From Clocks to Chaos

The Rhythms of Life

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Princeton
University
Press

Published by Princeton University Press, 41 William Street, Princeton,
New Jersey 08540
In the United Kingdom: Princeton University Press, Guildford, Surrey

This book has been composed in Linotron Times Roman by Syntax International
Clothbound editions of Princeton University Press books are printed on
acid-free paper, and binding materials are chosen for strength and durability.
Paperbacks, although satisfactory for personal collections,
are not usually suitable for library rebinding

Printed in the United States of America by Princeton University Press,
Princeton, New Jersey

Designed by Laury A. Egan

Library of Congress Cataloging-in-Publication Data

Glass, Leon 1943–
From clocks to chaos.

Bibliography: p. Includes index.
1. Biological rhythms. 2. Biological rhythms—
Mathematics. I. Mackey, Michael C., 1942–
II. Title.
QH527.G595 1988 574.1′882′0151 87-32803
ISBN 0-691-08495-5 (alk. paper)
ISBN 0-691-08496-3 (pbk.)

To Our Children

Contents

Preface

This book deals with the applications of mathematics to the study of normal and pathological physiological rhythms. It is directed toward an audience of biological scientists, physicians, physical scientists, and mathematicians who wish to read about biological rhythms from a theoretical perspective.

Throughout this volume, we discuss many biological examples and present selected mathematical models to emphasize main concepts. The biological examples have been chosen to illustrate the great variety of dynamic processes occurring in different organ systems. For most of the biological examples, a definitive theoretical interpretation is impossible at the current time. Consequently, the mathematical models are not intended to be exact descriptions of the real biological system, but are simplified approximations. We have tried to emphasize the main principles and to present them in the simplest way possible. It will remain for future researchers to determine whether more realistic models display the same dynamical properties as the simplified versions we present.

We assume a knowledge of calculus but try to explain all advanced concepts and intend the text to be intelligible to nonmathematicians. Equations are used sparingly, and we illustrate ideas with physiological examples and graphs whenever possible. Although there are frequent cross-references between chapters, the chapters are largely independent of one another and do not have to be read in the sequence presented. However, readers with little background in mathematics will need to refer back to chapters 2 and 3 for explanations of unfamiliar concepts. The Mathematical Appendix gives further details of some of the main mathematical techniques together with examples and problems to illustrate the application of these techniques in concrete situations.

Because of the large range of potential applications of the theory, it has been impossible to give exhaustive references. Rather, we have tried to give several key references for each topic to assist the reader in identifying the relevant literature. In order to preserve the flow of the text, we have collected the references in the separate Notes and References sections that follow each chapter.

Over the years we have benefited enormously from discussions and collaborations with students and colleagues. In particular we thank J. Bélair, P. Dörmer, A. Goldberger C. Graves, M. R. Guevara, U. an der Heiden, S. A. Kauffman, J. Keener, A. Lasota, J. G. Milton,

R. Perez, G. A. Petrillo, A. Shrier, T. Trippenbach, and A. T. Winfree. J. G. Milton, S. Strogatz, J. Tyson, and A. T. Winfree made many useful suggestions concerning presentation of the text, and J. G. Milton suggested the main title. The figures were drafted by B. Gavin, and S. James helped with the typing. We would like to thank Judith May and Alice Calaprice of Princeton University Press for their help and advice throughout the production of this book.

This book was partially written while LG was a visiting research scientist at the University of California at San Diego and MCM was a visiting professor at the Universities of Oxford and Bremen. We thank H. Abarbanel and A. Mandell (San Diego), J. D. Murray (Oxford), and H. Schwegler (Bremen) for their hospitality during this period of time. Finally, we have benefited from research grants from the Natural Sciences and Engineering Research Council (Canada), the Canadian Heart Association, and the Canadian Lung Foundation.

Montreal
August 1987

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From Clocks to Chaos

Chapter 1

Introduction: The Rhythms of Life

Physiological rhythms are central to life. Some rhythms are maintained throughout life, and even a brief interruption leads to death. Other rhythms, some under conscious control and some not, make their appearance for various durations during an individual's life. The rhythms interact with one another and with the external environment. Variation of rhythms outside of normal limits, or appearance of new rhythms where none existed previously, is associated with disease.

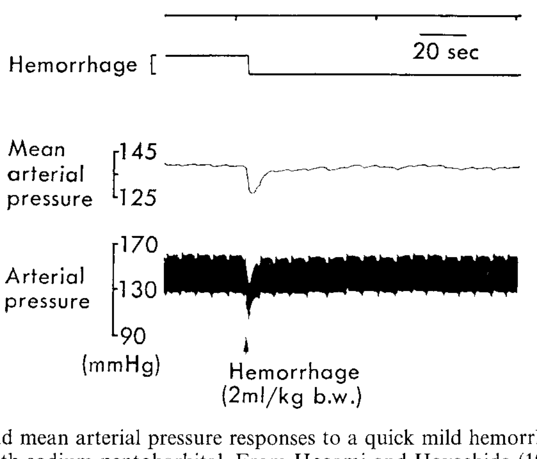
An understanding of the mechanisms of physiological rhythms requires an approach that integrates mathematics and physiology. Of particular relevance is a branch of mathematics called nonlinear dynamics. The roots of nonlinear dynamics were set by Poincaré at the end of the last century but have seen remarkable developments over the past 25 years. Unfortunately, the main features of nonlinear dynamics are usually presented in a format suitable for advanced students in mathematics and are thus difficult for the practicing physiologist. Yet many of the central ideas that are most relevant in physiology can be expressed and illustrated in concrete physiological examples. This book is intended to offer an introduction to recent advances in nonlinear dynamics as they have been applied to physiology, in a format intelligible to a nonmathematician. However, we also hope that those with a mathematical background will find the numerous physiological examples of interest, and that some will even find the many poorly understood phenomena in physiology which we discuss a stimulus for future research. In this chapter we give a brief outline of this book and summarize its themes by giving several physiological examples.

1.1 Mathematical Concepts

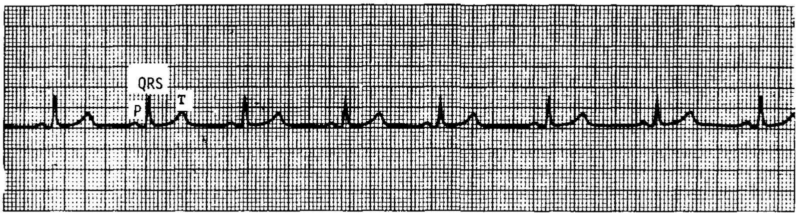
It is common to measure physiological observables as a function of time. Four main mathematical ideas have been developed to characterize such time series: steady states, oscillations, chaos, and noise.

Since the pioneering research of Bernard, Cannon, and others, it has become fashionable, if not obligatory, to discuss homeostasis near the beginning of physiology texts. *Homeostasis* refers to the relative constancy of the internal environment with respect to variables such as blood sugar, blood gases, electrolytes, osmolarity, blood pressure, and pH. The physiological concept of homeostasis can be associated with the notion of steady states in mathematics. *Steady states* refer to a constant solution of a mathematical equation. Elucidation of the mechanisms that constrain variables to narrow limits constitutes a key area of physiological research. As an example of a homeostatic mechanism, consider the response to a quick mild hemorrhage in an anesthetized dog (figure 1.1). Following the hemorrhage, reflex mechanisms are activated which restore blood pressure to near equilibrium within a few seconds.

Although the mean blood pressure is maintained relatively constant, as we all know, the contractions of the heart are approximately periodic. The periodic electrical activity of the heart can be visualized using an electrocardiogram. Figure 1.2 shows an example of a normal electrocardiogram. Likewise, all of us are familiar with the rhythms of heartbeat, respiration, reproduction, and the normal sleep-wake cycle. Less obvious, but of equal physiological importance, are oscillations in numerous other systems—for example, release of insulin and luteinizing hormone, peristaltic waves in the intestine and ureters, electrical activity of the cortex and autonomic nervous system, and constrictions in peripheral blood vessels and the pupil. Physiological oscillations are associated with periodic solutions of mathematical equations.

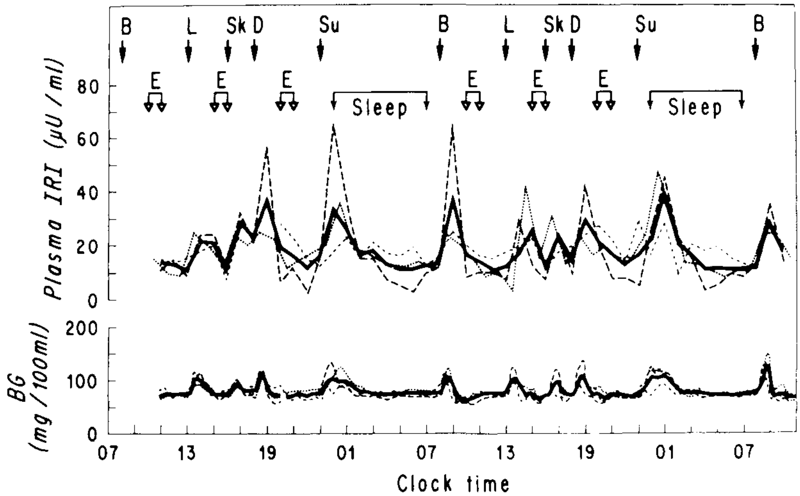


1.1. Arterial and mean arterial pressure responses to a quick mild hemorrhage in a dog anesthetized with sodium pentobarbital. From Hosomi and Hayashida (1984).



1.2. Normal electrocardiogram. The P wave corresponds to atrial depolarization, the QRS complex to ventricular depolarization, and the T wave to ventricular repolarization. One large box corresponds to 0.2 sec in the horizontal direction, and 0.5 mv in the vertical direction. From Goldberger and Goldberger (1986).

Of course, we all know that close measurement of any physiological variable will never give a time sequence that is absolutely stationary or periodic. Even systems that are assumed to be stationary or periodic will always have fluctuations about the fixed level or periodic cycle. In addition, there are systems that appear to be so irregular that it may be difficult to associate them with any underlying stationary or periodic process. One potential source of physiological variability is the fluctuating environment. As one eats, exercises, and rests, blood-sugar levels and insulin levels respond in a characteristic fashion (figure 1.3).

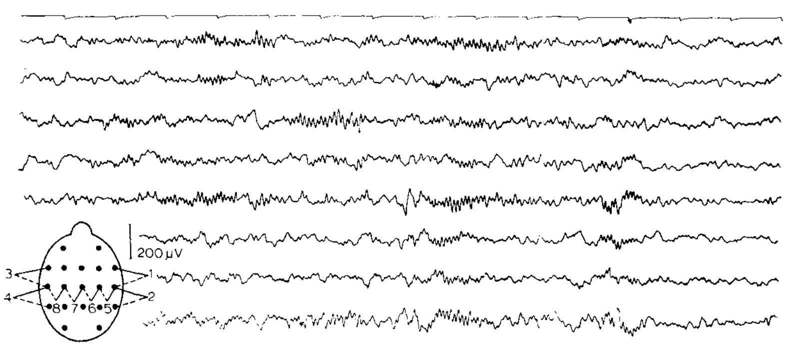


1.3. Immunoreactive insulin (IRI) and blood glucose (BG) in ambulatory normal subjects over a 48-hour period. Interrupted lines describe patterns for individual subjects; continuous lines show the group averages. Symbols: B = breakfast; L = lunch; Sk = snack; D = dinner; Su = supper; E = 1 hour of walking exercise. From Molnar, Taylor, and Langworthy (1972).

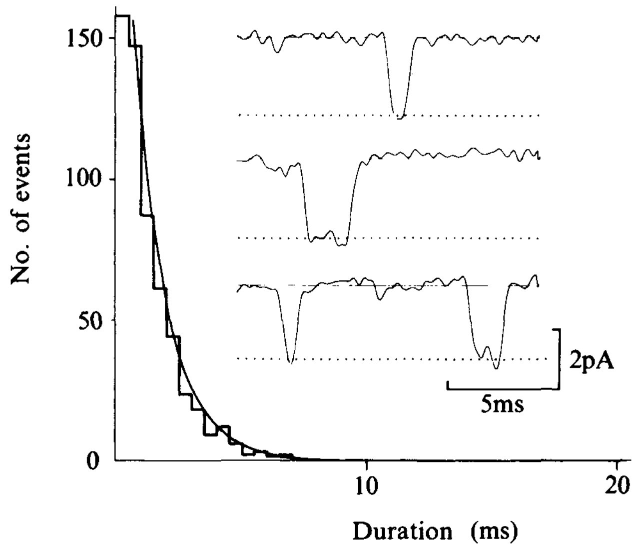
Similarly, the blood pressure responds to the changes in activity and posture. Physiological rhythms themselves can also act to perturb other rhythms. An example is respiratory sinus arrhythmia in which the heartbeat is quickened during inspiration. Although such variability is not necessarily easy to deal with theoretically, its origin is often readily understood.

More mysterious situations are those in which fluctuations are found even when environmental parameters are maintained at as constant a level as possible and no perturbing influences can be identified. For example, the electroencephalogram measures average electrical activity from the localized regions of the cortex and shows fluctuations over time which are often quite irregular (figure 1.4). These situations afford significant difficulties in understanding the mechanisms leading to the irregularities.

Mathematics offers us two distinct ways to think about the irregularities intrinsic to physiology. The more common of the two is *noise*, which refers to chance fluctuations. For example, such chance fluctuations are often associated with the opening and closing of channels in neurons and cardiac cells that carry ionic current (figure 1.5). Although "chaos" is often used as a popular synonym for noise, it has developed a technical meaning that is quite different. Technically, *chaos* refers to randomness or irregularity that arises in a deterministic system. In other words, chaos is observed even in the complete absence of environmental noise. An important aspect of chaos is that there is a sensitive dependence of the dynamics to the initial conditions. This means that although in principle it should be possible to predict future



1.4. Electroencephalogram recorded from a normal 17-year-old woman during natural sleep. There are 14 Hz spindles, which are independent on either side. The top line shows 1-sec intervals. Simultaneous recordings from the eight electrode positions indicated on the diagram are displayed. From Kiloh et al. (1981).



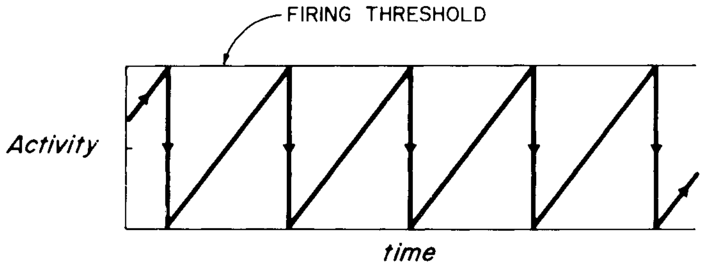
1.5. Currents flowing through an individual potassium channel from a single cell from dispersed AV node of rabbit heart. Short pulses of 2.4 pA amplitude at a resting potential of -20 mv. The histogram represents the distribution of current pulse durations and is fitted by a single exponential. From Sakmann, Noma, and Trautwein (1983).

dynamics as a function of time, this is in reality impossible since any error in specifying the initial condition, no matter how small, leads to an erroneous prediction at some future time.

Some equations display dynamics that are not periodic and fluctuate in irregular fashion. The existence of such equations was known to Poincaré and later mathematicians, but the recognition of these phenomena has only recently emerged in the natural sciences. The implications of such phenomena in biology and physiology are a topic of great current interest.

In practical situations, there are fluctuations about some mean value or oscillations which are more or less regular. It is not a trivial problem to go backwards from the observation of such dynamics to infer something about the underlying dynamical system.

Chapters 2 and 3 offer an introduction to the concepts of steady states, oscillations, noise, and chaos in mathematics. We show how these properties can arise in equations and how transitions between different types of dynamical behavior can occur. Since some of the material in chapters 2 and 3 is elementary, those with some knowledge of mathematics may wish to skip some of the sections. On the other hand, those with a weaker background in mathematics and those who really do not like



1.6. Integrate and fire model. The activity rises to a firing threshold and then resets to zero.

to read about mathematical ideas can skip ahead to other chapters, using chapters 2 and 3 as references as the need arises.

1.2 Mathematical Models for Biological Oscillators

There is a large literature that proposes many different types of models for the generation of physiological rhythms. The simplest type of model is called an *integrate and fire model.* In such models a quantity called the *activity* rises to a threshold leading to an event. The activity then instantaneously relaxes back to a second lower threshold. This process is represented schematically in figure 1.6. If the function determining the rise and fall of the activity between the two thresholds is fixed, and if the thresholds are fixed, then a periodic sequence of events will be generated at a readily determined frequency.

A physiological system that can be modeled by an integrate and fire mechanism is the one controlling the micturition reflex. As time proceeds, the bladder fills and eventually micturition takes place. Then the cycle starts anew. In the normal adult, micturition occurs 6–10 times/day with a voiding volume of 300–600 ml. However, pregnant women and patients with serious bladder or prostatic pathology often display increased frequency, reduced volume, and nocturia. In figure 1.7 we show the voided volume and micturition times recorded by a patient with carcinoma of the bladder. We are unaware of detailed quantitative studies or theoretical analysis of the micturition reflex or its pathological variants. A variety of other systems have been modeled by integrate and fire models, and we shall utilize such models in many different points in the text.

Although integrate and fire models are frequently used in physiology and will be discussed in several subsequent chapters, from a mathe-