Theory of non-Markovian stochastic resonance

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We consider a two-state model of non-Markovian stochastic resonance (SR) within the framework of the theory of renewal processes. Residence time intervals are assumed to be mutually independent and characterized by some arbitrary *nonexponential* residence time distributions which are modulated in time by an externally applied signal. Making use of a stochastic path integral approach we obtain general integral equations governing the evolution of conditional probabilities in the presence of an input signal. These equations generalize earlier integral renewal equations by Cox and others to the case of driving-induced nonstationarity. On the basis of these equations a response theory of two-state renewal processes is formulated beyond the linear response approximation. Moreover, a general expression for the linear response function is derived. The connection of the developed approach with the phenomenological theory of linear response for manifest non-Markovian SR put forward [I. Goychuk and P. Hänggi, Phys. Rev. Lett. **91**, 070601 (2003)] is clarified and its range of validity is scrutinized. The theory is then applied to SR in symmetric non-Markovian systems and to the class of single ion channels possessing a fractal kinetics.

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I. INTRODUCTION

The concept of stochastic resonance (SR) has been originally put forward in order to explain the periodicity of glacial recurrences on the Earth [1]. It has gained, however, an immense popularity in the context of signal transduction in nonlinear stochastic systems in physics and biology [2–4]. Paradoxically enough, the detection of beneficial input signals in the background stochastic fluctuations of a signal-transmitting physical system can be improved upon corrupting the information-carrying signal with input noise, or upon raising the level of intrinsic thermal noise. A first example of SR has been given for a continuous state bistable dynamics agitated by the thermal noise and periodically modulated by an external signal [1]. There exists a huge number of systems in physics, chemistry, and biology which do exhibit SR [2–4]. These range from the classical systems to the systems with distinct quantum features [5].

Experimentally, SR has been demonstrated in various macroscopic systems, see, e.g., in the reviews [2,4] and the references therein. For a mesoscopic system containing a finite number of molecules SR has been first demonstrated experimentally in Ref. [6]. The mesoscopic system in Ref. [6] consists of dynamically self-assembled alamethicin ion channels of variable size that are placed in a lipid membrane. Up to this date, however, there remains the challenge to demonstrate SR on the level of *single* stable molecules. Ion channels of biological membranes [7,8] present one of the most appealing objects for such *single-molecular* studies. The invention of patch clamp technique (Ref. [8]) made such investigations possible. The single-molecular SR experiments which have been performed under the conditions of variable *intrinsic* thermal noise intensity [9], did not arrive at the convincing conclusions. A recent *theoretical* study [10] suggested a parameter regime where SR effect should indeed occur for a Shaker K^+ channel under physiological conditions when *external* noise is added to the signal. This issue has further been examined theoretically in Ref. [11]. The present status calls for both theoretical and experimental investigations. Particularly, the presence of distinct memory effects in the dynamics of such single molecules as ion channels constitutes a major theoretical challenge [12]. The non-Markovian features caused by these memory effects may be crucial for the occurrence of stochastic resonance on the level of single molecules.

The gross features of the observed bistable dynamics can be captured by a two-state stochastic process $x(t)$ that switches back and forth between two values x_1 and x_2 at random time points $\{t_i\}$. Such a two-state random process can be directly extracted from filtered experimental data and then statistically analyzed. Basically, the process $x(t)$ is characterized as follows: The sojourn in the state x_1 alternates randomly at t_i into the sojourn in the state x_2, then $x(t)$ switches back to x_1 at time t_{i+1}, and so on. If the sojourn time intervals $\tau_i = t_{i+1} - t_i$ are *independently* distributed (a condition which we shall assume throughout the following), such two-state renewal processes are fully specified by two residence time distributions (RTDs) $\psi_{1,2}(\tau)$ [13]. In the simplest case, which corresponds to the dichotomic Markovian process, both RTDs are strictly exponential, i.e., $\psi_{1,2}(\tau) = \nu_{1,2}\exp(-\nu_{1,2}\tau)$, where $\nu_{1,2}$ are the transition rates which equal the inverse mean residence times (MRTs), which are given by

$$\langle \tau_{1,2} \rangle := \int_0^\infty \tau \psi_{1,2}(\tau) d\tau, \tag{1}$$

with $\nu_{1,2} = \langle \tau_{1,2} \rangle^{-1}$. The input signal $f(t)$ causes the transition rates $\nu_{1,2}$ to be time dependent, i.e., $\nu_{1,2} \to \nu_{1,2}(t)$. Moreover, the RTDs become functionals of the driving signal

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$$\psi_{1,2}(t-t')\to\psi_{1,2}(t,t')=\nu_{1,2}(t)\exp\left[-\int_{t'}^{t}\nu_{1,2}(\tau)d\tau\right]. \tag{2}$$

As a consequence, the time-dependent probabilities $p_{1,2}(t)$ of the states $x_{1,2}$ obey the master equations

$$\dot{p}_1(t)=-\nu_1(t)p_1(t)+\nu_2(t)p_2(t)$$

$$\dot{p}_2(t)=\nu_1(t)p_1(t)-\nu_2(t)p_2(t) \tag{3}$$

with the signal-dependent rates which under an adiabatic assumption obey the rate law [14]

$$\nu_{1,2}(t)=\nu_{1,2}^{(0)}\exp(-[\Delta U_{1,2}\mp\Delta x f(t)/2]/k_BT). \tag{4}$$

In Eq. (4), $\nu_{1,2}^{(0)}$ are the frequency prefactors, $\Delta U_{1,2}$ are the heights of the activation barriers, $\Delta x := x_2 - x_1 > 0$ is the amplitude of fluctuations, k_B is the Boltzmann constant, and T is the temperature. For a weak periodic signal

$$f(t)=f_0\cos(\Omega t), \tag{5}$$

the use of Eqs. (3) and (4) allows one to calculate within linear response theory the *asymptotic*, long-time response of the mean value $\langle x(t)\rangle = x_1p_1(t)+x_2p_2(t)$ to $f(t)$, i.e.,

$$\langle\delta x(t)\rangle=f_0|\tilde{\chi}(\Omega)|\cos(\Omega t-\varphi(\Omega)),\quad \text{as } t\to\infty. \tag{6}$$

In Eq. (6), $\tilde{\chi}(\Omega)$ is the linear response function in the frequency domain and $\varphi(\Omega)$ denotes the phase shift. The spectral amplification of signal, $\eta=|\tilde{\chi}(\Omega)|^2$, exhibits the effect of SR, i.e., a bell-shaped dependence vs increasing intrinsic thermal noise strength which is measured by the temperature T [2].

The above outlined two-state Markovian theory has been put forward by McNamara and Wiesenfeld [15]; this approach has proven very useful over the years as a basic, prominent model for SR research [2]. Remarkably enough, this simple model allows one to unify the various kinds of SR such as periodic, aperiodic [16], and even nonstationary SR—within a unifying framework of information theory [10].

Many *observed* bistable stochastic processes $x(t)$ are, however, truly not Markovian, as can be deduced from the experimentally observed RTDs. As a matter of fact, any deviation of RTDs from the strictly exponential form indicates a deviation from the Markovian behavior [17,18]. The profoundly non-Markovian case emerges when at least one of the RTDs possesses a large (diverging) variance $\mathrm{var}(\tau_{1,2}) = \int_0^\infty \tau^2\psi_{1,2}(\tau)d\tau - \langle\tau_{1,2}\rangle^2\to\infty$. The stochastic dynamics of single molecules is especially interesting in this respect. For example, the RTDs of the conductance fluctuations in biological ion channels are in many cases not exponential [19–21]. Usually, a sum of many exponentials, $\psi(\tau) = \sum_{i=1}^N c_i\nu_i\exp(-\nu_i\tau)$, $\sum_{i=1}^N c_i=1$ is needed to describe the experimental data [8]. Moreover, in some cases $\psi(\tau)$ can well be described by a stretched exponential [19], or by a power law $\psi(\tau)\propto 1/(b+\tau)^\beta, \beta>0$ [20,21]. The power law is especially remarkable. For example, in Ref. [21] such a power law behavior has been found for the closed time RTD of a large conductance (BK) potassium channel with a power law exponent $\beta\approx 2.24$ yielding formally $\mathrm{var}(\tau_{closed})=\infty$. This in turn implies that such conductance fluctuations should exhibit a characteristic $1/f^\alpha$ noise power spectrum $S(f)$ [22]. Indeed, this is the case of BK ion channel [23], as well as of some other ion channels [24].

What are the non-Markovian features of SR in similar systems? We address this question below using the just described non-Markovian generalization of McNamara-Wiesenfeld model characterized by some arbitrary nonexponential RTDs $\psi_{1,2}(\tau)$ and the corresponding survival probabilities $\Phi_{1,2}(\tau)=\int_\tau^\infty\psi_{1,2}(\tau')d\tau'$ [13]. Similar models with alternating renewal processes have been used previously in the SR theory for some particular stochastic dynamics contracted to the two-state dynamics [25,26]. Moreover, the class of colored noise driven stochastic resonance [27] is also intrinsically non-Markovian. All these prior studies have been restricted, however, to situations with finite memory effects on a finite time scale. A truly non-Markovian situation emerges when the memory effects extend practically to infinity, exhibiting a scale free, weak power law decay. A phenomenological linear response theory of such genuine non-Markovian SR (which does not presume a knowledge of the underlying microscopic dynamics) has been put forward recently in Ref. [28]. The present work provides further details and, additionally, presents a more general framework for the non-Markovian SR theory which extends beyond the linear response description.

II. GENERAL THEORY

A. Two-state renewal process

To start, let us consider a two-state renewal process (TSRP) $x(t)$ which takes initially, at time t_0, the value x_1, or the value x_2 with the probability $p_1(t_0)$, or $p_2(t_0)$, correspondingly. At a random time point t_1 the process switches its current state into another state and stays there until the next random time point t_2. Then, the renewal process proceeds further in time in the same manner. The survival probability to remain in the state 1, or the state 2 for the time $\tau_i = t_{i+1}-t_i$ is $\Phi_1(\tau_i)$, or $\Phi_2(\tau_i)$, correspondingly. These two survival probabilities completely specify the considered TSRP [13]. The functions $\Phi_{1,2}(\tau)$ must satisfy the following obvious restrictions: (i) $0\leq\Phi_{1,2}(\tau)\leq 1$, (ii) $\Phi_{1,2}(\tau+\Delta\tau)\leq\Phi_{1,2}(\tau)$, $\Delta\tau>0$ (nonincreasing function of time) (iii) $\Phi_{1,2}(0)=1$, (iv) $\lim_{\tau\to\infty}\Phi_{1,2}(\tau)=0$, but are otherwise arbitrary. One example is given by the stretched exponential law or Weibull distribution

$$\Phi(\tau)=\exp\{-[\Gamma(1+1/a)\nu\tau]^a\},\quad 0<a<1. \tag{7}$$

In Eq. (7), $\nu=1/\langle\tau\rangle$ is a rate parameter having the meaning of inverse MRT and $\Gamma(x)$ denotes the gamma function. Moreover, the power law dependence

$$\Phi(\tau)=\frac{1}{[1+\nu\tau/\gamma]^{1+\gamma}},\qquad \gamma>0 \tag{8}$$

corresponds to the Pareto distribution. Both Weibull and Pareto distributions typify the so-called fractal dependencies. In particular, such distributions have been detected for several different types of ion channels [19,21]. An interesting feature of the Pareto distribution is that for $0<\gamma<1$ it displays a diverging variance, $\mathrm{var}(\tau)=\infty$, whereas the MRT $\langle\tau\rangle$ is finite. The closed time intervals of a large conductance potassium ion channel studied in Ref. [21] seems to obey Eq. (8) with $\gamma\approx 0.24$. Other fractal-like distributions can be constructed from the expansion over exponentials

$$\Phi(\tau)=\sum_{i=1}^{\infty} c_i \exp(-\nu_i\tau), \quad \sum_i c_i=1, \tag{9}$$

assuming some recurrence scaling relations among the rate constants $\{\nu_i\}$, e.g., $\nu_{i+1}=a\nu_i$, and among the expansion coefficients $\{c_i\}$, e.g., $c_{i+1}=bc_i$, with some structural constants $0<a<1, 0<b<1$ [29,12,30]. If the hierarchy of rate constants is obtained from a fundamental rate constant ν_0 applying a recurrence scaling relation similar to one given above, the corresponding distribution can be characterized as a fractal in time. If the whole hierarchy is produced by a more complicated scaling law involving two, or more independent fundamental rate constants, the distribution is multifractal. The corresponding stochastic processes can be referred to as fractal renewal processes [22]. Such random processes presently attract renewed attention in physics and in mathematical biology [12].

The negative time derivative

$$\psi_{1,2}(\tau)=-\frac{d\Phi_{1,2}(\tau)}{d\tau} \tag{10}$$

yields the corresponding residence time distributions [13]. Next, let us assume that a number of alternations occurred before the starting time point t_0 and the considered process became homogeneous in time *before* the observation started at t_0. Then, for such persistent, *time-homogeneous* process the RTDs of the *first* time interval $\tau_0=t_1-t_0$, $\psi_{1,2}^{(0)}(\tau)$ must differ from $\psi_{1,2}(\tau)$ [13,18,30–32], namely [33],

$$\psi_{1,2}^{(0)}(\tau)=\frac{\Phi_{1,2}(\tau)}{\langle\tau_{1,2}\rangle}, \tag{11}$$

where $\langle\tau_{1,2}\rangle$ is given by Eq. (1). The corresponding survival probability of the first residence time interval reads

$$\Phi_{1,2}^{(0)}(\tau)=\frac{\int_\tau^\infty \Phi_{1,2}(t)dt}{\langle\tau_{1,2}\rangle}. \tag{12}$$

Moreover, if to choose $p_{1,2}(t_0)$ as the stationary values, $p_{1,2}(t_0)=p_{1,2}^{st}$, the considered persistent process is *stationary*. From Eq. (11) it follows that the two-state renewal process (TSRP) can be stationary only if the two mean residence times $\langle\tau_1\rangle$ and $\langle\tau_2\rangle$ are finite. A diverging mean residence time leads to anomalously slow diffusion (subdiffusion) in the multistate case [30,32,34]; such a situation is not considered here.

When a time-dependent input signal is switched on, the driven TSRP becomes a nonstationary process and the corresponding survival probabilities depend not only on the length of time intervals, but also on the initial time instant t' of any considered residence time interval, i.e., $\Phi_{1,2}(t-t')\to\Phi_{1,2}(t,t')$. The residence time distributions are then accordingly given by

$$\psi_{1,2}(t,t')=-\frac{d\Phi_{1,2}(t,t')}{dt}. \tag{13}$$

The corresponding conditional survival probabilities can be defined as $\Phi_{1,2}(\tau|t'):=\Phi_{1,2}(t'+\tau,t')$ (here the condition is different from that used in footnote [33]—in the absence of signal—notwithstanding the use of identical notations). The particular choice, $\Phi_{1,2}(t,t')=\exp(-\int_{t'}^{t}\nu_{1,2}(\tau)d\tau)$, leads to Eq. (2)—the only choice which is consistent with the Markovian assumption [17]. In the nonstationary driven case, the distinction between $\Phi_{1,2}^{(0)}(t,t')$ and $\Phi_{1,2}(t,t')$, $\psi_{1,2}^{(0)}(t,t')$ and $\psi_{1,2}(t,t')$ is not necessary. Nevertheless, we keep formally this distinction in the following, because when the driving is being switched off, the process $x(t)$ relaxes to its stationary state. This distinction becomes very important in order to construct the evolution operator for time-homogeneous initial preparations.

B. Integral equations of nonstationary renewal theory

Our immediate goal is to obtain the evolution equations for the considered stochastic process: we are looking for the forward evolution operator $\mathbf{\Pi}(t|t_0)$ (or the matrix of conditional probabilities) connecting the probability vector $\vec{p}(t)=[p_1(t),p_2(t)]^T$ at two different instants of time t and t_0, i.e.,

$$\vec{p}(t)=\mathbf{\Pi}(t|t_0)\vec{p}(t_0). \tag{14}$$

This evolution operator can be explicitly constructed by considering the contributions of all possible stochastic paths leading from $\vec{p}(t_0)$ to $\vec{p}(t)$. To start, let us separate these contributions as follows

$$\mathbf{\Pi}(t|t_0)=\sum_{n=0}^{\infty}\mathbf{\Pi}^{(n)}(t|t_0), \tag{15}$$

where the index n denotes the number of alternations that occurred during the stochastic evolution. The contribution with no alternations obviously reads,

$$\mathbf{\Pi}^{(0)}(t|t_0)=\begin{bmatrix}\Phi_1^{(0)}(t,t_0) & 0\\ 0 & \Phi_2^{(0)}(t,t_0)\end{bmatrix}. \tag{16}$$

Stochastic paths with a single alternation contribute as

$$\mathbf{\Pi}^{(1)}(t|t_0)=\int_{t_0}^{t}dt_1\mathbf{P}(t,t_1)\mathbf{F}^{(0)}(t_1,t_0), \tag{17}$$

where

$$\mathbf{P}(t,t_0)=\begin{bmatrix}\Phi_1(t,t_0) & 0\\ 0 & \Phi_2(t,t_0)\end{bmatrix} \tag{18}$$

and

$$\mathbf{F}^{(0)}(t,t_0)=\begin{bmatrix}0 & \psi_2^{(0)}(t,t_0)\\ \psi_1^{(0)}(t,t_0) & 0\end{bmatrix}. \tag{19}$$

Next, the paths with two alternations contribute to Eq. (15) as

$$\mathbf{\Pi}^{(2)}(t|t_0)=\int_{t_0}^{t}dt_2\int_{t_0}^{t_2}dt_1\mathbf{P}(t,t_2)\mathbf{F}(t_2,t_1)\mathbf{F}^{(0)}(t_1,t_0), \tag{20}$$

where

$$\mathbf{F}(t,t_0)=\begin{bmatrix}0 & \psi_2(t,t_0)\\ \psi_1(t,t_0) & 0\end{bmatrix}. \tag{21}$$

Contributions with higher n are constructed along the same line of reasoning.

This representation of the evolution operator $\mathbf{\Pi}(t|t')$ in terms of an infinite sum over the stochastic paths is exact, although not very useful in practice. The structure of the infinite series in Eqs. (15)–(21) implies, however, the following representation

$$\mathbf{\Pi}(t|t_0)=\mathbf{\Pi}^{(0)}(t|t_0)+\int_{t_0}^{t}dt_1\mathbf{P}(t,t_1)\mathbf{G}(t_1,t_0), \tag{22}$$

where the unknown auxiliary matrix function $\mathbf{G}(t,t_0)$ satisfies the matrix integral equation

$$\mathbf{G}(t,t_0)=\mathbf{F}^{(0)}(t,t_0)+\int_{t_0}^{t}dt_1\mathbf{F}(t,t_1)\mathbf{G}(t_1,t_0). \tag{23}$$

The equivalence of Eqs. (15)–(21) and Eqs. (22) and (23) can be readily checked by solving Eq. (23) with the method of successive iterations.

In components, Eq. (22) reads

$$\Pi_{11}(t|t_0)=\Phi_1^{(0)}(t,t_0)+\int_{t_0}^{t}\Phi_1(t,t_1)G_{11}(t_1,t_0)dt_1, \tag{24a}$$

$$\Pi_{22}(t|t_0)=\Phi_2^{(0)}(t,t_0)+\int_{t_0}^{t}\Phi_2(t,t_1)G_{22}(t_1,t_0)dt_1, \tag{24b}$$

$$\Pi_{12}(t|t_0)=\int_{t_0}^{t}\Phi_1(t,t_1)G_{12}(t_1,t_0)dt_1, \tag{24c}$$

$$\Pi_{21}(t|t_0)=\int_{t_0}^{t}\Phi_2(t,t_1)G_{21}(t_1,t_0)dt_1. \tag{24d}$$

It is worth to note that the set of Eqs. (24a)–(24d) is not independent. The conservation of probability implies that

$$\Pi_{11}(t|t_0)+\Pi_{21}(t|t_0)=1,$$
$$\Pi_{22}(t|t_0)+\Pi_{12}(t|t_0)=1. \tag{25}$$

The consistency of Eqs. (24a)–(24d) with the conservation law, Eq. (25), can be checked readily. The matrix integral equation (23) reads in components

$$G_{11}(t,t_0)=\int_{t_0}^{t}\psi_2(t,t_1)G_{21}(t_1,t_0)dt_1, \tag{26a}$$

$$G_{22}(t,t_0)=\int_{t_0}^{t}\psi_1(t,t_1)G_{12}(t_1,t_0)dt_1, \tag{26b}$$

$$G_{12}(t,t_0)=\psi_2^{(0)}(t,t_0)+\int_{t_0}^{t}\psi_2(t,t_1)G_{22}(t_1,t_0)dt_1, \tag{26c}$$

$$G_{21}(t,t_0)=\psi_1^{(0)}(t,t_0)+\int_{t_0}^{t}\psi_1(t,t_1)G_{11}(t_1,t_0)dt_1. \tag{26d}$$

From Eqs. (26a)–(26d) one can deduce independent scalar integral equations for each component of matrix function $\mathbf{G}(t,t_0)$. Indeed, after substituting $G_{21}(t,t_0)$ from Eq. (26d) into Eq. (26a) the closed equation for $G_{11}(t,t_0)$ follows as

$$G_{11}(t,t_0)=\xi_1^{(0)}(t,t_0)+\int_{t_0}^{t}\xi_1(t,t_1)G_{11}(t_1,t_0)dt_1. \tag{27}$$

In Eq. (27),

$$\xi_1^{(0)}(t,t_0)=\int_{t_0}^{t}\psi_2(t,t_1)\psi_1^{(0)}(t_1,t_0)dt_1 \tag{28}$$

and

$$\xi_1(t,t_0)=\int_{t_0}^{t}\psi_2(t,t_1)\psi_1(t_1,t_0)dt_1 \tag{29}$$

is a renewal density. Analogously,

$$G_{22}(t,t_0)=\xi_2^{(0)}(t,t_0)+\int_{t_0}^{t}\xi_2(t,t_1)G_{22}(t_1,t_0)dt_1, \tag{30}$$

where

$$\xi_2^{(0)}(t,t_0)=\int_{t_0}^{t}\psi_1(t,t_1)\psi_2^{(0)}(t_1,t_0)dt_1,$$

$$\xi_2(t,t_0)=\int_{t_0}^{t}\psi_1(t,t_1)\psi_2(t_1,t_0)dt_1. \tag{31}$$

Moreover, for the off-diagonal elements of $\mathbf{G}(t,t_0)$ we find

$$G_{12}(t,t_0)=\psi_2^{(0)}(t,t_0)+\int_{t_0}^{t}\xi_1(t,t_1)G_{12}(t_1,t_0)dt_1,$$

$$G_{21}(t,t_0)=\psi_1^{(0)}(t,t_0)+\int_{t_0}^{t}\xi_2(t,t_1)G_{21}(t_1,t_0)dt_1 . \quad (32)$$

Equations (27)–(31) together with Eqs. (24a)–(24d) present the first main result of this work. This set of equations generalizes the integral equations of renewal theory obtained by Cox [13] and others [18] to the case of nonstationary renewal processes modulated by external signals. The solution of the evolution operator $\mathbf{\Pi}(t|t_0)$ is thereby reduced to solve the set of independent scalar integral equations for $G_{ij}(t,t_0)$. This presents an essential simplification as compare to the case of an evaluation of infinite matrix integral series in Eqs. (15)–(21).

C. Time-homogeneous case

In the absence of a signal, all two-time quantities depend only on the time-difference $\tau=t-t_0$. In this case, the integral equations of renewal theory can be solved formally by use of the Laplace transform method and the evolution operator (i.e., its Laplace transform) can be found explicitly. Let us denote the Laplace transform of any function $F(\tau)$ below as $\tilde{F}(s):=\int_0^\infty \exp(-s\tau)F(\tau)d\tau$. Then, upon Laplace transforming Eqs. (24a)–(32), using Eqs. (11) and (12) and some well-known theorems of Laplace transform, one finds the explicit expression for the evolution operator $\tilde{\mathbf{\Pi}}(s)$. It coincides with the known result in the literature [13,18,28], reading

$$\tilde{\mathbf{\Pi}}(s)=\frac{1}{s}\begin{bmatrix} 1-\dfrac{\tilde{G}(s)}{s\langle\tau_1\rangle} & \dfrac{\tilde{G}(s)}{s\langle\tau_2\rangle} \\ \dfrac{\tilde{G}(s)}{s\langle\tau_1\rangle} & 1-\dfrac{\tilde{G}(s)}{s\langle\tau_2\rangle} \end{bmatrix}, \quad (33)$$

where

$$\tilde{G}(s)=\frac{(1-\tilde{\psi}_1(s))(1-\tilde{\psi}_2(s))}{(1-\tilde{\psi}_1(s)\tilde{\psi}_2(s))} \quad (34)$$

is an auxiliary function.

The existence of finite mean residence times $\langle\tau_{1,2}\rangle$ implies the following useful representation for the Laplace-transformed RTDs:

$$\tilde{\psi}_{1,2}(s):=1-\langle\tau_{1,2}\rangle s[1+g_{1,2}(s)]. \quad (35)$$

In Eq. (35), $g_{1,2}(s)$ are corresponding functions vanishing at $s\to 0$, i.e., $g_{1,2}(s)\to 0$. Note that the functions $g_{1,2}(s)$ are not necessarily analytical. For example, $g(s)\sim s^{\gamma}$ with some real-valued exponent, $0<\gamma<1$, is allowed, for an example, see below in Eq. (94). Such nonanalytical feature leads to diverging variance of RTDs. From the formal expression (33) a number of important results follows:

1. Stationary probabilities

The vector of stationary probabilities $\vec{p}^{\,st}=[p_1^{st},p_2^{st}]^T$ can be evaluated as $\vec{p}^{\,st}=\lim_{s\to 0}[s\tilde{\mathbf{\Pi}}(s)\vec{p}(0)]$. With Eqs. (33)–(35) one readily obtains the result

$$p_1^{st}=\frac{\langle\tau_1\rangle}{\langle\tau_1\rangle+\langle\tau_2\rangle},\quad p_2^{st}=\frac{\langle\tau_2\rangle}{\langle\tau_1\rangle+\langle\tau_2\rangle}. \quad (36)$$

2. Relaxation function

The generally nonexponential relaxation of $\langle x(t)\rangle =x_1p_1(t)+x_2p_2(t)$ to the stationary mean value $x_{st}=x_1p_1^{st}+x_2p_2^{st}$ is described by the relaxation function $R(\tau)$, i.e.,

$$p_{1,2}(t_0+\tau)=p_{1,2}^{st}+[p_{1,2}(t_0)-p_{1,2}^{st}]R(\tau), \quad (37)$$

where $R(\tau)$ obeys the Laplace transform

$$\tilde{R}(s)=\frac{1}{s}-\left(\frac{1}{\langle\tau_1\rangle}+\frac{1}{\langle\tau_2\rangle}\right)\frac{1}{s^2}\tilde{G}(s), \quad (38)$$

and $\tilde{G}(s)$ is given by Eq. (34). The validity of Eqs. (37) and (38) can be easily checked upon the use of Laplace transformed Eq. (14) and the result in Eqs. (33) and (34) along with the normalization condition $p_1(t_0)+p_2(t_0)=1$ and Eq. (36). It should be emphasized here that the relaxation function $R(t)$ for the considered *persistent* renewal process is unique, i.e., it does not depend on $p_{1,2}(t_0)$. This corresponds to the situation where the random process $x(t)$ has not been prepared at $t=t_0$ in a particular state x_1, or x_2, but rather has almost relaxed to its stationary state. In other words, a number of alternations occurred before $t=t_0$ and the probability $p_{1,2}(t_0)$ to measure the particular value $x_{1,2}$ of $x(t)$ at the instant of time t_0 is close to its stationary value $p_{1,2}^{st}$. This class of initial preparations, where the relaxation function does not depend on the actual initial probabilities, is termed the time-homogeneous preparation class. This preparation class [35,36] must be distinguished from strongly nonequilibrium initial preparations, where the system is prepared, for example, in a particular definite state, say in the state x_1, with the probability one, $p_1(t_0)=1$.

3. Stationary autocorrelation function and regression theorem

Let us consider next the normalized autocorrelation function, i.e.,

$$k(\tau)=\lim_{t\to\infty}\frac{\langle\delta x(t+\tau)\delta x(t)\rangle}{\langle\delta x^2\rangle_{st}} \quad (39)$$

of the stationary fluctuations, $\delta x(t)=x(t)-x_{st}$. In Eq. (39),

$$\langle\delta x^2\rangle_{st}=(\Delta x)^2\frac{\langle\tau_1\rangle\langle\tau_2\rangle}{(\langle\tau_1\rangle+\langle\tau_2\rangle)^2} \quad (40)$$

is the mean-squared amplitude of the stationary fluctuations and $\Delta x=x_2-x_1$ is the fluctuation amplitude. With $\langle\delta x(t+\tau)\delta x(t)\rangle=\langle x(t+\tau)x(t)\rangle-\langle x\rangle_{st}^2$, as $t\to\infty$, and

$$\lim_{t\to\infty}\langle x(t+\tau)x(t)\rangle=\sum_{i=1,2}\sum_{j=1,2}x_ix_j\Pi_{ij}(\tau)p_j^{st}, \quad (41)$$

we obtain the same result as in Ref. [38], i.e.,

$$\tilde{k}(s)=\frac{1}{s}-\left(\frac{1}{\langle\tau_1\rangle}+\frac{1}{\langle\tau_2\rangle}\right)\frac{1}{s^2}\tilde{G}(s). \quad (42)$$

Upon comparison of Eq. (38) with Eq. (42) we find the following regression theorem for these non-Markovian two-state processes, namely,

$$R(\tau)=k(\tau). \quad (43)$$

The regression theorem (43), which relates the decay of the *relaxation function* $R(\tau)$ to the decay of *stationary autocorrelations* $k(\tau)$, presents a cornerstone result for the derivation of phenomenological linear response theory for non-Markovian SR [28].

Usually, the Laplace transform (42) cannot be inverted analytically. If $k(t)\geqslant 0$ for all times t, one can define the mean correlation time

$$\tau_{corr}=\int_0^\infty k(t)dt=\lim_{s\to 0}\tilde{k}(s). \quad (44)$$

Assuming finite second moments of RDTs, $\langle\tau_{1,2}^2\rangle=\int_0^\infty\tau^2\psi_{1,2}(\tau)d\tau$ we obtain from Eqs. (42) and (44) the simple result

$$\tau_{corr}=R_{NM}\tau_M, \quad (45)$$

where

$$\tau_M=\frac{\langle\tau_1\rangle\langle\tau_2\rangle}{\langle\tau_1\rangle+\langle\tau_2\rangle} \quad (46)$$

is the correlation time of the Markovian process possessing the same MRTs $\langle\tau_{1,2}\rangle$ as the considered non-Markovian process. The coefficient

$$R_{NM}=\tfrac{1}{2}(C_1^2+C_2^2) \quad (47)$$

presents a numerical quantifier of non-Markovian effects in terms of the coefficients of variation of the corresponding residence time distributions, i.e.,

$$C_{1,2}=\frac{\sqrt{\langle\tau_{1,2}^2\rangle-\langle\tau_{1,2}\rangle^2}}{\langle\tau_{1,2}\rangle}. \quad (48)$$

For example, for the stretched exponential (7) the coefficient of variation emerges as

$$C=\sqrt{\frac{\Gamma(1+2/a)}{\Gamma^2(1+1/a)}-1}. \quad (49)$$

For the Pareto law distribution in Eq. (8) it reads

$$C=\begin{cases}\infty, \gamma\leqslant 1\\ \sqrt{\dfrac{\gamma+1}{\gamma-1}}, \gamma>1.\end{cases} \quad (50)$$

As a criterion for Markovian vs non-Markovian behavior one can propose to test the coefficients of variation $C_{1,2}$ of the experimentally determined RTDs $\psi_{1,2}(t)$. In the strict Markovian case we have $C_1=C_2=1$. Large deviations of any of the two coefficients of variation, $C_{1,2}$, from unity indicate the presence of strong non-Markovian memory effects. The proposed test-criterion appears experimentally to be more conveniently applied than the direct test of the Chapman-Kolmogorov-Smoluchowski equation [37]. For example, in the fractal model of the ion channel gating by Liebovitch *et al.* the closed residence time distribution is fitted by Eq. (7) with $a\approx 0.2$ [19]. This yields $C_{closed}\approx 15.84$. Thus, assuming that the open residence times are exponentially distributed, i.e., $C_{open}=1$, one obtains $R_{NM}\approx 126$. Furthermore, according to Ref. [21] BK ion channels display a closed residence time distribution following a Pareto law with $\beta=2+\gamma\approx 0.24$. In such a case, the memory effects should depict an infinite range since $\tau_{corr}=\infty$. In both cases, the observed two-state fluctuations do exhibit long-range temporal correlations. The gating dynamics is thus clearly non-Markovian within such a two-state description.

4. Power spectrum of fluctuations

For the power spectrum of fluctuations, i.e.,

$$S_N(\omega)=2\langle\delta x^2\rangle_{st}\int_0^\infty k(t)\cos(\omega t)dt=2\langle\delta x^2\rangle_{st}\mathrm{Re}[\tilde{k}(i\omega)], \quad (51)$$

the use of Eqs. (40) and (42) in Eq. (51) yields [22,26,28,36,38]

$$S_N(\omega)=\frac{2(\Delta x)^2}{\langle\tau_1\rangle+\langle\tau_2\rangle}\frac{1}{\omega^2}\mathrm{Re}[\tilde{G}(i\omega)]. \quad (52)$$

It is evident that asymptotically, in the limit $\omega\to\infty$, the power spectrum (52) is Lorentzian in the case of time-continuous RTDs [22,39],

$$S_N(\omega)\to\frac{2(\Delta x)^2}{\langle\tau_1\rangle+\langle\tau_2\rangle}\frac{1}{\omega^2}, \text{ as } \omega\to\infty. \quad (53)$$

This follows from the fact that $\lim_{\omega\to\infty}\psi_{1,2}(i\omega)=0$ and thus $\lim_{\omega\to\infty}\tilde{G}(i\omega)=1$ [39]. Practically this situation occurs for $\omega\gg\langle\tau_{1,2}\rangle^{-1}$. On the other hand, one can deduce from Eq. (51) that in the opposite limit for $\omega\to 0$,

$$S_N(\omega)\to S_N(0)=2\langle\delta x^2\rangle_{st}\tau_{corr}, \quad (54)$$

where $\langle\delta x^2\rangle_{st}$ is the mean-squared amplitude of stationary fluctuations given by Eq. (40) and τ_{corr} is given in Eq. (45). A very interesting situation emerges for $\tau_{corr}\to\infty$, implying $S_N(0)\to\infty$. This occurs when at least one of the residence

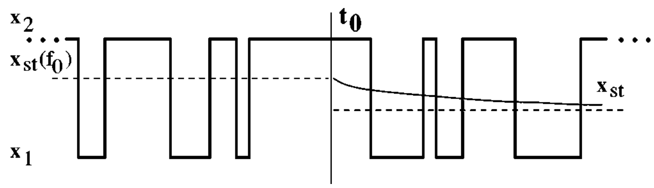

FIG. 1. Relaxation of a perturbed persistent renewal process $x(t)$. A constant force f_0 is applied long before and is released at $t=t_0$. The mean value $\langle x(t)\rangle$ relaxes from the constrained stationary value $x_{st}(f_0)$ to its true stationary value x_{st}.

time distributions possesses a diverging variance, cf. Eqs. (45)–(47). In such a case, for the low-frequency region $\omega < \langle \tau_{1,2}\rangle^{-1}$ the power spectrum drastically differs from the Lorentzian form. For example, for a symmetric TSRP with the survival probabilities given by the Pareto distributions (8) one can show [22] (see also below) that for $0<\gamma<1$, $S_N(\omega)\sim 1/\omega^{1-\gamma}$. For $\gamma\to 0$ this corresponds to celebrated $1/f$ noise [22,40].

III. PHENOMENOLOGICAL THEORY OF LINEAR RESPONSE

It is possible to predict the linear response of the underlying stochastic process $x(t)$ to the external driving $f(t)$ by referring only to information on its stationary properties, i.e., without explicit knowledge of the concrete mechanism at work by which the process $x(t)$ is perturbed by the external signal. The phenomenological theory of linear response for general stochastic processes [36,41] and for thermal physical systems [42] provides a very useful and widely applied tool to answer this question. It is also the only method available if no further detailed knowledge of the microscopic dynamics is at hand for the *observed* two-state dynamics. This is the common experimental situation. The common linear response approximation

$$\langle \delta x(t)\rangle := \langle x(t)\rangle - x_{st} = \int_{-\infty}^{t} \chi(t-t')f(t')dt', \quad (55)$$

holds independently of the underlying stochastic dynamics [36]. In Eq. (55), $\chi(t)$ denotes the linear response function in the time domain. The universality of the relation (55) allows one to find the linear response function $\chi(t)$ using a properly designed form of the perturbation $f(t)$. Within the phenomenological approach it can be obtained following an established procedure [42]: (i) First, apply a small static force f_0, (ii) then, let the process $x(t)$ relax to the constrained stationary state with mean value $x_{st}(f_0)$, and finally (iii) suddenly remove the force at $t=t_0$, see Fig. 1.

Then, in accord with Eq. (55) the response function reads

$$\chi(\tau) = -\frac{1}{f_0}\frac{d}{d\tau}\langle \delta x(t_0+\tau)\rangle, \quad \tau>0, \quad (56)$$

where $\langle \delta x(t_0+\tau)\rangle = x_1 p_1(t_0+\tau) + x_2 p_2(t_0+\tau)$ is determined by Eq. (37) with the initial $p_{1,2}(t_0)$ taken as $p_{1,2}(t_0) = \langle \tau_{1,2}(f_0)\rangle / [\langle \tau_1(f_0)\rangle + \langle \tau_2(f_0)\rangle]$. The limit $f_0\to 0$ is implicitly assumed in Eq. (56). Expanding $p_{1,2}(t_0)$ to first order in f_0 we find with $\Delta x = x_2 - x_1$

$$\langle \delta x(t_0+\tau)\rangle = \frac{\langle \delta x^2\rangle_{st}}{\Delta x}[\beta_2-\beta_1]R(\tau)f_0 + o(f_0), \quad (57)$$

where

$$\beta_{1,2} := \left.\frac{d\ln\langle \tau_{1,2}(f_0)\rangle}{df_0}\right|_{f_0=0}. \quad (58)$$

Note that in the derivation of this result it is tacitly assumed that the initial constrained stationary populations $p_{1,2}(t_0)$ at $t=t_0$ belongs to the class of time-homogeneous initial preparations [36] for the process $x(t)$ in the absence of applied force. This seems a natural and intuitively clear assumption in view of the facts that the limit $f_0\to 0$ has to be taken in Eq. (56) at the very end of calculation, and the considered process is persistent. Nevertheless, this commonly accepted assumption is a hidden hypothesis which, strictly speaking, cannot be proven within the phenomenological approach.

Upon combining Eq. (57) with the regression theorem (43) we obtain from Eq. (56), after taking the limit $f_0\to 0$, the *fluctuation theorem* [28]

$$\chi(\tau) = -[\beta_2-\beta_1]\frac{\theta(\tau)}{\Delta x}\frac{d}{d\tau}\langle \delta x(t+\tau)\delta x(t)\rangle_{st}, \quad (59)$$

wherein $\theta(t)$ denotes here the unit step function. The non-Markovian fluctuation theorem (59) presents a prominent result [28]; in particular, it does not assume thermal equilibrium [36]. In the frequency domain it reads

$$\tilde{\chi}(\omega) = \frac{(\beta_2-\beta_1)\langle \delta x^2\rangle_{st}}{\Delta x}[1 + i\omega\tilde{k}(-i\omega)], \quad (60)$$

where $\tilde{\chi}(\omega) = \int_{-\infty}^{\infty}\chi(t)e^{i\omega t}dt$ denotes the linear response function in the frequency domain, and $\tilde{k}(s)$ is given by Eq. (42). Substitution of Eqs. (42) and (40) in Eq. (60) yields

$$\tilde{\chi}(\omega) = \frac{(\beta_2-\beta_1)\Delta x}{\langle \tau_1\rangle + \langle \tau_2\rangle}\frac{i}{\omega}\tilde{G}(-i\omega), \quad (61)$$

where $\tilde{G}(s)$ is given in Eq. (34). The expression (61) together with Eq. (34) connects the linear response function $\tilde{\chi}(\omega)$ with the Laplace-transformed residence time distributions $\tilde{\psi}_{1,2}(i\omega)$, i.e., with the characteristic functions of the RTDs.

If, in addition, the mean residence times obey the thermal detailed balance relation

$$\frac{\langle \tau_1(f_0)\rangle}{\langle \tau_2(f_0)\rangle} = \exp\left(\frac{-\epsilon(T) - f_0\Delta x}{k_B T}\right), \quad (62)$$

where $\epsilon(T)$ is the free-energy difference between two metastable states, we recover for the fluctuation theorem in Eq. (59) the form that characterizes classical equilibrium dynamics [36,42,43], i.e.,

$$\chi(\tau)=-\frac{\theta(\tau)}{k_BT}\frac{d}{d\tau}\langle\delta x(\tau)\delta x(0)\rangle_{st}. \tag{63}$$

Equation (61) then yields

$$\tilde{\chi}(\omega)=\frac{(\Delta x)^2}{k_BT}\frac{1}{\langle\tau_1\rangle+\langle\tau_2\rangle}\frac{i}{\omega}\tilde{G}(-i\omega). \tag{64}$$

For example, this result is valid for an Arrhenius-like dependence of $\langle\tau_{1,2}\rangle$ on temperature T and force f_0, i.e.,

$$\langle\tau_{1,2}(f_0)\rangle=A_{1,2}\exp\left(\frac{\Delta U_{1,2}\mp\Delta x_{1,2}f_0}{k_BT}\right), \tag{65}$$

where $\Delta U_{1,2}$ are the heights of activation barriers, $\Delta x_1=z\Delta x$, $\Delta x_2=(1-z)\Delta x$ with $\Delta x=x_2-x_1$, $0<z<1$. Equation (63) presents a key result because it provides a link between the phenomenological theory of linear response theory and the actual physical processes which are in *thermal equilibrium* and do exhibit long-range time correlations. Let us assume, for example, the following situation: The observed two-state process results from thermally activated transitions in a complex potential energy landscape $U(\vec{x})$ possessing two domains of attraction (i.e., two metastable states) separated by distance Δx along the direction of the reaction coordinate x which describes transitions between the metastable states. Next, let us assume that the coupling of the external force $f(t)$ to the dynamics has the potential energy form $U_{int}=-xf(t)$. Then, the classical equilibrium fluctuation theorem (63) follows from first principles [42], or, likewise, from a mesoscopic starting point in terms of the generalized master equation for the thermal equilibrium dynamics [43]; in other words, it is exact. The nonexponential features of the RTDs in the described situation stems from the motions "perpendicular" to the above reaction coordinate x. In such a case, the thermodynamic relations like Eq. (62) are compatible with non-Markovian kinetics. This is the case where the phenomenological theory of linear response in non-Markovian systems has a firm foundation. The readers should be warned, however, that the phenomenological theory is not universally valid for nonequilibrium physical systems; see, for an example in Ref. [44]. Nevertheless, below we explicitly define an universality class of such systems (which are beyond the thermal equilibrium class) where its validity can be proven on a more general basis.

IV. ASYMPTOTIC RESPONSE THEORY BASED ON DRIVEN RENEWAL EQUATIONS

Starting from the driven renewal equations (24a)–(32) one can develop the theory of the linear and the nonlinear response which possesses a broader range of validity as compared to the above phenomenological theory. For a periodic signal (switched on in the infinite past) like in Eq. (5), the conditional survival probabilities $\Phi_{1,2}(\tau|t):=\Phi_{1,2}(t+\tau,t)$ acquire (at asymptotic times $t\gg t_0$) the time periodicity in t of the driving signal and therefore can be expanded into the Fourier series, i.e.,

$$\Phi_{1,2}(\tau|t)=\sum_{n=-\infty}^{\infty}\Phi_{1,2}^{(n)}(\tau)\exp[-in\Omega t],$$

$$\Phi_{1,2}^{(-n)}(\tau)=[\Phi_{1,2}^{(n)}(\tau)]^{*}. \tag{66}$$

Similar expansions hold also for the conditional residence time distributions $\psi_{1,2}(\tau|t)$ with the corresponding expansion coefficients $\psi_{1,2}^{(n)}(\tau)=-(d/d\tau)\Phi_{1,2}^{(n)}(\tau)$. Note that $\Phi_{1,2}^{(0)}(\tau)$ and $\psi_{1,2}^{(0)}(\tau)$ in this section denote the Fourier expansion coefficients with $n=0$. These quantities are clearly not related to the survival functions (12) and RTDs (11) of the first time interval. We hope that such use of notations will not confuse the readers. The corresponding Laplace-transformed quantities of the τ-dependent Fourier coefficients $\tilde{\psi}_{1,2}^{(n)}(s)$ and $\tilde{\Phi}_{1,2}^{(n)}(s)$ in Eq. (66) are related by

$$\tilde{\psi}_{1,2}^{(n)}(s)=\delta_{n,0}-s\tilde{\Phi}_{1,2}^{(n)}(s). \tag{67}$$

Our goal is to evaluate the asymptotic behavior of the populations $p_{1,2}^{(as)}(t)$ and of the mean value $\langle x^{(as)}(t)\rangle$. To do so, one needs to determine the asymptotic evolution operator $\Pi^{(as)}(t):=\lim_{t_0\to-\infty}\Pi(t|t_0)$. Obviously, $\Pi_{11}^{(as)}(t)=\Pi_{12}^{(as)}(t)$ and $\Pi_{22}^{(as)}(t)=\Pi_{21}^{(as)}(t)$. Moreover, $p_1^{(as)}(t)=\Pi_{11}^{(as)}(t)$, $p_2^{(as)}(t)=\Pi_{22}^{(as)}(t)$. Next, let us define the auxiliary quantity $\mathbf{G}^{(as)}(t)$ as $\mathbf{G}^{(as)}(t):=\lim_{t_0\to-\infty}\mathbf{G}(t,t_0)$. Then, Eqs. (24a) and (27) in the limit $t_0\to-\infty$ yield

$$p_1^{(as)}(t)=\int_{-\infty}^{t}\Phi_1(t,t_1)G_{11}^{(as)}(t_1)dt_1, \tag{68}$$

where $G_{11}^{(as)}(t)$ is solution of the integral equation:

$$G_{11}^{(as)}(t)=\int_{-\infty}^{t}\xi_1(t,t_1)G_{11}^{(as)}(t_1)dt_1, \tag{69}$$

with the renewal density $\xi_1(t,t_1)$ given in Eq. (29). The equation determining $p_2^{(as)}(t)$ likewise reads

$$p_2^{(as)}(t)=\int_{-\infty}^{t}\Phi_2(t,t_1)G_{22}^{(as)}(t_1)dt_1, \tag{70}$$

where $G_{22}^{(as)}(t)$ is the solution of integral equation

$$G_{22}^{(as)}(t)=\int_{-\infty}^{t}\xi_2(t,t_1)G_{22}^{(as)}(t_1)dt_1, \tag{71}$$

with $\xi_2(t,t_1)$ given in Eq. (31). Note that the conditional renewal densities $\xi_{1,2}(\tau|t):=\xi_{1,2}(t+\tau,t)$ also acquire a time periodicity in t and can be represented in the form like Eq. (66) with the corresponding expansion coefficients $\xi_{1,2}^{(n)}(\tau)$. One can show that the corresponding Laplace-transformed quantities $\tilde{\xi}_{1,2}^{(n)}(s)$ are related with the quantities $\tilde{\psi}_{1,2}^{(n)}(s)$ as follows:

$$\tilde{\xi}_1^{(n)}(s)=\sum_{m=-\infty}^{\infty}\tilde{\psi}_2^{(m)}(s)\tilde{\psi}_1^{(n-m)}(s+im\Omega),$$

$$\tilde{\xi}_2^{(n)}(s)=\sum_{m=-\infty}^{\infty}\tilde{\psi}_1^{(m)}(s)\tilde{\psi}_2^{(n-m)}(s+im\Omega). \qquad (72)$$

For periodic driving $f(t)$, both $p_{1,2}^{(as)}(t)$ and $G_{11,22}^{(as)}(t)$ must be periodic functions of time [2] and can be expanded into Fourier series

$$p_1^{(as)}(t)=\sum_{k=-\infty}^{\infty}p_{1,2}^{(k)}e^{-ik\Omega t},\quad p_{1,2}^{(-k)}=[p_{1,2}^{(k)}]^* \qquad (73)$$

and

$$G_{11,22}^{(as)}(t)=\sum_{k=-\infty}^{\infty}g_{1,2}^{(k)}e^{-ik\Omega t},\quad g_{1,2}^{(-k)}=[g_{1,2}^{(k)}]^*, \qquad (74)$$

respectively.

Using Eqs. (5) and (55) and the expansion (73) one can show that the coefficient $p_1^{(1)}$ in Eq. (73) determines the *linear response function* $\tilde{\chi}(\Omega)$ in the frequency domain as

$$\tilde{\chi}(\Omega)=-\frac{2\Delta x}{f_0}p_1^{(1)} \qquad (75)$$

in the limit $f_0\to 0$. Moreover, from the normalization condition $p_1^{(as)}(t)+p_2^{(as)}(t)=1$ it follows that

$$p_1^{(0)}+p_2^{(0)}=1,\quad p_1^{(n)}=-p_2^{(n)}\quad \text{for}\quad n\neq 0. \qquad (76)$$

Upon substituting Eqs. (73) and (74) and the expansions like Eq. (66) into Eqs. (68)–(71), performing the time integration and comparing the coefficients of the Fourier expansions on the left- and right-hand sides of the corresponding equations we finally end up with

$$p_1^{(k)}=\sum_{n=-\infty}^{\infty}\tilde{\Phi}_1^{(n)}(-ik\Omega)g_1^{(k-n)}, \qquad (77)$$

$$g_1^{(k)}=\sum_{n=-\infty}^{\infty}\sum_{m=-\infty}^{\infty}\tilde{\psi}_2^{(m)}(-ik\Omega)\times\tilde{\psi}_1^{(n-m)}(-i[k-m]\Omega)g_1^{(k-n)}, \qquad (78)$$

and

$$p_2^{(k)}=\sum_{n=-\infty}^{\infty}\tilde{\Phi}_2^{(n)}(-ik\Omega)g_2^{(k-n)}, \qquad (79)$$

$$g_2^{(k)}=\sum_{n=-\infty}^{\infty}\sum_{m=-\infty}^{\infty}\tilde{\psi}_1^{(m)}(-ik\Omega)\times\tilde{\psi}_2^{(n-m)}(-i[k-m]\Omega)g_2^{(k-n)}. \qquad (80)$$

The relations (77)–(80) also serve as the basis for a response theory without restriction on the linear response approximation. In order to apply these equations, one has to specify the expansion coefficients in Eq. (66), i.e., to specify the way how the external signal $f(t)$ enters the conditional residence time distributions $\psi_{1,2}(\tau|t)$, or, equivalently, the conditional survival probabilities $\Phi_{1,2}(\tau|t)$ to the required order in the signal amplitude f_0. It is worth noting that the solutions of Eqs. (78) and (80) are defined up to some arbitrary constants which can be fixed at the end of calculations by applying the normalization relations in Eq. (76).

In the linear response approximation, $\tilde{\Phi}_{1,2}^{(0)}(s)=\tilde{\Phi}_{1,2}(s)$, i.e., $\tilde{\Phi}_{1,2}^{(0)}(s)$ coincide with the unperturbed survival probabilities $\tilde{\Phi}_{1,2}(s)$. Moreover, $\tilde{\Phi}_{1,2}^{(1)}(s)\propto f_0$. All the higher order terms $\tilde{\Phi}_{1,2}^{(n\geq 2)}(s)$ can be neglected, being of higher order proportional to f_0^n, $n\geq 2$. The same holds true for $\tilde{\psi}_{1,2}^{(n)}(s)$. After some cumbersome algebra, one finds from Eqs. (77)–(80) an expression for $p_1^{(1)}$, which then by use of relation (75) yields

$$\tilde{\chi}(\Omega)=-\frac{2i\Delta x}{f_0\Omega}\frac{1}{\langle\tau_1\rangle+\langle\tau_2\rangle}\frac{\tilde{\psi}_2^{(1)}(-i\Omega)[1-\tilde{\psi}_1(-i\Omega)]-\tilde{\psi}_1^{(1)}(-i\Omega)[1-\tilde{\psi}_2(-i\Omega)]}{1-\tilde{\psi}_1(-i\Omega)\tilde{\psi}_2(-i\Omega)}. \qquad (81)$$

The result in Eq. (81) presents a second cornerstone result of this work. Note that this general result depends on the quantities $\tilde{\psi}_{1,2}^{(1)}(s)\propto f_0$ which do not follow directly from the characteristic functions of stationary RTDs, i.e., $\tilde{\psi}_{1,2}(s)$, but their knowledge requires one to specify a microscopic model. Generally, Eq. (81) is not mathematically reducible to the result (61) of the phenomenological theory. A question arises whether such a reduction is possible in practice and the phenomenological theory of linear response can be put on a more firm ground beyond the time-homogeneous preparation class result in Eq. (61) of which the thermal equilibrium result in Eq. (64) is a special case. Below we describe a rather broad class of relevant systems.

Models with form-invariant RTDs

Let us assume that the survival probability and the corresponding RTD can be parametrized by a single frequency parameter ν which has the meaning of an inverse mean residence time, i.e., $\nu=\langle\tau\rangle^{-1}$. Furthermore, we assume that a weak signal $f(t)$ causes ν to became time dependent, i.e.,

$$\nu\to\nu(t)=\nu[1-\beta f(t)], \qquad (82)$$

with $\beta\ll 1/f_0$ (the subscripts 1,2 are suppressed). Moreover, the survival probabilities become modified applying the following rule: $\nu\tau\to\int_t^{t+\tau}\nu(t')dt'$. More generally, let us consider arbitrary survival probabilities of the form (9) generalized to the time inhomogeneous case in the following way

$$\Phi(\tau) \rightarrow \Phi(\tau|t) = \sum_{i=1}^{\infty} c_i \exp\left(-\int_t^{t+\tau} \nu_i(t') dt' \right), \quad \sum_i c_i = 1. \tag{83}$$

In Eq. (83), we assume that (to leading order) neither the expansion coefficients c_i nor the ratios between any of $\nu_i(t)$ and $\nu_j(t)$ are modified by the applied signal $f(t)$, i.e.,

$$\frac{\nu_i(t)}{\nu_j(t)} = a_{ij}, \tag{84}$$

with a_{ij} being some structural constants. This covers fractal (although *not* multifractal) time distributions. Put differently, the scaling law which produces the whole hierarchy of rate constants out of a single rate constant is invariant of the applied signal. If the mean residence time $\langle \tau \rangle = \Sigma_i c_i / \nu_i$ exists, one can always set $\nu = \langle \tau \rangle^{-1}$ as the relevant rate constant in the absence of driving. This rate will acquire an explicit time dependence like in Eq. (82) when the signal is switched on. Given our assumptions, all the time-dependent rates $\nu_i(t)$ in Eq. (83) will be proportional to the rate $\nu(t)$ in Eq. (82). Then, in the lowest first order in βf_0, we find

$$\Phi(\tau|t) = \Phi(\tau) + \beta \psi(\tau) \int_t^{t+\tau} f(t') dt'. \tag{85}$$

From Eq. (85) we obtain upon observing Eq. (5)

$$\Phi_{1,2}^{(1)}(\tau) = \frac{1}{2} i \frac{\beta_{1,2} f_0}{\Omega} \psi_{1,2}(\tau) [\exp(-i\Omega\tau) - 1] \tag{86}$$

and

$$\tilde{\Phi}_{1,2}^{(1)}(s) = -\frac{1}{2} i \frac{\beta_{1,2} f_0}{\Omega} [\tilde{\psi}_{1,2}(s) - \tilde{\psi}_{1,2}(s + i\Omega)]. \tag{87}$$

Observing Eq. (67) by taking into account $\tilde{\psi}_{1,2}(0) = 1$ in Eq. (87) thus yields

$$\tilde{\psi}_{1,2}^{(1)}(-i\Omega) = -\tfrac{1}{2} \beta_{1,2} f_0 [1 - \tilde{\psi}_{1,2}(-i\Omega)]. \tag{88}$$

Substituting Eq. (88) into Eq. (81) we recover the result of the phenomenological theory in Eq. (61). In conclusion, for the considered class of models the nonequilibrium fluctuation theorem (61) is well justified. This model class can therefore be reconciled with the assumption of time-homogeneous initial preparations used in the phenomenological theory of linear response (see Sec. III). This assumption is naturally not always justified *a priori*. It rather delimits an important and rather broad class of corresponding physical systems. Nevertheless, the equilibrium fluctuation theorem (63) presents a fundamental relation which must be obeyed for all thermal equilibrium systems. This imposes a salient restriction on mesoscopic models leading to the observed equilibrium non-Markovian dynamics. In particular, if one knows that the considered system is in the thermal equilibrium, one must use the rigorous relation (64), rather than Eq. (81) for the calculation of the linear response. This constitutes the essence of the phenomenological theory of non-Markovian stochastic resonance developed in Ref. [28]. For other systems, e.g., for those modeling neuronal dynamics (which are far away from thermal equilibrium) the use of Eq. (81) is preferred. In order to apply Eq. (81), however, one must also specify the underlying nonequilibrium microscopic dynamics in the presence of a time-periodic stimulus. This means that the time-inhomogeneous conditional RTDs $\psi_{1,2}(\tau|t)$ must be measured, or modeled (to the linear order) in the driving signal strength. We next present a detailed study of non-Markovian stochastic resonance in *thermal equilibrium* systems that do exhibit prominent temporal long-range time correlations [28].

V. STOCHASTIC RESONANCE

In the presence of applied periodic signal (5), the spectral power amplification (SPA) [2,45], $\eta(\Omega) = |\tilde{\chi}(\Omega)|^2$ reads by use of the fluctuation theorem in Eq. (64) upon combining (39),(42),(40), (65) as follows

$$\eta(\Omega, T) = \frac{(\Delta x/2)^4}{(k_B T)^2} \frac{\nu^2(T)}{\cosh^4[\epsilon(T)/(2k_B T)]} \frac{|\tilde{G}(i\Omega)|^2}{\Omega^2}. \tag{89}$$

In Eq. (89), $\nu(T) = \langle \tau_1 \rangle^{-1} + \langle \tau_2 \rangle^{-1}$ denotes the sum of effective rates. The quantity $\epsilon(T) = \Delta U_2 - \Delta U_1 + T\Delta S$ denotes the free-energy difference between the metastable states which includes the entropy difference $\Delta S := S_2 - S_1 = k_B \ln(A_2/A_1)$. In the Markovian case we obtain $\tilde{G}(s) = s/(s+\nu)$ and Eq. (89) equals the known result, see in Refs. [2,45].

The signal-to-noise ratio (SNR) is given within linear response approximation by

$$R_{SN}(\Omega, T) := \frac{\pi f_0^2 |\tilde{\chi}(\Omega)|^2}{S_N(\Omega)}, \tag{90}$$

where $S_N(\omega)$, Eq. (51), is the spectral power of stationary fluctuations [2]. By use of Eq. (89), we obtain

$$R_{SN}(\Omega, T) = \frac{\pi f_0^2 (\Delta x/2)^2}{2(k_B T)^2} \frac{\nu(T)}{\cosh^2\left[\frac{\epsilon(T)}{2k_B T}\right]} N(\Omega), \tag{91}$$

where the term

$$N(\Omega) = \frac{|\tilde{G}(i\Omega)|^2}{\mathrm{Re}[\tilde{G}(i\Omega)]} \tag{92}$$

denotes a frequency- and temperature-dependent non-Markovian correction. For arbitrary continuous $\psi_{1,2}(\tau)$ the function $N(\Omega)$ approaches unity for high-frequency signals, $\Omega \gg \langle \tau_{1,2} \rangle^{-1}$. Thus, Eq. (91) reduces in this limit to the known Markovian result [2], i.e., the Markovian limit of SNR is assumed asymptotically in the high-frequency regime. More interesting, however, is the result for small frequency driving. In the zero-frequency limit we find $N(0)=1/R_{NM}$ with R_{NM} given in Eq. (47). With $R_{NM}=\infty$ as it is the case for the Pareto distribution (8) with $0<\gamma<1$, $N(0)=0$, i.e., $R_{SN}(\Omega=0,T)=0$ as well. Consequently, ultraslow signals are difficult to detect within the SNR-measure in a strongly non-Markovian situation.

A. Symmetric SR

As a first example, we address non-Markovian SR in a symmetric system with the survival probabilities $\Phi_{1,2}(\tau)$ described by the identical power laws (8) with $\nu=\langle\tau\rangle^{-1}$ determined from Eq. (4) with $f(t)=0$, $\nu_{1,2}^{(0)}=\nu_0$ and $\Delta U_{1,2}=\Delta U$. In this case, the Laplace-transformed RTDs read

$$\tilde{\psi}(s)=1-(\gamma\langle\tau\rangle s)^{\gamma+1}\exp(\gamma\langle\tau\rangle s)\Gamma(-\gamma,\gamma\langle\tau\rangle s), \quad (93)$$

where $\Gamma(x,y)$ is the incomplete gamma function [47]. For $0<\gamma<1$, the distribution (93) has a diverging variance; its small-s expansion reads

$$\tilde{\psi}(s)\approx 1-\langle\tau\rangle s+\gamma^{\gamma}\Gamma(1-\gamma)[\langle\tau\rangle s]^{1+\gamma}. \quad (94)$$

Using Eqs. (94) and (34) in Eq. (52) we obtain for the low-frequency part of the power spectrum

$$S_N(\omega)\approx\frac{1}{2}(\Delta x)^2\Gamma(1-\gamma)\sin(\pi\gamma/2)\frac{\gamma\langle\tau\rangle}{[\gamma\langle\tau\rangle\omega]^{1-\gamma}}. \quad (95)$$

To obtain the spectral amplification (89) and the SNR (91) numerically one has to use Eq. (93) in Eq. (34). For $\gamma>1$, the power spectrum of this process mimics a conventional Lorentzian. Moreover, for $\gamma\gg 1$, $C\approx 1$, cf. Eq. (50). Thus, one can expect that for large γ the considered situation does not differ much from the Markovian case, at least qualitatively. Indeed, for very large $\gamma\sim 100$ the discrepancy with the Markovian case in the SNR behavior vs noise intensity $D=k_BT$ is not detectable. The well-known bell-shaped stochastic resonance behavior is reproduced with the maximum at $D=\Delta U/2$. Nevertheless, in the behavior of $\eta(\Omega,T)$ some discrepancy still remains detectable even for such large γ (not shown).

Next, the case with $0<\gamma\leq 1$ is of major interest as it is qualitatively very distinct from the Markovian stochastic resonance, see Fig. 2. The reason is that the mean correlation time τ_{corr} in Eq. (44) becomes formally infinite and the power spectrum exhibits a typical $1/f^{\alpha}$- characteristics, with $\alpha=1-\gamma$, cf. Eq. (95). Nevertheless, an important time scale of the stochastic dynamics does still exist: It is defined by the mean time of stochastic turnovers between the metastable states, $\tau_0(D)=2\langle\tau\rangle$. Invoking the reasoning of a stochastic synchronization of stochastic resonance [45] one can expect stochastic resonance to occur when the time scale of stochastic turnovers $\tau_0(D)$ matches the period of external driving $\mathcal{T}=2\pi/\Omega$, i.e., $\tau_0(D)\sim\mathcal{T}$. Indeed, Fig. 2(a) unambiguously demonstrates the stochastic resonance phenomenon for a non-Markovian system with $\gamma=0.2$. Thus, the interpretation of SR as the phenomenon caused by stochastic synchronization between the time scales of the random, temperature driven transitions, and the external periodic modulations [2,45] can be extended even onto this extreme non-Markovian case (with diverging mean correlation time, $\tau_{corr}=\infty$). Note, however, that the maximal value of the spectral amplification of signal is strongly suppressed in the present case by the factor of about 20 as compared with the corresponding Markovian counterpart possessing the same $\langle\tau\rangle$, see Fig. 2(b).

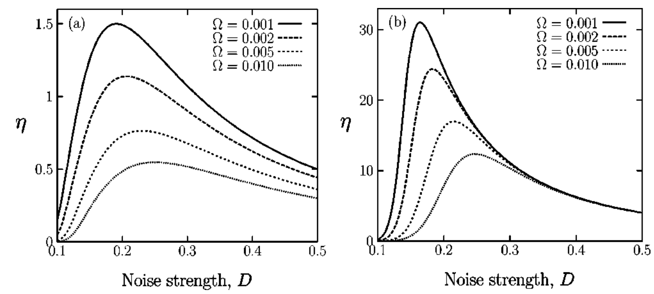

FIG. 2. The spectral amplification of the signal (in arbitrary units) is depicted vs the thermal noise intensity $D=k_BT$ at different driving frequencies Ω: (a) non-Markovian symmetric system and (b) its Markovian counterpart. In the non-Markovian case, both RTDs follow a Pareto law with $\gamma=0.2$. D is scaled in units of the barrier height ΔU; Ω is scaled in units of ν_0.

In contrast to the overall simpler behavior of the spectral amplification measure the SNR displays prime features, cf. Figs. 3(a) and 3(b). First, the SNR becomes frequency dependent. In the limit $\Omega\to 0$, we obtain for the form-factor $N(\Omega)$ in Eq. (92),

$$N(\Omega)\approx\frac{[\langle\tau\rangle\Omega]^{1-\gamma}}{2\sin(\pi\gamma/2)\gamma^{\gamma}\Gamma(1-\gamma)}. \quad (96)$$

In this limit, the signal-to-noise ratio can be approximated as

$$R_{SN}(\Omega,D)\approx\frac{\pi}{4}(f_0\Delta x/2)^2 \times\frac{(2\nu_0)^{\gamma}}{\sin(\pi\gamma/2)\gamma^{\gamma}\Gamma(1-\gamma)} \times\frac{\exp(-\gamma\Delta U/D)}{D^2}\Omega^{1-\gamma}. \quad (97)$$

This SNR expression (97) displays several nontrivial features: (i) the stochastic resonance peak occurs at smaller noise strength $D_{NM}(\Omega\to 0)=\gamma\Delta U/2$ as compare to the Markovian case, where $D_M=\Delta U/2$. (ii) The SNR displays a nontrivial, power law dependence on the angular driving frequency $R_{SN}(\Omega)\sim\Omega^{1-\gamma}$. Moreover, with the increasing angular frequency Ω of signal the signal-to-noise ratio $R_{SN}(\Omega)$ should approach its frequency independent Markovian limit. Thus, the resonance value $D_{NM}(\Omega)$ becomes frequency dependent for an intermediate range of frequencies and approaches the Markovian value D_M in the limit of high frequencies. This profound frequency dependence of non-

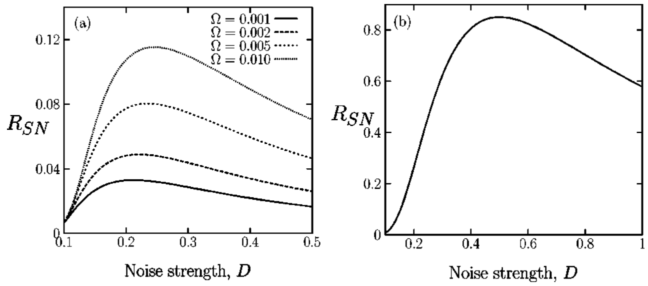

FIG. 3. Signal-to-noise ratio (in arbitrary units) vs thermal noise intensity $D=k_BT$ at different driving frequencies Ω: (a) non-Markovian symmetric system and (b) its Markovian counterpart. In the non-Markovian case, both RTDs follow a Pareto law with $\gamma=0.2$. D is scaled in the units of barrier height ΔU, Ω is measured in units of ν_0.

Markovian stochastic resonance is very distinct from its Markovian counterpart, compare Fig. 3(a) with Fig. 3(b).

B. SR in ion channels with fractal kinetics

Our second example pertains to the non-Markovian SR in an asymmetric system. An especially interesting case emerges when one of the RTDs is exponential, while the one presents a power law with a giant (divergent) dispersion. Interestingly enough, such a case apparently is realized in nature for the gating dynamics of the locust BK channel [21]. Indeed, this and some other ion channels exhibit a fractal gating kinetics together with the $1/f^{\alpha}$ noise power spectrum of fluctuations [21,23,24,46]. In the context of gating dynamics, $x(t)$ corresponds to the conductance fluctuations and the forcing $f(t)$ is proportional to the time-varying transmembrane voltage. For a locust BK channel the measured unperturbed closed time statistics $\psi_1(\tau)$ can be approximated by a Pareto law (8) with $\gamma\approx 0.24$ and $\langle\tau_1\rangle=0.84$ ms [21]. The open time RTD assumes an exponential form with $\langle\tau_2\rangle=0.79$ ms [21].

Unfortunately, neither the voltage, nor the temperature dependence of the mean residence times are experimentally available. For this reason, we employ here the common Arrhenius dependence in Eq. (65) with some characteristic parameters, namely, because the temperature dependence of open-to-closed transitions is typically strong [7], we assume a high activation barrier, i.e., $\Delta U_2=100$ kJ/mol ($\sim 40\ k_BT_{room}$). The closed-to-open transitions are assumed to be weakly temperature dependent with $\Delta U_1=10$ kJ/mol. Because $\langle\tau_1\rangle\sim\langle\tau_2\rangle$ at room temperature T_{room}, the difference between ΔU_1 and ΔU_2 is compensated by an entropy difference $\Delta S\sim -36k_B$. The physical reasoning is that the closed time statistics exhibits a power law, i.e., the conformations in the closed state form a self-similar hierarchy and are largely degenerate [46]. This in turn implies a larger entropy as compared to the open state.

The normalized autocorrelation function $k(t)$ and the power spectrum $S_N(\omega)$ of the current fluctuations are of prime interest. In the considered case, the auxiliary function (34) simplifies to

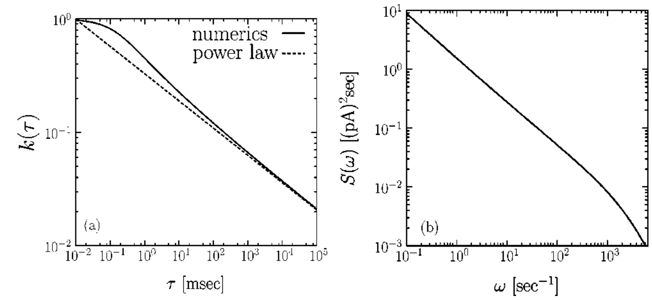

FIG. 4. (a) The normalized autocorrelation function of current fluctuations, see Eq. (39), and (b) the corresponding power spectrum for the studied model of locust BK channel. The amplitude of current fluctuations is taken to be 10 pA. The broken line in (a) corresponds to the long-time asymptotic, Eq. (100), being in agreement with the numerical result (full line) in long-time limit.

$$\tilde{G}(s)=\frac{\langle\tau_2\rangle s[1-\tilde{\psi}_1(s)]}{\langle\tau_2\rangle s+1-\tilde{\psi}_1(s)}, \tag{98}$$

where $\tilde{\psi}_1(s)$ is given by Eq. (93) with $\langle\tau\rangle=\langle\tau_1\rangle$. The Laplace transform of $k(t)$ can in the limit $s\to 0$ be approximated as

$$\tilde{k}(s)\to\frac{\gamma^{\gamma}\Gamma(1-\gamma)\langle\tau_1\rangle\langle\tau_2\rangle}{\langle\tau_1\rangle+\langle\tau_2\rangle}[\langle\tau_1\rangle s]^{\gamma-1}. \tag{99}$$

From Eq. (99) the long-time ($t\to\infty$) behavior of the autocorrelation function follows immediately by virtue of a Tauberian theorem [30], namely,

$$k(\tau)\to p_2^{st}\left(\frac{\tau}{\gamma\langle\tau_1\rangle}\right)^{-\gamma}, \tag{100}$$

where p_2^{st} is the channel's stationary opening probability. The result in Eq. (100) describes a power law decay with an exponent $\gamma=0.24$. In Fig. 4(a), this analytical result is compared with the numerical inversion of $\tilde{k}(s)$ with $\tilde{G}(s)$ in Eq. (98), obtained due to the Stehfest algorithm [48]. This figure shows that the long-time asymptotical behavior of $k(\tau)$ indeed obeys the power law in (100) for $\tau>10$ sec. However, for smaller $\tau<10$ sec some kind of transient behavior occurs which cannot be characterized by a simple power law. Nevertheless, the slow decay of correlations is clearly nonexponential.

For $\omega\gg\langle\tau_{1,2}\rangle^{-1}$ the power spectrum of fluctuations is expected to approach a Lorentzian tail, $S(\omega)\sim\omega^{-2}$. Indeed, this behavior starts in Fig. 4(b) for $\omega>500\ \mathrm{sec}^{-1}$. The nontrivial frequency dependence emerges for the sufficiently small $\omega\ll\langle\tau_{1,2}\rangle^{-1}$. In this case we obtain from Eq. (99)

$$S(\omega\to 0)\approx 2(\Delta x)^2\frac{\langle\tau_1\rangle^2\langle\tau_2\rangle^2}{(\langle\tau_1\rangle+\langle\tau_2\rangle)^3}\times\Gamma(1-\gamma)\sin(\pi\gamma/2)\frac{\gamma}{[\gamma\langle\tau_1\rangle\omega]^{1-\gamma}}. \tag{101}$$

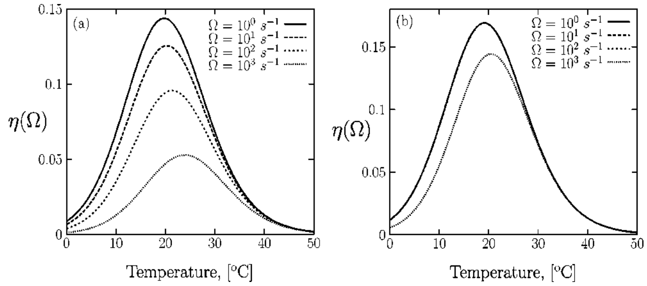

FIG. 5. (a) The spectral power amplification $\eta(\Omega)$, Eq. (89), (in arbitrary units) vs temperature (in °C) for the BK ion channel gating scenario (see text) and (b) its comparison with a corresponding Markov modeling.

Thus, for $\gamma=0.24$ we have $S(\omega\to 0)\propto 1/\omega^{\alpha}$ with $\alpha=1-\gamma=0.76$. This typical $1/f^{\alpha}$ noise behavior is depicted in Fig. 4(b). We should remark, however, that the experiment [23] gives a slightly different value of $\alpha\approx 1$. The reasons of this discrepancy are presently not clear. One possibility is that the durations of the subsequent open and closed time intervals are yet mutually correlated, contrary to the assumptions made in the present model. If this is the case indeed, the studied model should be generalized further to account for such correlations.

The spectral power amplification vs the temperature is depicted for various angular driving frequencies in Fig. 5(a). The panel in Fig. 5(b) corresponds to an overall Markovian modeling with an exponential $\psi_1(\tau)$ possessing the same mean residence time $\langle\tau_1\rangle$. We observe a series of striking non-Markovian features in Fig. 5: (i) A characteristic SR maximum occurs in the physiological range of varying temperatures. This maximum is caused by entropic effects which have not been addressed before in the theory of stochastic resonance. Because of the fact that the free-energy bias $\epsilon(T)$ is temperature dependent, due to a large entropic asymmetry between states, stochastic resonance in the spectral amplification occurs in a temperature regime where the populations of both states become approximately equal, $\epsilon(T)\approx 0$. Note that this effect occurs also in the Markovian case, cf. Figs. 5(a) and 5(b). Therefore, it is not caused by non-Markovian effects. (ii) Due to an intrinsic asymmetry the (angular) frequency dependence of the spectral amplification $\eta(\Omega,T)$ for the Markov modeling is rather weak for small frequencies $\Omega\ll\langle\tau_{1,2}\rangle^{-1}$ [2]. In contrast, the non-Markovian SR exhibits a distinct low-frequency dependence, thereby frequency resolving the three overlapping lines in Fig. 5(b). This feature constitutes an authentic non-Markovian effect. (iii) The evaluation of the SNR yields—in clear contrast to the frequency-independent Markov modeling—a profound, very strong non-Markovian SR frequency *suppression* of SNR towards smaller frequencies: The SNR maximum for the top line in Fig. 5(a) is suppressed by two orders of magnitude as compared to the Markov case, cf. Fig. 6. As a consequence, for a strong non-Markovian situation it is preferable to use low-to-moderate frequency inputs in order to monitor non-Markovian stochastic resonance with SNR.

VI. SUMMARY AND CONCLUSIONS

In the present work we have put forward a general theory of stochastic resonance for two state non-Markovian sys-

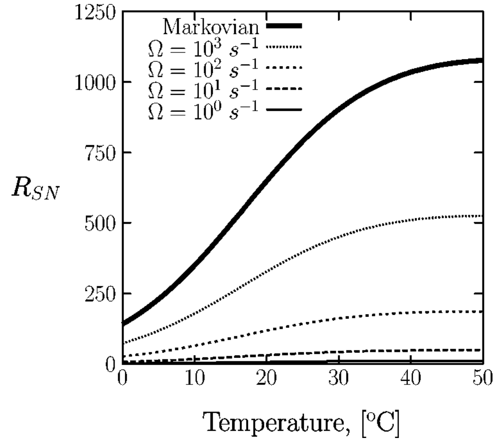

FIG. 6. The signal-to-noise ratio (R_{SN} in arbitrary units) vs temperature (in °C) for the studied model of Stochastic Resonance in a locust BK channel. The upper curve depicts the Markovian limit attained for large angular driving frequencies of the signal.

tems. The theory is based on time-inhomogeneous integral renewal equations governing the evolution of conditional probabilities in the presence of driving signal. These equations for driven renewal processes generalize earlier result by Cox [13] and others [18] for stationary renewal processes to include the signal influence on the residence time distributions. Based on these equations we presented a general outline of the theory of the linear and the asymptotic nonlinear response to the sinusoidal signal. In particular, we obtained a general expression for the linear response function $\tilde{\chi}(\omega)$, Eq. (81), which can be used for a variety of applications. The expression in Eq. (81) presents a major result of this paper. We note, however, that the explicit use of Eq. (81) requires one to specify explicitly the way in which the periodic signal modulates the asymptotic, nonequilibrium residence time distributions. For a class of nonequilibrium fractal distributions where the signal enters the RDTs through a single frequency parameter having the meaning of the inverse mean residence time, it has been shown that Eq. (81) reduces to the result (61) of the phenomenological theory of linear response developed previously in Ref. [28]. Moreover, if the mean residence times obey the thermal detailed balance condition (62), the expression (61) reduces further to Eq. (64) which can be obtained independently from the classical fluctuation-dissipation theorem (63) by use of the expression in Eq. (42) for the autocorrelation function of the considered non-Markovian stochastic process. Even though the microscopic (or mesoscopic) details of the thermal equilibrium dynamics leading to the observed two-state non-Markovian fluctuations are generally not known, the linear response function is determined uniquely by the characteristic functions of the residence time distributions $\tilde{\psi}_{1,2}(s)$ via Eqs. (64) and (34). For such equilibrium non-Markovian fluctuations, the knowledge of the equilibrium RTDs allows one to determine the linear response of the considered physical system to weak signals. This is the essence of the phenomenological theory of non-Markovian stochastic resonance put forward in Ref. [28]. For such equilibrium systems, the general expressions for the spectral power amplification, Eq. (89), and for the signal-to-noise ratio (SNR), Eq. (91), are available. We applied these general expressions to study the main features of stochastic resonance in several non-Markovian systems exhibiting long-range temporal correlations along with $1/f^{\alpha}$ power spectra of fluctuations.

In particular, for a symmetric non-Markovian system with a power law distributed residence time intervals the occurrence of stochastic resonance has been demonstrated to comply with a stochastic frequency synchronization similar to the Markovian case [2]. However, both the SPA measure and the SNR measure become strongly suppressed due to strong non-Markovian effects. The most striking feature of the non-Markovian SR is a distinct frequency dependence of the SNR measure. In particular, the SNR becomes immensely suppressed for low frequency signals. Thus, the use of signals with an intermediate frequency range matching the mean time of the stochastic escapes between states yields most distinct non-Markovian SR feature.

For asymmetric non-Markovian fluctuations pertinent to fractal gating dynamics of the locust BK ion channel several interesting features have been revealed. (i) The expected diminution of the SPA measure relative to the Markovian case does not occur. This can be attributed to the fact that one of the RDTs in the considered case is strictly exponential similar to the Markovian case. (ii) For asymmetric Markovian systems the SPA measure ceases to be frequency dependent for small adiabatic frequencies. The non-Markovian effects, however, introduce at low driving frequencies a distinct dependence, both for the SPA and the SNR. This latter phenomenon can be used to detect and establish a strong non-Markovian behavior in practice.

Our non-Markovian theory of stochastic resonance possesses a whole range of applications and we hope that it will be used by the practitioners in their further research work on stochastic resonance. Especially, we hope that our theory will guide experimentalists to find the proper and more interesting parameter regimes and to reveal the stochastic resonance effect on the level of single biomolecules.

ACKNOWLEDGMENT

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