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Random dynamics of the Hodgkin-Huxley neuron model

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Noise can alter the response of neurons, enhancing their ability to detect weak inputs. We analyze how the Hodgkin-Huxley equations, a canonical neuron model, respond to white noise stimulation. We show that this model possesses a stochastic attractor, reduced to a unique stochastic equilibrium point that attracts all trajectories.

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Neurons operate in fluctuating environments and are also subject to internal variability. Both sources of noise play an important part in shaping the response of neurons [1]. Notably, they can increase their sensitivity to weak stimuli [2], a feature that may present behavioral [3] and biomedical [4] advantages. The purpose of the present study is to analyze how neurons respond to noiselike inputs. The applications of the understanding gained in this way are twofold. On the one hand, it sheds light on the mechanisms underlying the influence of noise on neuronal coding. On the other hand, it determines how such inputs — which occur in central neurons [5], and have been extensively used in experiments [6,7] — are encoded. To carry out our program, we investigated the random dynamics of a canonical neuron model, namely the Hodgkin-Huxley (HH) equations [8].

The stochastic HH equations form a system of four differential equations:

$$\frac{dV}{dt} = G_{Na} m^3 h (V_{Na} - V) + G_K n^4 (V_K - V) + G_l (V_l - V) + \xi,$$

$$\frac{dx_i}{dt} = \frac{x_\infty^i(V) - x_i}{\tau_x^i(V)} \quad 1 \leqslant i \leqslant 3, \tag{1}$$

where C is the membrane capacitance, G_{Na}, G_K, and G_l are the maximal sodium, potassium, and leak conductances normalized by membrane capacitance, C, V_{Na}, V_K, and V_l are the corresponding reversal potentials, and ξ is the white Gaussian noise of intensity σ. In the second equation, x_1, x_2, and x_3 represent the gating variables m, h, and n. The parameter values and the auxiliary functions are the same as in [9,10]. They satisfy $0 < x_\infty^i < 1$ and $\tau_x^i > 0$. In the absence of noise, the HH model has a unique globally asymptotically stable equilibrium point, which represents the resting state of neuronal membrane.

The transition probability density function (PDF) associated with Eq. (1) represents the probability to reach any point $X = (V,m,h,n)$ at a time t, given the position of the system at a time s, with $s < t$. In the long run, i.e., $t \to \infty$ the transition PDF becomes independent from the initial state: it represents the stationary distribution p^* of the system. In other words, starting from any initial distribution $p_0 = p(V,m,h,n,0)$ of initial points, the density $p(V,m,h,n,t)$ of the solutions of Eq. (1) eventually stabilizes at p^*. Practically, p^* is the distribution of the values taken by any solution of Eq. (1) over a long time interval. For the HH model, p^* has a Gaussian-like shape centered on the equilibrium point, at low noise intensities. It takes on a different form due to noise induced firing at large noise levels. For instance the joint distribution of V and n presents a marked loop representing frequent noise induced suprathreshold excursions and the resulting action potentials. The progressive transformation from the former to the latter (Fig. 1) takes place in a narrow noise range, previously referred to as noise induced transition [9,10]. This phenomenon has been also observed and analyzed in other neuronal models, such as the FitzHugh-Nagumo, the active rotator and the leaky integrator, and its implication for neuronal coding, notably spike timing precision has been analyzed and discussed in [9–12].

The stationary distribution p^* contains only partial information about the behavior of the stochastic system Eq. (1) because it provides a static picture. The present work is concerned with dynamical aspects, notably the phase portrait of the random dynamical system (RDS) defined by Eq. (1). In a deterministic dynamical system, the phase portrait depicts the general organization of the trajectories in the phase space. It is constructed by computing the orbits of initial conditions. Similar studies are possible for RDSs. We provide a brief description of the concepts used in our study, and refer to the comprehensive monograph [13] for a thorough treatment.

We label by ω a given sample path of the noise $\xi(t)$,

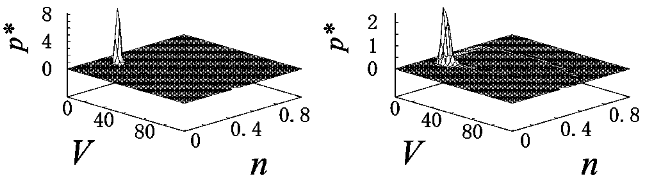

FIG. 1. Stationary distribution of the HH model. The joint distribution is shown in the V-n phase plane. Noise intensities are $\sigma = 1$ (left panel) and 2.5 $(\mathrm{ms})^{1/2}$ μA/cm^2 (right panel). Histograms were constructed from 10 000 simulated units using bin size 1 mV in along the V axis and 0.01 along n axis. V is expressed in mV, n is dimensionless, and the vertical axis is in 1/mV.

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formally, we write $\omega=\{\xi(t)\}_{-\infty<t<\infty}$, and we denote by Ω, the set of all ω. Schematically, for a fixed ω, Eq. (1) can be studied in the same way as a nonautonomous deterministic system. For instance, one can wonder whether it possesses an attractor, and if so, what the structure of this attractor is. Carrying such a task for all ω would be daunting. Fortunately, it is unnecessary. The random dynamical system theory provides the proper framework to derive the behavior of the system and representative phase portraits for typical sample paths ω, and even discuss qualitative changes in these based upon single solutions of Eq. (1). The following paragraphs clarify these general considerations; first through the discussion of a significant example, and then through the analysis of the stochastic HH dynamics. Rigorous definitions and mathematical analyses can be found in [13].

We consider a system satisfying

$$\frac{du}{dt}=-gu+\xi(t), \tag{2}$$

where $g>0$ is constant, and $\xi(t)$ is the white Gaussian noise of intensity σ. The solution of Eq. (2), taking the value u_0 at $t=t'$, and the noise sample path ω can be formally written as

$$u(t,t',u_0,\omega)=e^{-g(t-t')}u_0+\int_{t'}^{t}e^{-g(t-s)}\xi(s)ds. \tag{3}$$

Clearly, except for particular, unrepresentative realizations ω, these solutions do not stabilize at a constant or periodic behavior, but display sustained undamped irregular fluctuations throughout time. These oscillations not withstanding, for a fixed ω, the difference between any two solutions tends exponentially fast to zero: $u(t,t',u_0,\omega)-u(t,t',u_1,\omega)=\exp(-g(t-t'))(u_0-u_1)$. In fact all solutions converge to a single one $u^*(t,\omega)=\int_{-\infty}^{t}\exp[-g(t-s)]\xi(s)ds$. This specific solution plays an important part in the phase portrait of the stochastic system.

Each random selection of ω yields a different realization of u^*, so that u^* is a stochastic process. In fact, u^* is a stationary stochastic process, in the sense that its mean, variance, autocorrelation, and other higher order moments do not depend on time. In this respect, u^* is time-invariant and plays the same role as an equilibrium for deterministic dynamical systems. Such stationary processes solutions of stochastic differential equations are referred to as stochastic equilibrium points.

As pointed out above, solutions of Eq. (2) keep fluctuating throughout time. This makes it impossible to actually represent a stochastic equilibrium point by a single point as $t\to\infty$. More generally, one encounters the same difficulty for representing attractors of stochastic systems because they are time-dependent. The way out of this is the pull-back method: rather than starting the system at time $t'=0$ and examining the asymptotic regime as $t\to\infty$, the system is initiated at some time t' in the past, i.e., $t'<0$, and allowed to run until $t=0$, and the asymptotic behavior $t'\to-\infty$ is investigated. Let us illustrate this with Eq. (2). Taking $t=0$ and the limit $t'\to-\infty$ in Eq. (3) yields

$$\begin{aligned}\lim_{t'\to-\infty}u(t=0,t',u_0,\omega)&=\lim_{t'\to-\infty}e^{gt'}u_0+\int_{t'}^{0}e^{gs}\xi(s)ds\\&=\int_{-\infty}^{0}e^{gs}\xi(s)ds\\&=u^*(0,\omega).\end{aligned} \tag{4}$$

Thus the pullback shows that Eq. (2) has a unique stochastic equilibrium point which is globally asymptotically stable, i.e., attracts all other solutions. Furthermore, using the pullback method, this stochastic equilibrium is represented by $u^*(0,\omega)$, which does not depend on time any more: in other words, it is a random variable, rather than a stochastic process.

The above example illustrates the concept of stochastic fixed points and the pull-back method that can be used to obtain information about the phase portrait of noisy systems. A concept, more general than equilibria, used in the description of the asymptotic behavior of deterministic dynamical systems is that of attractor [14]. Essentially, a deterministic dynamical system possesses an attractor when all trajectories eventually enter and remain within some bounded region of the phase space. This concept can be extended to stochastic systems in the same way that was discussed for equilibria [13]. Schematically, a random dynamical system possesses a stochastic attractor $A(\omega)$ if for almost all ω, all trajectories started at $t'=-\infty$ are within a bounded region $B(\omega)$ at the time $t=0$. In such a case the stochastic attractor $A(\omega)$ is what ''remains'' at $t=0$ from the pull-back method when $t'\to-\infty$. For example, for Eq. (2), the stochastic attractor is a single point $A(\omega)=\{u^*(0,\omega)\}$. In the following, we argue that the situation is similar for the stochastic HH model. To this end, first we show the existence of a stochastic attractor for this model, and then determine its nature from numerical computations.

The fact that Eq. (1) possesses a stochastic attractor is due to two properties. The first is that the gating variables m, h, and n are bounded between zero and one, regardless of the noise realization ω. The second is the similarity between the first equation in Eq. (1) and Eq. (2). Indeed, the equation for the dynamics of V can be rewritten as

$$\frac{dV}{dt}=G(t)(a(t)-V)+\xi, \tag{5}$$

where $G(t)=G_{Na}m^3h+G_kn^4+G_l$, and $a(t)=(G_{Na}m^3hV_{Na}+G_kn^4V_K+G_lV_l)/G(t)$, so that $0<G_l<G(t)<(G_{Na}+G_K+G_l)$ and $\min(V_{rev})<a(t)<\max(V_{rev})$, where $V_{rev}=V_{Na}$, V_K or V_l. Defining v and y as $v(t)=\int_{-\infty}^{t}\exp(-\int_s^tG(r)dr)G(s)a(s)ds$ and $y=V-v-u^*$, we have

$$\frac{dy}{dt}=-G(t)y+(g-G(t))u^*(t,\omega), \tag{6}$$

so that for g satisfying $0<g<G_l$, there exist positive constants β and γ such that

$$\frac{dy^2}{dt} \leqslant -\beta y^2 + \gamma [u^*(t,\omega)]^2, \tag{7}$$

so that, with notations similar to Eq. (3), we have

$$y^2(t,t',y_0,\omega) \leqslant e^{-\beta(t-t')} y_0^2 + \gamma \int_{t'}^{t} e^{-\beta(t-s)} [u^*(s,\omega)]^2 ds. \tag{8}$$

Using the pull-back, method, i.e., setting $t=0$ and $t' \rightarrow -\infty$, we have

$$\lim_{t' \rightarrow -\infty} y^2(0,t',y_0,\omega) \leqslant \int_{-\infty}^{0} e^{\beta s} [u^*(s,\omega)]^2 ds. \tag{9}$$

The above shows that there is a bound $R(\omega)$ for the pullback of y. Given that $V = y + v + u^*$, and that the pullback of each of these three quantities is bounded, the same holds for that of V. Combining this with the boundedness of the gating variables suffices to establish the existence of a stochastic attractor $A(\omega)$ for Eq. (1) [13]. In the following, we discuss the structure of this attractor.

At the limit of zero noise, the stochastic attractor is reduced to the unique equilibrium point of the HH, and the system is globally asymptotically stable. The situation is the same at low noise levels, in the sense that the random dynamical system remains globally asymptotically stable with a unique stochastic equilibrium point playing the same role as that of the deterministic system. In other words, the low noise behavior of stochastic HH equations is similar to that of Eq. (2). Given that the shape of the stationary distributions p^* changes when noise is increased (Fig. 1), the question is whether this noise induced transition is concurrent with a qualitative change in the stochastic attractor of the model. Such a qualitative change is referred to as a dynamical stochastic bifurcation [13]. For a random dynamical system, stochastic bifurcations are detected as a sign change in the Lyapunov exponents of the system. These exponents are defined in a way similar to those of deterministic dynamical systems, and thanks to the ergodicity of the stochastic system, they take on the same value for almost all initial conditions and almost all noise sample path ω. This same ergodicity ensures in fact that when the dynamics of the system are confined within some bounded region, a negative leading Lyapunov exponent implies that the solutions eventually converge to a finite number of stochastic equilibria [15,16]. In this sense, a negative Lyapunov exponent in a random dynamical system is more restrictive than negative real parts of the eigenvalues of the Jacobian matrix at an equilibrium point of a deterministic dynamical system.

Figure 2 represents the Lyapunov exponents of Eq. (1) against the noise intensity. All four exponents are negative and remain so at all noise levels, thus ruling out the presence of dynamical stochastic bifurcations in this system. These results suggest that the stochastic attractor $A(\omega)$ is restricted to a single stochastic equilibrium point at all noise levels. Pull-backs (Fig. 3) and time reversed simulations run at several noise levels agreed with the above result (not shown).

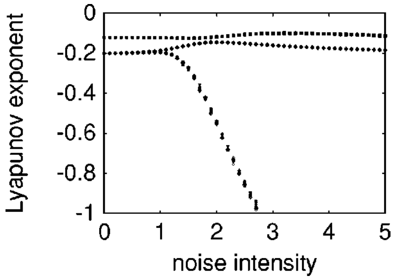

FIG. 2. The first three Lyapunov exponents of the HH model (in ms^{-1}) against noise intensity [in $(\mathrm{ms})^{1/2}\mu$ A/cm^2]. For each noise amplitude, the exponents were estimated from eight simulations lasting 100 000 ms, from which the starting 5 000 ms were discarded, using the algorithm in [17], with a step of 0.05 ms. The fourth Lyapunov exponent was also computed (not shown) and was found to decrease from -5.3 to -9.8 for the same noise range.

In conclusion, we analyzed the dynamics of a noisy canonical neuron model, namely the HH equations, from the perspective of random dynamical system theory. We showed that this system possesses a stochastic attractor that is in fact a single globally asymptotically stable stochastic equilibrium point. In the following paragraphs, we discuss first the generality of the results, and then their implications in terms of neuronal coding.

The first stage of our study consisted in proving the existence of a stochastic attractor for the HH model. The proof relied only on two properties of these equations, one that the gating variables are bounded, and second that the equation governing the dynamics of V has a linear dependence on this variable, with bounded coefficients. These two properties are actually shared by all HH-type equations, modeling electrical activity of cellular membranes, regardless of the number of gating variables and transmembranar currents they implement. So that, our work establishes that all such biophysical membrane models possess stochastic attractors. The nature of this attractor is model dependent. For the HH model, we

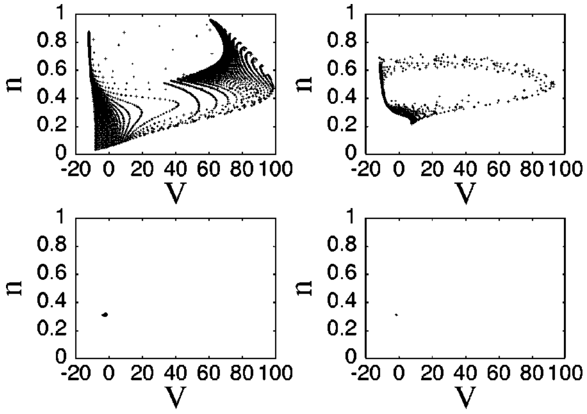

FIG. 3. Pullbacks of the noisy HH model for $\sigma = 3$, at $t = -1$ ms (upper left panel), $t' = -5$ ms (upper right panel), $t' = -20$ ms (lower left panel), and $t' = -50$ ms (lower right panel), for a starting grid of $N = 10\,000$ initial conditions positioned at $V(t') = V_K + (j-1)(V_{Na} - V_K)/N$, $m(t') = m_\infty(V(t'))$, $h(t') = n(t') = 1/2N + (k-1)/N$, with j, $k = 1, \cdots N$. Abscissae, V (in mV), ordinates, n (dimensionless).

found it to be a single stochastic equilibrium point. This result generalizes our previous analysis carried in the case of the leaky integrate and fire model [12].

For the HH model, our results reveal a striking difference between the response to periodic stimulation and fluctuating noise like inputs. Indeed, for the former, increasing the input amplitude leads to successive bifurcations separating regimes, such as subthreshold oscillations and suprathreshold phase lockings. In contrast, modifying the intensity of the noiselike inputs does not induce any dynamic stochastic bifurcation as attested by the constant sign of the Lyapunov exponents. From the standpoint of neuronal coding, this global asymptotic stability of the stochastic equilibrium point means that to each input realization ω, there corresponds a unique asymptotic response. In other words, if an HH model is presented with the same input realization ω at different occasions, it will present the same response (possibly after a transient), even if initially it was at a different state. In this sense, the response evoked by such inputs is reliable, a phenomenon that has been observed in a large number of experimental preparations, including invertebrate as well as vertebrate neurons [7].

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