# Dynamical diseases and Bifurcations: Understanding Functional Disorders in Physiological Systems

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Under normal conditions physiological variables, such as breathing frequency, blood cell concentration, neuronal activity, or heart beat frequency, display either a stationary or fairly regular periodic activity. In the course of a disease the behavior of these variables may undergo a sequence of distinct and characteristic oscillatory patterns.

We show here that despite dramatic pathological changes in the behavior, the underlying physiological control system may still be intact and unaltered, with the exception of a single parameter being out of its physiological range. As this parameter changes, a cascade of transitions between various types of behavior may occur that correspond to different stages of the disease.

This view is supported by consideration of a model that treats the *transitions* as *bifurcations* in dynamical systems and by the discussion of exemplary physiological systems.

**„Dynamische Krankheiten" und „Verzweigungen": Zum Verständnis von Funktionsstörungen in physiologischen Systemen.**

Cheyne-Stokes-Atmung, periodische Hämatopoiese, penicillininduzierte epileptische Anfälle und Herzrhythmusstörungen sind Beispiele für Krankheiten, die als Folge der Fehlfunktion eines physiologischen Regelsystems auftreten. Symptomatisch dabei ist, daß funktionell entscheidende Größen (wie Atemfrequenz, Blutkörperchen-Anzahl, neuronale Aktivität und Herzschlagfrequenz), die sich normalerweise nahezu konstant verhalten oder periodisch (mit definierter Frequenz) variieren, unter pathologischen Bedingungen veränderte, für die jeweilige Erkrankung typische Verhaltensmuster zeigen. Je nach Art und Verlauf der Erkrankung treten dabei verschiedene komplexe periodische oder aperiodische Muster mit charakteristischen Übergängen auf.

Wir zeigen hier, daß trotz solcher dramatischer pathologischer Veränderungen im Verhalten funktioneller Variablen das zugrunde liegende physiologische Regelsystem intakt und unverändert sein kann, mit Ausnahme eines einzelnen Parameters, der seinen physiologischen Bereich verlassen hat.

Solche qualitativen Wechsel im Verhalten eines Systems in Abhängigkeit von einer Parameteränderung werden in der Physik als *Phasenübergänge* bezeichnet. (Bekanntestes Beispiel ist der Übergang des Systems Wasser vom flüssigen in den festen Zustand, wenn der Parameter Temperatur eine kritische Schwelle unterschreitet.) In allgemeinerem Rahmen treten diese Phänomene in der Theorie dynamischer Systeme als *Bifurkationen* (Verzweigungen) auf. Anhand eines Modells, das in enger Beziehung zu den erwähnten physiologischen Kontrollsystemen steht, erläutern wir hier einige Konzepte dieser Theorie und demonstrieren ihre Relevanz an mehreren konkreten Beispielen.

Zweierlei streben wir mit dieser Darstellung an:
I. Ein tieferes Verständnis des Zusammenhanges von Struktur und Verhalten eines Systems. (Beispielsweise beruht die Wirksamkeit vieler Medikamente darauf, daß sie zur Änderung eines Systemparameters führen, die ihrerseits einen Wandel des Systemverhaltens impliziert.)
II. Systemanalyse als Grundlage einer erfolgreichen Therapie.

## 1 Introduction

There are three main goals of this paper. The first is to introduce the concept of *periodic disease* by way of illustrative examples in the following section. This serves to reemphasize that physiological systems which normally display a constant value of some variable may, in the laboratory

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or pathological state, have an oscillatory variation in that variable. Alternately, systems with normally periodic variables may show altered oscillatory patterns under some circumstances. In both cases the oscillatory states may be periodic or aperiodic.

Secondly, we wish to introduce a number of *dynamic properties* of models that may be employed in understanding the behaviour of biological systems. Though models of biological phenomena may be of divergent types, their behaviour may be qualitatively similar. Thus we focus our attention on a particular model as a paradigm, and use the behaviour of this model to illustrate several useful concepts concerning system dynamics. This material forms the core of Section 3.

In Section 4 we introduce the concept of a *dynamical disease*, which draws a connection between the periodic diseases of Section 2 and the dynamic model properties presented in Section 3. This correspondence is explored in depth for three of the examples of Section 2.

## 2 Periodic Diseases

Reimann [28, 29] appears to have been the first to systematically catalog and study periodic diseases. In this section we briefly illustrate the concept with four examples.

### 2.1 Cheyne-Stokes Respiration

Under constant conditions respiratory ventilation (in litres/min) is normally either constant or oscillates slowly [31]. However, in Cheyne-Stokes breathing there is a regular and large variation in ventilatory amplitude, with periods of high ventilation separated by distinct apneic episodes [16] as shown in Figure 1a. This pattern is often seen in patients with brainstem lesions, patients in congestive heart failure, and grossly obese individuals. Cheyne-Stokes breathing patterns were induced in the laboratory dog by Guyton [12].

### 2.2 Periodic Hematopoiesis

In the absence of stress, infection, bleeding or altered erythropoietic demand, the densities (in cells/kg) of the various circulating cells in the blood remain within certain bounds over time [32]. There is a rare but well characterized hematological disorder, periodic hematopoiesis, in which this is not the case [7]. As shown in Figure 2, in this disorder there is a dramatic oscillation of the neutrophil numbers from normal to low values. This oscillation is also present in the monocytes, lymphocytes, platelets and reticulocytes [14]. In the majority of patients the period of this oscillation is between 17 and 28 days.

There is a well studied animal model for human periodic hematopoiesis, the grey collie [1, 3, 4]. Periodic hematopoiesis in the grey collie is identical to that in the human except that the period is between 9 and 12 days.

### 2.3 Penicillin Induced Epileptic Discharge

In an effort to understand the sequence of events leading to petit mal and grand mal epileptic seizures, neurophysiologists have often employed the penicillin animal model [27].

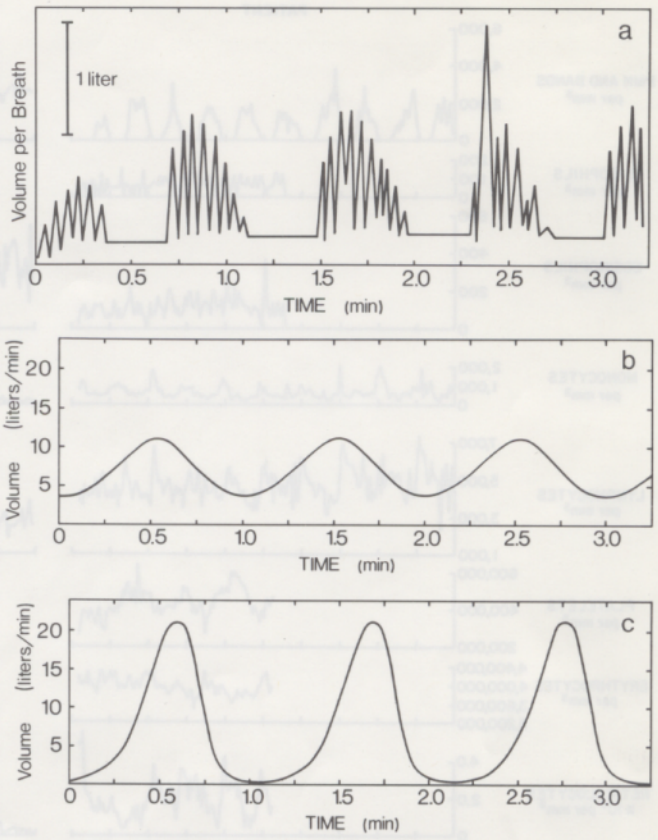


Fig. 1: Cheyne-Stokes breathing, 1a, Ventilation versus time in a 29 year old man with Cheyne-Stokes respiration (redrawn from Specht and Fruhman [31]), b and c, Human ventilation predicted from a simple model for arterial $CO_2$ control (see section 4.1), in b, $S^* = 7.7$ litre/min per mm Hg $CO_2$ increase, in c, $S^* = 10.0$ (reproduced from Mackey and Glass [22], by permission).

In this model, topical application of penicillin to various cortical areas results in a progressive approach of individual neuronal firing patterns to those seen during epileptic seizures. Figure 3 shows one example of the effects of penicillin on an individual cortical neuron in the cat, in which a low frequency firing pattern is gradually replaced by sustained high frequency firing.

### 2.4 Cardiac Arrhythmias

Though the heart normally beats in a regular and periodic fashion, it is capable of exhibiting a periodic beating as well as quite irregular behaviour [17] (see Figure 4). Such alterations in beating patterns are easily induced in laboratory animals, and an especially dramatic sequence is shown in Figure 5.

## 3 The Dynamic Behaviour of Models

This section illustrates a variety of dynamic behaviour that simple models for biological phenomena may display. We also introduce several concepts concerning system behaviour of use in describing and understanding biological phenomena generally, and periodic diseases in particular.

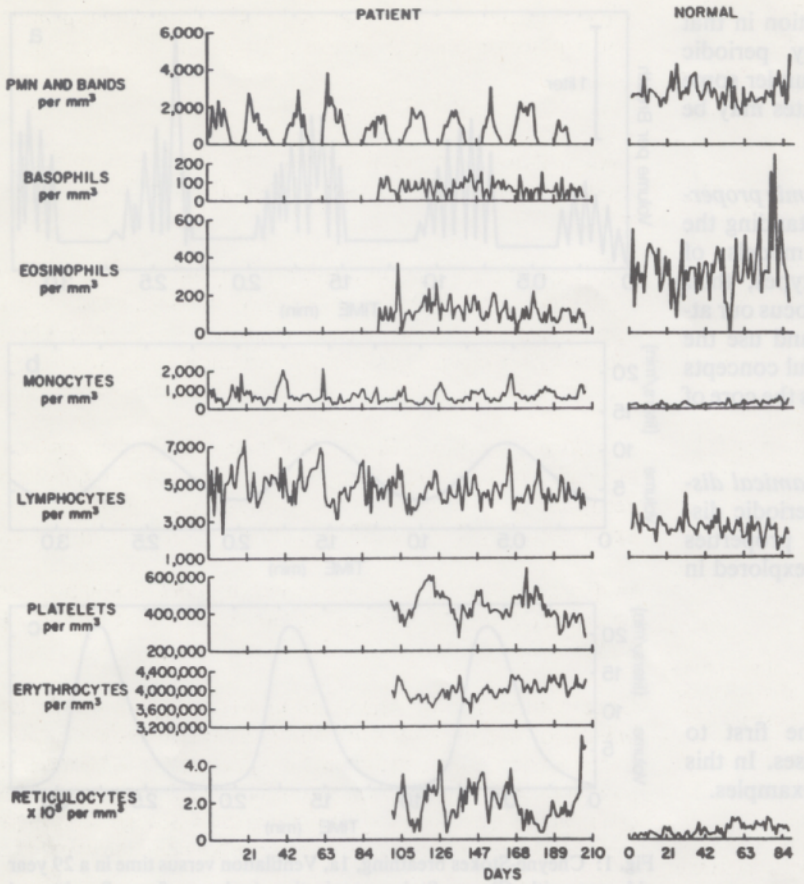


Fig. 2: A comparison between the circulating cell densities in a patient with periodic hematopoiesis (left) and in a normal individual (reproduced from Guerry et al. [7], by permission).

Biological processes are generally continuous in time and require continuous time models, often formulated as differential equations. Consider a simple system that regulates a single variable x(t), e.g. the concentration of some substance. The rate of change of x(t) with time is given by the difference between the production rate, p, and the destruction (or loss) rate, d, of x(t):

$$\frac{dx}{dt} = p - d \tag{1}$$

Generally p and/or d are functions of x due to feedback effects.

For example, the destruction rate is often linearly related to x, $d = ax(t)$, by a rate constant a; while the production rate depends on the value of x at some time $\tau$ in the past, $p = f(x[t-\tau])$. Such delays ($\tau$) in production may arise from a number of mechanisms as shown by the examples of Section 4. With these expressions for p and d, equation (1) can be written as

$$\frac{dx}{dt} = f(x[t-\tau]) - ax(t) \tag{2}$$

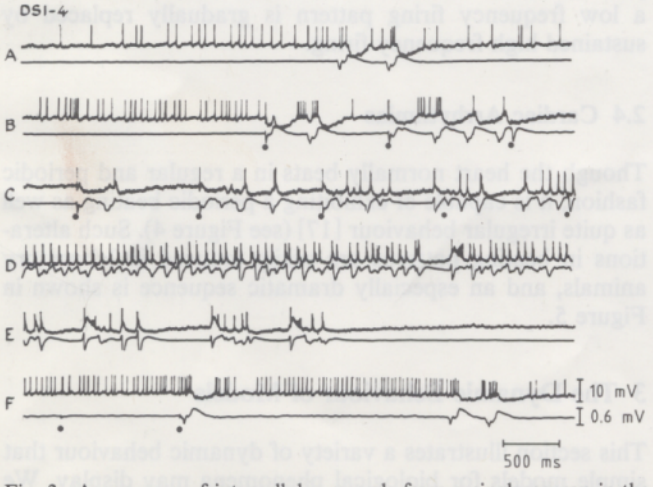


Fig. 3: A sequence of intracellular records from a single neuron in the pericruciate cortex of cat following the application of penicillin. The records, A–F, are not contiguous (reproduced from Prince [26], by permission).

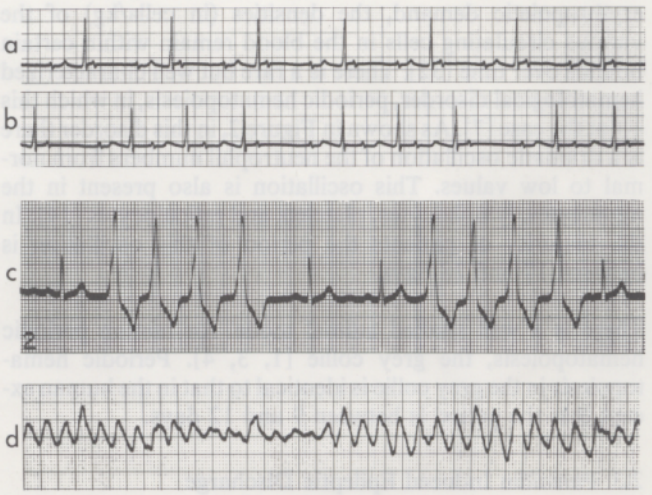


Fig. 4: Abnormal human electrocardiograms, a, 2:1 AV-block, b, the Wenckebach phenomenon, c, Ventricular tachycardia, d, Ventricular fibrillation (reproduced from Lindsay and Budkin [17], by permission).

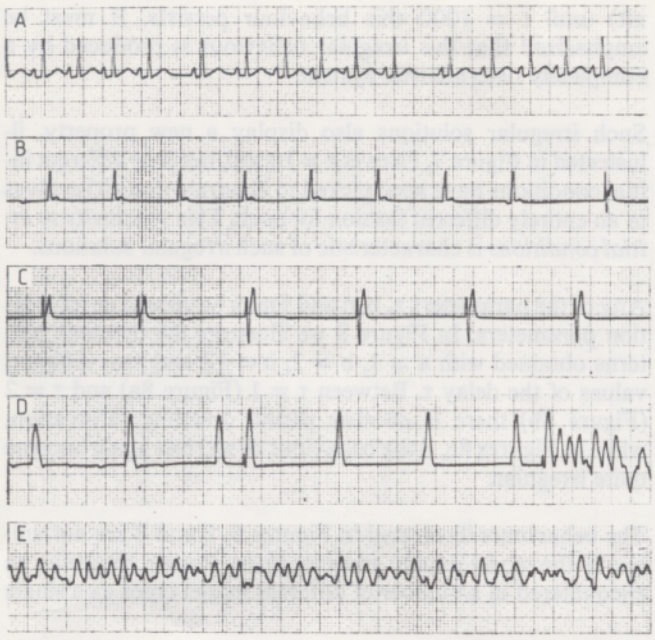


Fig. 5: A sequence of electrocardiograms taken from a dog at various times during the progressive hypoxia resulting from pentobarbital-induced respiratory arrest (from Guntheroth [9], reproduced from Rushmer [30], by permission).

The production rate f may take several different forms, depending on the nature of the feedback. The two extreme cases are those in which f is a strictly decreasing or increasing function of $x(t-\tau)$. The first case corresponds to pure *negative feedback*, while the second is characteristic of a *positive feedback* system. Generally, however, maximal production rates are attained at neither $x = 0$ (negative feedback) nor for very large values of x (positive feedback). Rather, maximal production occurs at some intermediate value of x. Therefore, the general situation is characterized by a production function f that is a „humped" function of $x(t-\tau)$, and thus the system displays mixed positive and negative feedback characteristics.

To illustrate the rich spectrum of behaviours that continuous time systems with mixed feedback characteristics may display, we have picked

$$f(x[t-\tau]) = b\,\frac{x(t-\tau)}{1+x^n(t-\tau)} \qquad (3)$$

where n and b are constants [6, 18–22].

By definition, a *steady state* is one in which there is no change with time. Thus, in a steady state is $(dx/dt) = 0$ and production (p) and loss (d) must exactly balance. By equating the destruction (ax) to the production function of equation (3), we get

$$ax = b\,\frac{x}{1+x^n} \qquad (4)$$

The terms $x(t-\tau)$ in the production function are replaced by x since, in a steady state, x(t) does not vary and thus $x(t) = x(t-\tau)$. Equation (4) gives the relation between the parameters a, b, and n and the steady state. In this case there are two values of x, call them $x_1^*$ and $x_2^*$, at which production and loss are equal. One is $x_1^* = 0$ and the other is

$$x_2^* = \sqrt[n]{\frac{b-a}{a}}$$

(Notice that $x_2^*$ has no biological meaning if $b < a$, so for the model to be realistic we require $b > a$. If $b = a$ then $x_1^* = x_2^* = 0$.)

For illustration, pick $b = 2$ and $a = 1$ so $x_2^* = 1$ irrespective of the value of n. When $0 < n \lesssim 5.04$, then the variable x(t) approaches the stable steady state $x_2^* = 1$, in either a damped or oscillatory fashion, for all initial conditions $x(t) > 0$ for all $t \leq 0$. We call $x_2^* = 1$ a *stable steady state.*

In contrast, we may pick an initial state of the system as close as we like to $x_1^* = 0$ (as long as the initial state is not exactly zero) and the solution x(t) will always deviate from $x_1^*$ and approach $x_2^* = 1$. Thus $x_1^*$ is called an *unstable steady state.*

In Figures 6 and 7 we show some numerical solutions to equation (2) with (3) for various values of n and $\tau$ with $a = 1$, and $b = 2$.

Once n exceeds 5.04, the solution x(t) has quite a different behaviour as shown for $n = 6$ in Figure 6a. Now for all initial states of the system, except $x(t) = x_1^*$ or $x(t) = x_2^*$ for $t \leq 0$, x(t) becomes periodic after an initial transitory phase. This behaviour occurs for all n in the range $5.04 \lesssim n \lesssim 7.2$ (though there are minor variations in the period), and we say that at n

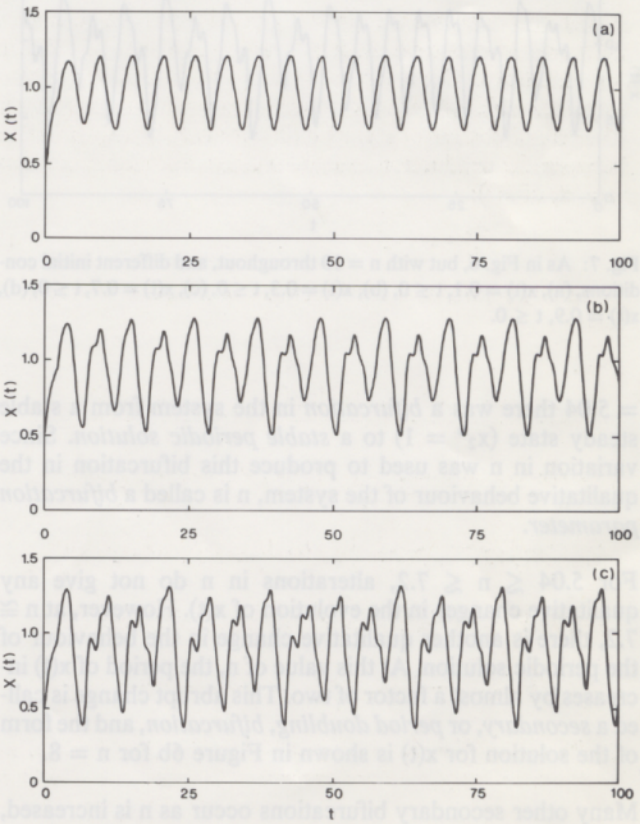


Fig. 6: The solutions x(t) versus of equations (3) and (4), left side, obtained with $a = 1$, $b = 2$, $\tau = 2$, using a predictor-corrector integration scheme and a step size of 0.05, for various values of n. In every case $x(t) = 0.5$, $t \leq 0$, (a), $n = 6.0$, (b), $n = 8.0$, (c), $n = 10.0$.

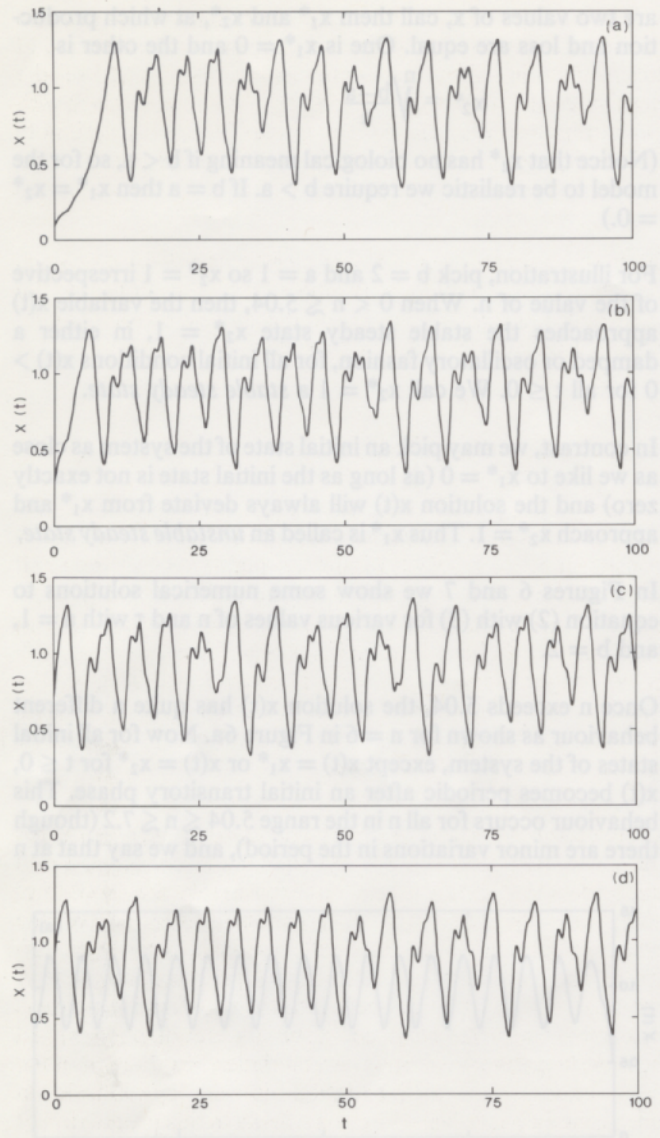


Fig. 7: As in Fig. 6, but with n = 10 throughout, and different initial conditions, (a), $x(t) = 0.1$, $t \leq 0$, (b), $x(t) = 0.3$, $t \leq 0$, (c), $x(t) = 0.7$, $t \leq 0$, (d), $x(t) = 0.9$, $t \leq 0$.

= 5.04 there was a *bifurcation* in the system from a stable steady state ($x_2^* = 1$) to a *stable periodic solution*. Since variation in n was used to produce this bifurcation in the qualitative behaviour of the system, n is called a *bifurcation parameter*.

For $5.04 \lesssim n \lesssim 7.2$, alterations in n do not give any qualitative changes in the evolution of x(t). However, at $n \cong 7.2$, there is another qualitative change in the behaviour of the periodic solution. At this value of n, the period of x(t) increases by almost a factor of two. This abrupt change is called a *secondary*, or *period doubling*, *bifurcation*, and the form of the solution for x(t) is shown in Figure 6b for n = 8.

Many other secondary bifurcations occur as n is increased, and an especially dramatic one is illustrated in Figure 6c for n = 10. Now over the period of time that x(t) is shown, there appears to be no periodic variation. Rather, x(t) has a somewhat irregular (chaotic) appearance and if one follows x(t) until t = 1000 this behaviour persists. It must be emphasized that this irregular behaviour is produced by a completely deterministic system.

Such irregular solutions also display a new property, illustrated in Figure 7. Here is n = 10 still, but four different initial conditions have been picked to illustrate that x(t) evolves in an entirely different fashion for each. This *sensitivity to initial conditions* is characteristic of such irregular solutions.

Any of the parameters a, b, n and τ may be viewed as bifurcation parameters. In Figure 8 we illustrate the dynamic patterns obtained with a = 1, b = 2, n = 12 and four different values of the delay τ. Between τ = 1 (Figure 8a) and τ = 2 (Figure 8b) there is another period doubling bifurcation, while in Figures 8c, d the behaviour of x(t) has again become quite irregular.

The behaviours illustrated in Figures 6, 7 and 8 are not unique to the model used to generate them. Rather, they may be encountered in a number of different model types as a single

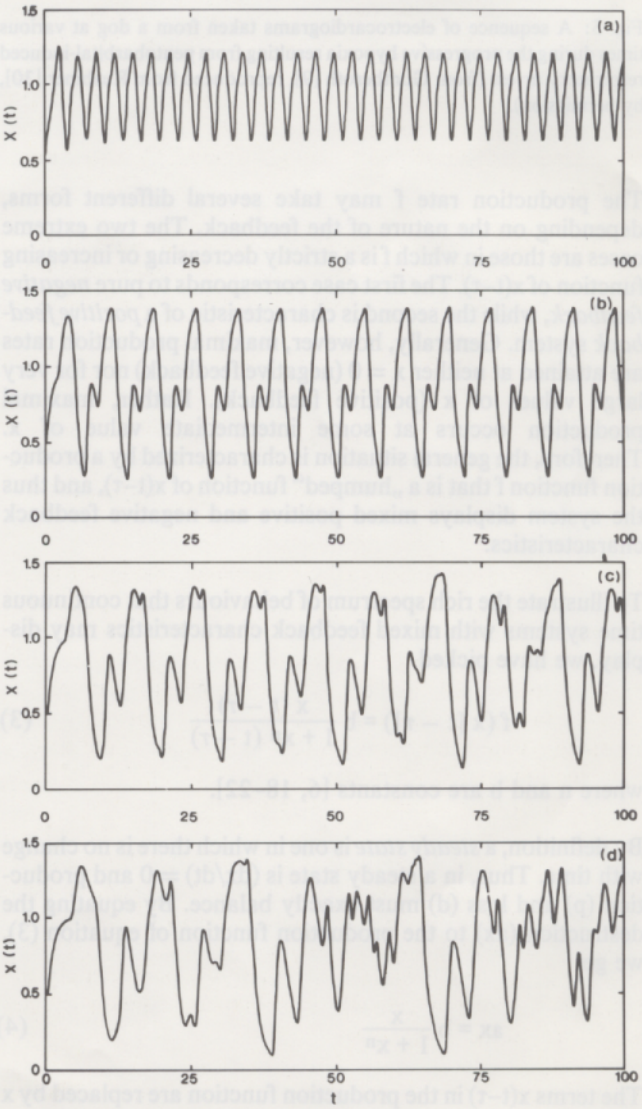


Fig. 8: As in Fig. 6, but with n = 12 and $x(t) = 0.5$, $t \leq 0$ throughout, and varying τ. The integration step size was equal to 0.025 τ in each case, (a), τ = 1, (b), τ = 2, (c), τ = 3, (d), τ = 4.

bifurcation parameter is varied [5, 10, 13, 25]. Though the specific behaviours may vary from model to model, the general concepts concerning stability, bifurcation, periodicity, and aperiodicity (chaos) have wide applicability.

## 4 Dynamical Diseases

Mackey and Glass [22] speculated that certain periodic diseases arose because of a bifurcation in the behaviour of a physiological control system. They called these *dynamical diseases*, and speculated that there was a clear link between diseases like those illustrated in Section 2, and system behaviours discussed in Section 3. Here, we consider this possible link for three of the examples of Section 2.

### 4.1 Cheyne-Stokes Breathing

In the simplest of models for the regulation of arterial $CO_2$, x(t) denotes the arterial $CO_2$ concentration, the $CO_2$ production rate (p) is constant under constant conditions, and the rate of $CO_2$ elimination is proportional to the product of x and the ventilation V. In this problem [22] it is important to note that the ventilation V is an increasing, non-linear function of arterial $CO_2$ levels some time $\tau$ in the past. This delay $\tau$ is due to the blood transit time from the brainstem (where ventilation is determined by the chemoreceptors and by the "respiratory oscillator") to the lungs (where $CO_2$ elimination takes place).

It is straightforward to show that the steady state arterial $CO_2$ concentration, $x^*$, will become unstable and be replaced by a stable periodic solution period of about (4 $\tau$) whenever

$$S^* > \frac{\pi V^*}{2p\tau} \tag{5}$$

In equation (5) $V^* = V(x^*)$ is the steady state ventilation, and $S^*$ is the slope of the ventilatory response curve at $x^*$. (For derivation of model equations and stability analysis see appendix, p. 163.)

The qualitative predictions of (5) are most interesting when compared with clinical findings in Cheyne-Stokes breathing. Equation (5) indicates there are four ways in which there may be a bifurcation from a stable steady state $x^*$ to a stable periodic solution: 1) An elevation in circulatory time $\tau$ or $CO_2$ production rate, p; 2) An increase in the sensitivity $S^*$ of the steady state ventilation, and 3) A decrease in the steady state ventilation $V^*$. All of the parameters ($\tau$, p, $S^*$, $V^*$) can be viewed as bifurcation parameters.

As pointed out in Section 2., Cheyne-Stokes breathing is observed in congestive heart failure (elevated $\tau$) and obesity (increased p). Furthermore, in patients with brain-stem lesions who display Cheyne-Stokes respiration, an $S^*$ elevated above normal has been found. Finally, experimentally increasing $\tau$ above a critical level induces Cheyne-Stokes respiration in the dog [12].

All of the parameters in this model can be estimated, and at their normal values the steady state $x^*$ is stable. Increasing $S^*$ beyond its critical value of 7.44 L/min per mm Hg $CO_2$ increase and holding all other parameters at their normal values gives model-predicted ventilatory responses as shown in Figure 1b, c. Note that for both values of $S^*$ the period of the oscillation is about one minute. Since $\tau$ is about 15 sec the predicted and computed periods are in good agreement with each other and with the clinical data of Figure 1a. Also note that in Figure 1c a distinct apneic period occurs once in each cycle.

Thus there seems to be a strong one-to-one correspondence between the bifurcation behaviour of a simple model for the control of arterial $CO_2$ levels and the occurrence of Cheyne-Stokes breathing in a diversity of disease states.

### 4.2 Periodic Hematopoiesis

A survey [18] of the available clinical and laboratory findings in periodic hematopoiesis suggests that they are most consistent with a defect within the pluripotential stem cell compartment, which gives rise to the differentiated precursors of the formed elements of the blood. This defect must be such that the differentiated cellular efflux from the stem cells is no longer stable as in normal individuals. Rather, the steady state efflux must be unstable, and replaced by a stable periodic oscillatory efflux with a period of 17–28 days in humans, or 9–11 days in dogs.

On the basis of the above survey and hypothesis, a model for the pluripotential stem cell dynamics was formulated and analyzed [18]. In this model, x(t) represents the number of stem cells available for differentiation into all of the hematopoietic cell lines. Loss of these cells is by either differentiation, or reentry of cells into the proliferative phase of the cell cycle. This flux of cells into the proliferative phase is determined by total stem cell numbers and displays mixed positive/negative feedback characteristics. Production of the cells capable of differentiation is *via* cytokinesis in proliferating phase cells. There is a delay in this production of cells due to the time required for cells triggered into the proliferative phase to complete DNA synthesis and mitosis.

All of the parameters for this stem cell model can be estimated for both humans and dogs, and in both cases the normal steady state efflux is stable. Furthermore, for both the dog and the human it is impossible to produce the characteristics of periodic hematopoiesis by varying only a single parameter in the model [18]. However, if the stem cell model parameters are held at their normal values and it is assumed that there is an abnormal death of cells during the proliferative phase of the cell cycle, then the consequences are remarkable. If $M^*$ (cells/kg per day) is the cellular efflux into the differentiated cell lines and $\gamma$ (per day) is the rate of postulated cell death from the proliferative phase, then increasing $\gamma$ leads to the following sequence of events. An increase in $\gamma$ from its normal value of zero leads to a progressive decrease in $M^*$, and $M^*$ remains stable. Eventually a critical $\gamma$, say $\gamma_1$, is reached at which $M^*$ is no longer stable and a stable periodic solution, which oscillates about this depressed level of $M^*$, appears. This stable periodic cellular efflux persists until a second value of $\gamma$, say $\gamma_2$, is reached and then $M^*$ becomes stable again. Further increase in $\gamma$ leads to progressive decreases in $M^*$ to zero.

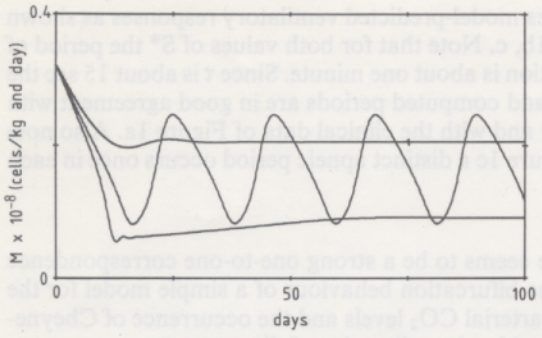


Fig. 9: Stem cell efflux into all differentiated cell lines as predicted by model for stem cell regulation in humans. The top curve which reaches a steady state corresponds to $\gamma = 0.20$ per day, the middle oscillatory flux is for $\gamma = 0.25$ per day, and the bottom curve is for $\gamma = 0.29$ per day (reproduced from Mackey [20], by permission).

Using parameters for the model derived from human data the *predicted period* of this oscillatory efflux into the differentiated cell lines is between 16 and 28 days, while for data from dogs it is between 9 and 14 days. In Figure 9, M* is shown as a function of time, computed from the stem cell model assuming normal human parameters, for three different values of $\gamma$.

Thus, the hypothesis of abnormal cellular death from the proliferating phase stem cells offers a sufficient explanation for the dynamics of periodic hematopoiesis in humans and the grey collie. The hypothesis further predicts that it should be possible to induce periodic hematopoiesis by using agents which kill proliferating phase stem cells. This has been amply demonstrated in humans [15], dogs [23, 24], and mice [11].

### 4.3 Penicillin Induced Alterations in Neuronal Activity

As in other cortical structures, application of penicillin to the hippocampus results in a remarkable sequence of events as revealed by intracellular recording from CA3 pyramidal cells. Normally the CA3 cells display bursting behaviour in which groups of action potentials are separated by silent periods. Following penicillin, this pattern becomes ever more irregular and complex, finally culminating in high sustained firing of the CA3 cells.

The CA3 pyramidal cells of the hippocampus comprise the output cell population of a recurrent inhibitory neuronal network whose excitatory input comes from the mossy fibres. The inhibitory interneurons are the basket cells, and the inhibitory transmitter is gamma-aminobutyric acid (GABA). Thus, excitation within the mossy fibers excites the CA3 cells, which in turn excite the interneurons *via* axon collaterals. This activity in the inhibitory interneurons feeds back to modulate the CA3 firing frequency.

The complicated sequence of activity within this recurrent inhibitory neural network in the presence of penicillin can be understood by analyzing a simple model [21]. In this model x(t) represents the frequency of action potential generation in the CA3 cells. The "production" of x is entirely due to excitatory activity in the presynaptic mossy fibres. The "destruction" of x is mediated by two processes: 1) The natural decay of activity because of the electrotonic properties of the cell membrane; and 2) A mixed positive/negative feedback due to the recurrent inhibition. It is important to realize that this feedback occurs with an appreciable delay due to the conduction times in the CA3 and basket cells.

This neural network has been intensively studied by neurophysiologists, and there exist data allowing one to estimate most of the parameters in the model except for the density of GABA receptors (T) on the CA3 cells. Since penicillin has a much higher binding affinity than GABA for these receptors, and thus penicillin will act to decrease (the "free") T, it is natural to identify T as a bifurcation parameter in this model (see 3).

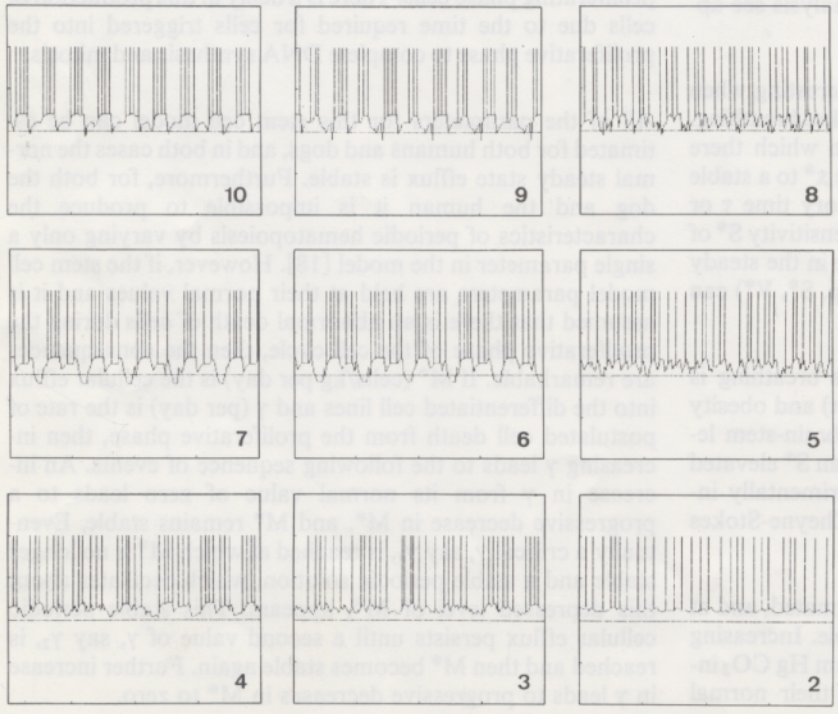


Fig. 10: Simulated effects of penicillin in a recurrent inhibitory neuronal network. Each panel shows 2 seconds of simulated membrane potential, with superimposed action potentials, as the density (T) of "free" receptors (see text) is reduced in steps of 1, from 10 (upper left) to 2 (lower right), by penicillin. In each panel the ordinate (membrane potential) ranges from −10 to +15 mV relative to the resting potential (solid horizontal line).

Assuming an initial density of T = 10 receptors per cell, the model predicted behaviour of the CA3 cells is shown in Figure 10 (upper left panel). Successive decreases of T, corresponding to reducing the number of "free" receptors from the population by penicillin, results in the sequence of events shown in the remainder of Figure 10. As T decreases, the initially periodic firing of the CA3 cells gives way to progressively more complicated asynchronous firing patterns. At very low receptor densities the model predicts that the CA3 cells will fire in a uniform and sustained fashion.

Thus, the sequence of events following the topical application of penicillin in the hippocampus is apparently explicable in terms of the altered recurrent inhibitory dynamics brought about by penicillin binding to the postsynaptic GABA receptor. It is important to note, however, that this model can only explain the transition from periodic bursting to sustained firing of the CA3 cells. It cannot offer any insight into the abrupt cessation of activity in these cells, which is presumably due to an unphysiological intra- and extracellular ionic accumulation, caused by the sustained activity.

In addition to the relevance of this model to understanding penicillin induced behaviour, interesting notions are raised *vis à vis* variability in neuronal activity. This variability is commonly attributed to stochastic membrane threshold variations or other stochastic sources. Yet, in this completely *deterministic* model for recurrent inhibition there are parameter values which produce highly irregular (stochastic-like) neuronal firing (see Figure 10). These observations raise the possibility that much of the variation observed in nervous electrical activity is not due to random stochastic events, but is a reflection of complicated neuronal feedback effects.

## 5 Discussion

Other periodic diseases have been analyzed within the framework of "dynamical" diseases. For both periodic chronic myelogenous leukemia [20] and periodic autoimmune hemolytic anemia [19], a plausible and sufficient hypothesis is that the disorder is due to a bifurcation in system dynamics. A similar hypothesis has been made for the origin of periodic schizophrenia [2].

In an attempt to understand the interaction of periodic inputs to a cardiac oscillator, Guevara and Glass [8] have analyzed the behaviour of a phenomenological model for the activity of the atrioventricular (AV) node of the heart. The rhythmic input of the sinoatrial (SA) node to the AV node is represented as a periodic input to the model. They have demonstrated that a variety of phase locking patterns in the AV node model may be obtained by variation of the amplitude and phase of the analog to the SA node input. These include a number of clinically observed transitions and patterns, including states where phase locking is unattainable. In this situation an aperiodic, or "chaotic", pattern reminiscent of ventricular fibrillation ensues.

We feel that the concept of "bifurcation" in physiological systems is important for understanding the origin and onset of a variety of phenomena observed in clinical and laboratory settings. It seems to be useful that all involved in the study of biological organisms recognize that even relatively "simple" systems may have very complicated behaviour. Complicated and unexpected behaviours should not necessarily be assumed to result from improper experimental or clinical procedures. They may reflect a heretofore unsuspected aspect of system behaviour under altered conditions, and thus give deeper insight into normal and abnormal regulation of physiological processes.

## 6 Appendix: Derivation of Model Equations for Respiratory Control and Stability Analysis

In this appendix the way how to derive the formulations (for the model described in 4.1) on the basis of experimental observations and theoretical concepts is outlined. Moreover a stability analysis of the steady states is given. The mathematical problems associated with the existence of periodic and aperiodic solutions are beyond the scope of this paper, and the reader is referred to the literature [34, 35].

Here x(t) denotes the arterial $CO_2$ concentration in the lungs at time t. Experimental studies [36] indicate that ventilation V is an increasing function of $CO_2$ concentration, which may be approximately described by

$$V(x) = V_{max}\, x^n/(\Theta^n + x^n), \tag{6}$$

where $V_{max}$ is the maximal ventilation and n and $\Theta$ are parameters chosen to agree with experimental data (see below). However, since the blood is oxygenated in the lungs, but the receptors, which are sensitive to the $CO_2$ concentration, are present in the brainstem, there is a time lag $\tau \cong 0.2$ min in the dependence of V on x:

$$V(t) = V(x(t-\tau)) = V_{max}\, x^n(t-\tau)/(\Theta^n + x^n(t-\tau)). \tag{7}$$

The production rate (p) of $CO_2$ is approximately constant under constant conditions, p = constans. The $CO_2$ elimination (d) is assumed to be proportional both to the $CO_2$ concentration x and the ventilation V:

$$d = \alpha \cdot x \cdot V \tag{8}$$

with a proportionality factor $\alpha$. The complete model now follows from the equations (1), (7), and (8):

$$\frac{dx}{dt}(t) = p - \frac{\alpha \cdot V_{max} \cdot x^n(t-\tau) \cdot x(t)}{\Theta^n + x^n(t-\tau)}. \tag{9}$$

Equations of type (9) and (2) are known in the mathematical literature as *differential-difference equations* [33]. Equation (9) admits a steady state solution $x^*$ characterized by $dx/dt = 0$,

$$p = \alpha \cdot V^* \cdot x^*, \tag{10}$$

where

$$V^* = V_{max}\,(x^*)^n/(\Theta^n + (x^*)^n) \tag{11}$$

is the steady state ventilation. For normal humans the literature [36] gives values $x^* = 40$ mm Hg, $V^* = 7$ liter/min, $p = 6$ mm Hg/min, $V_{max} = 80$ liter/min. The stability of the steady state $x^*$ is analyzed according to conventional methods [33] as following. Equation (9) has the form

$$dx(t)/dt = F(x(t), x(t-\tau)), \tag{12}$$

where F (x,y) is a function of two variables. Associated with (12) is the *characteristic equation*

$$\lambda - A - B\, e^{-\lambda\tau} = 0, \tag{13}$$

where $A = \frac{\partial F}{\partial x}(x^*, x^*)$, $B = \frac{\partial F}{\partial y}(x^*, x^*)$

are the partial derivatives at the steady state. The complex numbers $\lambda$ satisfying Equation (13) are called the eigenvalues of $x^*$. The general stability criterion says that $x^*$ is asymptotically stable if all eigenvalues of $x^*$ have negative real part, and $x^*$ is unstable if there is at least one eigenvalue with positive real part. Analysis [33] shows that all eigenvalues have negative real parts if and only if

$$\lambda^2 (B^2 - A^2) < \gamma^2, \tag{14}$$

where $\gamma$ is uniquely determined by the conditions

$$\pi/2 < \gamma < \pi \quad \text{and} \quad \gamma \cdot \cot \gamma = \tau \cdot A.$$

Using the abbreviation $S^* = dV(x^*)/dx$ we obtain

$$A = -p/x^*, \; B = -pS^*/V^*, \tag{15}$$

hence $x^*$ is stable if

$$\tau^2\lambda^2 (S^{*2}/V^{*2} - 1/x^{*2}) < \gamma^2. \tag{16}$$

With the parameters given above it turns out that $\tau\lambda/x^* \cong 0.0375$ and $\gamma \cong \pi/2$. Therefore, neglecting the small term, (16) is approximated by

$$\tau \cdot \lambda \cdot S^*/V^* < \pi/2. \tag{17}$$

The corresponding condition for instability is just the inequality (5). Figures 1b, c show numerical solutions to Equation (9) for two different values of $S^*$ in a region where $x^*$ is unstable. The parameters $\alpha$, n, and $\Theta$ may be computed from the given normal physiological parameters by the relations (10) and

$$n = \frac{x^* \cdot V_{max} \cdot S^*}{V^* (V_{max} - V^*)}, \tag{18}$$

$$\Theta = x^* \frac{(V_{max} - V^*)^{1/n}}{V^*}. \tag{19}$$

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## 7 References


[1] Cooper, G. W., in A. S. Gordon (ed.): *Regulation of Hematopoiesis*. Appleton-Century-Crofts, New York 1970, p. 1611.

[2] Cronin, J., *Bull. Math. Biol. 39*, 187 (1977).

[3] Dale, D. C., D. W. Alling, S. M. Wolff, J. *Clin. Invest. 51*, 2197 (1972).

[4] Dale, D. C., S. B. Ward, H. R. Kimball, S. M. Wolff, *J. Clin. Invest. 51*, 2190 (1972).

[5] Eckmann, J.-P., *Rev. Mod. Phys. 53*, 643 (1981).

[6] Glass, L., M. C. Mackey, *Ann. N.Y. Acad. Sci. 316*, 214 (1979).

[7] Guerry, D., D. C. Dale, M. Omine, S. Perry, S. M. Wolff, *J. Clin. Invest. 52*, 3220 (1973).

[8] Guevara, M. R., L. Glass, *Phase locking, period doubling bifurcations, and chaos in a mathematical model of a periodically driven biological oscillator: A theory for the entrainment of biological oscillators and the generation of cardiac dysrhythmias. J. Math. Biol.* (1982), in press.

[9] Guntheroth, W. G., *Pediatric electrocardiography*, W. B. Saunders Co., Philadelphia 1965.

[10] Gurel, O., O. E. Rössler, *Ann. N.Y. Acad. Sci. 316*, 1 (1979).

[11] Gurney, C. W., E. L. Simmons, E. O. Gaston, *Exp. Hematol. 9*, 118 (1981).

[12] Guyton, A. C., J. W. Crowell, J. W. Moore, *Am. J. Physiol. 187*, 395 (1956).

[13] Helleman, R. H. G., *Ann. N.Y. Acad. Sci. 357*, 1 (1980).

[14] Hoffman, H. J., D. Guerry, D. C. Dale, *J. Interdiscipl. Cycle Res. 5*, 1 (1974).

[15] Kennedy, B. J., *Blood 35*, 751 (1970).

[16] Lambertsen, C. J., in V. Mountcastle (ed.): *Handbook of Medical Physiology*. 13th edit., The C.V. Mosby Co., St. Louis 1974, p. 1522.

[17] Lindsay, A. E., A. Budkin, *The cardiac arrhythmias*. 2nd edit., Yearb. Med. Publ., Chicago 1975.

[18] Mackey, M. C., *Blood 51*, 941 (1978).

[19] Mackey, M. C., *Bull. Math. Biol. 41*, 829 (1979).

[20] Mackey, M. C., in J. Vassilova-Popova, E. V. Jensen (eds.): *Biophysical and Biochemical Information Transfer in Recognition*. Plenum Publ. Corp., New York 1979, p. 373.

[21] Mackey, M. C., *The dynamics of a recurrent inhibitory neural network*. 1982 (in preparation).

[22] Mackey, M. C., L. Glass, *Science 197*, 287 (1977).

[23] Morley, A., F. Stohlman, *Blood 35*, 312 (1970).

[24] Morley, A., E. A. King-Smith, F. Stohlman Jr., in F. Stohlman Jr. (ed.): *Hemopoietic Cellular Proliferation*. Grune and Stratton, New York 1970, p. 3.

[25] Ott, E., *Rev. Mod. Phys. 53*, 655 (1981).

[26] Prince, D. A., in H. H. Jasper, A. A. Ward, A. Pope (eds.): *Basic Mechanisms of the Epilepsies*. Little, Brown & Comp., Boston 1969, p. 320.

[27] Prince, D. A., *Ann. Rev. Neurosci. 1*, 395 (1978).

[28] Reimann, H. A., *Periodic diseases*. F. A. Davis, Philadelphia 1963.

[29] Reimann, H. A., *Clinical insight on the nature of periodic diseases, Mod. Med.*, April 40 (1975).

[30] Rushmer, R. F. *Cardiovascular dynamics*. 2nd edit., W. B. Saunders Co., Philadelphia 1970.

[31] Specht, H., G. Fruhman, *Bull. Physiol. Pathol. Respir. 8*, 1075 (1972).

[32] Wintrobe, M. M., *Clinical hematology*. Lea & Febiger, Philadelphia 1976.

[33] Bellmann, R., K. L. Cooke: *Differential-difference equations*. Academic Press, New York, London 1963.

[34] Heiden, U. an der, *J. Math. Biol. 8*, 345 (1979).

[35] Heiden, U. an der, M. C. Mackey, *The dynamics of production and destruction, J. Math. Biol.* (1982/83), in press.

[36] Kellog, R. H., in W. O. Fenn, H. Rahn (eds.): *Handbook of Physiology, Sect. 3*, Vol. 1, American Physiological Society, Washington, D. C., 1964.

([33–36] References to the Appendix)