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ON THE TRANSPORT NOISE OF HYDROPHOBIC IONS IN LIPID BILAYER MEMBRANES

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The effect of transit time on the electrical transport noise of a closed one-barrier model at equilibrium as proposed by Kolb and Läuger [6] is studied using the master-equation approach. A transit time is the time for an ion to cross the energy barrier (membrane interior) when the energy of the ion reaches the barrier height. Both the time correlation function and the noise power spectrum are obtained as functions of the transit time of the ions. Possible effects of transit time on the time correlation function of transport of dipicrylamine ions in lipid bilayers as reported by Bruner and Hall [13] and on the noise power spectrum as reported by Kolb and Läuger [6] are discussed.

1. Introduction

In recent years, measurements of current noise in biological membranes have attracted considerable attention in relation to the elucidation of membrane properties and transport mechanisms [1–4]. One type of noise which has been intensively studied both theoretically and experimentally is that related to the opening and closing of ion channels in the membrane. The channel in a membrane is a low-resistance pathway for ion transport and can exist in a number of open and closed states. The fluctuation in membrane currents reflects the fluctuation in the concentration of open channels in the membrane. Thus, the general concentration-fluctuation theory of chemical reactions can be applied directly to this channel noise problem and information such as unit conductance and mean lifetime of different states of the chennel can be obtained from membrane current noise data [4].

Another kind of noise which has also attracted extensive studies recently is the so-called 'transport noise' associated with the translocation steps of individual ions or carrier-mediated transport of ions through membranes or open channels [5–12]. The movement of an ion (or an ion-carrier complex) in the membrane may be described as a series of jumps from one binding site to the other over activation energy barriers. Each jump contributes with a single current pulse to the total current measured in the external circuit. Fluctuations of the total current therefore arise from fluctuations in the number of ions crossing the individual barriers. In terms of chemical kinetics, transport noise is related to the fluctuation of fluxes of the reactions while channel noise is related to the fluctuation of concentrations of the species.

The first measurements of transport noise in lipid bilayer membranes were reported by Kolb and Läuger [6] on dipicrylamine ions and by Szabo [10] on tetraphenylborate ions. The current noise spectra from these measurements were very different from those of the channel mechanism. In general, the noise power intensity is very small at low frequency and increases as f^2 (f, frequency) as f increases. At a high-frequency region, the noise power spectrum becomes independent of f (white noise). Thus, the spectrum looks like an inverted Lorentzian.

To explain the experimental results, Kolb and

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Läuger [6] proposed a single one-barrier transport model (the KL model) in which it is assumed that the ions are adsorbed in potential-energy minima at either membrane surface and are able to cross the central energy barrier by thermal activation. The adsorption and desorption processes of ions between the membrane and the bathing solutions are assumed to be very slow compared to the kinetics of ion translocation across the membrane. Thus, the ions on both sides of the membrane can be considered as a closed thermodynamic system at equilibrium. Using Langevin's formalism, they obtained a noise function that fits with experimental results. Later, Läuger [7] showed that the same equation could be derived using Nyquist's theorem. In another development, Frehland [8] showed that transport noise could be obtained directly from the usual kinetic equations. When applied to this equilibrium KL model of one barrier with two binding sites, Frehland's general formalism recovers the same noise equation as obtained by Kolb and Läuger [6] or by Läuger [7].

In these treatments, it was always assumed that the translocation of ions across the barrier was an instantaneous process. That is, the ions remain at the binding sites most of the time and cross the (central) barrier instantaneously when their energies reach the barrier height. In this paper we present a different treatment which is applicable to systems in which the translocation of ions is not instantaneous but requires a finite 'transit time' (denoted as Δ hereafter). Both the noise power spectrum, $G(\omega)$, and the time correlation function, $C(\tau)$, of the current fluctuations are obtained and expressed explicitly as functions of Δ. When Δ is set to zero, the noise functon of Kolb and Läuger is recovered. Thus, in a sense, the present theory is more general than those of Läuger [7], Kolb and Läuger [6], and Frehland [8].

Our interest in this transit-time problem was partly aroused by a recent report by Bruner and Hall [13], to which the time correlation function of transport noise of dipicrylamine ions was measured. One of the main points of the paper was to show that the measured $C(\tau)$ agreed with the theoretical $C(\tau)$ obtained from the $G(\omega)$ of Kolb and Läuger [6]. However, if one examines closely the results of Bruner and Hall (see fig. 2), it is easy to find that the experimental data do not agree completely with the theory. The theoretical $C(\tau)$ is larger (less negative) at low $|\tau|$ values and smaller (more negative) at large $|\tau|$ values than the experimental values (the deviation near $\tau = 0$ is about 5%). We thought that the discrepancy might be due to the omission of the transit time in the theory and that it might be worthwhile to have a transport noise theory applicable to systems with nonzero transit times.

Studies on the effect of a finite transit time on the noise power spectrum of other transport models have been reported by Stevens [14] and by Läuger [5]. The present report represents the first study on this closed one-barrier two-binding-site model (the KL model) applicable to the transport of hydrophobic dipicrylamine or biphenylborate ions across lipid bilayer membranes.

2. The KL model and the microscopic current

We summarize briefly the basic features of the KL model in fig. 1. As indicated in fig. 1a, the membrane is considered as a dielectric layer of thickness d interposed between two conducting phases (the aqueous electrolyte solutions) which are connected by an external measuring circuit. Then, if an ion of charge ze_0 (where z is the valence and e_0 the elementary electron charge) is moved in the dielectric over a distance s, a charge of magnitude ze_0s/d is displaced in the external circuit. (The external circuit is assumed to have an infinite response.) If we use i to denote an ion at the left binding site and ii at the right, then the translocation of ions is equivalent to the chemical reaction $\mathrm{i} \underset{\beta}{\overset{\alpha}{\rightleftarrows}} \mathrm{ii}$. For lipid bilayer membranes, $\alpha = \beta$ when the voltage across the membrane is zero. The barrier between the binding sites is assumed to be very steep and the two energy minima very sharp so that unsuccessful climbing of the ions does not produce any current pulse in the external circuit. Let us assume that the ions are positive charged and the external circuit is arranged in such a way that an ion translocation from the left to the right side (i → ii) produces a positive charge pulse of magnitude ze_0s/d and duration Δ (or a current pulse of $ze_0/s(d\Delta)$), while a translocation from

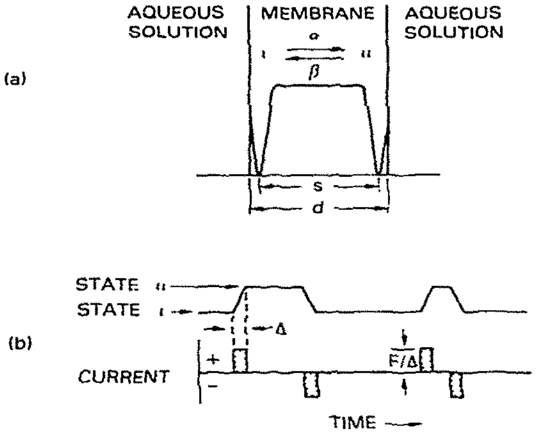

Fig. 1. (a) Schematic energy profile of hydrophobic ion in a lipid bilayer membrane. (b) The upper curve represents the state of the ion and the transition from one state to the other. The lower curve represents the current measured in the external circuit due to ion translocation. The time (transit time) for an ion to cross the barrier is denoted by Δ. F is defined as $F \equiv \frac{ze_0s}{d}$.

the right to the left side produces a negative charge pulse of the same magnitude and duration.

The duration Δ is called the transit time here. It is the time for an ion to diffuse between the sites, across the energy barrier, when the energy of the ion reaches the barrier height and an actual translocation occurs. One must note that this transit time is different from the mean occupation times of the ions. The mean times for an ion to stay in state i ($\bar{t}_{\mathrm{i}}$) and state ii ($\bar{t}_{\mathrm{ii}}$) are $1/\alpha$ and $1/\beta$, respectively. It is reasonable to assume that Δ is only a small fraction of $\bar{t}_{\mathrm{i}}$ or $\bar{t}_{\mathrm{ii}}$, since it involves processes in activated states. Fig. 1b shows the time behavior of a membrane containing only one ion. The upper graph shows the state of the ion as a function of time. The transition from one state to the other is not instantaneous, but requires a transit time Δ. The lower graph shows the current pulses due to the transition of states, as measured in the external circuit.

Since each ion translocation produces a current pulse of length Δ, in a membrane containing a large number (M) of ions the instantaneous current (as measured in the external circuit) at time t is the sum of the current pulses generated in the time interval Δ between $t-\Delta$ and t. Let n_{12} and n_{21} be the number of transitions of i → ii and ii → i, respectively. Then, the instantaneous current $I(t)$ at time t can be expressed in terms of the net i → ii transitions $n(=n_{12}-n_{21})$ as

$$I(t) = nze_0s/(d\Delta) \equiv nF/\Delta,$$

$$F \equiv ze_0s/d. \qquad (1)$$

3. The time correlation function and the noise power spectrum

The time correlation $C(\tau)$ of the measured external current is the ensemble average of the product of $I(t)$ and $I(t+\tau)$:

$$C(\tau) = \langle I(t)I(t+\tau)\rangle \qquad (2)$$

Substituting eq. 1 into eq. 2, we have

$$C(\tau) = \left(\frac{ze_0s}{\Delta d}\right)^2 \langle n(t)n(t+\tau)\rangle. \qquad (3)$$

Thus, in order to obtain the time correlation function $C(\tau)$, one needs the two-time joint probability function, $P(n,t;n',t+\tau)$, of the net number of i → ii transitions. That is, one needs the probability of finding exactly n net i → ii transitions at time t and exactly n' net i → ii transitions at $t+\tau$. Since the stochastic properties of fluxes (or the number of transitions) of chemical reactions are difficult to study, $P(n,t;n',t+\tau)$ is in general not readily available. Thus, we discard this line of pursuit and consider the probability of states instead of fluxes in evaluating $C(\tau)$. To do this, we have to find a way of replacing $n(t)$ and $n(t+\tau)$ in eq. 3 with N_2 (or N_1) where N_2 is the total number of ions in state ii (or the ions at the right side of the membrane). One must note that the system is closed so that N_2 (or N_1) alone is enough to specify the state of the system.

Since the system is closed, the net number of i → ii transitions ($n(t)$) between $t-\Delta$ and t is exactly equal to $N_2'-N_2$ where N_2 and N_2' are the number of ions in state ii at $t-\Delta$ and t, respectively. Similarly, $n(t+\tau)=N_2'''-N_2''$, where N_2'' and N_2''' are the number of ions in state ii at $t+\tau-\Delta$ and $t+\tau$, respectively. Thus, the time correlation function in eq. 3 can be expressed as

$$C(\tau)=\frac{F^2}{\Delta^2}\sum_{N_2,N_2',N_2'',N_2'''}(N_2'-N_2)(N_2'''-N_2'')P(N_2,t-\Delta;N_2',t;N_2'',t+\tau-\Delta;N_2''',t+\tau). \quad (4)$$

where $P(N_2,t-\Delta;N_2',t;N_2'',t+\tau-\Delta;N_2''',t+\tau)$ is the joint probability function of N_2 at the four time points: $t-\Delta$, t, $t+\tau-\Delta$ and $t+\tau$. For systems at stationary state, the probability functions are independent of the absolute value of t. Thus, after setting $t=\Delta$, eq. 4 becomes

$$C(\tau)=\frac{F^2}{\Delta^2}\sum_{N_2,N_2',N_2'',N_2'''}(N_2'-N_2)(N_2'''-N_2'')P(N_2,0;N_2',\Delta;N_2'',\tau;N_2''',\tau+\Delta). \quad (5)$$

For Markovian systems, the joint probability function is equal to a product of conditional probability functions. Thus, depending on whether τ is larger or smaller than Δ, P in eq. 5 for a stationary system can be expressed as

$$\begin{aligned}P(N_2,O;N_2',\Delta;N_2'',\tau;N_2''',\tau+\Delta)&\\ =P(N_2)W(N_2|N_2',\Delta)W(N_2'|N_2'',\tau-\Delta)&\\ \times W(N_2''|N_2''',\Delta)\text{ if }\tau>\Delta, &\quad (6)\\ =P(N_2)W(N_2|N_2'',\tau)W(N_2''|N_2',\Delta-\tau)W(N_2'|N_2''',\tau)&\\ \text{if }\tau<\Delta. &\quad (7)\end{aligned}$$

Here $P(N_2)$ is the equilibrium probability of having N_2 ions in state ii in the system.

Substituting eqs. 6 and 7 into eq. 5, we get

$$C(\tau)=\frac{F^2}{\Delta^2}\sum_{N_2,N_2',N_2'',N_2'''}(N_2'-N_2)(N_2'''-N_2'')P(N_2)\times W(N_2|N_2',\Delta)W(N_2'|N_2'',\tau-\Delta)W(N_2''|N_2''',\Delta)\quad \tau>\Delta. \quad (8)$$

$$C(\tau)=\frac{F^2}{\Delta^2}\sum_{N_2,N_2',N_2'',N_2'''}(N_2'-N_2)(N_2'''-N_2'')P(N_2)\times W(N_2|N_2'',\tau)W(N_2''|N_2',\Delta-\tau)W(N_2'|N_2''',\tau)\quad \tau<\Delta. \quad (9)$$

For chemically reacting systems, explicit expressions for the conditional probability functions are, in general, hard to obtain. However, as shown in Appendix A, for this simple two-state system $W(N_2|N_2',t)$ can be expressed as

$$W(N_2|N_2',t)=P(N_2)^{-1/2}P(N_2')^{1/2}\sum_{k=0}^{M}u_{N_2k}u_{N_2'k}e^{-\lambda_k t} \quad (10)$$

where u_{N_2k} is the (N_2,k_1) element of the unitary matrix which diagonalizes the symmetrized relaxation matrix of an equilibrium kinetic system composed of M independent subunits undergoing i ⇄ ii reactions (see Appendix A and ref. 15) and $\lambda_k(\equiv k(\alpha+\beta))$ is an eigenvalue of that relaxation matrix. In general, both $P(N_2)$ and u_{N_2k} can be expressed in terms of $n_\infty\equiv\alpha/(\alpha+\beta)$. But their exact expressions are not important here. The only relations that are useful here are

$$\sum_k u_{ik}u_{jk}=\delta_{ij}, \quad (11)$$

$$u_{i0}=P(i)^{1/2}, \quad (12)$$

and

$$\sum_j ju_{jk}P(i)^{1/2}=Mn_\infty\delta_{k0}-[Mn_\infty(1-n_\infty)]^{1/2}\delta_{k1}, \quad (13)$$

where $n_\infty=\alpha/(\alpha+\beta)$ and δ is the usual Kronecker delta function. Eqs. 11 and 12 have been discussed in ref. 15. Proof of eq. 13 is given in Appendix B.

Substituting eq. 10 into eqs. 8 and 9, and using eqs. 11–13, we obtain the time correlation functions

$$C(\tau)=-F^2Mn_\infty(1-n_\infty)e^{-\lambda(\tau-\Delta)}(e^{-\lambda\Delta}-1)^2/\Delta^2\quad(\tau>\Delta), \quad (14)$$

$$C(\tau)=F^2Mn_\infty(1-n_\infty)[e^{-\lambda\tau}(2-e^{-\lambda\Delta})-e^{-\lambda(\Delta-\tau)}]\Delta^2\quad(\tau\leq\Delta), \quad (15)$$

where $\lambda=\lambda_1\equiv\alpha+\beta$.

Using the Wiener-Khintchine theorem and eqs. 14 and 15, we obtain the noise power spectrum $G(\omega)$,

$$\begin{aligned}G(\omega)&=4\int_0^\infty C(\tau)\cos\omega\tau\,d\tau\\ &=8F^2Mn_\infty(1-n_\infty)\lambda\left[\frac{1-\cos(\omega\Delta)}{\Delta^2(\lambda^2+\omega^2)}\right] \quad (16)\end{aligned}$$

where $\omega=2\pi f$ and $f=$ frequency.

$C(\tau)$ and $G(\omega)$ for the special case $\Delta=0$ can be obtained easily from eqs. 14–16 as

$$\begin{aligned}C^0(\tau)=\lim_{\Delta\to0}C(\tau)&=-MF^2n_\infty(1-n_\infty)\lambda^2e^{-\lambda\tau}\\ &\quad(\tau>0) \quad (17A)\\ &=\infty\quad(\tau=0), \quad (17B)\end{aligned}$$

$$G^0(\omega)=\lim_{\Delta\to0}G(\omega)=\frac{4MF^2n_\infty(1-n_\infty)\lambda\omega^2}{\lambda^2+\omega^2}. \quad (18)$$

Eq. 18 is identical to eq. 8 of Kolb and Läuger [6] if one notes that $n_\infty = 1/2$ (as $\alpha = \beta$) and that our F, M, α and $1/\lambda$ here correspond to Kolb and Läuger's $\alpha z e_0$, n, k_i and τ_i, respectively.

The total fluctuation $C(0)$ can be obtained from eq. 15 directly or from $G(\omega)$ in eq. 16 by integration. The result is

$$C(0) = 2F^2 M n_\infty (1 - n_\infty)(1 - e^{-\lambda\Delta})/\Delta^2. \qquad (19)$$

When $\Delta = 0$,

$$\lim_{\Delta \to 0} C(0) = \lim_{\Delta \to 0} \frac{F^2 M n_\infty (1 - n_\infty)\lambda}{\Delta} = \infty. \qquad (20)$$

This agrees with eq. 17B and is consistent with the results of a white noise.

4. Comparisons with experiments

In this section the effect of Δ on the time correlation function $C(\tau)$ and the noise power spectrum $G(\omega)$ will be examined numerically using the parameters given by Bruner and Hall [13] and by Kolb and Läuger [6] for the transport of dipicrylamine ions across lipid bilayer membranes. The purpose is to see if it is possible to estimate the value of Δ from experimentally measured $C(\tau)$ and $G(\omega)$ curves. The values of MF^2 and λ for the two cases (BH case and KL case) are listed in table 1. One must note that the values of MF^2 are determined by the area of the membrane and the concentration of hydrophobic ions in the system. On the other hand, the values of λ are dependent on the temperature of the system. As hsown in table 1, the λ values of the two cases are varied by more than an order of magnitude.

Table 1

Values of MF^2 and λ used in numerical calculations

BH, dioleylphosphatidylcholine membrane of area 0.58 mm² with 0.1 M NaCl and 10^{-7} M dipicrylamine⁻ at 23°C; KL, dierucoyl lecithin membrane of area 0.36 mm² with 0.1 M NaCl and 3×10^{-8} M dipicrylamine⁻ at 5°C.

	MF^2 ($A^2 - s^2$)	λ (s^{-1})
BH case	9.92347×10^{-29}	751.8797
KL case	6.16×10^{-28}	22.72727

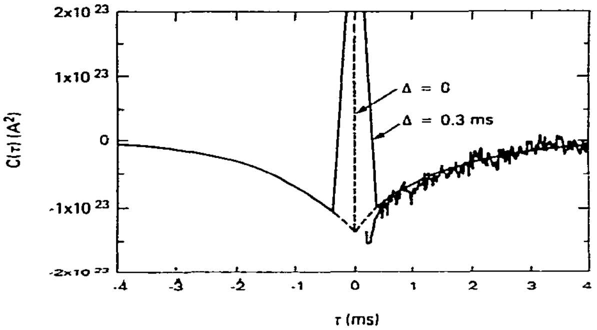

Fig. 2. The calculated time correlation functions of the BH case. Also included is the experimental curve obtained by Bruner and Hall [13]. The difference in the calculated $C(\tau)$ between $\Delta = 0$ and $\Delta = 0.3$ are too small to be seen in the figure for $\tau > 0.3$ ms.

As mentioned before, the value of Δ may be just a fraction of the time constant ($1/\lambda$) of the transport kinetics. Thus, Δ must be in the submillisecond range. For convenience, we consider the cases wieht $\Delta = 0.1$, 0.2 and 0.3 ms.

The calculated $C(\tau)$ curves for $\Delta = 0$ and 0.3 ms are plotted in fig. 2 (BH case) and fig. 3 (KL case). Note that the experimental result of Bruner

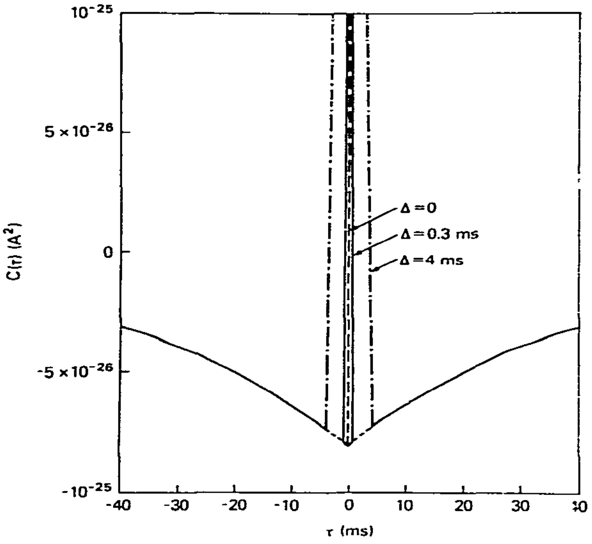

Fig. 3. The calculated time correlation function of the KL case.

and Hall is also shown in fig. 2. Before discussing the effects of Δ on $C(\tau)$, let us examine the general properties of $C(\tau)$. As one can see from the figures, the time correlation function $C(\tau)$ of this closed one-barrier two-binding-site model is quite different from that of the channel mechanism. In general, $C(\tau)$ is positive at $\tau = 0$ and decreases almost linearly as τ decreases. It becomes negative when τ is larger than τ_0, which can be obtained from eq. 15 as

$$\tau_0 = \frac{\ln(2e^{-\lambda\Delta} - 1)}{2\lambda}. \tag{21}$$

$C(\tau)$ reaches its minimum at $\tau = \Delta$ and then increases exponentially toward the value zero at $\tau = \infty$. The occurrence of a negative correlation in this system is a distinctive feature which one can never get in concentration-fluctuation measurements (channel noise). The concentration time correlation function is always positive and decays monotonically as τ increases [4]. This negative correlation is due to the occurrence of alternate positive and negative pulses of equal duration in the system as has been discussed by Frehland [18].

As shown in figs. 2 and 3, $C(\tau)$ of nonzero Δ is quite different from that of $\Delta = 0$ in the region $0 \leq \tau \leq \Delta$, but becomes indistinguishable from the $\Delta = 0$ case when τ is greater than Δ. That is, the time correlation function $C(\tau)$ is sensitive to Δ only at small τ. Since Bruner and Hall did not measure accurately $C(\tau)$ at τ smaller than 0.5 ms, their $C(\tau)$ results are not sufficient for the estimate of Δ.

Calculated noise power spectra for the two cases are shown in figs. 4 and 5. In general, $G(\omega)$ is very small when ω is small and increases monotonically and then reaches a plateau as ω becomes larger. This feature is quite different from the noise power spectrum of channel conductance fluctuations, in which the power density is large at low frequencies and decreases as ω increases (Lorentzian). For finite Δ values, $G(\omega)$ starts to decrease after ω becomes very large. Only when $\Delta = 0$ does $G(\omega)$ remain constant (white noise) at high frequencies. As one can see from figs. 4 and 5, the frequency at which $G(\omega)$ starts to fall after reaching the plateau is very sensitive to the value of Δ. In contrast, the rising phase at low frequencies seems to be completely independent of Δ. Thus, if one is to determine the Δ value, it is important to have $G(\omega)$ at high frequencies.

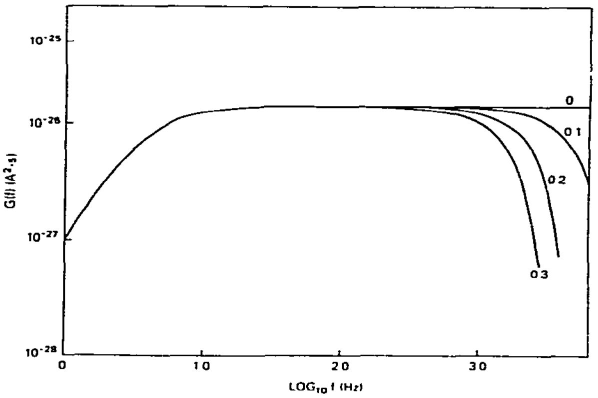

Fig. 4. The calculated noise power spectrum of the BH case. The values of Δ (in ms) are indicated beside the curves.

If one compares figs. 4 and 5, it is easy to find that the $G(\omega)$ curves of both BH and KL cases seem to fall off from the plateau at the same frequency for the same Δ value. This means that the $G(\omega)$ at the 'falling' phase (high-frequency

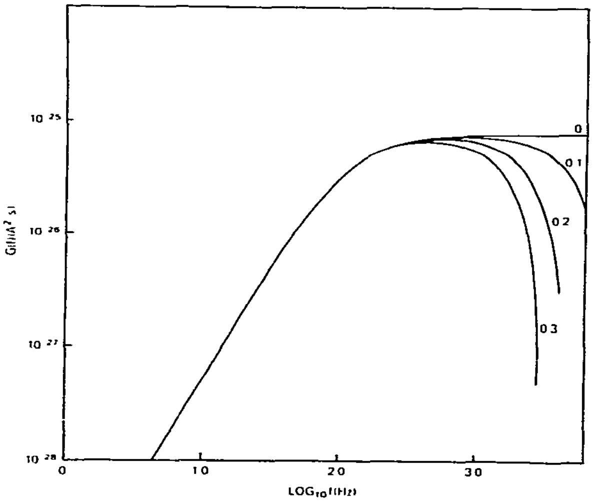

Fig. 5. The calculated noise power spectrum of the KL case. The values of Δ (in ms) are indicated beside the curves.

region) is not very sensitive to the value of λ (or temperature, since λ is a function of temperature only) and that it is possible to estimate the value of Δ without knowing the value of λ.

From the above arguments, it is clear that the existence of a falling phase in $G(\omega)$ at high frequencies after the plateau indicates the presence of a transit time in the translocation process. In principle, one has to analyze $G(\omega)$ in eq. 16 in order to evaluate the exact value of Δ. In practice, one can make a rough estimate of Δ based on the 'half frequency' ($f_{1/2}$) of $G(\omega)$ at the falling phase. The half frequency here is defined as the frequency at which $G(\omega)$ is decreased to one-half that of its plateau value. For both the BH and KL cases, the $f_{1/2}$ values for $\Delta = 0.1$, 0.2 and 0.3 ms were found to be approximately equal to 4.5, 2.5 and 1.5 kHz, respectively. Thus, if $\Delta = 0.3$ ms or larger. a measurement of $G(\omega)$ up to $f = 1.5$ kHz is enough to determine Δ. If Δ is 0.1 ms or less, then the measurement has to go up to more than 4.5 kHz.

5. Discussions

As mentioned in section 1, the experimental $C(\tau)$ for the transport of dipicrylamine ions across lipid bilayer membranes as reported by Bruner and Hall [13] was found to be slightly deviated from the theoretical $C(\tau)$ without the transit time (see fig. 1 of ref. 13). We thought that this deviation might disappear for nonzero Δ cases. As shown in fig. 2 and discussed in secton 4, it is apparent that this is not true. In fact, as long as the value of Δ is only a fraction of $1/\lambda$, the difference in $C(\tau)$ between a nonzero Δ and $\Delta = 0$ cases will be very small for $\tau > \Delta$. Thus, the small deviations may be due to the values of MF^2 and λ used in the calculation. In fact, we found that experimental BH results could be fitted rather well with $MF^2 = 9.45 \times 10^{-29}$ ($A^2 - s^2$) and $\lambda \simeq 796.5$ (s^{-1}) (data not shown). Of course, other factors such as deviations from the idealized rectangular-pulse model, etc., may also cause the deviation in $C(\tau)$. In any case, the deviations in $C(\tau)$ at the $\tau > 0$ region are not due to the existence of transit times.

Theoretical studies on transport noise with transit times have been reported by Stevens [14] and Läuger [5]. However, the transport mechanisms (and therefore the results) of these studies are quite different from that in this paper. Stevens [14] treated the unidirectional flow of ions through membranes (or channels) as a random jumping of ions from one side of the membrane to the other according to a Poisson process with a constant mean rate r. The process is thus identical to the jumping of electrons from the cathode to the anode in a vacuum tube and the usual shot noise analyses with transit times [16] can be applied to this case. Läuger extended the treatment to include a backward flow in the transport process. Assuming that the backward flow is independent of the forward flow, he obtained similar shot noise results. Again, the translocation step is assumed to be Poissonian. The basic assumption in a Poissonian translocation mechanism is that the proability of transporting an ion across the barrier between time t and time $t + dt$ is equal to $r dt$ where r is a constant independent of t [17]. In general, if the number of ions at one side of the barrier is $N(t)$ at time t, the probability that an ion will translocate from that side to the other between times t and $t + dt$ is equal to $\alpha N(t) dt$ where α is a constant. Thus, a Poisson process implies that $N(t)$ is a constant independent of time. For a membrane system to have this property, the adsorption and desorption processes of ions between the binding sites of the membrane and the bathing solutions must be fast compared to the time scale of the translocation kinetics of the ions. In thermodynamic terms,the system containing all the ions on the binding sites of the membrane is 'open'. In the present paper, the system is 'closed' and $N(t)$ is not independent of time. if one compares eq. A4 of ref. 5 and eq. 16, it is easy to see that the noise power intensity of this one-barrier two-binding-site model goes to zero as the frequency (f) approaches zero if the system is closed and remains constant if the system is open.

In conclusion, we have obtained the analytical expressions of the time correlation function and the noise power spectrum of the ion-translocation process in a closed one-barrier two-binding-site membrane model with a finite transit time. The results are new and can be used to evaluate the value of transit time when either the noise power spectrum at very high frequencies or the time correlation function at very small times is available.

Appendix A

A.1. The conditional probability function, for a system of i $\underset{\beta}{\overset{\alpha}{\rightleftarrows}}$ ii reactions

We consider a system at equilibrium containing a total of M molecules of i and ii, which can undergo isomeric reactions i $\underset{\beta}{\overset{\alpha}{\rightleftarrows}}$ ii. Let N_1 and N_2 be the numbers of molecules in states i and ii, respectively. Then owing to conservation, we have $N_1 + N_2 = M$. Thus, the system can be characterized by either N_1 or N_2 alone. We choose N_2 as the independent variable. Then the conditional probability function $W(N_2|N_2',t)$ of finding N_2' at time t when at time zero the system has exactly N_2 molecules of ii obeys the master equation

$$\begin{aligned}\frac{\mathrm{d}W(N_2|N_2',t)}{\mathrm{d}t} &= W(N_2|N_2'-1,t)(M-N_2'+1)\alpha \\ &\quad + W(N_2|N_2'+1,t)(N_2'+1)\beta \\ &\quad - W(N_2|N_2',t)[(M-N_2')\alpha + N_2'\beta] \qquad \text{(A1)} \\ &\quad N_2, N_2' = 0,1,2,\cdots,M\end{aligned}$$

The definition of a conditional probability function requires that

$$W(N_2|W_2',0) = \delta_{N_2 N_2'} \qquad \text{(A2)}$$

and

$$W(N_2|N_2',t) = 0 \text{ when } N_2' < 0 \text{ or } N_2' > M \qquad \text{(A3)}$$

For any particular N_2 value, we can obtain a set of M first-order differential equations from eq. A1:

$$\frac{\mathrm{d}W(N_2|N,t)}{\mathrm{d}t} = -A\,W(N_2|N,t) \qquad \text{(A4)}$$

where $W(N_2|N,t)$ is a column matrix of $M+1$ elements:

$$W(N_2|N,t) \equiv \begin{pmatrix} W(N_2|0,t) \\ W(N_2|1,t) \\ \vdots \\ W(N_2|M,t) \end{pmatrix}, \qquad \text{(A5)}$$

and

$$A \equiv \begin{pmatrix} M\alpha & -\beta & 0 & 0 & \cdots & 0 \\ -M\alpha & (M-1)\alpha+\beta & -2\beta & 0 & \cdots & 0 \\ 0 & -(M-1)\alpha & (M-2)\alpha+2\beta & -3\beta & \cdots & 0 \\ \vdots & & & & & \\ 0 & 0 & 0 & 0 & -\alpha & M\beta \end{pmatrix} \qquad \text{(A6)}$$

Matrix A ($M+1$ by $M+1$) corresponds to the relaxation matrix of a linear kinetic scheme,

$$\begin{matrix}[0] & \underset{\beta}{\overset{M\alpha}{\rightleftarrows}} & [1] & \underset{2\beta}{\overset{(M-1)\alpha}{\rightleftarrows}} & \cdots\cdot & \underset{M\beta}{\overset{\alpha}{\rightleftarrows}} & [M]. \\ P(0) & & P(1) & & & & P(M)\end{matrix} \qquad \text{(A7)}$$

The kinetic scheme in eq. A7 is equivalent to the scheme of a system containing M subunits each of which is undergoing the i $\underset{\beta}{\overset{\alpha}{\rightleftarrows}}$ ii reaction. The state $[j]$ with probability $p(j)$ has j subunits in state ii. As discussed in ref. 15, for this system eq. A4 can be solved and $W(N_2|N,t)$ can be expressed in terms of the fundamental matrix $\Phi(t)$ of eq. A6:

$$W(N_2|N,t) = \Phi(t)W(N_2|N,0) \qquad \text{(A8)}$$

where

$$\phi_{ij}(t) = P(i)^{1/2}P(j)^{-1/2}\sum_k u_{ik}u_{jk}e^{-\lambda_k t} \qquad \text{(A9)}$$

The $P(i)$ in eq. A9 are the same $P(i)$ as in eq. A7, and u_{ik} is the (i,k) element of the unitary matrix which diagonalizes the symmetrized relaxation matrix A of eq. A6. Explicit expressions for the u_{ik} are not required here, although a few have been given in the appendix of ref. 15 (the M here is equivalent to the x in ref. 15). The λ_k are the eigenvalues of matrix A. In general, there is one zero eigenvalue which is represented by λ_0. Other nonzero λ are all real positive numbers and $\lambda_k = k(\alpha+\beta)$. From eqs. A8 and A9, and using eq. A2, we have

$$\begin{aligned} W(N_2|N_2',t) &= \sum_{N_2''}\phi_{N_2'N_2''}(t)W(N_2|N_2'',0) \\ &= \sum_{N_2''}\phi_{N_2'N_2''}(t)\delta_{N_2N_2''} \qquad \text{(A10)} \\ &= \phi_{N_2'N_2} = P(N_2')^{1/2}P(N_2)^{-1/2}\sum_k u_{N_2k}u_{N_2'k}e^{-\lambda_k t}\end{aligned}$$

Eq. A10 is the desired result. It is easy to see that eq. A10 satisfies the condition, eq. A2:

$$\begin{aligned} W(N_2|N_2',0) &= P(N_2')^{1/2}P(N_2)^{-1/2}\sum_k u_{N_2k}u_{N_2'k} \\ &= P(N_2')^{1/2}P(N_2)^{-1/2}\delta_{N_2N_2'} \\ &= \delta_{N_2N_2'} \end{aligned}$$

At $t=\infty$, eq. A10 becomes

$$W(N_2|N_2',\infty) = P(N_2)^{1/2}P(N_2)^{-1/2}u_{N_20}u_{N_2'0} = P(N_2')$$

That is, at $t=\infty$ the conditional probability is independent of the initial condition and is equal to the steady-state probability as shown in eq. A7.

Appendix B

B.1. Proof of eq. 13

Let us denote $\sum_{j=0}^{M} ju_{jk}P(j)$ by h_k. Then h_k is equal to the square root of g_k in eq. 37 of ref. 15 when a_l is set equal to l. For systems composed of M i ⇄ ii subunits, the g_k has been expressed explicitly by eqs. 46, 48 and 49 of ref. 15. Thus,

$$h_k = \left\{\frac{x![n_\infty(1-n_\infty)]^k}{k!(x-k)!}\right\}^{1/2}\{\ \}_k \tag{B1}$$

$$\{\ \}_k = \sum_{j=0}^{x-k}\frac{(x-k)!(-n_\infty)^{x-k-j}H_{x-j}}{j!(x-k-j)!} \tag{B2}$$

$$H_{x-j} = \sum_{l=0}^{x-j}\frac{(x-j)!(-1)^l l}{l!(x-j-l)!} \tag{B3}$$

It is easy to show that H_{x-j} in eq. B3 is nonzero only when $x-j=1$, and then it is equal to -1. Thus

$$H_{x-j} = (-1)\delta_{x-j,1} \tag{B4}$$

Substituting eq. B4 into eq. B2, we have

$$\{\ \}_k = xn_\infty\delta_{k,0} - \delta_{k,1} \tag{B5}$$

With eqs. B5 and B1, eq. 13 can be proved easily.

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