Chaos in Neurobiology

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Abstract—**Deterministic mathematical models of neural systems can give rise to complex aperiodic ("chaotic") dynamics in the absence of stochastic fluctuations ("noise") in the variables or parameters of the model or in the inputs to the system. We show that chaotic dynamics are expected in nonlinear feedback systems possessing time delays such as are found in recurrent inhibition and from the periodic forcing of neural oscillators. The implications of the possible occurrence of chaotic dynamics for experimental work and mathematical modeling of normal and abnormal function in neurophysiology are mentioned.**

I. Introduction

RECENTLY, a flurry of interest has arisen in period-doubling bifurcations (in which the period of an oscillation doubles as a parameter is changed) and complex aperiodic ("chaotic") dynamics in simple deterministic mathematical models (for a general introduction see [1], [2]). Several reasons can be found for this interest. 1) To many, it is counterintuitive that complex dynamics can arise in simple mathematical models. 2) Many of the features of transitions from regular to chaotic dynamics have been shown to be independent of the details of the mathematical model, provided certain topological conditions are obeyed [3], [4]. 3) Experimental studies of chemical oscillators [5], [6], hydrodynamic systems [7], [8], periodically forced electronic systems [9], and periodically forced biological oscillators [10], [11] have demonstrated transitions from regular to irregular dynamics displaying these theoretically predicted features.

Although current interest in these problems was stimulated by the review by May [1], which discussed the possible existence of chaotic dynamics in ecological systems, the impact on biological research has been limited. On the other hand, in the past few years, several hundred articles dealing with the mathematics of chaos and the observation of chaos in physical systems have appeared (for reviews, see [3], [12], [13]).

This paper presents results on chaotic dynamics of direct relevance to neurobiology. In Section II complicated behavior in neurobiological models with feedback and time delays is discussed. In Section III, we show that periodic forcing of models of neural oscillators can lead to chaos. In Section IV we discuss the relevance of this work for neurobiology, with special reference to experimental studies, pathophysiology, and normal function. For recent reviews on related physiological topics see [14]–[16].

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II. Time Delays and Chaotic Behavior

A. Background

Many neurobiological processes have been modeled by systems of ordinary differential equations

$$\frac{dx}{dt} = F(x(t)), \qquad t > t_0 \tag{1}$$

with initial condition $x(t_0) = x_0$. Here x is a vector giving the state variables (e.g., neural firing frequency, concentration of transmitter, membrane voltage, membrane conductance), and F represents the interactions among the state variables. Often, F depends not only on the value of x at the present time but also on the past history of the system (e.g., due to finite conduction time along neural pathways). This may be formally represented by

$$\frac{dx}{dt} = F\big(x(t), x_{\{t'\}}(t)\big), \qquad t > t_0, \tag{2}$$

where $x_{\{t'\}}$ denotes the variable $x(t)$ at all t', $-\infty < t' < t$. In this case initial conditions must be specified in the form of a function $u(t')$ for $-\infty < t' \leqslant t_0$.

For some one-dimensional systems given by (2), the dependence on past history may be made explicit by writing

$$\frac{dx}{dt} = F(x(t), y(t)), \tag{3a}$$

where the function

$$y(t) = \int_{-\infty}^{t} g(t - t')x(t')\,dt' \tag{3b}$$

gives the prescription for calculating the total influence of the past history of the state variable x on the present dynamics. The function g (the kernel) specifies the weight to be attached to $x(t')$ at each point of time in the past. In the special case where the kernel has the form

$$g(\xi) = \frac{a^n \xi^{n-1} e^{-a\xi}}{(n-1)!}, \qquad a \geqslant 0, \quad n = 1, 2, \cdots,$$

then (3a), (3b) are equivalent to

$$\frac{dx_1}{dt} = F(x_1, x_{n+1})$$

$$\frac{dx_i}{dt} = a(x_{i-1} - x_i), \qquad i = 2, \cdots, n+1. \tag{4}$$

Equation (4) constitutes a set of $(n + 1)$ ordinary differen-

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tial equations, n of which are linear and one of which may be nonlinear [17]. Thus, in this special case, general consideration of a system with dynamics dependent on its prior history is closely related to the behavior of a multidimensional system with no explicit prior history dependence.

In situations where the effects of prior history are confined to a short interval of time, the kernel g is sharply peaked about some previous time, say $t - \tau$. In the limiting case where $g(t - t')$ can be approximated by a delta function $g(t - t') = \delta(t - t' - \tau)$, then (3) reduces to a time delay differential equation

$$\frac{dx}{dt} = F(x(t), x_\tau(t)), \tag{5}$$

where $x_\tau(t) \equiv x(t - \tau)$. Many applied problems [14], [15], [17]–[21] have been modeled by a single state variable $x(t)$, where the rate of change of x at a time t is equal to the balance between the loss $(-\alpha x(t))$ of x at a rate α and the production $(f(x_\tau(t))$ of x at a rate dependent on the value of x some time in the past $(x_\tau(t))$, so that

$$\frac{dx}{dt} = -\alpha x(t) + f(x_\tau(t)). \tag{6}$$

If $f(x_\tau)$ is a monotone decreasing function of x_τ, then (6) describes a system with pure negative feedback; while if $f(x_\tau)$ is monotone increasing the system is a positive feedback system. Often, however, $f(x_\tau)$ may be a nonmonotonic function of x_τ, and thus the system may display mixed positive and negative feedback characteristics. From numerical and analytic studies [14], [15], [18]–[24] it is known that when $f(x_\tau)$ is not monotonic, the solutions of (6) may have an extremely complicated evolution in time.

An early application of (4) was a model for schizophrenia with piecewise linear negative feedback [25], [26]. The possibility of periodic or aperiodic dynamics was raised, although no simulations of the system were presented. A recent paper suggests that schizophrenia may be associated with periodic and aperiodic dynamics in (4) and (6) [20]. The control functions, which are related to the control of dopamine synthesis, are not monotonic. Sparrow has examined nonmonotonic feedback in a system similar to that described by (4) and described both periodic and aperiodic dynamics [27]. Rapp has suggested that such feedback may operate on the level of a single nerve cell and give rise to chaotic dynamics [16], [28].

B. Model for Recurrent Inhibition [15], [21].

As a further example of the application of time delays to neurobiology we consider a model for recurrent inhibition developed by Mackey and an der Heiden [15], [21]. If a postsynaptic cell receives an excitatory input from a presynaptic cell and a recurrent inhibitory input from an inhibitory interneuron, resulting in excitatory postsynaptic potentials (EPSP's) and inhibitory postsynaptic potentials (IPSP's) $E(t)$ and $I(t)$, respectively, then it may be shown that the dynamics are approximated by

$$\frac{dI}{dt} = -\alpha I(t) + \beta F_\tau \frac{K}{K + F_\tau^n}, \tag{7}$$

where $F_\tau \equiv F(t - \tau)$, τ is the time required to transmit information around the recurrent inhibitory pathway, and

$$F(t) = \begin{cases} 0, & E - I \leqslant \theta \\ F_0[E(t) - I(t) - \theta], & E - I < \theta \end{cases} \tag{8}$$

is the postsynaptic cell instantaneous firing rate. In (7) the second nonlinear term gives the rate of change of $I(t)$ due to the recurrent inhibitory feedback. The amount of inhibitory transmitter released at the interneuron–postsynaptic cell synapse at time t is proportional to F_τ, and $[K/(K + F_\tau^n)]$ is the fraction of receptor sites available to be activated by that transmitter. In (7), α is the reciprocal of the postsynaptic cell membrane time constant, K is a constant related to the equilibrium constant of the inhibitory transmitter-receptor complex, n is the number of inhibitory transmitter molecules required to activate one receptor, and β is a constant proportional to the number of inhibitory receptors per cell. In (8), θ is the membrane threshold for the generation of action potentials, and F_0 is a constant.

An analysis of (7) and (8) shows that for constant presynaptic activity levels (E = constant), depending on parameter values, one, two, or three steady-state firing levels may exist in the postsynaptic cell [21]. These steady states may be stable or unstable, depending on parameter values, and extensive numerical studies of (7) and (8) indicate that a wide range of behavior may arise as even a single parameter is varied.

To illustrate, consider the hippocampal recurrent inhibitory circuit consisting of the mossy fiber, CA3 pyramidal cell, basket cell complex. Here the CA3 pyramidal cells (the postsynaptic cell) receive excitatory presynaptic input from the mossy fibers and recurrent inhibitory input from the basket cells via what is generally considered to be a monosynaptic pathway. The inhibitory transmitter is γ-aminobutyric acid (GABA) [29]. Many of the parameters in (7) and (8) can be estimated from existing data, and as discussed by Mackey and an der Heiden [21], we have $\tau = 100$ ms, $\alpha^{-1} = 10$ ms, $K = 1$ Hz^3, $\theta = 4$ mV, $F_0 = 2.25$ Hz/mV, $n = 3$, and $\beta = 2.4T$ mV, where T is the average number of GABA receptors per CA3 pyramidal cell.

Though the number of GABA receptors per cell is not known, Mackey and an der Heiden [21] conducted a numerical investigation of the effect of decreasing T starting from a value of $T = 1900$ and assuming that a constant level of presynaptic activity existed that gave $E = 1.6\theta = 8.4$ mV. This is analogous to the experimental situation where the number of functional GABA receptors is titrated by the application of penicillin [21]. The results are shown in Fig. 1.

Initially, with 1900 receptors per cell, the CA3 firing shows bursting behavior typical of these cells. The bursting in the model is due to the delays in the recurrent inhibitory network rather than intrinsic membrance properties of the cell. As the receptor density is decreased, the initially periodic firing pattern of the CA3 cells gives way to progressively more complicated firing patterns. At very low ($T = 1100$) receptor densities, the model predicts that the CA3 cells will fire in a sustained but erratic fashion. This

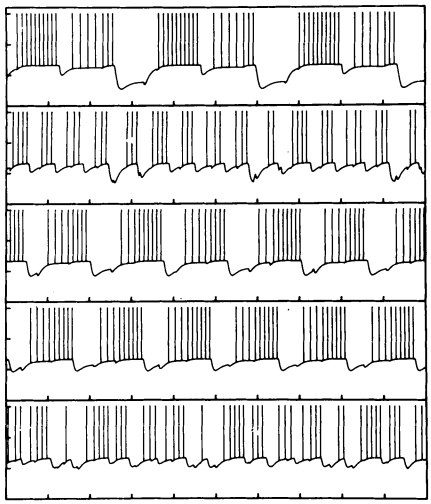

Fig. 1. Simulated effect of decreasing number (T) of CA3 GABA receptors in mossy fiber, CA3 pyramidal cell, basket cell complex. Each panel shows 1 s of simulated membrane potential [$E - I(t)$] of CA3 pyramidal cell, obtained by solving (7) and (8), with superimposed vertical lines where action potentials occur. From top to bottom, receptor density falls from $T = 1900$ to $T = 1100$ in steps of 200. In each panel ordinate (membrane potential) ranges from -5 to $+10$ mV relative to resting potential.

sequence of events is qualitatively very similar to the behavior found following the application of penicillin [30], and the model thus may offer some insight into the penicillin model for epilepsy. The examination of the effects of direct electrical synaptic connections in this specific case, as recently demonstrated by Taylor and Dudek [31], has not been carried out. Other theoretical models for epilepsy in which recurrent inhibition plays an important role have appeared [32].

Presently, the various models for chaos in neurobiology based on (4) and (6) must be viewed with caution. Systematic manipulations of experimental systems described by (4) or (6) have not yet been undertaken. Experimental results are needed to guide further modeling efforts.

III. Periodic Forcing of Neural Oscillators

A. Background

Oscillations in individual neurons, neural networks, and muscle cells underlie many of the main physiological functions (e.g., heartbeat, respiration, digestion, reproduction, mastication, locomotion). Since mathematicians have long known that the periodic forcing of nonlinear oscillators can give rise to complex phase-locking patterns, bifurcations, and aperiodic dynamics [33], [34], one anticipates that such behavior might be observable in forced physiological and neural oscillators. Consider the following examples. 1) Many experiments have been done on the entrainment of pacemaker and network neural oscillators to a periodic input. In these experiments, both phase-locked dynamics and irregular dynamics are often observed (see [10], [11], [35]–[43] for representative papers and references). 2) Physiological rhythms interact with one another and with external inputs, e.g., the heartbeat speeds up during inspiration (respiratory sinus arrhythmia [44]), and circadian rhythms in man are normally entrained to the light–dark cycle [45], [46]. 3) Periodic driving of the heart by an artificial pacemaker or of the respiratory rhythm by a mechanical ventilator are often required in clinical situations. Lack of entrainment between the forcing and the autonomous rhythms can have serious consequences.

Recent studies on the periodic forcing of biological oscillators have been interpreted in the context of current work on chaotic dynamics. Periodic electrical sinusoidal stimulation of an internodal cell from *Nitella* leads to phase locking, subharmonic, quasi-periodic, and aperiodic dynamics [11]. As a second example, consider the effects of stimulation of spontaneously beating cardiac cells with brief duration current pulses [10]. Injection of a single pulse of current resets the rhythm of the oscillation to a degree that depends on the phase of the cycle at which the stimulus is delivered. If ϕ is the phase of the oscillator immediately before the perturbation ($0 \leqslant \phi < 1$), and ϕ' the phase immediately after the perturbation, then the phase transition curve (PTC)

$$\phi' = h(\phi) \tag{9}$$

can be experimentally determined by systematically injecting isolated current pulses at different points in the cycle [10]. In response to a train of stimuli, and assuming that rapid relaxation back to the limit cycle oscillation occurs after a perturbation, we have

$$\phi_{i+1} = h(\phi_i) + \tau, \tag{10}$$

where ϕ_i is the phase of the oscillation immediately before the ith stimulus, τ is the time interval between successive stimuli (taking the intrinsic period of the oscillation = 1), and h is the PTC of (9) [10], [35], [47], [48]. Equation (10) is often called the Poincaré map. Iteration of (10) can be used to predict the effects of periodic stimulation at any given frequency. In particular, iteration of the Poincaré map for periodically stimulated aggregates of cardiac cells demonstrated the presence of period-doubling bifurcations and chaos at certain stimulation frequencies [10]. The fact that these dynamics were seen experimentally and that there was close agreement between theory and experiment gives *a posteriori* justification for the assumptions used in deriving (10) [47]. Period-doubling bifurcations, bistability, and chaotic dynamics are also observed if other simple functional forms for $h(\phi)$ are assumed in (10) [47]–[49].

B. Periodic Forcing of Neural Models

To illustrate the effects of periodic stimulation on neural oscillators, we have considered the effects of periodic stimulation of the Hodgkin–Huxley (HH) equations developed to model electrical activity of the squid axon membrane [50], and of the Bonhoeffer–van der Pol (BVP) equations, a reduced analog of models of excitable membranes [51].

The squid giant axon can generate a periodic train of action potentials if placed in a low-calcium solution or

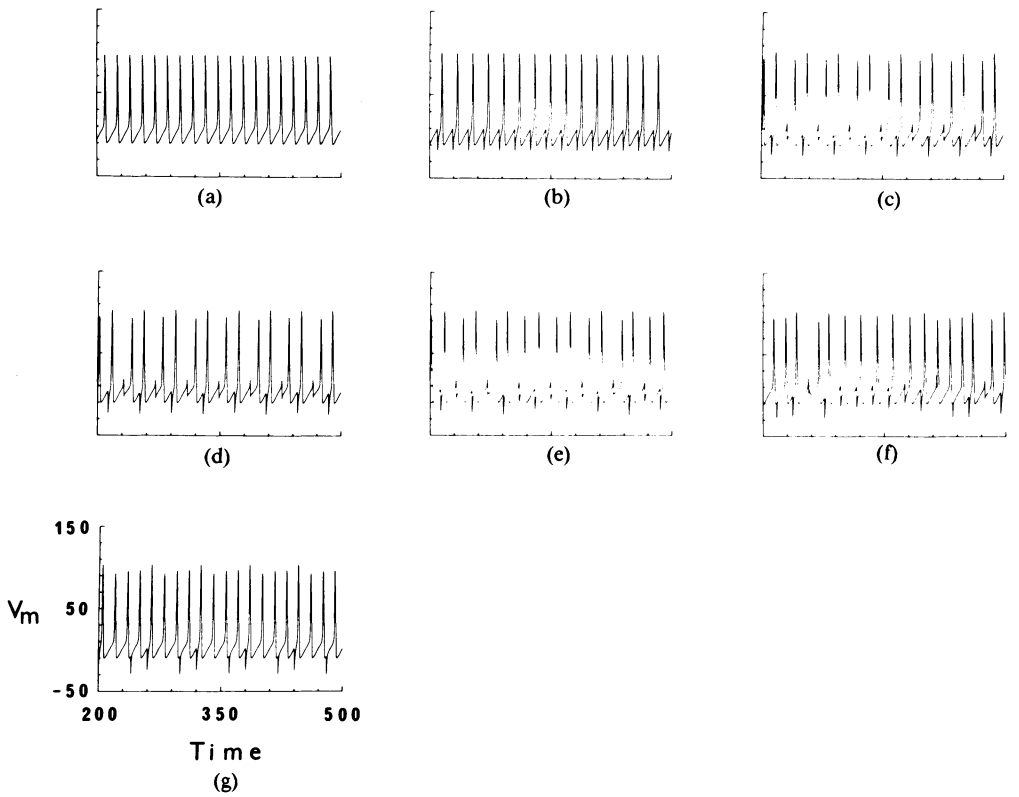

Fig. 2. Periodic stimulation of spontaneous oscillations in HH equations with train of hyperpolarizing current pulses. Spontaneous activity is elicited using constant bias current of 8.75 $\mu A/cm^2$. Pulse repetition rate is $1/\tau$. Pulse amplitude is 150 $\mu A/cm^2$, and pulse duration 0.2 ms. First pulse is injected at $t = 0$ ms, with $V_m(t = 0) = 5.0047$ mV, $m(t = 0) = 0.0277$, $h(t = 0) = 0.3813$, $n(t = 0) = 0.4637$. All of panels show $-V_m$ (in mV) plotted as function of time (in ms). Activity is only shown from $t = 200$ ms, to allow some time for transients to decay. Sharp downward deflections are synchronous with pulse train. (a) Spontaneous activity with period of oscillation equal to 15.39 ms. (b) 1 : 1 phase-locking ($\tau = 19.10$ ms). Fixed latency exists from each stimulus to following action potential. (c) 2 : 2 phase-locking ($\tau = 19.35$ ms). Latency alternates between two fixed values. (d) 4 : 4 phase-locking ($\tau = 19.37$ ms). (e) 8 : 8 phase-locking ($\tau = 19.40$ ms). (f) irregular patterns in which more action potentials exist than stimuli ($\tau = 19.75$ ms). (g) 3 : 4 phase-locking ($\tau = 20.00$ ms). Sharp downward deflection of every third stimulus is obscured by upstroke.

subjected to a constant depolarizing current [52], [53]. This spontaneous activity is reproduced by appropriate modifications in the HH equations [52], [53]. Fig. 2(a) shows a train of action potentials with period 15.39 ms generated in response to a constant depolarizing current of 8.75 $\mu A/cm^2$ in the HH equations. (The HH equations are as in Best [54] and were integrated using a first-order Euler method employing the Rush–Larsen algorithm with a time increment of 0.001 ms [55].)

Now consider the effect of periodic stimulation at frequencies lower than the frequency of spontaneous activity. The stimulus is a brief hyperpolarizing current pulse of amplitude 150 $\mu A/cm^2$ and duration 0.2 ms. For a period of stimulation (τ) sufficiently close to the spontaneous period, 1 : 1 phase locking results (Fig. 2(b), $\tau = 19.10$ ms). In N : M phase locking, M action potentials exist for each N stimuli, and the pattern is periodic in time with period $N\tau$. For τ slightly greater than the largest value of τ at which 1 : 1 locking can be maintained, 2 : 2 phase locking occurs, with the latency (the time from the beginning of a stimulus to the upstroke of the subsequent action potential) now strictly alternating between two values (Fig. 2(c), $\tau = 19.35$ ms). Locking is also observed in 4 : 4 (Fig. 2(d), $\tau = 19.37$ ms) and 8 : 8 (Fig. 2(e), $\tau = 19.40$ ms) ratios. As τ is increased, patterns are observed in which one action potential still exists for each stimulus but no obvious periodicity of low order. With further increases in τ, a region is encountered in which an occasional extra or "escape" action potential exists not immediately preceded by a stimulus (Fig. 2(f), $\tau = 19.75$ ms). This escape can be periodic, as in 3 : 4 phase locking (Fig. 2(g), $\tau = 20.0$ ms). The above catalog of the dynamics as the period of the stimulation is increased is not exhaustive, as other behaviors can be seen.

To analyze the dynamics, we consider the Poincaré map, which can be directly computed from the system equations as follows. The point $x = (V_m, m, n, h) = (5.0047$ mV, 0.02770, 0.3813, 0.4637) is on the limit cycle and is arbi-

trarily assigned a phase of zero. The HH equations are then integrated from this initial condition at $t = 0$ until $t = 15.40$ ms using a time increment of 0.01 ms.

The phase of each point $x(t)$ is defined to be t/T_0, where $T = 15.39$ ms is the period of the spontaneous oscillation. Thus a phase is assigned to each of 1540 points on the limit cycle. A second numerical integration is then carried out, with a single stimulus being applied at $t = 0$ and initial conditions on the limit cycle. The equations are then integrated forward in time using a time increment of 0.01 ms for a time τ. The point $\hat{x}$ is selected from the 1540 points initially determined, so that its distance from $x(t = \tau)$ as given by

$$\rho(\hat{x}, x) = \left[0.01(\hat{V}_m - V_m)^2 + (\hat{m} - m)^2 + (\hat{h} - h)^2 + (\hat{n} - n)^2\right]^{1/2}$$

is a minimum. We then approximate the phase of $x(t - \tau)$ to be the phase of $\hat{x}$. Repeating this second integration in turn with each of the 1540 points to which a phase was initially assigned as starting point $x(t = 0)$ leads to the Poincaré maps of Fig. 3. The details of the map in the region $0.562 < \phi < 0.564$ have not been resolved in this computation and can be rather complex (see [54] for further details).

Determination of the Poincaré map in this manner for $\tau > 19$ ms yields maps which are very close to being simple vertical translations of each other by an amount $\Delta\tau/T_0$, where $\Delta\tau$ is the difference in τ for two such maps and T_0 is the period of the spontaneous oscillation. This is a consequence of the fact that the relaxation back to the limit cycle is rapid, relative to the period of the oscillation [48]. Although it is, in principle, easy to iterate the Poincaré map in order to determine the dynamics resulting from periodic stimulation, even very simple models for phase-locking reveal complex bifurcations as stimulation amplitude and frequency are changed [47]–[49]. Consequently, we do not discuss in detail the bifurcations of the Poincaré map at the one level of stimulus amplitude and duration used but instead show how the map accounts for the features of the dynamics presented in Fig. 2.

If a point exists on the Poincaré map where $\phi_{i+1} = \phi_i = \phi^*$, then ϕ^* is said to be a steady state or a period 1 orbit. If $\left|(\partial\phi_{i+1}/\partial\phi_i)|_{\phi^*}\right| < 1$, the steady state is stable (Fig. 3(a)), as in stable 1 : 1 phase locking (Fig. 2(b)). For $\tau = 19.35$ ms, the steady state becomes unstable, since $(\partial\phi_{i+1}/\partial\phi_i)|_{\phi^*} < -1$, leading to a period doubling or "flip" bifurcation [1] and 2 : 2 phase locking (Fig. 2(c)). The period-doubling bifurcation produces a stable period 2 orbit on the Poincaré map, with two stable period 2 points ϕ_1 and ϕ_2 such that if $\phi_i = \phi_1$, then $\phi_{i+1} = \phi_2$, $\phi_{i+2} = \phi_1, \cdots$. As τ is increased beyond $\tau \approx 19.35$ ms, a sequence of period-doubling bifurcations to orbits of periods $4, 8, \cdots$ results. These bifurcations produce the 4 : 4 and 8 : 8 phase-locking patterns of Fig. 2(d) and Fig. 2(e), respectively. Though we have not examined the possibility, further increase of τ will presumably result in the appearance

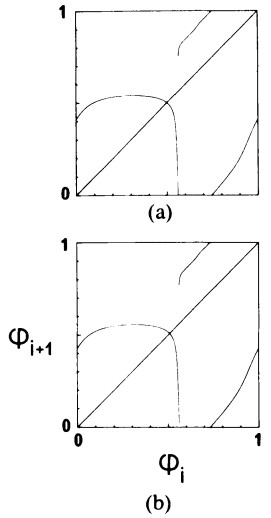

Fig. 3. Poincaré map for HH oscillator for pulse amplitude of 150 μA/cm^2 and pulse duration of 0.2 ms. Details of map in region $0.562 < \phi_i < 0.564$, have not been resolved in this computation. $\phi_i = 0$ is point $V_m = 5.0047$ mV, $m = 0.0277$, $h = 0.3813$, and $n = 0.4637$. (a) $\tau = 19.10$ ms: intersection of map with diagonal line ($\phi_{i+1} = \phi_i$) gives steady-state $\phi^* \approx 0.5$, which is stable, since $-1 < (\partial\phi_{i+1}/\partial\phi_i)|_{\phi^*} < +1$. This stable period 1 orbit corresponds to 1 : 1 locking shown in Fig. 2(b). (b) $\tau = 20.00$ ms, with stable period 3 orbit corresponding to 3 : 4 locking pattern of Fig. 2(g).

of orbits with higher order even ($\neq 2^n$) and odd periodicities [1]. For τ greater than approximately 19.55, period N orbits corresponding to $N : M$ phase-locking patterns with $N/M \neq 1$ can be seen (Fig. 3(b) corresponding to Fig. 2(g)), as well as more complex behavior corresponding to Fig. 2(f).

Next we consider the effects of periodic input to the BVP equations

$$\dot{x} = c\left(x - \frac{x^3}{3} + y + z\right)$$
$$\dot{y} = \frac{1}{c}(-x - by + a). \tag{11}$$

In these equations "x shares the properties of both membrane potential and excitability, while y is responsible for accommodation and refractoriness" [51]. The parameter z is the stimulus current while a, b, and c are constants. This model displays phenomena characteristic of electrically excitable cells such as regenerative excitability, refractoriness, quasi-threshold behavior, and anodal break excitation [51].

To investigate the response of the BVP equations to a periodic input, a predictor–corrector Euler integration scheme with a time increment of 0.001 was used [56]. For $a = -0.5$, $b = -0.8$, $c = 3$, and $z = 0$ the BVP equations possess a limit cycle, the period of which is 11.83 (Fig. 4(a)). The periodic input is a pulse train in z with amplitude 5.0, duration 0.2, and repetition frequency $1/\tau$. There are 1 : 1 (Fig. 4(b), $\tau = 12.0$), 2 : 2 (Fig. 4(c), $\tau = 12.4$), and 4 : 4 (Fig. 4(d), $\tau = 12.6$) phase-locked patterns, as well as complex behavior in which one event exists for each stimulus (Fig. 4(e), $\tau = 12.9$). As τ is increased further, a 1 : 1 pattern is again encountered (Fig. 4(f), $\tau = 13.0$),

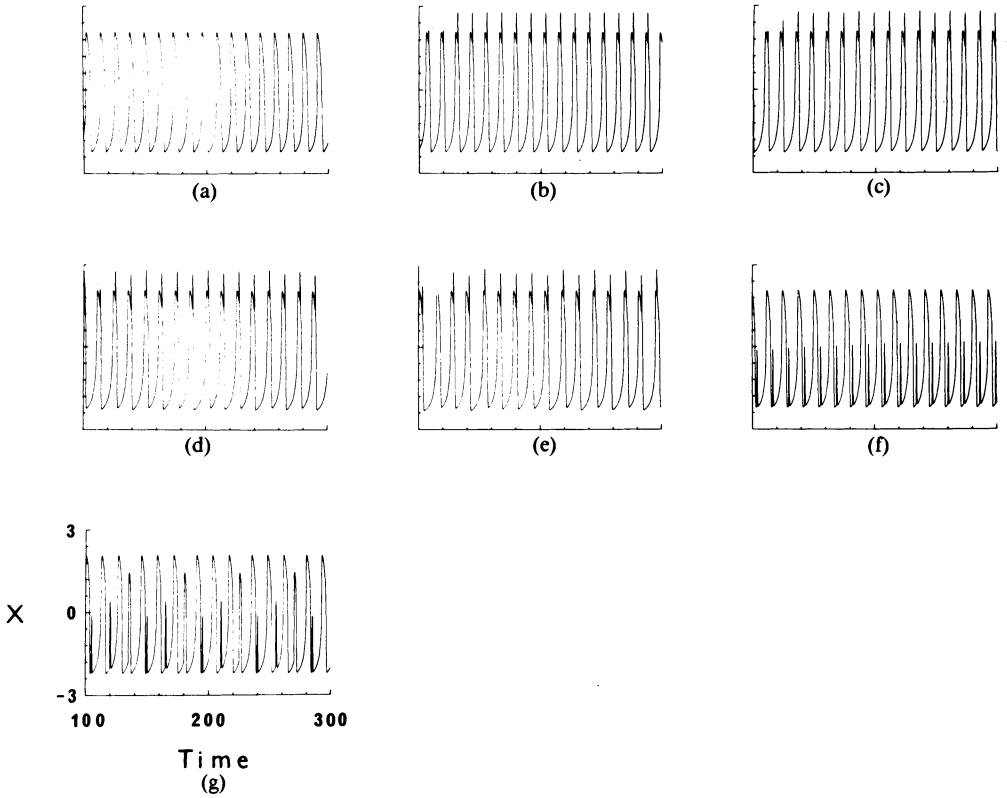

Fig. 4. Effect of periodic perturbation of BVP equations, with pulse of amplitude 5.0, duration 0.2, and repetition rate $1/\tau$. First pulse is injected at $t = 0$, with $x(t = 0) = -2.2127$, $y(t = 0) = -1.4652$. All panels of this figure show x as function of time, starting at $t = 100$ to allow some time for decay of transients. (a) Spontaneous unperturbed activity with period $T_0 = 11.83$. (b) 1 : 1 phase-locking ($\tau = 12.0$). (c) 2 : 2 phase-locking ($\tau = 12.4$). (d) 4 : 4 phase-locking ($\tau = 12.6$). (e) Irregular activity ($\tau = 12.9$). (f) 1 : 1 phase-locking ($\tau = 13.0$). (g) 3 : 3 phase-locking ($\tau = 15.0$).

which undergoes a sequence of period doubling bifurcations as τ is increased. Finally, 3 : 3 phase locking occurs (Fig. 4(g), $\tau = 15.0$).

The Poincaré map was also numerically computed for the BVP equations using the same procedure as described earlier for the HH equations. The point $(x, y) = (-2.2127, -1.4652)$ has phase zero. For $\tau = 12.4$, two stable fixed points of period 2 exist (Fig. 5(a)), corresponding to 2 : 2 phase locking (Fig. 4(c)). As τ increases, further period-doubling bifurcations eventually lead to the complicated dynamics of Fig. 4(e) ($\tau = 12.9$). At still higher values of τ, a stable period 1 orbit exists, corresponding to the 1 : 1 pattern of Fig. 4(f). Finally, at $\tau = 15.0$, the Poincaré map yields an orbit of period 3 (Fig. 5(b)), corresponding to 3 : 3 phase locking (Fig. 4(g)). A phenomenon often seen in the iteration of nonmonotonic maps is that different starting conditions can lead to different asymptotic behaviors [48], [49]. For example, at $\tau = 12.9$, in addition to the complex pattern of Fig. 4(e), 1 : 1 phase locking can also be seen for some other initial conditions. For τ slightly less than about 12.7, intermittent behavior with a long laminar phase can be observed.

We have only shown the Poincaré map for one level of stimulus amplitude and duration. As these two parameters are changed, the topology of the Poincaré map also changes [48]. Thus the sequence of bifurcations that occurs as τ is changed (for a fixed stimulus amplitude and duration) depends on these two stimulus parameters.

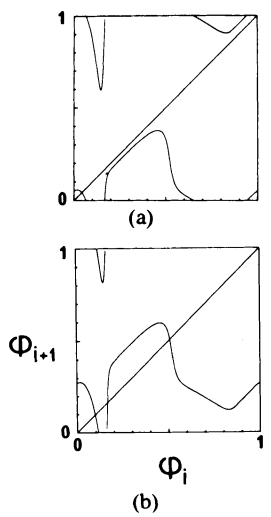

Fig. 5. Poincaré map for BVP oscillator for pulse amplitude of 5.0 and pulse duration of 0.2. (a) $\tau = 12.4$, with period 2 orbit, corresponding to 2 : 2 locking shown in Fig. 4(c). (b) $\tau = 15.0$, with period 3 orbit corresponding to 3 : 3 locking shown in Fig. 4(g).

On the basis of our experiments [10], theoretical work [47]–[49], and the numerical studies described earlier, we predict that period-doubling bifurcations, intermittency [57], bistability [49], and chaotic dynamics arising from the periodic forcing of neural oscillators will be widespread. Since the bifurcations often occur over small ranges in parameter space the phenomena can only be observed if one performs systematic studies on the effects of changing the amplitude, duration, and frequency of periodic pulsatile stimulation. The relevance, if any, of such phenomena to information processing in vivo in neural systems remains to be clarified.

IV. Relevance to Neurophysiology

We have given several examples in which deterministic models give rise to chaotic dynamics (which can even be aperiodic in the absence of any stochastic variation in inputs or control parameters). These observations raise the possibility that some of the observed variability in neural electrical activity may be a reflection of intrinsically chaotic dynamics. Theoretical techniques currently being developed should be capable of distinguishing the relative contributions of intrinsic "chaos" and "noise" (generated externally by the environment or internally by the system itself) to the aperiodic behavior experimentally observed [58]. To date, these techniques have not been applied in concrete situations. Bearing in mind that all irregular neural dynamics which can be observed are *not* necessarily associated with chaos in deterministic systems, we briefly discuss several examples in which chaotic dynamics may play a role.

A. Experimental Work

1) The properties of neurons depend on the chemical environment of the neuron. Consequently, abnormal electrolyte concentrations or the presence of hormonal or pharmacological agents may have strong effects on pacemaker neurons. In a recent study, the effects of 4-aminopyridine (4AP) on an identified molluskan pacemaker neuron were analyzed [59]. Under prolonged exposure to 4AP, an irregular bursting pattern developed. The properties of the pacemaker neuron were well-described by a modified Hodgkin–Huxley equation, and it was conjectured that the irregular dynamics reflected a chaotic trajectory in the deterministic system. The observed fluctuations bear a superficial resemblance to irregular dynamics attributed to chaos in chemical oscillations [5], [6] and to chaotic dynamics in simple chemical kinetic schemes [60]. However, a detailed experimental study of the transitions in dynamic behavior, in response to 4AP, and an interpretation in terms of bifurcations in the underlying equations was not made. The generation and transmission of periodic and chaotic firing activity in modified HH equations has been described by Carpenter [61]. Furthermore, period-doubling bifurcations of unstable limit cycles in the HH equations have been demonstrated [62]. These examples suggest that spontaneously chaotic dynamics may be observable in neural systems.

2) A second class of examples in which chaos may be important is in the periodic forcing of neural oscillators, as discussed above. The irregular dynamics which have been observed in these experiments are generally attributed to stochastic fluctuations of input or system parameters rather than to the presence of intrinsic chaos [37], [42], [43]. Since periodically forced nonlinear oscillators show period-doubling bifurcations and chaos, experimental studies of periodically forced neural oscillators bear reexamination in this light.

B. Dynamical Disease

A dynamical disease is defined as a disease that occurs in an intact physiological control system operating in a range of control parameters that leads to abnormal dynamics [14], [15], [18]. The signature of a dynamical disease is a change in the qualitative dynamics of some observable as one or more parameters are changed. These changes would correspond mathematically to bifurcations in nonlinear equations describing the physiological system. Theoretical analyses of Cheyne–Stokes respiration [14], [15], [18], schizophrenia [20], [25], [26], insomnia [45], [46], epilepsy [15], [21], [32], dyskinesia [16], AV heart block [47], [63], and some hematological disorders [14], [15], [18], [19], [64]–[66] suggest that these diseases may be classified as dynamical diseases. Since many neural disorders are characterized by changes in the normal patterns of behavior, it is tempting to propose that such diseases arise from bifurcations that may eventually result in "chaotic" dynamics. However, before such associations can be justified, it will be necessary to clinically observe changes in the qualitative dynamics and identify these changes with corresponding changes in the qualitative dynamics of mathematical models. Analysis of qualitative dynamics as a function of control parameters may lead to new therapies directed towards restoring normal dynamics. Thus the theoretical analysis is of potentially powerful diagnostic and therapeutic value. It will not be easy to convince a clinician to try a novel therapy suggested by a theoretician, and collaboration between mathematicians, clinicians, and basic scientists will be needed.

C. Normal Function

Neurophysiological systems are characterized by nonlinear feedback, oscillation, and coupling of oscillators. Why are the phenomena of chaotic dynamics so rarely observed in normal physiology? Two possible reasons, which are not mutually exclusive, bear consideration.

1) *The construction of normal physiological control systems has a large range of control parameters which give rise to stable dynamics (either steady-state equilibria or stable oscillations).* The coupling between oscillations is normally sufficiently weak (respiratory sinus arrhythmia [44]) so that perturbation of one rhythm by the other does not lead to

pathology, or sufficiently strong (in locomotion [40]) that 1 : 1 entrainment is found.

2) *Chaotic behavior normally occurs, but this is not now recognized.* Even cursory examination of data from many neural systems shows that variations in dynamics, from regular (periodic) to irregular (aperiodic) are possible and represent "normal" behavior. For example, spontaneous changes occur in the respiratory rhythm from very regular to irregular during different states of sleep and wakefulness. The mechanisms underlying these transitions are not well understood. The coding of sensory input gives a second example of the possible importance of chaotic dynamics in normal function. It is believed that the coding of the intensity of periodic sensory input may be accomplished by variable degrees of entrainment between the sensory input and the firing of the receptor [37], [38], [67]. If a given receptor is not in 1 : 1 synchronization with the input, it may have an extremely irregular firing pattern (for example, see [38, fig. 5]). Although it has been proposed that such irregular patterns are due to "noise" in the system [37], [42], the possibility of deterministic chaos should not be ignored. It has been proposed that complex EEG patterns which occur normally arise from interactions between a large number of neural relaxation oscillators [68]. As well, chaotic dynamics may occur in neuroendocrine systems with nonlinear feedback [69], [70]. Finally, since neurophysiological control systems are nonlinear systems with time delays due to sensory input, neural information processing and motor output, and since hormonal systems also possess inherent time delays, chaotic behavior is expected to occur in both neural and neurohumoral control systems.

The concept of chaos introduces a new perspective for the analysis of neural dynamics. We have discussed the implications of chaos for neural systems amenable to experimental electrophysiological study and theoretical modeling. We leave to others to analyze the relevance of chaos to higher cognitive function, originality, and free will.

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