Stochastic resonance in ion channels characterized by information theory

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(Received 21 September 1999)

We identify a unifying measure for stochastic resonance (SR) in voltage dependent ion channels which comprises periodic (conventional), aperiodic, and nonstationary SR. Within a simplest setting, the gating dynamics is governed by two-state conductance fluctuations, which switch at random time points between two values. The corresponding continuous time point process is analyzed by virtue of information theory. In pursuing this goal we evaluate for our dynamics the τ information, the mutual information, and the rate of information gain. As a main result we find an analytical formula for the rate of information gain that solely involves the probability of the two channel states and their noise averaged rates. For small voltage signals it simplifies to a handy expression. Our findings are applied to study SR in a potassium channel. We find that SR occurs only when the closed state is predominantly dwelled upon. Upon increasing the probability for the open channel state the application of an extra dose of noise monotonically deteriorates the rate of information gain, i.e., no SR behavior occurs.

PACS number(s): 87.16.−b, 87.10.+e, 05.40.−a, 02.50.Wp

I. INTRODUCTION

Stochastic resonance (SR) constitutes a cooperative phenomenon wherein the addition of noise to the information carrying signal can improve in a paradoxical manner the detection and transduction of signals in nonlinear systems (see, e.g., Ref. [1] for an introductory overview, and Ref. [2] for a comprehensive survey and references). Clearly, this effect could play a prominent role for the function of sensory biology. As such, the beneficial role of ambient and external noises has been addressed not only theoretically (see, e.g., Ref. [3]), but has also been manifested experimentally on different levels of biological organization—e.g., in human visual perception [4] and tactile sensation [5], in cricket cercal sensory systems [6], in the mammalian neuronal networks [7], and (even earlier) in the mechanoreceptive system in crayfish [8]. Presumably, the molecular mechanisms of biological SR have their roots in stochastic properties of the ion channel arrays of the receptor cell membranes [1]. This stimulates interest in a study of SR in biological ion channels. One of the outstanding challenges in SR research is therefore the quest to answer whether—and how—SR occurs in single and/or coupled ion channels.

These channels are evolution's solution enabling membranes made of fat to participate in electrical signaling. They are formed of special membrane proteins [9]. In spite of their great diversity, these naturally occurring nanotubes share some common features. Most importantly, the channels are functionally bistable, i.e., they are either *open*, allowing specific ions to cross the membrane, or are *closed* [9]. The regulation of the ion flow is achieved by means of the so-called gating dynamics, i.e., those intrinsic stochastic transitions occurring inside the ion channel that regulate the dynamics of open and closed states. The key feature of gating dynamics is that the opening-closing transition rates depend strongly on external factors such as the membrane potential (voltage-gated ion channels), membrane tension (mechanosensitive ion channels), or presence of chemical ligands (ligand-gated ion channels). This sensitivity allows one to look upon the corresponding ion channel as a kind of single-molecular sensor which transmits input information to the signal-modulated ion current response.

Recently, it was demonstrated experimentally by Bezrukov and Vodyanoy [10] that a parallel ensemble of independent, although *artificial* (alamethicin) voltage-gated ion channels does exhibit SR behavior, when the information-carrying voltage signal is perturbed by a noisy component. These authors put forward the so-called *nondynamical model* of SR. It is based on a statistical analysis of a ''doubly stochastic,'' periodically driven Poisson process with a corresponding voltage-dependent spiking rate [10,11]. Conceptually, such a model can be adequate to those situations only where the channel is closed on average with openings constituting relatively rare events. An experimental challenge is to verify whether the SR effect persists for *single* natural biological ion channels under realistic conditions. Moreover, a second challenge is to extend the theoretical description in Ref. [11] to account properly for a distribution of dwell times spent by the channel in the conducting state.

The previous research on SR in ion channels was exclusively restricted to the case of conventional SR, i.e., SR with a periodic input signal. In a more general situation, however, input aperiodic signals can be drawn from some statistical distribution. This case of the so-termed *aperiodic* SR was recently put forward for neuronal systems [6,12–14]. Note that the important assumption of dealing with a signal realization that is taken from a stationary process was made in all previous studies. In practice, however, one frequently encounters a situation where this stationarity assumption is not rigorously valid, because the signal has a finite duration on the time scale set by observation. In this *nonstationary* situation, both spectral and cross-correlation SR measures are inadequate. A preferable approach is then to look for SR from the perspective of statistical information transduction [6,14]. As elucidated in this work, information theory [15] can indeed provide a *unified* framework to address different types of SR, including *nonstationary* SR. It is the main purpose of this work to investigate the possibility to enhance the transmission of information in a *single* ion channel in the presence of a dose of noise. This task will be accomplished within a simplistic two-state Markovian model for ion channel conductance [9]. Already within such an idealization, our analysis in terms of information theory measures turns out to be rather involved.

II. TWO-STATE MODEL

In principle, a microscopic description of the gating dynamics should be based upon a detailed understanding of the structure of the channel's ''gating dynamics.'' The present state of the art assumes that voltage-sensitive gates are represented by mobile charged α-helix fragments of the channel protein which can dynamically block the ion conducting pathway. Therefore, the gating dynamics can be described by a diffusive motion of gating ''particles'' in an effective potential. Then Kramers diffusion theory [16,17] and its extension to the realm of *fluctuating barriers* (see, e.g., Ref. [18] for a review and further references) can be utilized to describe the gating dynamics. Such a type of procedure, however, is still in its infancy [19]. For our purpose, it suffices to follow a well-established phenomenological road provided by a discrete phenomenological modeling [20].

The simplest two-state model of this kind reflects the functional bistability of ion channels. Dichotomous fluctuations between conducting and nonconducting conformations of *single* ion channels were clearly seen in patch clamp experiments [20]. The statistical distributions of sojourn times of the open channel state and the closed channel state, respectively, are generically not exponentially distributed [20]. However, one can characterize these time distributions by an average time $\langle T_o(V)\rangle$ to dwell in the open (O) state, and by a corresponding average time $\langle T_c(V)\rangle$, to stay in the closed (C) state. These two averages depend on the transmembrane voltage V. Then the actual multistate gating dynamics can be approximately mapped onto the effective two-state dynamics described by the simple kinetic scheme

$$O \underset{k_c(V)}{\overset{k_o(V)}{\leftrightarrows}} C,$$

with corresponding voltage-dependent effective transition rates $k_c(V)=1/\langle T_o(V)\rangle$ and $k_o(V)=1/\langle T_c(V)\rangle$, respectively. Although such a two-state Markov description presents a rather crude approximation, it captures the main features of the gating dynamics of the voltage-sensitive ion channels—the dichotomous nature and the voltage-dependence of transition rates. Moreover, by construction this model yields the correct mean open (closed) dwell times, and the stationary probability for the channel to stay open, i.e., $P_o(V)=\langle T_o(V)\rangle/[\langle T_o(V)\rangle+\langle T_c(V)\rangle]$. An example of the experimental dependence of the transition rates on voltage V can be found for a K^+ channel in Refs. [21,22], and is depicted in Fig. 1. We note that, in contrast to the closing rate k_c, the opening rate has *no exponential* dependence on the voltage. In par-

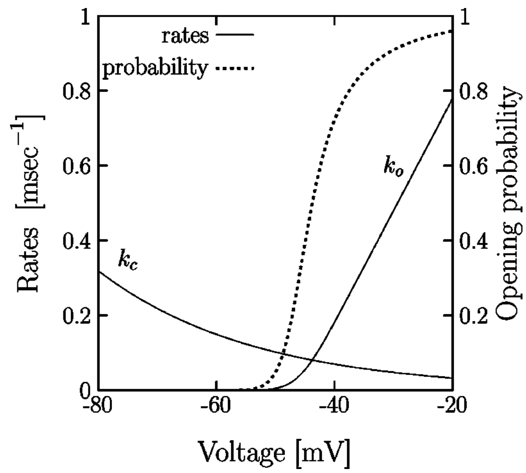

FIG. 1. Voltage dependence of the opening rate, k_o, and the closing rate, k_c, for a K^+ ion channel vs a static voltage V_0 (solid lines); cf. Eq. (A1). The corresponding probability for the channel in the open state is depicted by the dotted line.

ticular, these two rates are not symmetric (with respect to dependence on V; cf. Fig. 1). The reason for this is that the two-state description results in a *reduction* of an intrinsic multistate (or multiwell) gating dynamics, and thus presents only a shadow of the real behavior. In this sense, the Markovian approximation models the true non-Markovian dynamics on a coarse grained time scale.

To proceed, one has to generalize this working model to a case with time-dependent voltages $V(t)=V_0+V_s(t)+V_n(t)$. Here we distinguish among three components of the voltage: (i) the constant bias voltage V_0; (ii) some time-dependent, unbiased signal $V_s(t)$; and (iii) a noisy component voltage $V_n(t)$. The noisy voltage $V_n(t)$ is assumed to be a stationary Gaussian Markovian noise with zero average and root mean squared amplitude σ. Moreover, it possesses a frequency bandwidth f_n. Let us restrict our treatment to the situation where *both* the signal and the external noise are slowly varying on a time scale set by diffusive motions occurring within the open (or closed) conformation. This time scale τ_{con} typically lies in the μsec range, as manifested experimentally by the fast events in channel activation [19]. We thus can apply a *fluctuation rate* model [1,11], assuming that the transition rates $k_{o(c)}(t)\equiv k_{o(c)}[V(t)]$ follow the voltage $V(t)$ *adiabatically*. Furthermore, we assume that the applied Gaussian voltage $V_n(t)$ effectively presents ''white noise'' on the time scale set by the decay of autocorrelations of the ion current fluctuations. The autocorrelation time $\tau_I=1/[k_o(V_0)+k_c(V_0)]$ is typically of the order of milliseconds [20]. Then the choice of a noise bandwidth f_n satisfying $\tau_I^{-1}\ll f_n \ll \tau_{con}^{-1}$, i.e., $f_n\sim 10$–100 kHz, presents a consistent specification for the fluctuating rate description. The role of external noise is thus reduced within the same two-state approximation merely to forming new, noise-dressed time-dependent transition rates $\overline{k}_{\alpha=o,c}(t)\equiv\langle k_{\alpha=o,c}[V(t)]\rangle_n$. These result from taking the stochastic average of the fluctuating rates over the *external* noise. These effective rates now depend on the noise rms amplitude σ, the static voltage V_0, and the time-dependent signal $V_s(t)$. It turns out that within the given approximation the averaged transition rates do not depend on the noise bandwidth f_n; also see Appendix A.

Our models for the channel dynamics thus read

$$\frac{dP_o(t)}{dt} = -\overline{k_c}(t)P_o(t) + \overline{k_o}(t)P_c(t),$$
$$\frac{dP_c(t)}{dt} = -\overline{k_o}(t)P_c(t) + \overline{k_c}(t)P_o(t), \tag{1}$$

where $P_o(t)$ and $P_c(t)$ denote the time-dependent probabilities for a single ion channel to be open or closed, respectively. The stochastic process described by Eq. (1) is a *nonstationary* random telegraph noise with time-dependent transition rates. This model has been extensively studied in the literature, for example, to model conventional SR [2,23]. Moreover, this model was studied in Ref. [24] from the perspective of input-output cross-correlations as a simple model for *aperiodic* SR. However, to the best of our knowledge, a detailed analysis of this cornerstone model, using information theory [15,14] to specify the information transduction process, has not been developed previously.

III. STATISTICAL DISTRIBUTION OF CURRENT FLUCTUATIONS

How can we estimate the amount of information transmitted from the input voltage signal $V_s(t)$ to the output ion current $I(t)$? A comparative statistical analysis of the ion current fluctuations performed in the absence and presence of a signal allows one to answer this question.

When the channel is open, a large number of ions cross the channel, thus creating a finite, mean current $I_o(t)$. This current obeys the Ohmic law $I_o(t) = g_o[V(t) - V_k]$, where g_o is the conductivity of the open channel and V_k is the ''reversal'' potential (Nernst potential) for K^+ ion flow. When the channel is closed, the ion flow is negligible and the current is zero. We recall that the current passing through the open channel is generally time dependent in accordance with the externally applied signal $V_s(t)$. However, we will assume that information about the signal is encoded in the switching events of current between zero and $I_o(t)$, and *not* in the additional modulation of $I_o(t)$. In other words, the information is assumed to be encoded in the signal-modulated *conductance* fluctuations between g_o and zero [25].

Moreover, one can describe the resulting current fluctuations in terms of conductance fluctuations, i.e.,

$$I(t) = g(t)[V(t) - V_k], \tag{2}$$

wherein $g(t)$ is a two-state random point process [26,27]. The sample space of $g(t)$ within the time interval $[0,t]$ consists of stochastic trajectories which flip between zero and g_0 at randomly distributed switch-time points τ_i, $i = 1,2, \ldots$, i.e.,

$$0 < \tau_1 < \tau_2 < \cdots < \tau_s < t. \tag{3}$$

This defines a continuous time point process $\tau(\tilde{t})$, $0 \leq \tilde{t} \leq t$. Next we divide the sample space into two subspaces: (i) the subspace ''o'' contains all trajectories which finish in the open state at the end point t of the considered time interval, and (ii) the subspace ''c'' contains all trajectories which end in the closed state, respectively. Furthermore, within each subspace the trajectories are divided into the subclasses described by the number $s = 0,1,2, \ldots$, which enumerates the number of intermediate flips that occurred between open and closed states in order to arrive at the final state. The probability distribution on this space is given by a sequence of joint multitime probability densities $Q_s^{c(o)}(t,\tau_s, \ldots, \tau_1)$ for switches to occur at time $\tau_1, \tau_2, \ldots, \tau_s$, and to end up at time t in either the open state o or closed state c, respectively. This probability distribution is normalized, i.e.,

$$\sum_{\alpha=o,c}\left[Q_0^{\alpha}(t) + \sum_{s=1}^{\infty}\int_0^t d\tau_s \int_0^{\tau_s} d\tau_{s-1} \ldots \int_0^{\tau_2} d\tau_1 Q_s^{\alpha}(t,\tau_s, \ldots, \tau_1)\right] = 1. \tag{4}$$

The probability densities $Q_s^{c(o)}(t,\tau_s, \ldots, \tau_1)$ are readily constructed by taking into account the facts that the process $g(t)$ is (semi)-Markovian for any given realization of the voltage signal $V_s(t)$, with the switching time points τ_i being drawn alternatingly from two different *time-dependent* Poisson distributions [27]. In particular, the probability to stay in the closed conformation until time t, given that this conformation has been occupied initially with the probability $P_c(0)$, is

$$Q_0^c(t) = e^{-\int_0^t \overline{k_o}(\tau)d\tau} P_c(0). \tag{5}$$

To obtain the remaining probability densities, we introduce the conditional probability density

$$P_c(\tau_2|\tau_1) = \overline{k_o}(\tau_2)e^{-\int_{\tau_1}^{\tau_2}\overline{k_o}(\tau)d\tau} \tag{6}$$

for leaving the state ''c'' in the time interval $[\tau_2 + dt, \tau_2]$, given that this state was occupied with probability 1 at $\tilde{t} = \tau_1$. Analogous expressions, with indices changed from c to o, hold obviously also for the complementary quantities $Q_0^o(t)$ and $P_o(\tau_2|\tau_1)$. Then the multitime probability densities emerge as

$$Q_{2n}^c(t,\tau_{2n}, \ldots, \tau_1) = e^{-\int_{\tau_{2n}}^t \overline{k_o}(\tau)d\tau} P_o(\tau_{2n}|\tau_{2n-1}) \times P_c(\tau_{2n-1}|\tau_{2n-2}) \ldots P_o(\tau_2|\tau_1) \times P_c(\tau_1|0)P_c(0) \tag{7}$$

for a given even number of flips, and

$$Q_{2n+1}^c(t,\tau_{2n+1}, \ldots, \tau_1) = e^{-\int_{\tau_{2n+1}}^t \overline{k_o}(\tau)d\tau} P_o(\tau_{2n+1}|\tau_{2n}) \times P_c(\tau_{2n}|\tau_{2n-1}) \ldots P_c(\tau_2|\tau_1) \times P_o(\tau_1|0)P_o(0) \tag{8}$$

for an odd number of flips, respectively. The probability densities for the other subspace (labeled with o) can be written down by use of a simple interchange of the indices c and o in Eqs. (5)–(8).

The above reasoning yields a *complete* probabilistic description of the stochastic switching process that is related to the conductance fluctuations $g(t)$. In terms of the stochastic path description, the probability that the channel is open at the instant time t is therefore given by

$$P_o(t) = Q_0^o(t) + \sum_{s=1}^{\infty} \int_0^t d\tau_s \int_0^{\tau_s} d\tau_{s-1} \cdots \int_0^{\tau_2} d\tau_1 Q_s^o(t,\tau_s,\ldots,\tau_1). \tag{9}$$

An analogous expression also holds for the probability of the closed conformation $P_c(t)$. Upon differentiating $P_o(t)$ and $P_c(t)$ with respect to time t, one can check that these time-dependent probabilities indeed satisfy the kinetic equations (1).

IV. STOCHASTIC RESONANCE QUANTIFIED BY INFORMATION THEORY

In the following we derive a general theory for various information measures that can be used to quantify the information gain obtained from an input signal $V_s(t)$ being transduced by the ion channel current realizations $I(t)$ when $V_s(t)$ is switched on, versus the case with $V_s(t)$ being switched off. Intuitively, this information describes the difference in uncertainty about the current realizations in the absence and presence of the signal $V_s(t)$.

A. Preliminaries

We start out by reviewing the necessary background. Let us first consider a *discrete random variable* $\mathcal{A}$. As demonstrated by Shannon in 1948 [15] (his expression was discovered independently by Wiener), the information entropy

$$S(\mathcal{A}) = -\kappa \sum_{i=1}^{n} p_i \ln p_i \tag{10}$$

provides a measure of the uncertainty about a particular realization A_i of $\mathcal{A}$ [28]. In Eq. (10), the set p_i denotes the normalized probabilities for the realizations A_i to occur, $\Sigma_{i=1}^n p_i = 1$. The positive constant κ in Eq. (10) defines the unit used in the measurement. If the information entropy is measured in binary units, then $\kappa = 1/\ln 2$, natural units yield $\kappa = 1$, and digits give $\kappa = 1/\ln 10$. This measure attains a minimum (being zero) if and only if $p_i = 1$ for a particular value of i, and all others satisfy $p_i = 0$. It reaches a maximum if $p_i = 1/n$. The information entropy for a probability distribution is therefore a measure of how strongly it is peaked about a given alternative. The *uncertainty* is consequently large for spread out distributions, and small for concentrated ones.

The application of an external signal (perturbation) results in a change of probabilities p_i, and consequently in entropy $S(\mathcal{A})$. The gained information $\mathcal{I}$ is then defined by the corresponding change in entropy, i.e., $\mathcal{I} = S_{before} - S_{after}$.

The generalization of the information concept to the case of a continuous variable $A(x)$ presents no principal difficulties. In this case a proper definition of entropy reads

$$S(A) = -\kappa \int p(x) \ln[p(x)\Delta x] dx \equiv -\kappa \int p(x) \ln[p(x)] dx - \kappa \ln \Delta x, \tag{11}$$

wherein $p(x)$ is the probability density, and Δx denotes the precision with which the variable $A(x)$ can be measured (coarse graining of cell size). As clearly seen from Eq. (11), the *absolute* entropy of a continuous variable is not well defined since it diverges in the limit $\Delta x \to 0$. Nevertheless, the *entropy difference := information* is well defined, and *does not* depend on the precision Δx.

B. τ information

The generalization of information theory to the case of stochastic processes is not trivial. In our case, the proper definition of entropy of the switch-point process $\tau(\tilde{t})$, considered in the time interval $[0,T]$, is, by analogy with Eq. (11),

$$S_\tau[T|V_s] \equiv -\kappa \sum_{\alpha=o,c} \Big\{ Q_0^\alpha(T) \ln Q_0^\alpha(T) + \sum_{s=1}^{\infty} \int_0^T d\tau_s \int_0^{\tau_s} d\tau_{s-1} \cdots \times \int_0^{\tau_2} d\tau_1 Q_s^\alpha(T,\tau_s,\ldots,\tau_1) \times \ln[Q_s^\alpha(T,\tau_s,\ldots,\tau_1)(\Delta\tau)^s] \Big\}, \tag{12}$$

where $\Delta\tau$ denotes the precision of time measurement, and the symbol V_s indicates that the entropy is defined in presence of the signal $V_s(t)$. The presence of the time resolution $\Delta\tau$ in Eq. (12) gives the name "τ entropy" to this quantity [29]. It is very important that in the contrast to the case of a continuous variable, the contribution of the finite time resolution $\Delta\tau$ to the τ entropy cannot be recast in a form like $-\kappa \ln \Delta x$ [cf. Eq. (11)]. We note that its contribution *depends on the statistics of the random process* being different in the presence and absence of a signal. This is why not only the *absolute* entropy, but also the *difference* of entropies, become poorly defined for continuous time point random processes. As a result, the definition of information in this manner becomes rather ambiguous.

For a sufficiently large time interval T the averaged information transferred per unit time from the input voltage signal $V_s(t)$ to the output current signal $I(t)$ can be defined as follows [30,31]:

$$\mathcal{I}_\tau = \frac{S_\tau(T|V_s=0) - S_\tau(T|V_s)}{T}. \tag{13}$$

This information measure can be termed "τ information per unit time" to underline its dependence on the time resolution $\Delta\tau$. Upon taking the derivative of $S_\tau[t|V_s]$ in Eq. (12) with respect to time t, after some involved algebra (cf. Appendix B) we obtain the result

$$\frac{dS_\tau[t|V_s]}{dt} = -\kappa \sum_{\alpha=o,c} \overline{k}_\alpha(t)\ln[\overline{k}_\alpha(t)\Delta\tau/e]P_{\overline{\alpha}}(t), \quad (14)$$

where $\overline{\alpha}=o$, if $\alpha=c$, and vice versa. Together with Eq. (1) and the definition (13), the prominent result in Eq. (14) allows one to express the τ information for an arbitrary signal $V_s(t)$ through straightforward quadratures.

The τ-information concept was used to analyze the information transfer in neuronal systems in Refs. [30,31]. However, the strong dependence of τ information on the time precision $\Delta\tau$ [31] surely presents an undesirable *subjective* feature. In search of *objective* information measures, we consider information transfer in terms of the mutual information measure.

C. Mutual information

To introduce the reader to the mutual information concept, we follow the reasoning of Shannon [15]: the signals $V_s(t)$ are drawn from some statistical distribution characterized by the probability density functional $P[V_s(t)]$. Noting that the probability densities $Q_s^\alpha(t,\tau_s,\ldots,\tau_1)$ in Eqs. (5), (7), and (8) are in fact *conditional* with respect to the given realization of $V_s(t)$, one can define the joint probability densities, $Q_{joint}^{\alpha,s}[t,\tau_s,\ldots,\tau_1;V_s(t)] = Q_s^\alpha(t,\tau_s,\ldots,\tau_1)P[V_s(t)]$ for the corresponding stochastic processes $V_s(t)$ and $I(t)$. Moreover, one can define the averaged probability densities $\langle Q_s^\alpha(t,\tau_s,\ldots,\tau_1)\rangle_{signal}$ for the process $I(t)$ *in the presence of the process* $V_s(t)$, where the path integral $\langle\cdots\rangle_{signal} \equiv \int\mathcal{D}[V_s]\ldots P[V_s(t)]$ denotes stochastic averaging over the signal realizations. The mutual information between the stochastic process $V_s(t)$ and $I(t)$ can then be defined as the entropy difference

$$\mathcal{M}_T(V_s,I) = S_{av}(T) - \langle S_\tau(T|V_s)\rangle_{signal}, \quad (15)$$

where $S_{av}(T)$ is the τ entropy of an averaged process defined similarly to Eq. (12), but with the *averaged* probability densities $\langle Q_s^\alpha(t,\tau_1,\ldots,\tau_s)\rangle_{signal}$. Note that making use of the Bayes rules one can transform definition (15) into a form which makes transparent the fact that the mutual information $\mathcal{M}_T(V_s,I)$ is a symmetric functional of the processes $V_s(t)$ and $I(t)$, and provides a *nonlinear* cross-correlation measure between them [15]. However, we will take advantage of an equivalent form; it is obtained from Eq. (15) by using Eq. (12), yielding

$$\mathcal{M}_T(V_s,I) = \kappa\Bigg\langle \sum_{\alpha=o,c}\Bigg\{ Q_0^\alpha(T)\ln\frac{Q_0^\alpha(T)}{\langle Q_0^\alpha(T)\rangle_{signal}} + \sum_{s=1}^{\infty}\int_0^T d\tau_s \int_0^{\tau_s} d\tau_{s-1}\cdots \times\int_0^{\tau_2} d\tau_1 Q_s^\alpha(T,\tau_s,\ldots,\tau_1) \times\ln\frac{Q_s^\alpha(T,\tau_s,\ldots,\tau_1)}{\langle Q_s^\alpha(T,\tau_s,\ldots,\tau_1)\rangle_{signal}}\Bigg\}\Bigg\rangle_{signal}. \quad (16)$$

As clearly deduced from Eq. (16), Shannon's mutual information *does not* depend—due to its skillful definition in Eq. (15) – on the time resolution $\Delta\tau$. This underpins its advantage over the information measure in Eq. (13). Moreover, the functional form (16) inherits important connections between the mutual information and another prominent information measure: the (relative) Kullback entropy, also termed *information gain*.

D. Rate of information gain

Information gain [32] is given in terms of the relative entropy of the given statistical distribution with respect to some reference distribution. In our case, the reference distribution corresponds to stationary ion current fluctuations in the absence of the voltage signal $V_s(t)$. For a given signal $V_s(t)$, the information gain reads

$$\mathcal{K}_T[I|V_s] \equiv \kappa \sum_{\alpha=o,c}\Bigg\{ Q_0^\alpha(T)\ln\frac{Q_0^\alpha(T)}{Q_0^{(0)\alpha}(T)} + \sum_{s=1}^{\infty}\int_0^T d\tau_s\int_0^{\tau_s} d\tau_{s-1}\cdots \times\int_0^{\tau_2} d\tau_1 Q_s^\alpha(T,\tau_s,\ldots,\tau_1) \times\ln\frac{Q_s^\alpha(T,\tau_s,\ldots,\tau_1)}{Q_s^{(0)\alpha}(T,\tau_s,\ldots,\tau_1)}\Bigg\}, \quad (17)$$

where the index "(0)" in $Q_s^{(0)\alpha}$ refers to the case when no voltage signal is applied. The relative entropy can be regarded as a signal-induced deviation of the entropy of the random point process $\tau(\tilde{t})$ from its stationary value obtained in the absence of signal. Although the *absolute* entropy of such a switch-time point process $\tau(\tilde{t})$ depends strongly on the time resolution $\Delta\tau$ and thus is not well defined, the deviation of entropy from the steady-state value can be defined *independently* of $\Delta\tau$ via Eq. (17). For stochastic processes this relative entropy plays a role similar to the entropy difference, thus characterizing an information measure. This justifies its given name: information gain. In contrast to mutual information this measure can be defined for *deterministic* signals as well. Consequently, information gain can be used as an information measure both for conventional and aperiodic SR. Moreover, this measure is also well defined for *nonstationary* signals, and therefore can be used to quantify *nonstationary* SR as well.

In contrast to information gain, mutual information is more difficult to handle analytically. This is rooted in the fact that the *averaged* point process $\tau(\tilde{t})$ is a non-Markovian process, with corresponding joint probabilities not factorizing into products of conditional probabilities.

The following important inequality can be deduced:

$$\mathcal{M}_T(V_s,I) = \langle\mathcal{K}_T[I|V_s]\rangle_{signal} - \mathcal{K}_T[\langle I\rangle_{signal}] \le \langle\mathcal{K}_T[I|V_s]\rangle_{signal}. \quad (18)$$

In Eq. (18), $\mathcal{K}_T[\langle I\rangle_{signal}] \ge 0$ is the relative entropy of an *averaged* process $g(t)$ defined similarly to Eq. (17), but with averaged multitime probability densities $\langle Q_s^{\alpha}(T,\tau_s,\ldots,\tau_1)\rangle_{signal}$. The averaged information gain thus provides an upper bound for the mutual information. Moreover, applying a weak Gaussian signal, which can be regarded as a white noise on the time scale set by the ion current fluctuations, one can show that the difference between the mutual information and the averaged information gain in Eq. (18) is of order $O(A^4)$, where A denotes the rms amplitude of signals $A=\langle V_s^2(t)\rangle_{signal}^{1/2}$. On the other hand, it is shown below that the averaged information gain per unit time is of the order $O(A^2)$ and does not depend, within the given lowest order approximation, on other statistical parameters of signal. Thus the upper bound for mutual information in Eq. (18) can indeed be achieved with an accuracy of $O(A^2)$. This fact opens a way to calculate the informational capacity for weak signals [33].

The information gain can be evaluated from Eq. (17) without further problems. By differentiating $\mathcal{K}_T[I|V_s]$ with respect to T, we find, following the reasoning detailed in Appendix B, the remarkably simple, *main* result for the *rate of information gain*, i.e.,

$$\frac{d\mathcal{K}_t[I|V_s]}{dt}=\kappa\sum_{\alpha=o,c}\left[\overline{k}_\alpha(t)\ln\left(\frac{\overline{k}_\alpha(t)}{\overline{k}_\alpha(V_0)}\right)-\overline{k}_\alpha(t)+\overline{k}_\alpha(V_0)\right]P_{\bar{\alpha}}(t), \tag{19}$$

wherein $\overline{k}_\alpha(V_0)$ denotes the stationary transition rates in the absence of signal. Together with Eq. (1) this equation *completely* determines the information gain within the considered two-state model for any applied signal $V_s(t)$. For the case of a periodic signal $V_s(t)$ (conventional SR), or a stochastic stationary signal (aperiodic SR), one should additionally average Eq. (19) over the signal fluctuations and take the limit $t\to\infty$. In doing so, Eq. (19) yields the stationary rate of information gain. For weak stochastic signals this quantity also defines the informational capacity [33]

$$\mathcal{C}\approx\lim_{T\to\infty}\langle\mathcal{K}_T[I|V_s]\rangle_{signal}/T. \tag{20}$$

If the signal is deterministic and has a finite duration, one obtains the *total* information gain $\mathcal{K}$ by integrating Eq. (19) in a range from 0 to ∞.

V. STOCHASTIC RESONANCE IN SINGLE K^+ ION CHANNELS

In the following we apply our developed information theory concepts to investigate SR in a K^+ ion channel. We restrict our treatment to the case of weak signals with a time duration which strongly exceeds the autocorrelation time of current fluctuations τ_I. Then, after some elementary calculations in the lowest order of $V_s(t)$, Eqs. (19) and (1) yield

$$\frac{d\mathcal{K}_t[I(t)|V_s(t)]}{dt}=R(V_0,\sigma)V_s^2(t), \tag{21}$$

where the form factor

$$R(V_0,\sigma)=\frac{1}{8}\kappa\frac{\overline{k}_o(V_0)\overline{k}_c(V_0)}{\overline{k}_o(V_0)+\overline{k}_c(V_0)}[\beta_o^2(V_0)+\beta_c^2(V_0)] \tag{22}$$

depends on the static voltage V_0 and—via the rates $\overline{k}_\alpha(V_0)$—on the rms noise amplitude σ. In Eq. (22), $\beta_\alpha(V_0)=2(d/dV_0)\ln[\overline{k}_\alpha(V_0)]$, $\alpha=o$ and c, and the noise averaged rates $\overline{k}_{o(c)}(V_0)$ are given in the Appendix A for a K^+ channel in Eqs. (A2) and (A3).

In the case of stationary stochastic signals or for periodic driving, Eq. (21) provides—after stochastic averaging, or averaging over the driving period of applied voltage $V_s(t)$, respectively—the stationary rate of information gain. For signals of finite duration the total information gain is directly proportional to the total intensity of signal $\xi=\int_0^\infty V_s^2(t)dt$:

$$\mathcal{K}=R(V_0,\sigma)\xi. \tag{23}$$

As a result we find that weak signals of the the same intensity ξ produce equal information gains. The occurrence of three different kinds of SR behavior, i.e., periodic, aperiodic, and nonstationary SR, clearly depends on the behavior of the form function $R(V_0,\sigma)$ vs the rms noise amplitude σ. We recall that the static voltage (membrane potential) V_0 controls whether the ion channel is on average open or closed, cf. Fig. 1. In Fig. 2, we depict the behavior of the function $R(V_0,\sigma)$ vs the rms noise amplitude for different values of the applied static voltage. If the K^+ ion channel is closed, on average, we observe that the information gain becomes strongly amplified by noise, and can even pass through a maximum, i.e., SR occurs [cf. Fig. 2(a)]. In contrast, when the stationary probability for an open channel $P_o=k_o/(k_o+k_c)$ becomes appreciably large, the addition of an additional dose of noise can only deteriorate the detection of signal. As a result, the information gain decreases monotonically with increasing noise amplitude [cf. Fig. 2(b)]. This *no*-SR behavior occurs at a static bias of $V_0\approx-49$ mV, yielding $P_o\approx 0.08$. Note also, if the channel is predominantly open, that the information gain becomes practically insensitive to the external noise [cf. the bottom curve in Fig. 2(b)]. The occurrence of SR in the considered single ion channel thus requires that the channel is predominantly resting in its closed state.

VI. CONCLUSIONS

Let us now summarize the main results of this work. We have studied an illustrative two-state model for a single ion channel gating dynamics from an information theoretic point of view. The channel serves as an information channel, transducing information from the applied time-dependent voltage signal to the ion current fluctuations. Three different information theory measures have been developed to characterize stochastic resonance. From our viewpoint it is advantageous to use an information measure which is independent of time resolution $\Delta\tau$. We argued that the rate of information gain constitutes a unified characteristic measure for periodic (conventional), aperiodic, and nonstationary stochastic resonance. For conventional (periodic) SR and aperiodic SR this measure yields the averaged information gain per unit time.

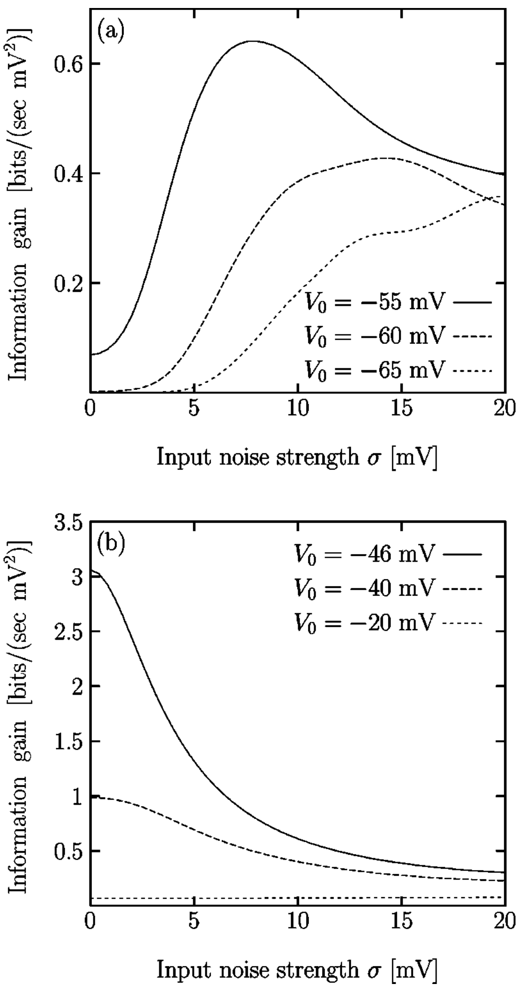

FIG. 2. Information gain versus rms amplitude of external noise σ at various static bias voltages V_0. The form function $R(V_0,\sigma)$ in Eqs. (21)–(23) is plotted vs the rms noise intensity σ.

Moreover, for weak stochastic signals it also gives the informational capacity, i.e., the maximal mutual information which can be transferred per unit time for random signals with a fixed rms amplitude. The concept of information gain can also be applied to the case of *nonstationary* deterministic signals with finite duration, i.e., nonstationary SR; cf. Eqs. (22) and (23).

Our main result is the closed formula for the rate of information gain in Eq. (19): it can be evaluated in a straightforward manner by using the corresponding probabilities of the two-state gating dynamics in Eq. (1). The information gain itself follows upon a time integration. In the presence of weak driving we derived handy analytical results given in Eqs. (21), (22), and (23). For voltage input signals referring to a stationary process the averaged rate of the information gain is determined by the rms amplitude of the signal input and by the form factor $R(V_0,\sigma)$. In the case of a nonstationary signal of finite duration, the total information gain is the product of this very form function and the integrated signal intensity ξ.

The experimental procedure for determining the rate of information gain can be formulated along the lines used for the τ entropy in Ref. [31]. First, one finds the corresponding probability histograms in the presence and absence of a signal, and then evaluates the information gain for the related stochastic chains. Naturally, this information gain will still depend on the time resolution $\Delta\tau$. However, in contrast to the τ information, this experimentally determined information gain should exhibit a much weaker dependence on the time resolution $\Delta\tau$. By using increasingly smaller time grids $\Delta\tau$, the experimentally obtained rate of information gain will approach a definite value.

Our theoretical results have been applied to investigate the phenomenon of stochastic resonance in a potassium-selective *Shaker IR* ion channel [21], as depicted within Figs. 2(a) and 2(b). Interestingly enough, we find that periodic, aperiodic, or nonstationary SR for this sort of ion channel, as quantified by the rate of information gain, is exhibited only for a situation in which the channel resides on average in a closed state. This type of behavior is rooted in the asymmetry of two rates k_o and k_c, with k_o depicting a characteristic steep, thresholdlike behavior; cf. Fig. 1.

Our SR feature is similar to the study of parallel SR in an array of alamethicin channels [10], although the two situations are not directly comparable. We note that the amount of transmitted information depends crucially on the membrane potential V_0. For the model studied the information transfer is optimized at zero noise level near $V_0 \approx -46$ mV when the opening probability becomes appreciable [note the upper curve in Fig. 2(b)]. However, under such optimal conditions the addition of external noise has the effect of only further deteriorating the rate of information transfer [Fig. 2(b)]. Upon further increasing the static bias V_0 the ion channel probability to stay open increases. The rate of information transfer then diminishes and becomes practically insensitive to the input noise level.

These results hopefully will motivate researchers to measure the predicted SR behavior in single potassium ion channels. Ever since the discovery of the SR phenomenon, the quest to use noise to optimize and control the transduction and relay of biological information has been one of the Holy Grails of SR research. Given this challenge, such and related experiments are much needed in order to settle the issue in question.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the support of this work by the German-Israel Foundation (GIF) through Grant No. G-411-018.05/95, as well as by the Deutsche Forschungsgemeinschaft, SFB 486 and HA1517/13-2.

APPENDIX A: MODEL FOR AVERAGED TRANSITION RATES IN A POTASSIUM CHANNEL

The opening and closing rates for the effective two-state model can be found from the voltage-dependent average dwell times. The latter can be determined from the experimental recordings. The experimental dependence of the effective transition rates on voltage V_0 for the potassium-selective channel *Shaker IR* embedded in the membrane of a *Xenopus* oocyte at *fixed* temperature $T = 18\,^\circ$C has been fitted [22,21] by a Hodgkin-Huxley type of data parametrization [34]. This corresponding fitting procedure yields

$$k_c(V)=a_1 e^{-b_1 V}, \quad a_1=0.015, \quad b_1=0.038, \tag{A1}$$

$$k_o(V)=\frac{a_2(V+V_2)}{1-e^{-b_2(V+V_2)}}, \quad a_2=0.03, \quad b_2=0.8, \quad V_2=46,$$

which are depicted in Fig. 1. Note that we replace the original fit of the closing rate k_c in Refs. [22,21] by a new expression in Eq. (A1). Unlike Ref. [22], our fit of experimental data in Ref. [22] is now also valid for positive voltages V. One should emphasize that the two rates in Eq. (A1) are strongly asymmetric with respect to their dependence on voltage. In particular, the opening rate $k_o(V)$ depicts a steep, thresholdlike behavior; see Fig. 1. In this work we explicitly use these experimental findings in our calculations. The rates in Eq. (A1) are measured in msec^{-1}, and the voltage in mV. According to our model study, the input voltage reads $V=V_0+V_n(t)$ when no additional signal is applied. Equations (A1) must be averaged over the realizations of $V_n(t)$ to obtain the noise averaged rates $\overline{k_o}(V_0)$ and $\overline{k_c}(V_0)$. For a Gaussian voltage noise $V_n(t)$ this averaging of the exponential in the first equation in Eqs. (A1) is governed by the second cumulant, yielding

$$\overline{k_c}(V_0)=a_1 e^{b_1^2\sigma^2/2-b_1 V_0}, \tag{A2}$$

where $\sigma=\langle V_n^2(t)\rangle^{1/2}$. The averaged opening rate

$$\overline{k_o}(V_0)=\frac{1}{\sqrt{2\pi}\sigma}\int_{-\infty}^{\infty}\frac{a_2(V_0+V_2+y)}{1-e^{-b_2(V_0+V_2+y)}}e^{-(y^2/2\sigma^2)}dy \tag{A3}$$

unfortunately cannot be analytically simplified further. However, this rate along with its derivative $d\overline{k_o}(V_0)/dV_0$ can readily be evaluated numerically from Eq. (A3).

APPENDIX B: CALCULATION OF ENTROPY AND INFORMATION GAIN

The purpose of this appendix is to provide the readers with some details of calculation of the entropic measures for the continuous time random point two-state process considered in this paper. First, we note two useful properties of the multitime probability densities which can be established from Eqs. (7) and (8). That is,

$$\frac{d}{dt}Q_s^\alpha(t,\tau_s,\ldots,\tau_1)=-\overline{k_{\bar\alpha}}(t)Q_s^\alpha(t,\tau_s,\ldots,\tau_1), \quad s\geqslant 0, \tag{B1}$$

and

$$Q_s^\alpha(t,t,\tau_{s-1},\ldots,\tau_1)=\overline{k_\alpha}(t)Q_{s-1}^{\bar\alpha}(t,\tau_{s-1},\ldots,\tau_1), \quad s\geqslant 1. \tag{B2}$$

The index α in Eqs. (B1) and (B2) takes the values $\alpha=o$ and c, and the index $\bar\alpha$ takes the value $\bar\alpha=o$, if $\alpha=c$, and vice versa. Using Eqs. (B1) and (B2), one can check that $P_{o(c)}$ given in Eq. (9) does satisfy Eq. (1).

Furthermore, let us consider the τ entropy in Eq. (12) as a sum of two contributions, $S_\tau[t|V_s]=\kappa\Sigma_{\alpha=o,c}S_\alpha(t)$, with $S_\alpha(t)$ defined from the corresponding partitioning in Eq. (12). Then, repeatedly using the relationships (B1) and (B2), after some straightforward, but lengthy calculations, we obtain

$$\frac{d}{dt}S_o(t)=-\overline{k_c}(t)S_o(t)+\overline{k_o}(t)S_c(t)+\overline{k_c}(t)P_o(t) - \overline{k_o}(t)\ln[\overline{k_o}(t)\Delta\tau]P_c(t) \tag{B3}$$

and

$$\frac{d}{dt}S_c(t)=-\overline{k_o}(t)S_c(t)+\overline{k_c}(t)S_o(t)+\overline{k_o}(t)P_c(t) - \overline{k_c}(t)\ln[\overline{k_c}(t)\Delta\tau]P_o(t). \tag{B4}$$

The addition of Eqs. (B3) and (B4) then yields Eq. (14). Likewise, splitting the information gain $\mathcal{K}_t[I|V_s]$ in Eq. (17) into the sum of two contributions, $\mathcal{K}_t[I|V_s]=\kappa\Sigma_{\alpha=o,c}K_\alpha(t)$, and invoking the properties (B1) and (B2) we obtain, after some algebra,

$$\frac{d}{dt}K_o(t)=-\overline{k_c}(t)K_o(t)+\overline{k_o}(t)K_c(t)-[\overline{k_c}(t) - \overline{k_c}(V_0)]P_o(t)+\overline{k_o}(t)\ln\left(\frac{\overline{k_o}(t)}{\overline{k_o}(V_0)}\right)P_c(t) \tag{B5}$$

and

$$\frac{d}{dt}K_c(t)=-\overline{k_o}(t)K_c(t)+\overline{k_c}(t)K_o(t)-[\overline{k_o}(t) - \overline{k_o}(V_0)]P_c(t)+\overline{k_c}(t)\ln\left(\frac{\overline{k_c}(t)}{\overline{k_c}(V_0)}\right)P_o(t). \tag{B6}$$

Adding Eqs. (B4) and (B5) results, after multiplying by κ, in our main result, in Eq. (19).

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