Time Delays, Oscillations, and Chaos in Physiological Control Systems

LEON GLASS
Department of Physiology, McGill University, Montreal, Quebec, Canada H3G 1Y6

ANNE BEUTER
Département de Kinanthropologie, Université du Québec à Montréal, Montréal, Québec, Canada H3C 3P8

AND

DAVID LAROCQUE
Department of Physiology, McGill University, Montreal, Quebec, Canada H3G 1Y6

Received 1 June 1987; revised 14 January 1988

ABSTRACT

Many physiological systems operate by feedback mechanisms in which there are time delays from the sensing of some disturbance to the mounting of an appropriate physiological response. Theoretical studies show that using either "mixed" feedback or multiple negative feedback loops with different delays, it is possible to generate complex periodic and aperiodic, chaotic rhythms. In an experimental study of finger tracking using visual feedback, a variable time delay can be added to the feedback circuit. As this delay is varied, complex rhythms of finger displacement are observed. We suggest that the complex dynamics observed in diverse physiological systems in normal individuals may be associated with chaotic dynamics arising from the interaction of multiple feedback loops.

I. INTRODUCTION

In the human body, there are many feedback mechanisms working to maintain key physiological variables within normal limits. In these feedback loops, there are delays which are associated with the time interval between the sensing of some disturbance and the mounting of an appropriate physiological response. The magnitude of such delays can vary widely. For example, the control of heart rate and blood pressure is mediated by various neural and hormonal mechanisms. Each mechanism has its own characteristic delay time and gain, and is effective over a well-defined range of blood pressure [15]. Even in normal circumstances it is believed that

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several different feedbacks may be operating simultaneously [1, 5, 19, 35]. Multiple feedback mechanisms are widespread and have been discussed in the context of control of ventilation [12, 26] and motor activity [32].

One means to study the effects of time delays in physiological control systems is to devise a means to alter a delay in a feedback loop. For example, Guyton et al. [16] increased the circulation time from the oxygenation of blood in the lung to the stimulation of chemosensitive sites in the brainstem by introducing a plastic tube in the carotid artery. In this fashion they were able to induce periodicities in the breathing rhythm of dogs. Manipulation of time delays in humans must be carried out using less invasive procedures. One technique which has been frequently employed is to study the operation of motor control following introduction of a time lag in a sensory feedback. Early studies showed that introduction of an auditory delay degrades speech and induces stuttering [24, 25], whereas a visual delay strongly impairs one's ability to trace a simple geometric figure [37, 38]. Introduction of a visual delay also changes characteristics of power spectra of tremor in subjects who were maintaining a fixed finger position under visual feedback [30].

Theoretical interpretation of feedback mechanisms in physiology is often undertaken in the context of linear systems theory [31, 32]. Although such methods may be useful in analyzing the onset of small amplitude oscillations, in order to theoretically treat larger amplitude fluctuations, nonlinear analysis is needed. An interesting observation is that systems with feedback control displaying a "mixed" feedback (both positive and negative feedback over appropriate ranges of the controlled variable) are capable of showing complex, aperiodic dynamics [8, 17, 28]. Such aperiodic dynamics in deterministic systems in which there is sensitive dependence of the temporal evolution on the initial conditions is called *chaos*. The occurrence of chaos in natural systems is now well recognized and has been the subject of intensive research in recent years [6].

The point of this article is to discuss several theoretical and practical aspects related to feedback control of physiological systems with time delays. In Section II, we discuss systems in which there is a single feedback loop with a single time delay and show that periodic oscillatory behavior as well as chaotic dynamics can both be found. In Section III we consider the dynamics in a system with multiple negative feedbacks. A theoretical formulation of such a system has been developed. This system shows periodic behavior, and in some instances apparently aperiodic, chaotic dynamics. Finally, in Section IV we describe experimental studies in which a subject maintains a constant position of his finger using visual feedback displayed on an oscilloscope screen, but with a time delay inserted in the feedback loop. Complex rhythms are observed. The results are discussed in Section V.

II. ONE VARIABLE DELAY DIFFERENTIAL EQUATIONS

First consider the simple ordinary differential equation

$$\frac{dx}{dt} = \lambda - \gamma x, \tag{1}$$

where x is a variable to be controlled, λ is a constant which represents a production rate, and γ is a constant which represents a decay rate. In the limit $t \to \infty$, starting from any initial condition, we have $x = \lambda/\gamma$. Thus, this system reaches a single stable equilibrium. In order to represent physiological systems one can assume that either λ or γ or both are nonlinear functions which depend on the value of x at some time in the past. We review the results of Mackey and Glass [8, 28] and then indicate some extensions.

In considering the control of the density of circulating blood cells, x, it was assumed that the production was a nonlinear function of the density at a time τ in the past, x_τ:

$$\frac{dx}{dt} = f(x_\tau) - \gamma x. \tag{2}$$

Two different forms for the nonlinear function were considered:

$$f(x_\tau) = \frac{\lambda\theta^n}{\theta^n + x_\tau^n}, \tag{3a}$$

$$f(x_\tau) = \frac{\lambda\theta^n x_\tau}{\theta^n + x_\tau^n}. \tag{3b}$$

Using the monotonically decreasing function in (3a), only periodic behavior or a stable steady state is observed. An appreciation of the periodic behavior is obtained by considering the piecewise linear limit which arises when $n \to \infty$. In this case, straightforward computations show that for $R = \lambda/\gamma\theta$, $R > 1$, there will be an oscillation with period

$$T = 2\tau + \frac{1}{\gamma}\left(\ln\frac{R - e^{-\gamma\tau}}{R-1} + \ln[R + (1-R)e^{-\gamma\tau}]\right) \tag{4a}$$

and amplitude

$$A = \frac{\lambda}{\gamma}(1 - e^{-\gamma\tau}), \tag{4b}$$

as shown in Figure 1.

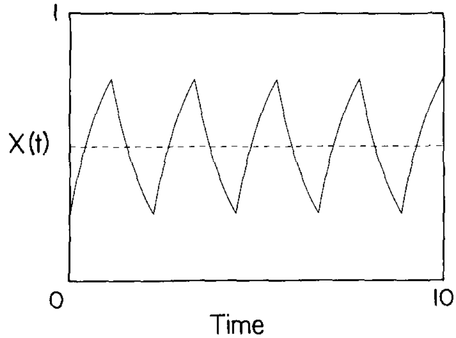

FIG. 1. Periodic oscillation which arises from the substitution of (3a) in (2) with $n \to \infty$, $\theta = 0.5$, $\lambda = \gamma = 1$, $\tau = 0.7$. The dashed horizontal line in this and some of the other figures represents the value of the threshold.

The situation using the nonmonotonic feedback in (3b) is very different. In this case, for some parameter values, numerical simulations showed highly complex behavior including period doubling bifurcations and chaotic dynamics (Figure 2). It was proposed that the observed oscillations in this case might correspond to abnormal fluctuations of blood cells observed in some leukemias. There are no proofs that the dynamics in the equation with the nonmonotonic feedback in (3b) are chaotic, but by using a piecewise linear nonmonotonic feedback function it has been possible to prove chaos [17]. Similar equations have been proposed by several workers as models for control of blood cell production [22, 27], feedback control in population growth, [14, 29, 34], and other areas (see references in [17]).

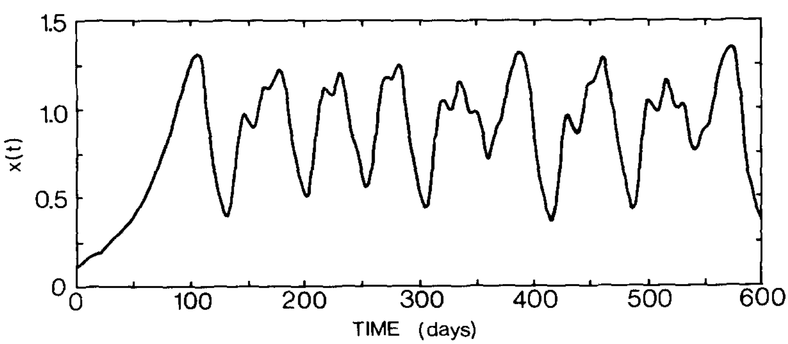

FIG. 2. Chaotic oscillation which arises from the substitution of (3b) in (2) with $n = 10$, $\theta = 1$, $\lambda = 0.2$, $\gamma = 0.1$, $\tau = 20$ (from [28]).

Time delay differential equations have been helpful in the testing of algorithms for the computation of quantitative measures which can be used to characterize complex dynamics in both model equations and physical and biological systems. One measure being intensively studied is the dimension. In delay differential equations, one must specify the initial conditions over a period of time, and the equations are therefore infinite dimensional. However, it is now well recognized that asymptotic dynamics in nonlinear equations can be characterized by a "dimension" which is not always an integer and may be less than the number of independent variables in the equations of motion. The first study of dimension in delay differential equations was carried out by Farmer [7], who showed that using the nonmonotonic decay in (3b), it was possible to determine the dimension, and that for certain parameters, the dimension appeared to increase linearly with the time delay. Thus, by increasing the time delay it is possible to obtain high (6–20) dimensions. However, the algorithms which have been used to compute the dimension in these systems are by no means straightforward. A recent study by Kostelich and Swinney [21] found it difficult to achieve convergence using a popular algorithm due to Grassberger and Procaccia [13], and favored an algorithm due to Badii and Politi [2]. In another study, it was suggested that in these equations the dimension can be approximated by dividing the delay time by a time constant approximately equal to the time it takes the autocorrelation function to decay to its first minimum [23].

In summary, the time delay equations considered in this section are conceptually simple and have been proposed as models in a number of different systems. However, it is not easy to characterize the dynamics or to prove asymptotic properties of the dynamics. Although it is believed that the delay equations represent a reasonable approximation to real biological systems, systematic experimental studies in which time delays or other variables corresponding to parameters in such equations are manipulated have not yet been reported (but see Section IV).

III. EQUATIONS WITH MULTIPLE DELAYS

Physiological systems have multiple feedbacks controlling key variables. Teleological arguments for multiple feedbacks are easy to find. They can provide backups if one system fails or is inadequate on its own. They can also provide flexibility of response, with some feedbacks operating rapidly and others with a longer delay. Previous considerations of the roles of multiple feedbacks and delays have been largely undertaken in the context of linear systems theory [1, 12, 26, 32, 35]. Thus different peaks in the power spectra of controlled variables have been associated with different feedback loops oscillating with different intrinsic frequencies. However, since multiple oscillations in nonlinear systems can interact to give rise to highly complex

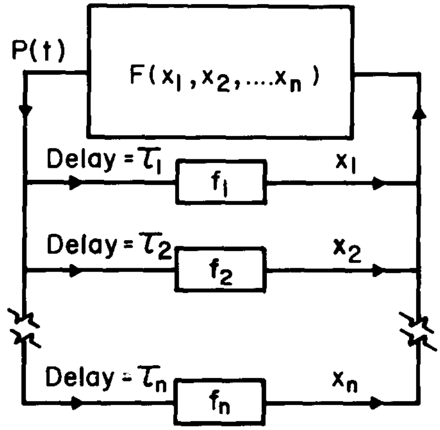

FIG. 3. Schematic diagram of a feedback system with multiple feedback loops.

chaotic dynamics, a simple interpretation of multiple peaks in power spectrum data must be viewed with caution. Indeed, it is not hard to imagine that mathematical models with multiple feedbacks with different delays may give rise to very complex dynamics. In order to illustrate this we consider a very simple piecewise linear model of a negative feedback system with multiple delays which can be easily integrated numerically.

Consider the schematic diagram in Figure 3. The multiple paths, each with its own time delay, act to stabilize the controlled variable P. We assume that

$$\begin{aligned} \varepsilon\frac{dP}{dt} &= \left[F(x_1, x_2, \ldots, x_N) - P\right], \\ \frac{dx_i}{dt} &= f_i(P_{\tau_i}) - \gamma x_i, \qquad i = 1, 2, \ldots, N, \end{aligned} \tag{5}$$

where the variables x_i are nonlinear functions of P at a time τ_i in the past, and the value of P tends to $F(x_1, x_2, \ldots x_N)$ with a time constant ε. With one variable in the limit $\varepsilon \to 0$, this reduces to Equation (2) considered in Section II.

We now consider a special case with multiple delays. Assume that:

(1) $\varepsilon = 0$.

(2) F is the average value of the x_i.

(3) Each of the control functions $f_i(P_{\tau_i})$ is a simple step function. It is one if $P(t - \tau_i) < \theta_i$ but is zero otherwise. θ_i is called the threshold for variable i.

(4) All the decay constants are equal.

With these assumptions, the equations of interest are

$$P = \frac{1}{N}\sum_{i} x_i,$$
$$\frac{dx_i}{dt} = \begin{cases} 1 - x_i & \text{if } P(t-\tau_i) < \theta_i, \\ -x_i & \text{if } P(t-\tau_i) \geqslant \theta_i. \end{cases} \qquad (6)$$

If at time t, $P(t-\tau_i) > \theta_i$, then we say that x_i is off at time t; otherwise we say it is on. These equations can be readily integrated. Either the dynamics will approach a steady state, in which case a subset of the x_i will be on and the others off, or the dynamics will fluctuate. In the case that the dynamics are fluctuating, P will continue to cross one or more of the thresholds. If a threshold i is crossed at time t, then at time $t + \tau_i$, x_i will be switched off if P was increasing when the threshold was crossed. If P was decreasing when the threshold was crossed, then x_i is switched on at a time τ_i afterwards. Therefore, each time a threshold is crossed, this will lead to a discontinuity in dP/dt after a delay. Say there is a discontinuity at time t_j. Then for $t_j < t < t_{j+1}$ we have

$$P(t) = \frac{1}{N}\sum_{i} x_i(t_j)e^{-(t-t_j)} + n_a[1 - e^{-(t-t_j)}], \qquad (7)$$

where n_a is the number of x_i that are on during the segment. The simple form of (7) allows one to explicitly compute the times for threshold crossing, and thus a precise integration of the dynamics is possible.

Analysis of these equations is still at an early stage. Since initial computations with this model (and others) containing two negative feedback loops did not display aperiodic dynamics, most attention to date has been given to the case in which there are three feedback loops. In this case there is not always a unique asymptotic behavior. This is demonstrated by considering the situation in which $\theta_1 = 0.05$, $\theta_2 = 0.3$, $\theta_3 = 0.4$, $\tau_1 = 1.3$, $\tau_2 = 1.8$, $\tau_3 = 1.5$. Any initial condition in which P is held in the interval $0.3 < P < 0.4$ for all times less than 0 will approach the stable steady state $P(t) = 0.33$ in the limit $t \to \infty$. Starting from other initial conditions, alternative behaviors can be found. This is demonstrated by starting at an initial condition in which all variables are set equal to the lowest threshold for all times less than 0. All variables are on at $t = 0$, and we assume that x_i will be turned off when $t = \tau_1 = 1.3$. Now as time proceeds the oscillation shown in Figure 4 is observed following a transient. This shows that depending on the initial condition, different asymptotic behaviors are possible.

Another interesting property is that (6) can show highly complex dynamic behaviors and bifurcations (i.e., changes in qualitative features of the dynamics) as parameters are varied. In Figure 5 we show the dynamics in (6)

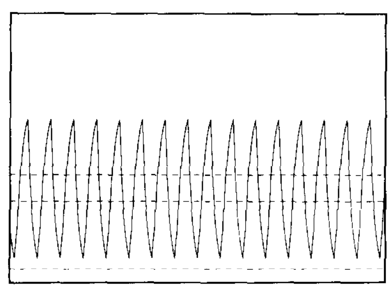

FIG. 4. Oscillation in (6) with $\theta_1 = 0.05$, $\theta_2 = 0.3$, $\theta_3 = 0.4$, $\tau_1 = 1.3$, $\tau_2 = 1.8$, $\tau_3 = 1.5$. In this and the following figure the initial condition is such that all three variables are set at the value of the lowest threshold (θ_1) for all times in the past. All three variables are on at $t = 0$. Following a time interval of τ_1, x_1 shuts off. Times for turning other elements on and off are found explicitly using the techniques described in the text. The plot shows the dynamics between $t = 450$ and $t = 525$. Computations were performed in double precision on an HP9816 computer.

with $\theta_1 = 0.4$, $\theta_2 = 0.5$, $\theta_3 = 0.6$, $\tau_1 = 0.56$, $\tau_3 = 0.87$, for several values of τ_2. In Figure 5(a) with $\tau_2 = 0.3$ there is a rapid low amplitude oscillation around 0.5. During this oscillation x_1 is always off and x_3 is always on, and x_2 switches on and off. As τ_2 increases, the amplitude of this oscillation increases until it crosses the thresholds for x_1 and x_3 [Fig. 5(b)]. As τ_2 continues to increase, there is a period-doubling bifurcation in which the period of the oscillation doubles, leading to alternate amplitudes on successive cycles [Figure 5(c)]. As τ_2 continues to increase, there is not a sequence of period doublings as found in other circumstances, but in this case a simple oscillation is again established [Figure 5(d)]. For $1.85 < \tau_2$ there are extremely complex sequences of bifurcations including oscillations of long periods [Figure 5(e), (h)] and periodic dynamics which do not converge even after integration for long times [Figure 5(f), (g)]. Thus, even after 3500 threshold crossings, it is still not possible to find periodic orbits for many values of τ_2. In addition, over some ranges of τ_2 there are extremely complex sequences of high period orbits. The bifurcations which are observed here do not appear to follow previously described bifurcation sequences, and the global structure of these bifurcations is not now understood. Although we do not have any proof that the dynamics in this example are chaotic, it is clear that there are very long cycles which are found over very narrow ranges of parameters. Further, for some parameter values, if there is not chaos, then there are either very long periods (we looked for cycles up to 500 threshold crossings), or very long transients, or both. A more detailed analysis of this system is clearly of interest.

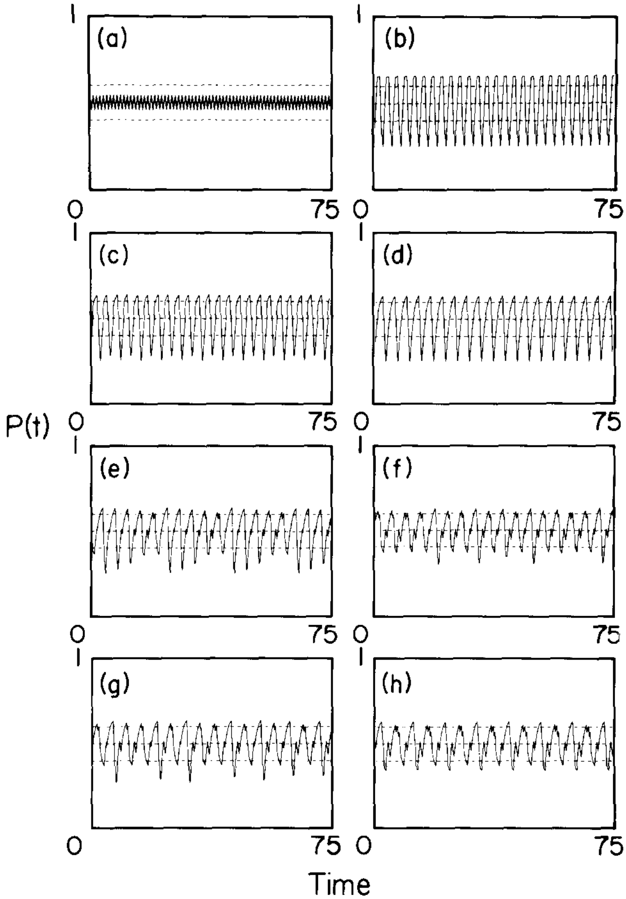

FIG. 5. Dynamics found in (6) with $\theta_1 = 0.4$, $\theta_2 = 0.5$, $\theta_3 = 0.6$, $\tau_1 = 0.56$, $\tau_3 = 0.87$, and varying τ_2. We designate the number of threshold crossings in a cycle by L. (a) $\tau_2 = 0.3$, $L = 2$; (b) $\tau_2 = 1.2$, $L = 6$; (c) $\tau_2 = 1.5$, $L = 12$; (d) $\tau_2 = 1.8$, $L = 6$; (e) $\tau_2 = 1.9$, $L = 40$; (f) $\tau_2 = 2.0$, aperiodic (g) $\tau_2 = 2.2$, aperiodic; (h) $\tau_2 = 2.3$, $L = 18$. For the parameters in (f) and (g) no periods with $L < 500$ were evident, even after 3500 threshold crossings. The plots show the dynamics between $t = 450$ and $t = 525$.

This example serves to illustrate that multiple negative feedback loops in a simple model system are capable of generating extremely complex dynamics.

IV. DELAYED VISUAL FEEDBACK AND MOTOR CONTROL

Experiments have been performed in which the effects of variable time delays were introduced in a tracking task. Here we give a brief summary of the results. A full description is in preparation and will appear elsewhere.

Briefly, the subject is seated in an upright position in a dark room with the left forearm supported in a trough and the index finger extended in a medical splint. The position of the finger is monitored using a linear variable displacement transducer (LVDT) weighing about 50 g (SE Labs), connected to the splint. The position of the extended finger is used to set the vertical position of a horizontal line displayed on an oscilloscope which is positioned approximately 120 cm from the subject. The screen of the oscilloscope is 10 cm wide, and a vertical displacement of the finger of 1 mm corresponds to about 16 mm vertical displacement on the screen. A baseline, representing zero displacement, is also displayed on the oscilloscope. Using the visual signal, the subject is instructed to maintain a constant finger position, relative to the stationary baseline. Inserted between the LVDT and the oscilloscope is an analogue delay line [a "bucket-brigade device" (BBD)] (EG&G Reticon—RD5108). The frequency of a tunable external clock sets the sampling time of the BBD, and in this fashion a variable delay is introduced. The magnitude of the delay is equal to $2048/f$, where f is the frequency of the tunable clock in Hz. To remove the artifact caused by the

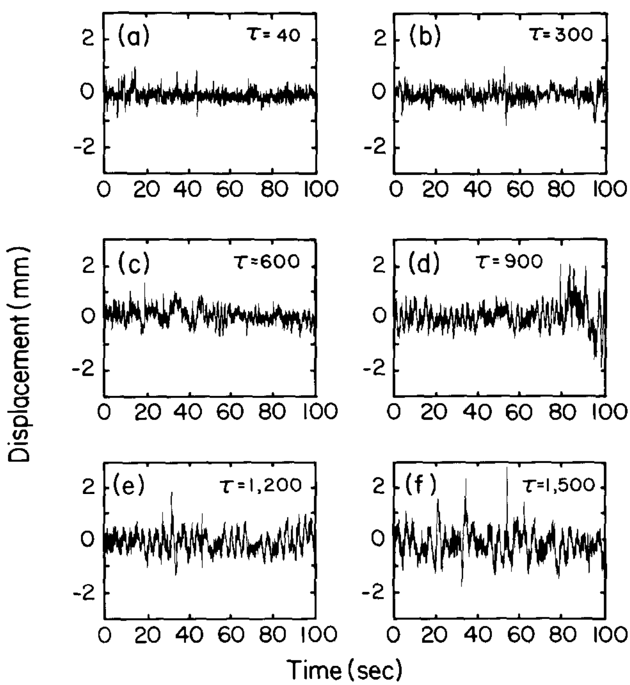

FIG. 6. Displacement of finger position as a function of time using the visual feedback discussed in the text. For each panel the delay (in msec) is shown.

clock, the output of the BBD is filtered using an 8 pole low pass Bessel filter (Frequency Devices 902LPF) with a corner frequency of 30 Hz. The signal from the LVDT is also sent directly to a 12 bit A/D converter (ISAAC Cyborg 91A) interfaced to an Apple IIe computer and sampled at a frequency of 100 Hz.

The subject is told that there is a delay present in the visual feedback, but does not know the magnitude of the delay. For each delay studied, the subject is first given 10–20 sec to stabilize the oscilloscope trace, and then 100 sec of data are recorded.

In Figure 6 we display a typical series of results recorded from a normal 23 year old women with time delays of 40, 300, 600, 900, 1200, and 1500 msec, presented in random order. As the time delay in the visual feedback path increases, an irregular low frequency oscillation arises with a period of approximately 2–4 times the delay. The amplitude of the oscillation increases as the delay in the visual feedback increases, and a regular oscillation is only observable intermittently. Although some subjects display oscillations which are a bit more regular than those here, in others the oscillations are less regular. In any case, the oscillations are never sustained in a clocklike fashion for the duration of any trial. Superimposed on the low frequency oscillations one can usually observe a low amplitude oscillation with a frequency of 8–12 Hz which is associated with physiological tremor.

V. DISCUSSION

Although early workers such as Bernard [3] and Cannon [4] stressed the importance of constancy (homeostasis) of the internal environment, more recently there has been much discussion of the apparent fluctuations continually occurring in physiological systems [1, 9–12, 18–20, 26, 33, 35, 36, 39]. Recently, Goldberger and colleagues have suggested that these fluctuations may even represent chaotic dynamics [9–11]. Supporting evidence for chaos in normal physiological function is still negligible. However, the presence of $1/f$ noise in the power spectra of the normal heartbeat [20] and the white blood cell count [10] has been taken as evidence for some underlying "chaotic" or "fractal" process. We suggest that the "mixed" feedback (Section II) and the multiple feedbacks with differing delays (Section III) offer a possible mechanism for generating complex dynamics that are experimentally observed in diverse physiological systems.

The results from the motor control experiments which are shown in Figure 6 can be thought of as a paradigmatic example of the sorts of fluctuations which are readily observable in other systems. Indeed, the time traces shown in Figure 6 bear at least qualitative similarities to time traces displaying blood pressure fluctuations [1, 5, 35], fluctuations in ventilation [12, 26], fluctuations in white blood cells [10], and fluctuations in blood glucose [33]. In all these situations there is fluctuation about a mean level, with some evidence for periodicity.

Such records provide a problem for further theoretical analysis and interpretation. One approach is to assume that oscillations at different frequencies correspond to instabilities in different feedback loops with different time delays [1, 12, 26, 35]. The problem with such an interpretation is that it assumes that the dynamics can be thought of in the context of low amplitude sinusoidal oscillations in linear systems. This is misleading for two reasons:

(1) Non-sinusoidal oscillations will give rise to higher harmonics in the power spectra. Thus, observation of higher harmonics of a fundamental frequency does not necessarily reflect multiple feedback loops.

(2) Physiological systems are nonlinear, and the dynamics in such systems may not simply be a superposition of oscillations from several different control loops.

An alternative viewpoint is that the complex fluctuations present in records such as Figure 6 may reflect deterministic chaos intrinsic in the physiological system. In the current case, there is both visual and proprioceptive input concerning the finger position, and the control of position is brought about by neural activity to the extensor and flexor muscles of the finger. The neural activity is not simply a reflection of primitive reflex loops, but may also be affected by cognitive processes including learning and anticipation [32]. Further study would be needed to determine if these multiple afferent and efferent pathways could lead to chaos.

An interesting observation which has emerged from recent theoretical and experimental studies is that increasing the time delays in feedback systems appears to increase the dimension of the dynamics [7, 23]. The theoretical and experimental studies reported here indicate that broad generalizations relating dimension to time delays may be difficult. The theoretical studies in Figure 5 show that as the time delay is increased, periodic and chaotic rhythms may alternate. Further, superficial visual examination of the records for finger displacement in Figure 6 (or in other subjects) do not reveal increasingly complicated dynamics as the delay is increased. Indeed, in some instances, the long delays appear to be associated with increasing regularity of the resulting dynamics.

Several lines of research are suggested by the hypothesis that complex dynamics in physiological systems may be associated with chaos. It is important to measure control functions and to incorporate such measured functions in appropriate mathematical models such as nonlinear delay differential equations. Experimental manipulation of the parameters of the control function could then be correlated with observed bifurcations of the dynamics. Another approach is to investigate the effects of blocking some feedback loops (for example, by using pharmacological means) but not others. Experiments of this sort have been carried out in studying the control of heart rate fluctuations [1, 35, 36]. Peaks in the power spectra changed in relative intensity following blockade of different feedback pathways. A related theoretical observation, which requires further study, is that using negative feedback only, we have not been able to find parameters which lead to complex aperiodic dynamics using less than three independent loops with three different time delays. This suggests that in experimental systems, it may be possible to convert complex fluctuating dynamics to a more regular, periodic behavior by removal of individual negative feedback loops.

In conclusion, it is well known that many physiological variables display complex fluctuations in time which are not easy to characterize. These fluctuations persist even in situations in which the environment is maintained as constant as possible. We suggest that such fluctuations may be due, at least partially, to chaotic dynamics which arise as a consequence of multiple feedback mechanisms in the nonlinear physiological control systems. Experimental studies of dynamics in feedback control systems in which the feedback is experimentally manipulated should provide rich data for theoretical interpretation.

We have benefited from financial support from the Natural Sciences Engineering and Research Council. We thank D. Lanteigne for assistance in constructing the delay line.

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