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Bidirectional shot noise in a singly occupied channel

E. Barkai,[1] R. S. Eisenberg,[2] and Z. Schuss[3]
[1]*School of Physics and Astronomy, Tel-Aviv University, Ramat-Aviv, Tel-Aviv 69978, Israel*
[2]*Department of Molecular Biophysics and Physiology, Rush Medical Center, 1750 West Harrison, Chicago, Illinois 60612*
[3]*School of Mathematical Sciences, Tel-Aviv University, Ramat-Aviv, Tel-Aviv 69978, Israel*
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We calculate the power spectrum of the noisy current in a narrow channel that admits one charge carrier at a time from the left L or right R reservoirs. The random positive and negative currents are produced by the random arrival and departure of discrete charges at a measuring device on one side. The unidirectional currents are not independent because the presence of one charge in the channel blocks the entrance of another. Four classes of trajectories are possible: the *trans* trajectories LR and RL and *cis* trajectories LL and RR. The power spectrum of the total current is described by explicit formulas, depending only on the statistics of the interarrival times and times spent in the channel. These formulas generalize those of shot (e.g., Schottky) noise and predict more complex behavior than the sum of the noises of the four types of trajectories, if they were independent: (i) the mean current and the intensity of fluctuations saturate as the arrival time on one side decreases and (ii) the noise intensity depends nonlinearly on the mean net current. Explicit formulas are given and special cases are analyzed. [S1063-651X(96)03808-1]

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I. INTRODUCTION

Shot noise is the noisy current produced by the random arrival of identical discrete (unit) charges at a measuring device. The classical mathematical theory of shot noise assumes that the interarrival times of charges are independent identically distributed (IID) positive random variables [1,2]. This is the main feature of classical shot noise theory. More generalized theories allow some dependence between interarrival times, but still require them to be identically distributed (see the generalized Campbell theorem on the mean current in [3]). In these theories charge carriers are counted as they arrive at the measuring device, where they are captured and cannot leave. The measuring device acts as a (mathematical) absorbing boundary. In classical shot noise the interarrival times at the measuring device are IID exponentially distributed random variables and the intensity K equals the mean current $\langle I\rangle$ (Schottky's formula [4])

$$K=\langle I\rangle. \tag{1.1}$$

If the interarrival times are IID random variables $\tau_1,\tau_2,\ldots,$ not necessarily exponentially distributed, then [2]

$$\langle I\rangle=\frac{1}{\langle\tau\rangle} \tag{1.2}$$

and

$$K=\frac{\langle\tau^2\rangle-\langle\tau\rangle^2}{\langle\tau\rangle^3}. \tag{1.3}$$

In more general situations the measuring device distinguishes between incoming and outgoing charge movements. Movements in one direction may separately be classical shot noises, but the combination may or may not. Landauer [5] considered the situation in which the sum is nearly a classical shot noise. He considered two independent sources of current, the first flowing from left to right I_{LR} and the second from right to left I_{RL}, both defined to be positive. In this case the net current is the difference $I=I_{RL}-I_{LR}$ and the intensity of the resulting noise is the sum

$$K=\langle I_{LR}\rangle+\langle I_{RL}\rangle. \tag{1.4}$$

In other situations the unidirectional currents are not independent and corrections are needed to Eq. (1.4). For example, if the unidirectional currents have to move one charge at a time through a channel to reach the measuring device, the motion in one direction blocks the motion in the other, so the movements are not independent. Together they are not classical shot noise and Eqs. (1.1)–(1.4) do not apply.

We analyze exactly this situation: a channel that admits one charge at a time from the left L or right R reservoir. The measuring device is on one side of the channel and counts incoming charges as positive and outgoing charges as negative. In our model, discrete charges arrive at each end of the channel from different populations in the reservoirs that may have different concentrations and therefore different interarrival times. They may enter the channel, if it is empty, and spend random times moving to one end of the channel or the other. These times are determined by the dynamics of motion outside (interarrival times) or inside the channel (full-channel times).

Motion inside the channel is determined by many factors that depend on the physical setup of the problem. A separate theory, for example [6], is needed to determine the statistics of the full-channel times, given the details of the motion. The full-channel times depend on the direction the charge moves: more precisely, they depend on the side they enter and exit. For example, if discrete charges cross the same channel but in different directions, they move, in time, over different potential profiles (even if their charge and other properties are the same), because the profiles are usually not symmetric. The different charge carriers can also have different proper-

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ties, e.g., different, mass, size, or friction. Thus different charge carriers spend different times in the channel. Carriers can cross the channel (i.e., enter at one side and exit the other, carrying a *trans* flux) or they can enter and leave the same side (either right R or left L, carrying a *cis* flux). This situation violates the assumptions of shot noise theory because the counting events are not identical (i.e., some events are positive and some are negative) and are not independent (i.e., carriers exclude each other in the channel). Small systems such as the (protein) channels of biological membranes have these characteristics [7,8].

The main result of this paper is a formula for the power spectral density function of current fluctuations in the single occupancy model described above [Eq. (3.33)] and for its intensity [Eq. (4.1)]. These formulas involve no approximations beyond those in the model itself. We compute the spectral density for the general case where the distribution of waiting and full-channel times are not necessarily described by simple rate laws, i.e., our model is not Markovian. In diffusion systems, such as channels, this reflects the fact that barriers are often small and so Markovian jump models do not apply [9]. Thus the dynamics in the channel can be general, ranging from ballistic to Brownian, or even Markovian dynamics.

Our intensity formula adds terms to Eq. (1.4), due to the dependence introduced by single occupancy and competition. The *cis* trajectories, included here, add a significant, sometimes dominant, contribution to the fluctuations. The power spectral density function is different from that of shot noise. It is not flat with frequency, but rather has a variety of shapes, depending on conditions, even when all distributions are exponential; noise intensity depends nonlinearly on the net current. The formulas are generalized to allow mixed populations of different species of charge carriers on both sides of the channel [Eq. (5.1)].

This paper is organized as follows. First, in Sec. II we define exactly the model under consideration. This includes the specification of the measuring device as a counter of charges. In Sec. III we calculate the spectral density and correlation functions. Section IV presents the main result of this paper: the spectral density of the measured current. A number of special cases are presented. Section V treats the case of several species, in which slow charge carriers may dramatically change the measured current. Our mathematical computation generalizes the analysis in [4], Chap 5, pp. 161–174, of correlations of electronic signals.

II. DEFINITIONS AND THE COUNTER MODEL

Our mathematical model describes a narrow channel that contains one charge carrier at a time. We assume that positive charges (with charge $+1$) arrive at the left end of the channel at IID random times, denoted generically Δ_L. Similarly, charges arrive at the right end of the channel at IID random times Δ_R. These are called *interarrival* times. They do not depend on whether or not the channel is occupied. If the channel is empty upon arrival of a charge carrier, the charge enters. If the channel is occupied, it is rejected and returned to the reservoir; it does not queue up. E is the time between the moment the channel empties and refills (from either side). If it refills from the left, we label it E and call it E_L, and if it refills from the right, we call it E_R. We call E_L and E_R *empty-channel times* or *waiting times*. We assume that the system is in the steady state, that is, the stochastic processes have been going on for an infinite time at the moment observation begins. If observation of the channel starts sometime during the period when the channel is empty, the time for the arrival of the first charge carrier from the left or from the right is called the *residual interarrival time*, denoted Δ_L^* or Δ_R^* [2].

The times that L or R charge carriers spend in the channel (i.e., charges that entered the channel from the left or right) are called *full-channel times*, denoted generically F_L and F_R. They are assumed to be (generally different) IID random variables. F_{LL} denotes the full channel times of those L charge carriers that exit on the left; F_{LR} denotes the full channel times of the other L charge carriers, namely, those that exit on the right. F_{RL} and F_{RR} are similarly defined. If observation starts some time after a charge carrier has entered the channel, but before it leaves, the (remaining) waiting times of charge carriers in the channel are called *residual full-channel times* F_{ij}^* $(i=L,R;\ j=L,R)$.

We assume, for the sake of simplicity, that the waiting process is renewed when the channel empties. The renewal assumption is justified if, for example, the waiting times have exponential distributions [10]. It is also justified if the initial state of the reservoir is the same after each charge carrier leaves the channel. The initial state is always the same if the population of charge carriers equilibrates very quickly after a charge carrier leaves the channel; that is to say, the equilibration time of the population is much less than the time the charge carrier spent in the channel, its full-channel time.

The empty- and full-channel times come in pairs. After every full-channel time the channel empties; therefore, each E_i is followed by a F_{ij} and after each F_{ij} comes an E_k. A typical realization of time intervals is

$$\{F_{LR}^*, E_L^1, F_{LR}^2, E_L^3, F_{LL}^4, E_R^5, F_{RL}^6, E_R^7, F_{RR}^8, \ldots\}. \tag{2.1}$$

In this realization, observation began at $t=0$, when the channel was already occupied, namely, by a charge carrier that had entered on the left and that will exit on the right. Events in this realization occur at times $t_0, t_1, \ldots$, specifically,

$$t_0 = F_{LR}^*, \quad t_1 = F_{LR}^* + E_L^1, \quad t_2 = t_1 + F_{LR}^2, \tag{2.2}$$

and so on.

We define the probability distribution of the empty channel time E_i as the joint probability

$$\Pr\{E_i < t\} = \Pr\{\Delta_i < t, \Delta_i < \Delta_{i^c}\} = W_i(t) \quad (i=L,R), \tag{2.3}$$

where the complementary index i^c is defined by

$$i^c = \begin{cases} R & \text{if } i=L \\ L & \text{if } i=R. \end{cases}$$

This notation describes the joint probability that an i charge carrier arrives before an i^c charge carrier in the competition for an empty channel and this occurs before time t. The comma in Eq. (2.3) is a logical *and*. The joint probability distribution function $W_i(t)$ can be expressed explicitly in terms of the probability densities $r_i(t)$ and $r_{i^c}(t)$ of the interarrival times Δ_i and Δ_{i^c}, respectively. Since Δ_i and Δ_{i^c} are assumed independent, their joint probability density function (PDF), which is the PDF of E_i, is $r_i(x)r_{i^c}(y)$ and then

$$W_i(t)=\int_{\substack{x<t\\x<y}}\int r_i(x)r_{i^c}(y)dx\,dy=\int_0^t dx\int_x^\infty dy\; r_i(x)r_{i^c}(y). \tag{2.4}$$

Setting

$$w_i(t)=W_i'(t)\quad(i=L,R),$$

we find, from Eq. (2.4), that

$$w_i(t)=r_i(x)\int_t^\infty r_{i^c}(y)dy=r_i(t)\left[1-\int_0^t r_{i^c}(y)dy\right]. \tag{2.5}$$

The probability that an i charge carrier arrives before an i^c charge carrier in the competition for an empty channel is

$$P(i)\equiv W_i(\infty)=\Pr\{\Delta_i<\Delta_{i^c}\}. \tag{2.6}$$

The functions $W_i(t)$, the probability distributions of the empty channel times E_i, are not proper distributions but rather *defective distributions* [and $w_i(t)$ are *defective densities*] (see [10], pp. 115 and 374) because they are not normalized to 1 [see Eq. (2.6)]; rather they are normalized together, collectively remedying each other's individual defect

$$W_L(\infty)+W_R(\infty)=1. \tag{2.7}$$

Defective distributions often arise in physical problems with flux at the boundaries, e.g., stochastic problems in which part or all of the boundaries are absorbing (see [2], pp. 222 and 234).

We denote by $\hat{w}_i(p)$ the Laplace transform of $w_i(t)$. Thus Eq. (2.6) is equivalent to

$$P(i)=\hat{w}_i(0) \tag{2.8}$$

and Eq. (2.7) is equivalent to

$$\hat{w}_L(0)+\hat{w}_R(0)=1.$$

The defective mean time for an i charge carrier to arrive at an empty channel after it has emptied is

$$\langle E_i\rangle=-\frac{d}{dp}\hat{w}_L(p)\bigg|_{p=0}=-\hat{w}_i'(0) \tag{2.9}$$

and the mean waiting time for *any* charge carrier is

$$\langle\tau_w\rangle=-\hat{w}_L'(0)-\hat{w}_R'(0). \tag{2.10}$$

For example, if Δ_L and Δ_R have exponential distributions with rates α_L and α_R, that is,

$$\Pr\{\Delta_i<t\}=1-e^{-\alpha_i t}\quad(i=L,R;\ t>0), \tag{2.11}$$

then

$$w_i(t)=\alpha_i e^{-(\alpha_L+\alpha_R)t},\quad \hat{w}_i(p)=\frac{\alpha_i}{\alpha_L+\alpha_R+p}. \tag{2.12}$$

In this case

$$P(i)=\hat{w}_i(0)=\frac{\alpha_i}{\alpha_L+\alpha_R},\quad -\hat{w}_i'(0)=\frac{\alpha_i}{(\alpha_L+\alpha_R)^2}. \tag{2.13}$$

In a special case, where charge carriers arrive at the channel by diffusion from the surrounding left and right baths (which form the reservoirs of our model), [11–13] show that

$$\alpha_i=2\pi\rho_i D_i R_i, \tag{2.14}$$

where the charge carrier concentration in the bath on side i is ρ_i, the diffusion coefficient is D_i, and R_i is the radius of the channel. Note that in this case the interarrival time Δ_L depends on the concentration ρ_L, while the empty-channel time E_L depends on both concentrations ρ_L and ρ_R.

Similarly, we denote by $Q_{LR}(t)$ the joint conditional probability that a charge carrier exits on the right before time t, given that it entered the channel on the left. Thus $q_{ij}(t)=Q_{ij}'(t)$ is the defective density function of the full channel time F_{ij} and $\hat{q}_{iL}(0)+\hat{q}_{iR}(0)=1$. In particular, $\hat{q}_{ij}(0)=Q_{ij}(\infty)$ is the probability that an charge carrier that entered the channel on side i exits on side j. We denote this probability by $P(j|i)$, that is,

$$\hat{q}_{ij}(0)=P(j|i). \tag{2.15}$$

The defective mean $-\hat{q}_{LL}'(0)$ is the mean time a charge carrier (that enters the channel on the left and exits on the left) spends in the channel. Thus the first two moments of the full-channel time of an i charge carrier are given by

$$\langle F_i\rangle=-\hat{q}_{ii}'(0)-\hat{q}_{ii^c}'(0),$$

$$\langle F_i^2\rangle=\hat{q}_{ii}''(0)+\hat{q}_{ii^c}''(0),$$

$$\langle F_{ii^c}\rangle=-\hat{q}_{ii^c}'(0) \tag{2.16}$$

and the mean time a charge carrier spends in the channel is

$$\langle\tau_F\rangle=P(L)\langle F_L\rangle+P(R)\langle F_R\rangle. \tag{2.17}$$

We define the mean renewal time

$$\langle t_P\rangle=\langle\tau_w\rangle+\langle\tau_F\rangle. \tag{2.18}$$

For example, if full-channel times are exponentially distributed with the four rates γ_{ij},

$$\hat{q}_{ij}(p)=\frac{\gamma_{ij}}{\gamma_{iL}+\gamma_{iR}+p},\quad P(i|i^c)=\frac{\gamma_{ii^c}}{\gamma_{iL}+\gamma_{iR}},$$
$$\langle F_i\rangle=\frac{1}{\gamma_{iL}+\gamma_{iR}},\quad \langle F_{ii^c}\rangle=\frac{\gamma_{ii^c}}{(\gamma_{iL}+\gamma_{iR})^2}. \tag{2.19}$$

The probabilities $P(i|j)$ and the mean full-channel times can be calculated once the physical system or model that defines them is specified. For a model of diffusion as a chemical reaction, Ref. [6] calculates both the probabilities

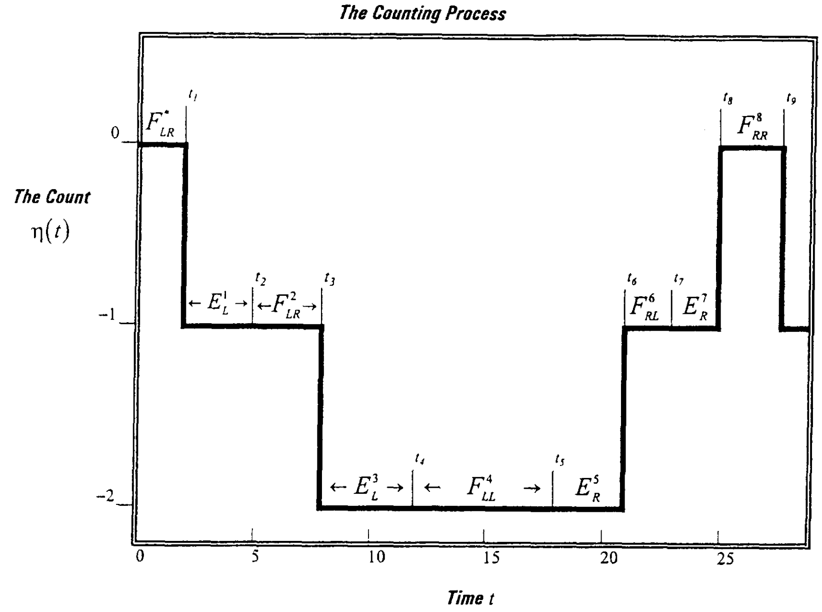

FIG. 1. Counting process $\eta(t)$ for the realization (2.1).

and the mean full-channel times. In an overdamped chemical reaction, the probabilities are given by

$$P(i|i^c)=\sqrt{2\pi kT}\,\frac{e^{\Phi(i^c)/kT}}{\int_L^R \gamma(x)e^{\Phi(x)/kT}dx},\qquad(2.20)$$

where k is Boltzmann's constant, T is the absolute temperature, $\Phi(x)$ is the electric potential in the channel, $\gamma(x)$ is the (displacement dependent) friction, and the reaction region is located in the interval $L<x<R$. In particular,

$$\frac{P(R|L)}{P(L|R)}=e^{-\Delta\Phi/kT},\qquad(2.21)$$

where $\Delta\Phi=\Phi(L)-\Phi(R)$ is the potential difference across the reaction region.

The measuring device as a counter

The measuring device is modeled as an ideal counter of discrete charge, placed at the right end of the channel. It counts (a) an LR charge carrier as 0 when it enters and as -1 when it exits the channel, (b) an LL charge carrier as 0 both when it enters and when it exits because an LL charge carrier does not reach the counter, (c) an RL charge carrier as $+1$ when it enters the channel and as 0 when it exits, and (d) an RR charge carrier twice, once as $+1$ when it enters the channel and again, as -1, when it departs. This particular model reflects the properties of the electrode in patch clamp measurements of biological channels [7]. Our calculations extend easily to include other configurations of the counter, e.g., where LL trajectories are also counted.

The counting process in the realization Eq. (2.1) is shown in Fig. 1. Counts occur at times $t_0,t_1,t_2,\ldots$ [see Eq. (2.2)].

To calculate the statistical properties of the current, we construct a cumulative counting process $\eta(t)$. The consecutive (random) times when an arrival or a departure occur are denoted t_i. The cumulative count $\eta(t)$ changes at times t_i by 1, -1, or 0, according to the recording of the counter.

The current is given by

$$I(t)\equiv\frac{d\eta(t)}{dt}=\sum_{i=0}^{\infty}\theta_i\delta(t-t_i),\qquad(2.22)$$

where the "counting function" θ_i can assume the three values

$$\theta_i=\begin{cases}0 & \text{if } t_i-t_{i-1}=E_L,\ F_{LL},\ \text{or } F_{RL}\\ 1 & \text{if } t_i-t_{i-1}=E_R\\ -1 & \text{if } t_i-t_{i-1}=F_{RR}\ \text{or}\ F_{LR}.\end{cases}\qquad(2.23)$$

If the charge carried by each particle is $+1$, the process $I(t)$ is the current flowing through the channel.

The unidirectional currents are given by

$$\langle I_{ii^c}\rangle\equiv\frac{\hat{w}_i(0)\hat{q}_{ii^c}(0)}{\langle t_P\rangle}=\frac{P(i)P(i^c|i)}{\langle t_P\rangle}\qquad(2.24)$$

and the net mean current is given by

$$\langle I\rangle=\langle I_{RL}\rangle-\langle I_{LR}\rangle,\qquad(2.25)$$

where the mean time $\langle t_p\rangle$ is given in Eq. (2.18) above. Equation (2.24) is a straightforward consequence of the calculations of Sec. III. This expression can be understood as follows. The expression $1/\langle t_P\rangle$ is the total number of renewals per unit time and the numerator in Eq. (2.24) represents the probability of counting an ii^c charge carrier. Thus their product is the unidirectional current.

If the interarrival times are exponentially distributed, with rates α_i [see Eq. (2.11)], then the unidirectional currents (2.24) are given by

$$\langle I_{ii^c}\rangle=\frac{\alpha_i P(i^c|i)}{1+\alpha_L\langle F_L\rangle+\alpha_R\langle F_R\rangle}.\qquad(2.26)$$

Note that the dependence of the unidirectional currents on microscopical times is different from that in classical shot noise theory, even if the unidirectional currents contain only *trans* trajectories.

The ratio of unidirectional fluxes has been very useful in some applications [7]. Equations (2.14), (2.21), and (2.26) imply that the Ussing flux ratio is

$$\frac{\langle I_{LR}\rangle}{\langle I_{RL}\rangle}=\frac{\alpha_L P(R|L)}{\alpha_R P(L|R)}=\frac{\rho_L D_L R_L}{\rho_R D_R R_R}e^{-\Delta\Phi/kT},$$

as predicted by the Nernst-Planck equation [7].

III. THE SPECTRAL DENSITY

We consider the case where the fluctuating current through the channel $I=I(t)$ is a stationary stochastic process. The spectral density of $I(t)$ is related to the spectral density of $I(t)-\langle I\rangle$ by the relation [4]

$$S(I,\omega)=S(I-\langle I\rangle,\omega)+4\pi\langle I\rangle^2\delta(\omega). \quad (3.1)$$

For $\omega\neq 0$, we have $S(I,\omega)=S(I-\langle I\rangle,\omega)$. This, together with the mean value of the current $\langle I\rangle$ (2.25), gives the spectral density of the process for all ω. The intensity of the current fluctuations, denoted K, is a useful property of the current; it is defined by [4], p. 23, Eq. (2.13), and gives the limiting low-frequency power of the current $I(t)$ once it is made zero mean by subtracting the average current $\langle I\rangle$

$$K\equiv\tfrac{1}{2}\lim_{\omega\to 0}S(I,\omega)=\tfrac{1}{2}\lim_{\omega\to 0}S(I-\langle I\rangle,\omega). \quad (3.2)$$

We now consider the Laplace transform of the process $I(t)$,

$$L(I,p)\equiv\int_0^\infty I(t)\exp(-pt)dt. \quad (3.3)$$

The spectral density of a stationary process can be calculated from its Laplace transform [see [4], p. 27, Eq. (2.27)]. For the stationary process $I(t)$, the spectral density is given by

$$S(I,\omega)=2\lim_{\epsilon\to 0}\epsilon\left\langle\left|L\left(I,\frac{\epsilon}{2}-i\omega\right)\right|^2\right\rangle, \quad (3.4)$$

where the Laplace transform of the current Eq. (2.22) is given by

$$L(I,p)=\sum_{i=0}^{\infty}\theta_i\exp(-pt_i). \quad (3.5)$$

Hence

$$|L(I,p)|^2=\sum_{i=0}^{\infty}\theta_i\exp(-pt_i)\sum_{k=0}^{\infty}\theta_k\exp(-\bar{p}t_k)$$
$$=\Sigma_0+\Sigma_++\Sigma_-, \quad (3.6)$$

where

$$\Sigma_0\equiv\sum_{i=0}^{\infty}\theta_i^2\exp[-(p+\bar{p})t_i], \quad (3.7)$$

$$\Sigma_+\equiv\sum_{i=0}^{\infty}\sum_{k=i+1}^{\infty}\theta_i\exp(-pt_i)\theta_k\exp(-\bar{p}t_k)$$
$$=\sum_{i=0}^{\infty}\sum_{l=1}^{\infty}\theta_i\exp(-pt_i)\theta_{i+l}\exp(-\bar{p}t_{i+l}), \quad (3.8)$$

$$\Sigma_-=\bar{\Sigma}_+, \quad (3.9)$$

where $\bar{p}$ and $\bar{\Sigma}_+$ mean complex conjugates. As shown below, Σ_0 produces a frequency-independent term in the spectral density (i.e., white noise), whereas Σ_+ contributes a frequency-dependent component of noise in the spectral density. We now proceed to calculate $\langle|L(I,p)|^2\rangle$, first calculating $\langle\Sigma_0\rangle$.

A. Calculation of $\langle\Sigma_0\rangle$

We first consider in detail the case when the channel is occupied at $t=0$. The time interval between $t=0$ and the time it empties is the residual F_{ij}^*. Setting $\epsilon\equiv p+\bar{p}=2\,\mathrm{Re}(p)$, we rewrite Eq. (3.7) as

$$\langle\Sigma_0\rangle=\sum_{i=0}^{\infty}\langle\theta_i^2\exp(-\epsilon t_i)\rangle$$
$$=\langle\theta_0^2\exp(-\epsilon t_0)\rangle$$
$$+\langle\exp(-\epsilon t_0)\rangle\sum_{i=1}^{\infty}\langle\theta_i^2\exp[-\epsilon(t_i-t_0)]\rangle. \quad (3.10)$$

The term $\langle\exp(-\epsilon t_0)\rangle$ can be factored from the sum because t_0 is statistically independent of the later time intervals.

The main part of the calculation is to determine the expectation

$$\langle\theta_i^2\exp[-\epsilon(t_i-t_0)]\rangle. \quad (3.11)$$

To exploit the fact that E_i and F_{ij} come in pairs, consider separately the case where i is odd or even. At $t=0$ the channel is occupied; hence when i is odd (even), the last time interval that determines the counting function θ_i must be a waiting time (full-channel time).

For $i=2n$, $n=1,2,\ldots$, we have

$$\langle\theta_{2n}^2\exp[-\epsilon(t_{2n}-t_0)]\rangle=\langle\exp[-\epsilon(t_{2n-2}-t_0)]\rangle$$
$$\times\langle\exp[-\epsilon(t_{2n}-t_{2n-2})]\theta_{2n}^2\rangle$$

and θ_{2n} is determined by a full-channel time. In this expression, we used the fact that the last two time intervals are statistically independent of the previous $2n-2$ time intervals. For the further calculation of θ_{2n}, we need consider only full-channel times of type RR and LR, since for other full-channel times $\theta_{2n}=0$. Using the identity Eq. (7.1) of Appendix A, we can write the expression (3.11) for $i=2n$ in terms of the Laplace transform of the defective density functions $\hat{w}_j(p)$ and $\hat{q}_{ij}(p)$ as

$$\langle\exp[-\epsilon(t_{2n}-t_0)]\rangle=C^n(\epsilon), \quad (3.12)$$

where the moment generating function of the renewal period is

$$C(\epsilon)\equiv\hat{w}_L(\epsilon)[\hat{q}_{LL}(\epsilon)+\hat{q}_{LR}(\epsilon)]+\hat{w}_R(\epsilon)[\hat{q}_{RL}(\epsilon)+\hat{q}_{LR}(\epsilon)]. \tag{3.13}$$

Since in this case $\theta_{2n}^2=1$,

$$\langle\theta_{2n}^2\exp[-\epsilon(t_{2n}-t_0)]\rangle=C^{n-1}(\epsilon)[\hat{w}_R(\epsilon)\hat{q}_{RR}(\epsilon)+\hat{w}_L(\epsilon)\hat{q}_{LR}(\epsilon)]. \tag{3.14}$$

A similar calculation is carried out for the case where i is odd. Here the last interval is a waiting time and we get a contribution only from times E_R. Summing up all terms appearing in Eq. (3.10), we get

$$\langle\Sigma_0\rangle=\langle\theta_0^2\exp(-\epsilon t_0)\rangle+\langle\exp(-\epsilon t_0)\rangle\times\frac{\hat{w}_R(\epsilon)+\hat{w}_R(\epsilon)\hat{q}_{RR}(\epsilon)+\hat{w}_L(\epsilon)\hat{q}_{LR}(\epsilon)}{1-C(\epsilon)}. \tag{3.15}$$

Note that

$$\langle t_P\rangle\equiv-C'(0)=-\sum_{i=L,R}\{\hat{w}_i'(0)+\hat{w}_i(0)[\hat{q}_{ii^c}'(0)+\hat{q}_{ii}'(0)]\}=\langle\tau_w\rangle+\langle\tau_F\rangle, \tag{3.16}$$

where $\langle\tau_w\rangle$ is mean waiting time (2.10) and $\langle\tau_F\rangle$ is the mean full-channel time, weighted by the probabilities of winning the empty channel, given in Eq. (2.17) [see Eq. (2.18)]. Similarly,

$$\langle t_P^2\rangle\equiv C''(0). \tag{3.17}$$

The second moment $\langle t_P^2\rangle$ depends on the second moments of the microscopic times.

B. Calculation of $\langle\Sigma_+\rangle$

First, we rewrite $\langle\Sigma_+\rangle$ as

$$\langle\Sigma_+\rangle=\langle\theta_0\exp(-\epsilon t_0)\rangle\sum_{l=1}^{\infty}\langle\theta_l\exp[-\bar{p}(t_l-t_0)]\rangle+\langle\exp(-\epsilon t_0)\rangle\sum_{i=1}^{\infty}\sum_{l=1}^{\infty}\langle\theta_i\exp[-p(t_i-t_0)]\theta_{i+l}\times\exp[-\bar{p}(t_{i+l}-t_0)]\rangle. \tag{3.18}$$

It is shown below that the only contribution to the spectral density comes from the second term in Eq. (3.18). We therefore define

$$\langle\Sigma_+^1\rangle\equiv\sum_{i=1}^{\infty}\sum_{l=1}^{\infty}\langle\theta_i\exp[-p(t_i-t_0)]\theta_{i+l}\times\exp[-\bar{p}(t_{i+l}-t_0)]\rangle,$$
$$\langle\Sigma_+^{\theta_0}\rangle\equiv\langle\theta_0\exp(-\epsilon t_0)\rangle\sum_{l=1}^{\infty}\langle\theta_l\exp[-\bar{p}(t_l-t_0)]\rangle. \tag{3.19}$$

To compute $\langle\Sigma_+^1\rangle$ we must first calculate the correlation function, defined by

$$C(i,i+l)\equiv\langle\theta_i\exp[-p(t_i-t_0)]\theta_{i+l}\exp[-\bar{p}(t_{i+l}-t_0)]\rangle. \tag{3.20}$$

1. Calculation of $C(i,i+l)$

To calculate the correlation function, it is convenient to consider four possibilities: (i) l is even and i is odd, (ii) l is odd and i is even, (iii) l and i are even, and (iv) both l and i are odd. For each case we must consider all the different values that the counting functions θ_i and θ_{i+l} can assume.

Consider in some detail the case when *both l and i* are even. Both θ_i and θ_{i+l}, appearing in (3.20), are determined by a full-channel time (recall that at t_0^+ the channel is empty). We partition the $i+l$ intervals into four parts, (i) the first $i-2$ intervals, (ii) the pair $i-1$ and i, (iii) the next $l-2$ time intervals, and (iv) the pair $i+l-1$ and $i+l$, because each part is statistically independent of all other parts. We therefore get

$$C(i\text{ is even, }i+l\text{ is even})=\langle\exp[-\epsilon(t_{i-2}-t_0)]\rangle[-\hat{w}_L(\epsilon)\hat{q}_{LR}(\epsilon)-\hat{w}_R(\epsilon)\hat{q}_{RR}(\epsilon)]\langle\exp[-\bar{p}(t_{l-2}-t_0)]\rangle\times[-\hat{w}_L(\bar{p})\hat{q}_{LR}(\bar{p})-\hat{w}_R(\bar{p})\hat{q}_{RR}(\bar{p})]. \tag{3.21}$$

Note that there is no contribution from the terms that contain LL and RL, because then $\theta_i=0$ and $\theta_{i+l}=0$. These terms describe the events where the particle exits from the left-hand side of the channel and hence is not counted by the counter on the right-hand side of the channel.

For i even and l odd, we determine θ_i and θ_{i+l} from a full-channel time and a waiting time, respectively. In this case, we have

$$C(i\text{ is even, }i+l\text{ is odd})=\langle\exp[-\epsilon(t_{i-2}-t_0)]\rangle[-\hat{w}_L(\epsilon)\hat{q}_{LR}(\epsilon)-\hat{w}_R(\epsilon)\hat{q}_{RR}(\epsilon)]\langle\exp[-\bar{p}(t_{l-1}-t_0)]\rangle\hat{w}_R(\bar{p}). \tag{3.22}$$

For i odd and l even, we have

$$\begin{aligned} C(i \text{ is odd, } i+l \text{ is odd}) &= \langle \exp[-\epsilon(t_{i-1}-t_0)]\rangle[\hat{w}_R(\epsilon)\hat{q}_{RL}(\bar{p}) \\ &\quad + \hat{w}_R(\epsilon)\hat{q}_{RR}(\bar{p})]\langle \exp[-\bar{p}(t_{l-2}-t_0)]\rangle \hat{w}_R(\bar{p}). \end{aligned} \tag{3.23}$$

Here the sign of θ_i and θ_{i+l} is determined by the waiting times.

For i odd and $l>1$ and odd, we have

$$\begin{aligned} C(i \text{ is odd, } i+l \text{ is even, } l>1) &= \langle \exp[-\epsilon(t_{i-1}-t_0)]\rangle[\hat{w}_R(\epsilon)\hat{q}_{RL}(\bar{p}) \\ &\quad + \hat{w}_R(\epsilon)\hat{q}_{RR}(\bar{p})]\langle \exp[-\bar{p}(t_{l-3}-t_0)]\rangle \\ &\quad \times[-\hat{w}_L(\bar{p})\hat{q}_{LR}(\bar{p})-\hat{w}_R(\bar{p})\hat{q}_{RR}(\bar{p})]. \end{aligned} \tag{3.24}$$

Here θ_i is determined by a waiting time, while θ_{i+l} is determined by a full channel time. For i *odd and* $l=1$, we have

$$C(i \text{ is odd, } l=1) = \langle \exp[-\epsilon(t_{i-1}-t_0)]\rangle \times[-\hat{w}_R(\epsilon)\hat{q}_{RR}(\bar{p})]. \tag{3.25}$$

2. *Calculation of* $\langle \Sigma_+^1 \rangle$

We now find the exact expression for $\langle \Sigma_+^1 \rangle$ by summing the correlation functions $C(i,i+l)$ (3.21)–(3.25). We use the identity

$$\begin{aligned} \langle \Sigma_+^1 \rangle &= \sum_{i=1}^{\infty}\sum_{l=1}^{\infty} C(2i,2(i+l)) + \sum_{i=1}^{\infty}\sum_{l=0}^{\infty} C(2i,2(i+l)+1) \\ &\quad + \sum_{i=0}^{\infty}\sum_{l=1}^{\infty} C(2i+1,2(i+l)+1) \\ &\quad + \sum_{i=0}^{\infty}\sum_{l=0}^{\infty} C(2i+1,2(i+l+1)) \end{aligned} \tag{3.26}$$

and Eqs. (3.12) and (3.13) to get

$$\begin{aligned} \langle \Sigma_+^1 \rangle &= \frac{1}{1-C(\epsilon)}\left\{ -\hat{w}_R(\epsilon)\hat{q}_{RR}(\bar{p}) + \frac{1}{1-C(\bar{p})} \right. \\ &\quad \left. \times[G(\epsilon,\bar{p})+H(\epsilon)][\hat{w}_R(\bar{p})+H(\bar{p})] \right\}, \end{aligned} \tag{3.27}$$

where we have defined

$$\begin{aligned} G(\epsilon,p) &\equiv \hat{w}_R(\epsilon)[\hat{q}_{RL}(p)+\hat{q}_{RR}(p)], \\ H(p) &\equiv -\hat{w}_L(p)\hat{q}_{LR}(p)-\hat{w}_R(p)\hat{q}_{RR}(p). \end{aligned} \tag{3.28}$$

C. The limit $\epsilon \to 0$

The spectral density is now determined from Eq. (3.4). According to Eqs. (3.6) and (3.9),

$$S(I,\omega) = 2\lim_{\epsilon\to 0}\epsilon\left\langle \Sigma_0\left(\frac{\epsilon}{2}-i\omega\right)\right\rangle + 4\lim_{\epsilon\to 0}\epsilon \mathrm{Re}\left\langle \Sigma_+\left(\frac{\epsilon}{2}-i\omega\right)\right\rangle. \tag{3.29}$$

We consider each term separately. First, from Eqs. (3.15) and (3.16),

$$2\lim_{\epsilon\to 0}\epsilon\langle \Sigma_0\rangle = \frac{2}{\langle t_P\rangle}[\hat{w}_R(0)+\hat{w}_R(0)\hat{q}_{RR}(0)+\hat{w}_L(0)\hat{q}_{LR}(0)]. \tag{3.30}$$

Note that in this calculation, the factor $\langle \exp(-\epsilon t_0)\rangle$ has been omitted. In the limit $\epsilon \to 0$ that factor is the probability that the channel is initially occupied, as was assumed in the calculations above. Similar calculations, conditioned on an initially empty channel, give the same result but with the factor $\lim_{\epsilon\to 0}\langle \exp(-\epsilon t_0)\rangle$ replaced by the probability that the channel is initially empty. It follows that the sum of these two cases is independent of this factor. Thus, in general, it can be set equal to 1.

It can be seen that $\lim_{\epsilon\to 0}\epsilon\langle \Sigma_+^{\theta_0}\rangle = 0$. This is so only if $\omega \neq 0$. Our calculation is restricted to this case. At $\omega=0$ the power spectral density contains a $\delta(\omega)$ multiplied by $\langle I\rangle^2$ [see Eq. (3.1)].

The next term is

$$2\lim_{\epsilon\to 0}\epsilon\langle \Sigma_+^1\rangle = \frac{2}{\langle t_P\rangle}\left\{ -\hat{w}_R(0)\hat{q}_{RR}(i\omega) + \frac{[G(0,i\omega)+H(0)][H(i\omega)+\hat{w}_R(i\omega)]}{1-C(i\omega)} \right\}. \tag{3.31}$$

Equation (3.31) is related to the exact expression needed for the calculation of the spectral density,

$$\lim_{\epsilon\to 0}\epsilon\langle \Sigma_+\rangle = \lim_{\epsilon\to 0}\epsilon\langle \exp(-t_0\epsilon)\rangle\langle \Sigma_+^1\rangle. \tag{3.32}$$

We can now collect all the different terms and get the main result so far

$$\begin{aligned} S(I,\omega) &= \frac{2}{\langle t_P\rangle}[\hat{w}_R(0)+\hat{w}_R(0)\hat{q}_{RR}(0)+\hat{w}_L(0)\hat{q}_{LR}(0)] \\ &\quad + \frac{4}{\langle t_P\rangle}\mathrm{Re}\left[-\hat{w}_R(0)\hat{q}_{RR}(i\omega) + \frac{F(i\omega)}{1-C(i\omega)} \right]. \end{aligned} \tag{3.33}$$

Here we have used the notation

$$F(p) \equiv [G(0,p)+H(0)][H(p)+\hat{w}_R(p)]. \tag{3.34}$$

Recall that the functions $G(0,p)$ and $H(p)$ have been defined in (3.28) and $\langle t_P\rangle$ in Eq. (3.16).

IV. ASYMPTOTIC PROPERTIES OF THE SPECTRAL DENSITY

First, we consider the limit $\omega \to 0$, because in most experimental situations it is easier to measure low frequencies accurately than high. This limit corresponds to the long-time asymptotics of the autocorrelation function of the current fluctuations. Taking the limit $\omega\to 0$ in Eq. (3.33), we get, from Eq. (3.2),

$$K=\langle I_{LR}\rangle+\langle I_{RL}\rangle+\frac{\langle t_P^2\rangle\langle I\rangle^2}{\langle t_P\rangle}+\frac{2\langle I\rangle}{\langle t_P\rangle}[X_{RL}-X_{LR}], \tag{4.1}$$

where

$$X_{ii^c}\equiv\hat{w}_i'(0)\hat{q}_{ii^c}(0)+\hat{w}_i(0)$$
$$=-\langle E_i\rangle P(i^c|i)-P(i)\langle F_{ii^c}\rangle, \tag{4.2}$$

the mean unidirectional and net currents $\langle I_{ii^c}\rangle$ and $\langle I\rangle$ are given by Eqs. (2.24) and (2.25), $\langle t_P\rangle$ is defined in Eq. (3.16), and $\langle t_P^2\rangle$ is defined in Eq. (3.17). Note that Eq. (4.1) adds two terms to Eq. (1.4). They reflect the dependence introduced by single occupancy.

The intensity appears to be a quadratic function of the total current flowing through the channel. However, the mean current in Eq. (4.1) is not an independent variable; rather both K and $\langle I\rangle$ are functions of the microscopic times, which in turn are functions of the physical variables that determine these times. In biological applications these may be concentrations and voltage across the channel. Thus Eqs. (2.25) and (4.1) give a nonlinear parametric dependence between the intensity and the mean current.

The expression of the intensity is symmetric in the sense that L and R are interchangeable. Changing the location of the counter does not alter the spectral density at $\omega\to 0$.

Note that the prefactor of $\langle I\rangle^2$ in Eq. (4.1) depends on second moments of the waiting and full-channel times and thus is more dependent on the details of the probability distributions of the microscopical times than the other terms in Eq. (4.1). In the particular case when the waiting times are negligible and so the channel is almost always occupied Eq. (4.1) simplifies significantly. For $\hat{w}_i'(0),\hat{w}''(0)\to 0$, we obtain, from Eqs. (4.1) and (4.2),

$$K=\langle I_{LR}\rangle+\langle I_{RL}\rangle+\frac{\langle\tau_F^2\rangle\langle I\rangle^2}{\langle\tau_F\rangle}$$
$$-\frac{2\langle I\rangle}{\langle\tau_F\rangle}[P(R)\langle F_{RL}\rangle-P(L)\langle F_{LR}\rangle], \tag{4.3}$$

because $\langle\tau_w\rangle\to 0$ in Eq. (2.18). This is a particularly useful equation because $P(i)$ is the probability that a charge enters from side i and can be independent of the dynamics of arrival.

The short-time behavior of the autocorrelation function corresponds to the asymptotic behavior of $S(I,\omega)$ for large ω. For $\omega\to\infty$, we get, using the normalization $\hat{q}_{RR}(0)+\hat{q}_{RL}(0)=1$,

$$\lim_{\omega\to\infty}S(I,\omega)=\frac{2}{\langle t_P\rangle}[\hat{w}_R(0)+\hat{w}_R(0)\hat{q}_{RR}(0)+\hat{w}_L(0)\hat{q}_{LR}(0)]$$
$$=\frac{2}{\langle t_P\rangle}[P(R)+P(R)P(R|R)+P(L)P(R|L)]$$
$$=\frac{2}{\langle t_P\rangle}[2P(R)P(R|R)+P(R)P(L|R)$$
$$+P(L)P(R|L)]. \tag{4.4}$$

In contrast to the case $\omega\to 0$, this result is sensitive to the location of the counter, that is to say, the side on which current is measured. The reason is that at high frequencies the counter is sensitive to the correlations that occur on the microscopic time scale. A factor of 2 multiplies the RR term, hence the RR terms contribute twice as much noise as the RL and LR trajectories. This is expected since the RR terms are counted twice, as they enter the channel and as they exit. The LL trajectories contribute to this expression only through the dependence of the mean pair time $\langle t_P\rangle$ on the full channel times.

A. Saturation

As the interarrival time on one side, say L, becomes shorter, the mean unidirectional current $\langle I_{LR}\rangle$ increases and saturates. From Eq. (2.26) we see that the condition for this saturation is

$$\alpha_L\langle F_L\rangle\gg 1+\alpha_R\langle F_R\rangle$$

and the saturation value is

$$\langle I_{LR}\rangle=\frac{P(R|L)}{\langle F_L\rangle}. \tag{4.5}$$

The mean unidirectional current $\langle I_{RL}\rangle$ decreases to zero as α_L increases indefinitely so that the net mean current $\langle I\rangle$ saturates at the value (4.5) when $\langle I_{RL}\rangle\ll\langle I_{LR}\rangle=P(R|L)/\langle F_L\rangle$. Equation (2.24) then implies the additional condition

$$\alpha_R P(L|R)\ll\alpha_L P(L|R).$$

If charges arrive by diffusion, the rate α_L varies as a function of concentration [see (2.14)]. Thus the current saturates as concentration increases on one side.

In this limit, we recover classical shot noise. Indeed, the net mean current is $\langle I_{LR}\rangle$ [as given in Eq. (4.5)], which is the mean current of classical shot noise with interarrival time τ_{SN} whose mean value is

$$\langle\tau_{SN}\rangle=\frac{\langle F_L\rangle}{P(R|L)}$$

[see Eq. (1.2)]. This is shot noise with nonexponential interarrival times.

In this limit Eq. (4.1) implies that K becomes independent of α_L and reaches saturation as well,

$$\lim_{\alpha_L\to\infty}K=\frac{P(R|L)}{\langle F_L\rangle}\left[1+\frac{P(R|L)\langle F_L^2\rangle}{\langle F_L\rangle^2}-2\frac{\langle F_{LR}\rangle}{\langle F_L\rangle}\right], \tag{4.6}$$

and is thus independent of all arrival rates. That is, the intensity, as a function of concentration on one side of the channel, saturates at the value given in Eq. (4.6). It can be written as (1.3)

$$K=\frac{\langle \tau_{\rm SN}^2\rangle-\langle \tau_{\rm SN}\rangle^2}{\langle \tau_{\rm SN}\rangle^3},$$

where

$$\langle \tau_{\rm SN}^2\rangle=\frac{P(R|L)\langle F_L^2\rangle+2\langle F_L\rangle\langle F_{LL}\rangle}{P^2(R|L)}.$$

A further simplification is obtained if no *cis* trajectories originate from L. Then $\hat{q}_{LL}(x)=0$, $\hat{q}_{LR}(0)=1$, and $\langle F_{LR}\rangle=\langle F_L\rangle$, so that charge carriers flow only from left to right. Equations (4.5) and (4.6) then simplify to

$$\langle I_{LR}\rangle=\frac{1}{\langle F_L\rangle} \tag{4.7}$$

and

$$\lim_{\alpha_L\to\infty} K=\frac{\langle F_L^2\rangle-\langle F_L\rangle^2}{\langle F_L\rangle^3}, \tag{4.8}$$

respectively [2]. For the special case where the full-channel times are described by normalized exponential distributions, we use

$$\hat{q}_{LR}(p)=\frac{\gamma_{LR}}{\gamma_{LR}+p} \tag{4.9}$$

to get $1/\langle F_L\rangle=\gamma_{LR}$, so that

$$\langle I_{LR}\rangle=\gamma_{LR}$$

and

$$\lim_{\alpha_L\to\infty} K=\gamma_{LR}=\langle I_{LR}\rangle, \tag{4.10}$$

which is the classical shot noise relation (1.1).

B. Noise intensity at zero net current

If the mean net current vanishes, the intensity depends only on the mean unidirectional currents as in Eq. (1.4). The mean unidirectional currents, in turn, do not depend on higher-order moments of the times E_i and F_{ij}. Thus the intensity K does not depend on higher-order moments of the waiting and full-channel times if $\langle I\rangle=0$.

In systems of electrochemistry and membrane biology the equilibrium case $\langle I\rangle=0$ occurs when the potential across the system has a particular value. We now determine the noise intensity in this situation. In this case, by Eq. (2.25),

$$\hat{w}_L(0)\hat{q}_{LR}(0)=\hat{w}_R(0)\hat{q}_{RL}(0) \tag{4.11}$$

or

$$P(L)P(R|L)=P(R)P(L|R).$$

When the arrival times are assumed to be described by exponential distributions, condition (4.11) becomes

$$\alpha_L P(R|L)=\alpha_R P(L|R) \tag{4.12}$$

or, using the relation Eq. (2.21),

$$\alpha_R=\alpha_L e^{-\Delta\Phi/kT}. \tag{4.13}$$

Equation (4.13) is called the Nernst equation in physical chemistry [14] and $\Delta\Phi$ is the *reversal potential* (at which the current is zero). Using Eqs. (2.20) and (4.13) in Eq. (4.1), we find that at the reversal potential the intensity is given by

$$K=\frac{2\alpha_L P(R|L)}{1+\alpha_L[\langle F_L\rangle+\langle F_R\rangle e^{-\Delta\Phi/kT}]}. \tag{4.14}$$

If $\alpha_L[\langle F_L\rangle+\langle F_L\rangle e^{-\Delta\Phi/kT}]\ll 1$, Eq. (4.14) reduces to,

$$K=2\alpha_L P(R|L)$$

and if $\alpha_L[\langle F_L\rangle+\langle F_L\rangle e^{-\Delta\Phi/kT}]\gg 1$, the intensity saturates at

$$K=\frac{2P(R|L)}{\langle F_L\rangle+\langle F_R\rangle e^{-\Delta\Phi/kT}}. \tag{4.15}$$

When the mean current is zero, as described in Eq. (2.25), the fluctuations cannot be described by fluctuations in ionic conductance, as defined in membrane physiology [15,16,7], because at the reversal potential conductance does not produce current.

Although K in Eq. (4.15) appears independent of concentration, it should be borne in mind that the potential $\Phi(x)$, the mean full channel times $\langle F_L\rangle$ and $\langle F_R\rangle$, and the probability $P(R|L)$ depend on the concentrations [17]. Nonetheless, it is an experimental fact that in many biological channels the reversal potential $\Delta\Phi$ in Eq. (4.13) does not change noticeably with concentrations if α_L/α_R is held constant [see Eq. (2.14)] [7].

C. The shape of the spectral density in symmetric systems

To investigate the shape of the power spectral density function $S(I,\omega)$, we consider a simplified idealized symmetric system in which

$$\begin{gathered}\hat{w}_R(p)=\hat{w}_L(p)\equiv\hat{w}(p),\quad \hat{w}(0)=\tfrac{1}{2},\\ \hat{q}_{LL}(p)=\hat{q}_{RR}(p)\equiv\hat{q}_{cis}(p),\\ \hat{q}_{LR}(p)=\hat{q}_{RL}(p)\equiv\hat{q}_{trans}(p),\\ \hat{q}_{cis}(0)+\hat{q}_{trans}(0)=1.\end{gathered} \tag{4.16}$$

These conditions can occur if the concentrations of charge carriers are the same on both sides of the channel [see Eq. (2.14)] and the potential in the channel is symmetric, that is, if the channel is located between the points $x=-d$ and d, then $\Phi(-x)=\Phi(x)$. In this case $\langle I\rangle=0$. This does not mean that the unidirectional currents vanish; indeed, these currents are the source of fluctuations. Defining $\hat{Q}(i\omega)\equiv\hat{q}_{cis}(i\omega)+\hat{q}_{trans}(i\omega)$ and using the result Eq. (3.33), we find that in this model the spectral density is

$$S(I,\omega)=\frac{2}{\langle t_P\rangle}\left\{1+\mathrm{Re}\left[-\hat{q}_{cis}(i\omega)-\frac{[\hat{Q}(i\omega)-1]^2\hat{w}(i\omega)}{1-2\hat{w}(i\omega)\hat{Q}(i\omega)}\right]\right\}. \tag{4.17}$$

The two limits $\omega\to 0$ and $\omega\to\infty$ are given by

$$\lim_{\omega\to 0} S(I,\omega)=\frac{2}{\langle t_P\rangle}\hat{q}_{trans}(0)\leq\lim_{\omega\to\infty} S(I,\omega)=\frac{2}{\langle t_P\rangle}. \tag{4.18}$$

We now consider in some detail the case when ω is small. We write

$$S(I,\omega)=\frac{2}{\langle t_P\rangle}\hat{q}_{trans}(0)+\frac{\omega^2}{\langle t_P^2\rangle}S_2+o(\omega^3), \tag{4.19}$$

where

$$S_2=\langle t_P\rangle\hat{q}''_{cis}(0)-\frac{\hat{Q}'(0)}{2\langle t_P\rangle}\{[4\hat{w}'(0)+\hat{Q}'(0)]\hat{Q}''(0)+2\hat{Q}'(0)[4\hat{w}'^2(0)-\hat{w}''(0)]\}.$$

The sign of S_2 determines whether the spectral density is a decreasing or increasing function of ω near $\omega=0$. We consider first the case when the arrival times are exponentially distributed. For this case $4\hat{\omega}'^2_{\exp}(0)-\hat{\omega}''_{\exp}(0)=0$; hence

$$S_2^{\exp}=\langle t_P\rangle\hat{q}''(0)_{cis}-\frac{\hat{Q}'(0)}{2\langle t_P\rangle}[4\hat{w}'_{\exp}(0)+\hat{Q}'(0)]\hat{Q}''(0). \tag{4.20}$$

This expression shows that the behavior of the spectral density changes when $S_2^{\exp}$ changes sign. The first term on the right-hand side of Eq. (4.20) is always positive, whereas the second is negative. If *cis* trajectories are not dominant in the process (i.e., the first term can be neglected), the spectral density is a decreasing function of ω near to $\omega=0$.

In the particular case where all processes, including the full-channel times, are exponentially distributed the Laplace transforms of the defective densities are

$$\hat{q}_{cis}(p)=\frac{\gamma_c}{\gamma+p},\quad \hat{q}_{trans}(p)=\frac{\gamma_t}{\gamma+p},\quad \hat{w}_i(p)=\frac{\alpha_0}{2\alpha_0+p}, \tag{4.21}$$

where $\gamma=\gamma_c+\gamma_t$ is the rate that determines the full-channel time. For this case

$$\langle t_P\rangle=\frac{1}{2\alpha_0}+\frac{1}{\gamma}.$$

A simple calculation gives the spectral density

$$S(I,\omega)=\frac{2}{\langle t_P\rangle}\left\{\frac{\omega^4+\omega^2(2\gamma^2+2\alpha_0^2+2\alpha_0\gamma-\gamma_c\gamma)+\gamma(\gamma+2\alpha_0)^2(\gamma-\gamma_c)}{[(\gamma+2\alpha_0)^2+\omega^2][\gamma^2+\omega^2]}\right\}. \tag{4.22}$$

Two types of behavior are observed. When the *cis* trajectories are dominant (i.e., $\gamma\simeq\gamma_c$), the spectral density is a monotonically increasing function of ω (for positive ω). When the *trans* trajectories become dominant, the spectral density is not monotonic; in fact, it has one extremum, a minimum in Fig. 2. For small ω Eq. (4.22) gives

$$S(I,\omega)=\frac{4\alpha_0(\gamma-\gamma_c)}{(2\alpha_0+\gamma)^2}+\omega^2\frac{4\alpha_0}{(2\alpha_0+\gamma)^3\gamma^2}\times[\gamma_c(2\alpha_0+\gamma)^2-2\alpha_0\gamma(\alpha_0+\gamma)]+o(\omega^3).$$

As γ_c traverses the critical value

$$\gamma_c^{\text{critical}}\equiv\frac{2\alpha_0\gamma(\alpha_0+\gamma)}{(2\alpha_0+\gamma)^2} \tag{4.23}$$

a transition occurs from a decreasing to an increasing spectral density near $\omega=0$.

Next, we consider another symmetrical case where the defective distribution functions describing the full-channel times are insensitive to the initial location of the particle. This means that once the particle has entered the channel the direction from which it entered is forgotten. This situation occurs, for example, if there are potential wells at the entrances to the channel. For this case, and when all defective distributions are exponentially distributed, memory plays no role. This case is characterized by

$$\hat{q}_{LL}(p)=\hat{q}_{RL}(p)\equiv\hat{q}_L(p),\quad \hat{q}_{RR}(p)=\hat{q}_{LR}(p)\equiv\hat{q}_R(p). \tag{4.24}$$

The above assumption means that once the particle has entered the channel, it (and the environment) instantaneously forgets the path in phase space it had followed prior to the entrance of the charge carrier into the channel. This can occur, for example, if the charge carrier is trapped in a deep potential well in which thermalization is reached very quickly.

Under the above assumptions, the following four functions determine the properties of the spectral density:

$$\hat{q}_i(p)=\frac{\gamma_i}{\gamma+p},\quad \hat{w}_i(p)=\frac{\alpha_i}{\alpha+p}. \tag{4.25}$$

Here α_i is the rate of arrival from the side i and γ_j is the rate with which a particle exit the channel on side j. We denote $\gamma\equiv\gamma_L+\gamma_R$ and $\alpha\equiv\alpha_L+\alpha_R$. The general result (3.33) reduces to

$$S(I,\omega)=\frac{2(\gamma\alpha_r+\alpha\gamma_r)}{(\gamma+\alpha)}-\frac{4(\alpha_r+\gamma_r)(\gamma^2\alpha_r+\alpha^2\gamma_r)}{(\alpha+\gamma)[(\alpha+\gamma)^2+\omega^2]}\,. \tag{4.26}$$

This spectral density is a combination of a white-noise term and an inverted Lorenzian. Hence, for the case where both *cis* and *trans* trajectories exist, the spectral density always increases close to $\omega=0$.

D. Intensity in a symmetric channel

The intensity varies in a complex way in an interacting system like this even in the simplified case of a symmetric channel. We assume that

$$\hat{q}_{LR}(p)=\hat{q}_{RL}(p),\quad \hat{q}_{LL}(p)=\hat{q}_{RR}(p),$$

but the empty-channel times are not equal, that is,

$$\hat{w}_L(p)\neq\hat{w}_R(p).$$

The statistical properties of the empty-channel times are assumed to be described by

$$\hat{w}_i(p)=\frac{\alpha_i}{\alpha+p},$$

where $\alpha=\alpha_L+\alpha_R$. For this case Eq. (4.1) is

$$K=A_1+A_2\langle I\rangle^2,\quad A_1\equiv\frac{\alpha\hat{q}_{LR}(0)}{1+\alpha\langle t_{\rm ch}\rangle},$$

$$A_2\equiv\frac{\alpha\langle t_{\rm ch}^2\rangle}{1+\alpha\langle t_{\rm ch}\rangle}-2\langle t_{trans}\rangle, \tag{4.27}$$

where

$$\langle t_{\rm ch}\rangle\equiv-\hat{q}'_{LR}(0)-\hat{q}'_{LL}(0),\quad \langle t_{\rm ch}^2\rangle\equiv\hat{q}''_{LR}(0)+\hat{q}''_{LL}(0),$$

$$\langle t_{trans}\rangle\equiv-\frac{\hat{q}'_{LR}(0)}{\hat{q}_{LR}(0)}.$$

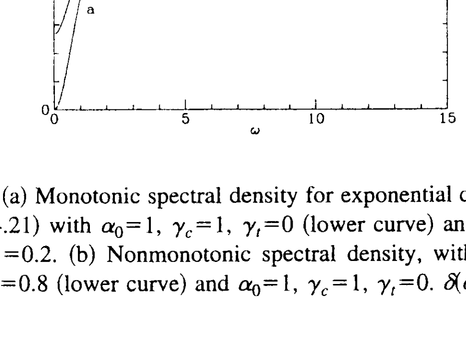

FIG. 2. (a) Monotonic spectral density for exponential defective densities (4.21) with $\alpha_0=1$, $\gamma_c=1$, $\gamma_t=0$ (lower curve) and $\alpha_0=1$, $\gamma_c=0.8$, $\gamma_t=0.2$. (b) Nonmonotonic spectral density, with $\alpha_0=1$, $\gamma_c=0.2$, $\gamma_t=0.8$ (lower curve) and $\alpha_0=1$, $\gamma_c=1$, $\gamma_t=0$. $\delta(\omega)$ is not shown.

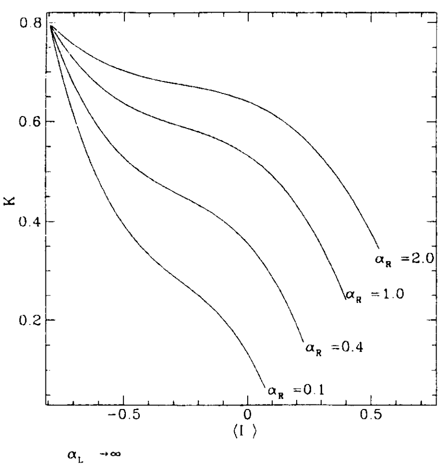

FIG. 3. Intensity vs mean current with $\hat{q}_{LR}(p)=\hat{q}_{RL}(p)=\gamma_t/(\gamma_t+\gamma_c+p)$, $\hat{q}_{LL}(p)=\hat{q}_{RR}(p)=\gamma_c/(\gamma_t+\gamma_c+p)$, and $\hat{w}_i(p)=\alpha_i/(\alpha_L+\alpha_R+p)$. $0\leq\alpha_L<\infty$, $\gamma_c=0.2$, and $\gamma_t=0.8$. α_R is shown in the figure.

Note than when varying both α_L and α_R while keeping $\alpha_L+\alpha_R$ fixed, the K vs $\langle I\rangle$ curve has the shape of a parabola. When $A_2<0$, the intensity achieves its maximum at $\langle I\rangle=0$. Such behavior does not occur if the unidirectional fluxes are independent. The graph of intensity vs mean current is shown in Fig. 3. In Fig. 3 only the rate of arrival α_L is varied while the other rates are kept constant. Note that the intensity does not always increase with $|\langle I\rangle|$. As $\langle I\rangle$ changes from positive to negative, K keeps decreasing (see explanation below). This is also the a feature of Eq. (1.4). As discussed in Sec. IV, the intensity saturates as $\alpha_L\to\infty$. Note further that the current saturates so that the graph cannot be extended beyond a limiting value. When $\alpha_L\to\infty$ the physical interactions and empty-channel times are not important. Even so, our result does not reduce to generalized shot noise due to the existence of the *cis* trajectories.

The case where the mean current $\langle I\rangle$ and channel times are held fixed and the rates of arrival α_L and α_R are varied is shown in Fig. 4. It can be seen that the intensity of the process always increases as $\alpha=\alpha_L+\alpha_R$ is increased. This can be proved directly from Eq. (4.27), for the more general case where channel times are not assumed exponentially distributed. For exponentially distributed channel times, intensity curves decrease with $\langle I\rangle$ (i.e., $A_2<0$). When the rate α is increased, the mean current $\langle I\rangle$ can either decrease or increase. Hence K does not always increase when $\langle I\rangle$ is increased (also see Fig. 3) because K reflects the total number of events rather than the excess of RL over LR charge carriers, i.e., the current.

E. *RR* trajectories only

Stratonovich [4] considers the case of the derivative of the random telegraph signal [1]. This counter is analogous to that for a channel with only RR trajectories, which occurs, for example, if the left-hand side of the channel is blocked. Then, only two normalized distribution functions are needed to describe the channel, $\hat{q}_{RR}(p)\equiv\hat{q}(p)$, $P(R|R)=1$ and $\hat{w}_R(p)\equiv\hat{w}(p)$, $P(R)=1$. For this special case Eq. (3.33) reduces to

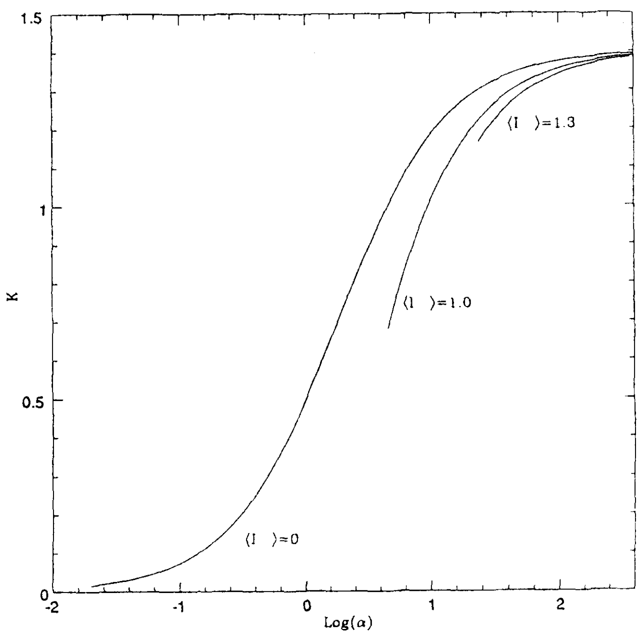

FIG. 4. Intensity vs log(α) for $\langle I\rangle$ constant. Defective densities are given in the caption to Fig. 3. Here $\gamma_c=0.4$ and $\gamma_t=1.4$. When $\langle I\rangle\neq 0$, α is bounded from below.

$$S(I,\omega)=\frac{4}{\langle t_P\rangle}\operatorname{Re}\left\{\frac{[1-\hat{q}(i\omega)][1-\hat{w}(i\omega)]}{1-\hat{w}(i\omega)\hat{q}(i\omega)}\right\}. \quad (4.28)$$

In this case $\langle t_P\rangle=-\hat{q}'(0)-\hat{w}'(0)$, that is, it is the sum of the mean full-channel time and the mean waiting time. Our result (4.28) reproduces that in [4].

V. THE CASE OF SEVERAL CHARGE CARRIER SPECIES: A BIOLOGICAL APPLICATION

Consider the case where different kinds of charge carrier species are kept at fixed concentrations on either side of the channel. In this case there are several currents flowing through the channel. This is the usual biological situation and describes the natural function of many biological membranes in nerve, muscle, and other cells [8,7].

We restrict our calculation to the case of only two species, both carrying identical charge. The full situation will be analyzed in a subsequent paper dealing with specific biological experiments. We present the stochastic core here in the context of our derivation and theory.

As in the previous calculation, the channel can be occupied by at most one charge carrier at a time. In the two species case, a typical sequence of time intervals is

$$\{\ldots;E_L^1,F_{LR}^1;\ldots;E_L^1,F_{LL}^1;E_R^2,F_{RL}^2;\ldots;E_R^2,F_{RR}^2;\ldots\}.$$

Here the upper index 1 or 2 identifies the charge carrier. Because both charge carriers carry the same charge, the counter is insensitive to the identity of the two particles. In this case our previous definitions of the counting process can be used for the multiple charge carrier case. The difference between the one charge carrier case and the two charge carrier case are the additional waiting and full-channel times that we consider below.

Four defective densities $w_i^\beta(t)$ ($\beta=1,2$) normalized by $\Sigma_{\beta=1,2}\Sigma_{i=L,R}\hat{w}_i^\beta(0)=1$, determine the waiting times. The probability that a particle arrives from i and is of type β is $\hat{w}_i^\beta(0)$. The statistical properties of the full-channel times are given by the defective distributions $q_{ij}^\beta(t)$. In terms of the Laplace transform the normalization of these functions is $\Sigma_{j=L,R}\hat{q}_{ij}^\beta(0)=1$. Therefore 12 functions describe the statistical properties of the waiting and full-channel times.

The calculation carried out above for a single species is now repeated for the case of two species. It does not impose any special difficulties. In Appendix B we give the calculation of $\langle\exp[-\epsilon(t_{2n}-t_0)]\rangle$ for the multiple species case; other parts of the calculation are straightforward. We therefore give the final result for this important case,

$$\begin{aligned}S(I,\omega)=&\frac{2}{\langle t_P\rangle}\sum_{\beta=1,2}[\hat{w}_R^\beta(0)+\hat{w}_R^\beta(0)\hat{q}_{RR}^\beta(0)\\&+\hat{w}_L^\beta(0)\hat{q}_{LR}^\beta(0)]+\frac{4}{\langle t_P\rangle}\\&\times\operatorname{Re}\left[-\sum_{\beta=1,2}\hat{w}_R^\beta(0)\hat{q}_{RR}^\beta(i\omega)+\frac{F(i\omega)}{1-C(i\omega)}\right].\end{aligned} \quad (5.1)$$

In this case

$$C(\epsilon)=\sum_{\beta=1,2}\sum_{i=L,R}\hat{w}_i^\beta(\epsilon)[\hat{q}_{iL}^\beta(\epsilon)+\hat{q}_{iR}^\beta(\epsilon)].$$

As in the case of a single species, $\langle t_P\rangle$ and $F(i\omega)$ are defined by Eqs. (3.16) and (3.34), respectively. The functions $G(\,)$ and $H(\,)$, which define $F(p)$, are given by

$$G(0,p)=\sum_{\beta=1,2}\hat{w}_R^\beta(0)[\hat{q}_{RL}^\beta(p)+\hat{q}_{RR}^\beta(p)],$$

$$H(p)=-\sum_{\beta=1,2}\hat{w}_L^\beta(p)\hat{q}_{LR}^\beta(p)-\sum_{\beta=1,2}\hat{w}_R^\beta(p)\hat{q}_{RR}^\beta(p). \quad (5.2)$$

A generalization of (5.1) to the case where more than two charge carrier species with identical charges can occupy the channel is straightforward. Generalizations to cases where charge carriers of different charges can occupy the channel are also possible. In this case the counting function θ_i assumes different values for different charge carriers.

If interarrival times are exponentially distributed with rates α_i^1,α_i^2 ($i=L,R$), we have

$$\hat{w}_i^j(p)=\frac{\alpha_i^j}{\sum_{i=L,R}\sum_{j=1,2}\alpha_i^j+p}\quad(i=L,R;\ j=1,2).$$

It follows that

$$\langle t_P\rangle=-C'(0)=\langle\tau_w\rangle+\langle\tau_F\rangle, \quad (5.3)$$

where, as in Eqs. (2.10)–(2.15),

$$\langle \tau_w \rangle = \frac{1}{\sum_{i=L,R} \sum_{j=1,2} \alpha_i^j}, \quad \langle \tau_F \rangle = P^j(i) \langle F_i^j \rangle, \tag{5.4}$$

and

$$P^j(i) = \frac{\alpha_i^j}{\sum_{i=L,R} \sum_{j=1,2} \alpha_i^j} \quad (i=L,R;\ j=1,2). \tag{5.5}$$

The current is given, as in Eq. (2.26), by

$$\langle I \rangle = \langle I_{LR} \rangle - \langle I_{RL} \rangle, \tag{5.6}$$

where the unidirectional currents are given by

$$\langle I_{LR} \rangle = \frac{\alpha_L^1 P^1(R|L) + \alpha_L^2 P^2(R|L)}{\Delta},$$

$$\langle I_{RL} \rangle = \frac{\alpha_R^1 P^1(L|R) + \alpha_R^2 P^2(L|R)}{\Delta}, \tag{5.7}$$

and

$$\Delta = 1 + \sum_{i=L,R} \sum_{j=1,2} \alpha_i^j \langle F_i^j \rangle. \tag{5.8}$$

For each species, $P^j(R|L)$ and $P^j(L|R)$ are given in the appropriate version of Eq. (2.20).

The noise intensity is given by Eq. (4.1) with $\langle t_P \rangle$, $\langle I \rangle$, $\langle I_{LR} \rangle$, and $\langle I_{RL} \rangle$ given in Eqs. (5.3)–(5.7) and

$$X_{ii^c} = -\sum_{j=1,2} P^j(i)[P^j(i^c|i)\langle \tau_w \rangle + \langle F_{ii^c}^j \rangle] \quad (i=L,R), \tag{5.9}$$

where $P^j(i)$ are given in Eq. (5.5), $P^j(i^c|i)$ in the appropriate version of Eq. (2.20), and $\langle F_{ii^c}^j \rangle$ are the mean time that *trans* charge carriers of either species spend in the channel (see [6]). This analysis will be exploited in future work to predict the power spectrum of noise observed in the presence of several charge carrier species in biological channels.

VI. SUMMARY AND DISCUSSION

In summary, we have developed a theory of noise for a single occupancy channel where *cis* and *trans* trajectories exist, given the statistics of the interarrival and full-channel times. The latter times have to be determined from separate theories. Some general features of the model, however, are independent of the details of the statistics. These are saturation, the nonlinearity in the dependence of intensity on mean current, fluctuations at zero mean current, and so on.

Saturation of intensity and mean current is found. This is due to the existence of two types of dynamics. When the arrival time increases, the finite channel time will cause the saturation and vice versa. The intensity and mean current depend on the channel and arrival times. This results in a general nonlinear parametric dependence between intensity and mean current. The properties of the power spectral density at $\omega \to 0$ do not depend on the location of the measuring device. Properties at high frequencies do.

The intensity of the noise in our model differs from that given in Eq. (1.4) for two independent shot noises. It contains additional terms that arise from the competition for the single occupancy channel.

The two typical shapes (for the symmetrical-exponential case) of the spectral density are monotonic and nonmonotonic. We have searched numerically for other shapes using the general result Eq. (3.33), assuming that exponential distributions describe channel and arrival times. For this case (3.33) depends on a set of six rates $(\alpha_L, \alpha_R, \gamma_{LR}, \gamma_{LL}, \gamma_{RL}, \gamma_{RR})$. We looked at 10 000 randomly chosen sets of interarrival and full-channel times. Each of the rates was in the interval $(0,1]$. We have not found in this limited search any qualitatively different shape other than those presented here.

For the general case K depends on six different probability densities describing the waiting times and the full-channel times. For the relatively simple case, when all processes are exponential, the result is controlled by six parameters. Our model does not reduce in this case to the usual rate model for biological channels [9]. To see this, note that the full-channel times are described in Eqs. (2.19) and (4.9) by four rates γ_{ij} $(i,j=L,R)$ that depend on the original location of the particle. Only when the full-channel times do not depend on the origin of the particle does our theory reduce to traditional rate theory of a singly occupied channel [7].

Our immediate goal in writing this paper was to describe the shot noise through a single file biological channel. The protein channels of biological membranes are a particularly well studied and interesting single file system [7,8]. These channel proteins have a hole down their middle that forms the channel's pore filled with a file of water molecules and charge carriers, typically sodium, potassium, or chloride. The hole is narrow enough to confer significant selectivity to the system and only one charge carrier can occupy the narrow region of the channel at a time. Because these channels regulate the movement of salts and charge across the membranes of cells, they are responsible for much of the behavior of many types of cells, whether nerve, muscle, cardiac, or epithelial. Many drugs act on protein channels, directly or indirectly, and they have been studied medically and biologically for more than a century.

Measurements can be made from ionic channels one molecule at a time using the patch clamp method [18]. The mean values of the current flow through such single channels can be predicted [17] by self-consistent theories of diffusion in an electric field akin to the drift diffusion equations of semiconductor (and much other) physics. One of the striking characteristics of single channels is the fluctuations in their current and those fluctuations change dramatically when slow charge carriers (e.g., blockers, [7]) are present. Although the fluctuations (often called "open channel noise" or "open channel block") have been studied extensively in Sigworth, Miller, and Yellen's laboratories [15,19,20] and elsewhere [16], theoretical analysis has (for the most part) used transition state theories that assume large barriers for current flow [9]. Recently, we [6] have learned how to compute the flux over barriers of any size or shape and how to compute the statistics of the underlying charge movements, e.g., the first-passage time and contents of the channel, but that theory did not predict the fluctuations in the current. Here we extend the analysis to a single occupancy model of a channel, relating the passage times (etc.) to the fluctuations in current. In later papers, we plan to relate the passage times to the structure of the channel and use the present results to predict the fluctuations in current observed experimentally. Theories of the mean current and theories of the fluctuating current use almost the same parameters and so a theory of the mean current should be able to predict the fluctuations, with no (additional) adjustable parameters, and it should be able to predict the response to trace concentrations of slow charge carriers *of a range of concentrations and concentration gradients* with one or two additional parameters. Specific predictions of such a wide range of experimental behavior provide a severe test of any theory and are our ultimate goal.

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APPENDIX A: CALCULATION OF $\langle\exp[-(t_{2n}-t_0)\epsilon]\rangle$

A sequence of $2n$ intervals consists of the following: (i) n waiting times for which there are (a) $0\leq k\leq n$ waiting times of the type L and (b) $n-k$ waiting times of the type R and (ii) n full-channel times out of which (a) $0\leq j\leq k$ are of the LR type and $k-j$ are of the LL type and (b) $0\leq m\leq n-k$ are of the RR type and $n-k-m$ are of the RL type. To determine $\langle\exp[-(t_{2n}-t_0)\epsilon]\rangle$, we partition the time interval $t_{2n}-t_0$ into $2n$ subintervals. The averaging procedure consists in integration over all time intervals, as well as summing over all possible arrangements, as specified. We obtain

$$\langle\exp[-(t_{2n}-t_0)\epsilon]\rangle=\langle\exp[-(E^1+F^2+E^3\cdots)]\epsilon\rangle.$$

Here E^i and F^j are empty- and full-channel times. Next, we introduce the classes enumerated above and the corresponding defective distribution functions defined previously in Sec. II. Averaging over all possible sequence of time intervals, we get

$$\langle\exp[-(t_{2n}-t_0)\epsilon]\rangle=\sum_{k=0}^{n}\sum_{j=0}^{k}\sum_{m=0}^{n-k}\binom{n}{k}\hat{w}_L^k(\epsilon)\hat{w}_R^{n-k}(\epsilon)\times\binom{k}{j}\hat{q}_{LR}^j(\epsilon)\hat{q}_{LL}^{k-j}(\epsilon)\times\binom{n-k}{m}\hat{q}_{RR}^m(\epsilon)\hat{q}_{RL}^{n-k-m}(\epsilon). \quad (A1)$$

Using this expression it can be shown that

$$\langle\exp[-(t_{2n}-t_0)\epsilon]\rangle=C^m(\epsilon),$$

where

$$C(\epsilon)=\sum_{i=L,R}\hat{w}_i(\epsilon)[\hat{q}_{ii^c}(\epsilon)+\hat{q}_{ii}(\epsilon)]. \quad (A2)$$

APPENDIX B: CALCULATION OF $\langle\exp[-(t_{2n}-t_0)\epsilon]\rangle$ FOR TWO SPECIES

A sequence of $2n$ intervals consists of the following: (i) n waiting times for which there are (a) $0\leq l_1\leq n$ waiting times of type L^1, (b) $0\leq l_2\leq n-l_1$ waiting times of type L^2, (c) $0\leq r_1\leq n-l_1-l_2$ waiting times of type R^1, and (d) $r_2=n-l_1-l_2-r_1$ waiting times of type R^2 and (ii) n full-channel times, out of which (a) $0\leq j^1\leq l^1$ are of type LR^1 and l^1-j^1 are of type LL^1, (b) $0\leq j^2\leq l^2$ are of type LR^2 type and l^2-j^2 are of type LL^2, (c) $0\leq s^1\leq r^1$ are of type RR^1 and r^1-s^1 are of type RL^1, and (d) $0\leq s^2\leq r^2$ are of type RR^2 and r^2-s^2 are of type RL^2. Using the same method as in Appendix A, we get

$$\langle\exp[-(t_{2n}-t_0)\epsilon]\rangle=C^n(\epsilon),$$

where $C(\epsilon)$ is given in Eq. (5.2).

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