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CURRENT NOISE IN TRANSPORT OF HYDROPHOBIC IONS THROUGH LIPID BILAYER MEMBRANES INCLUDING DIFFUSION POLARIZATION IN THE AQUEOUS PHASE

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An exact treatment of the current noise spectrum produced by transport of hydrophobic ions through membranes is presented, including the coupling of the diffusion processes through both the aqueous phase and the membrane. Both the equilibrium and the steady state noise spectra are computed. The theory contains previous results as limiting cases. The structure of the spectra is discussed with emphasis upon how noise measurements can be used to estimate kinetic parameters, especially the rate of desorption from the membrane. For this restricted model there is no low frequency divergence in the non-equilibrium current noise, i.e., for the model treated there is no $1/f$ noise.

1. Introduction

The measurement and interpretation of statistical fluctuations in membrane conductance is a topic of substantial current interest [1–5]. A problem which has generated speculation is the physical origin of the so-called $1/f$ noise reported for current and voltage fluctuations about the non-equilibrium steady state for ion transport through some biological and artificial membranes [1–3]. Model calculations have suggested that this feature of the membrane noise spectrum may be related to the effect that diffusion has on the kinetics of ion transport across a membrane [6–8]. However, these analyses treat diffusion separately from the membrane kinetics; as a result no theory of the noise spectrum incorporates the coupling of aqueous diffusion and membrane processes.

In this paper the current noise is calculated for an exactly soluble model of hydrophobic ion transport across a lipid bilayer membrane. This model, first suggested by Ketterer e.a. [9], describes transport as a five step process:

a) diffusion through the aqueous phase to the lipid membrane;
b) adsorption at the interface;
c) translocation across the membrane interior;
d) desorption into the bulk phase;
e) diffusion in the bulk solution.

As has been shown by Jordan and Stark [10] in their interpretation of voltage jump-current relaxation experiments, the Ketterer model is soluble without approximation if it is assumed that the only process affected by application of an external voltage is translocation. Under this restriction an exact expression for the relaxation current, including the effect of diffusion polarization, was found. By applying their analysis estimates of the desorption rate constants for the systems phosphatidylserine/tetraphenylborate and phosphatidylcholine/tetraphenylborate were obtained.

As the current noise is the Fourier transform of the current aurocorrelation function it should not be surprising that the Ketterer model as treated previously [10] also yields closed form expressions for the noise spectrum. In section 2 the equilibrium noise spectrum is computed and its structure, both in general and in some physically important limiting cases, discussed. In section 3 the current noise for fluctuations

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about a steady state is computed using a theory due to Frehland [11]. Comparison with the results of section 2 yields an exact formula for the excess noise; at least for this model system there is no $1/f$ dependence at low frequency. Section 4 recapitulates the major conclusions.

While the model is treated exactly, it remains a greatly simplified picture of physical reality. The restrictions and their physical significance have been discussed previously [10]; that discussion is not repeated here.

2. Equilibrum fluctuations

2.1. *Derivation of the power spectrum*

For systems fluctuating about *equilibrium* the power spectrum, $G(f)$, of electric *current* fluctuation at frequency f is, according to the Nyquist theorem, determined by the real part of the complex admittance, $Y(f)$ [12–16]

$$G(f) = 4k_B T \operatorname{Re} Y(f) , \tag{1}$$

here k_B is Boltzmann's constant and T is absolute temperature. The admittance is defined as the response of the system to a small voltage perturbation from its stationary value. Calculation of $Y(f)$ may be effected in many ways. For our purposes the easiest method is to assume a δ-function perturbation of intensity ζ,

$$\delta V(t) \equiv V(t) - V_s = \zeta\delta(t) , \tag{2}$$

from which the admittance is computed as the Fourier transform of the current response [15,16]

$$Y(f) = \frac{1}{\zeta}\int_{-\infty}^{+\infty} \exp(-2\pi i f t)\, \delta I(t)\, dt , \tag{3}$$

here $\delta I(t)$ is the difference between the current and its stationary value

$$\delta I(t) \equiv I(t) - I_s . \tag{4}$$

Calculation of $\delta I(t)$ requires solving the kinetic equations for the system being studied. The fundamental equations governing hydrophobic ion transport when a trans-membrane potential is applied are [10]

$$\partial C'/\partial t = D\partial^2 C'/\partial x^2 , \tag{5}$$

$$dN'/dt = \beta k C_0' - (k + k_i')N' + k_i''N'' , \tag{6}$$

where, as defined previously, C' (C'') and N' (N'') are the ion concentration in the aqueous phase and the ion surface density at the interface on the left (right) hand side of the membrane; $C_0 = C(0,t)$ is the ion concentration in the aqueous solution adjacent to the membrane. The desorption rate constant is k, that for adsorption is βk, the translocation rate constant from left to right (right to left) is k_i' (k_i'') and the aqueous diffusion coefficient is D. The condition which accounts for conservation of matter at the membrane interface is

$$D\partial C_0'/\partial x = \beta k C_0' - kN' , \quad x = 0 . \tag{7}$$

Analogous equations describe processes on the right hand side of the system; the superscripts $'$ and $''$ need only be interchanged. With concentrations and surface densities given in particulate (rather than molar) units the ion current is

$$I(t) = ze_0 A\,[k_i'N' - k_i''N''] \tag{8}$$

where z is the ionic valency, e_0 is the electronic charge and A is the membrane area. The assumption that only translocation is voltage dependent is explicit in eqs. (6) and (8); the adsorption and desorption rate constants are the same at both left and right hand sides of the membrane.

At equilibrium both the stationary value of the current and the voltage are zero; as a result the translocation rate constants k_i' and k_i'', the concentrations C' and C'' and the surface densities N' and N'' are equal. For a small voltage displacement, irrespective of the nature of the internal barrier to translocation, the rate constants may be written as

$$k_i' = k_i[1 + ze_0\delta V/2k_BT] ,$$

$$k_i'' = k_i[1 - ze_0\delta V/2k_BT] . \tag{9}$$

Because of the basic symmetry in the kinetic equations, the significant concentration variables are those introduced previously [10],

$$c(x,t) = \tfrac{1}{2}[C''(x,t) - C'(x,t)] ,$$

$$n(t) = \tfrac{1}{2}[N''(t) - N'(t)] . \tag{10}$$

Combining eqs. (5)–(10) yields

$$\partial c/\partial t = D\partial^2 c/\partial x^2 \,, \tag{11}$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \beta k c_0 - (k + 2k_\mathrm{i})n + k_\mathrm{i}\frac{ze_0\beta C}{k_\mathrm{B}T}\,\delta V \tag{12}$$

$$D\partial c_0/\partial x = \beta k c_0 - kn \,, \tag{13}$$

$$\delta I = ze_0 A\left[k_\mathrm{i}\frac{ze_0\beta C}{k_\mathrm{B}T}\,\delta V - 2k_\mathrm{i}n\right] , \tag{14}$$

from which the current response may be calculated Here C is the bulk ionic concentration far away from the membrane; as long as no voltage is applied $C_0' = C_0'' = C$ and $N' = N'' = \beta C$.

The solution to eqs. (11)–(14) is found using the Laplace transform method as applied before [10]; the current response, assuming a δ-function voltage pulse, is then

$$\delta I(t) = (k_\mathrm{i}z^2e_0^2A\beta C/k_\mathrm{B}T) \tag{15}$$

$$\times\,\zeta\left\{\delta(t) - \frac{\varkappa}{2\pi \mathrm{i}}\int \mathrm{d}z\, \mathrm{e}^{z\kappa t}\,\frac{1}{z + 1 + \sqrt{\omega z}/(1 + g\sqrt{\omega z})}\right\}$$

where

$$\kappa \equiv k_\mathrm{i}' + k_\mathrm{i}'' = 2k_\mathrm{i}\,, \quad \omega \equiv D/\kappa\beta^2\,, \quad g = \kappa/k \,. \tag{16}$$

Combining eqs. (1), (3) and (15), using the Laplace inversion approach outline in App. A of ref. [10], and integrating over t, the equilibrium power spectrum is

$$G(f) = G_\infty[1 - S(\nu)] \tag{17}$$

with

$$G_\infty = 4A\beta Cz^2e_0^2k_\mathrm{i}\,, \tag{18a}$$

$$S(\nu) = \frac{2\sqrt{\omega}}{\pi}\int_0^\infty \frac{\mathrm{d}u\; u^4}{u^4 + \nu^2}\;\frac{1}{\omega u^2[gu^2 - \gamma]^2 + (u^2 - 1)^2}\,, \tag{18b}$$

$$\nu = 2\pi f/\kappa\,, \qquad \gamma = g + 1\,. \tag{18c}$$

The structure function $S(\nu)$ may be expressed in closed form; the result, derived in the Appendix, is

$$S(\nu) = [P_1(\nu) - P_2(\nu)]/R(\nu) \tag{19}$$

with

$$P_1(\nu) = 1 + \nu^2 - \omega(\gamma + g)\nu^2 + \omega^2\gamma g(\gamma^2 + g^2\nu^2)\nu^2\,, \tag{20a}$$

$$P_2(\nu) = \sqrt{\omega\nu/2}\{[1 + 2\nu - \nu^2] + \omega[-\gamma^2 + 2g\gamma\nu + g^2\nu^2]\nu\}\,, \tag{20b}$$

$$R(\nu) = (1 + \nu^2)^2 - 4\omega(\gamma + g\nu^2)\nu^2 + \omega^2(\gamma^2 + g^2 + g^2\nu^2)^2\nu^2 . \tag{20c}$$

Eqs. (19) and (20), while complicated, are readily evaluated as functions of the scaled frequency ν for various values of the parameters g and ω. Only at low frequency is there a simple approximation to $G(f)$. From eqs. (16)–(20) $G(f)$, as $f \to 0$, is

$$G(f) = 2ACz^2e_0^2\sqrt{\pi Df} \times \{1 + (2\pi f/\kappa)[2 - \omega\gamma^2] + \ldots\}\,. \tag{21}$$

Two points should be noted. The equilibrium power spectrum is proportional to $f^{1/2}$ at low frequencies. This is a direct consequence of diffusion; were only first order relaxation processes significant the leading term would be proportional to f^2. Secondly, the limiting behavior at low frequency is independent of membrane kinetics, a result that mirrors the long time behavior of the relaxation current [10,17].

Eqs. (17)–(20) do not describe current fluctuations at arbitrarily small values of f since the current response function, as given by eq. (15), is derived assuming the system to be infinite in the aqueous phase [10]. We are therefore restricted to frequencies large enough that diffusion only occurs in the unstirred layers. For an unstirred layer of thickness L, the cut-off frequency can be estimated as $f \sim D/\pi L^2$. Given hydrophobic ions with $D \sim 5 \times 10^{-6}$ cm^2 s^{-1} and unstirred layers 100–300 μm thick, the cut-off occurs in the range 10^{-3}–10^{-2} Hz, i.e. at lower frequencies than those presently used experimentally [18,19]. Thus the power spectrum given by eqs. (17)–(20), while not valid everywhere, is applicable throughout the frequency range discussed in the published literature.

2.2. Interpretation

Of the four fundamental parameters that determine the equilibrium power spectrum, D, β, k and k_i, only D is lipid independent. The others must be determined from transport measurements involving membranes. Two relationships may be established from the limiting properties of the noise spectrum. From eq. (18a) βk_i may be calculated from the intensity of the white noise,

$$\beta k_i = G_\infty / 4ACz^2 e_0^2 \,. \tag{22}$$

There can, however, be a problem in exploiting this result, because, as previously indicated [10], the bulk concentration of hydrophobic ion is not accurately known since ions are continually being leached out of the aqueous solution into the torus surrounding the membrane. Unlike the case of current relaxation, there appears to be no simple general relation that establishes k_i from experimental data [10]. However, eq. (17), with eqs. (19) and (20), yields the general result

$$2k_i(k + 2k_i) = -\frac{1}{4\pi^2 G_\infty}\left(\frac{\mathrm{d}G}{\mathrm{d}(1/f^2)}\right)_{f=\infty} , \tag{23}$$

so that by plotting G versus $1/f^2$ in the high frequency region some information can be obtained, unfortunately not simply the value of k_i (unless desorption is significantly slower than translocation). But, as we shall see, the practical problem of determining k_i is often much simpler; in most interesting systems k_i may be readily deduced from the shape of the structure function.

Although the low frequency noise, eq. (21), is independent of k, k_i and β the approach to this limit is quite variable. The shape of the spectrum is a complicated function of g and ω. As in the case of current relaxation there are qualitative differences in the structure function $S(\nu)$ depending upon the magnitude of these parameters [10]. The distinctions reflect the same physical possibilities catalogued previously, i.e. whether diffusion, adsorption/desorption or translocation is most significant at relatively high frequency.

2.2.1. Rapid diffusion ($\omega g = D/k\beta^2 \gg 1$).

In this case the power spectrum, from eqs. (16)–(20), is

$$\frac{G(f)}{G_\infty} = 1 - \frac{\gamma g}{\gamma^2 + g^2\nu^2} = 1 - \frac{\kappa(\kappa + k)}{(\kappa + k)^2 + 4\pi^2 f^2} \,. \tag{24}$$

The spectrum is essentially a complementary lorentzian with characteristic frequency $(\kappa + k)/2\pi$ in exact analogy to the behavior of the relaxation current in this limit where there is a single relaxation with decay constant $\kappa + k$ [9]. At low frequency $G(f)$ approaches a constant (non-zero) limit, in apparent contradiction to the general result, eq. (21). This is an artifact of the limiting process; when ν is sufficiently small the quantities $\omega^2 g^2 \nu^2$ in eq. (20) no longer dominate the expressions for $P_1(\nu)$ and $R(\nu)$ and eq. (24) is no longer applicable. However, until the diffusive domain is reached, there is a *low frequency* region in which the noise intensity is constant.

2.2.2. Rapid interfacial equilibrium ($g = \kappa/k \ll 1$).

Here eqs. (17)–(20) do not simplify as drastically, the result is

$$\frac{G(f)}{G_\infty} = \frac{\sqrt{\omega\nu/2}\{1 + (2 - \omega)\nu - \nu^2\} + \nu^2\{\omega^2 - 3\omega + 1 + \nu^2\}}{1 + (\omega^2 - 4\omega + 2)\nu^2 + \nu^4} \tag{25}$$

Depending upon whether diffusion is fast or slow the noise spectrum is significantly altered. When diffusion is relatively slow ($\omega \to 0$), the power spectrum is again complementary lorentzian

$$\frac{G(f)}{G_\infty} = \frac{\nu^2}{1 + \nu^2} = \frac{4\pi^2 f^2}{\kappa^2 + 4\pi^2 f^2} , \tag{26}$$

with characteristic frequency $\kappa/2\pi$, in agreement with the results of Kolb and Läuger [19]; naturally this result mirrors the current relaxation with its decay time, κ^{-1} [10]. When diffusion is relatively fast eq. (25) becomes, with eqs. (16), (18c) and (22),

$$\frac{G(f)}{G_\infty} = \frac{\sqrt{bf}(1 - 2bf) + 4b^2 f^2}{1 + 4b^2 f^2} ,$$

$$b = \pi D(2ACz^2 e_0^2 / G_\infty)^2 , \tag{27}$$

an expression similar to that describing the relaxation current in the same physical limit (rapid interfacial equilibration and rapid diffusion) [10]. Whereas the relaxation current is established by knowledge of the initial current, the power spectrum is completely specified by the intensity of white noise.

2.2.3. Slow diffusion in the aqueous phase ($\omega = D/\kappa\beta^2 \ll 1$) or slow interfacial equilibrium ($g = \kappa/k \gg 1$).

Here the power spectrum, from eqs. (16)–(20), again yields the complementary lorentzian line shape, eq. (26), when the prescribed limits are taken. As with relaxation, the membrane is in either case effectively isolated from the bulk solution. The noise spectrum only reflects translocation kinetics.

The general purpose of noise analysis is to provide a different technique for characterizing the kinetics of membrane transport. As already noted, eq. (22), the limiting behavior at high frequency may be used to establish the product βk_i. No simple general relation (i.e. an analogue to eq. (30a) of ref. [10]) fixes k_i. However, as will become clear, k_i may often be determined by the high frequency line shape which is, for a broad range of g and ω values, complementary lorentzian. As long as the high frequency spectrum satisfies eq. (26) k_i may be estimated by solving

$$G(k_i/\pi) = G_\infty/2\ . \qquad (28)$$

If this is possible the determination of the desorption rate constant k depends upon how sensitive the power spectrum is to variation of k. As high frequency properties usually fix $\omega = D/\kappa\beta^2$, the most direct approach to k is to compute $G(f)/G_\infty$ for fixed ω and variable g. If calculated and measured curves are superposable g, and from eq. (16), k can be determined.

To illustrate the difficulties with this approach as well as to illuminate the structure of the power spectrum, the ratio $G(f)/G_\infty$ is plotted as a function of g for the ω-values 10^{-4}, 10^{-2}, 1, and 10^2 in fig. 1. When ω is 10^{-4} the high frequency spectrum is complementary lorentzian over a broad range and k_i is easily established from eq. (28). Determination of k is more difficult. Unless accurate measurements, differentiable from the background noise, are feasible at low power levels no distinction between g-values is possible. Assuming that intensity levels 0.1% of white noise are ascribable to membrane processes, distinctions between g-values can be made if they lie in the range 10^2–10^3; otherwise only lower or upper bounds on g can be given. Naturally if more accurate measurement is possible a larger range of g may be differentiated.

For $\omega = 10^{-2}$, the high frequency spectrum is still complementary lorentzian so that k_i can be established. The range of differentiable g-values is now larger. Assuming the 0.1% intensity level, distinctions are possible for $10 \lesssim g \lesssim 10^3$. For $\omega = 1$ the range of separable g's is greater, from ~1 to ~10^3; however there is a new problem. It becomes hard to determine k_i since the high frequency spectrum remains complementary lorentzian for only the first 10–15% of the intensity decrease. In effect the diffusive domain has encroached upon the high frequency one. Yet larger values of ω further complicate the determination of k_i since, unless $g \gtrsim 1$, there is no high frequency complementary lorentzian behavior.

The general conclusions are these:

a) Establishment of g is difficult at small ω. Assuming a detectable and differentiable noise level 0.1% of the white noise, marginal discrimination between different g is no longer possible for $\omega \lesssim 10^{-6}$.

b) At larger ω greater discrimination is possible. Under the best conditions g may be estimated as long as it is in the range $1 \lesssim g \lesssim 10^3$ (assuming background noise 0.1% of the white noise).

c) At small ω the high frequency spectrum is pure complementary lorentzian. The shift to the diffusive domain is gradual unless g is very large in which case a plateau separates the two regions.

d) At larger ω the three regions — diffusive, plateau and complementary lorentzian — are clearly distinguishable at smaller g values. However, for g too small the diffusive domain and the plateau dominate; there is no longer a clearly distinguishable complementary lorentzian region.

3. Non-equilibrium fluctuations

3.1. Derivation of the power spectrum

For fluctuations about a steady state the power spectrum must be computed in a totally different fashion. The Nyquist theorem no longer applies [20] and current fluctuations are not given by eq. (1). The system cannot be taken to be infinite in the aqueous phase since, under such constraints, eqs. (5)–(8) permit only one solution, $I_s = 0$, no matter what the external voltage.

Assuming unstirred layers of equal thickness L in contact with reservoirs in which the ion concentration is maintained at its bulk value C, the stationary concentration profile is that shown in fig. 2. Defining the gradients

$$\partial C'/\partial x = -\partial C''/\partial x = \alpha \qquad (29)$$

eqs. (5)–(8) and their right hand side analogues are readily solved for steady state values of the current, concentration displacement and surface density displacement. The results, using the definitions of eqs. (10), (16) and (18c), are

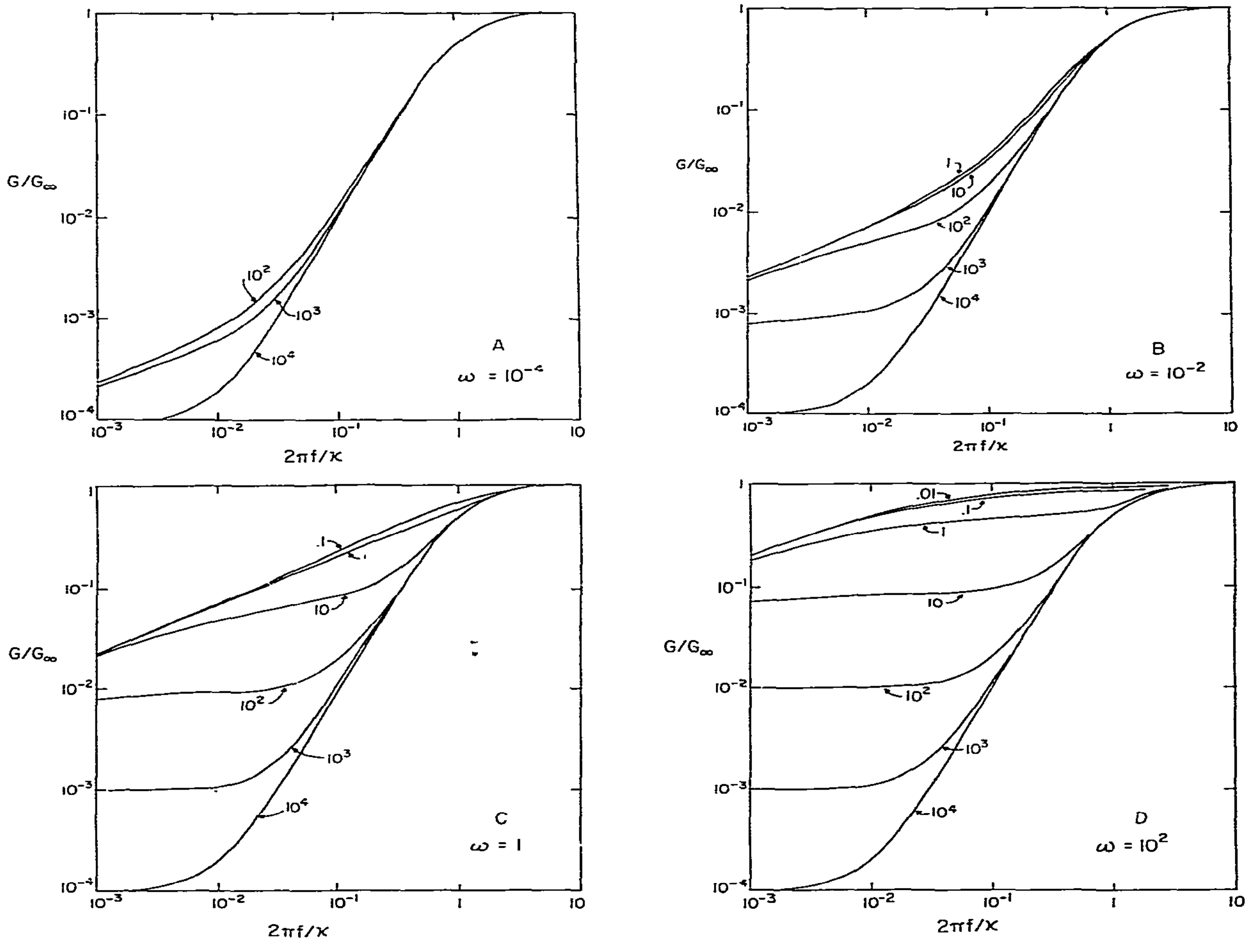

Fig. 1. Spectrum of reduced equilibrium current noise G/G_∞ as a function of reduced frequency $\nu = 2\pi f/(k_i' + k_i'') = 2\pi f/\kappa$ for various values of the parameters ω and g. A) $\omega = 10^{-4}$; B) $\omega = 10^{-2}$; C) $\omega = 1$; D) $\omega = 10^{2}$. The values of g are given in each graph. In each case there is no noticeable change in the noise spectrum if g is reduced below the smallest value given.

$$n_s = \frac{\Delta\beta C}{\kappa} - \frac{D\alpha}{\kappa} = \frac{\Delta\beta C}{\kappa}\left\{\frac{\beta\omega g + L}{\beta\omega\gamma + L}\right\}, \qquad (30a)$$

$$c_s = \frac{n_s}{\beta} - \frac{D\alpha}{k\beta} = \frac{\Delta C}{\kappa}\,\frac{L}{\beta\omega\gamma + L}, \qquad (30b)$$

$$I_s = ze_0 A\{\Delta\beta C - \kappa n_s\}$$

$$= ze_0 A\beta C\Delta\{\beta\omega/(\beta\omega\gamma + L)\} = ze_0 A D\alpha, \qquad (30c)$$

$$\alpha = c_s/L = \Delta C/[\kappa(\beta\omega\gamma + L)] \qquad (30d)$$

with

$$\Delta = k_i' - k_i''. \qquad (31)$$

For the problem at hand the current noise spectrum in the stationary state may be computed using a method developed by Frehland [11,20]; the system is treated as a sequence of separate energy barriers, precisely the approach required in one dimension. Instead of

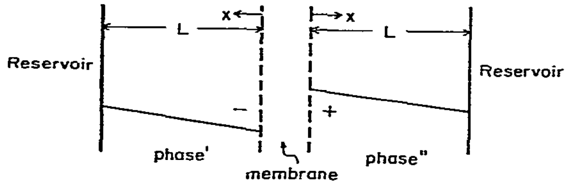

Fig. 2. Schematic steady state concentration profile for hydrophobic anions under an applied potential assuming unstirred layers of thickness L in contact with reservoirs containing anions at equal concentration. System polarity is indicated.

calculating the admittance, the regression of flux fluctuations is computed and related to the power spectrum via the Wiener–Khintchine theorem. The analysis is simplified because only those fluctuations which involve the movement of ions through a potential difference contribute to current noise. Applying Frehland's formalism to the Ketterer model (translocations are the only processes which produce *current* fluctuations), the power spectrum in the steady state can be written as

$$G(f) = 2z^2e_0^2\{[\varphi_{12}^{(s)} + \varphi_{21}^{(s)}] + 2k_i''[\varphi_{12}^{(s)}\langle\delta N_{21}\rangle - \varphi_{21}^{(s)}\langle\delta N_{22}\rangle] + 2k_i'[\varphi_{21}^{(s)}\langle\delta N_{12}\rangle - \varphi_{12}^{(s)}\langle\delta N_{11}\rangle]\}\,, \tag{32}$$

where $\varphi_{21}^{(s)}$ ($\varphi_{12}^{(s)}$) is the stationary translocation flux from left to right (right to left) and $\langle\delta N_{ij}\rangle$ is the Fourier transform of the surface density displacement at site i if, at $t = 0$, there is a unit surface density fluctuation at site j,

$$\langle\delta N_{ij}\rangle = \int_0^\infty \mathrm{d}t \cos 2\pi f t\, \delta N_{ij}(t)\,, \quad \delta N_{ij}(0) = \delta_{ij}\,. \tag{33}$$

The translocation fluxes can be written directly

$$\varphi_{21}^{(s)} = k_i'N'A = k_i'(\beta C - n_s)A\,, \tag{34a}$$

$$\varphi_{12}^{(s)} = k_i''N''A = k_i''(\beta C + n_s)A\,, \tag{34b}$$

with n_s, the stationary concentration displacement, given by eq. (30a). To compute the $\langle\delta N_{ij}\rangle$ requires solving eqs. (5)–(7) for the regression of the prescribed fluctuation about the steady state described by eq. (30). This calculation can be accomplished using the Laplace transform method [10]; it is simplified if symmetric and antisymmetric contributions to the decaying fluctuations are handled separately. Proceeding as in sect. 2 of ref. [10], the Laplace transforms of the displacement functions are found to be

$$\overline{\delta N}_{11}(s) = \{\overline{\Phi} + \overline{\Gamma} - (\Delta/\kappa)(\overline{\Phi} - \overline{\Gamma})\}/2\,, \tag{35a}$$

$$\overline{\delta N}_{21}(s) = \{\overline{\Phi} - \overline{\Gamma} + (\Delta/\kappa)(\overline{\Phi} - \overline{\Gamma})\}/2\,, \tag{35b}$$

$$\overline{\delta N}_{12}(s) = \{\overline{\Phi} - \overline{\Gamma} - (\Delta/\kappa)(\overline{\Phi} - \overline{\Gamma})\}/2\,, \tag{35c}$$

$$\overline{\delta N}_{22}(s) = \{\overline{\Phi} + \overline{\Gamma} + (\Delta/\kappa)(\overline{\Phi} - \overline{\Gamma})\}/2\,, \tag{35d}$$

where

$$\overline{\Phi}(s) = \frac{1}{s + kT(s)}\,, \qquad \overline{\Gamma}(s) = \frac{1}{s + \kappa + kT(s)}\,, \tag{36}$$

$$T(s) = \frac{\sqrt{sD}}{\sqrt{sD} + k\beta \tanh L\sqrt{s/D}}\,. \tag{37}$$

The function $\overline{\Gamma}(s)$ is precisely that which gives rise to the equilibrium power spectrum; in the limit that $L \to \infty$ it is the integrand of eq. (15) (identifying s as κz). The function $\overline{\Phi}(s)$ is new and accounts for any structural changes in the frequency dependence of the power spectrum due to the system being in a steady state rather than at equilibrium. Combining eqs. (32)–(35) and substituting from eqs. (16), (30a) and (31), the non-equilibrium power spectrum is

$$G(f) = 2z^2e_0^2A\left\{\frac{4k_i'k_i''\beta C}{\kappa}\times\left[1 - \int_0^\infty \mathrm{d}t \cos 2\pi f t\, \frac{\kappa}{2\pi \mathrm{i}} \int \mathrm{d}s\, e^{st}\overline{\Gamma}(s)\right] + \frac{\Delta}{\kappa} D\alpha\right\}. \tag{38}$$

Limiting consideration to frequencies large enough that the unstirred layer may be assumed infinite for purposes of Laplace transform inversion and substituting for α from eq. (30d), the result is

$$G(f) = \frac{8z^2e_0^2k_i'k_i''A\beta C}{k_i' + k_i''}\,[1 - S(\nu)] + \frac{2z^2e_0^2(k_i' - k_i'')^2}{k_i' + k_i''}A\beta C\,\frac{\beta\omega}{\beta\omega\gamma + L}\,. \tag{39}$$

The first term is structurally identical to the equilibrium current noise, eq. (17); the only change is that now $k_i' \neq k_i''$. The second term is the additional non-equilibrium contribution, it is positive semi-definite, vanishing only at equilibrium (when $k_i' = k_i''$) or if $L = \infty$.

3.2. Interpretation

According to eq. (39) there are two contributions to the non-equilibrium current noise. The first term is structurally identical to the equilibrium noise, eq. (17); the only difference is that the frequency scale is now proportional to $k_i' + k_i''$, not $2k_i$, reflecting the fact that translocation is voltage dependent. The second term is the so-called "excess noise"; it is, quite surprisingly, frequency independent. Non-equilibrium fluctuations increase the noise level by a constant amount; no singular behavior at low frequency is predicted. It is worth noting that terms involving $\overline{\Phi}(s)$, which contribute to the displacement functions $\overline{\delta N}_{ij}(s)$ of eq. (35), yield, when inverse Laplace transformed and Fourier transformed, spectral decompositions for which the intensity increases as the frequency drops. For frequencies large enough so that the unstirred layers may still be treated as infinitely thick, the frequency dependence of the ion surface density correlations in this region of the low frequency domain is proportional to $1/\sqrt{f}$.

In any event, solution of the Ketterer model including diffusive coupling indicates no low frequency singularities in the non-equilibrium current noise spectrum. Whether this result is general or if it simply reflects the restrictive assumption that only translocation processes contribute to current fluctuations is unclear. More general analysis, in which the voltage dependence of the adsorption/desorption process is incorporated is needed to answer this question. Thus the problem of whether diffusive coupling can lead to singular behavior of the low frequency excess noise in hydrophobic ion transport remains unresolved.

A final question is the relative importance of the equilibrium and non-equilibrium contributions to the power spectrum. From eq. (39) the relative intensity of the normal and excess contributions to the white noise is

$$R \equiv \frac{G_\infty(\text{excess})}{G_\infty(\text{normal})} = \frac{(k_i' - k_i'')^2}{4k_i'k_i''} \, \frac{\beta\omega}{\beta\omega\gamma + L} \, . \tag{40}$$

Assuming the barrier to translocation is both narrow and steep, the rate constants k_i' and k_i'' are [9]

$$k_i' = k_i e^{zu/2} \, , \quad k_i'' = k_i e^{-zu/2} \, ,$$

$$u = e_0 V/k_B T \, . \tag{41}$$

If unstirred layers are typically 100–300 μm thick, literature values of β and k_i [9,10,23] indicate that hydrophobic ion/membrane systems fall into two catagories.

3.2.1. Negative ions ($\beta\omega \ll L$)

For negative ions $\beta\omega$ is usually much less than L and, using eqs. (41) and (16), R is

$$R \sim (\beta\omega/L) \sinh^2 zu/2$$

$$= \frac{D}{2k_i\beta L} \, \frac{\sinh^2 zu/2}{\cosh\ zu/2} \, . \tag{42}$$

For excess noise to be measurable, R must be larger than the ratio of background to white noise. A favorable system is tetraphenylborate/phosphatidylserine for which the factor $D/2k_i\beta L$ is $\sim 10^{-2}$ [10]. Assuming, in line with the discussion of section 2.2, that the background noise is ~0.1% of the white noise, the excess noise would be above background for potentials greater than ~15 mV. As a result, moderate applied potentials could lead to significant increases in low frequency current noise. An unfavorable system is dipicrylamine/phosphatidylcholine for which $D/2k_i\beta L$ is $\sim 10^{-5}$ [9]. Here the excess noise does not reach the 0.1% level until a potential of ~250 mV is applied: non-equilibrium contributions are not measurable until the external potential is so large that membrane rupture becomes a distinct possibility.

3.2.2. Positive ions ($\beta\omega \gg L$)

For positive ions the published values of βk_i [23] suggest that $\beta\omega \gg L$; R, from eqs. (40), (41) and (16), is

$$R \sim (1/\gamma) \sinh^2 zu/2$$

$$= \frac{k}{k + 2k_i \cosh zu/2} \sinh^2 zu/2 \, . \tag{43}$$

Here the excess noise is significant even at low voltage (unless $k \ll k_i$) and should be easy to measure, assuming noise measurements on this class of systems to be at all feasible. Such measurements could directly answer the question of whether desorption or translocation is the faster process. The only difficulty is whether the equilibrium white noise is intense enough. From eqs. (18a) and (16), G_∞(norm) is proportional to $(\beta\omega)^{-1}$; as a result conditions favorable for measuring excess noise are problematical for determining the equilibrium white noise.

4. Recapitulation

Both equilibrium and non-equilibrium current noise spectra for the Ketterer [9] model of hydrophobic ion transport through membranes have been calculated. Only the translocation process is presumed to be voltage dependent.

The equilibrium spectrum is governed by aqueous diffusion at low frequency, $G \sim f^{1/2}$, and by membrane processes at high frequency, $G \sim f^2/(f_0^2 + f^2)$, with f_0 the characteristic relaxation frequency. Depending upon the relative rates of diffusion, adsorption, desorption and translocation the high and low frequency regions may be separated by a plateau. From the intensity of white noise βk_i can be estimated, eq. (22). If the plateau noise is substantially less intense than the white noise, k_i can be determined since the line shape of the high frequency noise is a complementary lorentzian. Depending upon the relative intensity of background and white noise, k may be measurable; if not bounds on k may often be obtained.

The steady state spectrum is comprised of two parts, a frequency dependent equilibrium-like term and a *constant* excess noise term. No low frequency singularity in the excess noise is predicted on the basis of the restricted Ketterer model; this may be a consequence of assuming that only translocations contribute to current fluctuations. The excess noise should be most readily observable for transport of *positive* ions; it may be totally masked by other noise sources for transport of negative ions unless the applied potential is so high that membrane rupture is likely.

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Appendix: Evaluation of S(v)

From eq. (18b), the structure function $S(\nu)$ may be written in alternate forms as

$$S(\nu) = \frac{\sqrt{\omega}}{\pi} \int_{-\infty}^{+\infty} \frac{\mathrm{d}u\, u^4}{u^4 + \nu^2} \frac{1}{\omega u^2 [g u^2 - \gamma]^2 + (u^2 - 1)^2} \, . \tag{A.1}$$

$$= \frac{1}{2\pi \mathrm{i}} \int_{-\infty}^{+\infty} \frac{\mathrm{d}u\, u^3}{u^4 + \nu^2} \times \left\{ \frac{g\sqrt{\omega} u - \mathrm{i}}{g\sqrt{\omega} u^3 - \mathrm{i} u^2 - \gamma\sqrt{\omega} u + \mathrm{i}} - \mathrm{c.c.} \right\} , \tag{A.2}$$

which are convenient for evaluation using contour integration methods with the contour illustrated in fig. 3. Since the contribution along the contour at $R = \infty$ is zero (the integrand of eq. (A.1) is proportional to R^{-4} along that path), $S(\nu)$ by the Cauchy theorem is found by computing the contribution from the residues at each pole in the upper half plane [24].

The function $g\sqrt{\omega} u^3 - \mathrm{i} u^2 - \gamma\sqrt{\omega} u + \mathrm{i}$ has three roots within the designated contour; its complex conjugate has none. Either all roots are pure imaginary or one is imaginary and two are complex. The conditions governing this distinction have been discussed before [10]. For analytical convenience consider the latter case in which the roots occur at

$$u_1 = \mathrm{i}a \, , \quad u_2 = r\mathrm{e}^{\mathrm{i}\varphi} \, , \quad u_3 = -r\mathrm{e}^{-\mathrm{i}\varphi} \, , \tag{A.3}$$

where

$$r^2 a = \xi \equiv 1/g\sqrt{\omega} \, , \quad 2r \sin\varphi + a = \xi \, ,$$

$$r(r + 2a \sin\varphi) = \eta \equiv \gamma/g \, . \tag{A.4}$$

The roots of $u^4 + \nu^2$ within the contour are

$$u_4 = \sqrt{\nu}\mathrm{e}^{\pi\mathrm{i}/4} \, , \quad u_5 = \sqrt{\nu}\mathrm{e}^{3\pi\mathrm{i}/4} \, . \tag{A.5}$$

Applying the Cauchy theorem to eq. (A.2) yields, after straightforward, but tedious, algebra

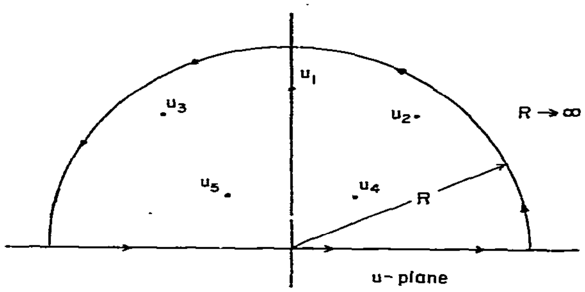

Fig. 3. Integration contour for evaluating $S(\nu)$. The position of the poles is indicated schematically for the case analyzed in the Appendix.

$$S(\nu)=\sum_{j=1}^{3}\frac{u_j^3(u_j-\mathrm{i}\xi)}{u_j^4+\nu^2}\prod_{k=1}^{3}{}'\frac{1}{(u_j-u_k)}-\frac{P_2(\nu)}{R(\nu)}, \quad \text{(A.6)}$$

where $P_2(\nu)$ and $R(\nu)$ are given in eq. (20) and the prime indicates that the term $k=j$ is excluded. Reformulation of the first term in eq. (A.6) is a bit complicated. From its functional form it can clearly be expressed as a fraction

$$\left(\prod_{j=0}^{2}A_j\nu^{2j}\right)\bigg/\left(\prod_{j=0}^{3}B_j\nu^{2j}\right), \quad \text{(A.7)}$$

in which, for convenience, we define $B_3\equiv 1$. With this definition the other B_j are readily identified as

$$B_0=\prod_{i=1}^{3}u_i^4, \quad B_1=\tfrac{1}{2}\sum_{i=1}^{3}\prod_{j=1}^{3}{}'u_i^4u_j^4,$$

$$B_2=\sum_{i=1}^{3}u_i^4. \quad \text{(A.8)}$$

From eqs. (A.8), (A.3) and (A.4) we find

$$B_0=r^8a^4=\xi^4, \quad \text{(A.9a)}$$

$$B_1=r^4(r^4+2a^4\cos 4\varphi), \quad \text{(A.9b)}$$

$$B_2=a^4+2r^4\cos 4\varphi. \quad \text{(A.9c)}$$

Simplification of B_1 and B_2 is not as easy as finding a compact form for B_0. Eq. (A.4) yields some relationships useful in further analysis

$$2r\sin\varphi=\xi-a, \quad 2ra\sin\varphi=\eta-r^2=a(\xi-a),$$
$$r^2=\xi/a=a^2-\xi a+\eta, \quad a^3=\xi a^2-\eta a+\xi. \quad \text{(A.10)}$$

Consider eq. (A.9c) which, using trigonometric identities, is

$$B_2=a^4+2r^4\{1-8\sin^2\varphi+8\sin^4\varphi\}. \quad \text{(A.11)}$$

Now using eq. (A.10) to eliminate the dependence on both r and $\sin\varphi$, B_2 is

$$B_2=a^4+2r^2\cdot r^2-4r^2(2r\sin\varphi)^2+(2r\sin\varphi)^4 \quad \text{(A.12)}$$
$$=a^4+\frac{2\xi}{a}(a^2-\xi a+\eta)-\frac{4\xi}{a}(\xi-a)^2+(\xi-a)^4.$$

Then, with the expression for a^3 in eq. (A.10), B_2 finally reduces to

$$B_2=\xi^4-4\xi^2(\eta-1)+2\eta^2, \quad \text{(A.13)}$$

which, when combined with eqs. (A.4) and (A.9a), yields the result

$$B_2=B_0[1-4g\omega+2g^2\gamma^2\omega^2]. \quad \text{(A.14)}$$

Similar analysis shows that

$$B_1=B_0[2-4\gamma\omega+\gamma^4\omega^2] \quad \text{(A.15)}$$

so that, by comparison with eq. (20c), we express the denominator of eq. (A.7) as

$$\prod_{j=0}^{3}B_j\nu^{2j}=B_0R(\nu)=\xi^4R(\nu). \quad \text{(A.16)}$$

The numerator of eq. (A.7) presents similar problems. Comparing the first term of eq. (A.6) with eq. (A.7) in the limit that $\nu\to 0$ yields

$$\frac{A_0}{B_0}=\sum_{j=1}^{3}\left(1-\frac{\mathrm{i}\xi}{u_j}\right)\prod_{k=1}^{3}{}'\frac{1}{(u_j-u_k)}, \quad \text{(A.17)}$$

which may be rewritten as

$$\frac{A_0}{B_0}=\frac{\mathrm{i}\xi}{(u_1-u_2)(u_2-u_3)(u_3-u_1)}$$
$$\times\left\{\frac{u_1-u_2}{u_3}+\frac{u_2-u_3}{u_1}+\frac{u_3-u_1}{u_2}\right\}, \quad \text{(A.18)}$$

which, after substitution from eq. (A.3), becomes

$$\frac{A_0}{B_0}=\frac{\xi}{r\cos\varphi[a^2-2ar\sin\varphi+r^2]}$$
$$\times\left\{\frac{r\cos\varphi}{a}+\frac{a\cos\varphi}{r}-\sin 2\varphi\right\}. \quad \text{(A.19)}$$

Now, simplifying and using eq. (A.4), we find

$$A_0 = B_0 \xi / r^2 a = B_0 \,. \tag{A.20}$$

In the same fashion A_1 and A_2 are evaluated; the results are

$$A_1 = B_0 \{1 - \gamma\omega + g\gamma^3\omega^2\} \tag{A.21a}$$

$$A_2 = B_0 \gamma g^3 \omega^2 . \tag{A.21b}$$

Thus the numerator of eq. (A.7), when compared with eq. (20a), is

$$\prod_{j=0}^{2} A_j \nu^{2j} = B_0 P_1(\nu) \tag{A.22}$$

and, using eq. (A.16), the first term in eq. (A.6) is $P_1(\nu)/R(\nu)$, precisely the desired result.

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