J. theor. Biol. (1989) **138**, 129–147

MINI REVIEW

Complex Dynamics and Bifurcations in Neurology

JOHN G. MILTON§‖¶, ANDRÉ LONGTIN†‖, ANNE BEUTER‡‖,
MICHAEL C. MACKEY§†‖ AND LEON GLASS§‖

§ *Department of Physiology, McGill University, Montreal, Quebec, Canada H3G 1Y6,*
† *Department of Physics, McGill University, Montreal, Quebec, Canada H3A 2T8,*
‡ *Département de Kinanthropologie, Université du Québec à Montréal, Montréal, Québec, Canada H3C 3P8, and*
‖ *Center for Nonlinear Dynamics in Physiology and Medicine, McGill University, Montreal, Quebec, Canada H3G 1Y6*

(*Received and accepted* 26 *January* 1988)

1. Introduction

The neurologist is often faced with patients who exhibit a bewildering array of abnormal oscillations and complex rhythms that pose therapeutic problems. These problems take many forms (Mackey & Milton, 1987; Glass & Mackey, 1988). Most commonly there is an appearance of an oscillation in a neurological control system not normally characterized by a rhythmic process. Examples include ankle clonus in patients with corticospinal tract disease (Dimitrijevic *et al.*, 1978), various movement disorders (e.g. essential and Parkinson's tremors, Marsden, 1984*a*,*b*), and the abnormal paroxysmal oscillations in the discharges of neurons which are associated with seizures (Ayala *et al.*, 1973). There can be a qualitative change in the oscillations produced by an already rhythmic process, for example, gait abnormalities (Beuter & Garfinkel, 1985), Cheyne-Stokes respiration (Cherniack & Longobardo, 1973), altered sleep-wake cycles (Wehr *et al.*, 1982) and rapid cycling manic-depressive illness (Wehr & Goodwin, 1983). In addition, there can be the disappearance of a rhythmic process as occurs in patients with depression in whom there is the disappearance of the diurnal rhythm in cortisol secretion (Hollister *et al.*, 1980). Finally, some clinical events recur in a seemingly random fashion, for example, seizures in adult epileptics (Milton *et al.*, 1987).

The traditional explanation given by the neurologist is to relate the appearance of abnormal dynamical behaviors to pathological processes which destroy or modify neural control mechanisms. The abnormal breathing patterns (Plum & Posner, 1980) and rhythmic movements of the palate (Lapresle & Hamida, 1970) which can occur

¶ To whom all correspondence should be addressed at Department of Physiology, McGill University, 3655 Drummond Street, Montreal, P.Q., Canada H3G 1Y6.

0022-5193/89/10012^{0}+19 $03.00/0

following certain brainstem strokes are examples of oscillations that arise because neural control mechanisms which normally suppress their appearance have been destroyed. On the other hand, the appearance of nystagmus and clonus in patients with multiple sclerosis are likely related to modifications in intact control mechanisms related to axonal demyelination (Rasminsky, 1984). However, in the majority of neural diseases there is both a destruction of neural pathways and modifications in those that remain. For example in Parkinson's disease there is both a loss of dopaminergic neurons in the basal ganglia and a depletion of dopamine in the remaining neurons (Alvord, 1968). Three approaches have been used to treat abnormal dynamical behaviors: (i) replacement of the deficient neurotransmitter (as in L-DOPA treatment in Parkinson's disease, Barbeau, 1969); (ii) modification of the balance between the remaining excitatory and inhibitory control mechanisms (as in pharmacological treatment of epilepsy, Woodbury *et al.*, 1982); and (iii) destruction of one or more of the remaining control loops (as in surgical treatment of various movement disorders, Molina-Negro, 1979).

In recent years a reinterpretation of the origin of the abnormal dynamical behaviors in neurological patients has been suggested (Mackey & Glass, 1977; Kaczmarek & Babloyantz, 1977; Glass & Mackey, 1979; an der Heiden *et al.*, 1981; Guevara, *et al.*, 1983; Chay, 1984; King *et al.*, 1984; Mackey & an der Heiden, 1984; Chay & Rinzel, 1985; Aihara & Matsumoto, 1986; Ermentrout, 1986; Mackey & Milton, 1987). These proposals have been based on studies of mathematical models of physiological systems in which qualitative changes in dynamics ("bifurcations") occur as certain parameters are varied. These behaviors range from stable equilibria to simple and complex periodic oscillations to aperiodic fluctuations ("chaotic" in the current vernacular). In this context, the abnormal oscillations in neurological patients arise because of either alterations in certain control parameters (such as neural conduction time, the number of membrane receptors and their affinities) and/or in the structure of the system.

In clinical situations, it is frequently difficult to identify the mechanism(s) leading to the observed dynamical abnormality and the abnormalities themselves are often difficult to characterize. For example, in epilepsy alterations in neural feedback are believed to be important in the genesis of seizure activity (Ayala *et al.*, 1973; Gloor, 1979). The fact that seizures can be triggered by fever, hyperventilation, photic stimulation and sleep deprivation (Aicardi, 1986; Niedermeyer & Lopes de Silva, 1987) shows that paroxysmal changes in neural dynamics can be brought about by transient alterations in physiological parameters. Anticonvulsant therapies attempt to prevent or abort seizure activity by modifying neural inhibitory and excitatory mechanisms either by the use of medications (Woodbury *et al.*, 1982) or biofeedback (Sterman & Friar, 1972; Forster, 1975) techniques. However, neither the identity of the control mechanism nor the altered physiological parameter are known. Characterization of an epileptic abnormality is based on clinical history and measurement of the electro-encephalogram (EEG) (Browne & Feldman, 1983; Aicardi, 1986). Although typically the recognition of a seizure either clinically or with the EEG poses little problem, even to an untrained person (Fig. 1), interpretation of the EEG changes in neuro-physiological terms is difficult since each EEG electrode simul-

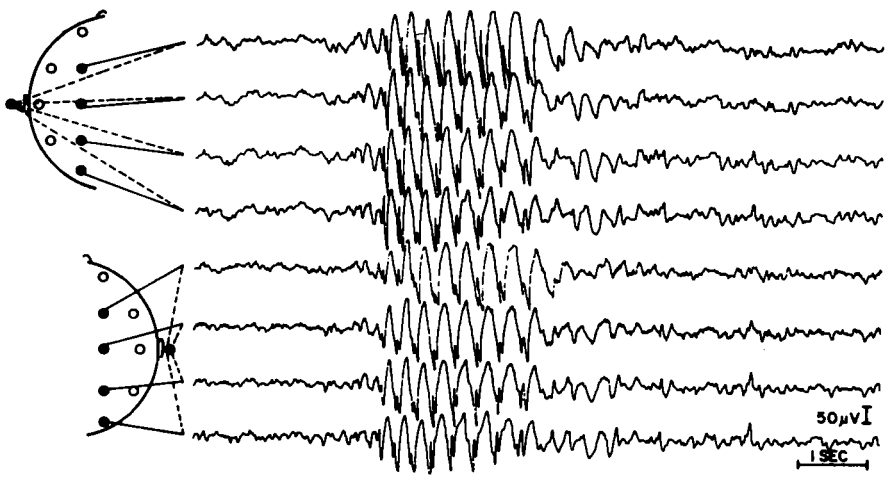

FIG. 1. Electroencephalographic recording (EEG) of a train of generalized 3 Hz spike and wave discharges in patient with a history of absence attacks and generalized tonic-clonic seizures. Note the abrupt change in the frequency and morphology of the EEG that is associated with the onset and offset of this train. (From Spehlmann, 1985, with permission from the publisher.)

taneously records from $\sim 6\,\mathrm{cm}^2$ of brain surface and hence millions of neurons (Cooper *et al.*, 1965).

In section 2 we describe quantitative measures used to characterize complex neural dynamics in neural systems. Using these measures it is difficult to determine underlying mechanisms. In section 3 we describe experimental models that have been used to induce bifurcations in neural control systems by changing control functions. In some situations, the observed dynamics are quite complex but an underlying theory can be developed. The relevance of these observations for future work is discussed in section 4.

2. Characterization of Neural Time Series

Traditional approaches to the quantitative analysis of neural time series are based on Fourier methods in which the time series is decomposed into its frequency components and the results displayed in the form of a power spectrum (Lopes da Silva, 1987). Measurements of the power spectra have been widely used, for example, to assess the background activity of the EEG (Duffy *et al.* 1979), to evaluate changes in the EEG during sleep (Dumermuth *et al.*, 1972; Mendelson *et al.*, 1987) and carotid endarterectomy (Blume & Sharbrough, 1987), and to describe the frequency content of various tremors (Halliday & Redfearn, 1956; Gresty & Findley, 1984), speech and auditory signals (Michelsen, 1985) and the electrical activity of muscle (Lindstrom & Magnusson, 1977).

In recent years, a new vocabulary and mathematical artillery has insinuated itself into the analysis of complex dynamical behaviours. These techniques are based on recent advances in nonlinear dynamics. Here we briefly indicate how two measures,

the Liapunov number and the dimension, are currently being used to characterize neural time series.

The *Liapunov number* measures the rate of divergence of solutions of deterministic dynamical systems for initial conditions that are very close (Wolf *et al.*, 1985). If, in such a system, the largest Liapunov number is negative, then there is either a stable steady state or a stable limit cycle. On the other hand, a positive Liapunov number is often taken as a definition of chaos (Wolf *et al.*, 1985). Positive Liapunov numbers have been observed experimentally for neural spike trains recorded from deafferented buccal-cerebral neurons and motor neurons of the cerebro-pleural ganglion of the sea slug (Mpitsos *et al.*, 1988) and for the human EEG recorded under a variety of conditions (Babloyantz *et al.*, 1985; Babloyantz & Destrexhe, 1986; Mayer-Kress & Holzfuss, 1987). Interpretation of these observations as evidence for determinstic chaos is not yet possible since the Liapunov number is positive for purely random processes such as a random walk. Further, the algorithm commonly used to compute Liapunov numbers (Wolf *et al.*, 1985) has many shortcomings; for example, it can give erroneous results in the presence of large time derivatives (Vastano & Kostelich, 1986; Wolf & Vastano, 1986).

The *dimension* is a quantity which is used to characterize the geometry of the steady state dynamics produced by deterministic systems (Russell *et al.*, 1980). For example, the dimension of an equilibrium point is 0 and that of a periodic orbit is 1. Various computer algorithms have been developed in an attempt to estimate the dimension when time series are very complex (for a review see Mayer-Kress, 1988). Applications of these algorithms to the study of neural dynamics typically yield noninteger values for the dimension. A geometrical object with a noninteger dimension is called a fractal (Mandelbrot, 1977). Fractal dimensions have been calculated for a variety of neural time series including finger tapping of parkinsonian and normal subjects (Kraus *et al.*, 1987), neural spike trains recorded from sea slugs (Mpitsos *et al.*, 1988) and the pre- and post-central gyri of monkeys (Rapp *et al.*, 1985), the EEG recorded from the olfactory bulb of rodents (Skarda & Freeman, 1987), and the human EEG under a variety of conditions (Babloyantz *et al.*, 1985; Albano *et al.*, 1986; Babloyantz, 1986; Babloyantz & Destrexhe, 1986, 1987; Layne *et al.*, 1986; Rapp *et al.*, 1986; Mayer-Kress & Layne, 1987; Mayer-Kress & Holzfuss, 1987; Watt & Hameroff, 1987). Although some chaotic systems (i.e. systems with a positive Liapunov number) have fractal dimensions, not all fractals are generated by chaos and not all chaotic systems are fractal (Grebogi *et al.*, 1984). There are a number of well recognized limitations associated with the computer algorithms used to estimate the dimension, e.g. the sensitivity of the algorithm to the number of data points, sampling interval and high derivatives; the effect of electronic filtering of the time series to remove artifact on the calculation of the dimension; and the stationarity of the time series (Caswell & Yorke, 1986; Layne *et al.*, 1986; Albano *et al.*, 1987; Kostelich & Swinney, 1987; Mayer-Kress, 1988; Mees *et al.*, 1988). Consequently, the relevance of the observations of a fractal dimension to the identification of chaotic dynamics is obscure at best.

Clinical interpretation of the EEG requires that attention to be given to the morphology, frequency and distribution of the various waveforms (Spehlmann,

1985; Niedermeyer & Lopes da Silva, 1987). However, in some applications a detailed reading of the EEG is not required since the only interest is to detect whether gross changes have occurred. An example is the use of the EEG to monitor carotid endarterectomy procedures (Blume & Sharbrough, 1987). Since the dimension in principle reduces the EEG to a single number, it has been suggested that the dimension may be useful to characterize changes in the morphology and frequency of waveforms during various surgical procedures (Layne *et al.*, 1986; Mayer-Kress & Layne, 1987; Mayer-Kress & Holzfuss, 1987). This is an intriguing possibility, but at present suitable high speed computers for the rapid calculation of the dimension are not available in most clinical settings and progress is slow.

Power spectra, Liapunov numbers and dimension provide descriptive measurements of time series. These quantities do not provide direct insight into the mechanisms which produce the measured time series. For example, the question as to whether the human EEG is chaotic during a seizure avoids the much more important question as to which neural inhibitory or excitatory mechanism(s) are actually involved in producing a seizure. Certainly one does not need to calculate the dimension of the EEG to determine if a seizure has occurred; this is usually obvious (Fig. 1). At present the mathematical properties of deterministic equations necessary for the production of chaotic dynamics are being uncovered (Guckenheimer & Holmes, 1983; Lasota & Mackey, 1985; Devaney, 1986). However, the identity of the neural mechanisms which are capable of generating chaotic signals, if they exist at all, are not known. Indeed, the complex neural time series measured experimentally may be chaotic; may arise from the interaction of several independent oscillators (e.g. quasi-periodicity); may reflect stochastic noise; or may reflect some combination of these possibilities. Clearly what is needed are methods to unravel the origins of these time signals.

3. Inducing Bifurcations in Neural Dynamics

A direct approach for studying bifurcations in neural dynamics is to experimentally induce changes in known parameters in neural control mechanisms. Most experiments of this type have been performed in invertebrate and animal preparations. Examples include (i) the generation of a variety of complex oscillations in the membrane potential of isolated invertebrate neurons by altering the frequency and amplitude of periodic electrical stimulation (Aihara & Matsumoto, 1987; Everson, 1987; Hayashi & Ishizuka, 1987; Matsumoto *et al.*, 1987) and by blocking K^+ channels with 4-aminopyridine (Holden *et al.*, 1982); and (ii) production of changes in breathing patterns in animals by either increasing the circulatory delay between the brain and lung (Guyton *et al.*, 1956) or by altering the frequency of mechanical ventilation in anesthestized animals (Petrillo & Glass, 1984; Petrillo *et al.*, 1983) and humans (Graves *et al.*, 1986).

Although the observation of abnormal dynamic behaviors in humans with neurological disease suggests that bifurcations can occur in human neural dynamics, there has been a paucity of human models in which it has been possible to directly assess the dynamics which arise from parameter manipulation. The strategies which have

been employed involve either manipulation of a time delay in a sensory feedback loop or of the gain in a feedback loop. Experiments in which a variable time delay has been inserted into a sensory feedback loop have typically focussed on a variety of motor tasks. Examples include the introduction of delayed auditory feedback causing stuttering in normal individuals (Lee, 1950, 1951) and of delayed visual feedback leading to poor hand writing (Smith, 1962; Smith *et al.*, 1960) and altered performance in tracking tasks (Merton *et al.*, 1967; Glass *et al.*, 1988).

Experiments in which the gain of a feedback loop has been manipulated have essentially been limited to the visual system. Examples include (i) the production of limit cycle oscillations in the visual smooth pursuit system by increasing the gain of the horizontal retinal feedback gain (Scotto & Oliva, 1984); (ii) "high gain" oscillations in pupil area, i.e. pupil cycling, induced by focussing a narrow light beam at the pupillary margin (Stern, 1944; Miller & Thompson, 1978); and (iii) simpler and complex oscillations in pupil area which occur when the pupil light reflex is "clamped" with external feedback (Stark, 1962; Longtin & Milton, 1988; Milton *et al.*, 1988; Reulen *et al.*, 1988).

In the remainder of this section we will discuss recent work in our laboratories involving experiments in which altered feedback has been introduced into two different situations: (i) the clamped pupil light reflex, and (ii) a visually guided motor tracking task.

3.1. BIFURCATIONS IN THE CLAMPED PUPIL LIGHT REFLEX

Studies of the pupil light reflex play an important role in current investigations of the properties of human neural feedback mechanisms (Stark, 1959, 1984). This reflex is a delayed negative feedback neural control mechanism which regulates the retinal light flux (equal to the light intensity multiplied by the pupil area) by changing the pupil area. The time delay, τ, or pupil latency is $\sim$300 msec (Milton *et al.*, 1988). Oscillations in pupil area with a period T, where $2\tau < T < 4\tau$, are predicted to occur once the gain and/or τ in the feedback loop become sufficiently large (Stark, 1959, 1962; Stark & Cornsweet, 1958; Longtin & Milton, in press). In the language of dynamical systems, the onset of the oscillations coincide with a supercritical Hopf bifurcation (Longtin & Milton, in press).

Direct experimental verification of the above predictions has been facilitated by the development of techniques to *clamp* the pupil light reflex (Stark, 1962; Longtin & Milton, 1988; Milton *et al.*, 1988; Reulen *et al.*, 1988). Clamping refers to a technique in which the feedback loop is first "opened" by focussing a small light beam onto the center of the pupil in order to circumvent the shading effects of the iris on the retina (Stark & Sherman, 1957). The feedback loop is then reclosed with an electronically constructed circuit, or clamping box, which relates measured changes in pupil area to changes in retinal illumination. By appropriate design of the clamping box, the reflex can be made unstable and the types of dynamical behaviors explored in a precisely controllable manner. With this technique it has been possible to gradually increase the gain in the feedback loop and verify that

oscillations occur once the gain becomes sufficiently large (Stark, 1962; Reulen *et al.*, 1988).

A simple design of the clamping box is shown in Fig. 2(a). This has been referred to as piecewise constant negative feedback since once pupil area exceeds an adjustable area threshold, θ_1, the light is turned on and the pupil will then become smaller (Milton *et al.*, 1988; Milton & Longtin, unpublished results). Piecewise constant negative feedback is an idealization of the traditional technique of producing pupil cycling by focussing a narrow light beam at the pupillary margin, but affords better control (Milton *et al.*, 1988). Measurements of pupil cycling are important as a clinical test for detecting pathology within the reflex arc (Stern, 1944; Miller & Thompson, 1978; Milton *et al.*, 1988). This observation has provided a major impetus for obtaining analytic insight into the properties of the oscillations in pupil area that occur under conditions of negative feedback.

Figure 2 shows the results of an experiment with piecewise constant negative feedback. Provided that $\tau > 0$ (which is always true), the condition for the onset of the oscillation is simply that θ_1 be less than the initial pupil area (Longtin & Milton, 1988; Milton *et al.*, 1988). As is shown the period and the amplitude of the oscillations depends on the value of θ_1 relative to the initial pupil area [compare Figs 2(c-f)] and the total time delay (equal to the pupil latency plus the machine delay) [compare Figs 2(f) and (g)].

The changes in pupil area, A, that occur under conditions of external piecewise constant feedback are given by the delay-differential equation (Longtin & Milton, 1988, in press)

$$\frac{dg}{dA}\frac{dA}{dt} + \alpha g(A) = F(A_\tau) \tag{1}$$

where τ is the total time delay and A_τ is the pupil area at a time τ in the past, i.e. $A_\tau = A(t-\tau)$. The rate constant for pupillary movements differs for constriction (α_c) and dilation (α_d). The function $F(A_\tau)$ has only one of two values depending on whether the light is on or off and the function $g(A)$ relates changes in neural activity in the reflex arc to changes in pupil area. Experimentally it is found that the time courses for constriction and dilation can each be approximated by a single exponential (Longtin & Milton, 1988) and thus eqn (1) can be written as

$$\frac{dA}{dt} + \alpha A = \begin{cases} A_{off}, & \text{if } A_\tau < \theta_1 \\ A_{on}, & \text{if } A_\tau > \theta_1 \end{cases} \tag{2}$$

where A_{on}, A_{off} are constants which depend on, among other things, the intensity of the light beam and the background illumination (Longtin & Milton 1988). The values of the constants α_c, α_d, A_{on}, A_{off} can be determined from plots of the maximum, or minimum amplitude of the oscillations in pupil area as a function of θ_1 as shown in Figs 2(b) and 3(b).

As can be seen in Fig. 2, the amplitude and period of the solutions of eqn (2) closely resemble those of the observed oscillations in pupil area produced by

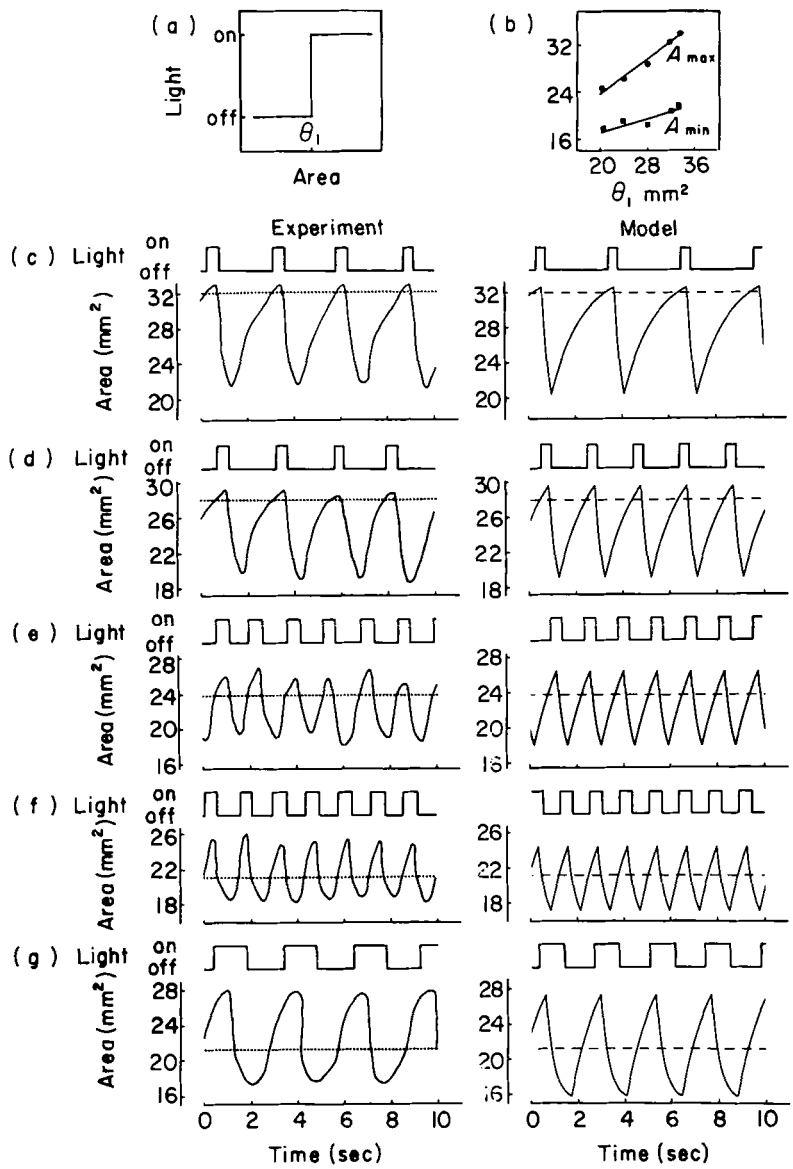

FIG. 2. Comparison of the changes in pupil area that occur as a function of time with imposed negative feedback to those predicted by eqn (2) (subject MC). The piecewise constant negative feedback is shown in (a). The pupil latency time was 285 msec. In (c-f) the machine delay was 100 msec ($\tau = 385$ msec) and in (g) the machine delay was increased to 579 msec ($\tau = 864$ msec). The area threshold, θ_1, was set at: (c) 32 mm², (d) 28·1 mm², (e) 23·8 mm², and 21·4 mm² in (f) and (g). For negative feedback, it can be shown (an der Heiden & Mackey, 1982; Milton & Longtin, unpublished results) that $A_{max} = \theta_1 \exp(-\alpha_d \tau) + A_{off}[1 - \exp(-\alpha_d \tau)]$ and $A_{min} = \theta_1 \exp(-\alpha_c \tau) + A_{on}[1 - \exp(-\alpha_c \tau)]$, where A_{max}, A_{min} are, respectively, the maximum and minimum amplitudes of the pupil area oscillations. The values of α_c, A_{on}, α_d, A_{off} used to calculate the solutions of eqn (2) were calculated from plots of A_{min}, A_{max} vs. θ_1 shown in (b) and were $\alpha_c = 3{\cdot}11\ \text{sec}^{-1}$, $\alpha_d = 0{\cdot}74\ \text{sec}^{-1}$, $A_{on} = 15{\cdot}7\ \text{mm}^2$, $A_{off} = 34{\cdot}5\ \text{mm}^2$. In (b) the values of A_{max}, A_{min} represent values averaged over a minimum of ten consecutive cycles.

changing either θ_1 or τ. These observations indicate that eqn (2) provides a good description of the dynamics observed in this experimental paradigm. However, the small cycle-to-cycle variations in pupil area are not predicted by eqn (2), and we believe that they reflect the influence of uncontrollable variations in the reflex arc, i.e. "noise".

A design of the clamping box which is better suited for the generation of complex dynamical behaviors is shown in Fig. 3(a) and corresponds to piecewise constant "mixed" feedback (an der Heiden & Mackey, 1982, 1987; Longtin & Milton, 1988). This type of feedback resembles negative feedback [Fig. 2(a)] except that once pupil area exceeds an area threshold $\theta_2 > \theta_1$, the light is turned off. The interest in studying this type of feedback stems from the analytic insight that has been gained into the properties of the equation

$$\frac{dA}{dt} + \alpha A = \begin{cases} A_{off}, & \text{if } A_\tau < \theta_1 \\ A_{on}, & \text{if } \theta_1 < A_\tau < \theta_2. \\ A_{off}, & \text{if } A_\tau > \theta_2 \end{cases} \tag{3}$$

For eqn (3) it has been possible to prove for simple initial conditions the existence of stable equilibria, of stable and unstable limit cycles, and Li and Yorke type chaos as well as mixing and exact motions as θ_1 and θ_2 are varied (an der Heiden, 1983, 1985; an der Heiden & Mackey, 1982, 1987). These latter aperiodic trajectories are unstable and thus would be expected to be difficult or impossible to observe experimentally. In numerical experiments we always observe complicated limit cycles in the parameter ranges where aperiodic dynamics exist. However, these limit cycles are stable only over extremely narrow parameter ranges and thus would be difficult to observe in real systems in which parameters may fluctuate.

Figure 3 shows the results of an experiment with mixed feedback. A variety of different oscillations, which are more complex than those produced with negative feedback (Fig. 2), occur as θ_1 and θ_2 are varied. For the parameter values measured experimentally, qualitatively similar solutions are produced by eqn (3). The agreement between the solutions of eqn (3) and experimental observations is best for the simpler oscillations shown in Figs 3(c) and (d). The more complex experimental oscillation shown in Fig. 3(e) has the same overall morphology as the corresponding solution of eqn (3), but possesses less detail. This presumably is a reflection of the inability of the slowest elements of the reflex arc to undergo rapid, sudden changes in direction. Indeed better agreement is obtained when eqn (3) is modified to include mechanical inertia (Milton & Longtin, unpublished results).

Although eqn (3) correctly predicts that very complex oscillations should be observed for certain choices of θ_1 and θ_2 [Fig. 3(f)], the predicted oscillations are periodic and clearly qualitatively very different. The origin of these complex oscillations in pupil area is currently under active investigation. One possible explanation is that this oscillation reflects the influences of uncontrolled irregular variations in certain of the parameters of eqn (3), i.e. multiplicative noise (Longtin & Milton, 1988). To illustrate the influence of parameter fluctuations, in Fig. 4 we show the effect of measured variations in A_{on} and A_{off} on the solutions of eqn (3). For the values of θ_1 and θ_2 which produce the complex oscillations shown in Fig. 3(f), the

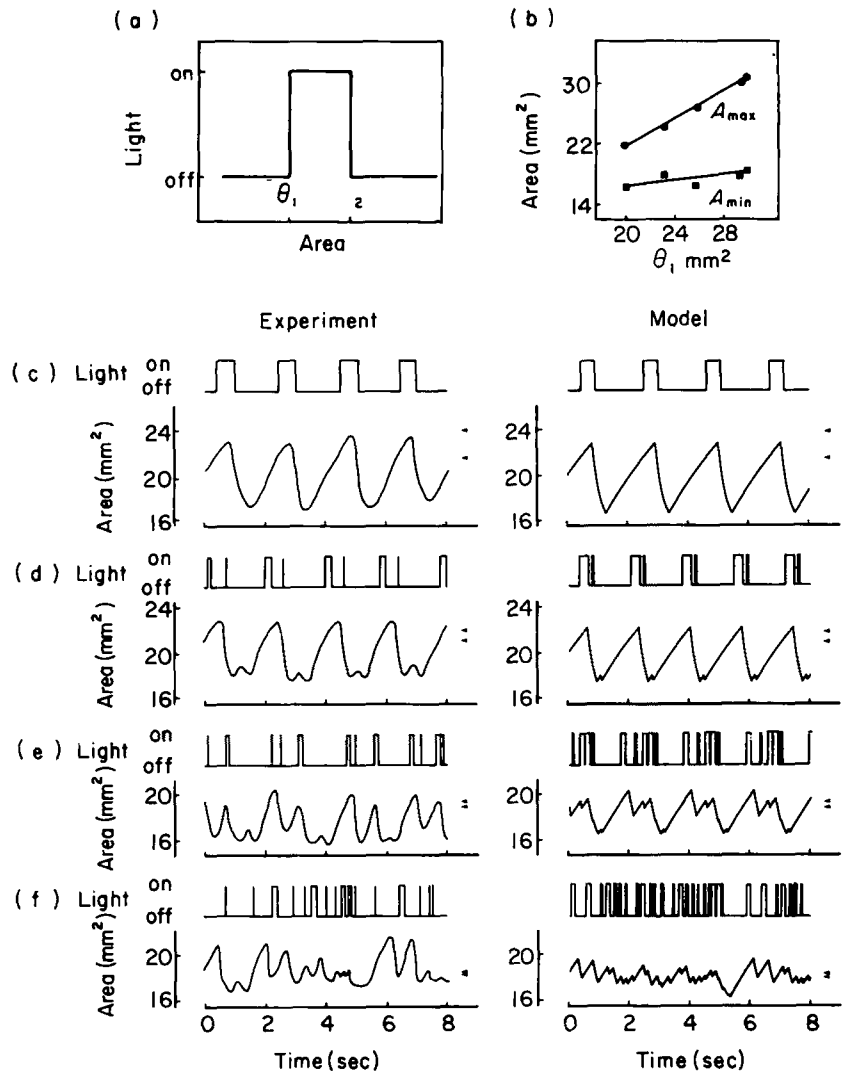

FIG. 3. Comparison of the changes in pupil area that occur as a function of time with imposed mixed feedback to those predicted by eqn (3) (subject JM). The piecewise constant mixed feedback is shown in (a). The parameter $\alpha_c = 3{\cdot}88\ \text{sec}^{-1}$, $\alpha_d = 0{\cdot}265\ \text{sec}^{-1}$, $A_{on} = 15{\cdot}5\ \text{mm}^2$, $A_{off} = 34{\cdot}2\ \text{mm}^2$ were measured in a preliminary experiment with piecewise constant negative feedback as discussed in the legend to Fig. 2 [data shown in (b)] and τ was 411 msec. The upper (θ_2) and lower (θ_1) area thresholds have been indicated by the "◀" at the right hand sides of the figure and were respectively: (c) 21·5 mm², 24·5 mm²; (d) 21 mm², 22 mm²; (e) 18·9 mm², 19·5 mm²; (f) 17·95 mm², 18·5 mm².

variations in A_{on} and A_{off} are large enough to induce transitions between qualitatively different solutions of eqn (3) [Fig. 4(d)]. Thus the observed oscillations could represent a combination of different solutions of eqn (3) plus transients. The simpler oscillations in Figs 3(c), (d) and (e) are less sensitive to these parameter variations because of the wider parameter intervals over which they are expected to occur

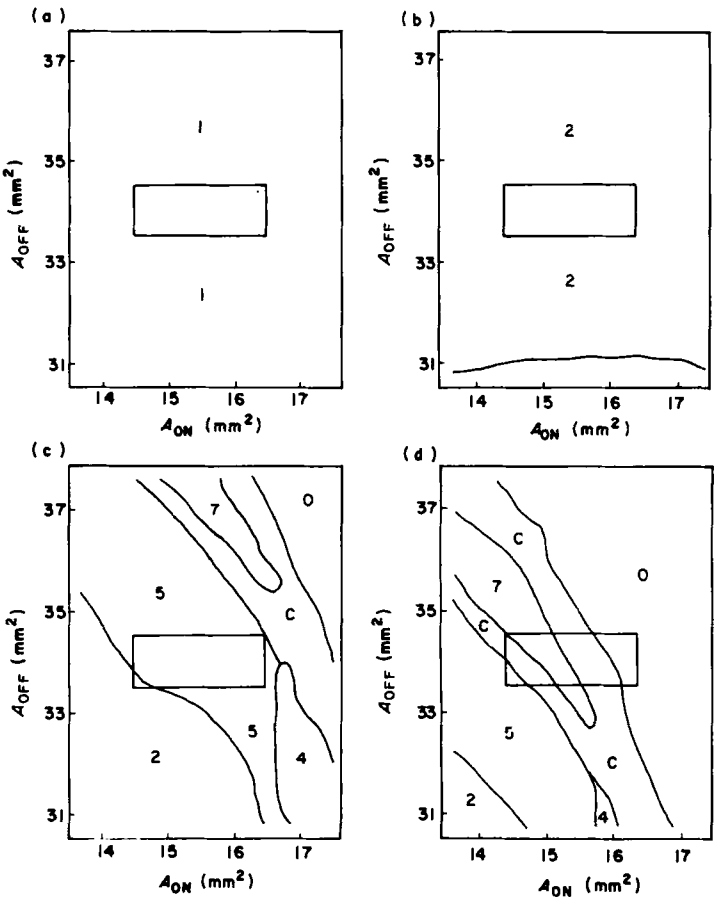

FIG. 4. The (A_{on}, A_{off})-parameter space for eqn (3) for the values of the area thresholds θ_1, θ_2 in Fig. 3 [(a), (b), (c), and (d) correspond, respectively, to Figs 3(c), (d), (e), and (f).] In constructing these parameter spaces the values of α_c, α_d, τ have been fixed and we have classified the periodic solutions of eqn (3) symbolically by the number of light pulses per period [i.e. Fig. 3(d) shows a type 2 solution since there are two light pulses per period]. The region labelled "C" contains very complex periodic solutions in close proximity as well as unstable mixing solutions. The rectangular boxes enclose the measured values of A_{on}, A_{off} ($\geq$10 consecutive values). Since in eqn (3), constriction and dilation occur as first order processes, it is possible to measure the values of A_{on}, A_{off} cycle to cycle using the values of, respectively, α_c, α_d (Longtin & Milton, 1988).

[Figs 4(a), (b), (c)]. We cannot exclude the possibility that the source of this multiplicative noise itself may represent the trace of a chaotic process (Lasota & Mackey, 1985, 1989) which is injected at some point into the reflex arc, for example, at the retina (Longtin & Milton, 1988) or the Edinger–Westphal nucleus (Stark *et al.*, 1958; Stanten & Stark, 1966).

The observations in Fig. 3 give a direct demonstration that qualitative changes in the dynamics of a neural control mechanism can arise as quantitative changes are made in the properties of neural feedback. The qualitative changes in dynamics

occur at approximately the same parameter values which produce bifurcations in a simple mathematical model for the pupil light reflex [eqn (3)]. Thus bifurcations in neural control mechanisms can be induced by parameter manipulation. However, these observations also emphasize that the different components of the observed dynamics must be carefully identified and evaluated before the aperiodic behaviors generated by the nervous system can be confidently assigned a determinstic origin.

3.2. VISUAL DELAYS IN MOTOR TRACKING TASKS

It is possible to alter dynamics in a process as complex as motor control by introducing a time delay into a sensory feedback loop. Figure 5 summarizes the results of an experiment in which a variable time delay is introduced into a simple motor tracking task (Merton *et al.*, 1967; Glass *et al.*, 1988; Beuter *et al.*, unpublished results). In this experiment subjects are required to adjust the position of their index finger to match the position of a target. However, the subjects are not able to directly assess the position of their index finger in relation to the target. Instead the subjects look at an oscilloscope screen on which two horizontal lines are displayed; one is stationary and corresponds to the target and the other is controlled by a micro-displacement tranducer attached to the index finger which is fixed by a lightweight medical splint so that movement only occurs at the metacarpo-phalangeal joint. The subjects are asked to match the two horizontal lines as closely as possible. A variable time delay is introduced by inserting an analog delay line between the transducer and the oscilloscope. Thus, by viewing the oscilloscope screen, the subjects are only able to judge the position of their index finger relative to the target at some time in the past. In addition, the feedback gain can be increased by amplifying finger movements so that relatively larger displacements are seen on the oscilloscope screen. In the experiments we discuss here, the gain has been adjusted so that a finger displacement of 1 mm corresponds to a displacement of $\sim$16 mm on the oscilloscope screen.

Figures 5(a) and (b) show the effect of an increase in the analog time delay by 300 msec and 1500 msec on the subject's performance during this visual tracking task. There are small rhythmic finger displacements in finger position with a mean frequency of 8–12 Hz [Figs 5(c), (d)]. These rhythms are present with or without the analog time delay (data not shown) and are associated with physiological tremor. As can be seen in Figs 5(c) and (d), the frequency of this tremor is not influenced by an increase in the analog time delay; however, the overall amplitude of finger displacements increases with the time delay.

Physiological tremor recorded in distal extremities is thought to involve complex mechanisms at the segmental level (i.e. spinal or brainstem) and central level (i.e. supra-spinal rhythmic input to motoneurons) (Lippold, 1970; Marsden, 1984*b*). Its amplitude can vary between subjects and is affected by both psychological (i.e. emotional state) and physiological factors (i.e. temperature disturbance or pharmacological agents such as beta-agonists) (Koller, 1984).

The addition of the analog time delay does result in the appearance of an increase in power in the power spectra below 1·5 Hz [Figs 5(c), (d)]. This is associated with

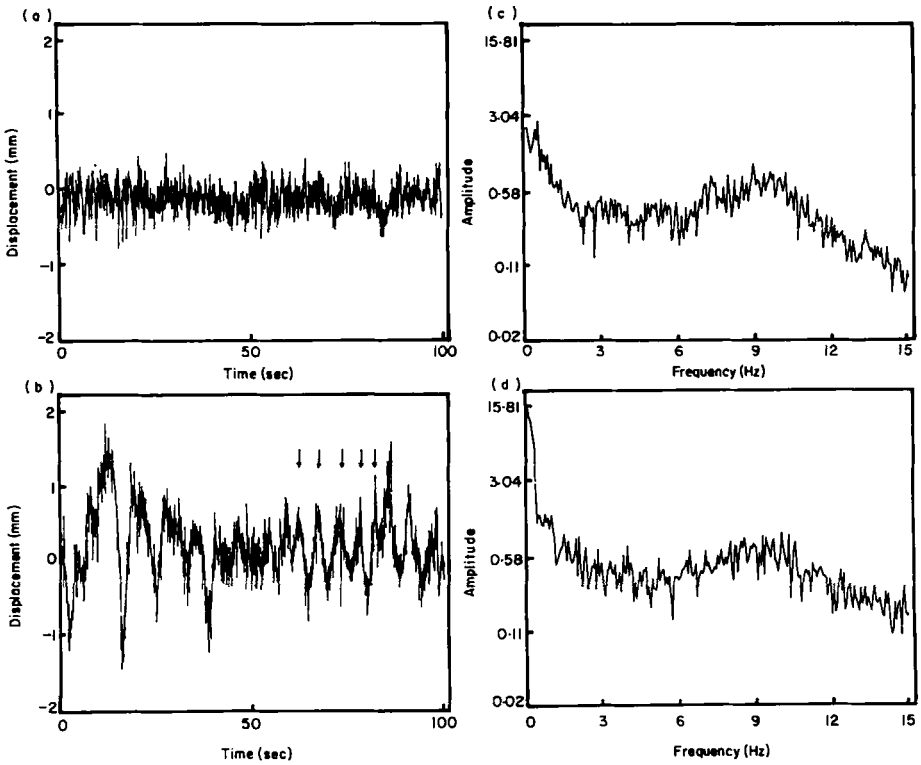

FIG. 5. (a), (b). Time series of the displacement of the index finger of a healthy subject (subject IT) performing the delayed visual tracking task described in the text with an added time delay of (a) 300 msec and (b) 1500 msec. The amplitude of the displacements in finger position increases with the time delay and in the case of the 1500 msec delay a regular low frequency oscillation appears intermittently (indicated by ↓). In (c) and (d) the power spectra of the finger displacement time series shown, respectively, in (a) and (b) is plotted for frequencies from 0–15 Hz. The logarithm of the amplitude of the power spectrum has been plotted in arbitrary units. With increasing delay, more power appears at frequencies $<1{\cdot}5$ Hz.

the appearance of a low frequency oscillation superimposed on the physiological tremor [Fig. 5(b)]. The amplitude and period of this low frequency oscillation increases as the time delay increases. This oscillation is not regular, but occurs intermittently. During the time intervals when this oscillation is more regular, the average inter-peak interval is found to increase continuously with the time delay and is found to be between two and four times the delay (Beuter *et al.*, unpublished results).

Since this delay does not appear to influence the frequency of the physiological tremor, it is likely that it is influencing a more central control mechanism. This interpretation is consistent with neuroanatomical considerations. The afferent signals arising from the proprioceptors and the retina travel by separate pathways to the cortex via separate thalamic nuclei. The likely first sites of interaction of this afferent information for the task of altering finger position are the association areas of the cortex, i.e. the parieto-occipital lobes. Thus, the increased time delay in our

experiment is probably affecting, as yet unknown, mechanisms in this region of the cortex. In addition, the cerebellum and basal ganglia are also likely to play a role. For example, the cerebellum modulates both descending efferent information to the spinal cord and finger via the corticospinal and rubrospinal tracts and ascending afferent information from vision (i.e. superior colliculus) and limb movements (i.e. spinocerebellar tracts).

Theoretically it can be shown that the period of an oscillation for a first order delayed feedback mechanism is at least two times the delay and, under certain conditions, may be bounded above by four times the delay (Hayes, 1950; Mackey & Glass, 1977; Glass & Mackey, 1979). This prediction is consistent with the period of the intermittent oscillation in finger position that occur when the delay is added (Fig. 5). However, in these simple mathematical models the observed cycle is a stable regularly occurring one (i.e. limit cycle), whereas the oscillation observed in this experiment is only intermittently regular. A number of neural mechanisms might account for this intermittency. The appearance and disappearance of the oscillation might be due to interactions between the multiple feedback loops which underlie the stabilization of the finger (Glass *et al.*, 1988). An alternative possibility is that the feedback loops are selectively activated depending on the current and past states of the system (Beuter *et al.*, unpublished results). For example, the relative importance of visual and proprioceptive mechanisms for maintaining finger position might fluctuate during the course of a single trial (Stephens & Taylor, 1974). Finally, the same reflex mechanisms may have different uses in different movement contexts (Lee *et al.*, 1983) and the volitional and motor planning of the subjects may also influence their motor responses through feedforward mechanisms (Hammond, 1956).

The above observations illustrate a general principle of neural control, i.e. there exist multiple mechanisms that influence the controlled activity at several levels in the nervous system. This principle is not unique to the control of finger movement but applies to virtually every neural behavior. A major problem is to unravel the interactions of the various central control loops and ultimately understand their contribution to the observed dynamics (as in Fig. 5). No foolproof strategy now exists to do this. One approach, not yet adequately tried, is to perform experiments in patients with known lesions that selectively eliminate neural pathways that control motor behavior (e.g. patients with cerebeller pathology or Parkinson's disease). These results can then be compared with those from normal subjects and in theoretical models with an effort at detecting qualitative changes in dynamics induced by the lesion.

4. Conclusions

Neurological systems generate complex dynamic behaviors. Although a variety of quantitative measures, such as power spectra, Liapunov exponents, dimension, have been used to describe these rhythms, these descriptions do not give a clear indication of the underlying mechanisms. We believe that an essential first step is the study of relatively simple model systems in which bifurcations can be induced. Here we have considered experiments in which alterations in the time delay and/or

gain of feedback loops are introduced using electronic circuits. It may also be possible to eventually develop experimental models in which bifurcations can be induced using pharmacological and/or surgical interventions. Neurological lesions provide another source of identifiable modifications in neural control. The goal of these experiments is not just to observe some novel behavior, but is to yield sufficient experimental data that theories based on known physiological mechanisms can be posed and then tested experimentally. In this way it should be possible to develop an understanding of the origins of dynamical behaviors seen in human disease and then, hopefully, devise more effective therapeutic strategies.

This work and A. Longtin were supported by the Natural Science and Engineering Research Council of Canada. Hamamatsu Photonics Systems, Inc. (Hamamatsu, Japan and Waltham, MA) provided the Binocular Iriscorder Model C-2515. We thank D. Lanteigne for constructing the delay line and the Neuro-electronics group at the Montreal Neurological Institute for their assistance. We are indebted to F. Andermann, N. Cashman, G. Francis, J. Gotman, M. Guevara, T. H. Kirkham, C. Polosa and N. So for their comments.

REFERENCES

AICARDI, J. (1986). *Epilepsy in Children.* New York: Raven Press.

AIHARA, K. & MATSUMOTO, G. (1987). Forced oscillations and routes to chaos in the Hodgkin-Huxley axons and squid giant axons. In: *Chaos in Biological Systems* (Degn, H., Holden, A. V. & Olsen, L. F., eds) pp. 121-131. New York: Plenum.

ALBANO, A. M., ABRAHAM, N. B., DE GUZMAN, G. C., TARROJA, M. F. H., BANDY, D. K., GIOGGIA, R. S., RAPP, P. E., ZIMMERMAN, I. D., GREENBAUM, N. N. & BASHORE, T. R. (1986). Lasers and brains: Complex systems with low-dimensional attractors. In: *Dimensions and Entropies in Chaotic Systems* (Mayer-Kress, G., ed.) pp. 231-240. New York: Springer-Verlag.

ALBANO, A. M., MEES, A. I., DE GUZMAN, G. C. & RAPP, P. E. (1987). Data requirements for reliable estimation of correlation dimensions. In: *Chaos in Biological Systems* (Degn, H., Holden, A. V. & Olsen, L. F., eds) pp. 207-220. New York: Plenum.

ALVORD, E. (1968). The pathology of parkinsonism. In: *Pathology of the Nervous System* (Minckler, J. ed.) pp. 1152-1161. New York: McGraw-Hill.

AYALA, G. F., DICHTER, M., GUMNIT, R. J., MATSUMOTO, H. & SPENCER, W. A. (1973). Genesis of epileptic interictal spikes. New knowledge of cortical feedback systems suggests a neurophysiological explanation of brief paraoxysms. *Brain Res.* **52**, 1-17.

BABLOYANTZ, A. (1986). Evidence of chaotic dynamics of brain activity during the sleep cycle. In: *Dimensions and Entropies in Chaotic Systems* (Mayer-Kress, G. ed.) pp. 241-245. New York: Springer-Verlag.

BABLOYANTZ, A. & DESTREXHE, A. (1986). Low-dimensional chaos in an instance of epilepsy. *Proc. natn. Acad. Sci. U.S.A.* **83**, 3513-3517.

BABLOYANTZ, A. & DESTREXHE, A. (1987). Strange attractors in the human cortex. In: *Temporal Disorder in Human Oscillatory Systems* (Rensing, L., an der Heiden, U. & Mackey, M. C., eds) pp. 48-56. New York: Springer-Verlag.

BABLOYANTZ, A., NICOLIS, C. & SALAZAR, M. (1985). Evidence of chaotic dynamics of brain activity during the sleep cycle. *Phys. Lett.* **111A**, 152-155.

BARBEAU, A. (1969). L-dopa therapy in Parkinson's disease. *Can. Med. Assoc. J.* **101**, 791-800.

BEUTER, A. & GARFINKEL, A. (1985). Phase plane analysis of limb trajectories in nonhandicapped and cerebral palsy subjects. *Adapted Phys. Activity Q.* **2**, 571-588.

BLUME, W. T. & SHARBROGH, F. W. (1987). EEG monitoring during carotid endarterectomy and open heart surgery. In: *Electroencephalography* (Niedermeyer, E. & Lopes da Silva, F., eds) pp. 645-656. Balitmore: Urban & Schwarzenberg.

BROWNE, T. R. & FELDMAN, R. G. (1983). *Epilepsy: Diagnosis and Management.* Toronto: Little, Brown.

CASWELL, W. E. & YORKE, J. A. (1986). Invisible errors in dimension calculations: Geometric and systematic effects. In: *Dimensions and Entropies in Chaotic Systems* (Mayer-Kress, G., ed.) pp. 123-136. New York: Springer-Verlag.

CHAY, T. R. (1984). Abnormal discharges and chaos in a neuronal model system. *Biol. Cybern.* **50,** 301-311.

CHAY, T. R. & RINZEL, J. (1985). Bursting, beating and chaos in an excitable membrane model. *Biophysics J.* **47,** 357-366.

CHERNIACK, N. S. & LONGOBARDO, G. S. (1973). Cheyne-Stokes breathing, and instability in physiological control. *New Engl. J. Med.* **288,** 952-957.

COOPER, R., WINTER, A. L., CROW, H. J. & WALTER, W. G. (1965). Comparison of subcortical, cortical and scalp activity using chronically indwelling electrodes in man. *Electroencephalogr. Clin. Neurophysiol.* **18,** 217-228.

DEVANEY, R. L. (1986). *An Introduction to Chaotic Dynamical Systems.* Don Mills, Ontario: Benjamin/Cummings.

DIMITRIJEVIC, M. R., SHERWOOD, A. N. & NATHAN, P. W. (1978). Clonus, peripheral and central mechanisms. In: *Physiological Tremor, Pathological Tremors and Clonus.* (Desmedt, J. E., ed.) pp. 173-182. New York: Krager.

DUFFY, F. H., BURCHFIELD, J. L. & LAMBROSO, C. T. (1979). Brain electrical activity mapping (BEAM). A method for extending the clinical use of EEG and evoked potential data. *Ann. Neurol.* **5,** 309-321.

DUMERMUTH, G., WALZ, W., SCOLLO LAVIZZARI, G. & KLEINER, B. (1972). Spectral analysis of EEG activity during sleep stages in normal adults. *Eur. Neurol.* **7,** 265-296.

ERMENTROUT, G. B. (1986). Period doublings and possible chaos in neural models. *SIAM J. Appl. Meth.* **44,** 80-95.

EVERSON, R. M. (1987). Quantification of chaos from periodically forced squid axons. In: *Chaos in Biological Systems* (Degn, H., Holden, A. V. & Olsen, L. F., eds) pp. 133-142. Plenum: New York.

FORSTER, F. M. (1975). *Reflex Epilepsy, Conditional Reflexes and Behavioural Treatment.* Springfield, Ill. Thomas.

GLASS, L. & MACKEY, M. C. (1979). Pathological conditions resulting from instabilities in physiological control systems. *Ann. N. Y. Acad. Sci.* **316,** 214-235.

GLASS, L. & MACKEY, M. C. (1988). *From Clocks to Chaos: The Rhythms of Life.* Princeton: Princeton University Press.

GLASS, L. BEUTER, A. & LAROCQUE, D. (1988). Time delays, oscillations and chaos in physiological systems. *Math. Biosciences* **90,** 111-125.

GLOOR, P. (1979). Generalized epilepsy with spike-wave discharge: A re-interpretation of its electrographic and clinical manifestations. *Epilepsia* **20,** 571-588.

GRAVES, C., GLASS, L., LAPORTA, D., MELOCHE, R. & GRASSINO, A. (1986). Respiratory phase locking during mechanical ventilation in anesthetized human subjects. *Am. J. Physiol.* **250,** R902-909.

GREBOGI, C., OTT, E., PELIKAN, S. & YORKE, J. A. (1984). Strange attractors that are not chaotic. *Physica* **13D,** 261-268.

GRESTY, M. A. & FINDLEY, L. J. (1984). Definition, analysis and genesis of tremor. In: *Movement Disorders: Tremor* (Findley, L. J. & Capildeo, R., eds) pp. 15-35. London: Macmillan.

GUCKENHEIMER, J. & HOLMES, P. (1983). *Nonlinear Oscillations, Dynamical Systems, and Bifurcations of Vector Fields.* New York: Springer-Verlag.

GUEVARA, M. R., GLASS, L., MACKEY, M. C. & SHRIER, A. (1983). Chaos in neurobiology. *IEEE Trans. Systems, Man Cybernetics* **SMC-13,** 790-798.

GUYTON, A. C., CROWELL, J. W. & MOORE, J. W. (1956). Basic oscillating mechanism of Cheyne-Stokes breathing. *Am. J. Physiol.* **187,** 395-398.

HALLIDAY, A. M. & REDFEARN, J. W. T. (1956). An analysis of the frequencies of finger tremor in healthy subjects. *J. Physiol.* **134,** 600-611.

HAMMOND, P. H. (1956). The influence of prior instruction to the subject on an apparently involuntary neuro-muscular response. *J. Physiol.* **132,** 17-18P.

HAYASHI, H. & ISHIZUKA, S. (1987). Chaos in molluscan neuron. In: *Chaos in Biological Systems* (Degn, H., Holden, A. V. & Olsen, L. F. eds) pp. 157-166. New York: Plenum.

HAYES, N. D. (1950). Roots of the transcendental equation associated with a certain difference-differential equation. *J. Lond. Math. Soc.* **25,** 226-232.

AN DER HEIDEN, U. (1983). Periodic, aperiodic, and stochastic behavior of differential-difference equations modeling biological and economical processes. In: *Differential-difference equations* (Collatz, L., Meinardus, G. & Wetterling, W, eds) pp. 91-108. Boston: Birkhäuser-Verlag.

AN DER HEIDEN, U. (1985). Stochastic properties of simple differential-delay equations. In: *Delay Equations, Approximation and Application* (Meinardus, G. & Nürnberger, G. ess) pp. 147-164. Basel: Birkhauser.

AN DER HEIDEN, U. & MACKEY, M. C. (1982). The dynamics of production and destruction: Analytic insight into complex behaviour. *J. math. Biol.* **16,** 75-101.

AN DER HEIDEN, U. & MACKEY, M. C. (1987). Mixed feedback: A paradigm for regular and irregular oscillations. In: *Temporal Disorder in Human Oscillatory Systems.* (Rensing, L., an der Heiden, U. & Mackey, M. C., eds) pp. 30–46. New York: Springer-Verlag.

AN DER HEIDEN, U., MACKEY, M. C. & WALTHER, H. O. (1981). Complex oscillations in a simple deterministic neuronal network. In: *Lectures in Applied Mathematics.* (Hoppensteadt, F., ed.) pp. 355–360. Providence: American Mathematical Society.

HOLDEN, A. V., WINLOW, W. & HAYDON, P. G. (1982). The induction of periodic and chaotic activity in a molluscan neuron. *Biol. Cybern.* **43,** 169–173.

HOLLISTER, L. E., DAVIS, K. L. & DAVIS, B. M. (1980). Hormones in the treatment of psychiatric disorders. In: *Neuroendocrinology.* (Kreiger, D. T. & Hughes, J. C., eds) pp. 167–175. Sunderland, MA: Sinauer.

KACZMAREK, L. K. & BABLOYANTZ, A. (1977). Spatiotemporal patterns in epileptic seizures. *Biol. Cybern.* **26,** 199–208.

KING, R., BARCHAS, J. D. & HUBERMAN, B. A. (1984). Chaotic behaviour in dopamine neurodynamics. *Proc. natn. Acad. Sci. U.S.A.* **81,** 1244–1247.

KOLLER, W. C. (1984). Diagnosis and treatment of tremors. *Neurol. Clin.* **2,** 499–514.

KOSTELICH, E. J. & SWINNEY, H. L. (1987). Practical considerations in estimating dimension from a time series. In: *Chaos and Related Natural Phenomena* (Procaccia, I. & Shapiro, M., eds) pp. 141–156. New York: Plenum.

KRAUS, P. H., BITTNER, H. R., KLOTZ, P. & PRZUNTEK, H. (1987). Investigation of agnositic/antagonistic movement in Parkinson's disease from an ergodic point of view. In: *Temporal Disorder in Human Oscillatory Systems* (Rensing, L., an der Heiden, U. & Mackey, M. C., eds) pp. 110–115. New York: Springer-Verlag.

LAPRESLE, J. & HAMIDA, M. B. (1970). The dentato-rubral pathway: Somatotopic relationship between the dentate nucleus and the contralateral inferior olive. *Arch. Neurol.* **22,** 135–143.

LASOTA, A. & MACKEY, M. C. (1985). *Probabilistic Properties of Deterministic Systems.* New York: Cambridge University Press.

LASOTA, A. & MACKEY, M. C. Stochastic perturbation of dynamical systems: The weak convergence of measures. *J. math. Appl.* **137** (in press).

LAYNE, S. P., MAYER-KRESS, G. & HOLZFUSS, J. (1986). Problems associated with dimensional analysis of electroencephalogram data. In: *Dimensions and Entropies in Chaotic Systems* (Mayer-Kress, G., ed.) pp. 246–256. New York: Springer-Verlag.

LEE, B. S. (1950). Effects of delayed speech feedback. *J. Acoust. Soc. Am.* **22,** 824–826.

LEE, B. S. (1951). Artificial stutter. *J. Speech Hearing Disorders* **16,** 53–55.

LEE, R. G., MURPHY, J. T. and TATTON, W. G. (1983). Long-latency myotactic reflexes in man: Mechanisms, functional significance, and changes in patients with Parkinson's disease or hemiplegia. In: *Motor Control Mechanisms in Health and Disease.* (Desmedt, J. E., ed.) pp. 489–508. New York: Raven Press.

LINDSTROM, L. H. & MAGNUSSON, R. I. (1977). Interpretation of myoelectric power spectra: a model and its applications. *Proc. IEEE* **65,** 653–662.

LIPPOLD, O. C. J. (1970). Oscillations in the stretch reflex arc and the origin of the 8–12 c/s component of physiological tremor. *J. Physiol.* **206,** 359–382.

LONGTIN, A. & MILTON, J. G. (1988). Complex oscillations in the human pupil light reflex with "mixed" and delayed feedback. *Math. Biosciences* **90,** 183–199.

LONGTIN, A. & MILTON, J. G. Insight into the transfer function, gain and oscillation onset for the pupil light reflex using nonlinear delay-differential equations. *Biol. Cybern.* (in press).

LOPES DA SILVA, F. (1987). EEG analysis: Theory and practice. In: *Electroencephalography* (Niedermeyer, E. & Lopes da Silva, F., eds) pp. 871–898. Baltimore: Urban & Schwarzenberg.

MACKEY, M. C. & AN DER HEIDEN, U. (1984). The dynamics of recurrent inhibition. *J. math. Biol.* **19,** 211–225.

MACKEY, M. C. & GLASS, L. (1977). Oscillation and chaos in physiological control systems. *Science, N.Y.* **197,** 287–289.

MACKEY, M. C. & MILTON, J. G. (1987). Dynamical Diseases. *Ann. N. Y. Acad. Sci.* **504,** 16–32.

MANDELBROT, B. B. (1977). *Fractals: Form, Chance, and Dimension.* San Francisco: W. H. Freeman and Co.

MARSDEN, C. D. (1984*a*). The pathophysiology of movement disorders. *Neurol. Clin.* **2,** 435–460.

MARSDEN, C. D. (1984*b*). Origins of normal and pathological tremor. In: *Movement Disorders: Tremor* (Findley, L. J. & Capildeo, R., eds) pp. 37–84. London: Macmillan.

MATSUMOTO, G., TAKAHASHI, N. & HANYU, Y. (1987). Chaos, phase locking and bifurcation in normal squid axons. In: *Chaos in Biological Systems.* (Degn, H., Holden, A. V. & Olsen, L. F., eds) pp. 143–156. New York: Plenum.

MAYER-KRESS, G. (1988). Application of dimension algorithms to experimental chaos. In: *Directions in Chaos* (Bai-Lin, H., ed.) Vol. 1. pp. 122-147. Singapore: World Scientific.

MAYER-KRESS, G. & HOLZFUSS, J. (1987). Analysis of the human electroencephalogram with methods from nonlinear dynamics. In: *Temporal Disorder in Human Oscillatory Systems.* (Rensing, L., an der Heiden, U. & Mackey, M. C., eds) pp. 57-68. New York: Springer-Verlag.

MAYER-KRESS, G. & LAYNE, S. P. (1987). Dimensionality of the human electrocephalogram. *Ann. N. Y. Acad. Sci.* **504,** 62-87.

MAYER-KRESS, G., YATES, F. E., BENTON, L., KEIDEL, M., TORSCH, W., PÖPPL, S. J. & GEIST, K. (1988). Dimensional analysis of nonlinear oscillations in brain, heart and muscle. *Math. Biosci.* **90,** 155-182.

MEES, A. I., RAPP, P. E. & JENNINGS, L. S. (1987). Singular-value decomposition and embedding dimension. *Phys. Rev.* **36A,** 340-346.

MENDELSON, W. B., SACK, D. A., JAMES, S. P., MARTIN, J. V., WAGNER, R., GARNETT, D., MILTON, J. & WEHR, T. A. (1987). Frequency analysis of the sleep EEG in depression. *Psychiatry Res.* **21,** 89-94.

MERTON, P. A., MORTON, H. B. & RASHBASS, C. (1967). Visual feedback in hand tremor. *Nature, Lond.* **216,** 583-584.

MICHELSEN, A. (ed.) (1985). *Time Resolution in Auditory Systems.* New York: Springer-Verlag.

MILLER, S. D. & THOMPSON, H. S. (1978). Edge-light pupil cycle time. *Br. J. Ophthalmol.* **62,** 495-500.

MILTON, J. G., GOTMAN, J., REMILLARD, G. M. & ANDERMANN, F. (1987). Timing of seizure recurrence in adult epileptic patients: A statistical analysis. *Epilepsia* **28,** 471-478.

MILTON, J. G., LONGTIN, A., KIRKHAM, T. H. & FRANCIS, G. S. (1988). Irregular pupil cycling as a characteristic abnormality in patients with demyelinative optic neuropathy. *Am. J. Ophthalmol.* **105,** 402-407.

MOLINA-NEGRO, P. (1979). Functional surgery of abnormal movements. In: *Functional Neurosurgery.* (Rasmussen, T. & Marino, R., eds) pp. 89-121. New York: Raven Press.

MPITSOS, G. J., BURTON, R. M., CREECH, H. C. & SOINILA, S. O. (1988). Evidence for chaos in spike trains of neurons that generate rhythmic motor patterns. *Brain Res. Bull.* **21,** 529-538.

NIEDERMEYER, E. & LOPES DA SILVA, F. (1987). *Electroencephalography: Basic Principles, Clinical Applications and Related Fields.* Baltimore: Urban & Schwarzenberg.

PETRILLO, G. A. & GLASS, L. (1984). A theory for phase locking respiration in cats to a mechanical ventilator. *Am. J. Physiol.* **246,** R311-320.

PETRILLO, G. A., GLASS, L. & TRIPPENBACH, T. (1983). Phase locking of the respiratory rhythm in cats to a mechanical ventilator. *Can. J. Physiol. Pharmacol.* **61,** 599-607.

PLUM, F. & POSNER, J. B. (1980). *The Diagnosis of Stupor and Coma.* Phildelphia. F. A. Davis.

RAPP, P. E., ZIMMERMAN, I. D., ALBANO, A. M., DE GUZMAN, G. C. & GREENBAUN, N. N. (1985). Dynamics of spontaneous neural activity in the simian motor cortex. *Phys. Lett.* **110A,** 335-338.

RAPP, P. E., ZIMMERMAN, I. D., ALBANO, A. M., DE GUZMAN, G. C., GREENBAUN, N. N. & BASHORE, T. R. (1986). Experimental studies of chaotic neural behaviour: Cellular activity and electroencephalographic signals. In: *Nonlinear Oscillations in Biology and Chemistry.* (Othmer, H. G., ed.) pp. 175-205. New York: Springer-Verlag.

RASMINSKY, M. (1984). Pathophysiology of demyelination. *Ann. N.Y. Acad. Sci.* **436,** 68-80.

REULEN, J. P. H., MARCUS, J. T., VAN GILST, M. J., KOOPS, D., BOS, J. E., TIESINGA, G., DE VRIES, F. R. & BOSHUIZEN, K. (1988). Stimulation and recording of dynamic pupillary reflex: the IRIS technique. Part 2. *Med. Biol. Eng. Comp.* **2,** 27-32.

RUSSELL, D. A., HANSON, J. D. & OTT, E. (1980). Dimension of strange attractors. *Phys. Rev. Lett.* **45,** 1175-1178.

SCOTTO, M. & OLIVA, G. A. (1984). Limit cycle oscillations of the human eye. *Biol. Cybern.* **51,** 33-41.

SKARDA, C. A. & FREEMAN, W. J. (1987). How brains make chaos in order to make sense of the world. *Behav. Brain Sci.* **10,** 161-195.

SMITH, K. U. (1962). *Delayed Sensory Feedback and Behavior.* Philadelphia: Saunders.

SMITH, W. M., MCCRARY, J. W. & SMITH, K. U. (1960). Delayed visual feedback and behavior. *Science, N.Y.* **132,** 1013-1014.

SPEHLMANN, R. (1985). *EEG Primer.* New York: Elsevier.

STANTEN, S. F. & STARK, L. (1966). A statistical analysis of pupil noise. *IEEE Trans. Biomed. Eng.* **13,** 140-152.

STARK, L. (1959). Stability, oscillations and noise in the human pupil servomechanism. *Proc. IRE* **47,** 1925-1939.

STARK, L. (1962). Environmental clamping of biological systems: pupil servomechanism. *J. Opt. Soc. Am.* **52,** 925-930.

STARK, L. (1984). The pupil as a paradigm for neurological control systems. *IEEE Trans. Biomed. Eng.* **31,** 919-924.

STARK, L. & CORNSWEET, T. N. (1958). Testing a servoanalytic hypothesis for pupil oscillations. *Science, N.Y.* **127,** 588.

STARK, L. & SHERMAN, P. M. (1957). A servoanalytic study of consensual pupil reflex to light. *J. Neurophysiol.* **20,** 17-26.

STARK, L., CAMPBELL, F. W. & ATWOOD, J. (1958). Pupil unrest: An example of noise in a biological servomechanism. *Nature, Lond.* **182,** 857-858.

STEPHENS, J. A. & TAYLOR, A. (1974). The effect of visual feedback on the physiological muscle tremor. *Electroencephalgr. Clin. Neurophysiol.* **36,** 456-464.

STERMAN, M. B. & FRIAR, L. (1972). Suppression of seizures in an adult epileptic following sensorimotor EEG feedback training. *Electroencephalgr. Clin. Neurophysiol.* **33,** 89-95.

STERN, H. J. (1944). A simple method for the early diagnosis of abnormality of the pupillary reaction. *Br. J. Ophthalmol.* **28,** 275-276.

VASTANO, J. A. & KOSTELICH, E. J. (1986). Comparison of algorithms for determining Lyapunov exponents from experimental data. In: *Dimensions and Entropies in Chaotic Systems.* (Mayer-Kress, G., ed.) pp. 100-107. New York: Springer-Verlag.

WATT, R. C. & HAMEROFF, S. R. (1987). Phase space analysis of human EEG during general anesthesia. *Ann. N. Y. Acad. Sci.* **504,** 286-288.

WEHR, T. A., GOODWIN, F. K., WIRZ-JUSTICE, A., CRAIG, C. & BREITMEIER, J. (1982). 48-Hour sleep-wake cycles in manic-depressive illness: Natrualistic observations and sleep deprivation experiments. *Arch. Gen. Psychiatry* **39,** 559-565.

WEHR, T. A. & GOODWIN, F. K. (1983). Biological rhythms in manic-depressive illness. In: *Circadian Rhythms in Psychiatry.* (Wehr, T. A. & Goodwin, F. K., eds) pp. 129-184. Pacific Groove, California: Boxwood Press.

WOLF, A. & VASTANO, J. A. (1986). Intermediate length scale effects in Lyapunov exponent estimation. In: *Dimensions and Entropies in Chaotic Systems.* (Mayers-Kress, G., ed) pp. 94-99. New York: Springer-Verlag.

WOLF, A., SWIFT, J. B., SWINNEY, H. L. & VASTANO, J. A. (1985). Determining Lyapunov numbers from a time series. *Physica* **16D,** 285-317.

WOODBURY, D. M., PENRY, J. K. & PIPPENGER, C. E. (eds) (1982). *Antiepileptic Drugs.* New York: Raven Press.