Oscillation and Chaos in Physiological Control Systems

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field orientations reflects the correspondence of early visual inputs between the two eyes for moderate amounts of relative rotation. Preliminary results from additional kittens suggest that even greater rotation (24°) may be more disruptive of binocularity; other investigators have reported similar results using large, surgically induced eye rotations (*9*) during early development.

Controversy has arisen concerning whether the orientation preferences of visual cortical neurons are innately determined (*10*) or whether such preferences directly reflect the orientations experienced during the visual sensitive period (*11*). Our results imply the existence of at least some plasticity in the development of cells' orientation preferences. It is possible, however, that innate mechanisms favor the systematic representation of all orientations in the visual cortex, that is, orientation hypercolumns (*12*), but that visual experience is crucial to the alignment of the two monocular orientation representations. Under this interpretation, the goggle experiences served to align these patterns of orientation representation so that the two monocular orientations differed systematically across the cortex.

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Oscillation and Chaos in Physiological Control Systems

Abstract. *First-order nonlinear differential-delay equations describing physiological control systems are studied. The equations display a broad diversity of dynamical behavior including limit cycle oscillations, with a variety of wave forms, and apparently aperiodic or "chaotic" solutions. These results are discussed in relation to dynamical respiratory and hematopoietic diseases.*

There are a number of chronic and acute diseases in which a primary symptom is the altered periodicity of some observable; for example, the irregular breathing patterns in adults with Cheyne-Stokes respiration (Fig. 1a) (*1*) and the fluctuations in peripheral white blood cell counts in chronic granulocytic leukemia (CGL) (Fig. 2a) (*2*). Previous theoretical studies of the control of respiration (*3*) and the control of hematopoiesis (*4*) have associated disease processes with oscillatory instabilities in mathematically complex models. Here we associate the onset of disease with bifurcations in the dynamics of first-order differential-delay equations which model physiological systems. We have two goals: (i) to bring to the attention of theoreticians two examples from medicine of complex and poorly understood dynamics; and (ii) to show that simple mathematical models of physiological systems predict the existence of regimes of periodic and aperiodic dynamics, similar to those encountered in human disease. This work is an extension of the work of Li and Yorke (*5*), May (*6*), May and Oster (*7*), and others on the periodic and aperiodic behavior encountered in discrete time population models (*8*).

Consider the ordinary differential equation

$$\frac{dx}{dt} = \lambda - \gamma x \qquad (1)$$

where x is a variable of interest, t is time, and λ and γ are positive constants giving the production and decay rates, respectively, of x. Then $x = \lambda/\gamma$ in the limit of $t \to \infty$. In many physiological systems, λ and γ are not constants but depend on the value of x at some earlier time (*3, 4*). Thus, the instantaneous rate of change of x at time t will depend on x_τ, the value of x at time $(t - \tau)$. We consider two complementary examples to illustrate the effects of allowing either λ or γ (but not both) to be nonlinear functions of x_τ. One is for the control of CO_2 elimination while the second embodies control of cell production.

In respiratory studies it has been established that the ventilation (V) is a sigmoidal function of arterial CO_2 concentration (x) (*9*). We assume that the CO_2 response curve is $V = V_m x^n/(\theta^n + x^n)$, where V_m is the maximum ventilation, and θ and n are parameters adjusted to fit experimental observations (*10*). We further assume that CO_2 is removed from the blood at a rate proportional to its concentration multiplied by the ventilation (*3*), and that the blood is a well-stirred fluid. Therefore we assume that the arterial CO_2 control system may be described by

$$\frac{dx}{dt} = \lambda - \frac{\alpha V_m x x_\tau^n}{\theta^n + x_\tau^n} \qquad (2)$$

where λ is the CO_2 production rate, τ is the time between oxygenation of blood in the lungs and stimulation of chemoreceptors in the brainstem, and α is a constant. The justification for Eq. 2 is heuristic: the equation reproduces certain qualitative features of normal and abnormal respiration.

As either the steepness of the CO_2 response curve or the delay time increases, the steady state becomes unstable and low-amplitude oscillations (Fig. 1b) or high-amplitude oscillations, in which there is a distinct apnea (Fig. 1c), are observed. Similar breathing patterns are observed clinically (*1, 3, 11*). Cheyne-Stokes respiration is often found in patients who have increased delay times between oxygenation of the blood in the lungs and stimulation of chemoreceptors in the brainstem, and also increased sensitivity to CO_2 (*11*). A phenomenon analogous to Cheyne-Stokes respiration in humans has been induced in dogs by inserting a circulatory delay between the heart and the brain (*12*). There are other pathological conditions in which highly irregular breathing patterns are observed; for example, apneic breathing in premature infants (*13*). We have not found a parameter range for Eq. 2 in which such complex patterns exist.

It is possible to analyze the stability of Eq. 2 in the neighborhood of the steady state (where $dx/dt = 0$). If at steady state x_0 is the CO_2 concentration, V_0 is the ventilation, and S_0 is the slope of the CO_2 response curve, then assuming parameters in the normal range (*14*), the instability condition can be computed (*15*) and is

$$S_0 > \frac{\pi V_0}{2\lambda\tau} \qquad (3)$$

For the parameter values cited we find instability for $S_0 > 7.44$ liter/min mm-Hg. At the instability the period of the oscillation is 4τ (*15*). These ana-

lytical results are similar to results found by numerical integration of more complex models of the respiratory system (*3*). Because of the crudeness of our mathematical model and experimental difficulties encountered in measuring respiratory control parameters, detailed numerical comparisons with experiments are difficult. However, our value for τ is comparable to that found in Cheyne-Stokes patients (*11*). Our critical value for S_0 lies above the generally accepted normal range of 2 to 6 liter/min · mm-Hg (*9*), and is comparable to sensitivities found in Cheyne-Stokes patients (*11*). The experimentally observed period of Cheyne-Stokes breathing is of the order two to three times the estimated τ (*11, 12*).

The dynamics of Eq. 2 illustrate familiar notions with respect to the destabilization of equilibrium points by time delays and the appearance of oscillatory behavior. In the next example a new phenomenon analogous to chaos in finite difference equations is found.

The regulation of hematopoiesis is the object of intense research (*16*). A pool of totipotent stem cells provides unipotent stem cells to the granulo-, erythro-, and thrombocytic lines. In each line unipotent stem cells supply cells to a number of nonproliferating differentiation compartments in the bone marrow before the release of a mature white blood cell, red blood cell, or platelet into the blood.

We consider a homogeneous population of mature circulating cells of density P. There is a significant delay τ between the initiation of cellular production in the bone marrow and the release of mature cells into the blood. Since the nature of the regulatory mechanisms in hematopoiesis is controversial, we consider two different possibilities

$$\frac{dP}{dt} = \frac{\beta_0 \theta^n}{\theta^n + P_\tau^n} - \gamma P \quad (4a)$$

$$\frac{dP}{dt} = \frac{\beta_0 \theta^n P_\tau}{\theta^n + P_\tau^n} - \gamma P \quad (4b)$$

where β_0, θ, n, and γ are constants. In Eq. 4a the production is a monotonic decreasing function of P_τ while in Eq. 4b the production is a single-humped function of P_τ (*17*).

Equations 4a and 4b display different qualitative dynamics. In both cases, as τ is increased an initially stable equilibrium becomes unstable and stable periodic solutions appear (Fig. 2b). In addition, in Eq. 4b as τ is further increased a sequence of bifurcations in the dynamics is found. These bifurcations appear to be strictly analogous to bifurcations found in first- and second-order finite difference equations (*5–8*). With these increases in τ in Eq. 4b we observed cycles with periods approximately 2, 4, 8, and 16 times the original one, as well as an apparently chaotic or aperiodic regime (Fig. 2c). In the aperiodic regime the choice of the initial conditions determines the evolution of the solutions, although for a given set of parameters the solutions always have the same bounds. In the midst of the aperiodic regime of

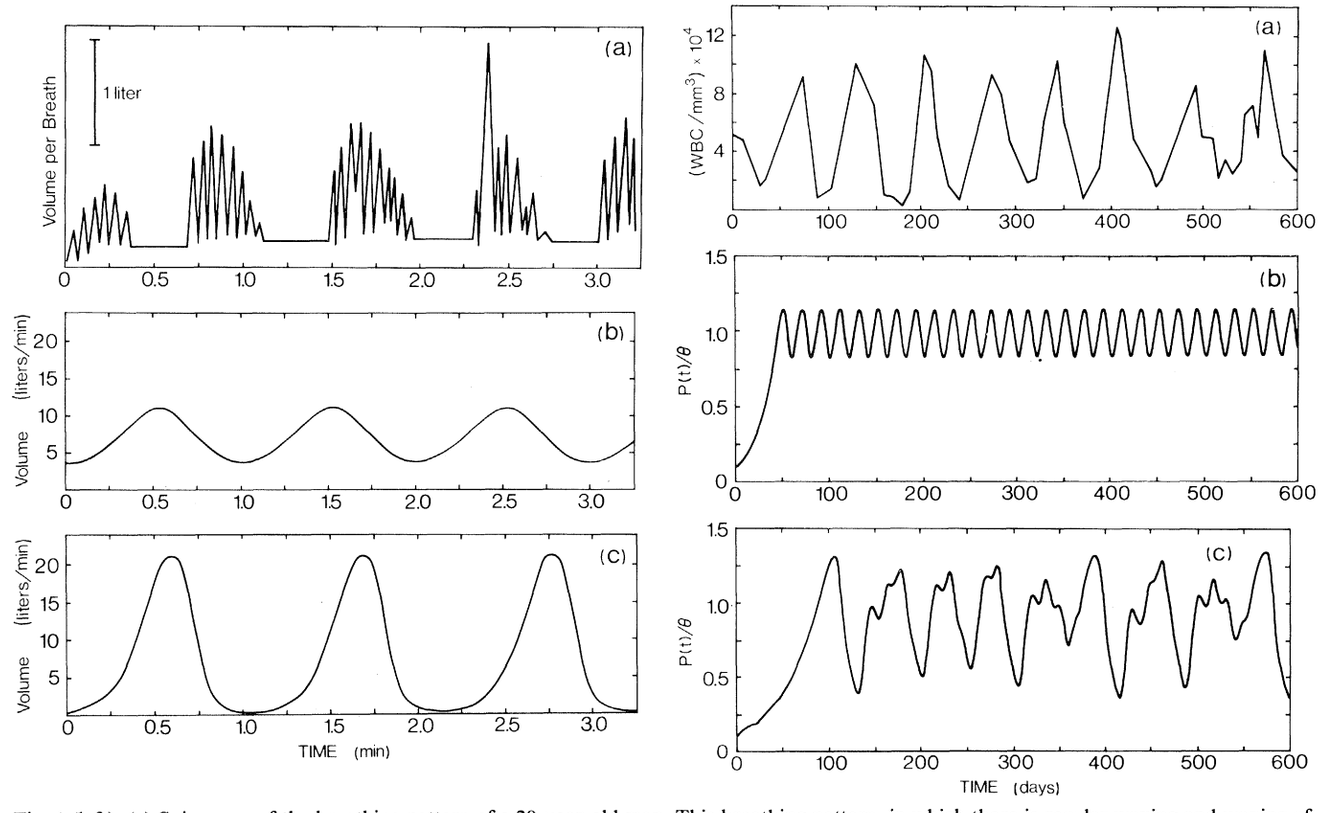

Fig. 1 (left). (a) Spirogram of the breathing pattern of a 29-year-old man. This breathing pattern, in which there is regular waxing and waning of inspiratory volume separated by distinct apneic spells, is termed Cheyne-Stokes respiration. The figure is redrawn from (*1*), which should be consulted for the original data and for other illustrations of respiratory oscillations. (b and c) Double precision numerical solutions of Eq. 2 using a predictor-corrector integration scheme, an integration step size of 0.01, an initial condition on x of 39 mmHg, and other parameters as described in (*14*). Decreases in integration step size, as well as computations using a Runge-Kutta scheme, convince us that the behaviors shown here and in Fig. 2, b and c, represent the properties of Eqs. 2 and 4b and are not due to numerical artifact. (b) A low-amplitude oscillation in ventilation $V(t)$ is found by integrating Eq. 2 with S_0 = 7.70 liter/min · mm-Hg. (c) A large-amplitude oscillation results from numerically integrating Eq. 2 with S_0 = 10.0 liter/min · mm-Hg. Fig. 2 (right). (a) Circulating white blood cell counts versus time in a 12-year-old girl with diagnosed chronic granulocytic leukemia. The period of the oscillation is about 72 days [redrawn from (*2*)]. (b) Numerical solutions to Eq. 4b obtained as detailed in Fig. 1, with an initial condition on P of 0.10, γ = 0.1 per day, β_0 = 0.2 per day, and n = 10. Parameter estimation for Eq. 4b is described in (*18*). With τ = 6 days, the equilibrium point $\bar{P} = \theta$ is unstable and the solution of Eq. 4b has a low-amplitude oscillation with a period of 20 days. (c) With the time delay increased to 20 days, the numerical solution of Eq. 4b now displays an aperiodic pattern.

Eq. 4b, stable but complex oscillations, which appear to be analogous to the stable oscillations of periods 3 and 6 found in finite difference equations, have also been observed over limited parameter ranges (*18*).

The solutions of Eqs. 4a and 4b are especially intriguing when considered in light of the clinical literature, where periodic fluctuations in circulating levels of platelets, red blood cells, and white blood cells have been observed. In particular, normal and pathological granulocyte production has been intensively studied (*16, 19, 20*). In normal healthy adults, circulating levels of granulocytes are either constant or show a mild oscillation with a period of 14 to 24 days (*16*). Cyclical neutropenia is a disease characterized by spontaneous oscillations in granulocyte numbers from normal to subnormal levels with a period of about 21 days (*19*). In some patients suffering from CGL circulating granulocyte numbers display large-amplitude oscillations with periodicities ranging from 30 to 70 days, depending on the patient (Fig. 2a) (*20*). In a number of CGL patients the cellular generation time is significantly increased, which would lead to an increase in τ (*21*). These long-term oscillations (Fig. 2a) occur in the absence of any clinical intervention. The variability in the maxima in Fig. 2a and the irregularities of the white blood cell counts over the last 100 days suggest, but not conclusively, that sequences of bifurcations may occur in patients with CGL.

We have shown how simple mathematical models of two physiological control systems can reproduce the qualitative features of normal and pathological function. We believe there is a large class of dynamical diseases, two of which have been considered here, characterized by the operation of a basically normal control system in a region of physiological parameters that produces pathological behavior (*22*). Our analysis suggests the following approaches: (i) demonstrate the onset of abnormal dynamics in animal models by gradual tuning of control parameters; (ii) gather sufficiently detailed experimental and clinical data to determine whether sequences of bifurcations similar to those found here actually occur in physiological systems; and (iii) attempt to devise novel therapies for disease by manipulating control parameters back into the normal range.

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14. With x_0, V_0, S_0, and V_m known, $n = x_0 S_0 V_m / V_0 (V_m - V_0)$, $\theta^n = x_0 (V_m - V_0)/V_0$, and $\alpha = \lambda / x_0 V_0$. For our numerical simulations we assumed $\lambda = 6$ mm-Hg per minute, $\tau = 0.15$ minute, $x_0 = 40$ mm-Hg, $V_0 = 7$ liter/min, and $V_m = 80$ liter/min, and varied S_0 [see (*9*)].
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18. A stability analysis of the steady states of Eqs. 4a and 4b indicates that destabilization occurs when n, β_0, and τ are increased or γ is decreased (*15*). In Eq. 4a destabilization is marked by the appearance of a stable oscillatory solution. Extensive numerical simulations of Eq. 4b indicate that the same sequence of bifurcations described in the text for increasing τ may be obtained by increasing n or β_0 or decreasing γ. For the numerical simulations we took $\gamma = 0.1$ per day, $\beta_0 = 0.2$ per day, $n = 10$, and $\theta = 1.6 \times 10^{10}$ cells per kilogram. This gives a total white blood cell density of 1.6×10^{10} cells per kilogram, a steady-state granulocyte turnover rate of 1.63×10^9 cells per kilogram per day, and a maximum granulocyte turnover rate of 3.66×10^9 cells per kilogram per day. See M. M. Wintrobe, *Clinical Hematology* (Lea & Febiger, Philadelphia, 1976).
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23. This research was supported by grant NRC-A-0091 from the National Research Council of Canada and a grant from the Cancer Research Society. We thank J. Milic-Emili, C. Polosa, and B. A. Cooper for helpful discussions.

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Fatty Acids and Their Prostaglandin Derivatives: Inhibitors of Proliferation in Aortic Smooth Muscle Cells

Abstract. *Prostaglandins are synthesized from eicosa-8,11,14-trienoic acid and eicosa-5,8,11,14-tetraenoic acid by smooth muscle cell cultures from guinea pig aorta. Production is inhibited by indomethacin. The precursor fatty acids and their prostaglandin derivatives inhibit proliferation of the cell cultures. The relative availability of fatty acids for prostaglandin biosynthesis may represent a control mechanism for cell proliferation.*

An important characteristic of the early or fatty streak lesion in the development of atherosclerosis is the presence of significant amounts of eicosa-8,11,14-trienoic acid ($C_{20:3}$) in addition to eicosa-5,8,11,14-tetraenoic acid ($C_{20:4}$) within the cholesteryl ester fraction (*1*). Cholesteryl esters of long-chain fatty acids are not surfactants (*2*) and these compounds form relatively inaccessible lipid droplets in the intimal lesions (*3*). $C_{20:3}$ is both an intermediate synthesized in the conversion of linoleic acid to $C_{20:4}$ and a precursor of prostaglandin E_1 (PGE_1) (*4*). The fatty acid $C_{20:4}$ is a precursor of prostaglandin E_2 (PGE_2) (*4*). Since only small amounts of $C_{20:3}$ are found in tissues (*1*), the amount of $C_{20:3}$ that is available for PGE_1 biosynthesis could be markedly diminished by