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# SHOT NOISE IN ION CHANNELS

P. LÄUGER

*Department of Biology, University of Konstanz, 775 Konstanz (G.F.R.)*

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## SUMMARY

A theoretical treatment of electrical noise originating from the discontinuous movement of ions through pore-like channels in a membrane is given. Two simple models are considered, a pore with a single energy barrier and a pore with a single binding site separated from the aqueous solutions by energy barriers on either side. The single-barrier pore acts as a white-noise source with a spectral density $S_J$ of the current that is proportional to the total rate of jumps over the barrier. At voltages near the equilibrium potential of the permeable ion, $S_J$ becomes equal to the spectral density of thermal (or Johnson) noise. On the other hand, in the limit of high voltages, $S_J$ approaches the spectral density of a Schottky noise source. A similar behaviour is found for channels with a double barrier in the limit of low frequencies $\omega$. At higher frequencies a dispersion of the spectral density near $\omega = 1/\tau_1$ occurs, where $\tau_1$ is the average lifetime of the occupied state of the channel.

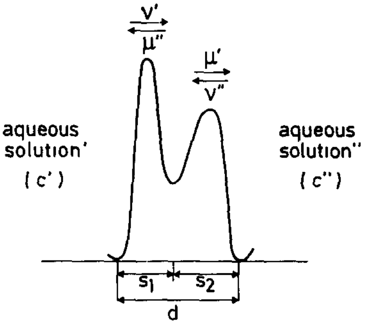
## INTRODUCTION

From the analysis of electrical noise which is associated with ion transport through membranes, information on the transport mechanism may be obtained. This possibility has prompted a number of experimental investigations in recent years. Extensive noise measurements have been carried out with nerve membranes [1–6] and with cholinergic synapses [7–9]. Similar studies have also been done with a membrane preparation involved in active transport of ions [10, 11] and with artificial lipid bilayer membranes [12, 13]. An excellent review on the experimental and theoretical aspects of noise in biological and artificial membranes has recently been published by Verveen and De Felice [14]. A principal difficulty in the analysis of noise measurements lies in the fact that the noise usually originates from several different sources. Despite numerous efforts [15–20] the theoretical basis for the analysis of the different noise sources in membranes is still incomplete.

In this paper we deal with noise originating from the movement of ions through discrete channels. An ion channel may be represented by a protein molecule which is embedded in the lipid matrix of the membrane and which offers to the ion a hydrophilic pathway through the apolar core of the membrane. Such a channel may be described as a series of binding sites where the ion is in an energetically favourable position and which are separated by activation energy barriers [21] Ions enter and leave the channel in a random fashion and pass through the channel by jumping from one binding site to the next. The electric current associated with the ion movement therefore consists of a sequence of short pulses and exhibits a noise component that is similar to the so-called shot noise in thermionic diodes [14, 18]*. In the following we give a theoretical treatment of shot noise for channels with one and two energy barriers

## DESCRIPTION OF THE MODEL

We assume that the membrane which separates two aqueous electrolyte solutions contains $n_c$ permanently open channels. Ions of only one kind are able to pass through these channels, the rest of the membrane being completely impermeable to ions The interaction of an ion with the channel is described by the potential energy profile of the channel [21] In the following, we restrict ourselves to two simple situations, namely, that the ion passing through the channel has to jump over a single energy barrier or over a double barrier (Fig. 1).



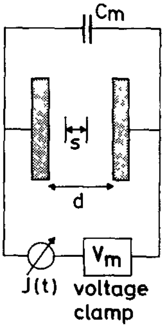


Fig 1 Energy profile of the ion channel $\mu'$, $\mu''$, $\nu'$ and $\nu''$ are the jump rates of the ion over the barriers

Fig. 2 Equivalent circuit of the membrane and the external measuring system

An ion jumping at time $t = 0$ within the channel over an energy barrier induces a current pulse $i(t)$ in the external measuring circuit. In order to calculate $i(t)$ we consider the following model (Fig 2). The membrane is represented by a dielectric sheet of thickness $d$ which is interposed between two conducting phases (the aqueous electrolyte solutions). The external circuit consists of a current meter and a device which clamps the membrane voltage at a preselected value $V_m$ We shall not deal here with instrumental limitations in the detection of the membrane noise; for this reason we treat the external circuit as noiseless and assume that the voltage-clamp device has virtually infinite bandwidth. The jump of the ion over an energy barrier in the membrane may be envisaged as a virtually instantaneous diplacement of a charge of

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* It should be noted that the term 'shot noise' which we use here for noise originating from the discontinuous movement of single charges has also been applied in the literature to the statistical opening and closing of ion channels [5, 7]

magnitude $ze_0$ ($z$ is the valency of the ion and $e_0$ the elementary charge) over a certain distance $\pm s$, normal to the surface of the membrane (Fig. 2). It may be shown by elementary electrostatic considerations that this displacement changes the charge on the membrane capacitance $C_m$ by an amount $q = \pm ze_0 s/d$. This charge is compensated by a current pulse $i(t)$ which is delivered by the voltage-clamp device in order to keep the membrane voltage constant. As we have assumed virtually zero rise-time of the voltage clamp, $i(t)$ has the form of a delta pulse that occurs at time $t = 0$:

$$i(t) = aze_0\delta(t)$$

$$\int_{-\infty}^{\infty} \delta(t)\mathrm{d}t = 1 \tag{1}$$

where $a = s/d$ for a jump from solution′ to solution″ and $a = -s/d$ for a jump from solution″ to solution′ (Fig. 1). The total current in the external circuit is given by the superposition of a large number of (positive or negative) pulses of the form $i(t)$.

## CHANNEL WITH A SINGLE BARRIER

In the simplest case the passage of the ion through the channel is equivalent to a jump over a single energy barrier. The current $J^*(t)$ flowing through a single channel may be generally written as the sum of a mean current $\overline{J^*}$ and a fluctuating current $\delta J^*(t)$:

$$J^*(t) = \overline{J^*} + \delta J^*(t) \tag{2}$$

If the $k$th current pulse $i_k$ occurs at time $t_k$, then $J^*(t)$ is given by

$$J^*(t) = \sum_k i_k(t-t_k) \tag{3}$$

In an actual experiment, the mean square of $\delta J^*(t)$ is measured over a certain interval of frequency $f$ (or angular frequency $\omega = 2\pi f$). The spectrum of the current fluctuations of a single channel is described by the spectral density $S_J{}^*(\omega)$ which is the contribution of the unit frequency interval centered at f to the mean square of $\delta J^*(t)$:

$$\overline{(\delta J^*)^2} = \int_0^{\infty} S_J^*(f)\mathrm{d}f = \frac{1}{2\pi}\int_0^{\infty} S_J^*(\omega)\mathrm{d}\omega \tag{4}$$

In order to calculate $S_J{}^*(\omega)$ we introduce the Fourier transform $\psi(\omega)$ of $i(t)$:

$$\Psi(\omega) = \int_{-\infty}^{\infty} i(t)\mathrm{e}^{-j\omega t}\mathrm{d}t \tag{5}$$

where $j = \sqrt{-1}$. As the single pulses are statistically independent, we may apply the generalized Carson theorem [22–24] which states that the spectral density $S_J{}^*$ is proportional to the mean rate at which the current pulses occur times the ensemble average of $|\Psi(\omega)|^2$:

$$S_J^*(\omega) = 2\nu\,\overline{|\Psi(\omega)|^2} \tag{6}$$

As the Fourier transform of a delta pulse is unity, one obtains from Eqns 1 and 5:

$$|\Psi(\omega)|^2 = (aze_0)^2 \tag{7}$$

If the membrane contains $n_c$ independent channels, then the spectral density of the total current is given by

$$S_J(\omega) = n_c S_J{}^*(\omega) \tag{8}$$

As $\overline{a^2} = s^2/d^2 = 1$ for a channel with a single barrier, Eqns 6–8 together yield

$$S_J(\omega) = 2n_c \nu z^2 e_0{}^2 \tag{9}$$

Thus, at low frequencies ($\omega^2 \tau_e{}^2 \ll 1$) the barrier behaves as a white-noise source with a spectral density

$$S_J(\omega) = S_J{}^0 = 2n_c \nu z^2 e_0{}^2 \tag{10}$$

The total jump rate $\nu$ is the sum of the rates $\nu'$ and $\nu''$ of jumps from solution′ to solution″ and from solution″ to solution′, respectively. Introducing the mean current $\bar{J}$:

$$\bar{J} = n_c \bar{J}^* = n_c(\nu' - \nu'')ze_0 \tag{11}$$

Eqn 10 may be written as

$$S_J^0 = 2ze_0 \bar{J} \frac{\nu' + \nu''}{\nu' - \nu''} \tag{12}$$

If an external voltage $V_m = \varphi' - \varphi''$ is applied to the membrane ($\varphi'$ and $\varphi''$ are the electrical potentials in the left-hand and right-hand solutions), and if $zV_m$ is large, then many more jumps from left to right than from right to left will occur ($\nu' \gg \nu''$). Conversely, for $zV_m \to \infty$, the relation $\nu'' \gg \nu'$ holds. Therefore,

$$S_J^0 = 2e_0 |z\bar{J}| \qquad (|V_m| \to \infty) \tag{13}$$

This is Schottky's equation for the noise generated by a saturated thermionic diode [25].

According to the theory of absolute reaction rates [21], the voltage dependence of $\nu'$ and $\nu''$ is given approximately by

$$\nu' = c'v \frac{kT}{h} e^{-E_0/kT} \cdot e^{zu/2} \tag{14}$$

$$\nu'' = c''v \frac{kT}{h} e^{-E_0/kT} \cdot e^{-zu/2} \tag{15}$$

where $k$ is Boltzmann's constant, $T$ the absolute temperature, $h$ Planck's constant, $E_0$ the barrier height at zero voltage, and $v$ a proportionality factor [26], $c'$ and $c''$ the concentrations of the permeable ion in solutions′ and ″, and $u$ the reduced voltage:

$$u = \frac{V_m}{kT/e_0} \tag{16}$$

The ohmic resistance $R_m$ of the membrane is defined by

$$R_{\mathrm{m}} = \left(\frac{V_{\mathrm{m}} - V_{\mathrm{m}}^{0}}{J}\right)_{V_{\mathrm{m}} \quad V_{\mathrm{m}}} \tag{17}$$

where $V_{\mathrm{m}}{}^{0}$ is the equilibrium potential at which $\bar{J} = ze_0 n_{\mathrm{c}}(v' - v'')$ becomes equal to zero:

$$zV_{\mathrm{m}}^{0} = \frac{kT}{e_0} \ln \frac{c''}{c'} = \frac{kT}{e_0} zu_0 \tag{18}$$

This relation is obtained from Eqns 15 and 16 by putting $v' = v''$. Using Eqns 11 and 15–19, Eqn 10 assumes the form

$$S_J^0 = \frac{4kT}{R_{\mathrm{m}}} \cosh \left[\frac{z}{2}(u - u_0)\right] \tag{19}$$

Thus, for potentials in the vicinity of the equilibrium potential ($u \approx u_0$), Eqn 19 reduces to Nyquist's theorem for thermal noise in a resistance $R_{\mathrm{m}}$ [27]·

$$S_J^0 = 4kT/R_{\mathrm{m}}.$$

## CHANNEL WITH A DOUBLE BARRIER

We now consider a channel with one binding site located between two energy barriers (Fig. 1). For instance, a pore with a single binding site has been proposed by Hille [28] as a model of the sodium channel in nerve. We assume that the ion concentrations $c'$ and $c''$ in the aqueous solutions are sufficiently small, so that a given channel is empty during most of the time. In this case the pulses occur in pairs which are separated by long, irregular time intervals. For instance, a pulse pair may consist in a jump from the left-hand solution into the binding site followed by a jump from the binding site back into the left-hand solution. Under these circumstances the theoretical treatment of current noise is complicated by the fact that the single pulses are no longer statistically independent. A general class of non-Poisson pulse sequences has been analyzed previously by Lukes [29], Heiden [30] and Schick [31]. Their treatment, however, is based on the assumption that the parameters of different pulses are uncorrelated, and is therefore not applicable to the present system.

In the following, we treat a pair of pulses originating from the entry of the ion into the binding site and the subsequent release as a single event which induces in the external circuit a current $i(t)$:

$$i(t) = ze_0[a_i\delta(t) + b_i\delta(t - \tau)] \tag{20}$$

The time interval $\tau$ between the two pulses of a pair has to be considered as a random variable (see below). Furthermore, a given event may be of any one of four classes which differ in the value of the parameters $a_1$ and $b_1$ (compare Fig. 1):

class 1: $a_1 = s_1/d, \quad b_1 = s_2/d$
class 2: $a_2 = -s_2/d, \quad b_2 = -s_1/d$
class 3· $a_3 = s_1/d, \quad b_3 = -s_1/d$
class 4: $a_4 = -s_2/d, \quad b_4 = s_2/d$

Class one corresponds to the entry of the ion from the left-hand solution, followed by the release to the right-hand solution, class two to the entry from the right-hand solution followed by the release to the left-hand solution, and so forth. As the events are statistically independent, we may apply Carsons theorem for the evaluation of $S_J(\omega)$ For this purpose we calculate the Fourier transform $\Psi_1(\omega, \tau)$ of $i(t)$ for an event of class $l$ ($l = 1, 2, 3, 4$) having an interval of length $\tau$ After $i(t)$ is introduced from Eqn 20 into relation 5, forward calculation yields the results

$$|\Psi_l(\omega, \tau)|^2 = z^2 e_0^2 (a_l^2 + b_l^2 + 2 a_l b_l \cos \omega\tau) \tag{21}$$

If $P_l(\tau)\mathrm{d}\tau$ is the joint probability that a given event is of class $l$ and has a pulse interval between $\tau$ and $\tau+\mathrm{d}\tau$, the average of $|\Psi|^2$ is given by

$$\overline{|\Psi(\omega)|^2} = \sum_{l=1}^{4} \int_0^\infty |\Psi_l(\omega, \tau)|^2 P_l(\tau) \mathrm{d}\tau \tag{22}$$

In order to calculate $P_l(\tau)$ we first introduce the probability $p_l$ that a given event is of class $l$, irrespective of the length of the pulse interval $\tau$ $P_l$ is determined by the average rates $\nu'$ and $\nu''$ of jumps from the left-hand and right-hand solutions into the binding site (Fig 1) and by the average rates $\mu'$ and $\mu''$ of jumps out of an occupied site. (If $n_c{}^*$ is the mean number of occupied channels in the membrane, the mean total rate of jumps from the site into the right-hand solution is equal to $n_c{}^*\mu''$) The probabilities $p_l$ are found to be·

$$\begin{aligned}
p_1 &= \frac{\nu'}{\nu'+\nu''} \cdot \frac{\mu'}{\mu'+\mu''} \\
p_2 &= \frac{\nu''}{\nu'+\nu''} \cdot \frac{\mu''}{\mu'+\mu''} \\
p_3 &= \frac{\nu'}{\nu'+\nu''} \cdot \frac{\mu''}{\mu'+\mu''} \\
p_4 &= \frac{\nu''}{\nu'+\nu''} \quad \frac{\mu'}{\mu'+\mu''}
\end{aligned} \tag{23}$$

(For instance, $p_1$ is equal to the probability $\nu'/(\nu'+\nu'')$ that an ion enters the binding site from the left side, times the probability $\mu'/(\mu'+\mu'')$ that the following jump out of the site goes to the right.)

We further define the probability $p(\tau)\mathrm{d}\tau$ that a given event has a pulse interval between $\tau$ and $\tau+\mathrm{d}\tau$. $p(\tau)$ is the same for all classes of events and is given by

$$p(\tau) = (\mu'+\mu'')\mathrm{e}^{-(\mu'+\mu'')\tau} \tag{24}$$

(see, for instance, Bhat [32]). $1/(\mu'+\mu'')$ is the mean life-time of the occupied state of the binding site and is equal to the relaxation time $\tau_1$ of a channel with one binding site [33]

$$\tau_1 = \frac{1}{\mu'+\mu''} \tag{25}$$

Eqn 24 may then be written in the form

$$p(\tau) = \frac{1}{\tau_1}\,e^{-\tau/\tau_1} \tag{26}$$

The meaning of the relaxation time $\tau_1$ is as follows. If in an assembly of channels the number $n_c{}^*$ of occupied channels is suddenly changed by an external perturbation, the change in $n_c{}^*$ decays to zero with an exponential time constant equal to $\tau_1$.

From the definitions of $P_l(\tau)$, $p_l$ and $p(\tau)$, it is obvious that $P_l(\tau) = p_l \cdot p(\tau)$. The right-hand side of Eqn 22 may then be evaluated by introducing expressions 23 and 26 for $p_l$ and $p(\tau)$. Using again Eqns 6 and 8, together with $v = v' + v''$, the following result is obtained:

$$S_J(\omega) = S_J^0\,\frac{1+Q\omega^2\tau_1^2}{1+\omega^2\tau_1^2} \tag{27}$$

$$S_J^0 = 2z^2e_0^2n_c\,\frac{v'\mu'+v''\mu''}{\mu'+\mu''} \tag{28}$$

$$Q = \left(\frac{s_1}{d}\right)^2\left(1+\frac{2v'\mu''}{v'\mu'+v''\mu''}\right) + \left(\frac{s_2}{d}\right)^2\left(1+\frac{2v''\mu'}{v'\mu'+v''\mu''}\right) \tag{29}$$

At low frequencies $\omega$ the double barrier acts as a white-noise source with spectral density $S_J{}^0$. We may again introduce the mean current density $\bar{J}$, which in this case is given [26] by·

$$\bar{J} = ze_0n_c\,\frac{v'\mu'-v''\mu''}{\mu'+\mu''} \tag{30}$$

so that

$$S_J^0 = 2ze_0\bar{J}\,\frac{v'\mu'+v''\mu''}{v'\mu'-v''\mu''} \tag{31}$$

At large values of $|zV_m|$ where either $v'\mu' \gg v''\mu''$ or $v'\mu' \ll v''\mu''$, Eqn 31 reduces to Schottky's relation (Eqn 13). For a further discussion of $S_J{}^0$ we introduce the voltage dependence of $v'$, $v''$, $\mu'$ and $\mu''$. Taking into account that the fraction $s_1/d$ of the total voltage acts on the first barrier and the fraction $s_2/d = 1 - s_1/d$ on the second barrier (Fig. 1), the jump rates are given by

$$v' = c'g'e^{zs_1u/2d} \qquad v'' = c''g''e^{-zs_2u/2d} \tag{32}$$

$$\mu' = h'e^{zs_2u/2d} \qquad u'' = h''e^{-zs_1u/2d} \tag{33}$$

where $g'$, $g''$, $h'$ and $h''$ are independent of concentration and voltage. If we denote the values of $v'$, $v''$, $\mu'$ and $\mu''$ at the equilibrium potential $u = u_0$ by $\bar{v}'$, $\bar{v}''$, $\bar{\mu}'$ and $\bar{\mu}''$, we obtain for the ohmic membrane resistance $R_m$ (Eqn 17) the expression

$$R_m = \frac{2kT}{z^2e_0^2n_c}\cdot\frac{\bar{\mu}'+\bar{\mu}''}{\bar{v}'\bar{\mu}'+\bar{v}''\bar{\mu}''} \tag{34}$$

Introduction of Eqns 32–34 into Eqn 28 then yields the result

$$S_J^0 = \frac{4kT}{R_m} \cdot \frac{\bar{\mu}' + \bar{\mu}''}{\mu' + \mu''} \cosh\left[\frac{z}{2}(u - u_0)\right] \tag{35}$$

Thus, for $u \approx u_0$ Eqn 35 reduces to the Nyquist formula $S_J{}^0 = 4kT/R_m$.

The frequency dependence of the spectral density is given by Eqn 27, which predicts that $S_J(\omega)$ approaches the value $Q \cdot S_J{}^0$ in the limit of high frequencies, the transition between $S_J(\omega) = S_J{}^0$ and $S_J(\omega) = Q \cdot S_J{}^0$ occurring in the vicinity of $\omega = 1/\tau_l$. It may be instructive to calculate $Q$ for some special cases under the assumption $s_1 = s_2 = d/2$.

$$v' = v'', \quad \mu' = \mu'' : Q = 1 \tag{a}$$

(From Eqn 30 it is seen that condition (a) requires that $\bar{J} = 0$, or $V_m = V_m{}^0$.) Thus, for this completely symmetrical case, the spectral density $S_J$ becomes independent of frequency.

$$|zV_m| \to \infty, \text{ so that either } v' \gg v'', \ \mu' \gg \mu'' \text{ or } v' \ll v'', \ \mu' \ll \mu'' : Q \approx 0.5 \tag{b}$$

$$V = V_m^0 : Q = \frac{1}{2} + \frac{1}{4}\left(\frac{\bar{v}'}{\bar{v}''} + \frac{\bar{v}''}{\bar{v}'}\right) = \frac{1}{2} + \frac{1}{4}\left(\frac{\bar{\mu}'}{\bar{\mu}''} + \frac{\bar{\mu}''}{\bar{\mu}'}\right) \tag{c}$$

(note that for $V_m = V_m{}^0$ the relation $\bar{v}'\bar{\mu}' = \bar{v}''\bar{\mu}''$ holds).

## DISCUSSION

In the preceding treatment of shot noise in ion channels we have considered two simple models, a pore with a single energy barrier and a pore with a single binding site separated from the aqueous solutions by energy barriers on either side. The main results of the analysis are contained in Eqns 9 and 27–29. The single-barrier pore behaves as a white-noise source with a spectral density $S_J$ that is proportional to the total rate of jumps over the barrier. At voltages near the equilibrium potential $V_m{}^0$ of the permeable ion, $S_J$ becomes equal to the spectral density of thermal (or Johnson) noise. On the other hand, in the limit of high voltages where the ion flow across the barrier becomes unidirectional, $S_J$ approaches the spectral density of a Schottky noise source.

The same behaviour (Johnson noise near the equilibrium potential, Schottky noise at large voltages) is found for channels with a double barrier in the limit of low frequencies. Channels with a double barrier, however, exhibit an additional feature, namely, a dispersion of the spectral density near $\omega = 1/\tau_1$ where $\tau_1$ is the average lifetime of the occupied state of the channel. Qualitatively, this dispersion may be understood as a consequence of the time correlation between subsequent jumps.

It is obvious from Eqn 35 that the low-frequency value $S_J{}^0$ of the spectral density contains little information which may not already be obtained by measuring the time-averaged properties of the membrane. Useful information, however, may be extracted from a measurement of the dispersion frequency $\omega = 1/\tau_1$, as $\tau_1$ is related to the rate constants of ion transport through the channel (Eqn 25) In that sense the noise analysis is equivalent to a macroscopic relaxation experiment.

At the moment it is difficult to compare the theoretical result with existing experiments. Most noise studies which have been carried out so far on nerve membranes and on artificial lipid membranes were mainly concerned either with $1/f$ noise or with noise originating from the statistical opening and closing of ion channels. A possible indication for shot noise from ion jumps over barriers would be the existence of dispersion regions in the spectral density $S_J(\omega)$. In many cases, however, the dispersion predicted by Eqn 27 will occur at very high frequencies, which may be experimentally inaccessible. For instance, from current estimates of the single-channel conductance of the sodium system in nerve [34], a transfer rate of about $10^6$–$10^7$ sodium ions per second through the open channel is calculated. This means that the average time which an ion spends at a binding site inside the channel is likely to be of the order of 1 $\mu$s or less. In this case the dispersion of $S_J(\omega)$ should occur in the MHz range, which is outside the experimental possibilities. Similar conclusions hold true for the gramicidin A channel for which the transfer rate of $Na^+$ or $K^+$ is estimated to be of the order of $10^7$ $s^{-1}$ [26, 35]. On the other hand, with ions that are more strongly bound to the channel, the characteristic time constants may fall into the experimentally accessible range. A further possible application of the (suitably modified) shot-noise theory could be future noise studies with artificial black lipid films in the presence of ion carriers or hydrophobic ions. In these systems the characteristic times are in the range of $10^{-4}$–$10^{-2}$ s [36, 37].

## APPENDIX: FINITE TRANSIT TIMES

In the treatment of the single barrier we have assumed that the jump over the barrier is an instantaneous event. We now consider the case of finite transit times, that is we assume that the transfer of the ion from left to right is equivalent to a movement of a charge $ze_0$ with constant velocity during time $t'$. Correspondingly, the transit time for a jump from right to left is denoted by $t''$. A similar treatment for the special case of unidirectional ion flow over a single barrier has been given by Stevens [18]. Eqn 1 has now to be replaced by

$$i(t) = \frac{aze_0}{t^*} \qquad (0 \leqq t \leqq t^*) \tag{A1}$$

$$i(t) = 0 \qquad (t < 0, t > t^*)$$

where $a/t^* = 1/t'$ for a jump from left to right and $a/t^* = -1/t''$ for a jump from right to left. This gives

$$|\Psi(\omega)|^2 = 2\frac{ze_0^2}{\omega t^*}(1-\cos \omega t^*) \tag{A2}$$

If $p' = v'/v$ and $p'' = v''/v$ are the probabilities of jumps from left to right and from right to left, and $\Psi'$ and $\Psi''$ the corresponding Fourier transforms, then

$$\overline{|\Psi(\omega)|^2} = p'|\Psi'(\omega)|^2 + p''|\Psi''(\omega)|^2 \tag{A3}$$

Using Eqns 6 and 8, one finally obtains

$$S_J(\omega) = 4z^2 e_0^2 n_c \left[ v' \frac{1-\cos \omega t'}{(\omega t')^2} + v'' \frac{1-\cos \omega t''}{(\omega t'')^2} \right] \tag{A4}$$

In the limit of short transit times ($\omega t' \ll 1$, $\omega t'' \ll 1$) this relation reduces to Eqn 9. For ion channels with a double barrier, a similar relation may be derived which contains in addition to $\tau_1$ the transit times $t'_1$, $t''_1$, $t'_2$ and $t''_2$ over the two barriers.

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