MODELS FOR $1/f$ NOISE IN NERVE MEMBRANES

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ABSTRACT A recently proposed model for $1/f(\omega^{-1})$ noise in nerve membranes (Clay and Schlesinger, 1976; Lundström and McQueen, 1974) is shown to be mathematically inconsistent in several respects. A self-consistent model based on similar membrane lipid orientation fluctuation effects is proposed.

Noise with a power spectrum $S(\omega) \propto \omega^{-1}$ has been repeatedly observed in nerve membranes. (See Verveen and DeFelice, 1974, for a summary of the experimental data and a reference list.) Recently, Lundström and McQueen (1974) have proposed a model for this noise based on membrane conductance fluctuations caused by fluctuations in the direction of the lipid hydrocarbons of the membrane bilayer. Clay and Schlesinger (1976) have modified this model by proposing that these same fluctuations give rise to ω^{-1} noise in the absence of membrane current due to the stochastic nature of ion transport through the membrane. (These papers are henceforth referred to as LM and CS.)

However, one may demonstrate that the derivations of the ω^{-1} behavior given by LM and CS are erroneous and that this model predicts noise having a steeper ω dependence. One may also demonstrate that the model of CS does not predict ω^{-1} noise in the absence of nonequilibrium currents even if the membrane resistance fluctuations are of the ω^{-1} type.

LM and CS propose that the local membrane conductance $g(\mathbf{r})$ is linearly related to fluctuations in the direction of the lipid hydrocarbon chains $\hat{n}(\mathbf{r})$ (the "director") by an equation $\delta g(\mathbf{r}) = \boldsymbol{\beta} \cdot \delta\hat{n}(\mathbf{r})$. $\delta\hat{n}(\mathbf{r})$ is assumed to obey a diffusion equation. It is further assumed that the fluctuations in $\hat{n}(\mathbf{r})$ exhibit instantaneous spatial correlation due to a relative suppression of short-wavelength fluctuations: $< |\delta\hat{n}(\mathbf{q})|^2> \propto 1/q^2$ where $\mathbf{q}$ is the wavevector of a Fourier component of the fluctuations (Martin et al., 1972).

Eq. 2 of LM contains an error. The correct equation relating the frequency spectrum of fluctuations to the spatial Fourier components is

$$S(\omega) \propto \int_{\mathbf{q}} \int_{\tau=0}^{\infty} |f(\mathbf{q})|^2 < \delta g(\mathbf{q},\tau)\, \delta g(\mathbf{q},0) > e^{i\omega\tau}\, \mathrm{d}\tau\, \mathrm{d}^2\mathbf{q}, \qquad (1)$$

where $f(\mathbf{q})$ is the Fourier transform of $f(\mathbf{r})$, the spatial weighting factor for fluctuations. In the frequently encountered case of diffusive fluctuations in variables without instantaneous spatial correlations (e.g., heat, carrier concentration), this becomes

$$S(\omega) \propto \int_{\mathbf{q}} |f(\mathbf{q})|^2 (q^2/[\omega^2 + Dq^4])\, d^2\mathbf{q}, \tag{2}$$

which appears, along with discussions of its derivation, in Richardson (1950) (Eq. 3.19) and Van Vliet and Fassett (1965) (Eq. 272*a*). For the case of spatially correlated functions a factor $< |\delta g(\mathbf{q})|^2 >$ must be included. Lundstrom et al. (1973) include this factor (as $< | P_1(q) |^2 >$) in their equation 6; however, both this paper and LM simply leave out $|f(\mathbf{q})|^2$. One of these factors, $< |\delta g(\mathbf{q})|^2 >$, gives the spectral distribution of the underlying fluctuations. The other factor, $|f(\mathbf{q})|^2$, gives the sensitivity of the observed variable to different Fourier components of the fluctuations. Eq. 7 of CS is correct, but Eq. 9 is not, since an unjustified $\delta(\mathbf{r} - \mathbf{r}')$ has been inserted. This error is equivalent to neglecting $|f(\mathbf{q})|^2$. Except in cases where $f(\mathbf{r})$ becomes arbitrarily large in the region of singularities (Weissman, 1975),[1] $f(\mathbf{q})$ falls off sufficiently rapidly for large q to produce $S(\omega) \propto \omega^{-\alpha}$ where $\alpha \geq 3/2$ for spatially uncorrelated fluctuations (Van Vliet and Fassett, 1965). The model of LM and CS uses spatially correlated fluctuations with relatively little ($\propto 1/q^2$) short-wavelength, high frequency components. One may easily verify that this model actually predicts $S(\omega) \propto \omega^{-2}$.

Eq. 2 of LM is correct in the special case in which $|f(\mathbf{q})|^2$ does not depend on $\mathbf{q}$. One may obtain such a result by assuming

$$f(\mathbf{r}) = \sum_{j=1} \boldsymbol{\beta}_j \delta(\mathbf{r} - \mathbf{r}_j), \tag{3}$$

and that $< \boldsymbol{\beta}_j \cdot \boldsymbol{\beta}_i > = 0$ for $i \neq j$. In effect, the ω^{-1} law is then a local phenomenon, requiring a lack of correlation between $\delta g(\mathbf{r})$ and $\delta g(\mathbf{r}')$ for $\mathbf{r} \neq \mathbf{r}'$. Although such an assumption contradicts the explicit model of LM and CS, it does lead to their result—that $S(\omega) \propto \omega^{-1}$ if $< |\delta \hat{n}(\mathbf{q})|^2 > \propto 1/q^2$. The possibility of obtaining a $\mathbf{q}$ independent $|f(\mathbf{q})|^2$ depends critically on two pecularities of the model. One is that the conductance occurs in localized channels (hence the delta functions). The other is that the fluctuating variable is a vector which allows randomly oriented channels to show no net cross-correlation in their fluctuations.

The interpretation of CS, however, ("a single channel does not produce $1/f$ noise in this model. In Eq. 9 we must integrate over the membrane patch to obtain the $1/f$ behavior.") is exactly opposite to the actual implications of the model. If one does not assume $< \boldsymbol{\beta}_i \cdot \boldsymbol{\beta}_j > = 0$ for $i \neq j$, the spectral shape will be very sensitive to such factors as the size and shape of the membrane patch as well as any correlations in positions of the channels. For example, if all the $\boldsymbol{\beta}_i$ are equal, for $\omega < Dc$ (D is the fluctuation diffusion coefficient, c is the channel concentration in centimeters^{-2}) the spectrum

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[1] Weissman, M. B. 1976. Dissertation, University of California, San Diego. In preparation.

should be close to that predicted for continuous conductivity, that is $S(\omega) \propto \omega^{-2}$. Using the estimates of D ($\sim 10^{-7}$ cm^2·s^{-1}) and c ($\sim 10^9$ cm^{-2}) from LM and CS, we find that over several decades of frequency observed in a typical experiment, the noise would probably be quite different from ω^{-1} if such effects occurred. Although the possibility of some distribution of correlated channel orientations and positions producing ω^{-1} noise cannot be ruled out, by far the simplest interpretation within this framework is that the orientations are uncorrelated, so that regardless of relative positions the ω^{-1} spectra of each channel's noise simply add to give the membrane spectrum.

The physical meaning of this model is then that the membrane contains discrete channels whose conductivity depends on the local hydrocarbon orientation. Each channel has a preferred direction $\boldsymbol{\beta}_j$ but the membrane as a whole has no preferred direction $\boldsymbol{\beta}$. It is necessary that each channel have a rotational diffusion time longer than the inverse of the lowest frequency for which the ω^{-1} law holds. Otherwise, the time dependence of $\boldsymbol{\beta}_j$ would lead to a loss of long-time correlation, causing a flattening out of $S(\omega)$ for $\omega < \tau_r^{-1}$, the inverse of the rotational diffusion time. In other words, each of the channels in which the ω^{-1} noise is produced must be a fairly stable constituent of the membrane, probably held in place by a protein network. This revised model remains, of course, highly speculative since, although none of the details are obviously implausible, none have been demonstrated experimentally.

The assertion of LM and CS that $< | \delta\hat{n}(\mathbf{q}) |^2 > \propto 1/q^2$, while reasonable, is not justified by their derivation, which starts from the proportionality of a term in the free energy density to $|\nabla \cdot \hat{n}(\mathbf{r})|^2$. This term limits the magnitude only of longitudinal waves, not shear waves. Some other term proportional to $| \nabla \times \hat{n}(\mathbf{r}) |^2$ must be invoked to obtain $< | \delta\hat{n}(\mathbf{q}) |^2 > \propto 1/q^2$. An obvious way around this difficulty would be to assume $\delta g(\mathbf{r}) \propto \nabla \cdot \hat{n}(\mathbf{r})$, but such an assumption would not lead to ω^{-1} noise in any simple way.

CS propose that the same mechanism that gives ω^{-1} noise when a current is flowing gives ω^{-1} noise in the absence of current by modulating the fluctuations δN in number of ions passing through each channel. In deriving this result, the authors neglect the time dependence of δN. However they state that the correlation time for δN is much less than the inverse of the highest frequency for which the ω^{-1} law holds. Thus the frequency spectrum of the fluctuations δN is flat over the frequency range of interest. The frequency spectrum of δN modulated by the conductance fluctuations is the convolution of the two spectra, which does not resemble ω^{-1}.

In fact, CS attempt to derive the ω^{-1} noise as an equilibrium phenomenon. Equilibrium noise (Johnson or Nyquist noise) is however determined by the fluctuation-dissipation theorem (e.g., Reif, 1965), with fluctuations in parameters such as resistance giving only small second-order corrections. That is, modulation of the Johnson noise by resistance fluctuations gives noise smaller than Johnson noise, which is itself small compared with the observed $1/f$ noise (Verveen and De Felice, 1974). Although recent AC impedance measurements on nerve membranes show that the impedance is frequency dependent (Fishman et al., 1976), this dependence would not give an ω^{-1}-like Johnson spectrum nor an ω^{-1}-like convolution with ω^{-1} resistance fluctuations.

Noise with a roughly ω^{-1} spectrum is a familiar problem in many electrical (and other) systems (Verveen and DeFelice, 1974) so that it may not be directly related to the membrane. However, if the explanation for the "zero-current" noise is to be found in the ω^{-1} resistance fluctuations of the nerve membrane, the system must be out of equilibrium. There must be some gradient in the potential of some ion across the membrane. If careful experiments demonstrate that some of the ω^{-1} noise persists in the absence of electrochemical gradients of all types, then an explanation other than membrane resistance fluctuations will be needed.

Real progress in understanding the mechanism of conduction in nerve membranes will require further experimental work both on nerves and on lipid bilayers. In particular, a set of experiments designed to demonstrate the dependence, if any, of the noise spectral shape on the geometry of the observed patch could greatly narrow the class of acceptable models.

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REFERENCES

CLAY, J. R., and M. F. SCHLESINGER. 1976. Theoretical model of the ionic mechanism of $1/f$ noise in nerve membrane. *Biophys. J.* **16**:121.

FISHMAN, H. M., L. E. MOORE, D. J. M. POUSSART, and E. SIEBENGA. 1976. Non first-order K^+ conduction impedance and noise feature in squid axon membrane. *Biophys. J.* **16** (2, pt. 2):26*a*. (Abstr.).

LÜNDSTROM, I., and D. MCQUEEN. 1974. A proposed $1/f$ noise mechanism in nerve cell membranes. *J. Theor. Biol.* **45**:405.

LÜNDSTROM, I., D. MCQUEEN, and C. KLASON. 1973. On low-frequency and $1/f$ noise from diffusionlike processes. *Solid State Commun.* **13**:1941.

MARTIN, P. C., O. PARODI, and P. S. PERSHAN. 1972. Unified hydrodynamic theory for crystals, liquid crystals, and normal fluids. *Phys. Rev.* **A6**:2401.

REIF, F. 1965. Statistical and Thermal Physics. McGraw-Hill, Inc., New York. Chapter 15.

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

VAN VLIET, K. M., and J. R. FASSET. 1965. *In* Fluctuation Phenomena in Solids. R. E. Burgess, editor. Academic Press, Inc., New York.

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.