Dissipative stochastic mechanics for capturing neuronal dynamics under the influence of ion channel noise: Formalism using a special membrane

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Based on the idea conveyed in the author's prior study [Fluct. Noise Lett. **6**, L147 (2006)], a physical approach for the description of neuronal dynamics under the influence of ion channel noise is developed in the realm of Nelson's stochastic mechanics when open to dissipative environments. The formalism therein is scrutinized using a special membrane with some tailored properties giving the Rose-Hindmarsh dynamics in the deterministic limit. Led by the presence of multiple number of gates in an ion channel, a dual viewpoint of channel noise is established. Then, stochastic mechanics is adopted to model those channel fluctuations emerging from the uncertainty in accessing the permissible topological states of open gates. A mutual interaction between the above fluctuations and the noise, emerging from the stochasticity in the movement of gating particles between the inner and the outer faces of the membrane, is portrayed within a system plus reservoir strategy. Induced by the interaction, renormalizations of the membrane capacitance and of a membrane voltage dependent potential are found to arise. Consequently, the equations of motion, for the expectation values of the variables and the pair correlation functions, are obtained in the collective membrane voltage space.

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I. INTRODUCTION

Neuronal activity is under the influence of noise of external and internal types. Internal noise, contrary to the external type of noise that arises from synaptic transmission and network effects, is specific to neurons and generates stochastic behavior on the level of neuronal dynamics. The major source of internal noise is due to the existence of a finite number of voltage-gated ion channels in a patch of neuronal membrane and that channels have one open state and one or more closed states. The number of open channels fluctuates in a seemingly random manner [1], implying a fluctuation in the conductivity of the membrane, which, in turn, implies a fluctuation in the *membrane voltage* (the voltage difference across the membrane, commonly termed as the membrane potential). The source of the apparent random behavior of these channels is believed to be thermal excitation of a molecule with multiple stable states.

Ion channels are water filled holes in the cell membrane that are formed by proteins embedded in the lipid bilayer, with the property that each type of ion channel is selective to conduct a particular ion species. The dynamics of the coupled system composed of ions, water, protein, and lipid molecules has been treated in various approaches: (1) Continuum approximation [2–4], (2) Brownian motion of each ion [5,6], (3) molecular dynamics that takes into account the motion of the involved particles [7,8], and (4) conceiving the ion channel as a quantum system with two or more states [9]. However, the gating of ion channels is typically modeled, without any reference to the molecular details, by means of a Markovian kinetic scheme, in which, stochastic state transitions depend instantaneously on the membrane voltage [1,2]. If a two-state (open or closed) ion channel specification is assumed, the Markovian transitions can fully be characterized by the following *residence time probability distributions* of staying in open and closed states, respectively: $\phi_o(\tau) = r_o \exp(-r_o\tau)$ and $\phi_c(\tau) = r_c \exp(-r_c\tau)$, where r_o is the opening rate and r_c is the closing rate. If a multistate (one open state and more than one closed states) ion channel specification is assumed, the autocorrelation function for single-channel conductance is a multiexponential function. The experimental investigations, using the patch clamp technique which permits measuring ionic currents through individual ion channels, reveal however that the closed state residence time distribution is actually not of exponential type [1]. Non-exponential distributions such as the stretched exponential $\phi_c(\tau) \propto -(d/d\tau)\exp(-(\nu\tau)^\alpha)$ and the power law $\phi_c(\tau) \propto \tau^{-\beta}$ have been proposed as alternatives to the Markovian scheme, where ν, α, and β are some parameters [10–13]. The parameters in these distributions are, however, far from being universal. For example, although it has been measured that $\beta = 1.5$ for a potassium channel [14], $\beta \approx 1.7$ for a gramicidin channel [15] and the values $\beta > 2$ in other experiments [16] were also reported. The ion channel gating for the case of power law distribution with $\beta = 1.5$ can be modeled using normal conformational diffusion over multiple degenerate substates [11,17–23]. A generalization of these discrete diffusion models has also been put forward, in which, depending on the chosen parameters, power-law-like residence time distributions with different characteristic time regimes in several types of ion channels are exhibited [24]. Additionally, a three state model of channel gating, in which an inactivated state from the closed state is accommodated with the assumption that the channel's inactivation occurs from the closed state with a voltage independent rate, was introduced [25].

Neuronal dynamics subject to ion channel noise has been modeled by means of representing the stochasticity of ion channels as an additional voltage dependent Gaussian noise term introduced into the deterministic equations of motion for the gating variables [26] or the conductances [27], in the Hodgkin-Huxley model [28]. Here, the term (*ion*) *channel noise* denotes how particular responses of populations of ion channels differ from the mean behavior. Fox and Lu [26]

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used a stochastic automaton model of the *channel gates* with exponential probabilities for the residences both in open and closed gate states, in which the voltage dependent rate constants are the same as of the Hodgkin-Huxley model. Despite the model does not yield the Hodgkin-Huxley equations in the deterministic limit, a good quantitative agreement between the two holds. Internal noise from ion channels has been shown to be sufficient to cause spontaneous activity (repetitive firing or bursting) in otherwise quiet neuronal models [27,29–36], and has been studied in the context of the coherence of the generated spike trains [37–41]. The effects of channel noise and temperature on more complicated behavior such as the coexistence of different dynamical states (in particular, the states of bursting and tonic firing) and noise-induced transitions among these dynamical states have attracted attention recently and have only started to be investigated within the past few years [42–45].

In a recent paper [46], we have proposed the utilization of Nelson's stochastic mechanics [47,48], in the presence of dissipation, for modeling the effects of ion channel noise on the voltage dynamics of the membrane. In that framework, the membrane voltage takes the place of the position and the momentum operator is defined in the membrane voltage space. Like in the extremely fruitful system plus reservoir strategies, often employed in the study of open systems, there are two systems coupled to each other, and influenced by the channel fluctuations: (1) The system of interest described in the membrane voltage space through a voltage dependent potential; (2) a system of microscopic dynamical variables causing dissipation in the number of open ion channels. Induced by the coupling between the two systems, some correction terms arise as a result of the renormalizations of the membrane capacitance and of a voltage dependent potential. The idea conveyed in Ref. [46], however, is in its infancy mainly because it relies on an ansatz and that the embracement of an open quantum mechanical type of formalism in it needs further justification. It is the central issue of the present treatise on the matter to elucidate the fundamentals of the proposal in Ref. [46], and to elaborate the raw formalism therein. In doing so, led by the presence of multiple number of gates in an ion channel, we establish a viewpoint, playing a vital role in the study, that conformational changes in ion channels are exposed to two kinds of noise that are different in character. The need for the adoption of stochastic mechanics to study the effects of channel noise follows from this viewpoint. The manuscript also covers derivation of the equations of motion for the pair correlation functions describing neuronal diffusion. We do not conduct an investigation into a certain type of biological neuron, but rather pursue a search for the possible universal mechanisms (independent of the structural details of the neuron) that might lie behind the profound effects of channel noise. In this respect, we adopt an idealized membrane tailored to highlight the most prominent features so that the whole analysis becomes more manageable and crispier. No particular residence time distribution is presupposed for the channels or for the gates, but a temperaturelike parameter, the value of which needs to be determined by phenomenological means, is introduced. In our analysis it is presumed, just for the sake of simplicity, that the Rose-Hindmarsh model [49], rather than the Hodgkin-Huxley model, is the proper model of the deterministic neuron.

This paper is organized as follows. Section II gives the description of our viewpoint that conformational changes in ion channels are subject to two different kinds of noise. Section III includes the basic concept of stochastic mechanics and covers a brief discussion on stochastic mechanics open to dissipative environments. Properties of the special excitable membrane that we use is the subject of Sec. IV. How having multigate channels necessitates the adoption of stochastic mechanics to study the effects of ion channel noise is discussed in Sec. V. A system, called the intrinsic system, that leads to dissipation in the channel dynamics is specified in Sec. VI. The equations of motion, for both the expectation values of the variables and the pair correlation functions, for the noisy voltage dynamics of our membrane are obtained in Sec. VII. Finally, Sec. VIII includes some concluding remarks and further discussion.

II. DUAL NATURE OF ION CHANNEL NOISE

Since the experimental detection of an electrical current flow within the membrane associated with the movement of some charged particles called *gating particles* [50–53], there is little doubt that the conducting state of a channel depends on the binding of a gating particle to a site (or channel gate) on the outer face of the membrane. For a four-gate channel, like the potassium channel, all the four gates must be occupied by gating particles in order for the channel to open. Upon depolarization of the membrane, the fraction of channels with a gating particle on the binding site will increase, as will the total ionic conductance of the membrane. Modeling gating kinetics and relating microscopic charge movement to macroscopic currents is an ongoing study. Alternatives to the traditional discrete-state Markov model in describing gating current kinetics of ion channels have been proposed. The use of Kramers' diffusion theory of reaction rates is one of them, in which a voltage dependent ion channel is treated as a Brownian motion particle undergoing spatial diffusion along a one-dimensional energy landscape [22,54]. Another alternative is the use of the Ramo-Shockley theorem that states a formula for the total current flowing into an electrode, held at a fixed voltage, in the voltage-clamp experiments [55].

It easily follows from the above perspective that conformational changes in ion channels are exposed to two different kinds of noise. First, voltage dependent movement of gating particles between the inner and the outer faces of the membrane is stochastic; therefore, gates open and close in a probabilistic fashion, that is it is the average number, not the exact number, of open gates over the membrane is specified by the voltage. The noise in this action will be coined as the *intrinsic noise*. The second kind of noise, entirely dissimilar in character to the intrinsic noise, comes up due to the presence of multiple number of gates in the channels. It is related to the fluctuations in the topology of open gates, rather than the fluctuations in the number of open gates. For example, in a toy membrane just having three potassium channels (twelve gates), nine open gates can be configured into a va-

riety of *topological states* with the possible results that none of the channels is open, one is open, or two are open. Since gating particles, throughout the dynamics, do not follow a prescribed order in occupying the available closed gates, and in vacating the open gates, the membrane at two different times may have the same number of open gates but two different conductance values. Hence, all the permissible topologies of open gates should be respected in determining the voltage dynamics. These fluctuations emerging from the uncertainty in accessing permissible topological states will be coined as the *topological noise*.

Since intrinsic and topological noises come up from different sources, their effects on the voltage dynamics should be formulated individually, nevertheless in a coupled form, as there is an interaction between the two through the membrane voltage. This is the main objective of the present paper. We note at this point that, in the currently available studies of other researchers that model the effects of channel noise on the voltage dynamics, topological noise is ignored or averaged out. In the seminal paper of Fox and Lu [26], for instance, the stochastic versions of the proportions of open gates, n for potassium and m for sodium, are introduced first in a master equation, and then, they are simply raised to the appropriate power, like n^4, to obtain the conductances in a Langevin description, in which the stochasticity of ion channels is represented by an additional voltage dependent Gaussian noise term introduced into the deterministic equations of motion for the gating variables. But then, undermining the fluctuations in n and m implies lack of fluctuations in the conductances. Likewise, in the frequently cited study of Chow and White [27], an additional voltage dependent Gaussian noise term is introduced for the conductances, and, if the covariance of the gate openness, over the ensemble of gates, is undermined then the channel covariance vanishes. That is to say, these models accommodate only the intrinsic noise.

III. DISSIPATIVE STOCHASTIC MECHANICS

A. Teaspoonful of stochastic mechanics

The subject named usually as *stochastic mechanics* was introduced by Nelson [47,48] and up to now many authors, such as Refs. [56–62], have proposed complementary or alternative works to Nelson's first formal approach. Stochastic mechanics provides a classical probabilistic description of quantum phenomena. For each quantum system, there is a corresponding Markov process. The spatial probability distributions of a quantum system and the corresponding Markov process coincide at any moment and, therefore, there is an agreement between the two in predicting all the observed correlations at different times. In Nelson's approach, a particle subject to Brownian motion is considered and when two Wiener processes, forward and backward, that describe Brownian motion are combined together they transform Newton's equation of dynamics into the Schrödinger equation and yield the complex nature of the wave function. In his derivation, Nelson studied Brownian motion in a medium with zero friction and used the Einstein-Smoluchowski theory for the kinematics, but for Newtonian dynamics he used the Ornstein-Uhlenbeck theory. It was assumed that the particle of mass m undergoes a Brownian motion with a diffusion constant D inversely proportional to m:

$$D = \frac{g}{2m}. \tag{1}$$

Here, g is normally identified with the Planck's constant $\hbar$ so that the derivation results precisely in the Schrödinger equation. The expectation values, which actually correspond to the average values of the observables over the whole ensemble of the classical sample paths, then follows from the probability density $|\psi(x,t)|^2$ of the stochastic position variable $x(t)$ at at any instant of time t, where ψ satisfies the Schrödinger equation

$$ig\frac{\partial\psi(x,t)}{\partial t} = -\frac{g^2}{2m}\frac{\partial^2\psi(x,t)}{\partial x^2} + U(x)\psi(x,t) \tag{2}$$

for the Newtonian potential $U(x)$.

In the approach of stochastic mechanics, pure states of isolated quantum systems, i.e., wave functions, are associated with Markovian random processes [63,64]. As an example, consider the isolated one-dimensional harmonic oscillator with Hamiltonian

$$H(q,\theta) = \frac{\theta^2}{2m} + \frac{1}{2}\omega^2 q^2. \tag{3}$$

The following wave function provides a coherent state associated with each solution $\{q(t),\theta(t)\}$ of the classical equations of motion of the oscillator:

$$\psi(x,t) = \left(\frac{\pi g}{m\omega}\right)^{-1/4}\exp\left[-\frac{m\omega}{2g}(x-q(t))^2 + \frac{i}{g}x\theta(t) - \frac{i}{2g}\theta(t)q(t) - \frac{i\omega}{2}t\right]. \tag{4}$$

Then, the diffusion process $x(t)$ corresponding to Eq. (4) obeys

$$\dot{x}(t) = \frac{\theta(t)}{m} - \omega(x(t)-q(t)) + \eta(t), \tag{5}$$

where the overdot denotes time derivative, and $\eta(t)$ is a Gaussian white noise with expectations

$$\langle\eta(t)\rangle = 0, \tag{6a}$$

$$\langle\eta(t)\eta(t')\rangle = \frac{g}{m}\delta(t-t'). \tag{6b}$$

The process can also be written in the following form [65,66]:

$$x(t) = \xi(t) + q(t), \tag{7}$$

where

$$\dot{q}(t) = \frac{\theta(t)}{m}, \tag{8a}$$

$$\dot{\theta}(t) = -m\omega^2 q(t), \tag{8b}$$

$$\dot{\xi}(t) = -\omega\xi(t) + \eta(t). \tag{8c}$$

The expectation values of the above stochastic variables satisfy $\langle\xi(t)\rangle=0$, $\langle x(t)\rangle=q(t)$, and $\langle\dot{x}(t)\rangle=\dot{q}(t)$. The variable $\xi(t)$ governed by Eq. (8c) is the stationary stochastic process associated with the ground-state of the harmonic oscillator. Thus, the process $x(t)$ for the coherent state of the harmonic oscillator, described by Eq. (4), is given by the classical deterministic trajectory $q(t)$ surrounded by the quantum noise of the ground state.

Even though a common goal of theories in stochastic mechanics lie on the possibility of finding a stochastic process that is equivalent to quantum mechanics, the approach can naturally be applied within the scope of classical statistical mechanics from which it originates. In the present paper, primarily, aspects of stochastic mechanics from the classical point of view and its correspondance with quantum mechanics in the mathematical sense will concern us, and therefore, it is not an absolute necessity to presume that stochastic mechanics and quantum mechanics are equivalent in the physical sense. Hence, we will make no attempt to pursue a discussion on the pros and cons of the stochastic interpretation of quantum mechanics in comparison with the widely accepted Copenhagen interpretation.

B. Stochastic mechanics open to dissipative environments

Early studies of stochastic mechanics in the presence of dissipative forces from the environment were based on a rather phenomenological approach in which it was presumed that thermal and statistic influence of the external world can be formulated without a detailed description of the interaction between the system and the external world [67,68], by means of the following nonlinear integro-differential equation known as the Schrödinger-Langevin equation:

$$ig\frac{\partial\psi(x,t)}{\partial t} = -\frac{g^2}{2m}\frac{\partial^2\psi(x,t)}{\partial x^2} + U(x)\psi(x,t) + \frac{\gamma g}{2mi}\left(\ln\frac{\psi(x,t)}{\psi^*(x,t)} - \left\langle\ln\frac{\psi}{\psi^*}\right\rangle_t\right)\psi(x,t), \tag{9}$$

where $\langle.\rangle_t$ denotes the expectation value at time t and γ is the friction coefficient. However, one can argue that the corresponding Schrödinger-Langevin equation can not be the correct description of the frictional phenomena on the grounds that it lacks the potential renormalization, as against the system plus reservoir strategies in open quantum systems [69,70]. In addition, if the potential function includes linear and quadratic terms of x, then the corresponding Schrödinger-Langevin equation, incorrectly, results in a time dependent diffusion constant; a time independent diffusion constant arises only for pure harmonic motion [71].

In addition to the Schrödinger-Langevin equation, Nelson's quantization method has also been extended, for the systems interacting with a thermal environment, in such a way that the states of the system are still described by random processes, with the important difference that randomness is partly of quantum origin, as for pure states, and partly due to the elimination of the degrees of the environment, as in the classical treatment of Brownian motion [72,73]. In this context, consider a system of $N+1$ particles with a quadratic Hamiltonian

$$H = \frac{1}{2}\mathbf{p}\cdot\mathbf{p} + \frac{1}{2}\sum_{n=0}^{N}\omega_n^2 q_n^2 + q_0\sum_{n=1}^{N}\kappa_n q_n, \tag{10}$$

where $\mathbf{q}=(q_0,q_1,\ldots,q_n)$ and $\mathbf{p}=(p_0,p_1,\ldots,p_n)$ are the position and momentum vectors for the entire system. This model, also known as the Ullersma model, describes a harmonic oscillator (central or Brownian) with frequency ω_0, linearly coupled with a thermal bath constituted by the ensemble of the remaining N oscillators, with frequencies ω_n. The stochastic quantization results for this system, based on the elimination of the degrees of the environment, are compatible (of course, when $g=\hbar$) with the quantum solution [73].

The quantum solution for the Ullersma model was obtained, regarding $q_n(t)$ and $p_n(t)$ as operators in the Heisenberg representation and considering an initial condition specified by thermal equilibrium for the entire system, using a system plus reservoir strategy, in which, the central oscillator corresponds to the system [74–77]. The solution was derived in the limit of large number of oscillators, $N\to\infty$, by introducing a continuum of frequencies characterized by the spectral strength function

$$\gamma(\omega)\Delta\omega = \sum_{\omega<\omega_n<\omega+\Delta\omega}\kappa_n^2 \tag{11}$$

and the expectation value $\langle q_0\rangle_t$ was found to obey the familiar Langevin type equation

$$\frac{d^2\langle q_0\rangle_t}{dt^2} = -\Omega^2\langle q_0\rangle_t - \Gamma\frac{d\langle q_0\rangle_t}{dt}, \tag{12}$$

where

$$\Gamma\delta(t) \cong \frac{1}{2}\int_0^\infty d\omega\frac{\gamma(\omega)}{\omega^2}\cos(\omega t) \tag{13}$$

and

$$\Omega^2 = \omega_0^2 - \int_0^\infty d\omega\frac{\gamma(\omega)}{\omega^2}. \tag{14}$$

It is important to note that frequency of the central oscillator appears in Eq. (12) as if it is Ω rather than ω_0; the frequency is renormalized to Ω as prescribed by Eq. (14). Arousal of such renormalizations is a common experience in open quantum systems as the coupling to the reservoir induces such effects [69,70]. The Schrödinger-Langevin equation, Eq. (9), on the other hand, does simply result in the Langevin equation with no renormalizations. The frequency renormalization also occurs when the Ullersma model is quantized using Nelson's quantization method [73] as follows:

$$\Omega^2 = \omega_0^2 - \sum_{n=1}^{N}\frac{\kappa_n^2}{\omega_n^2}, \tag{15}$$

which coincides with Eq. (14) in the limit of large reservoir. When this result is combined with the calculation of the pair

correlation functions, it is seen that stochastic quantization and quantum mechanics give the same result for the contribution of the thermal fluctuations [73].

Following the above discussed parallelism between stochastic mechanics and quantum mechanics, in both dissipative and non-dissipative cases, we shall adopt a formalism and terminology of (open) quantum mechanical type from this point onwards; but, keeping in mind that expectation values in stochastic mechanics are the ensemble averages of the classical stochastic paths. This adoption benefits from a direct use of the rich mathematical formulation of open quantum systems, which is more familiar to most researchers than stochastic mechanics. The theories developed throughout the years in open quantum systems—see Refs. [69,70] for an overview—give a simultaneous microscopic description of the frictional and diffusive phenomena. It is almost always the case that a system plus reservoir strategy is accommodated, which has been successfully used in many diverse fields of physics such as condensed matter physics, quantum optics, and nuclear physics. Although the quantum treatment of Brownian particle is an old problem, due to the renewed interest originated in the pioneering work of Caldeira and Leggett [78] on dissipative quantum tunnelling, the system plus reservoir strategy based formulation of the problem is often referred to as the Caldeira-Leggett model in the more recent literature. In order to narrow the diversity and also for aptness, we shall follow the terminology and the implementation of the strategy as it is often done in the study of statistical fluctuations in heavy ion collisions, in which, the system of interest (described by the macroscopic parameters such as the relative position of the two fragments) is referred to as the *collective system* and the reservoir (described by the microscopic internal parameters) is referred to as the *intrinsic system*. Employment of an intrinsic system, described by some microscopic internal parameters, rather than a conventional reservoir, will serve us better conceptually, later on, in the study of neuronal mechanisms.

The total Hamiltonian, corresponding to the entire system, is separated into intrinsic and collective Hamiltonians and a weak coupling:

$$H(x,p,\boldsymbol{\xi},\mathbf{p}_{\mathrm{int}}) = H_{\mathrm{coll}}(x,p) + H_{\mathrm{int}}(\boldsymbol{\xi},\mathbf{p}_{\mathrm{int}}) + xF(\boldsymbol{\xi}), \quad (16)$$

where $\boldsymbol{\xi}$ and $\mathbf{p}_{\mathrm{int}}$ denote the set of intrinsic coordinates and momenta, respectively; and $xF(\boldsymbol{\xi})$ describes the coupling (or interaction) between the collective and the intrinsic systems. Although systems with an interaction Hamiltonian more general than $xF(\boldsymbol{\xi})$ have been investigated [79], we will presume that the Hamiltonian given by Eq. (16) captures all the essentials to serve our purpose for the study of neuronal mechanisms. The intrinsic system is assumed to be in a state of large but nearly random excitation with the fluctuations being distributed as Gaussians. The Gaussian nature of the random forces is endorsed when the intrinsic system treated as a set of harmonic oscillators or when the interaction is the cumulative effect of large number of weak interactions where a central limit theorem can be applied. For the unperturbed system, with the associated Hamiltonian $H^0 = H_{\mathrm{coll}} + H_{\mathrm{int}}$, it is assumed that

$$\langle F \rangle_t^0 = 0. \quad (17)$$

The collective Hamiltonian in the absence of interaction is taken as

$$H_{\mathrm{coll}}(x,p) = \frac{p^2}{2m} + U(x), \quad (18)$$

where

$$p := -ig\partial/\partial x \quad (19)$$

is the collective momentum operator and $U(x)$ is the potential function. The total density operator, denoted by $\rho(t)$, satisfies the von Neumann (or Liouville–von Neumann) equation

$$ig\frac{\partial \rho(t)}{\partial t} = [H, \rho(t)]. \quad (20)$$

The aim is to reduce Eq. (20) to an effective one for the reduced density operator $\rho_{\mathrm{coll}}(t)$, defined by taking the trace of the total density operator over the intrinsic system,

$$\rho_{\mathrm{coll}}(t) = \mathrm{Tr}_{\mathrm{int}}\rho(t) \quad (21)$$

so that the expectation value of an operator A acting on the collective space can be simply determined through taking the trace over the collective system by virtue of

$$\langle A \rangle_t = \mathrm{Tr}(\rho(t)A) = \mathrm{Tr}_{\mathrm{coll}}(\rho_{\mathrm{coll}}(t)A). \quad (22)$$

Note that the parameter g in Eqs. (19) and (20) corresponds to the Planck's constant $\hbar$ in quantum mechanics, but this is not universally true in our case as g will be related to topological noise later in the paper. For $\rho_{\mathrm{coll}}(t)$ to be specified completely, the density operator of the intrinsic system in the absence of perturbation, $\rho_{\mathrm{int}}^0(t)$, needs to be defined. This is done by assuming that the intrinsic system is in thermal equilibrium with a temperature T. Thus $\rho_{\mathrm{int}}^0(t)$ is given by

$$\rho_{\mathrm{int}}^0 = \exp(-\beta H_{\mathrm{int}})/Z(\beta), \quad (23)$$

where $\beta := 1/T$ and $Z(\beta) := \mathrm{Tr}_{\mathrm{int}}(\exp(-\beta H_{\mathrm{int}}))$. Once the reduced density operator $\rho_{\mathrm{coll}}(t)$ is known, the equations of motion for the first and second cumulants of the collective variables can be derived. The first cumulants are the expectation values of the collective position and the collective momentum,

$$X := \langle x \rangle_t,$$

$$P := \langle p \rangle_t, \quad (24)$$

whereas the second cumulants are the collective pair correlation functions given by

$$\sigma_{xx} := \langle x^2 \rangle_t - X^2,$$

$$\sigma_{xp} := \frac{1}{2}\langle xp + px \rangle_t - XP,$$

$$\sigma_{pp} := \langle p^2 \rangle_t - P^2. \quad (25)$$

Cumulants higher than the second are identically zero for a one-dimensional Gaussian distribution.

The dynamics of the collective system, induced by the intrinsic system, has been investigated by means of the methods known as the linear response theory, as in Ref. [80], the first order time dependent perturbation theory, as in Ref. [71], and the Caldeira-Leggett master equation [78]. The sets of equations of motion, for both the first and the second cumulants, obtained through these methods are compatible with each other. The spirit of the linear response method (as it was used by Hofmann and Siemens [80]), however, is more appealing to our study, in which following the derivation of the equation for the reduced density operator, the commutators, by means of the correspondence principle, are replaced with the Poisson brackets and, consequently, a master equation for the classical probability density is obtained [80]. If the potential function $U(x)$ includes only polynomial terms of the order at most quadratic, then the resulting classical master equation is linear in x and p in the form of a typical Fokker-Planck equation. Therefore, the solution to the master equation is a Gaussian, in terms of the classical x and p, completely determined by the first and second cumulants. Then, equations of motion for the first cumulants read as

$$m\dot{X} = P, \tag{26a}$$

$$\dot{P} = -\frac{\gamma}{m}P - \left(1 - \frac{\varepsilon_m}{m}\right)\left\langle \frac{\partial U}{\partial x}\right\rangle_t + \varepsilon_u X. \tag{26b}$$

The terms with the coefficients ε_m and ε_u are correction terms which arise from the interaction of the collective system with the intrinsic system. The correction coefficients are subject to the constraint $\varepsilon_m > 0$, $\varepsilon_u > 0$. In Eq. (26b), the ε_m term can be thought of as a correction due to the mass renormalization, and the ε_u term as the curvature of an additional conservative potential in the form of an inverted parabola due to the potential renormalization. The second cumulants, which describe the diffusive behavior of the collective system, evolve in accordance with the dynamical equations

$$\dot{\sigma}_{xx} = \frac{2}{m}\sigma_{xp}, \tag{27a}$$

$$\dot{\sigma}_{pp} = 2\left(\varepsilon_u - \frac{\partial^2 U}{\partial x^2}\right)\sigma_{xp} - \frac{2}{m}\gamma\sigma_{pp} + 2\gamma T, \tag{27b}$$

$$\dot{\sigma}_{xp} = \left(\varepsilon_u - \frac{\partial^2 U}{\partial x^2}\right)\sigma_{xx} + \frac{1}{m}\sigma_{pp} - \frac{\gamma}{m}\sigma_{xp} - \frac{\varepsilon_m}{m}T. \tag{27c}$$

Note here that the second derivative of U in Eqs. (27b) and (27c) is independent of x since U was taken to be at most of quadratic order. In derivation of these equations, the system was taken in the high temperature limit, i.e., $g\omega/(2T) \ll 1$ for all relevant frequencies ω which contribute to the integrals. Because of this limit, the parameter g does not appear in the equations explicitly; normally, instead of the terms $2\gamma T$ in Eq. (27b) and $(\varepsilon_m/m)T$ in Eq. (27c), we would have some integral terms including g. Calculation of the correction coefficients ε_m and ε_u requires the knowledge of the eigenvalues of the intrinsic system and the matrix elements of $F(\boldsymbol{\xi})$ over the intrinsic eigenstates, through the equations

$$\varepsilon_m = 2g^2 \sum_{j>0} \frac{\langle 0|F|j\rangle\langle j|F|0\rangle}{\Omega_{j0}^3}, \tag{28}$$

$$\varepsilon_u = 2 \sum_{j>0} \frac{\langle 0|F|j\rangle\langle j|F|0\rangle}{\Omega_{j0}}, \tag{29}$$

where $\Omega_{j0} := E_j - E_0$ are decided from the eigenvalues of the unperturbed intrinsic Hamiltonian:

$$H_{\text{int}}|j\rangle = E_j|j\rangle. \tag{30}$$

If, as a special case, it is assumed that $F(\boldsymbol{\xi}) = \Sigma_n \kappa_n \xi_n$ and the harmonic potential is used, then it can be shown that the potential renormalization gives the same result as the frequency renormalization obtained by the stochastic quantization of the Ullersma model, that is Eq. (29) agrees with Eq. (15).

IV. PROPERTIES OF THE EXCITABLE MEMBRANE IN USE

The famous Hodgkin-Huxley model [28] of the neuron is based on a detailed analysis of ionic transport through the membrane and has proved to be very successful as the model of the deterministic neuron. However, reduced phenomenological models capable of describing the typical features of neuron dynamics, namely bursting and spiking, are also widely used. A popular model of this type is the Rose-Hindmarsh model [49], a three parameter model, where the three variables describe in dimensionless units the membrane voltage x, an auxiliary variable y representing the fast ion dynamics (e.g., potassium and sodium), and a slow variable z which captures the slower dynamics. The model is formulated in the form of a coupled set of dynamical differential equations as follows:

$$m\dot{x} = y - z - ax^3 + bx^2 + I, \tag{31a}$$

$$\dot{y} = -y - dx^2 + c, \tag{31b}$$

$$\dot{z} = -rz + rh(x - x_s), \tag{31c}$$

where a, b, c, d, r, h, and x_s are some constant parameters. I denotes the external current injected into the neuron and m, introduced here for convenience, denotes the membrane capacitance. The model is capable of exhibiting tonic firing and bursting, for a proper choice of the parameters, depending on the value of the current I. The dynamical behavior of the set of equations (31a)–(31c) has been studied extensively in connection with bursting, chaos and bifurcations [81,82].

In the present paper, our study of the effects of channel noise will be based on the Rose-Hindmarsh model as the underlying deterministic model of the neuron. $-ax^3 + bx^2$ part of $m\dot{x}$ in Eq. (31a) can be considered as the match of *leakage currents*, analogously with the Hodgkin-Huxley model. This leakage term includes all the terms in $m\dot{x}$ that are independent of the channel variables or the external current; in the same way as the leakage term in the Hodgkin-Huxley model

does, although the leakage there happens to be linear in x. We will assume that y and z currents are caused by some biophysically existing set of ion channels, to which, we shall refer as the *y channels* and *z channels*, respectively. All the open channels will be assumed to have the same conductance value irrespective of the type of channel. The channel variables y and z in Eqs. (31a)–(31c) are essentially measures of the number of open y channels and z *channels*, respectively; which we take to be as

$$y = \mu C^y + \nu^y \tag{32}$$

and

$$z = \mu C^z + \nu^z, \tag{33}$$

where μ is a constant proportional to the single channel conductance and C^y and C^z denote the number of open y channels and z channels, respectively. ν^y and ν^z are some constants. It is naturally supposed that both y and z channels are multigate (having more than one gate) channels, with equal number of gates per channel. The gating particles, binding to the y *gates* and the z *gates*, will be assumed to be identical and residing in the same pool. The proportion of the sum of the number of open y and z gates to the total number of y and z gates will be assumed to stay roughly the same throughout the dynamics.

Although it is possible, in principle, to conduct our approach using a membrane of the Hodgkin-Huxley type, the problem there, however, turns out to be physically a more difficult one. That is why we have tailored a special membrane as described above; but, still, we expect the results implied by our analysis, in connection with the effects of ion channel noise, to extend (in a qualitative sense) into the case of having a biophysically more realistic membrane.

V. STOCHASTIC MECHANICS AND THE TOPOLOGICAL NOISE

Let us assume for the time being that the deterministic membrane dynamics is not given by the set of equations (31a)–(31c), but instead, it is as follows:

$$m\dot{x} = y - z + I, \tag{34a}$$

$$\dot{y} = -dx^2 + c, \tag{34b}$$

$$\dot{z} = rh(x - x_s). \tag{34c}$$

In other words, we shall ignore the leakage currents [i.e., let $a=b=0$ in Eq. (31a)], and assume that the y channels or the z channels do not cause any dissipation [i.e., ignore $-y$ and $-rz$ terms in the right-hand sides of $\dot{y}$ in Eq. (31b) and $\dot{z}$ in Eq. (31c), respectively]. By a change of variables, it easily follows that this set of equations is equivalent to

$$m\dot{x} = \theta, \tag{35a}$$

$$\dot{\theta} = -dx^2 + c - rh(x - x_s) + \dot{I}, \tag{35b}$$

$$\theta(t_0) = y(t_0) - z(t_0) + I(t_0), \tag{35c}$$

where θ matches the overall current that the neuron experiences, and t_0 denotes the initial time.

Let us now introduce the topological noise to the deterministic system (35a)–(35c). The topological noise leads to fluctuations in the number of open channels, caused by the uncertainty in deciding the appropriate permissible topology of open gates. Thus, taking the variable θ in Eqs. (35a)–(35c) as representing the overall current in the average sense, a noise term, with zero expectation value, must be added to the right-hand side of Eq. (35a). In addition, a potential dependent term, that vanishes when the membrane voltage happens to be at its deterministic value (i.e., at $x=\langle x\rangle$), should be included. Then, we observe a strong resemblance between the voltage dynamics, subject to the topological noise, and the dynamics of the stochastic position variable $x(t)$ as it is expressed through Eqs. (5)–(7) and (8a)–(8c) when the potential is harmonic. The topological noise has an impulsive effect as a result of the movement through the stochastic paths, in the membrane voltage space, caused by the stochastic transitions among the permissible topological states. Putting all this together, we reach to the conclusion that the combined effect of topological noise, emerging from the fluctuations in the number of open y and z channels, on the membrane voltage is the same as the effect of a Brownian environment, with zero friction, on the position of a one-dimensional particle. This should substantiate the use of stochastic mechanics for modeling neuronal dynamics under the influence of ion channel noise. It is interesting to note here that Nelson's approach postulates the existence of a stochastic force responsible for random movement; the problem, however, is to explain the physical origin of such nondissipative stochasticity—and this is precisely the weakness of stochastic mechanics. In our use of stochastic mechanics, on the other hand, there is no such unexplained source of stochasticity: it is the topological noise.

Since, in our membrane, the sum of the number of open y and z gates stays roughly the same throughout the dynamics, the diffusion parameter g is approximately constant and voltage independent. Although the exact value of g can be calculated in principle, it is not so easy in reality. In addition to the conformational details of the membrane, issues such as the effects of ion-ion repulsion need to be taken into consideration; one gating particle in the channel may slow the entry (and speed the exit) of another.

Then, following Nelson [47,48], the membrane voltage obeys the following Schrödinger-type equation

$$ig\frac{\partial\psi(x,t)}{\partial t} = -\frac{g^2}{2m}\frac{\partial^2\psi(x,t)}{\partial x^2} + \tilde{U}(x,X,t)\psi(x,t), \tag{36}$$

where $|\psi(x,t)|^2$ is the probability density of finding the membrane voltage at the value of x at time t. The potential function $\tilde{U}(x,X,t)$ follows from Eq. (35b) as

$$\tilde{U}(x,X,t) = \frac{1}{3}dx^3 - cx + rh\left(\frac{1}{2}x^2 - x_s x\right) - \dot{I}x + U_{\mathrm{sqz}}(x,X) \tag{37}$$

in which the explicit time dependence is due to the external current. $U_{\mathrm{sqz}}(x,X)$ in $\tilde{U}(x,X,t)$ serves the purpose of *squeezing* the wave packet as it is defined by

$$U_{\mathrm{sqz}}(x,X) := \frac{1}{2}\alpha(x-X)^2, \tag{38}$$

where α is some positive constant specifying the amount of squeezing. The concept of squeezing the wave packet by the inclusion of an additional quadratic term into the potential function is borrowed from quantum optics [83]. It can be indeed shown that $U_{\mathrm{sqz}}(x,X)$, with its definition in Eq. (38), squeezes the spatial spread of the wave packet. If $\tilde{U}(x,X,t)$ were to contain $U_{\mathrm{sqz}}(x,X)$ only, i.e., if $\tilde{U}(x,X,t)=U_{\mathrm{sqz}}(x,X)$, then the equations of motion for the second cumulants would be

$$\dot{\sigma}_{xx} = \frac{2}{m}\sigma_{xp}, \tag{39a}$$

$$\dot{\sigma}_{pp} = -2\alpha\sigma_{xp}, \tag{39b}$$

$$\dot{\sigma}_{xp} = -\alpha\sigma_{xx} + \frac{1}{m}\sigma_{pp}. \tag{39c}$$

This system reaches to the steady state with the resulting values: $\sigma^*_{xp}=0$, $m\alpha\sigma^*_{xx}=\sigma^*_{pp}$, and $\dot{\sigma}^*_{xx}=\dot{\sigma}^*_{pp}=0$. Thus the squeezing potential $U_{\mathrm{sqz}}(x,X)$ forces the membrane voltage variance to attain a smaller value and evades ending up in a forever increasing variance. The existence of X in the definition of $U_{\mathrm{sqz}}(x,X)$ in Eq. (38) is in order to protect the first cumulants from the influence of the squeezing potential. $U_{\mathrm{sqz}}(x,X)$ has no effect on the first cumulant equations. The biophysical motivation behind introducing such a squeezing potential is as follows: movement of the charged particles in the intracellular and extracellular fluid counteract to a disturbance, trying to retain the variables as at their average, or the equilibrium, values.

The potential function $\tilde{U}(x,X,t)$ given by Eq. (37) contains a third order term in x. But we want to limit it to quadratic order. So, instead of this potential function, and the others that will appear later, the function $U(x,X,t)$ obtained by the following expansion of $\tilde{U}(x,X,t)$ around $x=X$:

$$U(x,X,t) = \tilde{U}(x=X,X,t) + (x-X)\left.\frac{\partial\tilde{U}(x,X,t)}{\partial x}\right|_{x=X} + \frac{1}{2}(x-X)^2\left.\frac{\partial^2\tilde{U}(x,X,t)}{\partial x^2}\right|_{x=X} \tag{40}$$

will be used. Since the squeezing potential forces a smaller membrane voltage variance, the presence of it greatly contributes to the validity of the expansion. Then, the solution to Eq. (36) is found to satisfy the following first cumulant equations:

$$m\dot{X} = P, \tag{41a}$$

$$\dot{P} = -dX^2 + c - rh(X - x_s) + \dot{I}, \tag{41b}$$

$$P(t_0) = y(t_0) - z(t_0) + I(t_0). \tag{41c}$$

Note, here, that even though X and P used in Eqs. (40) and (41a)–(41c) are defined by Eq. (24), they now have their meaning in the membrane voltage space, instead of the position space, as x now denotes the membrane voltage and the momentum operator p acts on the membrane voltage space. In the noise free limit, $g\to 0$, Eqs. (35a)–(35c) is rediscovered if θ is identified with the noise free momentum.

VI. INTRINSIC SYSTEM AND THE CHANNEL DISSIPATION

Comparing Eqs. (41a)–(41c) with Eqs. (35a)–(35c), one might be tempted, as far as the first cumulants are concerned, to think that the effect of incorporating the intrinsic noise into the Rose-Hindmarsh model will simply lead to the substitution of x by X in the set of equations (31a)–(31c). This, however, means nothing but the recognition of a Schrödinger-Langevin type equation, as in Eq. (9), as the correct equation of the frictional-diffusive phenomena, which is not the case as discussed in Sec. III B. On the other hand, the collective-intrinsic system approach seems to be the physically right scenario that fits to the nature of the problem. In this scenario, the collective system behaves in accordance with Eq. (36), for some potential function such as the one in Eq. (37), in the absence of interaction with the intrinsic system. If the deterministic model were described by Eqs. (34a)–(34c), then the collective system would give a complete specification of the neuron's behavior.

Due to the presence of the friction term $-y$ in it, $\dot{y}$ in Eq. (31b) can not be decided solely by the value of the membrane voltage x, for which, the knowledge of the set (or number) of open channels is required since the variable y is a measure of the number of open y channels. The potential function of the collective system, reflecting the global coupling of all ion channels through the membrane voltage, articulates the voltage dependent part of $\dot{y}$, whereas the frictional part of $\dot{y}$, due to its non-Hamiltonian character, is not accommodated by the collective system. This is because a non-Hamiltonian system can not be described by means of a velocity independent potential. The same argument applies also for the friction term $-rz$ in $\dot{z}$ in Eq. (31c).

Ion channels do not know each other's state and, therefore, a channel is not capable of adjusting its state in accordance with the states of the other channels for the fulfillment of a prescribed macroscopic friction. There must be a system (the intrinsic system) described by some microscopic dynamical variables and coupled to the collective system in order the friction term in the collective equations of motion to take place. The intrinsic system is nothing but a set of dynamical attributes describing the dynamics of the gating

particles. Then, the frictional parts of $\dot{y}$ and $\dot{z}$, or the non-Hamiltonian character of the channel activity, emerges from the part of coupling, between the collective and the intrinsic systems, that can not be characterized by a potential function. In physical terms, the intrinsic variables can be properly interpreted as the normal modes of the reservoir in the Rubin model often used as a prototype in nonequilibrium statistical mechanics [84] and open quantum mechanics [69]. In addition to the noisy behavior of ion channels led by the topological noise as stipulated in Sec. V, the intrinsic system, due to the intrinsic noise, exerts its own separate noisy action, i.e., both the collective and the intrinsic systems are noisy systems. Even though we are able to foresee certain types of random noise for the collective and the intrinsic systems separately when they are not perturbed by the existence of each other, some unpredictable effects must be expected to arise from the mutual interaction of these two noisy systems. Therefore, the voltage dynamics should be worked out from the dynamics of the entire (collective plus intrinsic) system through the use of reduced density operator techniques.

Let the intrinsic system coordinates be denoted by

$$\boldsymbol{\xi} = (\xi_j) \tag{42}$$

and the associated intrinsic momentum operator by

$$\mathbf{p}_{\text{int}} = (p_j), \quad p_j = -ig\frac{\partial}{\partial \xi_j}, \tag{43}$$

where the index j spans all the gating particles in a manner that some certain index values correspond to a certain gating particle. Although the diffusion coefficient associated with the intrinsic momentum operator does not need to be the same as the coefficient g in the collective momentum operator, a scaling over the intrinsic mass parameter is assumed for the avoidance of the discrepancy. We will treat the intrinsic system as a set of harmonic oscillators. Then, the intrinsic Hamiltonian is

$$H_{\text{int}} = \sum_j \left(\frac{p_j^2}{2m_j} + \frac{1}{2} m_j \omega_j^2 \xi_j^2 \right). \tag{44}$$

This Hamiltonian can equivalently be expressed in terms of the annihilation and creation operators, b_j and $b_j^\dagger$, respectively, of the intrinsic phonon modes:

$$H_{\text{int}} = g \sum_j \omega_j \left(b_j^\dagger b_j + \frac{1}{2} \right) \tag{45}$$

by using

$$\xi_j = \left(\frac{g}{2m_j\omega_j} \right)^{1/2} (b_j^\dagger + b_j) \tag{46}$$

and

$$p_j = i \left(\frac{g m_j \omega_j}{2} \right)^{1/2} (b_j^\dagger - b_j). \tag{47}$$

It is natural to assume that the intrinsic system is in thermal equilibrium and, therefore, its density operator in the absence of perturbation, ρ_{int}^0, is determined by the canonical distribution, in which the temperaturelike parameter, T, decides the average intrinsic energy density at equilibrium:

$$\rho_{\text{int}}^0 = \exp(-\beta H_{\text{int}})/Z(\beta), \tag{48}$$

where $\beta := 1/T$ and $Z(\beta) := \text{Tr}_{\text{int}}(\exp(-\beta H_{\text{int}}))$. The temperature parameter T simply can be thought of as a measure of how fast the gating particles, after a temporary external perturbation, regain the equilibrium distribution between the inner and the outer faces of the membrane.

VII. COLLECTIVE EQUATIONS OF MOTION FOR THE NOISY MEMBRANE VOLTAGE DYNAMICS

A. First cumulants

The Rose-Hindmarsh model, Eqs. (31a)–(31c), can be equivalently written as

$$m\dot{x} = \theta, \tag{49a}$$

$$\dot{\theta} = -\left(\frac{3a}{m}x^2 - \frac{2b}{m}x + 1 \right)\theta - ax^3 + (b-d)x^2 - rh(x - x_s) + c + I + \dot{I} - (1-r)z, \tag{49b}$$

$$\dot{z} = -rz + rh(x - x_s), \tag{49c}$$

$$\theta(t_0) = y(t_0) - z(t_0) - a(x(t_0))^3 + b(x(t_0))^2 + I(t_0). \tag{49d}$$

The leakage currents have their influence on both the frictional part and the potential part of $\dot{\theta}$ in Eq. (49b). The influence on the potential part emerges due the presence of the variables y and z in Eq. (31a).

We now couple the collective and the intrinsic systems described in the previous two sections. The resulting formalism should yield

$$m\dot{x} = \theta, \tag{50a}$$

$$\dot{\theta} = -\theta - ax^3 + (b-d)x^2 - rh(x - x_s) + c + I + \dot{I} - (1-r)z, \tag{50b}$$

$$\dot{z} = -rz + rh(x - x_s), \tag{50c}$$

$$\theta(t_0) = y(t_0) - z(t_0) - a(x(t_0))^3 + b(x(t_0))^2 + I(t_0) \tag{50d}$$

in the deterministic limit (i.e., the limit $g \to 0$ followed by $T \to 0$). Equations (50a)–(50d) are obtained from Eqs. (49a)–(49d) simply by removing the influence of leakage on the friction coefficient. This is because the leakage currents are known at all times as a function of the membrane voltage and, therefore, leakage is not associated with the intrinsic system. The potential function, by virtue of Eq. (50b), follows as

$$\tilde{U}^y(x,t) = \frac{1}{4}ax^4 - \frac{1}{3}(b-d)x^3 + \frac{1}{2}rhx^2 + [-rhx_s - c - I - \dot{I} + (1-r)z]x. \quad (51)$$

In Eq. (51), some z currents appear as if they are time dependent external forces embedded into the potential and that their effect does not come out in the friction coefficient. This occurs because of the difference between the friction coefficients of y and z currents. In fact, when the friction coefficients are the same, i.e., $r=1$, the z currents do not appear in the potential. The superscript y in $\tilde{U}^y(x,t)$ is used to indicate that the scheme employed absorbs all the y currents into the momentum θ. Since $\tilde{U}^y(x,t)$ contains terms higher than the quadratic order in x, we use instead the following potential function obtained from $\tilde{U}^y(x,t)$ through the employment of the expansion (40):

$$U^y(x,X,t) = f_1(X,t) + [aX^3 - (b-d)X^2 + rh(X-x_s) - c - I - \dot{I} + (1-r)z](x-X) + \frac{1}{2}[3aX^2 - 2(b-d)X + rh] \times (x-X)^2 + U_{\mathrm{sqz}}(x,X), \quad (52)$$

where the function $f_1(X,t)$ is irrelevant. Here, the squeezing potential $U_{\mathrm{sqz}}(x,X)$ is included for the reasons explained in Sec. V.

Consider the total Hamiltonian

$$H^y(x,p,X,t,\boldsymbol{\xi},\mathbf{p}_{\mathrm{int}}) = H^y_{\mathrm{coll}}(x,p,X,t) + H_{\mathrm{int}}(\boldsymbol{\xi},\mathbf{p}_{\mathrm{int}}) + [x - X_{\mathrm{eq}}(I)]F^y(\boldsymbol{\xi}), \quad (53)$$

where

$$H^y_{\mathrm{coll}}(x,p,X,t) = \frac{p^2}{2m} + U^y(x,X,t) \quad (54)$$

is the collective Hamiltonian, and $[x-X_{\mathrm{eq}}(I)]F^y(\boldsymbol{\xi})$ describes the coupling between the collective and the intrinsic systems. Equation (53) implies that that the renormalization potential is

$$U^y_{\mathrm{ren}}(x,I) = -\frac{1}{2}\varepsilon^y_u[x - X_{\mathrm{eq}}(I)]^2, \quad (55)$$

where ε^y_u is the correction coefficient of the potential renormalization. The function $X_{\mathrm{eq}}(I)$ corresponds to the value of membrane voltage when the entire system is in equilibrium, or equivalently, when the condition $\langle F^y\rangle^0_t = 0$, analogous to Eq. (17), is satisfied. Taking the interaction Hamiltonian as $xF^y(\boldsymbol{\xi})$ as in Eq. (16) leads to the location of the extremum of the renormalization potential be at $x=0$. It can be argued however that the extremum of the renormalization potential should coincide with the extremum of the collective potential. In other words, the extremum should be identified as the quasistatic or equilibrium state of the entire system. A detailed physical discussion on the issue can be found in Ref. [85]. We assume that the stationary solution of the set of equations (31a)–(31c) identifies the equilibrium state of the system. Solving Eqs. (31a)–(31c) subject to the condition $\dot{x} = \dot{y} = \dot{z} = 0$, results in that $X_{\mathrm{eq}}(I)$ must obey

$$aX^3_{\mathrm{eq}} - (b-d)X^2_{\mathrm{eq}} + h(X_{\mathrm{eq}} - x_s) - c - I = 0. \quad (56)$$

The Rose-Hindmarsh model for a feasible set of commonly used model parameters gives a unique fixed point in three dimensions [81], and, therefore, Eq. (56) results in a solution uniquely defined in such a parameter regime for a given I. In the first cumulant equations (26a) and (26b), there is no parameter corresponding to $X_{\mathrm{eq}}(I)$ since in that formulation it was assumed that the equilibrium occurs at $X=0$. Even though X_{eq} was set to zero in Ref. [46], it is more convincing to take it as defined by Eq. (56).

Following our discussion in Sec. III B, the first cumulants in the membrane voltage phase space are expected to obey the dynamics given by

$$m\dot{X} = P, \quad (57a)$$

$$\dot{P} = -P + \left(1 - \frac{\varepsilon^y_m}{m}\right)[-aX^3 + (b-d)X^2 - rh(X-x_s) + c + I + \dot{I} - (1-r)z] + \varepsilon^y_u[X - X_{\mathrm{eq}}(I)], \quad (57b)$$

$$\dot{z} = -rz + rh(X-x_s) + \eta^z, \quad (57c)$$

$$P(t_0) = y(t_0) - z(t_0) - a(X(t_0))^3 + b(X(t_0))^2 + I(t_0) \quad (57d)$$

analogously to Eqs. (26a) and (26b). The correction terms with the coefficients ε^y_m and ε^y_u are now due to the renormalizations of the membrane capacitance and the voltage dependent potential, respectively. η^z in Eq. (57c) is a Gaussian white noise with zero mean and mean square given by

$$\langle \eta^z(t)\eta^z(t')\rangle = 2rmT\delta(t-t'). \quad (58)$$

Equation (58) is obtained by means of the classical fluctuation-dissipation theorem using that the friction coefficient of the z channels is rm. X and P in Eqs. (57a)–(57d) do not actually correspond to the conventional expectation values of the overall dynamics. But rather they match to the expectation values for a particular deterministic choice of the part of z currents that appear as if time dependent external forces in the potential. This deterministic choice is dictated by Eq. (57c) for a given time course of $\eta^z(t)$. In other words, X and P are the expectation values of the voltage dynamics for a specific given time course of $\eta^z(t)$, and there is a separate (X,P) for each time course.

It is also instructive to give the mean square of the noise for the proportion of open z channels defined by

$$R^z := C^z/N^z, \quad (59)$$

where C^z is the number of open z channels, as before, and N^z denotes the total number of z channels. Then, it follows from Eqs. (33) and (57c) that

$$R^z = -rR^z - \frac{r\nu^z}{\mu N^z} + \frac{rh}{\mu N^z}(X - x_s) + \eta_R^z, \tag{60}$$

where

$$\eta_R^z = \frac{\eta^z}{\mu N^z}. \tag{61}$$

It follows from Eq. (58) that

$$\langle \eta_R^z(t)\, \eta_R^z(t') \rangle = \frac{2rm_0T}{\mu^2 d^z N^z}\delta(t - t'), \tag{62}$$

where m_0 and d^z are the membrane capacitance and the number of z channels, respectively, per unit membranous area. Note here that the temperature parameter T can be dependent on m_0 and d^z, therefore, Eq. (62) alone can not specify the dependence of the mean square onto m_0 or d^z. But the equation says that the effect of intrinsic noise decreases with the number of channels, or equivalently, with the size of the membrane. Unlike the case in the analysis of Fox and Lu [26], where the Gaussian noise terms for the gating variables are voltage dependent, Eq. (62) has no voltage dependence. This is because, contrary to the Hodgkin-Huxley model, the friction coefficients in the deterministic dynamics of our membrane are voltage independent.

Adoption of Eqs. (28) and (29) for the correction coefficients ε_m^y and ε_u^y gives

$$\varepsilon_m^y = 2g^2 \sum_{j>0} \frac{\langle 0|F^y|j\rangle\langle j|F^y|0\rangle}{(\Omega_{j0})^3} \tag{63}$$

and

$$\varepsilon_u^y = 2 \sum_{j>0} \frac{\langle 0|F^y|j\rangle\langle j|F^y|0\rangle}{\Omega_{j0}}, \tag{64}$$

where

$$\Omega_{j0} := E_j - E_0 \tag{65}$$

are obtained from the eigenvalues of the unperturbed intrinsic Hamiltonian in the same way as in Eq. (30). Since the couplings of the intrinsic modes add up in Eqs. (63) and (64), the weak perturbation of individual intrinsic modes does not mean that the influence of the intrinsic system on the collective system is weak as well. As a result, the correction coefficients ε_m^y and ε_u^y need not to be small enough to be ignored; therefore, the correction terms, in principle, can play a major role in the dynamics of the noisy neuron. The dependence of the correction coefficients on g is imposed by the form of $F^y(\boldsymbol{\xi})$. If, as a special case, it is assumed, for some constants κ_n^y, that

$$F^y(\boldsymbol{\xi}) = \sum_n \kappa_n^y \xi_n \tag{66}$$

then it can be shown by virtue of Eqs. (63) and (64) that the correction coefficients ε_m^y and ε_u^y are independent of the diffusion parameter g. This however does not mean that the correction terms will emerge also in the deterministic model; in the classical equations of motion for the central oscillator in the Ullersma model the appearance of a time dependent additive noise term, containing the intrinsic parameters, is inevitable. This noise term is not zero identically unless $\kappa_n = 0$ for all possible values of n; the presence of the correction terms implies the presence of an intrinsic noise term, and vice versa. Besides, when $F^y(\boldsymbol{\xi})$ is not restricted to the special case given by Eq. (66), the correction coefficients will depend on g. For example, if $F^y(\boldsymbol{\xi})$ consists of a linear combination of the quadratic terms ξ_n^2, then both ε_m^y and ε_u^y attain some values proportional to g.

After introducing back the influence of leakage on the friction coefficient, that was ignored in Eq. (50b), into Eq. (57b), we obtain the following dynamics of the first cumulants:

$$m\dot{X} = P, \tag{67a}$$

$$\dot{P} = -\left(\frac{3a}{m}X^2 - \frac{2b}{m}X + 1\right)P + \left(1 - \frac{\varepsilon_m^y}{m}\right)[-aX^3 + (b-d)X^2 - rh(X - x_s) + c + I + \dot{I} - (1-r)z] + \varepsilon_u^y[X - X_{\mathrm{eq}}(I)], \tag{67b}$$

$$\dot{z} = -rz + rh(X - x_s) + \eta^z, \tag{67c}$$

$$P(t_0) = y(t_0) - z(t_0) - a(X(t_0))^3 + b(X(t_0))^2 + I(t_0). \tag{67d}$$

The friction coefficient γ in Eq. (67b) is $3aX^2 - 2bX + m$. The presence of $3aX^2 - 2bX$ term in it is a result of leakage, while the presence of m comes from the interaction with the intrinsic system. Here, it is assumed that the leakage does not cause an additional noisy action.

Like the dynamical system given by Eqs. (49a)–(49d) the following system is also equivalent to the Rose-Hindmarsh model described by Eqs. (31a)–(31c):

$$m\dot{x} = \theta, \tag{68a}$$

$$\dot{\theta} = -\left(\frac{3a}{m}x^2 - \frac{2b}{m}x + r\right)\theta - rax^3 + (rb - d)x^2 - rh(x - x_s) + c + rI + \dot{I} - (1-r)y, \tag{68b}$$

$$\dot{y} = -y - dx^2 + c, \tag{68c}$$

$$\theta(t_0) = y(t_0) - z(t_0) - a(x(t_0))^3 + b(x(t_0))^2 + I(t_0). \tag{68d}$$

The potential function of the dynamical system (68a)–(68d) is

$$\tilde{U}^z(x,X,t) = \frac{1}{4}rax^4 - \frac{1}{3}(rb - d)x^3 + \frac{1}{2}rhx^2 + [-rhx_s - c - rI - \dot{I} + (1-r)y]x. \tag{69}$$

In the same manner of going from Eqs. (49a)–(49d) to Eqs. (67a)–(67d), we obtain the following first cumulant equations

$$m\dot{X} = P, \tag{70a}$$

$$\dot{P} = -\left(\frac{3a}{m}X^2 - \frac{2b}{m}X + r\right)P + \left(1 - \frac{\varepsilon_m^z}{m}\right)[-raX^3 + (rb-d)X^2 - rh(X-x_s) + c + rI + \dot{I} - (1-r)y] + \varepsilon_u^z[X - X_{\mathrm{eq}}(I)], \tag{70b}$$

$$\dot{y} = -y - dX^2 + c + \eta^y, \tag{70c}$$

$$P(t_0) = y(t_0) - z(t_0) - a(X(t_0))^3 + b(X(t_0))^2 + I(t_0), \tag{70d}$$

where the potential function $U^z(x,X,t)$, obtained from $\tilde{U}^z(x,X,t)$ by virtue of the expansion (40), is used:

$$U^z(x,X,t) = f_2(X,t) + [raX^3 - (rb-d)X^2 + rh(X-x_s) - c - rI - \dot{I} + (1-r)y](x-X) + \frac{1}{2}[3raX^2 - 2(rb-d)X + rh](x-X)^2 + U_{\mathrm{sqz}}(x,X) \tag{71}$$

in which the function $f_2(X,t)$ is irrelevant and $U_{\mathrm{sqz}}(x,X)$ is the squeezing potential as before. On the contrary to the potential (52), here some y currents, instead of the z currents, appear as if they are time dependent external forces embedded into the potential. The effect of these embedded currents does not come out in the friction coefficient. The friction coefficient γ in Eq. (70b) is $3aX^2-2bX+rm$. The presence of $3aX^2-2bX$ term in it is a result of leakage, while the presence of rm comes from the interaction with the intrinsic system. η^y in Eq. (70c) is a Gaussian white noise with zero mean and mean square given by

$$\langle \eta^y(t)\eta^y(t')\rangle = 2mT\delta(t-t') \tag{72}$$

through the classical fluctuation-dissipation theorem using that the friction coefficient of the y channels is m.

The first cumulants of the system having the Hamiltonian

$$H^z(x,p,X,t,\boldsymbol{\xi},\mathbf{p}_{\mathrm{int}}) = H^z_{\mathrm{coll}}(x,p,X,t) + H_{\mathrm{int}}(\boldsymbol{\xi},\mathbf{p}_{\mathrm{int}}) + [x - X_{\mathrm{eq}}(I)]F^z(\boldsymbol{\xi}) \tag{73}$$

evolve as given by Eqs. (70a)–(70d), where the collective Hamiltonian is

$$H^z_{\mathrm{coll}}(x,p,X,t) = \frac{p^2}{2m} + U^z(x,X,t). \tag{74}$$

However, the contribution to the friction coefficient is twofold coming partly from the interaction Hamiltonian $[x-X_{\mathrm{eq}}(I)]F^z(\boldsymbol{\xi})$ and partly from the leakage, as mentioned above. The correction coefficients ε_m^z and ε_u^z, induced by the intrinsic system $(\boldsymbol{\xi},\mathbf{p})$, read as

$$\varepsilon_m^z = 2g^2\sum_{j>0}\frac{\langle 0|F^z|j\rangle\langle j|F^z|0\rangle}{(\Omega_{j0})^3} \tag{75}$$

and

$$\varepsilon_u^z = 2\sum_{j>0}\frac{\langle 0|F^z|j\rangle\langle j|F^z|0\rangle}{\Omega_{j0}}, \tag{76}$$

where Ω_{j0} is the jth eigenvalue of the unperturbed intrinsic Hamiltonian, relative to the ground state eigenvalue, as given by Eq. (65).

Instead of the two different sets of dynamical equations (67a)–(67d) and (70a)–(70d), we desire a single formulation. It can be argued that Eqs. (67a)–(67d) give a better description of the neuronal dynamics, in comparison with Eqs. (70a)–(70d). This is because the constant parameter r has a value close to zero and, therefore, the leakage free part of the friction coefficient γ in Eq. (67b) is greater than the one in Eq. (70b); that is, Eqs. (67a)–(67d) accommodate most of the frictional effects within the scope of system plus reservoir strategies. An approximate scheme, better than the simple preference of Eqs. (67a)–(67d) over Eqs. (70a)–(70d), however, can be asserted through some mixing of the two dynamical equations. Our assertion is as follows. First, take a *mixing coefficient*, denoted by k, with the value

$$k = \frac{1}{1+r} \tag{77}$$

obtained by taking the ratio of the leakage free part of the friction coefficient γ in Eq. (67b) to the sum of the leakage free friction coefficients in Eqs. (67b) and (70b). Then, add the right hand sides of Eqs. (67b) and (70b) after multiplying them with k and $1-k$, respectively, in order to obtain the equation for $\dot{P}$ in the new scheme. Ultimately, the following first cumulant equations are obtained:

$$m\dot{X} = P, \tag{78a}$$

$$\dot{P} = -\left(\frac{3a}{m}X^2 - \frac{2b}{m}X + S_0\right)P - S_1aX^3 + S_2X^2 + S_6X - S_3X_{\mathrm{eq}}(I) + S_1I + S_5\dot{I} + S_7 - (1-r) \times \left[k\left(1 - \frac{\varepsilon_m^y}{m}\right)z + (1-k)\left(1 - \frac{\varepsilon_m^z}{m}\right)y\right], \tag{78b}$$

$$\dot{y} = -y - dX^2 + c + \eta^y, \tag{78c}$$

$$\dot{z} = -rz + rh(X - x_s) + \eta^z, \tag{78d}$$

$$P(t_0) = y(t_0) - z(t_0) - a(X(t_0))^3 + b(X(t_0))^2 + I(t_0), \tag{78e}$$

where

$$S_0 := k + (1-k)r, \tag{79}$$

$$S_1 := S_0 - \left[k\frac{\varepsilon_m^y}{m} + (1-k)r\frac{\varepsilon_m^z}{m}\right], \tag{80}$$

$$S_2 := k\left(1 - \frac{\varepsilon_m^y}{m}\right)(b-d) + (1-k)\left(1 - \frac{\varepsilon_m^z}{m}\right)(rb-d), \tag{81}$$

$$S_3 := k\varepsilon_u^y + (1-k)\varepsilon_u^z, \tag{82}$$

$$S_4 := k\frac{\varepsilon_m^y}{m} + (1-k)\frac{\varepsilon_m^z}{m}, \tag{83}$$

$$S_5 := 1 - S_4, \tag{84}$$

$$S_6 := S_3 - S_5 rh, \tag{85}$$

$$S_7 := (rhx_s + c)S_5. \tag{86}$$

Finally, in order to eliminate the appearance of $\dot{I}$ in Eq. (78b), we employ the operator π defined by

$$\pi := p - S_5 I \tag{87}$$

and substitute P in Eqs. (78a), (78b), and (78e) in terms of the expectation value Π,

$$\Pi := \langle \pi \rangle_t, \tag{88}$$

with the result

$$m\dot{X} = \Pi + S_5 I, \tag{89a}$$

$$\dot{\Pi} = -\left(\frac{3a}{m}X^2 - \frac{2b}{m}X + S_0\right)(\Pi + S_5 I) - S_1 aX^3 + S_2 X^2 + S_6 X - S_3 X_{\text{eq}}(I) + S_1 I + S_7 - (1-r) \times \left[k\left(1 - \frac{\varepsilon_m^y}{m}\right)z + (1-k)\left(1 - \frac{\varepsilon_m^z}{m}\right)y\right], \tag{89b}$$

$$\dot{y} = -y - dX^2 + c + \eta^y, \tag{89c}$$

$$\dot{z} = -rz + rh(X - x_s) + \eta^z, \tag{89d}$$

$$\Pi(t_0) = y(t_0) - z(t_0) - a(X(t_0))^3 + b(X(t_0))^2 + (1 - S_5)I(t_0). \tag{89e}$$

Although Eqs. (89a)–(89e) seem to be describing a four dimensional dynamical system, the set of possible initial values in it describes a three dimensional manifold since $\Pi(t_0)$ is uniquely specified by $X(t_0)$, $y(t_0)$, and $z(t_0)$. Note that in the deterministic limit, i.e., when $\varepsilon_m^y = \varepsilon_u^y = \varepsilon_m^z = \varepsilon_u^z = \eta^y = \eta^z = 0$, the solution to X from Eqs. (89a)–(89e) is the same as the solution to x from Eqs. (31a)–(31c), (49a)–(49d), and (68a)–(68d). That is, the deterministic limit results in the Rose-Hindmarsh model.

B. Second cumulants

Instead of using the second cumulants as defined by Eq. (25), it is more appropriate to redefine them through the operator π as follows:

$$\sigma_{xx} := \langle x^2 \rangle_t - X^2,$$

$$\sigma_{x\pi} := \frac{1}{2}\langle x\pi + \pi x \rangle_t - X\Pi = \sigma_{xp},$$

$$\sigma_{\pi\pi} := \langle \pi^2 \rangle_t - \Pi^2 = \sigma_{pp}. \tag{90}$$

The second cumulants tell us the neuron's diffusive behavior. Equations of motion for the second cumulants of the system described by the Hamiltonian H^y in Eq. (53) are given, in a manner analogous with Eqs. (27a)–(27c), as

$$\dot{\sigma}_{xx} = \frac{2}{m}\sigma_{x\pi}, \tag{91a}$$

$$\dot{\sigma}_{\pi\pi} = 2[\varepsilon_u^y - 3aX^2 + 2(b-d)X - rh - \alpha]\sigma_{x\pi} - 2\sigma_{\pi\pi} + 2mT, \tag{91b}$$

$$\dot{\sigma}_{x\pi} = [\varepsilon_u^y - 3aX^2 + 2(b-d)X - rh - \alpha]\sigma_{xx} + \frac{1}{m}\sigma_{\pi\pi} - \sigma_{x\pi} - \frac{\varepsilon_m^y}{m}T \tag{91c}$$

in the high temperature limit. The value of the friction coefficient, namely m, used in Eqs. (91b) and (91c) is taken from Eq. (57b). Similarly, the second cumulants corresponding to the system described by the Hamiltonian H^z in Eq. (73) are given by

$$\dot{\sigma}_{xx} = \frac{2}{m}\sigma_{x\pi}, \tag{92a}$$

$$\dot{\sigma}_{\pi\pi} = 2[\varepsilon_u^z - 3raX^2 + 2(rb-d)X - rh - \alpha]\sigma_{x\pi} - 2r\sigma_{\pi\pi} + 2rmT, \tag{92b}$$

$$\dot{\sigma}_{x\pi} = [\varepsilon_u^z - 3raX^2 + 2(rb-d)X - rh - \alpha]\sigma_{xx} + \frac{1}{m}\sigma_{\pi\pi} - r\sigma_{x\pi} - \frac{\varepsilon_m^z}{m}T, \tag{92c}$$

where the value of the friction coefficient used is rm. Following the discussion in the previous subsection, we remark here that the second cumulant equations (91a)–(91c) and (92a)–(92c) actually give the diffusive behavior for specific given time courses of $\eta^y(t)$ and $\eta^z(t)$, rather than the diffusive behavior of the overall dynamics. Therefore, there is a separate $(\sigma_{xx}, \sigma_{\pi\pi}, \sigma_{x\pi})$ for each time course of $\eta^y(t)$ and $\eta^z(t)$.

Finally, Eqs. (91a)–(91c) and (92a)–(92c) are combined together using the mixing coefficient given by Eq. (77), in the sense of combining the first cumulant equations (67a)–(67d) and (70a)–(70d) into Eqs. (78a)–(78e), as follows:

$$\dot{\sigma}_{xx} = \frac{2}{m}\sigma_{x\pi}, \tag{93a}$$

$$\dot{\sigma}_{\pi\pi} = 2(S_8 - 3S_0 aX^2 + S_9 X)\sigma_{x\pi} - 2S_0\sigma_{\pi\pi} + 2mS_0 T, \tag{93b}$$

$$\dot{\sigma}_{x\pi} = (S_8 - 3S_0 a X^2 + S_9 X)\sigma_{xx} + \frac{1}{m}\sigma_{\pi\pi} - S_0\sigma_{x\pi} - S_4 T, \tag{93c}$$

where S_0 is defined by Eq. (79); S_8 and S_9 are given by

$$S_8 := S_3 - \alpha - rh \tag{94}$$

and

$$S_9 := 2(S_0 b - d). \tag{95}$$

VIII. CONCLUDING REMARKS

In this paper, we have advocated a physical approach for the description of neuronal dynamics under the influence of ion channel noise, adopting dissipative stochastic mechanics. In this framework, the membrane voltage took the place of the position and the momentum operator was defined in the membrane voltage space. Two noisy systems, namely the collective and the intrinsic systems, were identified. The collective system had its identity in the membrane voltage phase space, whereas the intrinsic system was formed by a set of dynamical attributes associated with the gating particles. Ion channel noise played a twofold role in the dynamics of the collective system, or equivalently, in the membrane voltage dynamics. Due to the presence of multiple number of gates in the channels, the collective system has taken to be under the influence of those fluctuations emerging from the uncertainty in accessing the permissible topological states of open gates. We coined this kind of noise as the topological noise, and have argued for the use of Nelson's stochastic mechanics in modeling neuronal dynamics under the influence of topological noise. The noisy behavior of the intrinsic system followed from the stochasticity in the movement of gating particles between the inner and the outer faces of the membrane. The voltage dynamics experienced this kind of noise through the interaction between the collective and the intrinsic systems. For the coupling of the collective and the intrinsic systems we followed a system plus reservoir strategy in the realm of stochastic mechanics open to dissipative environments. The coupling between the collective and the intrinsic states induced renormalizations of the membrane capacitance and of the voltage dependent potential, as well as the channel dissipation. In consequence of these renormalizations, some correction terms appeared in the equations of motion for the first and the second cumulants of the voltage dynamics. The formalism developed in the study was based on a special excitable membrane that gives the Rose-Hindmarsh model in the deterministic limit. The adoption of dissipative stochastic mechanics, conducted throughout the paper, seems to be capable of serving as a theoretical framework for modeling the effects of channel noise in neurons. The resulting model offers itself as a promising candidate for the use in further investigation of the computational aspects of internally noisy neuronal systems and their applications. We note here that the use of two different kinds of noise in our formalism may give a misguided impression of the so-called *doubly stochastic resonance* [86]. In doubly stochastic resonance, two noise

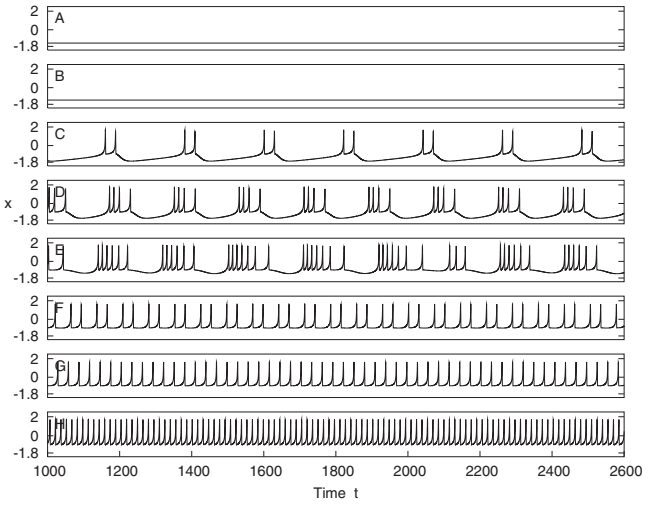

FIG. 1. Membrane voltage time series of the deterministic Rose-Hindmarsh model for the parameter values $m=1$, $a=1$, $b=3$, $c=1$, $d=5$, $x_s=-1.6$, $r=0.004$, and $h=4$ using various constant input current values: (A) 0.8, (B) 1.2, (C) 1.4, (D) 2.2, (E) 3.2, (F) 3.4, (G) 3.6, and (H) 4.4.

terms, one multiplicative and the other additive, are included into the Langevin equation in the strong damping limit. For ion channel noise, on the other hand, the topological noise introduces uncertainty into the overall current that the membrane experiences, whereas the intrinsic noise introduces Langevin type of fluctuations into the time derivative of the current. This results in a formulation completely different than the one of doubly stochastic resonance.

Let us leave a detailed numerical study of the model developed in this paper to a future article. But still it is worth mentioning here the following findings obtained from the numerical solution of Eqs. (89a)–(89e). The noisy neuron displays bursting in a wider range of input currents in comparison with its deterministic counterpart. This leads to the coexistence of two distinct regions of input current values, in which, the behavioral states of the deterministic and the noisy neurons are different. In one region, where input current values are low, the deterministic neuron is in the quiescent state, but the neuron with channel noise is in the bursting state. In the other region, having higher values of the input current, the deterministic neuron is in the state of tonic firing but the noisy neuron is still in the bursting state. These channel noise-induced transitions among the dynamical behavioral states can be seen by comparing Fig. 1 and Fig. 2. Figure 1 shows membrane voltage time series of our model in the deterministic limit, i.e., when $\varepsilon_m^y=\varepsilon_u^y=\varepsilon_m^z=\varepsilon_u^z=\eta^y=\eta^z=0$ (or equivalently, of the deterministic Rose-Hindmarsh model) using various constant input current values. Figure 2 shows time series of X for the correction coefficients $\varepsilon_m^y=0.3$, $\varepsilon_u^y=0.5$, $\varepsilon_m^z=0.003$, $\varepsilon_u^z=0.005$, and the temperature $T=1$. Comparison of Figs. 1(a) and 1(b) to Figs. 2(a) and 2(b) shows that ion channel noise causes activity (in the form of bursting) within some range of input currents, for which, the deterministic model is quiet. When Figs. 1(f) and 1(g) are compared with Figs. 2(f) and 2(g), it is seen that ion channel noise causes a transition from tonic firing to bursting

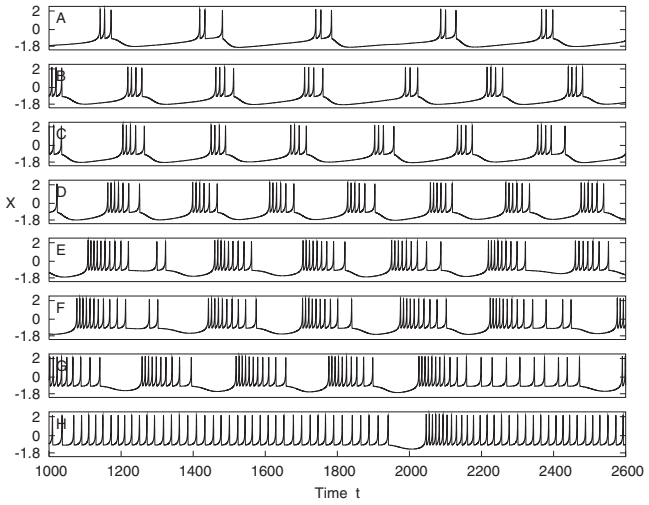

FIG. 2. Time series of X in our noisy neuron model for $\varepsilon_m^y=0.3$, $\varepsilon_u^y=0.5$, $\varepsilon_m^z=0.003$, $\varepsilon_u^z=0.005$, and $T=1$, and the Rose-Hindmarsh parameter values the same as in Fig. 1, using various constant input current values: (A) 0.8, (B) 1.2, (C) 1.4, (D) 2.2, (E) 3.2, (F) 3.4, (G) 3.6, and (H) 4.4.

within some other range of higher input currents. Both the renormalization effects, i.e., the correction terms, and the Gaussian white noise, i.e., $\eta^y(t)$ and $\eta^z(t)$, contribute to the above behavioral transitions; but in a manner that while the white noise terms cause irregularity in the time course of the voltage dynamics, the renormalization corrections force a regular (or coherent) dynamics just having the local fluctuations. Thus, topological noise, or having multi-gate channels, makes a profound effect on the behavioral state of the neuron and yet retaining a regular dynamics. Figure 3 shows time series of X for vanishing values of the correction coefficients, i.e., when the topological noise is ignored. Comparison of

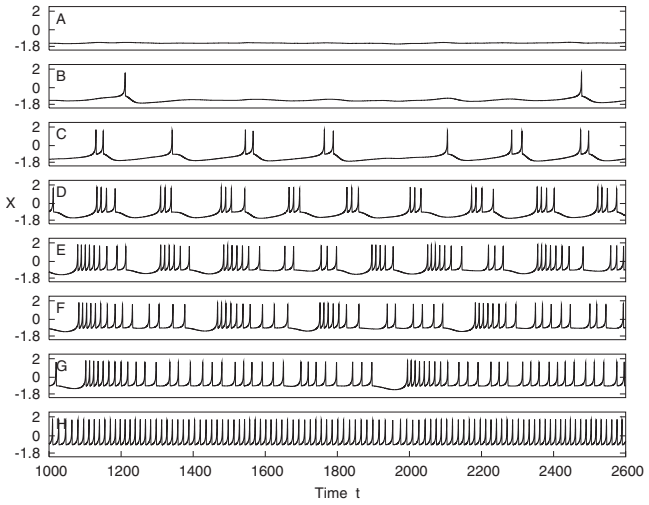

FIG. 3. Time series of X in our noisy neuron model for $\varepsilon_m^y=\varepsilon_u^y=\varepsilon_m^z=\varepsilon_u^z=0$, and $T=1$, and the Rose-Hindmarsh parameter values the same as in Fig. 1, using various constant input current values: (A) 0.8, (B) 1.2, (C) 1.4, (D) 2.2, (E) 3.2, (F) 3.4, (G) 3.6, and (H) 4.4.

Fig. 1(b) with Fig. 3(b) shows that the intrinsic noise can cause firing activity in otherwise quiet deterministic model. For larger values of the temperature parameter T, the firing activity takes place for smaller values of the input current and results in spontaneous activity. That is, the effect of the intrinsic noise in our model is essentially the same as the effect of channel noise reported using the currently available channel noise models [29,30,32–36] for the Hodgkin-Huxley membrane. Note that, as it was discussed in Sec. II, the underlying models of these studies make no use of the topological noise. Comparison of Fig. 2(a) with Fig. 3(a) shows that the inclusion of topological noise results in firing activity at even smaller input current values. It follows from the comparison of Figs. 2(g) and 2(h) with Figs. 3(g) and 3(h) that the inclusion of topological noise also results in prolongation of bursting for larger input current values. When the plots in Fig. 2 are compared with the plots in Fig. 3, it is seen that the topological noise, unlike the intrinsic noise, favors a coherent dynamics. This effect can be seen more noticeably using smaller values for the temperature T. Some early numerical results were reported in Ref. [87], but there the formulation did not include the noise terms $\eta^y(t)$ and $\eta^z(t)$, and also that the mixing coefficient was taken as $k=1/2$ instead of the one given by Eq. (77).

Our formulation has no explicit dependence onto the conformational and microscopic details of the membrane. This facilitates the investigation of the probable universal effects of ion channel noise as, some of which, just mentioned above, and appeals particularly to computational neurosciences. Of course, a possible estimation of the values of the parameters g, T, α, and the correction coefficients ε_m^y, ε_u^y, ε_m^z, ε_u^z from the membranous details would still be invaluable. In addition to the value of g and the knowledge of the exact nature of the intrinsic system, forms of the interaction operators $F^y(\boldsymbol{\xi})$ and $F^z(\boldsymbol{\xi})$ need to be known for the determination of the correction coefficients. The incidence of correction terms is a universal phenomenon that is to occur irrespective of the underlying deterministic model, but of course their precise impact on the dynamics will depend upon the model. Even though the regime we have pursued, in principle, pertains to the Hodgkin-Huxley type of membrane, the form of the deterministic differential equations and the more complicated membrane properties there create some additional complications and, therefore, physically the problem turns out to be a considerably more difficult one. But, still, the emergent renormalization corrections should be expected to play a role not very different than the Rose-Hindmarsh case. We expect that our theoretical findings will stimulate experimental works to verify the effects of the renormalization corrections in real neurons. As seen in Fig. 2, although the correction terms alter the neuron's quantitative behavior, the repertoire of basic behavior patterns remains the same under the renormalization effects. Therefore, a direct experimental verification of these possible effects may not be an easy task. However, following our above comparative findings from Figs. 1–3, any prospective experiment that might provide discrepant data for the input current values of the behavioral transitions in comparison with the current theoretical predictions, and data showing a voltage dynamics more coherent than the dynamics predicted by these theories, would authenticate our theory.

[1] B. Sakmann and N. Neher, *Single-Channel Recording*, 2nd ed. (Plenum, New York, 1995).
[2] B. Hille, *Ionic Channels of Excitable Membranes*, 3rd ed. (Sinauer Associates, Sunderland, 2001).
[3] P. Graf, A. Nitzan, M. G. Kurnikova, and R. D. Coalson, J. Phys. Chem. B **104**, 12324 (2000).
[4] G. Moy, B. Corry, S. Kuyucak, and S. H. Chung, Biophys. J. **78**, 2349 (2000).
[5] K. E. Cooper, E. Jakobsson, and P. Wolynes, Prog. Biophys. Mol. Biol. **46**, 51 (1985).
[6] S. Kuyucak and T. Bastug, J. Biol. Phys. **29**, 429 (2003).
[7] B. Roux and M. Karplus, Annu. Rev. Biophys. Biomol. Struct. **23**, 731 (1994).
[8] D. P. Tieleman, P. C. Biggin, G. R. Smith, and M. S. P. Sansom, Q. Rev. Biophys. **34**, 473 (2001).
[9] H. Haken, Fluct. Noise Lett. **4**, L171 (2004).
[10] L. S. Liebovitch and J. M. Sullivan, Biophys. J. **52**, 979 (1987).
[11] G. L. Millhauser, E. E. Salpeter, and R. E. Oswald, Proc. Natl. Acad. Sci. U.S.A. **85**, 1503 (1988).
[12] L. S. Liebovitch and A. T. Todorov, Critical Reviews in Neurobiology **10**, 169 (1996).
[13] S. B. Lowen, L. S. Liebovitch, and J. A. White, Phys. Rev. E **59**, 5970 (1999).
[14] M. S. P. Sansom, F. G. Ball, C. J. Kerry, R. McGee, R. L. Ramsey, and P. N. R. Usherwood, Biophys. J. **56**, 1229 (1989).
[15] A. Ring, Biochim. Biophys. Acta **856**, 646 (1986).
[16] E. Gorczynska, P. L. Huddie, B. A. Miller, I. R. Mellor, H. Vais, R. L. Ramsey, and P. N. R. Usherwood, Pflügers Archiv. Eur. J. Physiol. **432**, 597 (1996).
[17] P. Läuger, Biophys. J. **53**, 877 (1988).
[18] D. G. Levitt, Biophys. J. **55**, 489 (1989).
[19] C. A. Condat and J. Jäckle, Biophys. J. **55**, 915 (1989).
[20] W. Nadler and D. L. Stein, Proc. Natl. Acad. Sci. U.S.A. **88**, 6750 (1991).
[21] R. Shirokov, G. Ferreira, J. Yi, and E. Rios, J. Gen. Physiol. **111**, 807 (1998).
[22] D. Sigg, H. Qian, and F. Bezanilla, Biophys. J. **76**, 782 (1999).
[23] I. Goychuk and P. Hänggi, Proc. Natl. Acad. Sci. U.S.A. **99**, 3552 (2002).
[24] I. Goychuk and P. Hänggi, Phys. Rev. E **70**, 051915 (2004).
[25] I. Goychuk, P. Hänggi, J. L. Vega, and S. Miret-Artes, Phys. Rev. E **71**, 061906 (2005).
[26] R. F. Fox and Y. N. Lu, Phys. Rev. E **49**, 3421 (1994).
[27] C. C. Chow and J. A. White, Biophys. J. **71**, 3013 (1996).
[28] A. L. Hodgkin and A. F. Huxley, J. Physiol. Paris **117**, 500 (1952).
[29] L. J. DeFelice and A. Isaac, J. Stat. Phys. **70**, 339 (1992).
[30] A. F. Strassberg and L. J. DeFelice, Neural Comput. **5**, 843 (1993).
[31] S. M. Bezrukov and I. Vodyanov, Nature (London) **378**, 362 (1995).
[32] J. Rubinstein, Biophys. J. **68**, 779 (1995).
[33] J. E. Levin and J. P. Miller, Nature (London) **380**, 165 (1996).
[34] J. A. White, R. Klink, A. Alonso, and A. R. Kay, J. Neurophysiol. **80**, 262 (1998).
[35] C. Koch, *Biophysics of Computation: Information Processing in Single Neurons* (Oxford University Press, Oxford, 1999).
[36] S. L. Ginzburg and M. A. Pustovoit, Fluct. Noise Lett. **3**, L265 (2003).
[37] G. Schmid, I. Goychuk, and P. Hänggi, Europhys. Lett. **56**, 22 (2001).
[38] P. Jung and J. W. Shuai, Europhys. Lett. **56**, 29 (2001).
[39] S. Wu, W. Ren, K. He, and Z. Huang, Phys. Lett. A **279**, 347 (2001).
[40] A. M. Lacasta, F. Sagués, and J. M. Sancho, Phys. Rev. E **66**, 045105 (2002).
[41] B. Lindner, L. Schimansky-Geier, and A. Longtin, Phys. Rev. E **66**, 031916 (2002).
[42] P. F. Rowat and R. C. Elson, J. Comput. Neurosci. **16**, 87 (2004).
[43] H. A. Braun, M. T. Huber, N. Anthes, K. Voight, A. Neiman, X. Pei, and F. Moss, BioSystems **62**, 99 (2001).
[44] U. Feudel, A. Neiman, X. Pei, W. Wojtenek, H. A. Braun, M. T. Huber, and F. Moss, Chaos **10**, 231 (2000).
[45] O. V. Sosnovtseva, S. D. Postnova, E. Mosekilde, and H. A. Braun, Fluct. Noise Lett. **4**, L521 (2004).
[46] M. Güler, Fluct. Noise Lett. **6**, L147 (2006).
[47] E. Nelson, Phys. Rev. **150**, 1079 (1966).
[48] E. Nelson, *Dynamical Theories of Brownian Motion* (Princeton University Press, Princeton, NJ, 1967).
[49] J. L. Hindmarsh and R. M. Rose, Proc. R. Soc. London, Ser. B **221**, 87 (1984).
[50] M. Schneider and W. K. Chandler, Nature (London) **242**, 244 (1973).
[51] C. M. Armstrong and F. Bezanilla, Nature (London) **242**, 459 (1973).
[52] C. M. Armstrong and F. Bezanilla, J. Gen. Physiol. **63**, 533 (1974).
[53] R. D. Keynes and E. Rojas, J. Physiol. Paris **239**, 393 (1974).
[54] D. Sigg and F. Bezanilla, Biophys. J. **84**, 3703 (2003).
[55] W. Nonner, A. Peyser, D. Gillespie, and B. Eisenberg, Biophys. J. **87**, 3716 (2004).
[56] F. Guerra and L. M. Morato, Phys. Rev. D **27**, 1774 (1983).
[57] P. Blanchard, S. Golin, and M. Serva, Phys. Rev. D **34**, 3732 (1986).
[58] M. S. Wang, Phys. Rev. A **38**, 5401 (1988).
[59] T. Fukumi, Phys. Rev. A **40**, 530 (1989).
[60] L. S. F. Olavo, Phys. Rev. A **61**, 052109 (2000).
[61] B. Pavon, J. Math. Phys. **41**, 6060 (2000).
[62] N. C. Petroni and L. M. Morato, J. Phys. A **33**, 5833 (2000).
[63] F. Guerra, Phys. Rep. **77**, 263 (1981).
[64] E. Nelson, *Quantum Fluctuations* (Princeton University Press, Princeton, NJ, 1985).
[65] P. Ruggiero and M. Zannetti, Phys. Rev. Lett. **48**, 963 (1982).
[66] P. Ruggiero and M. Zannetti, Phys. Rev. B **27**, 3001 (1983).
[67] B. Skagerstam, J. Math. Phys. **18**, 308 (1977).
[68] K. Yasue, Ann. Phys. (N.Y.) **114**, 479 (1978).
[69] U. Weiss, *Quantum Dissipative Systems* (World Scientific, Singapore, 1999).
[70] H. P. Breuer and F. Petruccione, *The Theory of Open Quantum Systems* (Oxford University Press, Oxford, 2002).
[71] R. W. Hasse, Nucl. Phys. A **318**, 480 (1979).
[72] P. Ruggiero and M. Zannetti, Phys. Rev. A **28**, 987 (1983).
[73] S. De Martino, S. De Siena, P. Ruggiero, and M. Zanetti, J. Phys. A **22**, 2521 (1989).
[74] W. Eckhardt, Physica A **141**, 81 (1987).
[75] G. W. Ford and M. Kac, J. Stat. Phys. **46**, 803 (1987).
[76] P. S. Riseborough, P. Hänggi, and U. Weiss, Phys. Rev. A **31**,

471 (1985).
[77] F. Haake and R. Reibold, Phys. Rev. A **32**, 2462 (1985).
[78] A. O. Caldeira and A. J. Leggett, Physica A **121**, 587 (1983).
[79] Z. Kanokov, Y. V. Palchikov, G. G. Adamian, N. V. Antonenko, and W. Scheid, Phys. Rev. E **71**, 016121 (2005).
[80] H. Hofmann and P. J. Siemens, Nucl. Phys. A **275**, 464 (1977).
[81] H. Holden and P. J. Fan, Chaos, Solitons Fractals **2**, 349 (1992).
[82] H. Holden and P. J. Fan, Chaos, Solitons Fractals **3**, 439 (1993).
[83] M. O. Scully and M. S. Zubairy, *Quantum Optics* (Cambridge University Press, Cambridge, UK, 1996).
[84] R. Zwanzig, *Nonequilibrium Statistical Mechanics* (Oxford University Press, Oxford, 2001).
[85] H. Hofmann, Phys. Rep. **284**, 137 (1997).
[86] A. A. Zaikin, J. Kurths, and L. Schimansky-Geier, Phys. Rev. Lett. **85**, 227 (2000).
[87] M. Güler, Dynamics of Continuous Discrete and Impulsive Systems A Suppl. **14**(**SI**), 664 (2007).