Oscillation and Chaos in Physiological Control Systems

Michael C. Mackey; Leon Glass


Stable URL: http://links.jstor.org/sici?sici=0036-8075%2819770715%293%2A197%3A4300%3C287%3AOACIPC%3E2.0.CO%3B2-0

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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 these 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.

PAUL G. SHINNMAN
CHARLES J. BRUCE
Department of Psychology,
University of North Carolina,
Chapel Hill 27514.

References and Notes
8. We represented each interocular difference as lying in the range +90° to 90°; this conversion has the advantage that the expected mean of a random distribution is zero but the disadvantage of accentuating values at the extremes (±90°). For this reason, two cells with disparities larger than 80° (one in each 16° condition) were discarded. Statistical conclusions reported are unaffected by the exclusion of these cells.
13. Supported by NIH grants ME-17276 to P.S.G., ME-4269 to the Experimental Psychology Program (HD-01) to the Biological Sciences Research Center, and ME-11107 to the Neurology Program, and by a grant from the Office of Research and Development to P.S.G.
15 January 1977

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 leukaemia (CGL) (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), and May and Oster (7), and others on the periodic and aperiodic behavior encountered in discrete time population models (8).

Consider the ordinary differential equation

$$\frac{dx}{dt} = -\lambda + \gamma x$$  

where $x$ is a variable of interest, $t$ is time, and $\lambda$ and $\gamma$ are positive constants giving the production and decay rates, respectively, of $x$. Then $x = x/f(x)$ in the limit of $t \to \infty$. In many physiological systems, $\lambda$ and $\gamma$ are not constants but depend on the value of $x$ at some earlier time ($t - \delta$). Thus, the instantaneous rate of change of $x$ at time $t$ will depend on $x$, the value of $x$ at time $t - \delta$, and we consider two complementary examples to illustrate the effects of allowing either $\lambda$ or $\gamma$ (but not both) to be nonlinear functions of $x$. One is for the control of CO2 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 CO2 concentration ($x$) (9). We assume that the CO2 response curve is $V = V_0 x^n/(\theta^2 + x^n)$, where $V_0$ is the maximum ventilation, and $\theta$ and $n$ are parameters adjusted to fit experimental observations (10). We further assume that CO2 is removed from the blood at a rate proportional to its concentration multiplied by the ventilation ($J$), and that the blood is a well-stirred fluid. Therefore we assume that the arterial CO2 control system may be described by

$$\frac{dx}{dt} = -\lambda + \frac{\alpha V_0 x^n}{\theta^2 + x^n}$$  

where $\lambda$ is the CO2 production rate, $\tau$ is the time between oxygenation of blood in the lungs and stimulation of chemoreceptors in the brainstem, and a 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 CO2 response curve or the delay time increases, the steady state becomes unstable and high-amplitude oscillations (Fig. 1b) or high-amplitude oscillations, in which there is a distinct phase (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 CO2 (11). A phenomenon analogous to Cheyne-Stokes respiration in humans has been induced in dogs by inserting a circular 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 visualize the stability of Eq. 2 in the neighborhood of the steady state (where $dx/dt = 0$). If at steady state $x_s$ is the CO2 concentration, $V_s$ is the ventilation, and $S_b$ is the slope of the CO2 response curve, then assuming parameters in the normal range (14), the instability condition can be computed (15) and is

$$S_b > \frac{\pi V_0}{2\lambda \tau}$$  

For the parameter values cited we find instability for $S_b > 7.44$ liter/minute mm-Hg. At the instability the period of the oscillation is 4$\tau$ (15). These ana-
lytical results are similar to results found by numerical integration of more complex models of the respiratory system (1). 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 \( r \) 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 liters/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 \( r \) (17, 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 granulocyte, erythrocyte, and thrombocytic lines. Each line unipotent stem cell contributes 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 \( \tau \) 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

\[
\frac{dP}{dt} = \frac{\beta_0 P_0 - \gamma P}{\theta^2 + P^2} \quad (4a)
\]

\[
\frac{dP}{dt} = \frac{\beta_0 P - \gamma P}{\theta^2 + P^2} \quad (4b)
\]

where \( \beta_0, \theta, n, \) and \( \gamma \) are constants. In Eq. 4a the production is a monotonic decreasing function of \( P \), while in Eq. 4b the production is a single-humped function of \( P \) (17).

Equations 4a and 4b display different qualitative dynamics. In both cases, as \( r \) is increased an initially stable equilibrium becomes unstable and stable periodic solutions appear (Fig. 2b). In addition, in Eq. 4b as \( r \) 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 \( r \) 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 behavior of the initial conditions determines the evolution of the solution, although for a given set of parameters the solutions always have the same bounds. In the midst of the aperiodic regime of

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Fig. 1 (left). (a) Spirogram of the breathing pattern of a 79-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 mm-Hg, and other parameters as described in (74). Decreases in integration step size, as well as computations using a Runge-Kutta scheme, convince us that the behavior shown here and in Fig. 2 a and c, which is found by integrating Eq. 2 with \( S_0 = 7.7 \) liter/min - mm-Hg, is not due to numerical artifact. (b) A low-amplitude oscillation in ventilation \( V(t) \) is found by integrating Eq. 2 with \( S_0 = 10.6 \) 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 12 days (redrawn from (1)). (b) Numerical solutions to Eq. 4b obtained as detailed in Fig. 1, with an initial condition on \( P \) of 0.1 liter/min per day, \( \beta_0 = 0.2 \) per day, and \( r = 10 \). Parameter estimation for Eq. 4b is described in (18).

With \( r = 6 \) days, the equilibrium point \( \bar{P} = 6 \) 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.
Fatty Acids and Their Prostaglandin Derivatives: Inhibitors of Proliferation in Aortic Smooth Muscle Cells

Abstract. Prostaglandins are synthesized from eicosan-8,11,14-trienoic acid and eicosan-5,8,11,14-tetraenoic acid by smooth muscle cells 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 eicosan-8,11,14-trienoic acid (C_20:3) in addition to eicosan-5,8,11,14-tetraenoic acid (C_20:4), within the cholesterol ester fraction (l). Cholesteryl esters of long-chain fatty acids are not surfactants (2) and these compounds form relatively inaccessible lipid droplets in the internal 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_2 (PGE_2) (4). The fatty acid C_20:4 is a precursor of prostaglandin E_2 (PGE_2) (4). Since only small amounts of C_20:4 are found in tissues (l), the amount of C_20:4 that is available for PGE_2 biosynthesis could be markedly diminished by