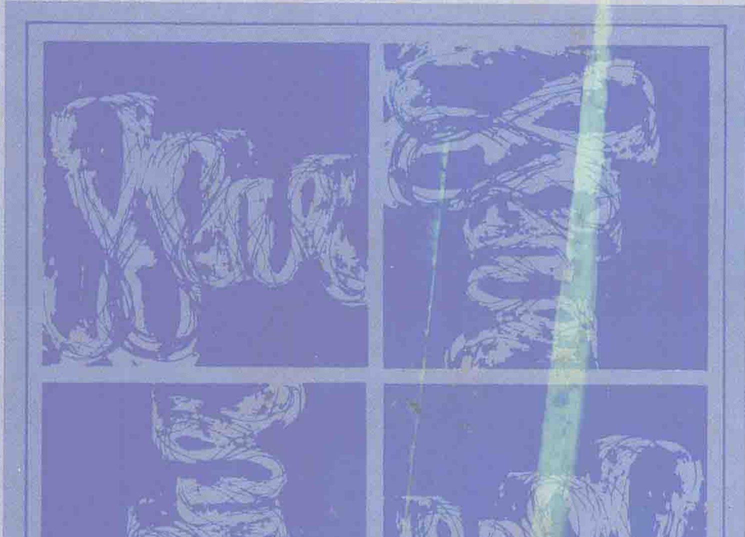
PRINCIPLES OF BIOLOGICAL REGULATION

An Introduction to Feedback Systems



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Preface

The objective of this book is to provide the life scientist with some understanding of control, regulatory, and feedback mechanisms in biological systems. The concepts to be introduced are related to the dynamic behavior of both individual biological processes and systems of processes that make up an organism. A further objective is the description of characteristics of biological feedback systems with emphasis upon the physical concepts, and thus with a minimum of mathematical formalism. It will become clear, however, that although a qualitative treatment of these ideas is adequate for some discussions, it is not sufficient for those concepts that turn upon the relative magnitudes of several quantities. As a consequence, it is hoped that the reader will sense the need for mathematical tools and techniques of greater power if he is to refine his understanding of the behavior of complex systems having many component processes.

The terms biological and physiological are used somewhat interchangeably. Although most of the examples are physiological, many of the concepts can be extended to a variety of biological problems, as is suggested on occasion. Genetics, ontogeny, and ecology are all fields in which many of the concepts described have already appeared.

At many points the discerning reader may detect exceptions to the relations and concepts described. With the sole view of presenting basic concepts in a simplified language, I have taken the liberty of making rather general statements on occasion without surrounding them with adequate restrictions and qualifying phrases. The hazards are obvious, but at the same time the reader is hereby warned that constraints on the general applicability of many statements do exist, and he is urged to seek out the exceptions or limitations. And perhaps he may even be encouraged to delve deeper into many topics so as to confront the author at some future encounter. As an aid in such further study a brief résumé of the salient points in a mathematical analysis will be found at the end of most chapters.

With the above objectives, it has been impossible to describe specific physiological examples in great detail. To do so would have expanded this text beyond all reasonable bounds. It is probably accurate to state that no one of the physiological systems has been described with the completeness and detail needed for clinical use, but it is hoped that this volume may contribute in some small way to that development.

Physiological examples have been introduced at numerous points in the hope that they will lend substance to the argument. For the most part they have been chosen to illustrate some system concept, however crudely. In most instances the examples have been greatly simplified, but not, it is hoped, to the point of unrecognizability or irrelevance to life processes.

Acknowledgments

This book is dedicated to the reader in the hope that it may smooth his passage through a portion of the vast literature of physiology, guided by the one concept of homeostasis. However, this dedication would be an impossibility were it not for the continued guidance of my mentors, especially Dr. John S. Gray, Dr. Christina Enroth-Cugell, and Dr. Miriam Eubank-Jones. To this I can only add my thanks to many classes of students who have patiently watched this text grow from small beginnings, and unknowingly contributed to that development.

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Biology as a Science of Organization 1.1

Current developments in the biological sciences make it increasingly clear that organization, or system theory, is a fundamental component of biology. It is axiomatic that biology is rooted in physical and chemical processes, but classical physics and chemistry are not enough to describe the evolution, development, and physiology of an organism. The component processes, such as diffusion, mass transport, and protein synthesis, are inadequate in themselves to account for the physiology of the entire organism, to say nothing about its organized behavior. To these components must be added the organizational framework—the manner in which the subsidiary processes are related and coupled. Numerous writers have described the two extreme viewpoints, that of molecular biology on the one hand, and organismic, systemic biology on the other. Simpson (1963, 1967) has provided an especially thoughtful examination of this situation, and has even elevated it to the position of a crisis in biology.

There are several reasons for this seeming concern. In the first place, an understanding of biological organization is only now developing, and so a full description of the role of organization in biological processes is at most in embryonic form. Second, in systems of many components, organization connotes complexity, and there is some feeling that we do not have the language necessary to describe these highly interrelated processes. At best, the mathematical language which appears most suitable at the present time is not an intellectual tool of most life scientists.

Among the many types of organization that characterize biological processes in cell, organism, and population, that termed regulatory, or homeostatis, is most ubiquitous. This fact, together with some similarity to existing technological systems, makes regulatory biology a reasonable first choice in developing a broader theory of biological organization.

There are four factors that prompted the writing of this book.

(1) It is apparent that feedback system theory is becoming of increasing significance to most life scientists, whether they are biologists concerned with the classical problems of cell, organ, organism, and population, or medical practioners concerned with human problems of health and disease. The wide prevalence of regulatory processes, and in particular the feedback mechanisms with which they are associated, make a study of such systems mandatory. It is possibly the first item on any agenda devoted to a study of organization.

(2) With very few exceptions, existing texts develop the concepts of regulatory behavior with the techniques, terminology, and mathematics of the engineering profession. The present text has been written with the hypothesis that most of the concepts can be developed in a qualitative nonmathematical form that is intuitively clear. The emphasis, then, is upon physical concepts, presented in such a manner (it is hoped) that the basic ideas can be translated into a biological context. How-

ever, biological systems do not lend themselves to a direct application of engineering concepts, but rather require careful study to assure that the result has biological relevance. It may well be that significant modification and extension of basic feedback theory will evolve as a consequence.

(3) The existence of feedback in any physical system has profound effects on its behavior, so that the responses to stimuli and disturbances are quite unlike those of individual components. Feedback accentuates certain properties of a system and endows it with others it did not have. Furthermore, feedback greatly complicates the interpretation of experimental findings, since a given response may not be attributable solely to the component being measured because it may also contain contributions from components located remotely in the feedback loop. These aspects of feedback suggest that experimental biologists need at least a basic understanding of feedback phenomena.

(4) The concept of regulation or homeostasis has been extended in the biological literature far beyond its original context. While some of these extensions offer exciting vistas to the investigator, others seem to cloud the issue and lead to an imprecision of discourse that impedes the development of clear ideas. In this and later chapters, some definitions will be discussed with a view to clarifying the discussion and promoting further study of regulatory problems and their bearing upon organization.

Although these factors appear to me as sufficient justification for another book, it should also be pointed out that the framework of this text, as well as the present state of knowledge, imposes severe limitations. Our knowledge of homeostasis is still extremely elementary and the reader is here forewarned that feedback theory does not provide the one ingredient that will unlock (or unleash) all biological secrets. Rather, it should be looked upon as another tool to assist in finding some answers, to lead on occasion to new and intriguing questions, and to provide integrating viewpoints within the family of biological sciences. An understanding of dynamic behavior and of feedback theory is but another tool for the life scientist. It is a tool in the same sense as is a microscope that reveals structure, the spectrograph as it depicts composition, or the recording electrode measuring neural signals. Each of these methods permits the examination of one facet of life, and each contributes to a deeper understanding of the whole.

Regulatory Biology 1.2

Although more precise definitions will be found in subsequent chapters, the following terms are introduced here in a descriptive manner. *Regulation,* when used to describe the property of a *system,* refers to the fact that certain changes brought about by disturbances to the system are minimized. Regulation may also refer to the *mechanisms* by which this minimization is effected. The terms *homeostasis* and *homeostat* are used in similar senses, but in a biological context. There is a relative component to these terms that implies the possibility of specifying those portions of the system that endow it with this property of regulation. To say that a given system is regulated is meaningless, unless a mechanism is identified in whose absence the system becomes less well regulated. In a broad sense, the homeostat has acquired mechanisms that improve its ability to resist disturbances.

Homeostatic mechanisms are the means whereby organisms have achieved relative freedom from the constraints of their environments. Having acquired greater freedom in this manner, that is, by evolving homeostatic processes, the organism has acquired a greater variety of functions, not only those required to maintain the homeostasis, but also those permitted by the enlarged environmental exposure.

This independence of the environment is a relative matter. Organisms do not become completely independent, but only more nearly independent of environmental factors, as they acquire the ability to maintain a constant internal environment in which most of their cells live. One finds that organisms have acquired not one homeostat, but a very large number, each related to some physical aspect of their internal affairs or of their behavior regarding the environment. Furthermore, each of the homeostats has its own limits within which it can maintain its integrity, and excursions beyond these limits are almost invariably fatal.

The biological quantities that are regulated fall into three broad categories, and we will want to discuss not only the differences but the similarities in the regulatory processes for these several types of regulating systems. In addition, we shall pay attention to the aspects which distinguish biological regulators from their technological counterparts. Although extended use will be made of analogous processes, the reader is forewarned that the use of the mistaken analog is a grave and present danger to biology.

The *quantity or concentration of the materials* making up the organism, that is, the many types of molecules or chemical species, is for the most part closely regulated by means of a large number of homeostatic processes. The need for regulation arises from the "mismatch" between supply and demand, and reflects changes in the intake, use, and excretion of specific molecules. Although the body contains stores of many chemical species, these cannot act as effective regulators without the addition of facultative processes to enhance or inhibit the synthesis and movement of material through appropriate pathways within the organism.

The *energy balance* within the body is carefully regulated in those organisms known as homeotherms. Changes in body temperature serve to indicate corresponding changes in the energy balance and thus in energy production, energy absorption, or energy dissipation. As is well known, slight changes in body temperature may be lethal, so that a means must be available for correcting any changes in the energy flow pattern in order not to upset the body temperature.

The various *muscular control mechanisms* involved in the control of posture and movement are also found to be well regulated, and thus we can subsume these processes under the term homeostasis.

An organism may exhibit the properties of homeostasis by means of a number of different mechanisms. Although the discussion of the first chapters will be related to feedback systems, it is well to point out that this is only one of several possible ways of controlling the perturbations in a biological system. Some of these other methods, such as rigidity, compensation, buffering, and stochastic regulation, are briefly discussed later.

The major portion of this text is devoted to homeostatic systems that function to maintain a relative constancy in a physical or chemical process. However, there is a growing awareness that this may be too limited a view. It is becoming increasingly apparent that oscillatory phenomena play a significant, if not an essential, role in many life processes. We refer here not to the obvious cardiac and respiratory rhythms, but to the so-called circadian (approximately 24-hr) rhythms which have been shown to exist widely in metabolic and activity patterns (Pittendrigh, 1961). The prevalence of this phenomenon has led to the hypothesis that organisms should be viewed as systems of coupled oscillators. This matter will be touched upon briefly in later chapters.

Historical Development 1.3

Like many fundamental concepts, biological regulation, or homeostasis, has an ancient and honorable ancestry. Its development from Greek to modern times has been admirably described by Adolph (1961), who has also discussed the many interpretations of the homeostatic concept and related ideas.

Possibly the first to recognize the prevalence of regulatory processes within the organism and to state the concept in reasonably precise and modern terms was Claude Bernard (1865, 1878).

> The organism is merely a living machine so constructed that, on the one hand, the outer environment is in free communication with the

inner organic environment, and, on the other hand, the organic units have protective functions, to place in reserve the materials of life and uninterruptedly to maintain the humidity, the warmth and other conditions essential to vital activity. Sickness and death are merely a dislocation or disturbance of the mechanism which regulates the contact of vital stimulants with organic units.

Bernard coined the phrase *fixite du milieu interieur* and stated that it was the condition for a free life.

The next major step in the development of this concept was taken by Cannon (1929), who coined the word *homeostasis,* which he defined as the "coordinated physiological reactions which maintain most of the steady states in the body." The term may be somewhat misleading, since the first portion *homeo* is an abbreviation meaning "like" or "similar, but not the same," and the second word *stasis* implies something static, immobile, and stagnant. It was not Cannon's intention to imply something static, and he points this out in his article. Cannon was well aware that these homeostatic mechanisms are dynamic in character, continually modifying various processes in order to meet the changing needs of the organism (Cannon, 1939).

Among the first attempts to refine these notions are the paper by Rosenblueth *et al.* (1943), and the book by Wiener (1948) that introduced the term *cybernetics.* Unfortunately, this term has been seized upon by many writers in as many fields, with the result that its precise meaning is now well-diluted and its utility is of doubtful value. The texts by Grodins (1963), Hughes (1964), Yamamoto and Brobeck (1965), Kalmus (1966), and Bayliss (1966) constitute significant contributions from biologists and physiologists to a growing borderland between biological and technological regulation. The texts by Milhorn (1966) and Milsum (1966) approach this territory with somewhat more of an engineering stance. The origins of selected homeostats are discussed by Adolph (1968).

Epitome 1.4

1. An organism is viewed as an organized collection of many physicochemical processes. The viability and behavior exhibited by the organism is a direct consequence of the manner in which these component processes are organized and interrelated.

2. Among the many kinds of biological organization, those termed regulatory, or homeostatic, are prevalent at all biological levels. The similarities between these homeostatic systems and technological regulators provide a starting point for the study of homeostatic mechanisms.