.

Sodium Concentration and Drugs Which Affect Sodium Conductance

The sodium conductance g_{Na} is another parameter which influences the threshold fluctuations by altering the position of the singular point. Experimentally g_{Na} can be varied in two ways: by changing the external sodium concentration or by applying a drug which blocks the sodium channels. Tetrodotoxin (TTX) is known to block the Na channels (Narahashi et al., 1964), and urethane is thought to have a similar effect (Hagiwara and Saito, 1959). Changes in external sodium change both g_{Na} and V_{Na}, whereas TTX only lowers g_{Na} without affecting V_{Na}. Figs. 4–5 *b* show how the

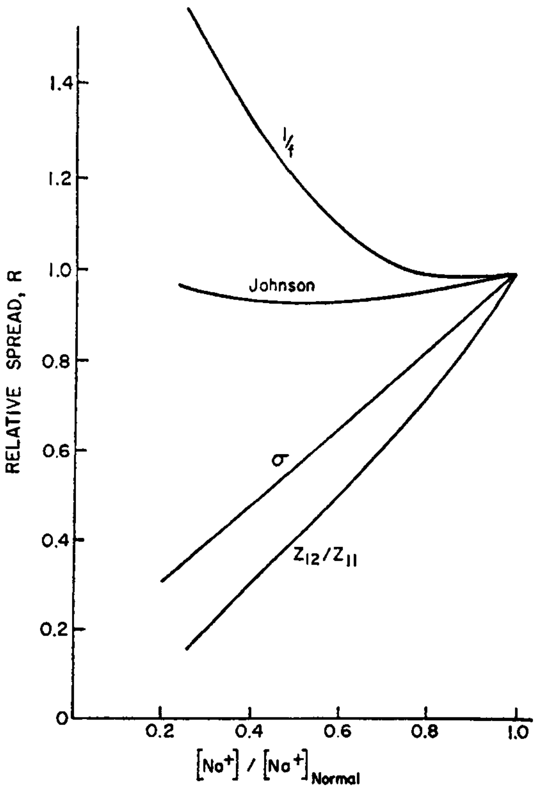

FIGURE 4 The effects of removal of Na+ from the bathing solution. There is a marked reduction in the relative spread related to Na+ conductance fluctuations. This is primarily because of changes in the slope of the threshold separatrix, leading to diminution of the importance of σ fluctuations. Note that there is no change in relative spread due to Johnson noise, but there is a slight *increase* in relative spread due to $1/f$ excess noise. The data of Dodge and Frankenhaeuser (1959) have been used to obtain the dependence of g_{Na} on $[Na]_o$.

elative spread varies with changing external sodium concentration and with application of g_{Na}-blocking drugs.

Urethane is reported to decrease the relative spread but increase the threshold so hat the product of the two is constant. From Fig. 5 *a* we see that when Na channels re blocked there are marked decreases in relative spread corresponding to Johnson noise or Na conductance fluctuations, whereas there is relatively little change for a $1/f$ noise source. In Fig. 5 *b* we have plotted the quantity $V_\theta{}^* \cdot R$, which is roughly proportional to the product of the relative spread and the threshold voltage. In accord with experiment, this quantity is seen to be approximately constant for a noise source dominated by conductance fluctuations.

Conclusions

In Table II we summarize the results of our calculations and compare them with experimental data. Some qualitative features, such as the decrease of fluctuations with

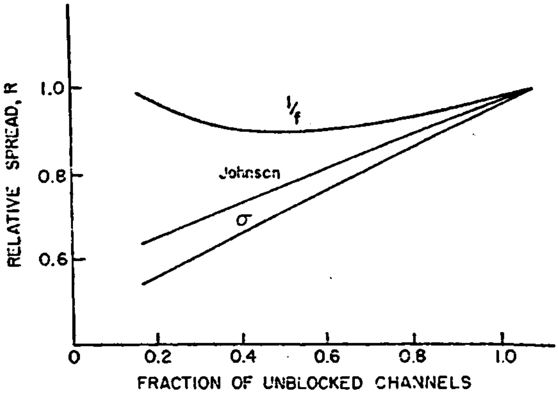

FIGURE 5 *a* Change in relative spread as sodium channels are blocked by addition of drugs such as TTX or urethrane. Normalized relative spread R as a function of the fraction of channels not being blocked.

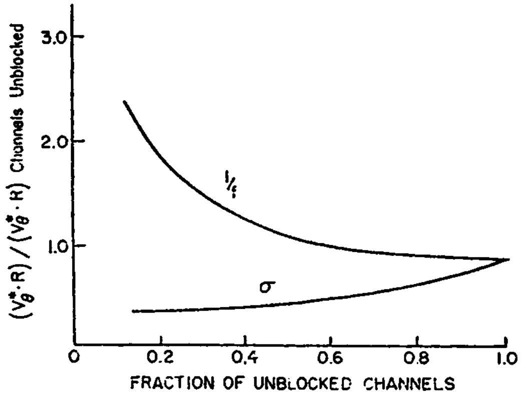

FIGURE 5 *b* The product ($R \cdot V_\theta^*$) as sodium channels are blocked by addition of drugs such as tetrodotoxin or urethane. Note that for σ fluctuations this quantity is almost a constant, as has been reported by Verveen (1962) for application of urethane.

increasing temperature and the predicted increase of fluctuations when Ca is removed, are more strongly dependent on the dynamics of the system than on the nature of the noise sources. The theory explains these features but shows that such experiments do not provide tools for identifying the dominant noise source.

On the other hand, the estimate of the magnitudes of the relative spread, the estimates of the temperature coefficients, and the predictions for Na-blocking agents all point to Na conductance fluctuations as the dominant noise source for causing threshold fluctuations. Additional evidence to test this point should come from an experiment in which threshold fluctuations are measured as a function of external Na concentration.

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TABLE II

SUMMARY OF EFFECTS OF VARIOUS AGENTS ON RELATIVE SPREAD

Parameter	Effect on relative spread			
	Theoretical Johnson noise	Theoretical $1/f$ noise	Theoretical σ fluctuations	Experiment
Decrease temperature	increase	increase	increase	increase[*]
$Q_{10} = \frac{RS(T+10) - RS(T)}{RS(T)}$	−0.18	−0.65	−0.30	−0.3−−0.4[*]
Urethane	decrease	little change	decrease	decrease[‡]
Product: $RS \times V_\theta^*$ (urethane)	—	increase	~ constant	~ constant[‡]
Lower ext. Na^+	~ constant	increase	decrease	—
Lower ext. Ca^{++}	increase	increase	increase	—
Absolute value,[§] %	0.2	0.3	4.0	2–5[*][‖][¶]

[*] Erlanger et al., 1941; however, see also Verveen and Hickey, 1963.

[‡] Verveen, 1962.

[§] Using standard parameters given in Table I.

[‖] Poussart, 1968.

[¶] Verveen and Derksen, 1965.

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