Non-Markovian Stochastic Resonance

Igor Goychuk and Peter Hänggi
Institute of Physics, University of Augsburg, Universitätsstrasse 1, D-86135 Augsburg, Germany
(Received 19 March 2003; published 14 August 2003)

The phenomenological linear response theory of non-Markovian stochastic resonance (SR) is put forward for stationary two-state renewal processes. In terms of a derivation of a non-Markov regression theorem we evaluate the characteristic SR-quantifiers; i.e., the spectral power amplification (SPA) and the signal-to-noise ratio (SNR), respectively. In clear contrast to Markovian-SR, a characteristic benchmark of genuine non-Markovian SR is its distinctive dependence of the SPA and SNR on small (adiabatic) driving frequencies; particularly, the adiabatic SNR becomes strongly suppressed over its Markovian counterpart. This non-Markovian SR-theory is elucidated for a fractal gating dynamics of a potassium ion channel possessing an infinite variance of closed sojourn times.

DOI: 10.1103/PhysRevLett.91.070601 PACS numbers: 05.40.–a, 82.20.Uv, 87.16.Uv

The concept of stochastic resonance (SR), originally put forward for the description of the periodicity of the Earth's glacial recurrences [1], has acquired an immense popularity in the context of weak signal transduction in stochastic nonlinear systems [2]. The phenomenon of SR is seemingly rather paradoxical: an optimal dose of either external or internal noise can considerably boost signal transduction. The archetypical situation of SR involves a periodically rocked, continuous state bistable dynamics driven by thermal, white noise [2]. The essential features of the perturbed bistable dynamics can be captured by a two-state stochastic process $x(t)$ that switches forth and back between two metastable states x_1 and x_2 at random time points $\{t_i\}$. This two-state random process can be directly extracted from filtered experimental data and subsequently statistically analyzed.

If the sojourn time intervals $\tau_i = t_{i+1} - t_i$ are *independently* distributed (an assumption being invoked throughout the following), the resulting two-state renewal process is specified by two residence time distributions (RTDs) $\psi_{1,2}(\tau)$ [3]. Commonly, one follows the reasoning of McNamara and Wiesenfeld [4] i.e., one approximates the reduced dynamics by a two-state Markovian process with the corresponding RTDs being strictly exponential, $\psi_{1,2}(\tau) = \nu_{1,2}\exp(-\nu_{1,2}\tau)$. Here, $\nu_{1,2}$ are the transition rates which are given by the inverse mean residence times $\langle\tau_{1,2}\rangle := \int_0^\infty \tau\psi_{1,2}(\tau)d\tau$ i.e., $\nu_{1,2} = \langle\tau_{1,2}\rangle^{-1}$. The input signal $f(t)$ yields time-dependent transition rates $\nu_{1,2} \to \nu_{1,2}(t)$. The probabilities $p_{1,2}(t)$ of the states $x_{1,2}$ obey the Markovian master equation [2,4], i.e.,

$$\begin{aligned}\dot p_1(t) &= -\nu_1(t)p_1(t) + \nu_2(t)p_2(t),\\ \dot p_2(t) &= \nu_1(t)p_1(t) - \nu_2(t)p_2(t),\end{aligned} \tag{1}$$

with the time-dependent rates. Applying a weak periodic signal of the form $f(t) = f_0\cos(\Omega t)$ yields for the asymptotic linear response $\langle\delta x(t)\rangle = f_0|\tilde\chi(\Omega)|\cos[\Omega t - \varphi(\Omega)]$. Here, $\tilde\chi(\Omega)$ is the linear response function in the frequency domain and $\varphi(\Omega)$ denotes the phase shift. For adiabatic, Arrhenius-like transition rates $\nu_{1,2}(t)$ that depend on temperature T and driving signal $f(t)$, the linear response function $\tilde\chi(\Omega)$ is known explicitly [4]. The SPA [5,6], $\eta = |\tilde\chi(\Omega)|^2$, then displays the phenomenon of SR, i.e., the quantity η depicts a bell-shaped behavior on the thermal noise strength T [2]. This appealing two-state Markovian SR theory due to McNamara and Wiesenfeld [4] enjoys great popularity and widespread application in SR research [2]. Moreover, this seminal Markovian scheme has recently been generalized in order to unify the various situations of SR—such as periodic or aperiodic SR [7] and nonstationary SR—within a unified framework based on information theory [8].

One may encounter, however, an ample number of other physical situations where the observed stochastic two-state dynamics $x(t)$ exhibits strong temporal long range correlations that are manifestly *non-Markovian* in nature with profoundly nonexponential, experimentally observed RTDs [9–12]. In principle, any deviation of RTDs from a strictly exponential behavior constitutes a deviation from a Markovian two-state behavior [9], although in practice it can be rather small. A clearcut, genuine non-Markovian situation emerges when, e.g., one of RTDs possesses a very large, possibly infinite variance $\mathrm{var}(\tau_{1,2}) = \int_0^\infty(\tau - \langle\tau_{1,2}\rangle)^2\psi_{1,2}(\tau)d\tau \to \infty$. As a specific example, this situation occurs for the stochastic dynamics of the conductance fluctuations in biological ion channels for which the RTDs generally assume a nonexponential behavior. The corresponding RTD $\psi(\tau)$ can either be described by a stretched exponential [10], or possibly also by a power law $\psi(\tau) \propto 1/(b+\tau)^\beta$, $\beta > 0$ [11]. The case with a power law is particularly interesting: In Ref. [11] one finds that the closed time RTD for a large conductance (BK) potassium channel assumes a power law with an exponent $\beta \approx 2.24$ implying that $\mathrm{var}(\tau_{\mathrm{closed}}) = \infty$. As a consequence, the conductance fluctuations are expected to exhibit a characteristic $1/f^\alpha$ noise power spectrum $S(f)$ [12]. Indeed, this result has been confirmed for the BK ion channel [13], as well as for other types of ion channels [14].

 0031-9007/03/91(7)/070601(4)$20.00

What are the characteristic signatures of non-Markovian SR in these and several other, manifestly non-Markovian phenomena? To address this challenge we herewith put forward the non-Markovian generalization of the well-known McNamara-Wiesenfeld two-state Markov theory to the case with arbitrary, nonexponential (!) RTDs $\psi_{1,2}(\tau)$ and corresponding survival probabilities $\Phi_{1,2}(\tau) = \int_\tau^\infty \psi_{1,2}(\tau')d\tau'$, respectively [3]. There do exist a few prior studies of non-Markovian SR based on a contraction of a (Markovian) stochastic dynamics onto a non-Markovian process; see, e.g., in [2,6,15,16]. However, the case of genuine non-Markovian SR with an infinite variance of sojourn times has not been investigated previously. Moreover, in clear contrast to these prior studies [6,15,16] we do *not* presume here any knowledge of the underlying microscopic or mesoscopic dynamics. In practice, such a mesoscopic dynamics is not accessible, or is simply not known. Instead, we pursue with this work a phenomenological scheme of non-Markovian SR which is solely based on the experimentally observed RTDs $\psi_{1,2}(\tau)$ in the absence of an input signal.

Propagator for two-state renewal processes.—A first challenge presents the derivation of the propagator $\mathbf{\Pi}(t|t_0)$ of the unperturbed persistent two-state renewal process $x(t)$. The quantity $\mathbf{\Pi}(t|t_0)$ relates 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., $\vec{p}(t) = \mathbf{\Pi}(t|t_0)\vec{p}(t_0)$. One can explicitly find $\mathbf{\Pi}(t \mid t_0)$ by considering the various contributions of all possible stochastic paths that lead from $\vec{p}(t_0)$ to $\vec{p}(t)$. Let us split up these contributions as follows

$$\mathbf{\Pi}\,(t|t_0) = \sum_{n=0}^{\infty} \mathbf{\Pi}^{(n)}(t|t_0), \qquad (2)$$

where the index n denotes the number of corresponding switches that occurred during the stochastic evolution. The contribution with zero alternations is obviously given by

$$\mathbf{\Pi}^{(0)}(t|t_0) = \begin{bmatrix} \Phi_1^{(0)}(t-t_0) & 0 \\ 0 & \Phi_2^{(0)}(t-t_0) \end{bmatrix}. \qquad (3)$$

Stochastic paths with a single alternation contribute the weight

$$\mathbf{\Pi}^{(1)}(t|t_0) = \int_{t_0}^{t} dt_1 \mathbf{P}(t-t_1)\mathbf{F}^{(0)}(t_1-t_0), \qquad (4)$$

where

$$\mathbf{P}\,(t-t_0) = \begin{bmatrix} \Phi_1(t-t_0) & 0 \\ 0 & \Phi_2(t-t_0) \end{bmatrix} \qquad (5)$$

and

$$\mathbf{F}^{(0)}(t-t_0) = \begin{bmatrix} 0 & \psi_2^{(0)}(t-t_0) \\ \psi_1^{(0)}(t-t_0) & 0 \end{bmatrix}. \qquad (6)$$

Note that for the persistent renewal process to be strictly *stationary* [17], the survival probability $\Phi_{1,2}^{(0)}(\tau)$ of the *first* residence time interval $\tau_0 = t_1 - t_0$ in Eq. (3) and the corresponding RTD $\psi_{1,2}^{(0)}(\tau) = -d\Phi_{1,2}^{(0)}(\tau)/d\tau$ in Eq. (6) must be chosen differently from all subsequent ones. Stationarity requires that [3,9,17],

$$\psi_{1,2}^{(0)}(\tau) = \frac{\Phi_{1,2}(\tau)}{\langle \tau_{1,2} \rangle}, \qquad (7)$$

where $\Phi_{1,2}(\tau) = \int_\tau^\infty \psi_{1,2}(t)dt$ are the given survival probabilities. From (7) it follows that the mean residence time $\langle \tau_{1,2} \rangle$ must assume finite values, $\langle \tau_{1,2} \rangle \neq \infty$. This imposes a salient restriction. Next, the paths with two switches contribute to Eq. (2) as

$$\mathbf{\Pi}^{(2)}(t|t_0) = \int_{t_0}^{t} dt_2 \int_{t_0}^{t_2} dt_1 \mathbf{P}(t-t_2)\mathbf{F}(t_2-t_1) \times \mathbf{F}^{(0)}(t_1-t_0), \qquad (8)$$

where

$$\mathbf{F}\,(t-t_0) = \begin{bmatrix} 0 & \psi_2(t-t_0) \\ \psi_1(t-t_0) & 0 \end{bmatrix}, \qquad (9)$$

and, likewise, for all higher n. Because $\mathbf{\Pi}(t|t_0)$ depends only on the time difference, $\tau = t - t_0$, the infinite, multiple-integral series (2)–(9) can be summed exactly by use of a Laplace transform. If we denote the Laplace transform for a function $A(\tau)$ by $\tilde{A}(s) := \int_0^\infty \exp(-st)A(\tau)d\tau$ we find

$$\tilde{\mathbf{\Pi}}(s) = \frac{1}{s}\begin{bmatrix} 1 - \frac{\tilde{G}(s)}{s\langle\tau_1\rangle} & \frac{\tilde{G}(s)}{s\langle\tau_2\rangle} \\ \frac{\tilde{G}(s)}{s\langle\tau_1\rangle} & 1 - \frac{\tilde{G}(s)}{s\langle\tau_2\rangle} \end{bmatrix}, \qquad (10)$$

where

$$\tilde{G}(s) = \frac{[1-\tilde{\psi}_1(s)][1-\tilde{\psi}_2(s)]}{[1-\tilde{\psi}_1(s)\tilde{\psi}_2(s)]}, \qquad (11)$$

in agreement with the known result in Refs. [3,9].

Non-Markov Regression Theorem.—From (10) and (11) one finds the stationary probabilities as $\vec{p}^{st} = \lim_{s\to 0}[s\tilde{\mathbf{\Pi}}(s)\vec{p}(0)]$. These explicitly read $p_{1,2}^{st} = \langle\tau_{1,2}\rangle/[\langle\tau_1\rangle + \langle\tau_2\rangle]$. The generally nonexponential relaxation of $\langle x(t)\rangle$ to the stationary mean value $x_{st} = x_1 p_1^{st} + x_2 p_2^{st}$ is described by the unique relaxation function $R(\tau)$, i.e.,

$$p_{1,2}(t_0+\tau) = p_{1,2}^{st} + [p_{1,2}(t_0) - p_{1,2}^{st}]\, R(\tau), \qquad (12)$$

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

$$\tilde{R}(s) = \frac{1}{s} - \left(\frac{1}{\langle\tau_1\rangle} + \frac{1}{\langle\tau_2\rangle}\right)\frac{1}{s^2}\tilde{G}(s). \qquad (13)$$

Let us consider next the autocorrelation function

$$k(\tau) = \lim_{t\to\infty} \frac{\langle \delta x(t+\tau)\delta x(t)\rangle}{\langle \delta x^2\rangle_{st}} \qquad (14)$$

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

$$\lim_{t\to\infty}\langle x(t+\tau)x(t)\rangle = \sum_{i=1,2}\sum_{j=1,2} x_i x_j \Pi_{ij}(\tau) p_j^{st} \tag{15}$$

we find the same result as in Ref. [18]; i.e.,

$$\tilde{k}(s) = \frac{1}{s} - \left(\frac{1}{\langle\tau_1\rangle} + \frac{1}{\langle\tau_2\rangle}\right)\frac{1}{s^2}\tilde{G}(s). \tag{16}$$

Upon comparison of (13) with (16) the following regression theorem holds for these non-Markovian two-state processes, namely

$$R(\tau) = k(\tau). \tag{17}$$

The regression theorem (17), which relates the decay of the relaxation function $R(\tau)$ to the decay of stationary fluctuations $k(\tau)$, presents a first main result, yielding the cornerstone for the derivation of linear response theory for non-Markovian SR.

Linear Response Theory.—The common linear response approximation

$$\langle\delta x(t)\rangle := \langle x(t)\rangle - x_{st} = \int_{-\infty}^{t} \chi(t-t')f(t')dt', \tag{18}$$

clearly holds independently of the underlying stochastic dynamics [19]. In (18), $\chi(t)$ denotes the linear response function in the time domain. It can be found following an established procedure [20]: (i) apply a small static "force" f_0, (ii) let the process $x(t)$ relax to the constrained stationary equilibrium $\langle x(f_0)\rangle$, and (iii) suddenly remove the force at $t = t_0$. Then, in accord with (18) the response function reads

$$\chi(\tau) = -\frac{1}{f_0}\frac{d}{d\tau}\langle\delta x(t_0+\tau)\rangle, \qquad \tau > 0, \tag{19}$$

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 (12) with the initial $p_{1,2}(t_0)$ taken as $p_{1,2}(t_0) = \langle\tau_{1,2}(f_0)\rangle/[\langle\tau_1(f_0)\rangle + \langle\tau_2(f_0)\rangle]$. Expanding $p_{1,2}(t_0)$ to first order in f_0 we obtain

$$\langle\delta x(t_0+\tau)\rangle = \frac{\langle\delta x^2\rangle_{st}}{\Delta x}[\beta_2 - \beta_1]R(\tau)f_0 + o(f_0), \tag{20}$$

where $\Delta x = x_2 - x_1$ is the fluctuation amplitude and

$$\langle\delta x^2\rangle_{st} = (\Delta x)^2\frac{\langle\tau_1\rangle\langle\tau_2\rangle}{(\langle\tau_1\rangle + \langle\tau_2\rangle)^2}, \tag{21}$$

is the mean squared amplitude of the stationary fluctuations. Moreover, $\beta_{1,2} := d\ln\langle\tau_{1,2}(f_0)\rangle/df_0|_{f_0=0}$ in (20) denotes the logarithmic derivative of mean residence time with respect to the input-signal strength. Upon combining (20) with the regression theorem (17) we obtain from (19) the *fluctuation theorem*

$$\chi(\tau) = -[\beta_2 - \beta_1]\frac{\theta(\tau)}{\Delta x}\frac{d}{d\tau}\langle\delta x(t+\tau)\delta x(t)\rangle_{st}. \tag{22}$$

$\theta(t)$ denotes the unit step function. The non-Markovian fluctuation theorem (22) presents a second main result of this work; in particular, it does not assume thermal equilibrium [19]. If, in addition, the mean residence times commonly obey an Arrhenius-like dependence on temperature T and force f_0; i.e.,

$$\langle\tau_{1,2}(f_0)\rangle = A_{1,2}\exp\left(\frac{\Delta U_{1,2} \mp \Delta x_{1,2}f_0}{k_B T}\right), \tag{23}$$

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 $0 < z < 1$, we recover for the fluctuation theorem in (22) the form which, in particular, holds true for a classical equilibrium dynamics [19,20]; i.e.,

$$\chi(\tau) = -\frac{\theta(\tau)}{k_B T}\frac{d}{d\tau}\langle\delta x(\tau)\delta x(0)\rangle_{st}. \tag{24}$$

Spectral Power Amplification.—In the presence of an applied periodic signal, see below (1), the spectral power amplification (SPA) [5], $\eta(\Omega) = |\tilde{\chi}(\Omega)|^2$, where $\tilde{\chi}(\omega) = \int_{-\infty}^{\infty}\chi(t)e^{i\omega t}dt$, reads by use of the FT in (24) upon combining (14), (16), (21), and (23) as follows

$$\eta(\Omega, T) = \frac{(\Delta x/2)^4}{(k_B T)^2}\frac{\nu^2(T)}{\cosh^4[\epsilon(T)/(2k_B T)]}\frac{|\tilde{G}(i\Omega)|^2}{\Omega^2}. \tag{25}$$

In (25), $\nu(T) = \langle\tau_1\rangle^{-1} + \langle\tau_2\rangle^{-1}$ is the sum of effective rates and $\epsilon(T) = \Delta U_2 - \Delta U_1 + T\Delta S$ 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 (25) equals the known result; see in [2].

Signal-to-Noise Ratio.—The signal-to-noise ratio (SNR) within linear response theory is given by $\mathrm{SNR}(\Omega, T) := \pi f_0^2|\tilde{\chi}(\Omega)|^2/S_N(\Omega)$, where $S_N(\omega)$ is the spectral power of stationary fluctuations [2]. In the present case, $S_N(\omega) = 2\langle\delta x^2\rangle_{st}\mathrm{Re}[\tilde{k}(i\omega)]$ with $\langle\delta x^2\rangle_{st}$ from (21) and $\tilde{k}(s)$ given in (16). By use of (25), we obtain

$$\mathrm{SNR}(\Omega, T) = \frac{\pi f_0^2(\Delta x/2)^2}{2(k_B T)^2}\frac{\nu(T)}{\cosh^2[\frac{\epsilon(T)}{2k_B T}]}N(\Omega), \tag{26}$$

where the term $N(\Omega) = |\tilde{G}(i\Omega)|^2/\mathrm{Re}[\tilde{G}(i\Omega)]$ denotes a frequency and temperature dependent non-Markovian correction. For arbitrary continuous $\psi_{1,2}(\tau)$ and the high-frequency signals $\Omega \gg \langle\tau_{1,2}\rangle^{-1}$, the function $N(\Omega)$ approaches unity. Then, Eq. (26) reduces to the known Markovian result [2], i.e., the Markovian limit of SNR is assumed asymptotically in the high-frequency limit. More interesting, however, is the result for small frequency driving. In the zero-frequency limit we obtain $N(0) = 2/[\mathrm{var}(\tau_1)/\langle\tau_1\rangle^2 + \mathrm{var}(\tau_2)/\langle\tau_2\rangle^2]$. With $\mathrm{var}(\tau_{1,2}) = \langle\tau_{1,2}^2\rangle - \langle\tau_{1,2}\rangle^2 = \infty$, $N(0) = 0$; i.e., $\mathrm{SNR}(0, T) = 0$ as well. Consequently, ultraslow signals are difficult to detect within the SNR measure.

Application: fractal ion channel gating.—Let us next illustrate our main findings for the case of a manifestly non-Markovian gating dynamics of ion channels that exhibit a fractal gating kinetics together with a $1/f^\alpha$

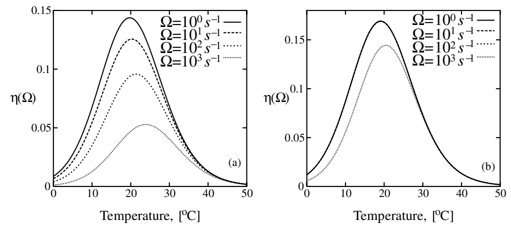

FIG. 1. (a) The spectral power amplification $\eta(\Omega)$, Eq. (25) (in arbitrary units) vs temperature (in °C) for the BK ion channel gating scenario (see text) and (b) its comparison with a corresponding Markov modeling.

noise spectrum of fluctuations [11,13]. In this context, $x(t)$ 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 can be approximated by a Pareto law; i.e., $\psi_1(\tau) = \langle\tau_1\rangle^{-1}(1+\gamma^{-1})/[1+\gamma^{-1}\tau/\langle\tau_1\rangle]^{2+\gamma}$ with $\gamma \approx 0.24$ and $\langle\tau_1\rangle = 0.84$ ms. The open time RTD assumes an exponential form with $\langle\tau_2\rangle = 0.79$ ms [11]. For low ω, the noise power reads $S_N(\omega) \propto 1/\omega^{1-\gamma}$. Unfortunately, neither voltage, nor temperature dependence of mean residence times are experimentally available. Thus, we employ here the Arrhenius dependence in (23). Namely, because the temperature dependence of the open-to-closed transitions is typically strong [21], we assume a rather high activation barrier; i.e., $\Delta U_2 = 100$ kJ/mol ($\sim 40\ k_B T_{\rm room}$). 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 $T_{\rm room}$, the difference between ΔU_1 and ΔU_2 is compensated by an entropy difference $\Delta S \sim -36\ k_B$. The physical reasoning is that the closed time statistics exhibits a power law; i.e., the conformations in the closed state are largely degenerate. This in turn yields a larger entropy as compared to the open state.

For these parameters, the spectral power amplification versus the temperature is depicted for various driving frequencies in Fig. 1(a). Furthermore, Fig. 1(b) corresponds to an overall Markovian modeling with an exponential $\psi_1(\tau)$ possessing the same $\langle\tau_1\rangle$. We observe a series of striking features in Fig. 1. (i) A distinct SR maximum occurs in the physiological range of varying temperatures (caused by the entropy effects). (ii) Because of a profound intrinsic asymmetry, the frequency dependence of the spectral amplification $\eta(\Omega, T)$ for the Markov modeling is very 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. 1(b)]. (iii) The evaluation of the SNR yields—in clear contrast to the frequency-independent Markov modeling—a very strong non-Markovian SR frequency suppression of SNR towards smaller frequencies. The SNR maximum for the top line in Fig. 1(a) is suppressed by 2 orders of magnitude as compared to the Markov case (not shown). As a consequence, for a strong non-Markovian situation it is preferable to use low-to-moderate frequency inputs in order to monitor SR.

In conclusion, we have put forward the phenomenological two-state theory of non-Markovian stochastic resonance. This approach carries great potential for many applications in physical and biological systems exhibiting temporal long range correlations, such as they occur in life sciences and geophysical phenomena (e.g., earthquakes), to name but a few. In clear contrast to Markovian-SR, a benchmark of genuine non-Markovian SR is its distinct strong frequency dependence of corresponding SR quantifiers within the adiabatic driving regime; cf. Fig. 1(a).

This work has been supported by the DFG *Sonderforschungsbereich* 486.

[1] R. Benzi, A.Sutera, and A. Vulpiani, J. Phys. A **14**, L453 (1981).
[2] L. Gammaitoni, P. Hänggi, P. Jung, and F. Marchesoni, Rev. Mod. Phys. **70**, 223 (1998).
[3] D. R. Cox, *Renewal Theory* (Methuen, London, 1962).
[4] B. McNamara and K. Wiesenfeld, Phys. Rev. A **39**, 4854 (1989).
[5] P. Jung and P. Hänggi, Phys. Rev. A **44**, 8032 (1991).
[6] P. Hänggi, P. Jung, C. Zerbe, and F. Moss, J. Stat. Phys. **70**, 25 (1993).
[7] J. J. Collins, C. C. Chow, and T. T. Imhoff, Nature (London) **376**, 236 (1995); Phys. Rev. E **52**, R3321 (1995).
[8] I. Goychuk and P. Hänggi, Phys. Rev. E **61**, 4272 (2000).
[9] M. Boguna, A. M. Berezhkovskii, and G. H. Weiss, Physica (Amsterdam) **282A**, 475 (2000).
[10] L. S. Liebovitch and J. M. Sullivan, Biophys. J. **52**, 979 (1987).
[11] S. Mercik and K. Weron, Phys. Rev. E **63**, 051910 (2001).
[12] S. B. Lowen and M. C. Teich, Phys. Rev. E **47**, 992 (1993).
[13] Z. Siwy and A. Fulinski, Phys. Rev. Lett. **89**, 158101 (2002).
[14] S. M. Bezrukov and M. Winterhalter, Phys. Rev. Lett. **85**, 202 (2000).
[15] V. I. Melnikov, Phys. Rev. E **48**, 2481 (1993).
[16] B. Lindner and L. Schimansky-Geier, Phys. Rev. E **61**, 6103 (2000).
[17] J. K. E. Tunaley, Phys. Rev. Lett. **33**, 1037 (1974).
[18] R. L. Stratonovich, *Topics in the Theory of Random Noise I* (Gordon and Breach, New York, 1963), p. 176.
[19] P. Hänggi and H. Thomas, Phys. Rep. **88**, 207 (1982).
[20] M. Toda, R. Kubo, and N. Saito, *Statistical Physics II* (Springer, Berlin, 1991).
[21] B. Hille, *Ionic Channels of Excitable Membranes* (Sinauer Assoc., Sunderland, MA, 2001), 3rd ed.