THEORETICAL MODEL OF THE IONIC MECHANISM OF $1/f$ NOISE IN NERVE MEMBRANE

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ABSTRACT A model is presented for the ionic mechanism of low frequency $1/f$ electrical noise which has been observed in axonal membranes. The model consists of narrow channels which open randomly throughout the membrane and remain open for only a short time compared with f_{max}^{-1} where $f_{max} \sim 2$ kHz is the maximum frequency for which $1/f$ noise is observed. The fluctuation in channel formation is coupled to low frequency normal mode vibrations in liquid crystals which have properties similar to nerve membranes. Ionic current flow through the channels is assumed to occur via single file diffusion. The diffusion process is regarded as a non-Markovian random walk on a one-dimensional lattice which is mathematically decomposed into its spatial and temporal components. This technique allows calculation of the mean and variance of the number of ions which flow through any single short-lived channel. The final result for the current noise power spectrum, S, is $S(f) = (A + k|\bar{I}|^2)/f$, where $\bar{I}$ is the mean membrane current and A and k are parameters which are independent of membrane voltage. The theoretical result is consistent with observations of $1/f$ noise in lobster axon by Poussart (1971, *Biophys. J.* **11**:212.) on the dependence of $S(f)$ on the mean steady-state current and the external potassium concentration. We also calculate the mean channel density and the Frank elastic constant of the membrane. This work is an extension of a macroscopic model of Lundström and McQueen (1974, *J. Theor. Biol.* **45**:405.) who obtain a spectral density of the form $S \sim |\bar{I}|^2/f$.

INTRODUCTION

Low frequency electrical noise having a spectral density of the type $1/f$ (f = frequency) has been observed in the resting membrane of the frog node (Verveen and Derksen, 1965; Siebenga and Verveen, 1971) and the giant axon of the lobster (Poussart, 1971) and the squid (Fishman, 1973). These observations have indicated that the noise is related to the flow of potassium current across the membrane. Consequently, a useful approach to the study of this phenomenon has been the direct measurement of the current noise spectrum by use of the voltage clamp technique. In Poussart's experiment the membrane potential was clamped to a slowly increasing voltage ramp, which has been shown by simulation of the Hodgin-Huxley equations to inactivate sodium current (Demko, 1968). Therefore, the membrane may be assumed to be essen-

tially a potassium electrode with slight modifications caused by leakage current. This method yields direct quantitative information about the dependence of the noise amplitude on the magnitude of potassium current and potassium concentrations within and outside of the nerve cell. Inferences may then be made about the molecular mechanisms responsible for the flow of potassium current through the membrane.

For example, Poussart (1971) found that the amplitude of the current noise spectrum $S(f)$ over the frequency range 20 Hz to 2 kHz is given by

$$S(f) = (A + k|\bar{I}|^r)/f, \tag{1}$$

where $\bar{I}$ is the average membrane current and A, k, and r are parameters which are independent of the membrane voltage V. The exponent r lies in the range $1 \lesssim r \lesssim 2$, with a mean value of 1.5 and the parameter A increases with increasing external potassium concentration. However, the statistical significance of the mean value $r = 1.5$ is difficult to ascertain from the experiment, and the uncertainty in the area of the patch of membrane from which the noise is measured obscures the potassium concentration dependence of A.

The observation that Eq. 1 is apparently valid for inward as well as outward currents in unmyelinated fibers suggests that the noise is not related to active membrane processes. Moreover, Fishman (1973) has shown that it is probably not related to potassium conductance fluctuations. In fact, his experiment raises some obvious questions about the connection between $1/f$ noise and the potassium system. Using internally perfused squid axons, Fishman (1973) observed relaxation noise of the type $(\zeta^2 + f^2)^{-1}$, ζ a constant, superimposed on a $1/f$ noise background. Addition to the internal perfusate of tetraethylammonium ions (TEA), which are known to block potassium conductance changes (Armstrong and Binstock, 1965), removed the relaxation noise without affecting the $1/f$ spectrum. Therefore, $1/f$ noise does not seem to be related to potassium conductance mechanisms, at least for squid. Poussart (1971) did not observe simple relaxation noise in the lobster axon. If the $1/f$ noise is caused by intrinsic membrane leakage current, as Fishman's experiment suggests, then the difference between the two experiments may perhaps be explained by a larger leakage conductance in lobster axon, as compared with squid axon. The $(\zeta^2 + f^2)^{-1}$ spectrum in lobster might be completely obscured by the $1/f$ noise.

Nevertheless, the experimental evidence for a link between $1/f$ noise and the potassium system is convincing. Even Fishman (1973) suggests that the noise is probably a manifestation of potassium current flow in the membrane. However, without resorting to the unattractive hypothesis of a substantial intrinsic difference between squid and lobster giant axon membrane, the only consistent explanation for both Fishman's and Poussart's data seems to be that $1/f$ noise is caused, at least partially, by a *potassium* component of the leakage current.

A compelling theoretical explanation of $1/f$ noise in nerve membrane was recently developed by Lundström and McQueen (1974). They have shown that the noise may very plausibly be caused by a coupling between potassium conductance and low fre-

quency hydrodynamic fluctuations of the constituent lipid molecules of the nerve membrane. However, their theory is not completely consistent with the experimental data represented by Eq. 1. Their theoretical expression for the power spectrum of the current fluctuations is of the form

$$S(f) \sim |\bar{I}|^2/f, \tag{2}$$

which does not contain a current (voltage)-independent term. The most distinctive feature of the lobster $1/f$ data is that the noise is present even when $\bar{I} = 0$. In fact, the noise is present in the complete absence of electrical and chemical gradients, that is, when the external potassium concentration $[K]_e$ is equal to the internal potassium concentration $[K]_i$ and the transmembrane potential is clamped at zero volts (Poussart, 1971).

We have developed a microscopic model of ion flow across the membrane which incorporates the ideas of Lundström and McQueen (1974). Our theoretical expression for the power spectrum given by Eq. 30 is consistent with the experimental data summarized by Eq. 1. This is not a trivial extension of their work since our theory permits a detailed comparison with many aspects of the experimental data such as the external potassium concentration dependence of the parameters A and k.

MODEL

We assume that the ions which produce $1/f$ noise diffuse or leak across the membrane through dynamic short-lived channels which are formed randomly throughout the membrane. The time τ for which any channel remains open is taken to be much smaller than f_{max}^{-1}, where $f_{max} \sim 2$ kHz is the observed high frequency cutoff of $1/f$ noise. The time τ must also be greater than the time any single ion remains within the membrane. Simple model calculations suggest that the ion transit time across the membrane at room temperature is about 10^{-7} s (Hille, 1970; Stevens, 1972). Therefore, 10^{-7} s $< \tau < 0.5 \times 10^{-3}$ s. Perhaps τ corresponds to a membrane time constant typical of short range ordering of lipid molecules or perhaps to a conformational time constant of a protein molecule which gates the leakage current, as in a fluid mosaic model of nerve membrane (cf. Singer and Nicolson, 1972).

The motion of ions through any open channel is assumed to occur by single file diffusion (Hodgkin and Keynes, 1955; Macey and Oliver, 1967) or hopping of ions between a few specialized sites, n, within the membrane channel. The time for sites to be filled by ions immediately after a channel opens is assumed to be much smaller than τ, which is plausible if n is only 2 or 3, as suggested by Hodgkin and Keynes (1955) for potassium channels. Motion of the row of ions is assumed to occur only when an ion from the internal or external fluid strikes the corresponding end of the channel. Since ions hit the membrane at random times, and since the electric field within the membrane affects the direction of motion, perhaps randomly, the number of ions, N, which traverse the channel during τ is a stochastic quantity.

The membrane current in this model for ions with a single unit charge is

$$I(t) = N/\tau \int_M \beta(\mathbf{r}, t)\, d\mathbf{r}, \tag{3}$$

where β is the density of open channels, and M is the membrane patch area. The time τ is taken to be essentially instantaneous with respect to f^{-1} for 20 Hz $\lesssim f \lesssim$ 2 kHz. Fluctuations in the transit times of individual ions across the membrane, which give rise to a shot noise spectrum (cf. Rice, 1954) at higher frequencies are ignored. Our microscopic formulation for the membrane current is to be contrasted with the macroscopic expression used by Lundström and McQueen (1974). They assume the membrane current is of the form

$$I(t) = (V - V_0) \int_M g(\mathbf{r}, t)\, d\mathbf{r}, \tag{4}$$

where g is the conductance per unit area of the membrane, $\mathbf{r}$ is a two-dimensional vector in the plane of the membrane, and V_0 is assumed to be the nonfluctuating resting membrane voltage. Eq. 4 will not yield a current independent term in the expression for the power spectrum because $(V - V_0)$ is assumed to be nonstochastic. However, our expression for the current will yield this term because the quantity N is stochastic.

In our formulation the average current is given by

$$\bar{I} = \bar{N}/\tau \int_M \bar{\beta} d\mathbf{r} = \bar{\beta} M \bar{N}/\tau,$$

where $\bar{\beta}M$ is the average number of open channels at any time t, and $\bar{N}$ is the average number of ions which any single channel contributes to the net ion flux in time τ.

The fluctuation in $I(t)$ is given by

$$\delta I(t) = \frac{(\bar{N} + \delta N)}{\tau} \int_M \delta\beta(\mathbf{r}, t)\, d\mathbf{r} + \bar{\beta}\delta N M/\tau, \tag{5}$$

where δN is the fluctuation in the number of ions which flow through any single channel and $\delta\beta$ is the fluctuation in the density of open channels ($\overline{\delta N} = \overline{\delta\beta} = 0$, and δN is independent of $\delta\beta$). The second term in Eq. 5 is a spurious artifact caused by neglecting the shot noise spectrum. It will give rise to a zero frequency delta function term in the expression for the spectral density, which is outside the range of frequencies under consideration. Consequently, it will not be discussed further.

The power density is defined as (Wang and Uhlenbeck, 1954)

$$S(f) = 4\, Re \int_0^\infty <\delta I(t)\delta I(0)> e^{2\pi i f t}\, dt \tag{6}$$

where $< >$ denotes a long time average of the quantity inside the brackets. Using Eqs. 5 and 6 we obtain

$$S(f) = 4[(\bar{N}^2 + \overline{\delta N^2})/\tau^2]\, \mathrm{Re} \int_0^\infty \int_M \int_M <\delta\beta(\mathbf{r}, t)\delta\beta^*(\mathbf{r}', 0)> e^{2\pi i f t} dt\, d\mathbf{r}\, d\mathbf{r}'. \tag{7}$$

The fluctuation $\delta\beta(\mathbf{r}, t)$ is related to the fluctuation of the motion of molecules within the membrane. Nerve membranes undoubtedly belong to the class of physical systems called liquid crystals (cf. Träuble and Eibl, 1974, and references therein). The parameter which is used to specify local properties of these systems is a unit vector $\hat{n}(\mathbf{r}, t)$ (the "director" in liquid crystal terminology) which gives the instantaneous direction of constituent membrane molecules at $\mathbf{r}$ at time t. Therefore, we define a coupling constant α such that

$$<\delta\beta(\mathbf{r}, t)\delta\beta(\mathbf{r}, 0)> = \alpha <\delta\hat{n}(\mathbf{r}, t) \cdot \delta\hat{n}(\mathbf{r}, 0)> \tag{8}$$

where $\delta\hat{n}(\mathbf{r}, t)$ is the fluctuation in the orientation of the director. We cannot compute α exactly, so we estimate it by observing that Eq. 8 must hold for all times, i.e., $\alpha = <\delta\beta^2(\mathbf{r}, 0)> / <\delta\hat{n}^2(\mathbf{r}, 0)>$. In this model the opening of channels is essentially an independent random event so a reasonable estimate of the mean square fluctuation in the density of open channels is $<\delta\beta^2(\mathbf{r}, 0)> = \bar{\beta}/M$. The fluctuation $<\delta\hat{n}^2>^{1/2} = \gamma^{1/2}$ is probably a small perturbation to the equilibrium orientation of the membrane molecules. If a typical fluctuation is some small angle θ about the equilibrium orientation, then $\gamma \cong \theta^2$, since $\hat{n}$ is a unit vector.

Eq. 7 for the power spectrum now becomes

$$S(f) = [4\bar{\beta}(\bar{N}^2 + \overline{\delta N^2})/\gamma M\tau^2] \operatorname{Re} \int_0^\infty \int_M \int_M <\delta\hat{n}(\mathbf{r}, t) \cdot \delta\hat{n}^*(\mathbf{r}', 0)> \delta(\mathbf{r} - \mathbf{r}') \cdot e^{2\pi i f t} dt d\mathbf{r} d\mathbf{r}'. \tag{9}$$

The evaluation of the integral in Eq. 9 is now identical to the work of Lundström and McQueen (1974). The main assumption in the evaluation of this correlation integral is that the membrane acts mechanically as a smectic-A type liquid crystal. This implies that $\delta\hat{n}$ satisfies a two-dimensional diffusion equation (Forster et al., 1972). The free energy fluctuations per unit area are given by (Frank, 1958)

$$\delta F = (dK_1/2)[\nabla \cdot \delta\hat{n}]^2,$$

where d is the membrane thickness, and K_1 is the Frank elastic constant. In the calculation of the correlation integral the membrane surface is treated as being infinite. The above assumptions coupled with the equipartition theorem (Landau and Lifshitz, 1969) give

$$S(f) = [\bar{\beta} M k_B T(\bar{N}^2 + \overline{\delta N^2})]/[2\pi\gamma d K_1 \tau^2 f], \tag{10}$$

where k_B is the Boltzmann constant and T is absolute temperature.

Eq. 10 is valid only for a finite range of frequencies. The finite size and curvature of the membrane provides a lower frequency limit. The breakdown of hydrodynamics for distances smaller than the size of membrane molecules yields an upper frequency limit.

The main part of this paper is the calculation of $\bar{N}$ and $\overline{\delta N^2}$ so that $S(f)$ may be compared with the observed dependence of $1/f$ noise in lobster on the potassium system.

DETERMINATION OF $\bar{N}$ AND $\overline{\delta N^2}$

We now turn our attention to a single open channel with some constant number of ions n. We emphasize that the current flowing through a single channel does not produce $1/f$ noise in this model. In Eq. 9 we must integrate over the membrane patch area to obtain the $1/f$ behavior. Also ours is not a "long pore" model, as n can even equal one. We do require that the number of ions in an open channel be fixed, and that the ions are not allowed to slip past one another. The large electric field within the membrane will obviously influence motion of the ions but we will assume that the channel ions do not move until intra- or extracellular ions collide with the corresponding end of the row with sufficient energy to overcome static forces which tend to keep the ions in place. That is, the potential energy of each ion is locally minimum at each lattice site (Fig. 1 A). The electric field will asymmetrize the potential energy function, but we assume that it will not completely abolish the minima, at least not within the range of physiological membrane voltages (Fig. 1 B). Presumably, when $V = 0$, the potential function is symmetrical.

The assumed ponderomotive collisions which displace the ions from their equilibrium positions are a necessary feature of our theoretical picture. These could, in fact, be collisions between bare ions, since the high dielectric constant of water greatly reduces the electrostatic repulsion between univalant ions so that their collision frequency is about the same order of magnitude as that of neutral species, all other conditions being equal (Frost and Pearson, 1961). Another possibility is that water molecules are situated between the membrane surface and the end ion so that the collisions occur between ions and electrically neutral water molecules.

The final assumption which is required for a self consistent physical model is that the direction of motion is not necessarily determined by the fluid from which the colliding ion emerged. In the situation pictured in Fig. 1 B, an ion from fluid 1 which collides with the channel ions may not transfer sufficient energy to the row to move it one or more lattice positions toward fluid 2. However, when the row returns to the equi-

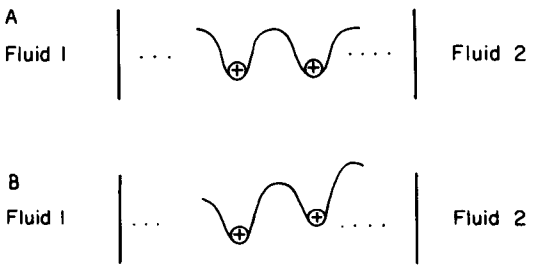

FIGURE 1 Schematic representation of electrostatic energy wells for two adjacent ions within a membrane channel. In example A, the membrane voltage, $V = 0$, so that the electrostatic barrier to motion is the same in either direction. In example B, $V \neq 0$. Specifically, $V < 0$, since fluid 1 is taken to correspond to the cellular interior. Consequently, E_{21}, the electrostatic barrier to motion toward fluid 1, is less than E_{12}, which is the barrier to motion of the channel ions toward fluid 2.

librium position, the ions may yet have sufficient energy, despite probably some dissipation, to overcome the barrier in the opposite direction. We assume that whenever a successful collision takes place, the row moves only one lattice site and that the ion which leaves the channel is replaced by another at the opposite end. That is, if motion occurs in the direction away from the fluid from which the colliding ion emerged, then that ion itself is assumed to enter the channel. However, if the motion is toward the same fluid from which the colliding ion emerged, then we assume that the row drags along an ion from the other fluid. Therefore, the channel is fully occupied at all times.

Consequently, the net number of ions $N(\tau)$ which traverse a single channel in time τ can be directly related to a random walk on an infinite one-dimensional lattice. That is, given that the distribution of times between steps that the walker takes is precisely the same as the distribution of times between collisions of extramembrane ions with the channel then the number of lattice sites between the initial and final locations of the random walker is identically $N(\tau)$ if the duration of the random walk is τ.

The net effect of this description of the ion flux is to decompose the motion of the channel ions into two parts: the times at which it occurs and the direction it takes at those times. The collisions of the extramembrane ions with the channel are the time determining factors and the electric field within the membrane as well as the relative difference between the internal and external ion concentrations are the primary direction determining factors. We regard both the collision times and the resulting directions of motion as random events. Therefore, we define two probability functions $\psi(t)$ and $p(\mathbf{l})$, where $\psi(t)\,dt$ is the probability that a collision occurs from either side of the membrane within the infinitesimal time interval $(t, t + dt)$ and $p(\mathbf{l})$ is the probability that the ions move a vector distance $\mathbf{l}$ at the time of that collision. We assume that the probability of two collisions within the interval $(t, t + dt)$ is $0[(dt)^2]$ and that ions move only one lattice site per collision. Therefore, the function $p(\mathbf{l})$ is given by

$$p(\mathbf{l} = \mathbf{L}) = \xi, p(\mathbf{l} = -\mathbf{L}) = 1 - \xi, \quad \text{and} \quad p(\mathbf{l} \neq \pm\mathbf{L}) = 0, \tag{11}$$

where L is the distance between two ions and ξ is a positive number ($0 \leq \xi \leq 1$) which is determined by the membrane potential, the ratio of the internal to external ion concentration, and perhaps the physical characteristics of the channel itself.

The probability density $\psi(t)$, as shown in Appendix A, is in general a bimodal function, since the time between collisions on one side of the membrane is different from that of the other side, if the ion concentrations are unequal. The exact form of ψ is not known. We make the assumption that the times of occurrence of collisions from either side of the membrane are independent of each other. As shown in Appendix A, the simplest form of ψ is

$$\psi(t) = (a_1 + a_2)\exp[-(a_1 + a_2)t], \tag{12}$$

where a_1 is proportional to the interior ion concentration $[C]_i$ and a_2 is proportional to the exterior ion concentration $[C]_e$. The precise form of ψ is not required to compute $\bar{N}$ and $\overline{\delta N^2}$. Only the first two moments are required (Shlesinger, 1974).

We now take advantage of the equivalence between the single channel flux and a one dimensional random walk by using the mathematical analysis which has been developed for the latter case (Montroll and Weiss, 1965; Montroll and Scher, 1973; Shlesinger, 1974). The goal of the calculation is to determine the mean distance and the mean squared fluctuations in the distance that the random walker moves in a time τ.

The average position of a random walker on a lattice at time t is

$$<\mathbf{l}(t)> = \sum_{\mathbf{l}} \mathbf{l} P(\mathbf{l}, t), \tag{13}$$

where $P(\mathbf{l}, t)$ is the probability that the walker is at the point denoted by the vector $\mathbf{l}$ at time t, and the summation is over all lattice points. Clearly, $\bar{N}$ and $\overline{\delta N^2}$ will be related to the first and second moments of $P(\mathbf{l}, t)$, respectively.

To expedite the analysis, we define two new functions $\gamma(\mathbf{k}, t)$ and $\lambda(\mathbf{k})$ such that

$$\gamma(\mathbf{k}, t) = \sum_{l} P(\mathbf{l}, t) e^{i\mathbf{l}\cdot\mathbf{k}} \quad \text{and} \quad \lambda(\mathbf{k}) = \sum_{l} p(\mathbf{l}) e^{i\mathbf{l}\cdot\mathbf{k}}. \tag{14}$$

That is, γ and λ are Fourier transforms of $P(\mathbf{l}, t)$ and $p(\mathbf{l})$, respectively. Eq. 14 gives as an alternative form for the average position,

$$<\mathbf{l}(t)> = -i\partial\gamma/\partial\mathbf{k} \Big|_{\mathbf{k}=0}. \tag{15}$$

The motivation for defining these functions is that the moments of the walk $\langle \mathbf{l}^n(t) \rangle$ are simply related to γ as, for example, in Eq. 15. Also, as shown in Appendix B, γ can be expressed in the closed analytical form

$$\gamma(\mathbf{k}, t) = \mathfrak{L}^{-1}[(1 - \psi^*(\mu))(\mu(1 - \lambda(\mathbf{k}))\psi^*(\mu))^{-1}], \tag{16}$$

where $\psi^*(\mu)$ is the Laplace transform of $\psi(t)$ and $\mathfrak{L}^{-1}$ denotes the inverse Laplace transform operation. The average position of the walker now becomes (Montroll and Scher, 1973)

$$<l(t)> = \bar{l}\,\partial\gamma/\partial\lambda \Big|_{\lambda=1}, \tag{17}$$

where

$$\overline{l^n} = \sum_{\mathbf{l}} (\mathbf{l})^n p(\mathbf{l}). \tag{18}$$

Using Eq. 16 together with Eq. 17 yields

$$<l(t)> = \bar{l}\,\partial/\partial\lambda\left[\mathfrak{L}^{-1}\left\{\frac{1 - \psi^*(\mu)}{\mu(1 - \lambda\psi^*(\mu))}\right\}\right]_{\lambda=1} = \bar{l}\,\mathfrak{L}^{-1}[f(\mu)], \tag{19}$$

where

$$f(\mu) = \psi^*(\mu)/(\mu(1 - \psi^*(\mu))). \tag{20}$$

Since the long time behavior of $\psi(t)$ is responsible for noise at low frequencies, it is appropriate to study the small μ behavior of $\psi^*(\mu)$. That is,

$$\psi^*(\mu) \sim 1 - \mu\bar{t} + \mu^2\overline{t^2}/2 + \cdots, \tag{21}$$

where

$$\overline{t^n} = \int_0^\infty x^n \psi(x)\, dx. \tag{22}$$

Consequently, $f(\mu)$ as defined by Eq. 20 is given by

$$f(\mu) \sim (\mu^2\bar{t})^{-1} + (\mu\bar{t})^{-1}(\tfrac{1}{2}\overline{t^2}/\bar{t} - \bar{t}). \tag{23}$$

Taking the inverse Laplace transform of Eq. 23 and using Eq. 19 gives

$$<l(t)> \sim [\bar{l}/\bar{t}]t + \bar{l}[\tfrac{1}{2}\overline{t^2}/\bar{t} - \bar{t}], \quad \sim [\bar{l}/\bar{t}]t. \tag{24}$$

for $t \leq \tau \gg \bar{t}$. The fluctuation in the average position is

$$\sigma(t) = [<l^2(t)> - <l(t)>^2]^{1/2}, \tag{25}$$

which can be shown to be (Montroll and Scher, 1973)

$$\sigma^2(t) = \overline{l^2}\partial\gamma/\partial\lambda \Big|_{\lambda=1} + \bar{l}^2[\partial^2\gamma/\partial\lambda^2 - (\partial\gamma/\partial\lambda)^2]_{\lambda=1}. \tag{26}$$

Combining Eq. 16 with Eq. 26 by performing the indicated differentiations and then applying Eq. 21 in the resulting expression finally yields

$$\sigma(t) \cong [\overline{l^2}/\bar{t} + (2\bar{l}^2/\bar{t})(\tfrac{1}{2}\overline{t^2}/\bar{t}^2 - 1)]^{1/2}t^{1/2}. \tag{27}$$

The quantities $\bar{N}$ and $\overline{\delta N^2}$ are given by

$$\bar{N}(t) = <l(t)>/L, \qquad \overline{\delta N^2}(t) = \sigma^2(t)/L^2. \tag{28}$$

The mean steady-state current through one channel is given by

$$\bar{I}_1 = e\bar{N}(t)/\bar{t} = e\bar{l}/L\bar{t}$$

where we have now explicitly included the charge on the ion. The total mean current through the membrane patch M is given by

$$\bar{I} = \bar{\beta}M\bar{I}_1. \tag{29}$$

Using Eqs. 28 and 29 in our expression for the power spectrum in Eq. 10 we find

$$S(f) = (1/f)[k_B T/2\pi d\gamma K_1]\{e^2\bar{\beta}M/\bar{t}\tau + [\bar{I}^2/\bar{\beta}M][1 + (2/\tau)((\overline{t^2}/2\bar{t}) - \bar{t})]\}, \tag{30}$$

where we have used the fact that for nearest neighbor steps in a random walk $\overline{l^2}/L^2 = 1$. Finally, we note that Eq. 30 is of the form

$$S(f) = (A + k|\bar{I}|^2)/f. \tag{31}$$

DISCUSSION

The most direct experimental test of Eq. 31 is the current dependence. The data of Poussart (1971) suggest a 3/2 power law, although several of his preparations exhibited a quadratic or near-quadratic relationship consistent with Eq. 31. Nevertheless, if the exponent, r in Eq. 1, is determined in future experimental tests to be statistically inconsistent with a value of $r = 2$, then our theory will have been demonstrated to be fundamentally incorrect.

Other experimental tests of Eq. 31 are the potassium concentration dependence of the parameters A and k, assuming that the $1/f$ noise is produced by potassium current. The parameter A is proportional to $\bar{\tau}^{-1}$ so if $\psi(t)$ is given by Eq. 12, then

$$A \sim ([K]_e + [K]_i), \tag{32}$$

where $[K]_{e(i)}$ is the external (internal) potassium concentration. In Fig. 2 we have plotted the relative $[K]_e$ dependence of A for the range 10 mM < $[K]_e$ < 500 mM using $[K]_i$ = 235 mM which is a typical value for the lobster axon (Brinley, 1965). The smooth curve represents the theoretical result in Eq. 32 which we have crudely fitted to the experimental points. All of the data show a great deal of scatter, represented by the vertical lines, except for the case of $[K]_e$ = 244 mM. However, Poussart (1971) has only three experimental points for this concentration, whereas several points are given for the others. The data have not been corrected for variation in area of the different

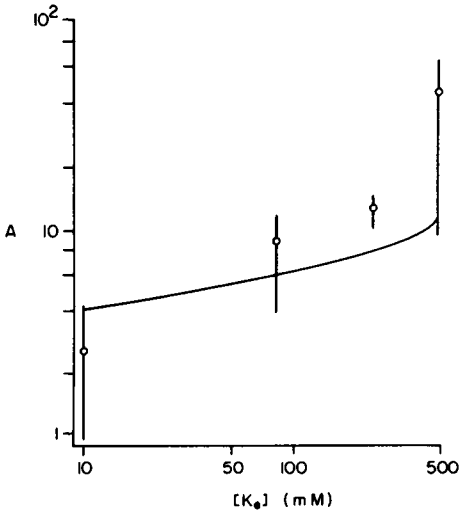

FIGURE 2 Relative comparison of the theoretical dependence of the parameter A on external potassium concentration with the experimentally determined concentration dependence. The vertical lines represent the data taken from Fig. 17 of Poussart (1971). The values of $[K]_e$ in the experiment are 10, 80, 244, and 478 mM. Each circle represents a rough average for the corresponding $[K]_e$. The extent of each line represents the experimental scatter and is not meant to imply any statistical measure of the data. The solid curve is a rough fit to the data of the theoretical expression for A given by Eq. 32 in the text.

preparations, which may be a significant cause of the scatter in the experimental points. As shown in Appendix A, more complicated forms of $\psi(t)$ can be obtained which may improve the agreement of theory to experiment. However, the present status of the experimental data for the parameter A is adequately fitted by Eq. 32.

The parameter k can also be tested. From Eqs. 30 and 31 we have

$$k \sim 1 + 2/\tau(\overline{t^2}/2\bar{t} - \bar{t}). \tag{33}$$

The second term in Eq. 33 reduces to zero for the special case of $\psi(t)$ given by Eq. 12, as can be readily seen by using the expressions for $\bar{t}$ and $\overline{t^2}$ given in Appendix A. Moreover, the quantity $(\overline{t^2}/2\bar{t}^2 - 1)$ is nearly zero even for more complicated forms of $\psi(t)$ (Shlesinger, 1975). Consequently, the external potassium concentration dependence of k is small, which seems to be consistent with the lobster axon data (Poussart, 1971).

The approximate number of noise producing channels can also be computed from our theory, since the ratio $A/k\bar{I}^2$ is independent of the parameters K_1 and γ. We have that

$$A/k\bar{I}^2 = e^2\bar{\beta}^2M^2/\bar{t}\tau\bar{I}^2 = S_{I=0}/(S_I - S_{I=0}). \tag{34}$$

From Poussart's Fig. 12

$$fS(f) = 4.5 \times 10^{-22}\,\text{amperes}^2 = A, \tag{35}$$

for $[K]_e = 10$ mM and $f = 640$ Hz. Also $k\bar{I}^2 = 2 \times 10^{-22}$ amperes^2 for $\bar{I} = 400$ nanoamperes. Using $\tau = 10^{-5}$s and $\bar{t} = 10^{-8}$s, and $e = 1.6 \times 10^{-19}$C, we obtain $\bar{\beta}M \cong 10^5$ channels. Since $M \sim 10^4\,\mu\text{m}^2$, $\bar{\beta} \cong 10$ channels/μm^2. This is about the same order of magnitude as the potassium channel density in axonal membrane (Hille, 1970). However, we emphasize that our hypothetical noise channels need not necessarily be equated with the usual potassium conductance channels.

Using the above estimate for $\bar{\beta}$, we may now compute the Frank elastic constant, K_1. If the membrane molecules fluctuate about their equilibrium orientation with a root mean square value of $\sim 5°$, then the parameter $\gamma = 0.01$. Using a membrane thickness of $d = 100$ Å, $\bar{\beta}M = 10^5$, $M = 10^4\,\mu\text{m}^2$, and $\bar{t}\tau = 10^{-13}$ s^2, gives $K_1 \sim 10^{-6}$ dyn. This value is consistent with measured values of elastic moduli for typical liquid crystals (Stephen and Straley, 1974).

Finally we note that the second term in Eq. 31 is of the form $S(f) \sim \bar{I}^2/N_c f$, where N_c is the total number of channels within the membrane patch. Since each channel contains the same number of ions, n, we have that $S(f) \sim \bar{I}^2/N_T f$, where N_T is the total number of charge carriers. This is the same as Hooge's law (Hooge, 1969) which is a phenomenological expression that attempts to express all $1/f$ noise measurements in one simple formula.

We have not conclusively shown that our formulation is the only one which will give an expression for the power spectral density which is consistent with Eq. 1. However, we have given one possible mechanism of $1/f$ noise which offers a useful framework for future noise measurements.

APPENDIX A

In this Appendix we will calculate a general form for the waiting time density $\psi(t)$ for collisions of ions in an internal and external fluid with a membrane channel. We shall call particles in the internal fluid type 1, and those in the external fluid type 2. We start our clock at an arbitrary time which we call $t = 0$. The last hit of the membrane channel may have occurred from the internal or external fluid at any time in the past. When one enters an ongoing stochastic process of this type at an arbitrary time then the probability density $h_i(t)\,dt$ of a hit by a particle of type i in the time interval $(t, t + dt)$ is (Feller, 1971)

$$h_i(t) = (1/\bar{t}_i)[1 - \int_0^t \phi_i(x)\,dx], \tag{36}$$

where $\phi_i(t)\,dt$ is the probability density of a hit by a particle of type i in the time interval $(t, t + dt)$ if the last hit of type i occurred at $t = 0$, and $\bar{t}_i = \int_0^\infty t\phi_i(t)\,dt$. Note that for $\phi(t) = ae^{-at}$, that $\phi(t) = h(t)$. So the probability density $\psi(t)$ for a hit from either side of the membrane in the interval $(t, t + dt)$ is

$\psi(t)\,dt$ = Prob. [hit from type 1 in $(t, t + dt)$] Prob. [no hit from type 2 in $(0, t)$] + Prob. [hit from type 2 in $(t, t + dt)$] Prob. [no hit from type 1 in $(0, t)$]

$$= h_1(t)\,dt\left[1 - \int_0^t h_2(x)\,dx\right] + h_2(t)\,dt\left[1 - \int_0^t h_1(x)\,dx\right]. \tag{37}$$

The simple Markovian case is $\phi_i(t) = h_i(t) = a_i \exp(-a_i t)$, which yields

$$\psi(t) = [a_1 + a_2]\exp[-(a_1 + a_2)t]. \tag{38}$$

The first two moments of this $\psi(t)$ are given by

$$\bar{t} = (a_1 + a_2)^{-1} = (\bar{t}_1^{-1} + \bar{t}_2^{-1})^{-1}, \tag{39 A}$$

and

$$\overline{t^2} = 2(a_1 + a_2)^{-2}, \tag{39 B}$$

where

$$\overline{t^n} = \int_0^\infty x^n \psi(x)\,dx. \tag{40}$$

A $\phi_i(t)$ of the more general form $\phi_{i,m}(t) = a_i^{m+1} t^m \exp(-a_i t)/m!$ yields

$$\psi_m(t) = \left\{\left[a_1 \exp(-a_1 t)\sum_{j=0}^{m} \{a_1 t\}^j/j!\right][m + 1]^{-2}\left[a_2 \exp(-a_2 t)\sum_{k=0}^{m}\sum_{j=0}^{k} a_2^{j-1} t^j/j!\right]\right\} + \{a_1 \leftrightarrow a_2\}, \tag{41}$$

with the first two moments

$$\bar{t}_m = (a_1a_2)(m+1)^{-2}\sum_{k=0}^{m}\sum_{j=0}^{m}[(m-j+1)(k+j+1)!(k!j!)^{-1}(a_1+a_2)^{-j-k-2} \cdot (a_1^k a_2^{j-1} + a_2^k a_1^{j-1})], \quad (42)$$

$$\overline{t_m^2} = (a_1a_2)(m+1)^{-2}\sum_{k=0}^{m}\sum_{j=0}^{m}[(m-j+1)(j+k+2)!(k!j!)^{-1}(a_1+a_2)^{-j-k-3} \cdot (a_1^k a_2^{j-1} + a_2^k a_1^{j-1})]. \quad (43)$$

APPENDIX B

The purpose of this Appendix is to derive Eq. 16 of the text. The analysis follows closely that of Montroll and Weiss (1965) and Montroll and Scher (1973). We begin with a one-dimensional lattice consisting of N points. We wish to cast the function $\gamma(\mathbf{k}, t)$ in closed analytical form, where

$$\gamma(\mathbf{k}, t) = \sum_{\mathbf{l}} P(\mathbf{l}, t)e^{i\mathbf{l}\cdot\mathbf{k}}. \quad (44)$$

The function $P(\mathbf{l}, t)$ is the probability that the walker is at site l at time t and the summation is over all N lattice points. We define another probability function $Q(\mathbf{l}, t)$, which is the probability that the random walker reaches the site $\mathbf{l}$ at precisely the time t. Also, let $\Psi(t)$ be the probability that the walker remains fixed during the time interval $(0, t)$. That is,

$$\Psi(t) = 1 - \int_0^t \psi(x)\,dx, \quad (45)$$

where, as in the text, $\psi(x)$ is the probability density of time interval x between ion collisions with the membrane channel. Then,

$$P(\mathbf{l}, t) = \int_0^t Q(\mathbf{l}, \tau)\Psi(t-\tau)\,d\tau, \quad (46)$$

or

$$P^*(\mathbf{l}, \mu) = Q^*(\mathbf{l}, \mu)(1 - \psi^*(\mu))/\mu, \quad (47)$$

where the starred variables are Laplace transforms of their unstarred counterparts. We observe that $Q(\mathbf{l}, t)$ is the sum of probabilities for each path that the walker may take from its starting position at time $t = 0$ to position $\mathbf{l}$ at time t. That is,

$$Q(\mathbf{l}, t) = P_0(\mathbf{l})\delta(t) + P_1(\mathbf{l})\psi(t) + P_2(\mathbf{l})\int_0^t \psi(\tau)\psi(t-\tau)\,d\tau + \cdots + \cdots P_j(\mathbf{l})\psi_j(t) + \cdots, \quad (48)$$

where $P_j(\mathbf{l})$ is the probability that the random walker is at $\mathbf{l}$ after step j. Also,

$$\psi_j(t) = \int_0^t \psi(\tau)\psi_{j-1}(t-\tau)\,d\tau,$$

$j = 1, 2, 3\ldots$, and $\psi_0(t) = \delta(t)$, where $\delta(t)$ is the Dirac delta function. The functions $\psi_j(t)$ are the probability densities for the occurrence of the jth step at time t. The Laplace transform of $\psi_j(t)$ is given by $[\psi^*(\mu)]^j$. Therefore,

$$Q^*(\mathbf{l}, \mu) = \sum_{j=0}^{\infty} P_j(\mathbf{l})[\psi^*(\mu)]^j. \tag{49}$$

The advantage of Eq. (49) is that it is in the form of generating function for the random walk. Generating functions are commonly used in random walk theory because they can often be expressed in a closed analytical form, whereas the functions $P_j(\mathbf{l})$ cannot. The generating function for the one-dimensional random walk under consideration in this Appendix B, is given by

$$P(\mathbf{l}, z) = \sum_{j=0}^{\infty} P_j(\mathbf{l}) z^j, \tag{50}$$

where z is a dummy variable such that $|z| \leq 1$. The functions $P_j(\mathbf{l})$ satisfy the recursion formula

$$P_{j+1}(\mathbf{l}) = \sum_{\mathbf{l}'} p(\mathbf{l} - \mathbf{l}') P_j(\mathbf{l}), \tag{51}$$

where $p(\mathbf{l})$ is the probability of vector displacement $\mathbf{l}$ when a collision occurs. If we multiply Eq. (51) by z^j and sum over all j, we obtain the discrete Green's function equation

$$P(\mathbf{l}, z) - z \sum_{\mathbf{l}'} p(\mathbf{l} - \mathbf{l}') P(\mathbf{l}', z) = \delta_{\mathbf{l},0}, \tag{52}$$

where we have used the initial condition $P_0(\mathbf{l}) = \delta_{\mathbf{l},0}$, i.e. the walker starts from a specified origin. Eq. 52 can be solved by defining a function

$$u(z, 2\pi\mathbf{l}/N) = \sum_{\mathbf{l}'} P(\mathbf{l}', z) \exp(2\pi i \mathbf{l} \cdot \mathbf{l}'/N). \tag{53}$$

If we multiply Eq. 52 by $\exp(2\pi i \mathbf{l} \cdot \mathbf{l}'/N)$ and sum over $\mathbf{l}'$, we obtain

$$u(z, 2\pi\mathbf{l}/N) = (1 - z\lambda(2\pi\mathbf{l}/N))^{-1}, \tag{54}$$

or

$$P(\mathbf{l}, z) = N^{-1} \sum_{\mathbf{s}} \frac{\exp(-2\pi i \mathbf{l} \cdot \mathbf{s}/N)}{1 - z\lambda(2\pi\mathbf{s}/N)}, \tag{55}$$

where λ is the Fourier transform of $p(\mathbf{l})$. That is,

$$\lambda(2\pi\mathbf{l}/N) = \sum_{\mathbf{s}} p(\mathbf{s}) \exp(2\pi i \mathbf{l} \cdot \mathbf{s}/N). \tag{56}$$

If we take the limiting case of an infinite lattice, Eq. 55 becomes

$$P(\mathbf{l}, z) = 1/(2\pi) \int_{-\pi}^{\pi} \frac{\exp(-i\mathbf{l} \cdot \mathbf{k})\, d\mathbf{k}}{1 - z\lambda(\mathbf{k})}. \tag{57}$$

Since Eq. 49 is of the same form as Eq. 50 only with z replaced by $\psi^*(\mu)$, we have that

$$Q^*(\mathbf{l}, \mu) = 1/(2\pi) \int_{-\pi}^{\pi} \frac{e^{-i\mathbf{l}\cdot\mathbf{k}}\, d\mathbf{k}}{1 - \psi^*(\mu)\lambda(\mathbf{k})}, \tag{58}$$

or using Eq. 47

$$P^*(\mathbf{l}, \mu) = 1/(2\pi) \int_{-\pi}^{\pi} \frac{e^{-i\mathbf{l}\cdot\mathbf{k}}\, d\mathbf{k}}{1 - \psi^*(\mu)\lambda(\mathbf{k})} \frac{1 - \psi^*(\mu)}{\mu}. \tag{59}$$

Finally, in the limit $N \to \infty$,

$$\gamma(\mathbf{k}, t) = \sum_{\mathbf{l}} P(\mathbf{l}, t) e^{i\mathbf{l}\cdot\mathbf{k}},$$

$$= 1/(2\pi) \int_{-\pi}^{\pi} \sum_{\mathbf{l}} e^{i\mathbf{l}(\mathbf{k}-\mathbf{k}')} \mathcal{L}^{-1}\left[\frac{1 - \psi^*(\mu)}{\mu(1 - \lambda\psi^*(\mu))}\right] d\mathbf{k}', \tag{60}$$

or

$$\gamma(\mathbf{k}, t) = \mathcal{L}^{-1}\left[\frac{1 - \psi^*(\mu)}{\mu(1 - \lambda\psi^*(\mu))}\right], \tag{61}$$

which is the desired result.

Note added in Proof: Conti, DeFelice, and Wanke (1975) have recently found that the relaxation noise is eliminated *and* the $1/f$ noise is decreased in depolarized squid giant axons by TEA. This finding suggests that $1/f$ noise is produced not only by leakage current, but also by the flow of ions through the voltage-dependent conductance channels. Consequently, it should be possible to model this result by adding a stochastic gate molecule to our $1/f$ channels and applying a stochastic analysis similar to that of Stevens (1972) or Hill and Chen (1972). Work along these lines is in progress.

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