BRIEF COMMUNICATION

A MECHANISM FOR $1/f$ NOISE IN DIFFUSING MEMBRANE CHANNELS

MICHAEL B. WEISSMAN, *Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138 U.S.A.*

ABSTRACT The diffusion polarization effect is shown to produce $1/f$ (ω^{-1}) noise in the conductance of membranes containing diffusing ion channels. The magnitude and frequency range of the effect are calculated.

The origin of noise with a frequency spectrum $S(\omega) \propto \omega^{-1}$ in a variety of electrical systems is a long-standing puzzle. It is generally agreed that in most cases satisfactory explanations have not been found (Verveen and DeFelice, 1974). In this note I derive from first principles a prediction of ω^{-1} noise in lipid membrane resistors containing ionophoric channels. The magnitude of this noise may be predicted without adjustable parameters. It is not claimed that the mechanism proposed here accounts for the ω^{-1} noise observed in biological membranes, since it is shown that such noise is unlikely to arise from any source affecting separate channels independently.

The outline of the theory is as follows. Conducting channels in membranes perturb the concentration of the ions they conduct, with the perturbation varying inversely with the distance from the channel, due to the diffusion polarization effect (see e.g., Neumcke, 1975). The current flowing in a channel then depends on how far away that channel is from each other channel. These distances vary as the channels diffuse in the membrane, producing current noise whose spectrum and magnitude may be calculated.

The standard linear fluctuation theory of noise (Richardson, 1950) gives the relationship between noise in an observed variable $I(t)$ and fluctuations in an underlying variable $g(\mathbf{r}, t)$ where $I(t) = \int g(\mathbf{r}, t) f(\mathbf{r}) d^n\mathbf{r}$, where n is the dimension of the system. It has recently been demonstrated (Weissman, 1975, 1977) that when $f(\mathbf{r})$ contains singularities, fluctuation transport produces noise of the form $S(\omega) \propto \omega^{-\alpha}$, $0 < \alpha < 2$. In particular, for $n = 2$, when the singularities have the form

$$f(\mathbf{r}) = f_0 + \frac{h}{|\mathbf{r} - \mathbf{r}_s|} \tag{1}$$

then $\alpha = 1$ (Weissman, 1977). For diffusive transport the ω^{-1} law holds for approximately $D/R^2 < \omega < D/a^2$, where D is the diffusion coefficient and R and a are the maximum and minimum values of $|\mathbf{r} - \mathbf{r}_s|$ for which Eq. 1 holds.

The fluctuating variable that we shall consider is the local channel concentration, $g(\mathbf{r}, t) = \sum_{i=1}^{N} \delta(\mathbf{r} - \mathbf{r}_i(t))$, where N is the number of channels and $\mathbf{r}_i(t)$ is the position of the i^{th} channel at time t. We must extend the previous theory slightly, since we wish to consider a time-dependent weighting function $f(\mathbf{r}, t)$ that gives the current which flows through a channel if it is present at $\mathbf{r}$ at time t. This extension is necessary since it is the diffusing channels themselves that produce the singularities in $f(\mathbf{r})$. Since, however, only the relative positions of the channels affect the noise, no modification of the previous theory is required except to replace the channel diffusion coefficient D with the pairwise diffusion coefficient $2D$.

Neumcke (1975)[1] has derived the magnitude of the effect of diffusion polarization on ionic concentrations, from which the effect on current flowing through neighboring channels may be trivially calculated. From Eqs. 43–66, we obtain that the current flowing through two channels at distance r is reduced from that at infinite separation by a factor $(1 - b/r)$, where the scaling factor b is roughly the "cell constant" of the channel. That is, $b \approx g/\sigma_k$, where g is the channel conductance and σ_k is the conductivity in bulk solution due to the ion(s) which the channel conducts. For typical ion-selective channels, as in Neumcke's numerical examples, $b \approx 3 \cdot 10^{-9}$ cm. Somewhat larger values of b are possible, but no channels more than an order of magnitude larger have been found to be ion-selective. We note that $(1 - b/r)$ is of the form of Eq. 1, so that ω^{-1} noise is predicted from the interaction of diffusing channels.

We may now calculate the magnitude of the fractional current fluctuations in a collection of N channels in a region of radius R with a closest distance of approach a. First, we calculate the current noise in a single channel confined to distances $a < r < R$ from a singularity of the form $(1 - b/r)$ by assuming an equal probability density $(1/\pi(R^2 - a^2))$ for the channel to be at any point in the allowed region, with the current at radius r given by $I_1(r) = I_0(1 - b/r)$:[2]

---

[1] Neumcke's paper attempts to derive ω^{-1} noise from the effects of conductance fluctuations in single channels on the time-dependent diffusion polarization. He treats the case in which "there are no interferences between the ion fluxes of neighboring pores," in contrast to this paper, which is exclusively concerned with such interference. Neumcke fails to consider the stationary nature of membrane conductance fluctuations, and thus arrives at the mistaken conclusion that fast fluctuations in channel conductance can give low-frequency ω^{-1} noise (M.B. Weissman, unpublished note).

[2] Here I_0 is the current that would flow through the channel if this one perturbation were removed. Since I_0 includes the effects of the other perturbing channels, it is in general less than the current through an isolated channel. The reduction is by a factor of $(1 + \Omega_s/\Omega_m)^{-1}$, where $\Omega_s = 1/2\, R\sigma_k$ is the spreading resistance of the patch and $\Omega_m = 1/\pi R^2 bc\sigma_k$ is the transmembrane patch resistance, where c is the channel concentration. For $Rbc \gtrsim 1$, it may be seen that the net current reduction is not equal to the sum over all channel pairs of the first-order reduction. Although this fact does not affect our calculation of the noise produced in each pair, it does lead to a reduction in the total patch noise from that calculated in Eq. 4, due to higher order effects involving three or more channels. Roughly speaking, what we calculate below is $\langle(\delta\Omega_m)^2\rangle / \langle\Omega_m\rangle^2$, which should be corrected by a factor $(1 + \Omega_s/\Omega_m)^{-2}$, for large patches, to obtain the net fractional resistance fluctuations.

$$<(\delta I_1)^2> = <I_1^2> - <I_1>^2 = <I_1>^2$$

$$\cdot \left(\left\{ \left[\int_a^R (1 - b/r)^2 2\pi r \, dr/\pi(R^2 - a^2) \right] \Big/ \left[\int_a^R (1 - b/r) 2\pi r \, dr/\pi(R^2 - a^2) \right]^2 \right\} - 1 \right)$$

$$= <I_1>^2 \cdot \left(\frac{2b^2}{R^2 - a^2} \ln R/a - \frac{4b^2}{(R + a)^2} \right) \Big/ \left(1 - \frac{2b}{R + a} \right)^2$$

$$\approx <I_1>^2 \cdot 2 \, (b^2/R^2) \, (\ln R/a - 2), \qquad (2)$$

where the approximate equality holds for $R \gg a, b$.

To obtain the total fractional current fluctuations, we consider that there are $N(N - 1)/2$ pairs of channels, with each pair generating four times the mean square noise calculated in Eq. 2. The total mean square current is of course N^2 times the single channel current, so that for the whole patch

$$<(\delta I)^2>/<I>^2 \approx (4/2) \, N(N - 1)/N^2 \cdot (2b^2/R^2)(\ln R/a - 2)$$

$$\approx 4 \, (b^2/R^2) \, (\ln R/a - 2). \qquad (3)$$

We have not considered edge effects since, as the $\ln R/a$ term shows, nearly all the noise comes from nearby channels, not those at distances of order R.

The magnitude of the ω^{-1} noise, given by the dimensionless parameter $M = S_I(\omega)\omega/I^2$, may now be easily calculated using the formula of Clarke and Voss (1974) $M = [<(\delta I)^2>/<I>^2]/(\ln \omega_1/\omega_0 + 3)$, where ω_1 and ω_0 are the upper and lower frequencies for which the ω^{-1} dependence breaks down. This gives

$$M \approx 4 \, (b^2/R^2)(\ln R/a - 2)/(2 \ln R/a + 3). \qquad (4)$$

The factor in parenthesis is always < 0.5 and, for any reasonable values of a and R ($a < 10^{-6}$ cm, $R > 10^{-4}$ cm), it is > 0.21 so that the experimentally somewhat inaccessible parameter a scarcely enters into the predicted M.

For experimentally plausible values of a ($2.5 \cdot 10^{-7}$ cm), b ($3 \cdot 10^{-9}$ cm), and R ($3 \cdot 10^{-3}$ cm), we calculate $M \approx 1.5 \cdot 10^{-12}$, comparable to the fractional fluctuation magnitude observed in some synthetic membranes (Michalides et al., 1973) and much larger than the fractional noise observed in some aqueous pores (Feher and Weissman, 1973). With about 10^{10} channels/cm^2 and a current of 2 pA/channel (e.g., Zingsheim and Neher, 1974), $S_I(\omega) \approx 6 \cdot 10^{-25} \, A^2/\omega$, should be obtained. This absolute current noise amplitude is also large enough to be observed (Conti et al., 1976). To avoid competing channel number fluctuation noise, the ω^{-1} noise should be observed in channels which lack on-off reactions and which are constrained to remain within the observed bilayer patch. Dimeric ionophores such as gramidicin would not be suitable.

The frequency range for which the ω^{-1} law holds is determined by a, R, and D (Weissman, 1975, 1977). For $a = 3 \cdot 10^{-7}$ cm, $R = 3 \cdot 10^{-3}$ cm, and $D = 10^{-10}$ cm^2/s (Axelrod et al., 1976), we find $S(\omega) \propto \omega^{-1}$ for $2 \cdot 10^{-5}$ Hz $\lesssim \omega/2\pi \lesssim 2 \cdot 10^3$ Hz, using the value of $D(2.4)^2/r^2$ for the characteristic ω of diffusion in a circular region of radius r, where 2.4 is the first root of the lowest order Bessel function.

Several difficulties arise if one attempts to account for the ω^{-1} noise observed in nerve membranes by this mechanism. First, it has not been unambiguously established that the Na^+ and K^+ channels are free to diffuse. Second, even if these channels do diffuse, so that this noise source would be present, it would account for only about 10^{-6} of $S(\omega)$ observed in typical experiments (Conti et al., 1976). Only if the channels formed clumps of $\sim 10^3$ channels (b scales as the conductance of a single localized channel or clump) could this mechanism account for the ω^{-1} noise known to arise from K^+ channels.

In fact, any mechanism which generates ω^{-1} noise independently in separate channels is unlikely to account for the observed magnitude. In one experiment for example, $M > 10^{-4}$ was observed in a sample with $N > 10^4$ (Conti et al., 1976) while in another $MN \approx 40$ (Conti et al., 1975) was observed. Since if the noise from the separate channels is independent, $<(\delta I_1)^2>/<I_1>^2 \approx 10 \cdot MN$, (see Eq. 4) no theory in which the channels independently undergo ω^{-1} conductance fluctuations of less than order unity can account for the observed noise. This suggests the likelihood that the noise is generated in batches of channels coherently. Although comparisons of noise from different membrane preparations are risky, the similar values of M found by Fishman (1973) and Conti et al., (1975) for patches with areas different by more than three orders of magnitude suggest that the noise mechanism may operate coherently over the entire patch, which would not be accounted for by this model nor by any other that I am familiar with.

Thus it is unclear whether the mechanism described in this note is of much direct practical significance. Nevertheless, it may be of importance in that it represents a source of ω^{-1} noise that may be derived from previously known phenomena in familiar systems, with the noise magnitude given in terms of independently measurable parameters.

Two types of generalizations may be fruitful. First, there may be other situations in which fluctuations in the distances between some diffusing objects produce $\omega^{-\alpha}$ noise due to pairwise effects on conductivity. Impurities in semiconductors, for example, may be such a case. Second, there may be other sources of singularities in membranes which give rise to larger ω^{-1} noise. For example, electrostatic interactions between closely clustered pores could cause a larger effect.

I thank B. Neumcke for sending me a draft of a review on 1/f membrane noise. This work was supported by a postdoctoral fellowship from the National Science Foundation.

Received for publication 16 September 1977.

REFERENCES

Axelrod, D., R. Ravdin, D. E. Koppel, J. Schlessinger, W. W. Webb, E. L. Elson, and T. R. Podelski. 1976. Lateral motion of fluorescently labeled acetylcholine receptors in membranes of developing muscle fibers. *Proc. Natl. Acad. Sci. U.S.A.* **73**:4594.

Clarke, J. and R. F. Voss. 1974. $1/f$ noise from thermal fluctuations in metal films. *Phys. Rev. Lett.* **33**:24.

Conti, F., L. J. DeFelice, and E. Wanke. 1975. Potassium and sodium current noise in the membrane of the squid giant axon. *J. Physiol. (Lond.).* **248**:45.

Conti, F., B. Hille, B. Neumcke, W. Nonner, and R. Stämpfli. 1976. Measurement of the conductance of the sodium channel from current fluctuations at the node of Ranvier. *J. Physiol. (Lond.).* **262**:699.

Feher, G., and M. Weissman. 1973. Fluctuation spectroscopy: determination of chemical reaction kinetics from the frequency spectrum of fluctuations. *Proc. Natl. Acad. Sci. U.S.A.* **70**:870.

Fishman, H. M. 1973. Relaxation spectra of potassium channel noise from squid axon membranes. *Proc. Natl. Acad. Sci. U.S.A.* **70**:876.

Michalides, J. F., R. A. Wallaart, and L. J. DeFelice. 1973. Electrical noise from PVC membranes. *Pflügers Arch. Eur. J. Physiol.* **341**:97.

Neumcke, B. 1975. $1/f$ membrane noise generated by diffusion processes in unstirred solution layers. *Biophys. Struct. Mechanism.* **1**:295.

Richardson, J. M. 1950. The linear theory of fluctuations arising from diffusional mechanisms—an attempt at a theory of contact noise. *Bell Syst. Tech. J.* **29**:117.

Verveen, A. A., and L. J. DeFelice. 1974. Membrane noise. *Prog. Biophys. Mol. Biol.* **28**:189.

Weissman, M. B. 1975. Simple model for $1/f$ noise. *Phys. Rev. Lett.* **35**:689.

Weissman, M. B. 1977. A model for $1/f$ noise from singularities in the fluctuation weighting function. *J. Appl. Phys.* **48**:1705.

Zingsheim, H. P., and E. Neher. 1974. The equivalence of fluctuation analysis and chemical relaxation measurements: a kinetic study of ion pore formation in thin lipid membranes. *Biophys. Chem.* **2**:197.