

Mechanisms of stochastic phase locking

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Periodically driven nonlinear oscillators can exhibit a form of phase locking in which a well-defined feature of the motion occurs near a preferred phase of the stimulus, but a random number of stimulus cycles are skipped between its occurrences. This feature may be an action potential, or another crossing by a state variable of some specific value. This behavior can also occur when no apparent external periodic forcing is present. The phase preference is then measured with respect to a time scale internal to the system. Models of these behaviors are briefly reviewed, and new mechanisms are presented that involve the coupling of noise to the equations of motion. Our study investigates such stochastic phase locking near bifurcations commonly present in models of biological oscillators: (1) a supercritical and (2) a subcritical Hopf bifurcation, and, under autonomous conditions, near (3) a saddle-node bifurcation, and (4) chaotic behavior. Our results complement previous studies of aperiodic phase locking in which noise perturbs deterministic phase-locked motion. In our study however, we emphasize how noise can induce a stochastic phase-locked motion that does not have a similar deterministic counterpart. Although our study focuses on models of excitable and bursting neurons, our results are applicable to other oscillators, such as those discussed in the respiratory and cardiac literatures. © 1995 American Institute of Physics.

I. INTRODUCTION

Biological oscillators exhibit a variety of dynamical behaviors that can be accessed experimentally through changes in the physicochemical parameters describing their internal and external environments. The oscillation may be endogenous to the system, such as for a pacemaker cell. The system may be normally quiescent, but excitable: if sufficiently perturbed, it will become activated and then return to its resting state. The system may exhibit bursting, in which periods of activity, such as neural firing or the secretion of insulin from pancreatic beta cells, alternate with periods of quiescence. The same system may exhibit all these behaviors in different parameter ranges. Periodic forcing causes a competition between time scales of the system proper and that of the stimulation. Simple or complex phase-locked motion, or chaotic motion can then ensue. The mathematical models for these systems undergo bifurcations as parameters are varied, and one can associate these qualitative changes in motion with those observed experimentally. Further, in the context of dynamical diseases, bifurcations can correlate with the onset of pathology. The goal of these comparisons between data and models is to help build mathematical models with better predictive capabilities. This is possible because certain behaviors and bifurcations are characteristic signatures of certain kinds of nonlinearities.

Noise is traditionally seen as a nuisance that blurs or smears out known patterns of behavior. We like to think that, were the noise to disappear, the predictable pure pattern would be restored. While it is true that this can happen, it is also true that noise can move bifurcation points, or induce dynamical behaviors with no deterministic counterpart. These noise-induced transitions¹ are especially important near bifurcation points. Noise is often present in large amounts in physiological systems, but even in minute amounts it can significantly alter the observed behaviors

(Sec. VI). It is useful then to view noise sources as important dynamical components that must be appropriately coupled to the other equations of motion. Further, the characteristics of noise such as probability density, intensity, and bandwidth must be viewed as parameters on equal footing with the deterministic parameters of the system.

The present study discusses mechanisms by which noise can produce stochastic phase locking in autonomous and periodically forced systems. This pattern is found in the vicinity of bifurcations where different dynamical behaviors coexist, as well as of bifurcations where they do not coexist. Bifurcation points and multistability are crucial concepts of dynamical diseases, thus the relevance of our study to this topic. Each mechanism studied here is found to have its own signature in the distribution of times between the events of interest. Other signatures, such as those associated with the return maps of interevent times, will be discussed elsewhere. We illustrate our findings on various neuron models in the vicinity of bifurcations commonly found in models of biological oscillators.

A. Stochastic phase locking or "skipping"

Many types of neurons exhibit stochastic phase locking or "skipping." Figure 1 is one possible simulation of the behavior of a skipping neuron using the Fitzhugh–Nagumo model (FHN) in the excitable regime (see Sec. III). The membrane voltage oscillates in response to a periodic current. Broadband noise is also driving this system. Near the peak of this noisy oscillation, action potentials or "spikes" are sometimes seen. The neuron may skip an integer number of cycles of the oscillation before spiking again. The multimodal histogram of interspike intervals (ISIH), seen in Fig. 1(B), is a characteristic signature of skipping. Because of the phase preference, the interspike intervals (ISIs) are grouped at integer multiples of the oscillation period T_0 . The ISIH also contains information on the amplitude and frequency of

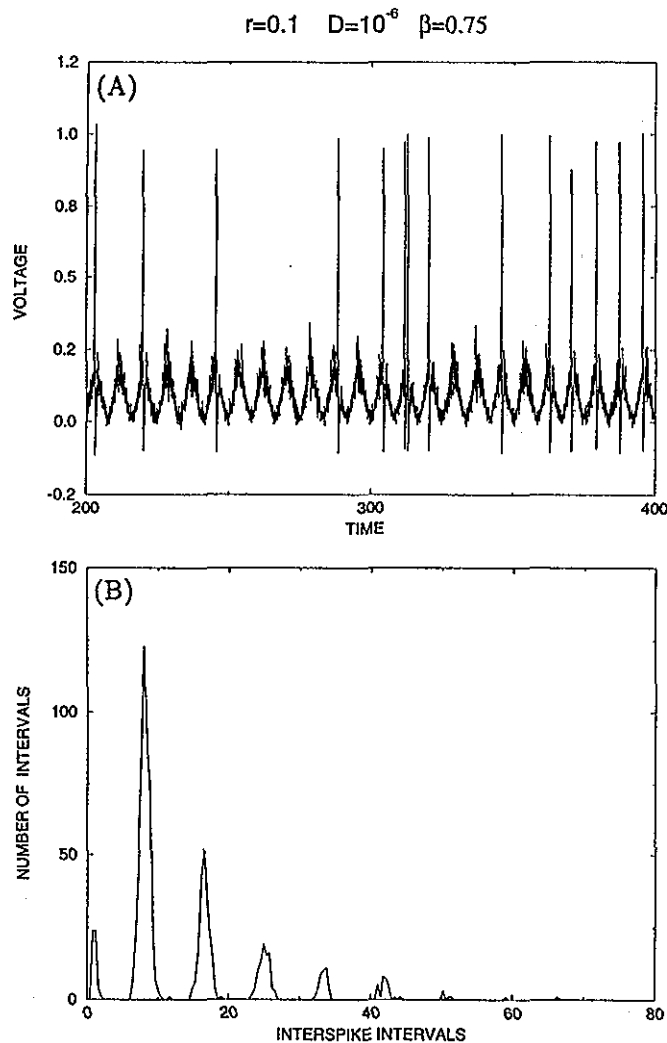


FIG. 1. Time series (upper panel) from low-frequency forcing of the Fitzhugh–Nagumo equation with periodic and stochastic forcing [Eqs. (1)–(3)]. The noiseless solution is a fixed point; an increase in b_0 brings on a limit cycle through a supercritical Hopf bifurcation. The ISIH peaks (lower panel) are at integer multiples of the driving period. Parameters are $a=0.5$, $b=0.12$, $d=1.0$, $r=0.1$, $\beta=0.75$, and $\epsilon=0.005$. Solutions for all the figures were obtained using a fixed step fourth-order Runge–Kutta method. The integration time step here is 0.005; 1000 steps were discarded as transients. A spike is counted when the positive going solution crosses the threshold value of 0.5. The ISIH was constructed from five realizations of 5×10^5 time steps.

the oscillation.² The peak widths are proportional to the noise intensity D . The rate of decay of the peak heights depends sensitively on D and the forcing amplitude. Also, when this amplitude increases, the ISIs get shorter, since the voltage spends more time near the spiking threshold during each stimulus cycle. The first peak in the ISIH is not always the highest, nor is it necessarily present, especially if the frequency is high (see Fig. 2). Spike generation is, in fact, determined by the amount and duration of the depolarization produced at the axon hillock.

Origins of skipping may be arbitrarily divided into two categories: autonomous and nonautonomous. The nonautonomous case applies when there is periodic forcing. This has been reported in a variety of systems, such as auditory

fibers,^{3,4} mammalian mechanoreceptor afferents,⁵ visual cortical neurons,⁶ and crayfish mechanoreceptors.⁷ When the driving frequency is not too high, the peaks of these ISIHs are “tunable,” lining up at the integer multiples of the driving period. In the autonomous case, there is no obvious external periodic forcing, although firings may be synchronized to an internal (autonomous) oscillation of the membrane potential. Examples include shark multimodal sensory cells⁸ and neurons in the cat lateral geniculate nucleus.⁹ All these ISIHs are robust features of the neurons under nonpathological conditions.

Various forms of stochastic phase locking are also seen in the populations of cells involved in the generation of the cardiac and respiratory rhythms, especially in diseased states (see Refs. 11 and 12 for a review). In one example of mechanical ventilation, the number of phrenic bursts per ventilator cycle can alternate randomly between one and two. This would produce a histogram of intervals between phrenic bursts, with one peak at half the pump period and another at the pump period. The mechanisms studied in this paper may shed more light on such behaviors.

In our study, the stimulus and noise are modeled as currents that cause voltage fluctuations. Our results can be understood by knowing how the noiseless system bifurcates when a constant bias current increases. In the case of FHN (Sec. III), there is a supercritical Hopf bifurcation at a current value I_H , beyond which the neuron fires repetitively. If the total bias current is not constant, but rather fluctuates due to periodic and stochastic forcing then there exist time intervals during which the total bias exceeds I_H . Thus, depending on the activation rate constants and the distance between the voltage and the spiking threshold when $I > I_H$, the excitable s system can produce one or more spikes.

In Sec. II we review earlier modeling studies of skipping behavior. In Sec. III we study skipping in the FHN model near a supercritical Hopf bifurcation, and examine the tunability of the ISIH. In Sec. IV we look at skipping near the subcritical Hopf bifurcation in the Morris–Lecar equations. Skipping without periodic forcing is studied in the autonomous Hindmarsh–Rose model in Sec. V. Skipping in the vicinity of a period-doubling route to chaos is studied in the Plant model of slow-wave bursting in Sec. VI. In Sec. VII we briefly discuss the relevance of stochastic resonance (SR) when skipping is present. The paper concludes in Sec. VIII.

II. PREVIOUS MODELS OF SKIPPING

A simple model for skipping is simply the convolution of a Gaussian process, which accounts for the width of the peaks, and of a discrete Poisson process, which accounts for the skipping. To our knowledge, the earliest model of skipping is the integrate-and-fire (IF) model of Gerstein and Mandelbrot.³ It accounted for the skipping response of primary auditory neurons to “clicks” of sound (short pulses of broadband noise). In this model, the periodic stimulus modulates the bias of the random walk of the voltage toward the threshold. Deletion models¹⁰ have also been proposed for multimodal ISIHs such as those of Ref. 9. These models are based on the effect of individual synaptic events, and tend to produce multimodal ISIHs whose structure degrades with in-

creasing ISI. Glass *et al.*¹¹ have reported that a simple IF oscillator with periodic input and noise can have patterns with irregular skipped beats. Descriptions of skipping based on stochastic point processes (in which there are no dynamical variables) can be found, in the context of auditory data, in Ref. 13. Dynamical modeling of skipping in auditory neurons has been done using stochastic Fitzhugh–Nagumo equations¹⁴ and stochastic Hodgkin–Huxley-type equations.¹⁵ Modeling of skipping in the context of bistability, excitability, and stochastic resonance (see Sec. VII) has been reported in Refs. 16–18, and 2.

Skipping can occur in completely deterministic models as well, when the dynamics are chaotic. This is the case for the forced Duffing equation.¹⁶ The histogram of times between successive crossings from a given well to the other well in this double-well motion exhibits peaks near but not exactly at integer multiples of the driving period. The alignment with the multiples of T_0 gets better at larger ISIs. This is probably due to inertia and finite damping, since with infinite damping the peaks do line up.² While this example is not a good model for an excitable neuron, it indicates what to expect when a bistable neural system with higher-order dynamics is periodically forced.

III. THE FITZHUGH–NAGUMO EQUATIONS AND TUNABILITY

The skipping neuron can often be “tuned” to the external frequency.⁴ This is illustrated in Fig. 1, which is a simulation of the stochastic Fitzhugh–Nagumo model¹⁹ in the excitable regime:

$$\epsilon \frac{dv}{dt} = v(v-a)(1-v) - w + \eta(t), \quad (1)$$

$$\frac{dw}{dt} = v - dw - (b + r \sin \beta t), \quad (2)$$

$$\frac{d\eta}{dt} = -\lambda \eta + \lambda \xi(t), \quad (3)$$

where $\langle \xi(t) \rangle = 0$ and $\langle \xi(t) \xi(s) \rangle = 2D \delta(t-s)$. We chose the exponentially correlated Ornstein–Uhlenbeck process $\eta(t)$ for the noise throughout this paper, because its variance $D\lambda$ and correlation time $\tau_c = \lambda^{-1}$ can be controlled. The power spectrum of $\eta(t)$ is flat up to the cutoff frequency λ . The ISI histograms are constructed from many different realizations of the stochastic process in Eqs. (1)–(3) (using a different seed for each realization). Equations (1)–(2) are taken from Ref. 19, in which the periodic forcing is on the slow variable. The ensuing behavior is qualitatively similar to that obtained by forcing the fast variable if the frequency is less than the relaxation rate of the fast variable ϵ .

The periodic forcing alone cannot produce spikes for the parameters in Fig. 1. If the bias b were increased, the model would bifurcate to a limit cycle of period 0.77 through a supercritical Hopf bifurcation. The effect of this limit cycle can already be seen with low-frequency forcing, as in Fig. 1(A), where two spikes ride one of the crests of the low-frequency modulation around the fixed point. Such multiple firings produce the peak at small ISIs. At higher forcing fre-

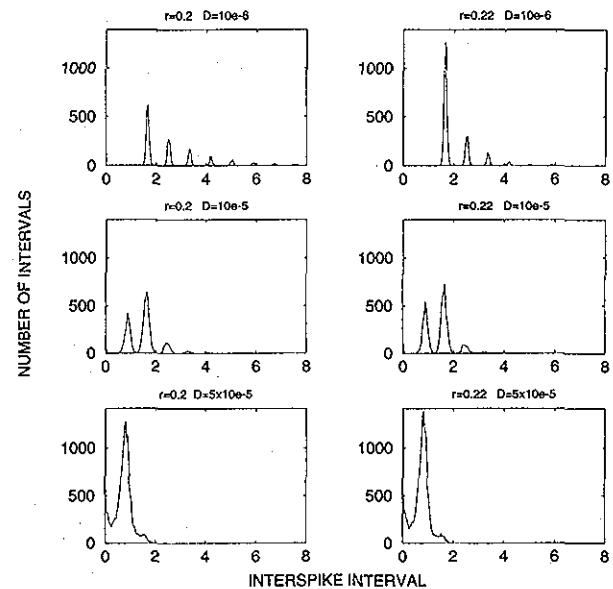


FIG. 2. Effect of phase locking on tunability: high-frequency forcing near a supercritical Hopf bifurcation. Multimodal ISI histograms from the numerical integration of the FHN system with periodic and stochastic forcing [Eqs. (1)–(3)]. The simulation parameters are as in Fig. 1, except for r and β . The left panels, for a forcing amplitude $r=0.2$ characterize the noise-induced limit cycle. The right panels, for $r=0.22$, characterize the perturbed limit cycle, which has period 1.675 s when $D=0$. This is twice the forcing period of 0.837 s ($\beta=7.5$), i.e., the solution is a 2:1 phase locking. The model is also tunable, but the first peak is suppressed at low noise.

quencies, the time scale of the limit cycle and that of the forcing can compete, leading to phase-locked spiking solutions.^{19,14,15} Note that phase-locked solutions can also arise even if the nonforced system is excitable.²⁰ Figure 2 shows two sets of ISI histograms as the noise is increased. The frequency is ten times greater than in Fig. 1. The deterministic motion underlying the right panels is a 2:1 phase-locked solution (one spike for every two cycles of the stimulus), while that underlying the left panels is a fixed point modulated by the small periodic forcing (i.e., no spiking). With noise, there is not much difference between these sub- and superthreshold cases, except at zero noise, where the former gives an empty ISI histogram and the latter a sharp peak at the period 1.675 of the 2:1 phase-locked solution (not shown).

IV. MORRIS–LECAR EQUATIONS

The Morris–Lecar equations (see Ref. 21) are a hybrid of the Hodgkin–Huxley and FHN equations. We study the behavior, with stochastic and periodic forcing, of the fast voltage variable $v(t)$ in the vicinity of a subcritical Hopf bifurcation, where a fixed point and limit cycle (repetitive firing) coexist. Without noise ($D=0$) and periodic forcing ($r=0$), $v(t)$ goes to the fixed point or travels along the limit cycle, depending on the initial conditions. With $D>0$, the behaviors shown in Figs. 3(B)–3(D) do not depend on the initial conditions. Rather than choose a low frequency, for which the behavior is similar to that in Fig. 1, we focus on the vicinity of the phase-locked regime. For $r=0.015$ and $D=0$, the motion is phase locked with a very large period [Fig. 3(A)]. The presence of noise [Figs. 3(B)–3(C)] deletes

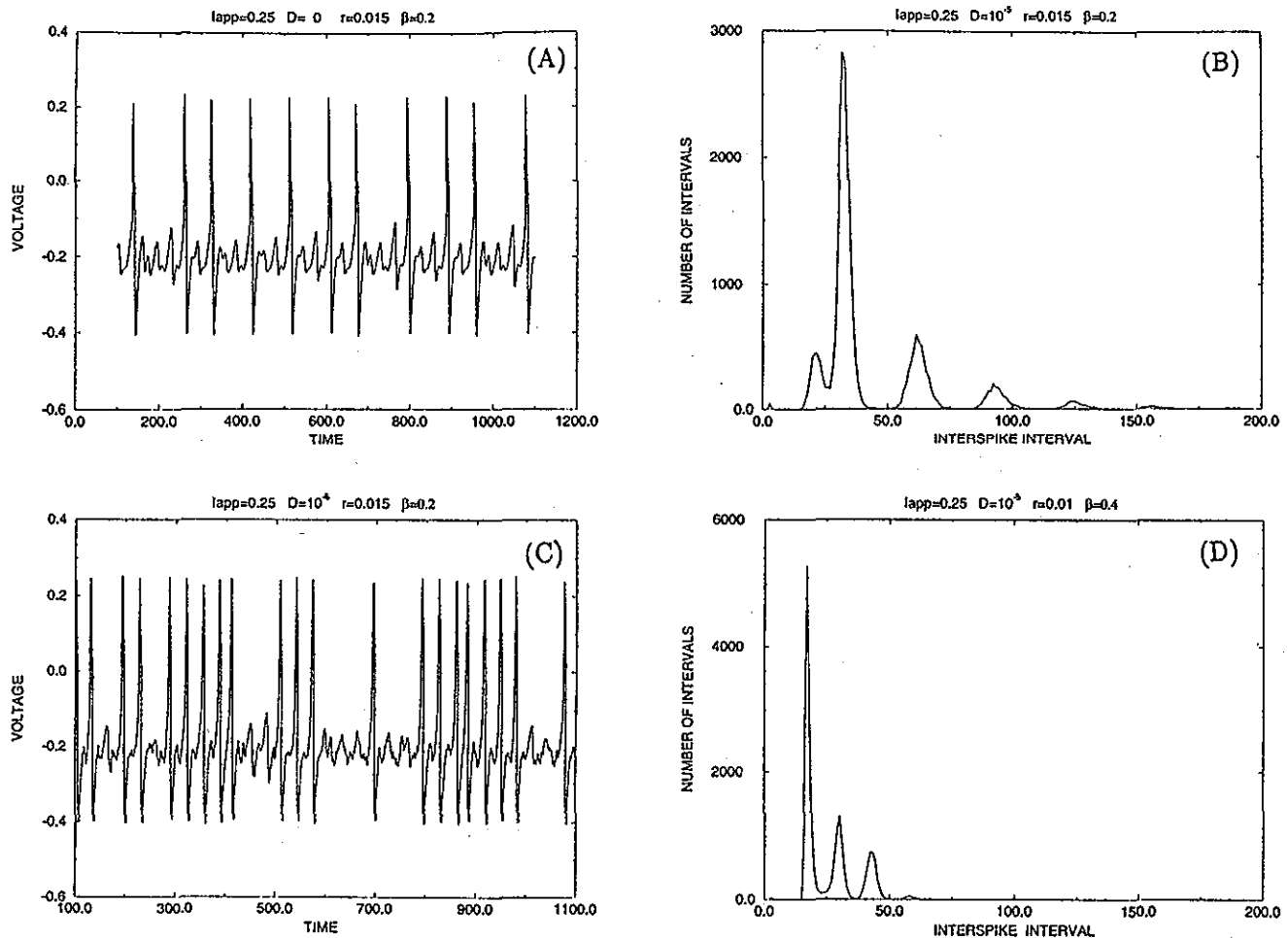


FIG. 3. Subthreshold forcing near a subcritical Hopf bifurcation: time series and ISIHs for the Morris–Lecar equations. The current $I=0.25$ is chosen, such that, in the absence of periodic and stochastic forcing, a limit cycle LC1 (repetitive firing) and a fixed point coexist. (A) A periodic phase-locked solution of high period (perhaps chaotic) when $D=0$ for forcing amplitude $r=0.015$ and angular frequency $\beta=0.2$ (period is 31.4). (B)–(C) ISIH and time series for the same parameters as in (A), but $D=10^{-5}$. The ISIH is multimodal, with peaks at integer multiples of 31.4. The small peak at 20.9 corresponds to the period of the limit cycle LC1. (D) Here $r=0.01$ and $\beta=0.4$ (forcing period 15.7). The underlying noiseless motion is a 5:3 solution of period 78.5. The peaks at 17.1, 30.15, 43.2, and 58.3 are near the multiples of 15.7, but appear perturbed by LC1. Parameters are as in Ref. 21: $v_1=-0.01$, $v_2=0.15$, $v_3=0$, $v_4=0.3$, $\bar{g}_{Ca}=1.1$, $\bar{g}_K=2.0$, $\bar{g}_L=0.5$, $v_K=-0.7$, $v_L=-0.5$, and $\phi=2$. Integration time step is 0.05, $\tau_c=0.01$, and the spiking threshold is 0.1. Integration involves 100 realizations of 220 000 time steps for $\beta=0.2$ and 50 realizations for $\beta=0.4$.

some spikes and induces others, the result being the familiar multimodal ISIH with peaks at multiples of the driving period T_0 . There is also another peak in the flank of the T_0 peak, due to the presence of the limit cycle. In other words, sometimes the forcing brings this system into its limit cycle behavior, which may then impose its own time scale on the spiking. When $r=0.01$, the noiseless motion is a small modulation of the fixed point at the same frequency β ; the ISIH with noise is like Fig. 3(B) but the limit cycle peak is more prominent and the perturbed phase-locked motion less prominent (not shown). If the frequency is then doubled [Fig. 3(D)], tunability is more degraded, presumably due to closeness of the limit cycle and forcing periods.

V. HINDMARSH–ROSE MODEL OF BURSTING

In this and the next section, we investigate how skipping can arise in the presence of noise, but without periodic stimulation. This possibility is examined in one of many models of bursting neurons: the Hindmarsh–Rose model:²²

$$\frac{dx}{dt} = y - ax^3 + bx^2 + I - z + \eta(t), \quad (4)$$

$$\frac{dy}{dt} = c - dx^2 - y, \quad (5)$$

$$\frac{dz}{dt} = r[s(x - x^*) - z]. \quad (6)$$

This model is studied with stochastic forcing of the fast variable $x(t)$. A transition from one to three singular points occurs through a saddle-node bifurcation as I increases. At the same time, the system goes from fixed point to bursting to pacemaker activity. Bursting occurs for a given I because the adaptation current z causes a modulation of the nullclines, such that either one or three singular points coexist. The

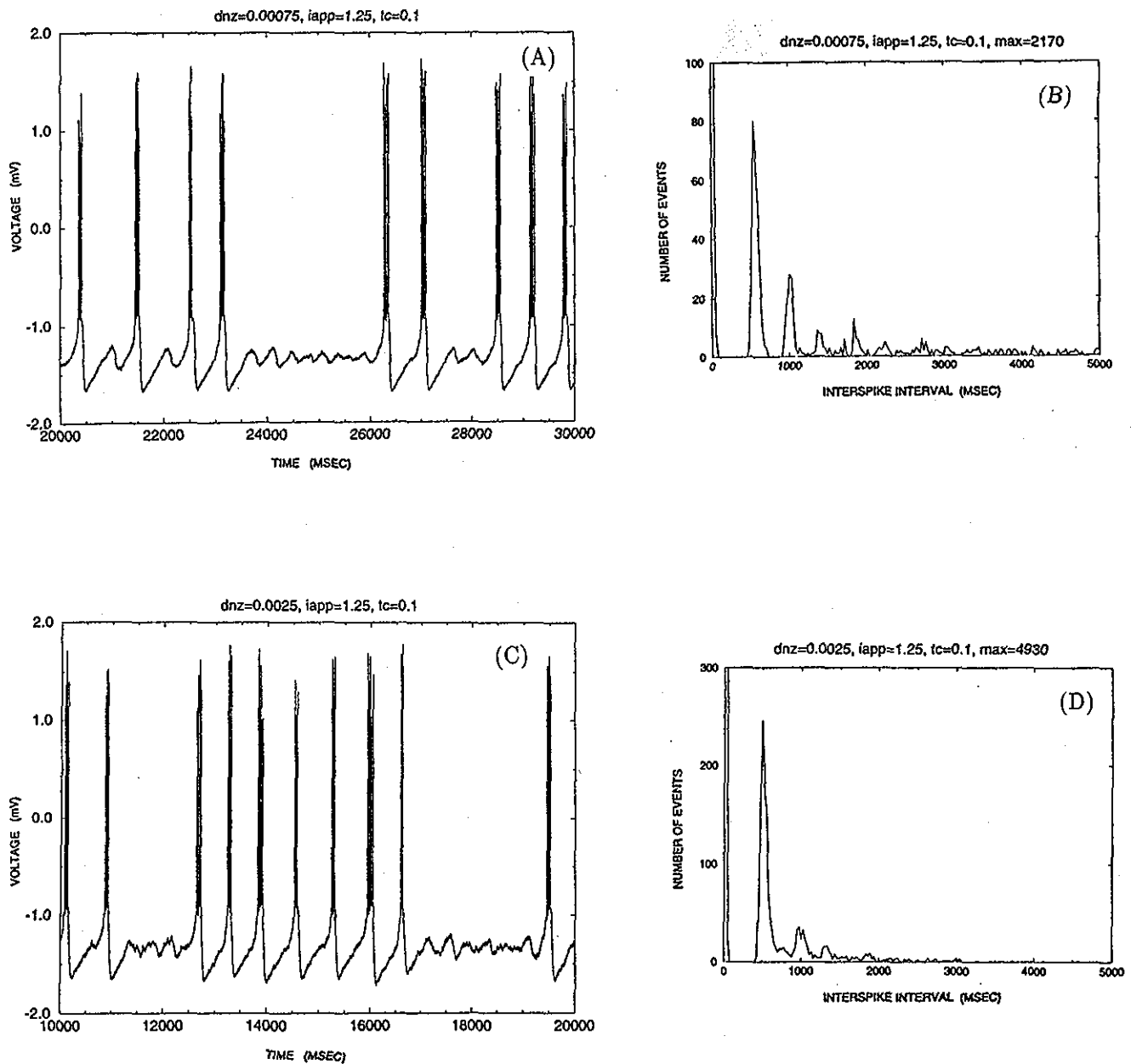


FIG. 4. Skipping near a saddle-node bifurcation in the Hindmarsh-Rose model Eqs. (4)–(6) of bursting behavior. Here there is only stochastic forcing. With $D=0$, the solution is a fixed point with complex eigenvalues having a negative real part. This explains the small oscillations seen (when $D>0$) between the larger waves. (A)–(B) Time series and corresponding ISIH for the noise level $D=dnz=7.5\times 10^{-4}$. (C)–(D) The same as in (A)–(B), but $D=2.5\times 10^{-3}$. The peaks are at integer multiples of the period of the nearby deterministic bursting pattern. For large D , counts are concentrated in the first mode. The counts in the first bins are due to the short ISIs inside the bursts. The maximum of these bins is indicated above the panel. Parameters are $a=1.0$, $b=3$, $c=1$, $d=5$, $s=4$, $r=0.001$, $I=1.25$, and $x^*=-1.6$. The integration time step is 0.05, and the spike threshold is 1.0. Five realizations of 5.5×10^6 time steps were used to construct the ISIHs.

skipping patterns seen in Fig. 4 are possible when I is set at a value near but below that for the onset of bursting. The noise induces skipping between active and quiescent phases of the bursting pattern. Since the induced behavior is bursting, multiple spikes appear on top of each wave that has reached the threshold. The small oscillations seen between the bursts are a consequence of the complex eigenvalues with negative real part characterizing the behavior around the fixed point near -1.4 . An increase in noise concentrates the probability into the first bins. This autonomous system thus behaves in many ways like the periodically driven systems above.

VI. PLANT'S “SLOW-WAVE BURSTER” MODEL

Chaos can appear in models for bursting cells. In the chaotic regime, the ISIs are distributed continuously rather than discretely. A bit of noise can smooth out the ISIH structure into a multimodal ISIH. This is illustrated here in Plant’s model²³ for slow-wave bursting, originally proposed to explain the firing behavior of the R-15 pacemaker neuron of Aplysia. Its autonomous five-dimensional dynamics are significantly more complicated than the other models studied up to now in this paper. The equations and parameters used can be found in Ref. 23. Again, the fast variable is forced by a

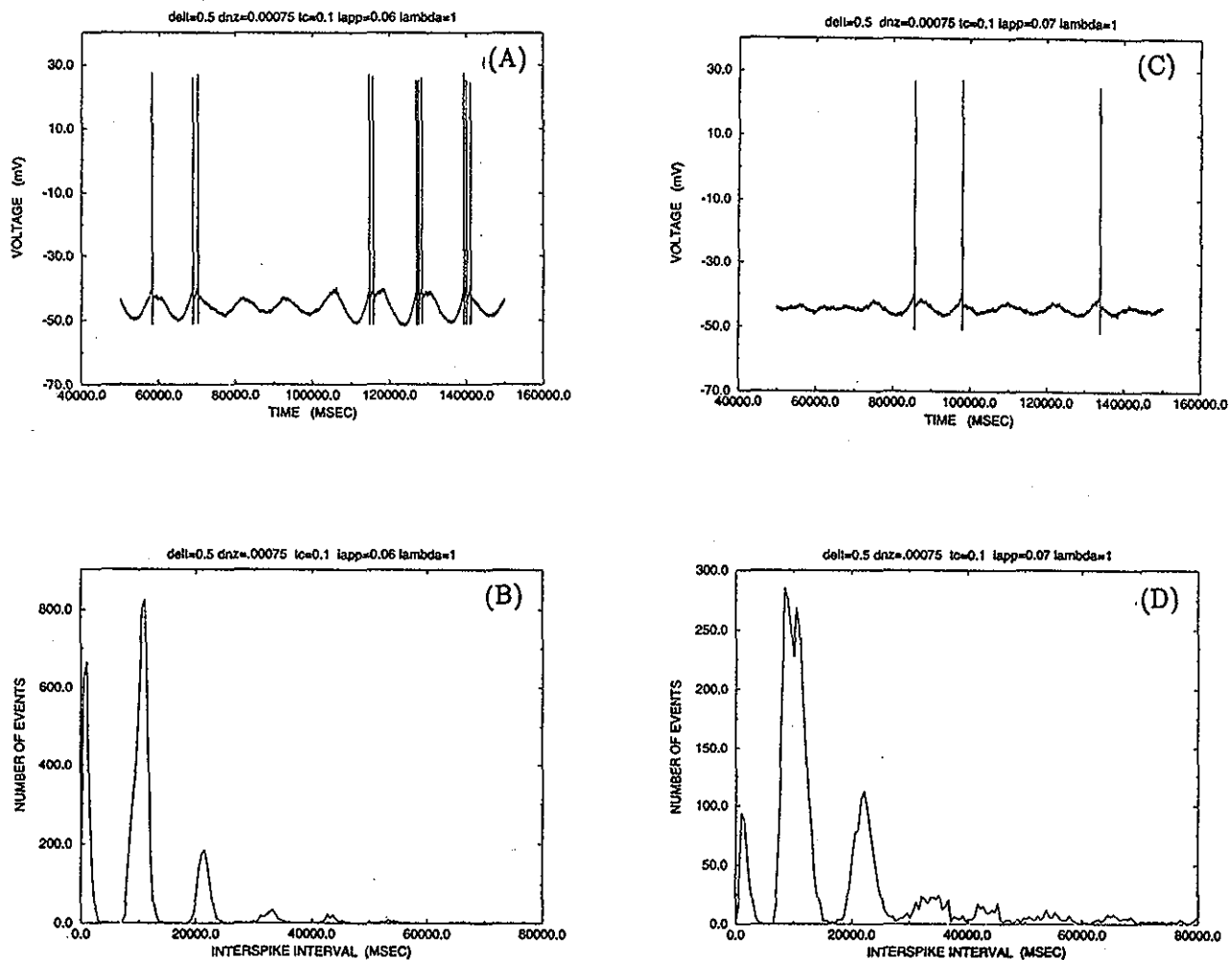


FIG. 5. Stochastic forcing near a chaotic regime: skipping in the Plant model of slow-wave bursting. Stochastic forcing with $D=7.5 \times 10^{-4}$ is present. (A)–(B) Time series and ISIH for the applied current $I_{app}=0.06$. When $D=0$, the solution is a period-doubled version of a solution having only one spike per burst. When $D>0$, the ISIH peaks are at integer multiples of the slow-wave underlying the bursting behavior. (C)–(D) The same as (A)–(B), but $I_{app}=0.07$. The noiseless solution here appears chaotic to the accuracy of our simulation (in double precision). Again the ISIH is multimodal, as in (B). Notice the counts in the first bins, corresponding as in Fig. 4 to the ISIs in the brief active phases induced by the noise. Parameters are as in Ref. 23; $\tau_c=0.1$, and the spike threshold is 10. Ten realizations of 4×10^6 integration steps (minus 5×10^4 transient steps) were used, with a time step of 0.5.

bias current and noise. The bursting mechanism here is different from that of the Hindmarsh–Rose model. But these systems are similar in that they can exhibit simple limit cycle motion, the time scale of which governs the skipping. Skipping can arise when the parameters are chosen such that the motion belongs to a period-doubling route to chaos. For $I_{app}=0.06$ and $D=0$, the ISIH has two close sharp peaks characteristic of the first period-doubled solution. As D increases (not shown), the peaks broaden, then merge; then peaks at integer multiples of this peak appear, and the number of short ISIs increases. At higher values of D , the probability bunches up into the first peak (which is also wider). This behavior is similar to that of the noisy FHN system with low-frequency forcing, when the underlying deterministic behavior is a limit cycle (i.e., as in Fig. 1, but with a larger value of b). We find also that if I_{app} changes to 0.07, skipping

is again seen, but the peaks are wider. Abrupt transitions to other ISIHs can be seen as I_{app} increases beyond 0.07.

VII. STOCHASTIC RESONANCE

All the systems studied above may, due to their stochastic switching properties, exhibit stochastic resonance (SR). This is a nonlinear effect in which the presence of a deterministic oscillation in the state variable is enhanced by noise. This presence can be measured, e.g., by the power spectrum of $V(t)$, from which a signal-to-noise ratio (SNR) can be extracted. As D increases from zero, the SNR goes through a maximum (at the “resonance”), leading to the paradoxical notion that an increase in noise can increase the SNR. This is possible if the deterministic forcing cannot by itself induce the neuron to fire (i.e., it is subthreshold). Hence, without

noise, no firings occur. As D increases, more firings occur, and they are more correlated with the small driving signal over a certain range of D . If the noise becomes too strong, this correlation decreases. Skipping is not SR, nor is it a sufficient condition for SR. SR has been suggested to occur in real neurons in Ref. 24; it was studied in the context of excitable models in Refs. 17 and 18, and was shown to occur experimentally in Ref. 7.

VIII. CONCLUSION

Skipping can occur with or without external periodic forcing, depending on the regimes of neural activity that can be "accessed" through noise (fixed point, excitable, pacemaker, and bursting). It is somewhat striking that it appears in the vicinity of so many noisy bifurcations; this may underlie its ubiquity in neurobiology. The best way to uncover its mechanism in an experimental setting is probably to vary system parameters (as is the case to demonstrate chaos in any system). The different ISIHs thus obtained are characteristic of the underlying dynamics. For example, as the applied current is changed in Plant's model, the ISIH structure can change drastically. This is not the case for the FHN model near a Hopf bifurcation.

Our study of skipping was not intended to be comprehensive. It is, first of all, limited to situations where the noise and deterministic oscillation bring the soma voltage closer to the spiking threshold. Spikes can also arise out of postinhibitory rebound, and skipping may occur when rebound events are deleted from a periodic pattern of such events. And pacemaker activity at a noisy inhibitory synapse²⁵ can produce skipping. The insights our study offers into skipping will potentially be useful for the interpretation of this and other physiological data. For example, in the cardiac arrhythmia known as concealed bigeminy,¹² there is a putative 2:1 entrainment between the sinus and ectopic rhythms. Fluctuations in refractory time are thought to cause skipping in the ectopic rhythm. The results of Secs. III–IV indicate that this could also occur if the origin of the 2:1 entrainment were noise induced rather than deterministic. The study of stochastic phase locking has¹¹ and will continue to benefit from the powerful concepts found in the theory of circle maps. Moreover, we suspect there exists a deeper connection between resonances in circle maps and stochastic resonance, as both involve the interaction of specific time scales.

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