Journal of Statistical Physics, Vol. 15, No. 2, 1976

A Statistical Theory of Excitable Membranes. Nonlinear Force–Flux Relation and Fluctuation

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Received November 25, 1975

A statistical theory of an excitable membrane is proposed under the assumptions that the membrane is composed of an ensemble of a number of active patches, and that the flip-flop transition of an active patch is governed by the dissipative interaction caused by an electric eddy current. By the method of expanding the master equation in the system size together with the Gaussian approximation, the time course of an excitation and the steady N-shaped relation between current and voltage are derived from the ensemble theory of open systems. The fluctuation of electric current under a fixed voltage becomes anomalously large in the marginal state at the threshold potential. The fluctuation associated with an action potential increases sharply at the jump-up transition, but it is not so large at the flip-back catastrophe. The fluctuation-dissipation relation at the steady state of the membrane system is discussed on the basis of a variational principle.

KEY WORDS: Excitable membrane; action potential; N-shaped *I–V* relation; open system; ensemble theory; fluctuation-dissipation relation; Onsager principle; system-size expansion.

1. INTRODUCTION

Since the technique of intracellular perfusion was introduced in the study of the electrophysiology of squid giant axon in 1961,[(1)] the excitation of living membrane has been studied theoretically in the framework of phase transition theory in thermal equilibrium.[(2)] Recent physicochemical studies carried out with internally perfused squid axon and with excitable protoplasmic droplets isolated from Nitella, however, have revealed that the process of excitation is accompanied by variations in the molecules constituting the membrane.[(3)] This implies that the theoretical treatment based on the

This study was supported partly by a grant from the Ministry of Education, Japan.

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equilibrium theory is insufficient to account for the process of excitation, and that, in turn, a concept of transition of state in a wider sense than the phase change of the membrane may be necessary.

In a previous paper[4] (hereafter called paper I) we proposed a method by which the excitation of a membrane is described as a transition between nonequilibrium steady states, where the dissipative interaction caused by the electric eddy current between the excited and the resting parts was taken into consideration.[4] The model used was as follows. The structure of the membrane is not uniform along the axon surface, and many excited patches coexist with the resting parts. Each domain of the membrane is able to take two distinct states, i.e., excited and resting states, and both the potential and the electrical resistance are quite different in these two states. Therefore, the local membrane potential varies from one position to another along the membrane surface. This nonuniform distribution of the membrane emf along the membrane surface creates the local electric current even if there is no net current across the membrane.[5] As a consequence of this long-range interaction by the electric current each domain changes its state from exciting to resting, or vice versa. The flip-flop (or birth and death) process of an active patch is assumed to be stochastic. In paper I, which was concerned with the ensemble theory of a dissipative open system, however, we did not study the fluctuation in physical properties such as the transmembrane current and the fraction of the excited region. In this paper we consider the potential and current fluctuations in the membrane system based on the theoretical model proposed in paper I. In Section 2 the master equation is derived for the flip-flop process of an active patch. The evolution equation and the steady fluctuation of the electric current are obtained for the Markovian case by means of the system-size expansion.[6] The time course of the fluctuation accompanied by an action potential is given in Section 3. The results are discussed in Section 4, where the fluctuation-dissipation relation in the membrane system is pointed out.

2. BIRTH AND DEATH MODEL AND ENSEMBLE THEORY OF EXCITABLE MEMBRANES

2.1. Expansion of the Master Equation in the System Size

The conservation law of probability in a birth and death process of a macrovariable X is generally described by the following master equation:

$$\partial P(X,t)/\partial t = -\Big\{\sum_R W(X,R)P(X,t) - \sum_R W(X-R,R)P(X-R,t)\Big\} \tag{1}$$

For the sake of simplicity we consider the case where a single variable X is involved. $P(X, t)$ is the probability density function and $W(X, R)$ is the transition probability per unit time from X to $X + R$. By use of the Kramers–Moyal expansion, Eq. (1) is rewritten as

$$\partial P(X, t)/\partial t = -\sum_R (1 - e^{-R\partial/\partial X}) W(X, R) P(X, t) \tag{2}$$

If we introduce new functions w and ψ and a variable x defined by

$$w(x, R) = W(X, R)/\Omega, \qquad \psi(x, t) = P(X, t)/\Omega, \qquad \text{and} \qquad x = X/\Omega \tag{3}$$

we can expand Eq. (2) in power series of ϵ $(=\Omega^{-1})$ to give

$$\begin{aligned} \frac{\partial \psi(x, t)}{\partial t} &= -\epsilon^{-1} \sum (1 - e^{-R\epsilon\partial/\partial x}) w(x, R) \psi(x, t) \\ &= \sum_{n=1}^{\infty} \frac{\epsilon^{n-1}}{n!} \left(-\frac{\partial}{\partial x}\right)^n C_n(x) \psi(x, t) \end{aligned} \tag{4}$$

where

$$C_n(x) = \sum_R R^n w(x, R) \tag{5}$$

Here the extensive quantity Ω stands for the system size. The set of Eqs. (4) and (5) is equivalent to Eq. (1). At this stage we introduce the generalized entropy S by the following:

$$\psi(x, t) \propto e^{\Omega \cdot S(x,t)} \tag{6}$$

Then Eq. (4) is rewritten as

$$\frac{\partial S(x, t)}{\partial t} = -\sum_R (1 - e^{-R\partial S/\partial x}) w(x, R) = \sum_{n=1}^{\infty} \frac{(-)^n}{n!} C_n(x) \left(\frac{\partial S}{\partial x}\right)^n \tag{7}$$

where the higher order terms in ϵ have been neglected. This relation gives an expression for the generalized entropy production. Furthermore, if we denote the most probable path of $x(t)$ by $y(t)$ and the variance by $\epsilon\beta(t)$ $(=\langle x^2 \rangle - y^2)$, the generalized entropy is given by the following equation:

$$S(x, t) = -\tfrac{1}{2}\beta^{-1}(t)[x - y(t)]^2 \tag{8}$$

under the Gaussian approximation. In the derivation of Eq. (8) the difference between $y(t)$ and the mean value of $x(t)$ has been neglected since the difference is a small quantity of the order of ϵ. Introducing Eq. (8) into Eq. (7) and comparing the respective terms of ϵ, we obtain the following set of equations:

$$\frac{dy}{dt} = C_1(y) \tag{9}$$

$$\frac{d\beta}{dt} = C_2(y) + 2\frac{dC_1(y)}{dy}\beta \tag{10}$$

These equations are referred to as evolution equations, and the kinetic property of the statistical distribution is determined by them. The assumptions used in Eqs. (6)–(10) are equivalent to the condition of normal fluctuation, which obeys the central limit theorem in the same way as in the equilibrium system. Equations (7), (9), and (10) describe the irreversible evolution not only in a state near equilibrium, but also in a state far from equilibrium, provided that the assumptions introduced above are permissible and the system is in the thermodynamic limit ($\Omega \to \infty$).

In this paper we assume that the state of the membrane satisfies the conditions mentioned above during the process of excitation, and that the method of the system-size expansion is applicable to our system.

2.2. Evolution Equation of Excitation

The state of the membrane is determined by the number of excited patches N_a $(=X)$ or the mean excited fraction x $(=N_a/N)$, where N is the total number of patches. The probability density $P(N_a, t)$ obeys the master equation given by Eq. (1). The transition probability $W(N_a, R)$ is determined approximately if we introduce the detailed balance conditions at the steady state,

$$W(N_a, R)P_s(N_a) = W(N_a + R, -R)P_s(N_a + R) \tag{11}$$

where P_s is the steady-state distribution function.[7] As illustrated in paper I, the steady state is given by the following distribution function:

$$P_s(N_a) \propto A \exp(-\gamma Q) \tag{12}$$

where γ is a positive constant, Q is the energy dissipation of the system, and A is the probability of the configuration:

$$A \propto N!/[N_a!\,(N - N_a)!] \tag{13}$$

If the Weiss approximation is applied to the interpatch interaction as a first approximation,[4] the energy dissipation Q is represented by

$$\begin{aligned} Q = {} & \{N_a g_a (V - E_a)^2 + (N - N_a) g_r (V - E_r)^2\} \Delta A \\ & + \tfrac{1}{2} g n (1/N)(E_a - E_r)^2 N_a (N - N_a) \end{aligned} \tag{14}$$

Here g_a and g_r are the conductances (mho/cm^2) of the excited and resting domains and E_a and E_r are the emf (volts) of the excited and resting domains, respectively. ΔA is the area (cm^2) of a patch, V is the clamped voltage, n is the number of nearest neighboring patches, and g is the interpatch conductance. Using Eqs. (12)–(14), we obtain the transition probability as follows:

$$\begin{aligned} W(N_a, 1) &= f N_a \exp[-(\mu/2) - (\alpha/4N)(2N_a - N)] \\ W(N_a, -1) &= f(N - N_a) \exp[-(\mu/2) + (\alpha/4N)(2N_a - N)] \\ W(N_a, R) &= 0 \qquad (\text{for } R \neq \pm 1) \end{aligned} \tag{15}$$

where α and μ are new parameters given by

$$\alpha = \gamma g n (E_a - E_r)^2 \qquad \mu = -\gamma \Delta A\{g_a(V - E_a)^2 - g_r(V - E_r)^2\} \tag{16}$$

and f is a function of N_a and R. Here the transition subjected to $R \neq \pm 1$ is neglected. For the sake of simplicity f is taken as a constant in the subsequent argument.

By the scaling $x = N_a/N$, the transition moment $C_n(x)$ is derived as

$$C_n(x) = \begin{cases} 2f\{(1 - 2x)\cosh K(x, V) + \sinh K(x, V)\}, & \text{odd } n \\ 2f\{\cosh K(x, V) + (1 - 2x)\sinh K(x, V)\}, & \text{even } n \end{cases} \tag{17}$$

where

$$K(x, V) = \tfrac{1}{2}\mu + \tfrac{1}{4}\alpha(2x - 1)$$

This allows us to write the evolution equation (9) as follows:

$$\frac{dy}{dt} = C_1(y, V) = 2f\{(1 - 2y)\cosh K(y, V) + \sinh K(y, V)\} \tag{18}$$

Equation (18) holds even if the membrane potential V varies with time, provided that the variation of V is slow enough in comparison with that of a flip-flop process of a patch. Since the time variation of the membrane potential V must satisfy the continuity equation of electric current I (A/cm^2) across the membrane, we have

$$C\frac{dV}{dt} = -\{g_a y(V - E_a) + g_r(1 - y)(V - E_r)\} + I \tag{19}$$

where C is the membrane capacitance (F/cm^2). The process of excitation is obtained from Eqs. (18) and (19). At the steady state given by $dy/dt = 0$ and $dV/dt = 0$, I and V satisfy the following equations:

$$I = g_a y_s(V - E_a) + g_r(1 - y_s)(V - E_r) \tag{20}$$

$$\tanh K(y_s, V) = 2y_s - 1 \tag{21}$$

where y_s denotes the steady value of y. In the case of $I = 0$ there are three steady states satisfying Eqs. (20) and (21). The upper and lower values of y_s correspond to the excited ($y_s = y_a$) and resting states ($y_s = y_r$), respectively, and the intermediate state represents the threshold level ($y_s = y_c$ and $V = V_c$). The right-hand side of Eq. (18) is approximated as follows:

$$C_1(y) \propto (V - V_c)(y - y_r)(y_a - y) \tag{22}$$

under the following assumption:

$$y = y_a \qquad \text{for} \quad V \geqslant V_c$$

$$y = y_r \qquad \text{for} \quad V < V_c$$

In the case where $y_r = 0$ and $y_a = 1$, Eq. (18) leads to the Markovian equation proposed in paper I,

$$\frac{dy}{dt} = k(V - V_c)y(1 - y) \tag{23}$$

2.3. Steady Fluctuation of the Nonlinear *I–V* Relation

Equations (20) and (21) lead to the N-shaped *I–V* relation shown in Fig. 1. The steady fluctuation of the excited fraction β_s is given by Eqs. (10) and (17) as follows:

$$\beta_s = -\frac{C_2(y_s)}{2C_1'(y_s)} = \frac{y_s(1 - y_s)}{1 - \alpha y_s(1 - y_s)} \tag{24}$$

Here α is defined by Eq. (16). On the other hand, the steady fluctuation of electric current λ $(=\langle I^2\rangle - \langle I\rangle^2)$ is derived from Eq. (19) as follows:

$$\lambda = \{g_a(V - E_a) - g_r(V - E_r)\}^2\beta_s \tag{25}$$

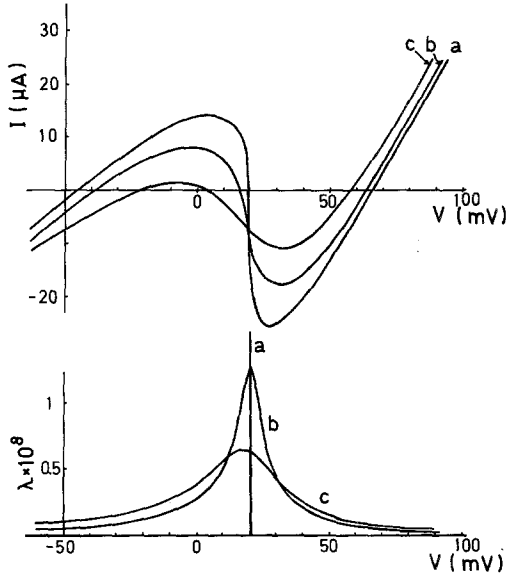

Fig. 1. The *I–V* and λ–*V* relations. (a) $\alpha = 4$, (b) $\alpha = 3.44$, and (c) $\alpha = 2.88$. The characteristic constants of the membrane were taken as follows: $E_a = 70$ mV, $E_r = -50$ mV, $g_a = 10^{-3}$ mho/cm^2, $g_r = 5 \times 10^{-4}$ mho/cm^2, $ng = 2 \times 10^9$ mho, and $\Delta A = 10^{-6}$ cm^2.

Equations (21), (24), and (25) give the relation of λ vs. V. Figure 1 shows the current fluctuation λ for various cases of the I–V relation. In the case where $\alpha > 4$ the I–V relation becomes multivalued, and consequently λ takes a negative value in a certain region of clamped voltage V. We limit our discussion to the case of $\alpha \leqslant 4$, since an I–V relation with hysteresis has not been observed in biological membranes. For the case of $\alpha = 4$, the current fluctuation λ diverges at

$$y_s = 1/2 \{\text{or at} \quad V = V_c^* \equiv [E_a + E_r(g_r/g_a)^{1/2}]/[1 + (g_r/g_a)^{1/2}]\}$$

as follows:

$$\lambda \propto 1/(1 - 2y_s)^2 \propto 1/(V - V_c^*)^2 \tag{26}$$

Here V_c^* does not agree with V_c of Eq. (22) in general (Fig. 1 shows the case of $V_c < V_c^*$), but the difference between V_c and V_c^* is very small. The λ–V relation will be discussed in a later section in reference to the fluctuation-dissipation relation and the stability of the steady state of the membrane.

3. PHENOMENOLOGICAL EQUATION AND THE TIME EVOLUTION OF FLUCTUATION

In the preceding section we derived the dynamics of excitation based on the ensemble theory of the excitable membrane. In the dynamical or time-dependent phenomena of excitation, however, the non-Markovian and nonlocal effects play an essential role.[5] As illustrated in paper I, the phenomenological process of excitation is given by the following set of equations:

$$\frac{\partial y}{\partial t} = k_1(V - V_c)y(1 - y) - k_2 y \int_0^t [V(t') - E_r]e^{-(t-t')/\tau}\, dt' \tag{27}$$

$$C\frac{\partial V}{\partial t} = -\{g_a y(V - E_a) + g_r(1 - y)(V - E_r)\} + I \tag{28}$$

where the k_i and τ are, respectively, rate constants and the time constant of irreversible ion accumulation at the membrane surface. Equation (27) is compared to Eq. (23) in the Markovian case. In this section we define the transition probability from a phenomenological consideration which is different from the assumption of detailed balance at the steady state introduced in the previous section. The scaled transition probability $w_1(x, R)$ derived from the first term of the right-hand side of Eq. (27) is given by

$$w_1(x, R) = \begin{cases} \frac{1}{2}k_1 x(1 - x)\{R(V - V_c) + |V - V_c|\}, & R = \pm 1 \\ 0, & R \neq \pm 1 \end{cases} \tag{29}$$

There is a positive or negative jump depending on whether $V > V_c$ or $V < V_c$. As a matter of course, $w_1(x, R)$ is nonnegative because $0 < x < 1$. The second (non-Markovian) term of Eq. (27) is derived by use of the following transition probability:

$$w_2(x, R) = \begin{cases} k_2 x \int_0^t [V(t') - E_r] e^{-(t-t')/\tau} \, dt', & R = -1 \\ 0, & R \neq -1 \end{cases} \tag{30}$$

Here we assumed $V \geqslant E_r$. Therefore the total transition probability $w(x, R, t)$ is given by

$$w(x, R, t) = w_1(x, R) + w_2(x, R) \tag{31}$$

The time dependence of the transition probability is attributed to the non-Markovian term of Eq. (30).

The most probable path given by Eq. (31) is equivalent to Eqs. (27) and (28), which was studied in previous papers. In this section we are mainly concerned with the fluctuation around the most probable motion $y(t)$. From Eqs. (10) and (31) the time course of the variance $\epsilon\beta$ $(=\langle x^2 \rangle - \langle x \rangle^2)$ is given by

$$\frac{\partial \beta}{\partial t} = k_1 |V - V_c| y(1 - y) + 2k_1 (V - V_c)(1 - 2y)\beta + k_2 y \Gamma(t) - 2k_2 \Gamma(t)\beta \tag{32}$$

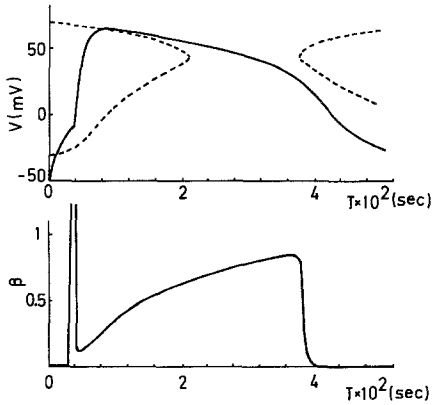

Fig. 2. The time courses of fluctuation and of an action potential with $k_1 = 10^6$, $k_2 = 6 \times 10^9$, and $\tau = 10^{-2}$ sec. The dashed lines show the quasisteady states. The upper dashed curve denotes the excited level and the lower gives the threshold level. Parameters used are as follows: $E_a = 70$ mV, $E_r = -50$ mV, $g_a = 10^{-3}$ mho/cm^2, $g_r = 10^{-4}$ mho/cm^2, $V_c = -30$ mV, and $C = 10^{-6}$ F/cm^2.

where $\Gamma(t) = \int_0^t [V(t') - E_r]e^{-(t-t')/\tau}\, dt'$. The time course of the fluctuation depends on the most probable motion, and consequently Eq. (32) must be calculated simultaneously with Eqs. (27) and (28).

Figure 2 shows an example of the time evolution of an action potential V and of the variance β. The current I is fixed 15 μA for $0 < t < 3$ msec and 0 for $t > 3$ msec. Values of parameters are listed in the figure legend. Just before the transition from the resting level to the excited level the fluctuation grows extremely large, then decreases sharply. During excitation the fluctuation increases gradually with time until the flip-back catastrophe occurs. When the flip-back transition occurs, the fluctuation does not diverge but diminishes sharply. The non-Markovian term of Eq. (32) seems to keep the fluctuation normal at the flip-back transition.

4. DISCUSSION

In this paper we have studied the fluctuation of the excitable membrane based on the theoretical model proposed in paper I. In general the fluctuation is closely connected to the stability of the state as well as a variational principle.[7,8] In this section we will briefly discuss the stability of the membrane system. In the stationary state ($\partial S/\partial t = 0$) the generalized entropy defined by Eq. (16) must satisfy the following equation:

$$-\frac{\partial S(y_s, V)}{\partial y_s} = \ln \frac{(1 - y_s)\exp[(\mu/2) - (\alpha/4)(2y_s - 1)]}{y_s \exp[-(\mu/2) + (\alpha/4)(2y_s - 1)]} \tag{33}$$

under the condition of Eq. (15). This is easily solved to give

$$S(y_s, V) = Q^* - (1/\gamma)S^* \tag{34}$$

where Q^* is the mean value of energy dissipation:

$$\begin{aligned} Q^* = N\{&[y_s g_a(V - E_a)^2 + (1 - y_s)g_r(V - E_r)^2]\,\Delta A \\ &+ \tfrac{1}{2}gn(E_a - E_r)^2(y_s - y_s^2)\} \end{aligned} \tag{35}$$

and S^* is the mixing entropy under the mean field approximation:

$$S^* = -N\{y_s \ln y_s + (1 - y_s)\ln(1 - y_s)\} \tag{36}$$

As mentioned in paper I, the variational principle given by

$$\frac{\partial S(y_s(I, V), V)}{\partial I} = 0 \tag{37}$$

leads to the I–V relation derived in Section 2. Here $S(y_s, V)$ was written as $S(y_s(I, V), V)$ with the aid of the continuity equation (20). Equation (37) is compared to the Onsager principle in the linear region,

$$(\partial/\partial I)(\tfrac{1}{2}G_d^{-1}I^2 - VI) = 0$$

where the electrical conductance G_d is obtained from Nyquist's theorem in terms of the current fluctuation λ:

$$G_d = (4k_BT)^{-1}\lambda$$

Here k_B is the Boltzmann constant and T is the absolute temperature. In the membrane system also the assumption of detailed balance enables us to derive the analogous relation between fluctuation and dissipation[7]:

$$G_d \equiv \partial I/\partial V = [y_s g_a + (1 - y_s)g_r] - 2\gamma\lambda \tag{38}$$

As mentioned in paper I, however, γ is not equal to $(k_BT)^{-1}$. In other words, the current fluctuation in the membrane system arises not only from the thermal motion of molecules in equilibrium, but also from the nonthermal motion of membrane macromolecules or active patches far from equilibrium. The force–flux relation in nonequilibrium has a physical meaning similar to the state equation in an equilibrium system. Therefore, the system becomes unstable when G_d or λ diverges, which follows a discrete change in physical properties such as a transmembrane current occurring at the critical point.

When an action potential is elicited, the memory effect stemming from ion accumulation at the membrane surface plays an indispensable role. In this case we use the Markovian master equation with a time-dependent transition probability, using the approximation that the flip-flop process of an active patch is very fast in comparison with the time evolution of the membrane potential. This approximation is permissible if we limit our discussion to a prolonged action potential. The fluctuation becomes large at the moment of the drastic change of the membrane potential. Just before the jump-up transition the system becomes extremely unstable but is relatively stable when the flip-back transition occurs. The non-Markovian effect of ion accumulation causes the gradual increase of the fluctuation. At the same time it moderates the instability at the flip-back catastrophe. In this paper the discussion was limited to the simple theoretical model proposed in a previous paper. It would be necessary to explore the advanced theory of fluctuations for a more realistic model in order to understand the diversity of instability behavior in the membrane system.

REFERENCES

1. I. Tasaki, *Nerve Excitation*, Thomas, Springfield, Illinois (1968).
2. J. P. Changeux, J. Thiery, Y. Tung, and C. Kittel, *Proc. Natl. Acad. Sci. U.S.* **57**:335 (1967); T. L. Hill, *Proc. Natl. Acad. Sci. U.S.* **58**:111 (1967); R. Blumenthal, H. P. Changeux, and R. Lefever, *Comp. Rend.* **270**:389 (1970).
3. I. Inoue, Y. Kobatake, and I. Tasaki, *Biophys. Chem.* **2**:116 (1974); H. Gainer, E. Carbone, I. Singer, K. Sisco, and I. Tasaki, *Comp. Biochem. Physiol.* **46A**:259, (1973); I. Inoue, N. Ishida, and Y. Kobatake, *Biochim. Biophys. Acta* **367**:24 (1974); T. Ueda, M. Muratsugu, and Y. Kobatake, *Biochim. Biophys. Acta* **373**:286 (1974).

4. Y. Aizawa and Y. Kobatake, *Prog. Theor. Phys.* **52**:1094 (1974).
5. Y. Aizawa, Y. Shimatani, and Y. Kobatake, *Prog. Theor. Phys.* **53**:305 (1975).
6. N. G. van Kampen, *Can. J. Phys.* **39**:551 (1961); in *Fluctuation Phenomena in Solids*, R. E. Burgess, ed., Academic Press, New York (1965); R. Kubo, K. Matsuo, and K. Kitahara, *J. Stat. Phys.* **9**:51 (1973).
7. M. Suzuki and R. Kubo, *J. Phys. Soc. Japan* **24**:51 (1968); G. S. Agarwal, *Z. Physik.* **252**:25 (1972).
8. R. Graham, *Springer Tracts in Modern Physics*, Vol. 66, Springer, New York (1973).