CRC

Handbook of Engineering in Medicine and Biology

Editors:

David G. Fleming

Barry N. Feinberg

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David G. Fleming

Professor, Biomedical Engineering in Pediatrics
Case Western Reserve University
Cleveland, Ohio

Barry N. Feinberg

Associate Professor, Electrical Engineering
Director, Clinical Engineering Program
Cleveland State University
Cleveland, Ohio

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FOREWORD

As an identifiable professional activity, biomedical engineering is a shade more than 20 years old, and many of the "old timers" who gave form and substance to the field are still far from retirement and continue to contribute to the literature.

The Annual Conference on Engineering in Medicine and Biology has just published its 28th Proceedings and those of us fortunate enough to have participated in, or have access to its early records, can only marvel at the awesome growth and current vitality of the meeting. In 15 years, its sponsorship has grown from 3 engineering societies, the IRE, ISA, and AIEE to 24 Constituent Associations representing a broad spectrum of engineering and medical societies.

The earliest federally funded training programs are celebrating their 18th birthday and formal educational programs now exist in over 100 institutions from community colleges to professional schools.

Educational opportunities exist leading to associate degrees for equipment technicians, to the B.S. degree in Bioengineering, to the M.S. degree in Clinical or Biomedical Engineering, and to the doctorate in Biomedical Engineering. Programs leading to the simultaneous awarding of the M.D. plus a Ph.D. in engineering are available in a number of universities. This picture presents a sharp contrast from the situation in 1960 when there were no formally trained biomedical engineers and everyone working in the field was either a retreaded physiologist, a diverted physician, or an engineer in search of new challenges. The first book in the field was yet to appear and the only regularly published journal in the field was the Transactions of the Group on Engineering and Medicine biology of the IEEE. At the present time the number of journals, textbooks, and monographs in the field are virtually too numerous to count.

This rapid growth has not been without problems for the student and senior investigator alike. Data may appear in a wide variety of publications, some only remotely related to biomedical engineering. The problem, while distressing, is not difficult to understand since biomedical engineering in its broadest definition includes all activities in which there is significant interfacing between the basic and clinical biomedical sciences with engineering theory and practice.

Academically, there is still little agreement on the content of the "educational core" at the undergraduate level or indeed if one exists at all. Graduate programs varying enormously in content and structure are part of the rubric of biomedical engineering, and post-educational professional activities may be equally diverse.

For example, recent publications by one of the editors include: 1) the application of modern systems theory to modeling neuromuscular control mechanisms; 2) the design, fabrication, and clinical evaluation of plastic nasal canula used for treating respiratory distress in premature infants. These two illustrations are presented because they demonstrate two extremes of the application of engineering to biology and medicine. Both examples represent instances in which either a method of engineering analysis or a method of modern technology is used 1) for the understanding of biological systems or 2) to solve an important problem in patient care.

A field whose scope includes nasal prongs and visual perception, ground fault detectors and cardiovascular fluid mechanics, hip pins and microcomputers is not easily organized into a coherent body of knowledge. The editors and contributors to the handbook share the belief that a body of information almost unique to biomedical engineering exists at the present time and that a project to bring much of it together is worth an investment of time and energy.

In Volume I, concepts of information, control, materials, mechanics and measurement are present. Volume II will be concerned with applications to instrumentation, clinical engineering, patient monitoring, and prostheses. Successive volumes in the series are to be devoted to specific topics and will coherently and concisely represent the state of knowledge in a given area at the time of publication. If the handbook fulfills its objective, it will to the extent possible provide a data base useful to the student and professional in biomedical engineering and be a source of information for investigators and practitioners in the allied health care and engineering fields.

David Fleming
Barry Feinberg

Cleveland, Ohio
November 1975

THE EDITORS

David G. Fleming is Professor of Biomedical Engineering in Pediatrics and Associate Director of Biomedical Engineering in Pediatrics and Associate Director of the Biomedical Electronics Resource at Case Western Reserve University.

Dr. Fleming received his A.B. in Zoology in 1948 and his Ph.D. in Physiology in 1952, both from University of California at Berkeley. He received his M D. from Case Western Reserve University in 1973.

From 1968 to 1970 Dr. Fleming was President of the IEEE Group on Engineering in Medicine and Biology. During the same time, Dr. Fleming also served as Chairman of the ASEE's Bio-and-Medical Engineering Committee. He also was a member of the Joint Committee on Engineering in Medicine and Biology from 1965 to 1970, acting as chairman in 1967.

Dr. Fleming's major research interest is biomedical instrumentation for high-risk infants and studies of physiological systems. He has authored many articles in these areas and holds numerous patents in the area of instrumentation.

Barry N. Feinberg is Associate Professor of Electrical Engineering and Director of the Clinical Engineering Program at Cleveland State University. He has been a visiting professor at the University of Edinburgh in Scotland and at the Academish Ziekenhuis, Leuven, Belgium.

Dr. Feinberg received a B.S. in both Electrical Engineering and Mathematics from the University of Michigan in 1962. He received a Masters in Electrical Engineering from the University of Louisville in 1964 and a Ph.D. in Engineering from Case Institute of Technology of Case Western Reserve University in 1968.

Dr. Feinberg is a member of the Institute of Electrical and Electronic Engineers and the Association for the Advancement of Medical Instrumentation, as well as other honorary organizations.

Dr. Feinberg is currently conducting research in biomedical and clinical engineering and has authored numerous papers in these areas.

CONTRIBUTORS

John Aldridge, M.D.
Department of Electrical Engineering
Princeton University
Princeton, NJ 08540

John Bligh, Ph.D.
Institute of Animal Physiology
Babraham, Cambridge
England

Albert Burstein, Ph.D.
Assistant Professor of Orthopedic Surgery
Case Western Reserve University
Cleveland, OH 44106

John Busser, Ph.D.
Alliance for Engineering in Medicine and Biology
5454 Wisconsin Avenue
Chevy Chase, MD 20015

Cesar A. Caceres, M.D.
Clinical Systems Associates, Inc.
1759 Que Street, NW
Washington, DC 20009

Lawrence Chik, Ph.D.
Department of Obstetrics and Gynecology and the Perinatal Clinical Research Center
Cleveland Metropolitan General Hospital/Case Western Reserve University
Cleveland, OH

Donald F. Gibbons, Ph.D.
Professor of Material Science
Case Western Reserve University
Cleveland, OH 44106

Norman Hurt, Ph.D.
Associate Professor of Mathematics
Cleveland State University
Cleveland, OH 44115

Stephan A. Kallis, Jr.
Digital Equipment Corporation
146 Main Street
Maynard, MA 01754

Peter G. Katona, Ph.D.
Associate Professor of Biomedical Engineering
Case Western Reserve University
Cleveland, OH 44106

Wen C. Lin, Ph.D.
Professor of Computer Engineering
Case Western Reserve University
Cleveland, OH 44106

Robert Plonsey, Ph.D.
Professor of Biomedical Engineering
Case Western Reserve University
Cleveland, OH 44106

Robert Rosen, Ph.D.
Center for Theoretical Biology
SUNY – Buffalo
Amherst, NY 14226

Robert J. Sokol, M.D.
Department of Obstetrics and Gynecology and the Perinatal Clinical Research Center
Cleveland Metropolitan General Hospital/Case Western Reserve University
Cleveland, OH

Jean Stojkov, B.S.
Department of Obstetrics and Gynecology and the Perinatal Clinical Research Center
Cleveland Metropolitan General Hospital/Case Western Reserve University
Cleveland, OH

Peter A. Torzilli, Ph.D.
Research Associate
Biomechanics Laboratory
Case Western Reserve University
Cleveland, OH 44106

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PHILOSOPHICAL, HISTORICAL AND THEORETICAL CONSIDERATIONS OF REGULATION AND CONTROL IN BIOLOGY AND MEDICINE

Robert Rosen

I. INTRODUCTION

Regulation and control processes are at the heart of the basic questions of biology and medicine. The present article is intended to provide a brief review of the presently employed techniques for the modelling of regulatory and control mechanisms, illustrated by some typical biomedical applications of these techniques. This material will be presented in Section II. In Section III, we will undertake a critical review of these techniques in the light of their historical and philosophical underpinnings, and suggest some directions for further development.

II. THEORETICAL STUDY OF REGULATORY AND CONTROL MECHANISMS IN BIOLOGY AND MEDICINE

1. Systems, States and Dynamics

We will here develop the basic concepts and terminology required for an understanding of biological control and regulatory processes.

For our purposes, a *system* of interest will merely comprise some isolable aspect of the world which we wish to study. Thus, for example, a typical system might be an individual organism, or a population of such organisms, or a cell or organ of an organism. These represent systems which can be separated physically from their natural environment. We might also be interested in studying systems which cannot be physically isolated from the organism, but which form a conceptual unity capable of separate study, such as a pool or compartment representing the distribution of a particular metabolite in an organism. We shall find many examples of both kinds of systems as we proceed.

The study of such systems takes many forms, as we shall see, but underlying all of them are two basic notions:

a. the *state* (or *instantaneous state*) of the system of interest, which involves the specification of what our system is like at an instant in time;

b. the *dynamics* of the system, which specifies how the instantaneous state changes in time as a function of the forces or inputs imposed upon the system.

Let us begin with the concept of *state*. In practice, the information which we can obtain about our system at an instant of time typically comes from allowing our system to interact with an appropriate kind of measuring instrument. The reading obtained from that instrument as a result of this interaction can be represented in the form of a numerical value, and this number thus conveys some information about the state of our system at the instant the measurement was made. A second such measurement, using a different measuring instrument, will in general convey more information about the state than a single one; a third measurement will convey still more. In this way, it is reasonable to identify the state of the system at an instant of time with the set of all numerical values which arise by interacting our system at the instant in question with all possible measuring instruments. Of course, this is an idealization, but for the moment it is plausible to regard the states of any system of interest as being represented or encoded by sets of numbers; these numbers in turn correspond to the values of observable quantities which are measured on the system at the instant in question.

Of course, much of this idealized information regarding the state of our system at an instant of time will be redundant; the values arising from some of the measurements we make may be functions of the values of other measurements, and hence are determined when the values of those others are known. Thus, we are led to seek the most parsimonious kind of state description, utilizing only sets of measurable quantities which have the following properties:

a. Every measurable quantity pertaining to the system is to be a function of those entering into our state description;

b. None of the quantities entering into our description is to be a function of the other quantities in the description.

The quantities entering into such a minimal description of the states of our system at an instant of time are called a set of *state variables* for our system. In general there are many possible sets of state variables.

Systems may be classified by the size of the set of state variables necessary to characterize their instantaneous states. The simplest kinds of systems are those which require only a finite set of state variables. For these systems, then, a state can be represented by an n-tuple of real numbers, where n is the (finite) number of state variables required for the most parsimonious specification of the states of the system. In this way, the set of states of such a system can be identified with some subset S of Euclidean n-dimensional space; by the familiar mathematical *abus de langage,* this subset S is called the *state space* of our system.

Thus, for example, a system of N mechanical particles in space is known from mechanics to be completely represented by a state space (called, in mechanics, a phase space) of 6N dimensions; a set of state variables for the system comprises the 3N components of displacement of each of the particles in the three spatial directions from some origin of spatial coordinates, and the corresponding 3N components of momentum or velocity. A system of N interacting chemical species may be represented by an N-dimensional state space, in which the state variables are the concentrations of the individual reactants. In this last example, it should be noted that not every mathematically available N-tuple of numbers can correspond to a state of the system (since concentrations must be nonnegative), and that therefore the set of those N-tuples which can in fact represent states must be carefully specified.

More complex systems cannot be represented by any finite set of state variables. For example, in a chemical reaction system which is inhomogeneous and spatially extended, merely knowing the total concentrations of the reactants in the system is not in general adequate. For such a system, we would have to specify the concentrations of the reactants at each point in the reaction vessel. The treatment of such spatially extended, or *distributed* systems, raises severe technical difficulties, but the basic strategy of approach to them is the same as that for finitely characterizable systems. Therefore we shall stress the treatment of the finite systems in this article.

Having decided on how to characterize our system at an instant of time (i.e., having specified an appropriate state space S) we must now turn our attention to considering how our states change in time. To do this, we shall exploit the mathematical properties of the state space, which we remember is a subset of Euclidean n-dimensional space. As such, it possesses a rich mathematical structure, including a topology (which allows a discussion of continuity or continuous change of state), a metric (which allows us to speak of states being close to each other) and, most importantly, a differentiable structure, which allows us to speak of time derivatives of functions defined on the state space; most importantly, of the state variables themselves.

Let us suppose that our system is in the state $(x_1(t_o), x_2(t_o), \ldots, x_n(t_o))$ at an instant t_o, where $x_1, \ldots, x_n$ represent a set of state variables for the system. To speak about the change of state of the system, it is necessary to specify how fast the state variables are changing when the system is in the given state. That is, we wish to talk about the rates of change of the state variables, represented intuitively by the derivatives dx_i/dt, evaluated in the given initial state.

Here again, we may make a classification of different kinds of systems. The simplest assumption we can make is the following: *the rates of change of the state variables, evaluated in a state, depends only on that state.* That is, in the neighborhood of any state, we could write a set of n equations of the form

$$\frac{dx_i}{dt} = f_i(x_1, \ldots, x_n), \quad i = 1, \ldots, n. \tag{1}$$

Here the functions $f_1, f_2, \ldots, f_n$ represent the mode of functional dependence of the rates of change of the state variables on the state. We should notice that these equations, as we have motivated them, are meaningful only locally, in the vicinity of an individual state; there is no reason a priori why the same set of functions $f_1, \ldots, f_n$ should specify the rates of change of the state variables in the neighborhood of some other state remote from the first. Nevertheless, it is intuitively clear that we can "patch together" such locally valid functions to get functions $f_1, \ldots, f_n$ valid over the entire state space, and we may therefore just as well assume that equations of the form (1) hold globally. Systems with a finite set of state variables whose change of state is specified by systems of equations of the form (1) are typically called *dynamical systems.* They provide the most accessible framework for the study of control and regulation in all kinds of systems, and exhibit the basic ideas most clearly. Therefore in what follows, we shall emphasize these systems in our study.

Naturally, we can make many other kinds of assumptions about the manner in which the rates of change of the state variables depend on the states. We could assume, for example, that the rate of change of a state variable in a state depends on the entire past history of the system leading up to that state, or on some part of that history. Such systems could be meaningfully said to possess a *memory.* In systems of the form (1), on the other hand, the present rate of change of state depends only on the state, and not on any prior (or subsequent) states; therefore these systems are *memoryless.* Nevertheless, as we shall see, the systems of the class (1) are sufficiently rich so that many important phenomena can be represented in them.

The equations (1), which we shall assume to be satisfied by all systems with which we deal, are called the *dynamical equations* or *equations of motion* of the system. They are completely determined by the functions $f_1, f_2, \ldots, f_n$, which specify the dependence of rate of change of state upon state. Intuitively, these functions f_i represent the *forces* acting on the system, causing the states to change. Such equations cannot be directly obtained by observations of the system, but must be written down on the basis of general principles. For instance, in a system consisting of N material particles, the dynamical equations are written down in accordance with Newton's laws of motion. In a chemical kinetic system, dynamical equations can be written down from an assumed stoichiometry of the reactions involved, together with the Law of Mass Action. Such a set of dynamical equations represents a *model* of the system of interest, and we attempt to infer properties of the real system from properties of the model. If the predictions obtained from the model are verified in the real system, the model is satisfactory for our purposes; otherwise we must change the model by revising the dynamical laws (i.e., altering our specification of the forces acting on the system), by making more complex assumptions regarding the dependence of rate of change of state upon state, by enlarging the state description, or by any combination of the above.

Let us now take systems of the form (1) as our point of departure and consider their properties in more detail. The fundamental kind of prediction we would like to make from such a representation is to specify the state of our system at any time t, knowing the present state. If we assign a state to each time instant t, it is clear that we will obtain a curve, which we may designate as C(t), which winds through the state space in some fashion. Knowing this curve, we could read off the corresponding state at any time we wished. Curves C(t) of this character are called *system trajectories.* Thus, the prediction problem reduces to the determination of the system trajectories. This in turn involves the specification of each of the state variables x_i as an explicit function of time, $x_i(t)$. Indeed, any system trajectory is just an n-tuple of such functions:

$$C(t) = \left\{ x_1(t), x_2(t), \ldots, x_n(t) \right\}.$$

In order to solve the prediction problem, then, we must determine the functions $x_i(t)$, and this obviously requires an integration of the dynamical equations (1).

It is worthwhile to pause at this point to give a geometrical interpretation of these concepts. Let us suppose that the state space S is two-dimensional; i.e., a subset of the plane. Let the state variables be denoted by x_1, x_2, and let us consider the time t as the independent variable. The dynamical equations then take the form

$$\frac{dx_1}{dt} = f_1(x_1, x_2)$$

$$\frac{dx_2}{dt} = f_2(x_1, x_2). \qquad (2)$$

Solutions of this system, obtained by integration of these equations, will consist of pairs of functions $x_1(t)$, $x_2(t)$. Consider the following diagram:

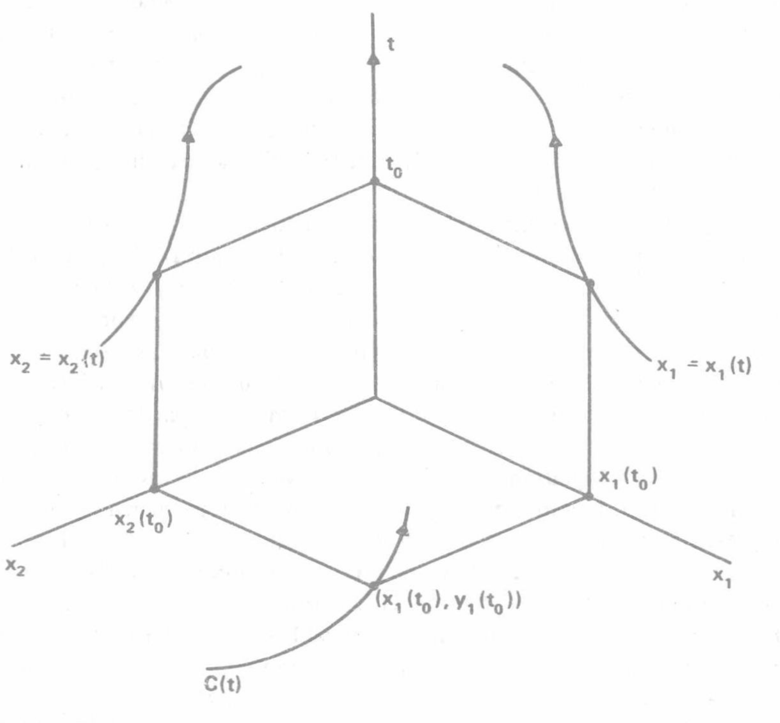

FIGURE 1. Diagrammatic representation of the relation between solutions and traje

Here the function $x_1 = x_1(t)$ is represented as a curve in the (x_1, t) plane; the function $x_2 = x_2(t)$ is represented as a curve in the (x_2, t) plane. The corresponding system trajectory is obtained as a curve in the x_1, x_2 plane as indicated: for each value of t, the corresponding values $x_1(t)$, $x_2(t)$ are read off the solution curves; these values uniquely determine a point (i.e., a state of the system) in the (x_1, x_2) plane. We shall consider some explicit examples shortly when we come to deal with linear systems.

The mathematical properties of the dynamical equations (1) are in accord with the intuitive picture we have given. Under very weak assumptions on the functions $f_1, \ldots, f_n$ (namely, that they be bounded and uniformly continuous on the state space), then the basic existence theorem for dynamical systems[1] holds that through each state there passes a trajectory. In the presence of a further weak condition (Lipschitz condition[1]) it can be stated that through every state there passes exactly one trajectory. This *unique trajectory property* is a statement of causality in these systems; two trajectories cannot cross, and hence every state has only one past which could give rise to it, and only one future which can emanate from it (assuming always, of course, that the forces on the system, as expressed in the dynamical equations, are not changing).

2. Stability

We now approach that aspect of dynamical system theory which is crucial from the standpoint of regulation. For our purposes, *regulation* shall be regarded as an autonomous system property related to the response of the system to a perturbation of state. The appropriate machinery for discussing such regulatory properties lies in the notion of the *stability properties* of the system, and we now turn to a discussion of these properties.

Stability refers to a relation between a given trajectory and those trajectories which are, in a certain sense, "nearby". Let us suppose we are given a trajectory C(t) of a system (1). At an instant t_0, let us modify, or perturb, the state of the system, so that instead of the system being in the state $C(t_0)$, it is in some other state $C'(t_0)$ close to $C(t_0)$. By the unique trajectory property, the new state $C'(t_0)$ determines an entire trajectory, which we may denote by $C'(t)$. Stability theory is concerned with the asymptotic behavior of the distances between C(t) and $C'(t)$ for $t > t_0$; i.e., with the discrepancy between what the unperturbed behavior of the system would be, and the actual behavior of the perturbed system.

There are several possibilities:

(a) $\lim_{t\to\infty} \|C(t) - C'(t)\| \to 0$ for all "nearby" trajectories $C'(t)$. In this case, the trajectories $C'(t)$ arising by perturbation all approach the unperturbed trajectory C(t). In this case, we say that C(t) is *asymptotically stable.* Such a trajectory possesses inherent regulatory properties, in that the effects of any perturbation of state will become vanishingly small. This situation is diagrammed in Figure 2.

(b) $\lim_{t\to\infty} \|C(t) - C'(t)\| < M$ for all "nearby" trajectories. In this case, the perturbed trajectories do not return to the unperturbed trajectory, but they do not get too far away. This is a kind of *neutral stability* of the unpertubed trajectory C(t), a weaker regulatory property than asymptotic stability. This situation is diagrammed in Figure 3.

(c) $\lim_{t\to\infty} \|C(t) - C'(t)\| \to \infty$ for at least one "nearby" trajectory. In this case C(t) is said to be *unstable.* We distinguish between the case in which only some of the nearby trajectories diverge from C(t) (*conditional instability,* cf, Figure 4), and the case in which all nearby trajectories diverge from C(t) (*asymptotic instability,* Figure 5).

Asymptotic stability has been invoked to account for many kinds of biological regulatory mechanisms. For instance, Waddington[2] has invoked the term *homeorrhesis* to

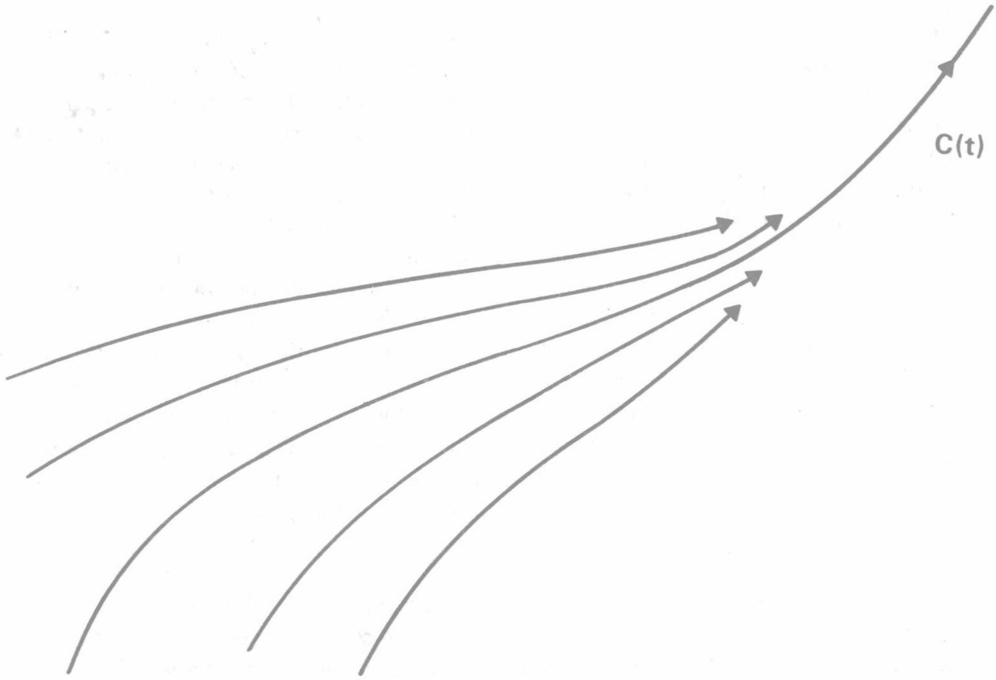

FIGURE 2. Behavior in the neighborhood of an asymptotically stable trajectory.

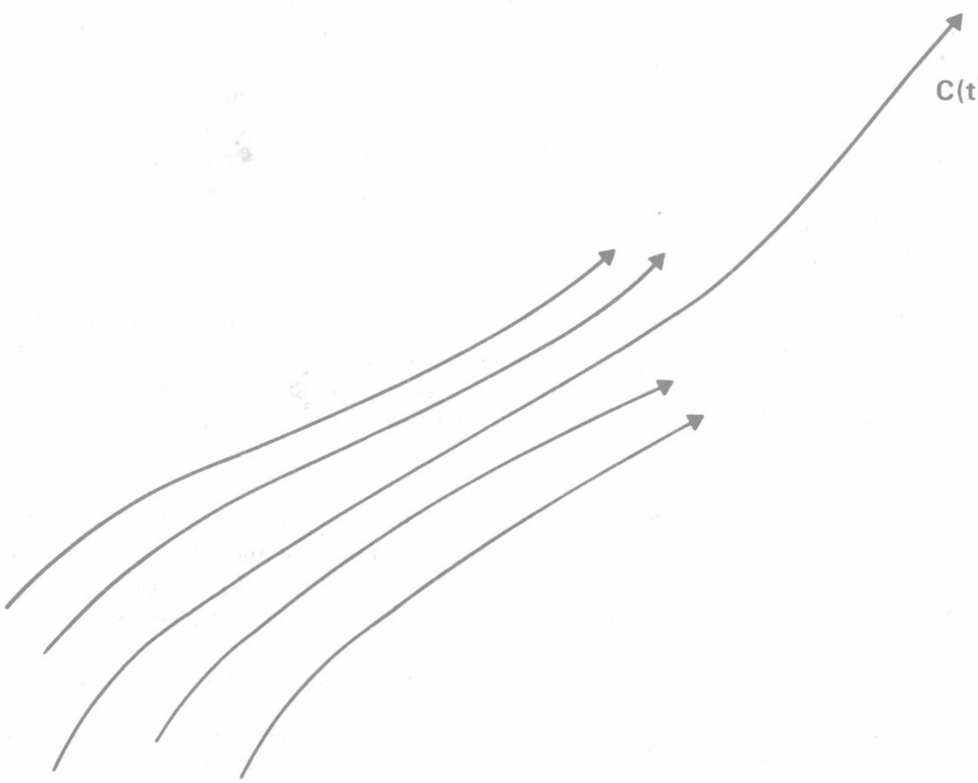

FIGURE 3. Behavior in the neighborhood of a neutrally stable trajectory.

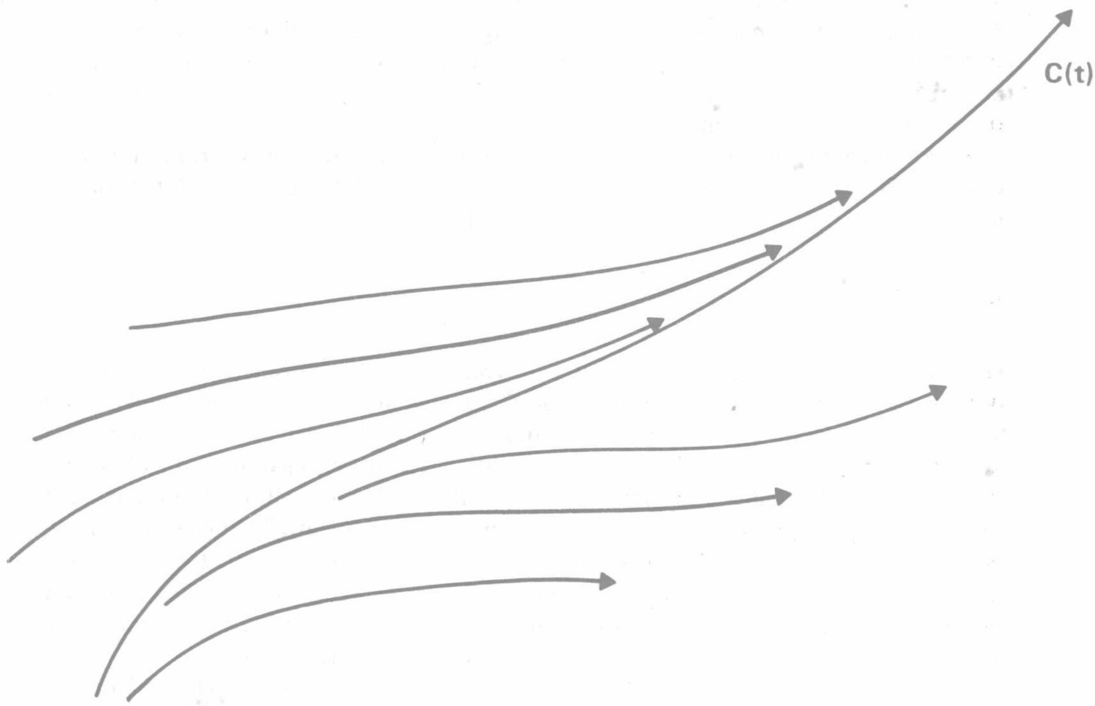

FIGURE 4. Behavior in the neighborhood of a conditionally unstable trajectory.

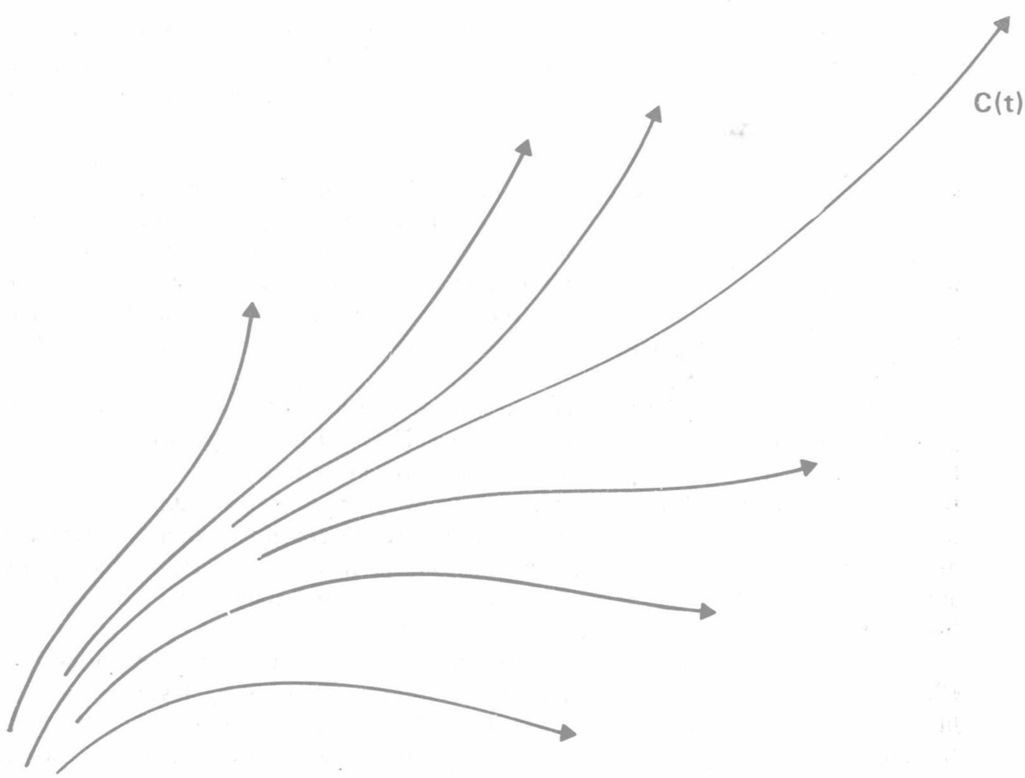

FIGURE 5. Behavior in the neighborhood of an asymptotically unstable trajectory.

account for the persistence of developmental pathways in embryology, despite experimental interference with the developing embryo, and pointed out that such homeorrhesis is an automatic consequence of an asymptotically stable developmental trajectory. Similar arguments can be invoked for related phenomena, such as the healing of wounds[3] and regeneration.[4]

In order to approach this last problem, let us shift consideration to a particular class of special trajectories of systems like (1). If we set the rates of change of the state variables equal to zero in (1), we obtain a set of algebraic equations of the form

$$f_i(x_i, \ldots, x_n) = 0, \quad i = 1, \ldots, n. \tag{3}$$

The solutions of these equations (if any exist) represent states in which none of the state variables are changing. Thus a system placed initially in such a state will remain there forever. Such states therefore represent entire trajectories (though of a degenerate kind), and are referred to as the *steady states* of the system. As entire trajectories, it makes sense to talk about the stability properties of steady states, and indeed all our definitions carry over directly, and we can talk about asymptotically stable, neutrally stable, or unstable steady states. Intuitively, an asymptotic steady state is one to which the system will return following a perturbation away from it; a neutrally stable steady state is one from which a perturbed trajectory will not diverge too far, and an unstable steady state is one which diverges further and further from the steady state as time proceeds.

The steady states of a system are important for many reasons. One reason not commonly appreciated is the fact that, given a dynamical system of the form (1), the stability properties of a trajectory C(t) of that system can be reduced to the problem of the stability of a steady state of an associated system.[5] The basic idea here is to contract the trajectory C(t) to a point, while maintaining the distances between C(t) and the neighboring trajectories. Thus the stability of steady states occupies a central conceptual role in the theory of stability, in addition to its importance in determining the properties of individual model systems.

As we shall see later (Section II 8) there is a close relation between the asymptotic stability of a steady state and the theory of feedback-control systems regulated by a set-point. Indeed, feedback control can be regarded as modifying the dynamics of a controlled system (by coupling to another system, or controller) in such a way that a particular desired state becomes asymptotically stable. Around such a state, the system may be said to exhibit *homeostasis*. Consequently, most attention in control theory has been paid to systems exhibiting such asymptotic stability, at least in a region surrounding the steady state.

However, biological regulation often crucially involves instability. For instance, models proposed by Rashevsky[6] and Turing[7] for the generation of inhomogeneities proceed by forcing a steady state, corresponding to a homogeneous situation, to become conditionally stable, so that random perturbations away from that steady state become magnified by the system. This amounts to a positive feedback situation, in which the distance of the state of the perturbed system from the homogeneous steady state grows autocatalytically. Excitatory phenomena such as nerve and muscle excitation can be likewise understood in terms of instability.[8]

Neutral stability is a special case of a situation in which certain solutions of the system (1) are *periodic*, so that the corresponding trajectories are *closed*. Such closed trajectories, like steady states, represent a limiting behavior of trajectories around them (it is a theorem[1] that a bounded trajectory can approach only a steady state or a closed trajectory), and are generally called *limit cycles*. A stable limit cycle is thus one which is approached asymptotically by all nearby trajectories. Such limit cycles are important in biological regulation because they can represent potential *clocks* for rhythmic or periodic processes, such as cell division or circadian rhythms. An extensive literature exists on this subject.[9] Such oscillations can also generate waves, whose relative phases may play a role in conveying information in the organism.[10]

3. Stability of Steady States, Linearization

In order to characterize the stability properties of the steady states of arbitrary dynamical systems, we may proceed in several ways. One way, of course, is to integrate the equations of motion and explicitly determine the asymptotic relationships between trajectories. This is often unfeasible. Another way is to utilize an indirect method, such as Lyapunov's Theorem,[1,5,11] which allows stability properties to be determined without directly integrating the dynamical equations. However, this method requires the fabrication of a function defined on the state space and possessing special properties (Lyapunov function), and this can often be difficult; we shall discuss the notion of a Lyapunov function in more detail in the next section. For most purposes, the most effective line of attack is the one we now proceed to describe, which reduces the general question of stability of steady states to a far more restricted class of systems, and one for which a complete analytical theory exists.

Let then $(x_1{}^0, x_2{}^0, \ldots, x_n{}^0)$ be a steady state of the system (1); we may as well assume it to be the origin, since by resetting the scales of the instruments which measure the state variables we can transform the origin of the state space to this point. We then have by definition that $f_i(0, 0, \ldots, 0) = 0$ for each index $i = 1, \ldots, n$. We can expand each of these functions f_i in a Taylor series about the origin, to obtain

$$f_i(x_1, \ldots, x_n) = f_i(0, \ldots, 0) + \sum_{j=1}^{n} \frac{\partial f_i}{\partial x_j}(0, \ldots, 0)\, x_j + \ldots \tag{4}$$

Sufficiently close to the origin, we can neglect the higher-order terms, to obtain

$$\frac{dx_i}{dt} = \sum_{j=1}^{n} \frac{\partial f_i (0, \ldots, 0)}{\partial x_j}\, x_j \quad i = 1, \ldots, n \tag{5}$$

where we have substituted these relations back into the system (1). We find then that the dynamical equations of the system, close to the origin, are themselves approximated by new and simpler dynamical equations of the form

$$\frac{dx_i}{dt} = \sum_{j=1}^{n} a_{ij} x_j \quad i = 1, \ldots, n \tag{6}$$

where we have written

$$a_{ij} = \frac{\partial f_i (0, \ldots, 0)}{\partial x_j}.$$

Systems of the form (6) are called *linear* dynamical systems. We shall now briefly set down the stability properties of the origin for such systems, and then turn to the question of how far these properties can be transferred to the original system (1), of which the system (5) is the *linearization* around the origin.

The stability properties of (6) are completely determined by the matrix of coefficients $A = (a_{ij})$, and in particular, on the eigenvalues of this matrix. If the eigenvalues are all distinct, then we can introduce new coordinates $u_i, \ldots, u_n$ into the neighborhood of the