SYSTEM IDENTIFICATION AND SAMPLING STRATEGIES APPLIED TO THE DEVELOPMENT OF COMPARTMENT MODELS

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COMPARTMENT MODELS

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CHAPTER I

INTRODUCTION

The influence of large-scale engineering projects on the biosphere has created a need for the management of ecosystems. Therefore, many aspects of the fields of systems analysis and ecology have been integrated and synthesized, resulting in systems ecology, a viable science of ecosystem design and management. Among the principles emerging from this "biosociation" (Patten, 1971, p. xiv) is the unfoldment of state models for environmental systems. This development has paralleled the use of compartment models for biological systems in general (Mohler, 1974). Practical applications of such systems methods are a potential mechanism for guiding management and analyses of environmental impact, provided that sampling and identification methods are developed to satisfy the modeling demands.

Laboratory and field microecosystems have definite boundaries and can be manipulated and replicated, producing useful models for the dynamical behavior of natural ecological systems (Odum, 1971, p. 20). The synthesis of research in biological modeling (microcosms) and mathematical modeling, with particular emphasis on the simulation and prediction of the behavior of ecological processes in response to natural and perturbed environmental conditions, is progressing to a high degree of sophistication. Systems analysis and mathematical modeling of biological processes introduce diverse research problems on a scale

not generally encountered in engineering and physical science. Fundamental principles must therefore be provided for systems ecology.

The construction of a model for an ecological process requires a theory for sampling ecological variables as a function of time, the ultimate objective being identification of the state model which relates ecosystem structure and function. Methods of systems identification for compartment models exist, including schemes presented by Halfon (1974 and 1975), Leary and Skog (1972), Milanese and Molino (1974), and Cobelli and Romanin-Jacur (1976), but their application is limited because of the absence of a general sampling theory to guide data collection. The basic principle of state identification is discussed in detail by Lee (1964) and Sherif and Wu (1974). There are also specific theories of sampling designed for system identification, which for the most part rely on the Nyquist theory, including a sampling strategy considered by Ng and Goodwin (1976) based upon the design methods of Mehra (1974).

With the advent of the modern high-speed digital computer, many engineering systems have become discretized in both time and magnitude. Examples include satellite and space probe telemetry and communication systems and the telephone networks which link central offices. With such data acquisition and information processing systems it is almost impossible to sample too rapidly. Unlike these engineering problems, the sampling period is not generally the only limiting factor in the analysis of ecosystems. In other words, it is possible to sample ecological structure both too slowly and too rapidly. It is not sufficient, as with many engineering systems, to merely fix the sampling frequency according to the Nyquist rate and then decide the arithmetic

precision of the sample quantization based upon required accuracy or fidelity criteria. For ecological systems the Nyquist rate is rarely known, a priori, and furthermore the sampling frequency can be shown to be dependent upon the sample quantization.

Based upon the specific identification scheme presented by Lee (1964), an associated sampling theory has been developed which can be extended for the implementation of specialized, and perhaps more effective, identification schemes (see Astrom and Eykhoff, 1971; Nieman, Fisher and Seborg, 1971; and Bellman and Astrom, 1970).

The sampling theory yields a priori computable bounds for which the sampling period may be determined for data collection. These upper and lower bounds for time invariant systems are shown to be dependent upon the arithmetic precision of the samples, the dimension of the ecosystem, and some intuitive bounds on the system dynamics, i.e., the entity turnover.

Chapter II presents a review of the literature pertaining to the problem to be discussed in this thesis. The concepts of systems ecology and model formulation are explored, stressing the need for the study of functional change in relation to ecosystem structure. Chapter III contains a discussion of the algorithm selected for the determination of compartmental rate coefficients for the input-output tracer analysis of biological systems. The algorithm is based upon a single-dose tracer input and a new deterministic sampling theory for data acquisition, both of which are presented in Chapter IV.

A tie between theory and experiment is given in Chapter V wherein the conditions for structural identifiability of a compartmental system are developed. Chapter VI concerns the design of a system for the

tracer technique of constant infusion.

Several examples illustrating the use of the identification scheme, the sampling theory, and the conditions for identifiability are considered in Chapter VII; and in Chapter VIII, the conclusions and recommendations for future areas of research are provided. The computer code which implements the identification algorithm is described in the Appendix.

CHAPTER II

REVIEW OF RELATED LITERATURE

Introduction

The discipline of systems ecology has led to the discovery of several general principles which express certain aspects of the behavior of an ecosystem. This chapter contains a review of previous research which aids in understanding the basic concepts of this study. The literature reviewed concerns the modeling of ecosystem structure and function, including the assumptions which underlie the models and their implications. The postulation of a basic formulation is presented, with major emphasis placed upon the analysis of tracer input-output experiments applied to microcosms. The first section pursues the development of the literature concerning ecological systems analysis. This is followed by sections which detail the major principles of ecosystem structure and function, compartment modeling, and tracer analysis.

History

The word "system" refers to an organized collection of components interacting and functioning as a whole, which is, in some sense, purpose or goal directed. The concept of state-space analysis of a system is recognized in fields where the time behavior of a physical process is of interest. One such discipline is modern ecology, the basic unit of

study being the ecosystem. The ecosystem concept has received considerable theoretical and experimental attention since 1940, although its development extends back to the 19th century. Systems ecology is a new approach in which state-space concepts may be utilized in describing and analyzing interrelations which emerge at the ecosystem level. The ultimate objective of systems ecology is the development of a science of ecosystem design, synthesis, and management. Probably the earliest actual applications of the idea of simulating the dynamics of ecosystems on computers were those of J. S. Olson (1965). G. M. Van Dyne, J. S. Olson, and B. C. Patten organized one of the first training programs in systems ecology in the 1960's at the Oak Ridge National Laboratory and the University of Tennessee where they formulated radioactive tracer studies of physiological systems (Patten, 1966). These pioneers together with K. E. F. Watt (1966, 1968), in resource management, C. S. Holling (1966), who studied population dynamics, and H. T. Odum (1960), by conducting energy flow research, revolutionized the field of ecology by providing a vital link with engineering systems analysis procedures.

Successful analysis of a dynamic system proceeds from a model which represents the essential aspects of a system under study and can be validated by comparison of the simulated response to the response of the physical reality. Models may be phenomenological, empirical, or analytical depending on their purpose, the available techniques that can be used, and the amount and quality of available knowledge. For many years laboratory ecosystems, including microcosms and controlled seminatural or artificial systems on a small scale, have served as useful models for the dynamic behavior of natural ecological systems. Coupling these biological models (microcosms) to mathematical models

and systems analysis, with the ultimate objective being to simulate and predict the behavior of ecosystems in response to natural and perturbed environmental conditions, provides an integrated guide for the measurement of structure and function of ecological processes.

A diversity of mathematical models exists for ecosystems. Nonlinear differential equations of the form of Volterra-Lotka are used to represent interacting populations, Markov processes and finite state models describe ecological succession, input-output models borrowed from economics give equilibrium constraints, and compartment models prescribe the dynamics of mass and energy balance. Compartment models, originally arising in biology, are viewed by many ecologists as playing a pivotal role in ecosystem analysis. The fundamental step in compartment model development involves conceptually separating the system into a number of distinct, interconnected, homogeneous and uniform components which are assumed to have distinguishable kinetics of transformation or energy transfer. The concepts of microcosms, tracer analysis, and compartment models are not unrelated. Atkins (1969) traces the origins of compartment modeling in tracer studies to the work of Hevesey (1923) who demonstrated the uptake and loss process of lead ions in plant roots. The first applications of compartment analysis to animals, involving the metabolism of radioactive bismuth in rabbits, were also made by Hevesey (Christiansen, Hevesey, and Lomholt, 1924). For his pioneering research in this area, George de Hevesey was awarded the Nobel Prize for Chemistry in 1943.

The term compartment was first used by Sheppard (1948). A great deal of literature on the general structural properties of compartmental models and tracer analysis have been published, including Sheppard and

Householder (1951), Hearon (1963), and Berman and Schoenfeld (1956). The fundamental aspects of ecosystem compartment modeling practiced today are presented by Patten (1971) in his "Primer for Ecological Modeling and Simulation."

The early applications of compartment modeling were primarily confined to tracer studies of biochemical and physiological systems. Although the compartment analysis approach to studying ecological systems is sometimes traced back to the early work of Kostitzin (1935), it was much later when the high-precision measurement methods employing radioactive tracers were used in compartment analyses of laboratory microcosms. The experiments by Whittaker (1961) dealing with radiophosphorus in aquarium microcosms and the analysis of radioactive cesium kinetics in terrestrial microcosms by Patten and Witkamp (1967) represent classic studies. With the tracer studies conducted at Oak Ridge National Laboratory, ecologists became more cognizant of the insight that systems analysis offers when applied to ecology; and its popularity increased.

In October, 1966, the United States International Biological Program (IBP) recognized a need for the development of models for large-scale, natural systems which are now referred to as Biomes. With the advent of these Biome studies, research shifted from microcosms and basic ecological processes to the analysis and mathematical modeling of these highly interconnected natural ecosystems. A framework was created requiring a holistic, systematic approach functioning both between and within Biomes (Neuhold, 1975). Perhaps the first attempt at a total ecosystem model, including the feedback of nutrients through a detritus food chain, was the model formulated for the Grassland Biome

study. Using the data base established for the shortgrass prairie ecosystem, Bledsoe et al. (1971) constructed the nonlinear model called PWNEE which was not totally acceptable as a useful simulation tool. A more successful model called LINEAR followed shortly through the efforts of Patten (1972a) and a team of ecologists from the University of Georgia. Innis (1975, 1978) describes in detail the development and implementation of the third total ecosystems model (ELM), which evolved from its predecessors. The multivolume work edited by Patten (1971, 1972b, 1975a, 1976), the paper by Weigert (1974), and the Alta Conference proceedings edited by Levin (1974) all survey other modeling efforts of both small- and large-scale environmental systems. Unfortunately, a detailed document of the modeling synthesis is not yet available, the best description being given in Patten (1975a). Thus, with this inexhaustive survey of research in systems ecology, mathematical modeling of natural ecosystems is observed to have matured of late into an area of biological modeling which in some sense is quite separate from that of tracer analysis or physiological kinetics.

Application of the substantial advances in the mathematical modeling of ecological systems to the analysis of microcosms is considered in this study. A new theory for the measurement of structure and the determination of function using tracer analysis is presented. It is hoped that the theory can be extended to future applications in the sampling, measurement, and analysis of large-scale natural ecosystems.

Ecosystem Structure and Function

In an address to the Ecological Society of Japan, E. P. Odum (1962) defines ecology as the study of ecosystem structure and function.

Ecological structure is divided into the composition of the biotic community, the quantity and distribution of the abiotic materials, and the gradient of environmental conditions. Ecological function depends on the throughput of energy flow, the rate of material or nutrient cycling, and biological regulation and reaction to regulation. Structure is therefore implicitly a static concept; whereas function is dynamic, being dependent upon time as a variable. However, both structure and function are ultimately time dependent because of environmental forcing functions which are time varying.

In the beginning stages of ecological research, ecologists were content with a descriptive approach, leading from a mere species list to more mathematical realizations of species diversity involving, for example, Shannon's formula. Emphasis on the function of an ecosystem, dealing with studies ranging from production to community metabolism to total energy budgets, matured later. The search for a bridge for the existing gap between these two schools of ecology has dominated much of the recent ecosystem research.

In modern ecology, the concept of the ecosystem as the basic unit of study has led to the discovery of several general principles which express certain aspects of the behavior of natural systems. These principles are for the most part based upon models for structure and function of the ecosystem. Odum (1971, p. 17) gives the best known model as

$$\text{throughput} = \text{turnover} \times \text{content}. \qquad (2.1)$$

This model defines ecological function to be linearly proportional to ecological structure, with the constant of proportionality equal to

turnover. In steady-state systems, turnover equals the reciprocal of the time required for throughput to completely replace compartmental content.

When properly applied, Equation (2.1) provides a powerful tool for ecosystem analysis. The basic study of functional change in ecological systems is related to the idea of ecological stability, a fundamental principle of ecosystem analysis. Stability is not one concept, but many, all meaning the ecosystem is well behaved in some sense. For quite some time researchers believed ecological stability to be directly correlated with the structural concept of diversity (Odum, 1971, p. 148), but the exact relationship proved to be elusive (Woodwell and Smith, 1969). Using one commonly accepted definition of ecological stability based upon the choice of pathways for throughput (MacArthur, 1955), Rutledge, Basore, and Mulholland (1976) developed from first principles of information theory a new index for stability. This index relates stability to the diversity of throughput, an initial measure of the uncertainty (choice) of the sources for ecosystem throughput, minus the uncertainty resolved by knowledge of the pathways for throughput, i.e., the food web structure. The diversity of throughput is measured by the Shannon formula, and the resolved uncertainty is equated to the average mutual information. Using (2.1) to compute the diversity of throughput in terms of the diversity of content, Rutledge's model provides a useful relationship between stability and diversity.

Compartment Models

Another example of the application of Equation (2.1) is exemplified by the compartment modeling principle, a useful technique when depicting

mass or energy transfer in biological systems. A compartment model is defined by considering the component parts of an ecosystem representing the various biological or geophysical aspects as lumped entities, i.e., the compartments, which are able to receive and distribute energy, biomass, or materials and which accumulate these quantities at a rate proportional to the net balance of inflows and outflows. It is assumed that the compartments are homogeneous with instantaneous mixing, each acting as a storage element for the quantities flowing into and out of it. When a conservation of matter or energy law is applied to the system, a rate equation is obtained for each compartment. Although nonlinear and time-varying functions more accurately describe nature, the assumption of linearity is often a good approximation to real systems, providing valuable insight into the more complex nonlinear system through the local application of linear systems analysis. If the compartmental outflows are constrained to be linearly proportional to the amount of stored matter or energy in the donor (or source) compartment, then the so-called linear donor controlled model results. This type of compartment model represents the ecological condition of ultimate resource limitation (Patten, 1975b). The mathematical model is realized by the following expression

$$\dot{x}_i = \sum_{j=1}^{n}{}' a_{ij} x_j - a_{ii} x_i + u_i \quad (i = 1, \ldots, n), \tag{2.2}$$

where there are n compartments in the ecosystem, the prime notation indicates summation for all $j \neq i$, a_{ij} is the rate coefficient for transfer from compartment j to compartment i, x_i represents the content of compartment i and $\dot{x}_i$ its time rate of change, u_i expresses any possible exogenous inputs to compartment i, and

$$a_{ii} = \sum_{j=1}^{n,} a_{ji} + a_{oi}, \tag{2.3}$$

where a_{oi} indicates a transfer from compartment i out of the ecosystem to the environment, i.e., the exogenous turnover.

The compartment model described by (2.2) has the properties of $a_{ij} \geq 0$ for $i \neq j$, $a_{ii} > 0$, and $u_i \geq 0$, from which it can be proven that initially positive compartmental contents, $x_i(0) > 0$ ($i = 1, \ldots, n$), implies positive contents for all future time, $x_i(t) > 0$ ($i = 1, \ldots, n$) for all $t \geq 0$ (Mulholland and Keener, 1974). It can also be shown that a_{ii} represents the turnover for compartment i, or

$$a_{ii} = 1/T_i \quad (i = 1, \ldots, n), \tag{2.4}$$

where T_i is the turnover time for compartment i. There are essentially two interpretations of turnover involving either steady-state or transient ecosystem operating conditions.

In steady-state each compartment in the ecosystem is balanced with respect to inputs and outputs, and the content of each compartment is constant. Hence, $\dot{x}_i = 0$ for all t, and from (2.3)

$$a_{ii}\, x_i = \sum_{j=1}^{n,} a_{ij}\, x_j + u_i. \tag{2.5}$$

In Equation (2.5), the right side of the equality expresses total influx to compartment i as the sum of the exogenous input (u_i) and endogenous inputs (summation). In steady-state, compartmental input equals output which in turn both equal throughput. Denoting throughput by z_i, (2.5) becomes

$$a_{ii}\, x_i = z_i \quad (i = 1, \ldots, n) \tag{2.6}$$

which is clearly the same as (2.1) when a_{ii} is interpreted as the compartmental turnover.

Under transient operating conditions, compartment i is assumed to be isolated from the rest of the ecosystem, so that (2.2) becomes

$$\dot{x}_i = -a_{ii}\, x_i \tag{2.7}$$

Note that both exogenous and endogenous inputs to compartment i are now zero. The solution of (2.7) is

$$x_i(t) = x_i(0)\, e^{-t/T_i}, \tag{2.8}$$

where $x_i(0)$ is the compartment content at $t = 0$, and a_{ii} is given by (2.4). Equation (2.8) prescribes the compartment content at time $t = T_i$ to be 36.8 percent of the initial value. The turnover time T_i also prescribes the half-life T_o of the contents of the isolated compartment to be

$$T_o = T_i \ln 2. \tag{2.9}$$

Tracers

The steady-state and transient conditions described often do not represent natural ecological phenomena involving the throughput and content of energy, biomass, or material. Therefore, in order to study the kinetics of the system it is necessary to label the material flows in the ecosystem with radioactive isotopes. In compartmental analysis these labels are called tracers, and to be useful they must be easily detected by an observer. A tracer may be either radioactive or stable. Ideally, these tracers (1) should be metabolically indistinguishable

from the mother substance, (2) must be small enough so that the system under observation will not be perturbed, and (3) must be uniformly distributed throughout the tracee (Atkins, 1969, p. 15). Various aspects of the tracer method are presented by Sheppard (1962), Jacquez (1972), Resigno and Beck (1972), and Shipley and Clark (1972).

Equation (2.2) is taken as the material balance equation for the label (tracer). The basic assumption is that (2.2) holds equally for the material as for its label so that the rate coefficients (a_{ij}) of material transfers are identical. This implies that the material and its isotope label are ecologically equivalent.

Mathematically, the use of isotope labels corresponds to a linearizing assumption mainly because the superimposed isotope levels are generally small in magnitude when compared to the material transfers within the ecosystem. Thus, even though the ecosystem structure and function are known to obey a steady-state nonlinear relationship, the introduction of the isotope represents a perturbation for which the linear approximation (2.2) holds true (Patten, 1975b).

Through the use of radioactive tracers, experiments can be designed to measure the rate coefficients of (2.2) given time series data for the compartment contents and inputs. Compartment content plus the associated rate coefficients determine material transfers as defined by the assumed model for ecosystem structure and function (2.1), or equivalently (2.2).

Shipley and Clark (1972) describe two methods of analysis using radioactive tracers, the single dose method and the constant-infusion method. The single-dose method is usually applied through the instantaeous introduction of tracer into each of the n compartments of the

biological system. This generates n solutions of (2.2) which depend only upon the initial conditions (each single dose) because all exogenous inputs are zero after the abrupt introduction of tracer. Exponential functions are then fitted to the measured time series data for the compartmental contents. The coefficients and exponents of these functions are used to compute the rate constants of (2.2). For the constant-infusion method, tracer is introduced, in turn, into each of the n compartments at a constant rate until a steady-state is reached as indicated by constant radioactivity in all compartments. This gives n equations resembling (2.5) in which all x_j ($j = 1, \ldots, n$) have been measured. The n^2 rate coefficients a_{ij} ($i, j = 1, \ldots, n$) are then determined by n^2 algebraic equations.

Ecosystem experiments differ from the tracer methods of physiology and biochemistry in that it is not always possible to introduce tracer directly into all compartments within the system. Indeed, natural inputs to ecosystems are typically limited to one or two compartments. This fact requires the development of different experimental design and sampling methods for ecosystem analysis. A consideration of these methods constitutes the subject of this study.

Summary

The preceding review has covered a small fraction of the total literature concerning the development of mathematical models as quantitative and qualitative tools with which to study ecosystems. A universal algorithm is desired which will relate ecosystem structure to ecosystem function for the evaluation of laboratory systems used as models of nature. The modeling principles and theoretical techniques

reviewed in this chapter provide a foundation for the development of such an identification scheme and its associated sampling theory. The description of tracer methods available for the acquisition of laboratory data is meant to form a basis for an experimental design for the proposed model identification and sampling schemes.

CHAPTER III

STATE IDENTIFICATION METHODS

Introduction

The problem of determining the function of an ecosystem from time series measurements of its structure has become known as a system identification problem. This chapter describes a computational strategy which has been used in this research for the identification of compartmental rate coefficients for the tracer analysis of biological systems. The algorithm is restricted to those systems whose processes may be characterized by one or more linear first-order ordinary differential equations.

Special inputs rather than those of normal operation are necessary for the off-line identification of tracer analysis. These input signals are reviewed, and basic experimental designs which coexist with theoretical techniques of data collection and identification are presented. In the remainder of the chapter, identification schemes are proposed for specific system structures with either a single-dose or a constant-infusion tracer input.

Input Signals for Identification

The determination of a model relating structure and function of an ecosystem from experimental time series observations of the state is

known as system identification. It includes the estimation of system parameters for both observable and unobservable components within the biological system. One of the fundamental problems of system identification is whether or not the parameters can be determined uniquely (Lee, 1964). If unique estimates cannot be obtained (the system is not identifiable), then the experimental procedures should be altered. Determination of structure from function results from an input-output tracer experiment. The different identification schemes that are available can be classified according to the basic elements of the problem and the input signals, the earliest methods being those based on frequency, step, and impulse responses. Special inputs rather than those of normal operation are necessary for these schemes, so the techniques are termed off-line identification and therefore apply only to linear stationary processes where input/output relations which hold for one set of inputs are good for all inputs (Graupe, 1972).

For the purposes of tracer analysis the local model is a linear donor controlled biological compartment model defined by

$$\dot{\underline{x}} = \underline{A}\underline{x} + \underline{B}\underline{u} \tag{3.1}$$

where the state $\underline{x}$ is an n-dimensional vector of the compartmental contents, the coefficient matrix $\underline{A} = (a_{ij})$ is an ordered array of the compartmental rate coefficients, the input $\underline{u}$ defines the ecosystem inputs as an m-dimensional vector, and the input connection matrix $\underline{B} = (b_{ij})$ is of n rows and m columns with entry b_{ij} equal to one if input u_j enters compartment i, if not, the entry is zero.

In (3.1), the inputs $\underline{u}$ and their entry into the ecosystem compartments, the $\underline{B}$ matrix, are known. The solution of the identification

problem for (3.1) requires a method to determine the entries in $\underline{A}$, containing the rate coefficients, given sufficient measurements of the state $\underline{x}$.

The use of sinusoidal or random (white noise) inputs for identification involves the frequency domain technique of spectral analysis to obtain system parameters. Sinusoidal, as well as random, inputs are difficult, if not impossible to implement for tracer laboratory experiments as performed on biological and ecological systems.

The frequency-response identification requires sine-wave inputs having variable frequencies. The sinusoidal inputs require experimental means of generating sine-wave input disturbances and varying the frequency over a range of interest.

Perhaps the simplest input signal to apply is the step input. A step input is given by

$$u(t) = \begin{cases} 0 & \text{for } t < 0 \\ 1 & \text{for } t \geq 0. \end{cases} \tag{3.2}$$

The ideal step forcing function consists of a zero-duration rise-time which is impossible in practice, so all practical step inputs are approximations in which the error is negligible if the initial rise-time is of a duration much shorter than the period of highest frequency of interest in the identification (Graupe, 1972). The transient or free response of the system after the input is then observed to determine certain unknown parameters. Other system parameters can be found from the steady-state response obtained as $t \to \infty$.

The impulse-response identification scheme follows closely the identification of linear processes by means of their step response.

This method is defined by Nieman, Fisher, and Seborg (1971) as the response of the system output variable to a Dirac delta function input, i.e., an input pulse of height h and duration 1/h in the limit as h tends to infinity. Obviously, delta functions cannot be realized because of their infinite amplitude, but an experimental approximation is made by using input pulses of finite width and unit area. An impulse response has the same nature as a system's free, transient response when excited by some equivalent initial condition. The Dirac delta function has a uniform frequency content and hence will excite all the system modes, making it an ideal function for system identification.

The possibility of finding a unique solution to the identification problem depends not only on the input signal, but also on the structure of the system. The identifiability of the model structure of (3.1) as discussed by Bellman and Astrom (1970) requires the assumption that the system is observable and controllable in the sense of Kalman. Also assuming the system to be initially at rest, that is, $x(0) = 0$, the input-output relation is then uniquely given by the impulse response. A more meaningful discussion of the identifiability, controllability, and observability of the compartment structure under discussion will be pursued subsequently.

Single Dose and Constant Infusion Experiments

The use of radioactive tracers in compartmental studies provides two types of experimental design for the identification problem when inputs to all n compartments are available, i.e., when $\underline{B} = \underline{I}$, the n-th order identity matrix, in the system model given by

$$\dot{\underline{x}} = \underline{A}\underline{x} + \underline{B}\underline{u}. \qquad (3.3)$$

In the biological literature, these two experiments are known as the single-dose (slug) method and the constant-infusion (continuous) method (Shipley and Clark, 1972), while in system theory these methods correspond to transient and steady-state analysis respectively. Interpretation of the two techniques with respect to toxic transfers leads to assessment of acute and chronic toxicity. In fact, the mathematical details of the constant infusion method are directly applicable to continuous bioassay tests.

The single-dose method requires that an instantaneous induction of tracer be delivered sequentially to each of the n compartments of the biological system, resulting in n transient responses of the system which depend only upon the initial conditions because all exogenous inputs are zero after the rapid introduction of tracer. This method simulates an impulse input function (Schwarz and Friedland, 1965, p. 120). Therefore, Equation (3.1) becomes

$$\dot{\underline{x}} = \underline{A}\underline{x} \tag{3.4}$$

since $\underline{u} = 0$ for all time $t > 0$. The solution of (3.4) is

$$\underline{x}(t) = \underline{\Phi}(t)\ \underline{x}(o) \tag{3.5}$$

where $\underline{\Phi} = (\phi_{ij})$ is the $n \times n$ state transition matrix, shown by the method of successive approximations (Picard's Method) to be given by the matrix exponential:

$$\underline{\Phi}(t) = e^{\underline{A}t}. \tag{3.6}$$

The single-dose method is most easily described by writing out the matrix product defined by (3.5) for each of the n compartments:

$$x_i(t) = \sum_{j=1}^{n} \phi_{ij}(t)\, x_j(o), \quad (i = 1, \ldots, n). \tag{3.7}$$

Since a single dose of tracer is injected at t = 0 into only one compartment (k) per experiment and it is assumed that the tracer mixes homogeneously and instantaneously, the resulting situation is described mathematically by the following conditions:

$$x_j(0) = \begin{cases} 0, & \text{for } j \neq k \\ 1, & \text{for } j = k \end{cases} \tag{3.8}$$

where the single dose of tracer to compartment k is normalized to unity. Incorporating the conditions of (3.8) into (3.7) yields

$$x_i(t) = \phi_{ik}(t), \quad (i = 1, \ldots, n) \tag{3.9}$$

since all terms in the summation are zero except j = k.

When a single dose of tracer is applied to compartment k, the time series of compartmental contents, $x_i(t)$ for i = 1, . . . , n, define the n entries in the k-th column of the $\underline{\Phi}$ matrix. If a single dose of tracer is then successively applied to the other (n - 1) compartments in the biological system, the remaining (n - 1) columns of $\underline{\Phi}$ can be identified. This requires an interpretation of (3.9) for k = 1, . . . , n. The identification scheme results in time series data for each ϕ_{ij} entry in the $\underline{\Phi}$ matrix. Relating these data for the n^2 entries in $\underline{\Phi}$ to closed form mathematical relationships requires the further identification of the coefficients and exponents of the exponential functions known to comprise each entry. These coefficients and exponents can be identified by various techniques, including graphical methods (curve peeling) and computer techniques based upon slope and intercept

measurements of the compartmental time series data (Shipley and Clark, 1972). As a result, the rate coefficients for the transfer of the tracer between compartments can be calculated. These coefficients will then define the $\underline{A}$ matrix of (3.4).

The entries in the $\underline{\phi}$ matrix have been presented as continuous time functions. However, discrete time series samples of compartment tracer levels are usually obtained as the experimental results. Thus, in order to use these discrete data for identifying the coefficients of the $\underline{A}$ matrix, a sampling theory is needed. A unified sampling theory and identification algorithm for tracer analysis is discussed in detail later. This sampling theory also applies to the implementation of the single dose-method.

The second method, known as the constant-infusion method, involves a continuous input of tracer to each of the n compartments, in turn, at a constant rate until the system is observed to be in steady-state as indicated by constant radioactivity in all compartments. For open systems, steady-states are observed when input equals output over non-zero time intervals.

The constant-infusion method is based upon the steady-state analysis of the linear non-homogeneous system described by (3.1) where $\underline{B} = \underline{I}$, the identity matrix. Consider the typical case where labeled material is infused into compartment k at a constant rate and no other inputs to the system are allowed. In mathematical terms, this situation is described by Equation (3.3) where

$$\underline{u} = \underline{e}_k \tag{3.10}$$

and $\underline{e}_k$ is the column vector of all zeros except the k-th entry which is

unity. In terms of the components of the input vector $\underline{u}$, (3.10) is expressed as

$$u_j = \begin{cases} 0, & \text{for all } j \neq k \\ 1, & \text{for } j = k, \end{cases} \tag{3.11}$$

where the infusion rate of the k-th compartment has been normalized to unity. After the input of (3.10) has been applied to the model (3.3), the system is allowed to reach steady-state as indicated by $\dot{x} = 0$, which is an asymptotic condition with increasing time. Equation (3.3) then becomes

$$\underline{0} = \underline{A}\underline{x}_k + \underline{e}_k \tag{3.12}$$

where $\underline{x}_k$ is the steady-state response to the input $\underline{e}_k$. The quantity of tracer stored in each compartment in steady-state, described by $\underline{x}_k$, can be measured by standard radiological methods. Thus, (3.12) gives n equations in the n^2 unknown entries in $\underline{A}$. The experiment is now repeated (n - 1) times, so that (3.12) is obtained for $k = 1, \ldots, n$. The result is n^2 independent equations to determine all n^2 entries in the $\underline{A}$ matrix. These equations are linearly independent because the set of inputs $\underline{e}_1, \ldots, \underline{e}_n$ provide an algebraic basis for the solution space.

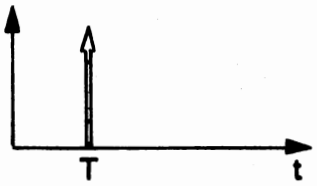
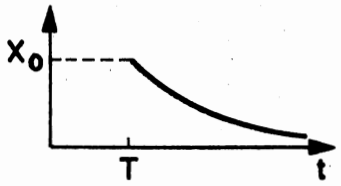
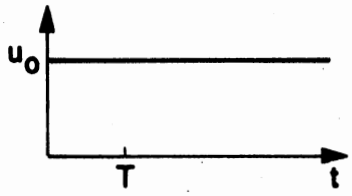
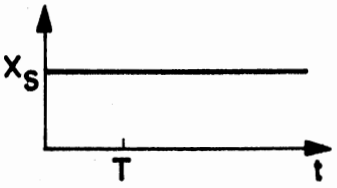
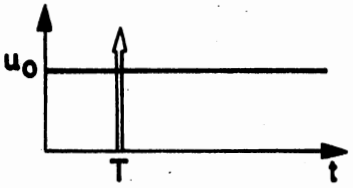
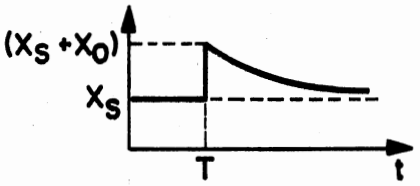
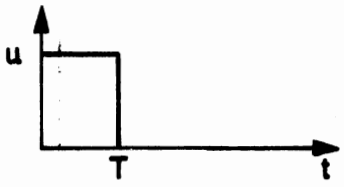
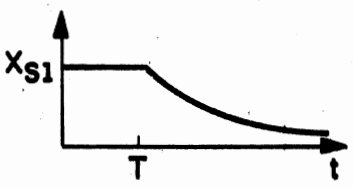
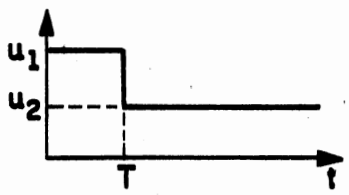
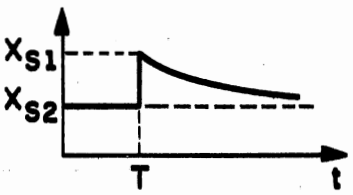
The constant inputs of the constant-infusion method result in a system steady-state generated by n experiments giving n measured and distinct steady-states. Hence, experimental design is concerned with ensemble samples of steady-states rather than time samples of transient states. It should be noted that this corresponds to a steady-state step input response for identification.

Basic Experiments

The use of radioactive tracers is prone to varying experimental procedures, especially with the advent of highly sophisticated instruments and new radioisotopes. Practical experiments must be designed to coexist with developed theoretical techniques. The Environmental Protection Agency Environmental Research Laboratory (Athens, Georgia) (Hill, 1977) has developed three basic experiments to assess the environmental impact on aquatic microcosms of toxic material inputs. As shown in Table I, the first test input represents a slug of toxic material, the second considers a constant chronic input level of toxin, and the third forms the superposition of the aforementioned experiments. The microcosm responses to the three basic inputs are also shown in Table I. The toxic slug of part (a) elicits a transient response with initial condition x_0, and the constant input level of part (b) gives rise to a steady-state defined by x_s. By assuming a linear model for the microcosm system, part (c) of Table I illustrates the resultant superposition principle. It should be noted that the basic microcosm experiments contain information regarding the validity of the linear modeling assumption. For linear models, the microcosm responses to the inputs of Table I, parts (a) and (b), should sum to give the response to the input of part (c). If this superposition is in fact true, the single-dose method [the input of part (a)] can be effectively used to identify the numerical model for the microcosm. Therefore, the validity of the linear state model (3.1) should be clear from the outcomes of the basic experiments of Table I. Generally, a local linear model can be identified for small perturbations (x_0 is small compared to x_s)

TABLE I

BASIC MICROCOSM EXPERIMENTS

	Input	Response
(a)		
(b)		
(c)		
(d)		
(e)		

caused by impulse inputs at a given system loading defined by u_o. A local model defined in this way will be dependent upon the system loading.

Also in Table I, two new experiments are proposed for linear model identification using tracers or toxic material flows as microcosm inputs. These inputs, based upon step functions, have been designed for ease of application in the laboratory and mathematical convenience for system identification. Indeed, as will be shown in the next chapter, these basic experimental inputs lead to a sampling theory which is essential to the successful application of standard identification schemes. This result, in turn, prescribes an experimental design for the <u>a priori</u> determination of the period for data collection in the laboratory.

It is desirable to establish an equivalence between the basic experiments of Table I. For $x_{s1} = x_o$, the responses of parts (a) and (d) are the same for $t > T$. This results in a relationship between the strength of the toxic slug input and the level u_1. For $t > T$, the model of (3.1) is applied to part (a):

$$\begin{aligned} \dot{\underline{x}} &= \underline{A}\underline{x} \\ \underline{x}(T) &= \underline{x}_o \end{aligned} \tag{3.13}$$

and part (d):

$$\begin{aligned} \dot{\underline{x}} &= \underline{A}\underline{x} \\ \underline{x}(T) &= \underline{x}_{s1}. \end{aligned} \tag{3.14}$$

For mathematical simplicity consider the tracer analysis assumption that all compartments have input pathways. Assume $\underline{B} = \underline{I}$ in (3.1) and apply

n unit impulse inputs, so that

$$\dot{\underline{x}} = \underline{Ax} + \underline{e}\ \delta(t) \tag{3.15}$$

where $\underline{e}$ is an n × 1 vector given by

$$\underline{e} = \sum_{i=1}^{n} \underline{e}_i . \tag{3.16}$$

Integrating through the state discontinuity at t = T:

$$\dot{\underline{x}}\ dt = \int_{T-}^{T+} \underline{Ax}\ dt + \int_{T-}^{T+} \underline{e}\ \delta(t)dt \tag{3.17}$$

yields

$$\underline{x}(T^+) - \underline{x}(T^-) = \underline{e}. \tag{3.18}$$

However, it is noted that $\underline{x}(T^+) = \underline{x}_o$ and $\underline{x}(T^-) = 0$ so that

$$\underline{x}_o = \underline{e}. \tag{3.19}$$

Now from (3.1), $\underline{x}_{s1}$ is obtained when $\dot{\underline{x}} = \underline{0}$:

$$\underline{x}_{s1} = -\underline{A}^{-1}\ \underline{u} \tag{3.20}$$

where $\underline{u}$ is an n × 1 with n-components to be prescribed. Then for the response equivalence, $\underline{x}_{s1} = \underline{x}_o$ implies

$$\underline{e} = -\underline{A}^{-1}\ \underline{u}, \tag{3.21}$$

yielding

$$\underline{u} = -\underline{Ae}. \tag{3.22}$$

State identification using the basic experiment of part (d), which describes the impulse response, assumes a global linear model for the

microcosm. While global linearity is an attractive mathematical assumption, it may be unreasonable in a biological sense. However, regardless of the applicability of the basic experiment of part (d) to the model identification problem, the experiment is useful as a laboratory test for estimating the time necessary for the return to a natural steady-state of microcosms for which toxic inputs have been totally removed.

The basic experiment of part (e) of Table I is analogous to the superposition of impulse and constant inputs for part (c). This basic experiment involves the transition between two microcosm steady-states defined by x_{s1} and x_{s2} defined by the inputs u_1 and u_2, respectively. The transition is mathematically accomplished by a step function, while in the laboratory the transition is easily obtained by instantaneously changing the pump infusion rate driving the microcosm. By setting $x_o = x_{s1}$, as before, and $x_{s2} = x_s$, it is clear that for $t > T$ the experiments of part (c) and part (e) are the same. Input equivalence can be obtained by using the method previously employed for the global transition to the zero state, giving

$$\underline{u}_1 = -\underline{A}\underline{e} \tag{3.23}$$

$$\underline{u}_2 = \underline{u}_o \tag{3.24}$$

which is obtained for $\underline{B} = \underline{I}$ in (3.1).

The basic experiment of part (e) has been designed as an identification technique for local linear models. Linearity can be tested in the laboratory by observing response superposition as a result of adding two microcosm inputs.

As previously noted, the basic experiments of parts (d) and (e)

have been designed for ease of application in the laboratory and to aid in the development of a sampling theory. It turns out that under certain conditions these basic experiments also avoid the problem in tracer analysis of having input access to each compartment. However, the equivalence between the inputs of Table I is essential in eliminating the so-called precursor problem. In Figure 1 an example of a two-compartment model with a single-dose input into the precursor compartment is shown in part (a) along with the input and compartment response plots in part (b).

The precursor problem deals with the impossibility of estimating the maximum value (x_m) of the response of compartment x_2 to the impulse input to compartment x_1. In order to develop an effective laboratory data collection strategy, it is necessary to have known rules for amplitude and time descretization. Because x_m is unknown before the experiment is completed, it is very difficult in ordinary tracer analysis to develop a rule for amplitude quantization. Given a sample period, data on microcosm structure is collected at discrete times; and the values of these data are quantized by the finite arithmetic precision of the measuring instruments. However, the quantization of time and amplitude are not sequential processes; they are in fact related to one another. This gives rise to the commonly used laboratory procedure for single-dose experiments of taking microcosm samples very rapidly at first until x_2 reaches its maximum and then more slowly to accommodate the compartmental dynamics inherent in the free response. The asynchronous sampling procedure described is difficult to analyze, particularly when the propagation of measurement errors through the identification algorithm is required. A periodic sampling scheme would

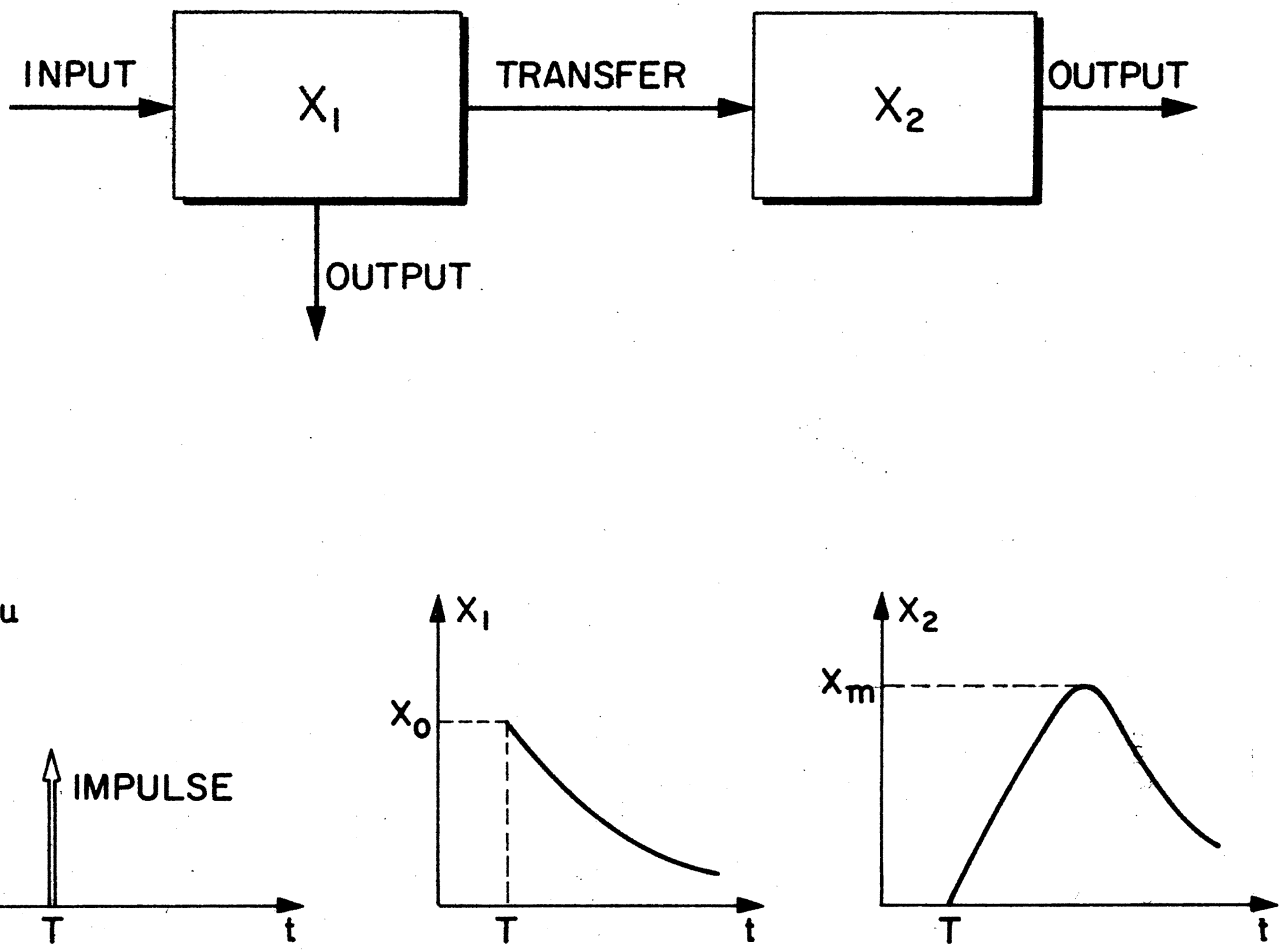


Figure 1. Two-Compartment System With Precursor

be more desirable.

The basic experiments (d) and (e) of Table I eliminate the precursor problem. This follows from the fact that transitions between steady-states in compartmental systems are monotonic and bounded by the initial and final states (Thron, 1972). Therefore, the amplitude quantization process is well defined, and a periodic sampling strategy is possible. The data collection, sampling theory, and model identification algorithms using the basic experiments of Table I are discussed in more detail in the sequel.

Direct Method

The mathematical model given by (3.1) is presumed to be the local model of a biological system where any possible exogenous inputs, such as introduction of tracer, and their entry into one or more of the compartments, the $\underline{B}$ matrix, are known. The solution of the identification problem for (3.1) requires a method to determine the entires in $\underline{A}$, containing the rate coefficients, given sufficient measurements of the state $\underline{x}$. The tracer method of biochemistry and physiology provides a solution of the identification problem when inputs to all n compartments are available, i.e., when $\underline{B} = \underline{I}$, the n-th order identify matrix, but for a typical ecosystem model where pathways to certain compartments are inaccessible, i.e., $m < n$, the tracer method cannot be fully employed.

Consider the following experiment in which a constant (known) input is applied to the ecosystem modeled by (3.1). After sufficient time has elapsed, a steady-state is observed, as indicated by $\dot{\underline{x}} = \underline{0}$. Denote this steady-state by the vectors $\underline{x}_s$, which is the solution of

$$\underline{0} = \underline{A}\underline{x}_s + \underline{B}\underline{u}. \tag{3.25}$$

In the experiment under discussion, the input is assumed to be a constant rate of infusion of labeled material. It is also assumed the steady-state can be measured using standard radiological methods. On a new time scale, the experiment is re-started at time t = 0 by removing all inputs to the ecosystem. Thus, before t = 0 the system is in steady-state $\underline{x}(0) = \underline{x}_s$, while for t > 0 the state of the system is governed by the solution of

$$\dot{\underline{x}} = A\underline{x} \tag{3.26}$$

because $\underline{u} = \underline{0}$ for t > 0. The labeled contents of the compartments of the ecosystem start at t = 0 with values determined by $\underline{x}_s$ and decrease exponentially as t becomes large as all the labeled material flushes from the system along the pathways for material transfer (see Table I).

It is assumed the input $\underline{u}$ which generates the steady-state $\underline{x}_s$ can be chosen so that $\underline{x}_s$ does not lie in a proper subspace of the n-dimensional state space of solutions of (3.1). This assumption is satisfied by systems (3.1) which are completely controllable, that is, systems capable of being driven by inputs to any state in state space. Johnson (1976) shows that open systems are generally controllable if the matrix of the intercompartmental rate coefficients (which exclude environmental transfers) is of rank n-1.

Despite the fact the state of the system, under the experimental conditions described, is governed by the differential equation (3.26), the problem is basically one of algebra. This is because the solution of (3.26) is prescribed by

$$\underline{x}(t) = \Phi(t)\underline{x}(0) \tag{3.27}$$

where the matrix exponential is denoted by the n × n matrix

$$\underline{\Phi}(t) = e^{\underline{A}t} \tag{3.28}$$

and called the state transition matrix. Thus, any future state $\underline{x}(t)$ at $t > 0$ is defined by the initial state $\underline{x}(0)$ through the transformation $\underline{\Phi}(t)$ defined by (3.28).

Consider (3.27) with $t = \tau$, for which

$$\underline{x}(\tau) = \underline{\Phi}(\tau)\underline{x}(0). \tag{3.29}$$

Now let $t = 2\tau$, giving

$$\underline{x}(2\tau) = \underline{\Phi}(2\tau)x(0) = \Phi^2(\tau)\underline{x}(0) = \underline{\Phi}(\tau)x(\tau) \tag{3.30}$$

Thus, for any positive integer i, it is clear that

$$\underline{x}(i\tau) = \underline{\Phi}\ \underline{x}[(i - 1)\tau] \quad (i = 1, 2, \ldots), \tag{3.31}$$

where $\underline{\Phi} = \underline{\Phi}(\tau)$ and (3.27) with $t = i\tau$ is the solution of this difference equation.

A continuous record of the state $\underline{x}(t)$ is not required in order to determine $\underline{\Phi}$, which through (3.28) gives $\underline{A}$. Since $\underline{\Phi}$ is an n × n constant matrix, constraint equations numbering n^2 are required to prescribe the entries in this matrix. The problem reduces to finding $\underline{A}$ from a finite number of discrete and regularly spaced samples of the state, given at times $t = 0, \tau, 2\tau, \ldots, k\tau$ where τ is the sample period. Substitution of these state samples into (17) gives

$$\underline{x}(\tau) = \underline{\Phi}\ \underline{x}(0)$$

$$\underline{x}(2\tau) = \underline{\Phi}\ \underline{x}(\tau)$$

$$\begin{matrix} \cdot & \cdot \\ \cdot & \cdot \\ \cdot & \cdot \end{matrix} \qquad (3.32)$$

$$\underline{x}(k\tau) = \underline{\Phi}\, \underline{x}[(k-1)\tau].$$

This linear algebraic system contains n^2 unknowns (all ϕ_{ij} entries of $\underline{\Phi}$) and k independent vector equations of n components each, for a total of kn equations. For $k < n$ no unique solution of (3.32) exists, and the system is overdetermined for $k > n$. Thus, $k = n$ or $(n + 1)$ discrete samples of the state are necessary and sufficient to determine $\underline{\Phi}$. And, from (3.28)

$$\underline{A} = (1/\tau)\, \ell n\, \underline{\Phi}, \qquad (3.33)$$

which identifies the rate coefficient matrix.

It is possible to re-write system (3.32) in the following more standard algebraic form

$$\underline{X}_2 = \underline{\Phi}\, \underline{X}_1, \qquad (3.34)$$

where $\underline{X}_1$ is an $n \times k$ matrix formed by columns from the first k state samples,

$$\underline{X}_1 = \{\underline{x}(0), \underline{x}(\tau), \ldots, \underline{x}[(k-1)\tau]\}, \qquad (3.35)$$

and $\underline{X}_2$ is similarly obtained from the next k state samples delayed by one sample period,

$$\underline{X}_2 = \{\underline{x}(\tau), x(2\tau), \ldots, x(k\tau)\}. \qquad (3.36)$$

For $k = n$ in (3.34) the solution for $\underline{\Phi}$ is obtained by inverting the

matrix $\underline{X}_1$. This assumes n linearly independent state samples which is indeed the case when the ecosystem model defined by (3.26) applies. Thus, the identification problem is solved by

$$\underline{A} = (1/\tau)\ \ell n(\underline{X}_2\underline{X}_1^{-1}) \tag{3.37}$$

under these stated conditions.

It is mathematically necessary and sufficient to make (n + 1) discrete state measurements in order to solve for $\underline{\Phi}$. At least (n + 1) measurements are required for a unique solution. However, on occasion it may be desirable to obtain more than (n + 1) state samples. For example, when significant experimental error is suspected in the state data, it may be of use to increase the dimension of the data set beyond (n + 1). Under these conditions k > n, and there are more equations than unknowns in (3.32). A Gaussian least squares estimate for the solution of (3.34) can then be obtained by multiplying (on the right) by the matrix transpose of X_1, denoted by X_1^T. This results in

$$\underline{X}_2\underline{X}_1^T = \underline{\Phi}\ \underline{X}_1\underline{X}_1^T. \tag{3.38}$$

The model identified by the solution of (3.38) is then given by

$$\underline{A} = (1/\tau)\ \ell n[\underline{X}_2\underline{X}_1^T)(\underline{X}_1\underline{X}_1^T)^{-1}]. \tag{3.39}$$

This model produces a minimum in the error defined as the square of the difference between predicted state values and measured state values on the time interval t = 0 to t = kτ (Lee, 1964).

It should be noted that some care is required in the application of (3.33) to ecosystem analysis. The identification scheme discussed is unconstrained with respect to the entries in the $\underline{A}$ matrix, that is,

(2.3) does not constrain the columns of the identified matrix. Also, (3.1) is an approximate linear relationship, which is not generally viewed as being universally applicable to ecosystem analysis (Bledsoe, 1976). Thus, transfer matrices with confused ecological meaning are possible as outcomes of the computation defined by (3.33). However, the ecological validity of the identified $\underline{A}$ matrix always can be judged by whether or not the constraint (2.3) holds. The problems associated with unconstrained identification are known (Halfon, 1974), and constrained identification methods which for the most part overcome these problems exist (e.g., Halfon, 1975). Indeed, the single-dose and constant-infusion methods of biochemistry and physiology (Shipley and Clark, 1972) are both constrained by (2.3). The obvious disadvantage of the constrained identification methods is that they force all ecosystems to obey (3.1). A detailed comparison of the applicability of the constrained versus unconstrained identification methods to ecosystem analysis is not available. However, both methods are hampered by the lack of a suitable sampling theory, which is the subject of the next chapter.

The proposed technique for the analysis of compartmental flows has been based upon complete time series measurements of the state which lead to direct identification of the transfers. An indirect identification scheme is proposed in the following section for the determination of the $\underline{A}$ matrix from knowledge of the accumulation of the state in compartments external to the biological system.

Indirect Method

An identification algorithm is desired for the case wherein a tracer element is superimposed, diffuses through a closed biological

system, and eventually amasses in given compartments. Time series measurements of only the accumulative entities are proposed to indirectly identify the unknown rate coefficients of the system. The local biological model of (2.2) is incorporated, and by designating the system of Figure 2 to describe the post-experimental data, the linear dynamic observer yielding a system identification technique is given by

$$\dot{\underline{y}}(t) = \underline{K}\,\underline{x}(t) \tag{3.40}$$

where $\underline{x}(t)$ is an n-dimensional vector of the compartmental states and $\underline{K} = \text{diag}\{k_1, \ldots, k_n\}$ defines an $n \times n$ diagonal matrix of the n rate coefficients describing the transfers to the compartments in which tracer is accumulating as defined by the n-dimensional vector $\underline{y}$. Integrating (3.40) gives its solution as

$$\underline{y}(t) = \underline{K}\,\underline{A}^{-1}[\underline{\Phi}(t) - \underline{I}]\underline{x}(0) \tag{3.41}$$

where $\underline{A} = (a_{ij})$ is the $n \times n$ matrix of rate coefficients defined by (2.2) and (2.3), $\underline{\Phi}(t) = e^{\underline{A}t}$ as defined in (3.28), $\underline{I}$ is the n-th order identity matrix, and $\underline{x}(0)$ is the nominal measurement of the state $\underline{x}(t)$. Note that there is assumed to be no tracer in the output compartments initially, i.e., $\underline{y}(0) = \underline{0}$.

The total amount of tracer accumulated in the observer system state $\underline{y}(t)$ will be defined by

$$\underline{y}(\infty) = -\underline{K}\,\underline{A}^{-1}\,\underline{x}(0), \tag{3.42}$$

since the matrix exponential of (3.41) vanishes as $t \to \infty$ when maximum accumulation is complete. Thus, any future state of the observer at $t > 0$ is prescribed by

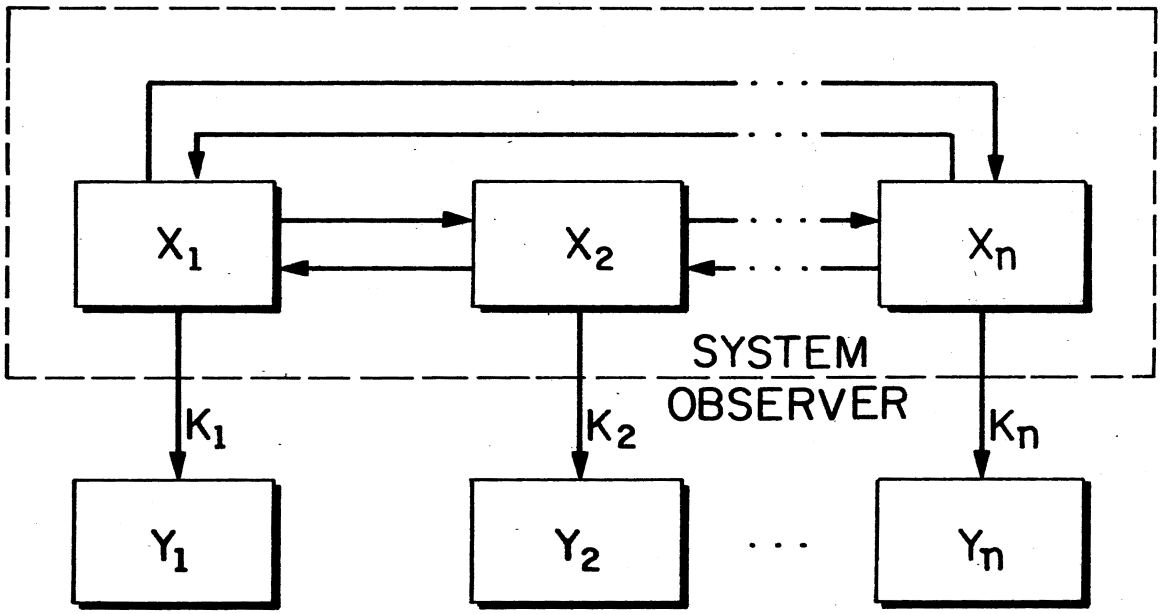


Figure 2. System Observer

$$\underline{y}(t) = \underline{K}\,\underline{A}^{-1}\,\underline{\Phi}(t)\,\underline{x}(0) + \underline{y}(\infty). \tag{3.43}$$

Consider (3.43) with $t = \tau$, for which

$$\underline{y}(\tau) = \underline{K}\,\underline{A}^{-1}\,\underline{\Phi}\,\underline{x}(0) + \underline{y}(\infty), \tag{3.44}$$

where $\underline{\Phi}(\tau) = \underline{\Phi}$. Now let $t = 2\tau$, giving

$$\underline{y}(2\tau) = \underline{K}\,\underline{A}^{-1}\,\underline{\Phi}\,\underline{x}(\tau) + \underline{y}(\infty) \tag{3.45}$$

Likewise, for any positive integer i,

$$\underline{y}(i\tau) = \underline{K}\,\underline{A}^{-1}\,\underline{\Phi}\,\underline{x}[(i-1)\tau] + \underline{y}(\infty) \quad (i = 1, 2, \ldots). \tag{3.46}$$

Given a finite number of discrete, regularly sampled measurements of the state at times $t = 0, \tau, 2\tau, \ldots k\mathrm{T}$, a linear algebraic system is formulated as follows:

$$\begin{aligned}
\underline{y}(\tau) &= \underline{K}\,\underline{A}^{-1}\,\underline{\Phi}\,\underline{x}(0) + \underline{y}(\infty) \\
\underline{y}(2\tau) &= \underline{K}\,\underline{A}^{-1}\,\underline{\Phi}\,\underline{x}(\tau) + \underline{y}(\infty) \\
&\;\;\vdots \qquad\qquad \vdots \\
\underline{y}(k\tau) &= \underline{K}\,\underline{A}^{-1}\,\underline{\Phi}\,\underline{x}[k-1)\tau] + \underline{y}(\infty).
\end{aligned} \tag{3.47}$$

Designating the $n \times k$ matrix formed by the first k observer state samples as $\underline{Y}_1$ and similarly obtaining $\underline{Y}_2$ from the next k measurements of the observer states delayed by one sample period, there results

$$\underline{Y}_1 = \{\underline{z}(\tau), \underline{z}(2\tau), \ldots, \underline{z}(k\tau)\} \tag{3.48}$$

and

$$\underline{Y}_2 = \{\underline{z}(2\tau), \underline{z}(3\tau), \ldots, \underline{z}[(k+1)\tau]\} \tag{3.49}$$

where $\underline{z}(i\tau) = \underline{y}(i\tau) - \underline{y}(\infty)$.

Recalling the system of equations developed for direct identification of the rate coefficients, it is clear that

$$\underline{Y}_1 = \underline{K}\,\underline{A}^{-1}\,\underline{\Phi}\,\underline{X}_1 = \underline{K}\,\underline{A}^{-1}\,(\underline{X}_2\,\underline{X}_1^{-1})X_1 = \underline{K}\,\underline{A}^{-1}\,\underline{X}_2 \tag{3.50}$$

and similarly,

$$\underline{Y}_2 = \underline{K}\,\underline{A}^{-1}\,\underline{\Phi}\,\underline{X}_2. \tag{3.51}$$

However, assuming the existence of the inverse of the observation matrix $\underline{K}$,

$$\underline{X}_2 = \underline{A}\,\underline{K}^{-1}\,\underline{Y}_1 \tag{3.52}$$

implies that

$$\underline{Y}_2 = \underline{K}\,\underline{\Phi}\,\underline{K}^{-1}\,\underline{Y}_1. \tag{3.53}$$

This results in

$$\underline{Y}_2\,\underline{Y}_1 = \underline{K}\,\underline{\Phi}\,\underline{K}^{-1} = e^{\underline{K}\,\underline{A}\,\underline{K}^{-1}\tau}. \tag{3.54}$$

Thus the matrix of rate coefficients identified by the measurements of $y(k)$ is

$$\underline{K}\,\underline{A}\,\underline{K}^{-1} = \underline{A}' = \frac{1}{\tau}\,\ell n\,(\underline{Y}_2\,\underline{Y}_1)^{-1}, \tag{3.55}$$

obtained by solving the identification problem without sampling the states of the system. Again, it is necessary and sufficient to make $(n+1)$ discrete measurements for a unique solution of Equation (3.55).

Equation (3.55) not only identifies the $\underline{A}'$ matrix from observer measurements only, but the scheme also identifies the $\underline{A}$ matrix of the biological system. The entries in the $\underline{A}'$ matrix are

$$a'_{ij} = (k_i/k_j)a_{ij} \quad (i, j = 1, \ldots, n) \tag{3.56}$$

where a_{ij} is the i-th row and j-th column entry in $\underline{A}$ and k_i is the i-th diagonal entry in $\underline{K}$. Furthermore, since k_i is a transfer from the system to the observer, this term has been previously defined as a_{oi} in (2.3). Note that $a'_{ij} = a_{ij}$. Thus, (2.2) and (3.56) provide $(n^2 + n)$ constraints for the same number of unknowns from which the $\underline{A}$ matrix entries can be obtained.

When applicable, the obvious advantage of indirect identification derives from the ability to compute transfers within a biological system from external measurements. Applications of this method include the analysis of organisms in which an introduced (labeled) substance is metabolized, and the substance plus metabolites accumulate in closed pools.

Approximation Method

The proposed identification schemes are based upon a discrete-time model for ecosystem structure which is used to compute $\underline{\Phi}$ which is defined by (3.28). The expression (3.33) relates the matrix $\underline{\Phi}$ to the unknown coefficient matrix $\underline{A}$, describing the material transfers between compartments. The solution of (3.33) requires knowledge of the step size τ and the computation of the natural logarithm of the matrix $\underline{\Phi}$. Noting that

$$\underline{\Phi} = \sum_{k=0}^{\infty} (\underline{A}\tau)^k/k!, \tag{3.57}$$

it is evident that the use of finite precision arithmetic affects the termination of the above infinite series representation for $\underline{\Phi}$ and $\underline{A}$. Consider the case where τ is chosen small enough to eliminate terms of $k \geq 2$ within the finite precision of the arithmetic, then from (3.57),

$$\underline{\Phi} = \underline{I} + \underline{A}\tau. \tag{3.58}$$

This prescribes

$$\underline{A} = (\underline{\Phi} - \underline{I}) \frac{1}{\tau} \tag{3.59}$$

as an approximation of the exact relationship given by (3.33). The conditions on τ for this representation are discussed in the sequel.

Constant Infusion

The proposed techniques for the determination of biological function based upon a finite number of measurements of structure utilize the single-dose method of tracer input. Constant infusion of tracer into a single compartment yields only n independent equations, thereby generally requiring n separate experiments for a unique solution to the identification problem. Hence, experimental design is concerned with ensemble samples of steady-states. Assuming an n-compartment system with the infusion rate normalized to unity, (3.12) becomes

$$\underline{A}\underline{x}_k = -\underline{e}_k. \tag{3.60}$$

Repeating the experiment (n - 1) times so that results are obtained for $K = 1, \ldots, n$ yields n^2 linearly independent equations of the form

$$\underline{A}\,\underline{X} = -\underline{I} \tag{3.61}$$

where

$$\underline{X} = \{\underline{x}_1, \ldots, \underline{x}_n\}$$

and

$$\underline{I} = \{\underline{e}_1, \ldots, \underline{e}_n\}.$$

Solving for the unknown matrix of rate coefficients, one observes from (3.61) that

$$\underline{A} = -\underline{X}^{-1} \tag{3.62}$$

if and only if $\underline{A}$ is the matrix of coefficients of an open system, i.e., $\underline{A}$ is invertible.

For the tracer analysis problem only infusion into single compartments leading to n sequential experiments,

$$\underline{u} = \underline{e}_k, \quad k = 1, \ldots, n. \tag{3.63}$$

is considered. However, it may be desirable to infuse tracer into more than one compartment for certain experiments, wherein

$$\underline{u} = \underline{u}_k, \quad k = 1, \ldots, n. \tag{3.64}$$

describes the n experiments for which corresponding steady-states are measured. Equation (3.61) then becomes

$$\underline{A}\,\underline{X} = -\underline{u} \tag{3.65}$$

and if the inputs $\{u_k\}$ span the state space and the system is open, then

$$\underline{A} = -\underline{u}\,\underline{X}^{-1}. \tag{3.66}$$

When inputs into all compartments are not possible, then the

question of identifiability arises. This question has been investigated for the single-dose method (Bellman and Astrom, 1970), but remains open for constant infusion.

With respect to constant levels of chronic toxicity and continuous bioassay methods for laboratory ecosystems, it would be of use to determine how the statistical errors in the ensemble samples propagate through the identification algorithm to the entries of the resultant modal transfer matrix. Sharp (1977) has propagated errors in the $\underline{A}$ matrix given errors of the observed states.

Summary

This chapter has dealt with a linear model relating biological structure and function. The results are ideally suited to the tracer analysis of compartmental systems wherein the tracer element represents a small perturbation superimposed upon the material flows within the system. Implementation of the identification algorithms are founded upon the basic experiments which have been characterized by such tracer inputs.

The two basic tracer inputs from which discrete measurements of the system state may be obtained, i.e., single dose and constant infusion, led to separate identification strategies. For identification resulting from single-dose inputs, periodic data is obtained directly from the transient response of a single experiment on a biological system or from measurements of the response to the input of an associated observer system. A constant infusion of tracer gives an ensemble of steady-states from which the system may be identified.

A computer code implementing the single-dose identification technique is found in the Appendix. The limiting capabilities of both approaches to parameter identification are discussed in subsequent chapters.

CHAPTER IV

SAMPLING THEORY

Introduction

This chapter is concerned with experimental design and limitations of the model identification theory. Problems of precision and accuracy of the state samples are of prime concern. Because the periodic samples are obtained from radiological measurement instruments, these data are of finite arithmetic precision. In other words, each sample $\underline{x}(k\tau)$ is a number rounded to a fixed number of decimal places. This roundoff error affects the sample period τ, or the rapidity with which the ecosystem is sampled, as required for identification. The sample period is also affected by the maximum and minimum compartmental turnovers within the ecosystem. These turnovers indicate the extent of the ecosystem dynamic behavior, hence their relationship to the sample period is clear. In that which follows, the relationships between the dynamic range of compartmental turnovers, the finite arithmatic precision of state samples, and the sample period are explored. These relationships are to be used as a guide for choosing the proper sample period for the solution of the identification problem.

The compartment model identification schemes discussed in the previous chapter were based upon a discrete data set. These data are discrete in both time and magnitude. For ecological systems it is not

sufficient, as with many engineering systems, to first decide the sample period according to the Nyquist rate (Carlson, 1975, p. 298) and then decide the arithmetic precision of the sample quantization based upon required accuracy or fidelity criteria. Before testing an ecological system, the bandwidth or Nyquist rate is rarely known. Therefore, a non-Nyquist sampling theory would be extremely useful for model identification.

Amplitude Bounds

Before discussing the non-Nyquist sampling theory, it is necessary to compute bounds on the magnitude of compartmental content variations in response to input perturbations. The inputs designed for model identification involve only transitions between system steady-states. That is, the non-Nyquist sampling theory will be developed exclusively for the basic experiments described in Table I. It will be shown that compartmental transitions between steady-states are monotonic, with exponential bounds depending on the maximum compartmental turnover and the minimum exogenous compartmental turnover. These bounds on compartmental variations determine how the finite arithmetic precision of the samples affects the amplitude quantization, which is an important first step toward computing the sample period for data collection.

The state transition matrix of (3.6) is given by

$$\underline{\Phi}(t) = \underline{L}\,\underline{\Psi}(t)\,\underline{L}^{-1} \tag{4.1}$$

where

$$\underline{\Psi}(t) = e^{\underline{\Lambda}\,t} \tag{4.2}$$

and $\underline{L}$ is an invertible n × n matrix of the eigenvectors of $\underline{A}$, and $\underline{\Lambda}$ is a diagonal n × n matrix of the eigenvalues, so that

$$\underline{L}^{-1} \underline{A} \underline{L} = \underline{\Lambda}. \tag{4.3}$$

The n eigenvalues of $\underline{A}$ are defined as the roots of the polynomial

$$|\underline{I}\lambda - \underline{A}| = 0. \tag{4.4}$$

These eigenvalues, which describe the ecosystem dynamics, are related to the compartmental turnovers. This relationship, in part, follows from a theorem by the Russian mathematician Gerschgorin: The eigenvalues λ_1, . . . , λ_n of the matrix $\underline{A} = (a_{ij})$ lie in one of the circular regions of the complex λ-plane described by

$$|\lambda + a_{jj}| \leq \sum_{i=1}^{n}{}' |a_{ij}|, \ (j = 1, \ . \ . \ . \ , n). \tag{4.5}$$

The right side of (4.5) is the sum of the absolute values of all the entries in the j-th column of $\underline{A}$ except the principal diagonal entry $-a_{jj}$. Let

$$r_j = \sum_{i=1}^{n}{}' |a_{ij}| \tag{4.6}$$

Then, (4.5) is the closed circular region in the λ-plane of radius r_j and center $-a_{jj}$. It should be noted that the theorem is also true for row sums (Wilf, 1962, p. 39).

In the development of the sampling scheme, it is assumed that the eigenvalues of the $\underline{A}$ matrix are real. This assumption simplifies the analysis of the sampling problem. For example, the controllability of the continuous system (3.1) with real eigenvalues implies the controllability of the discrete system (3.32) regardless of the sample period

value τ (Kalman, 1963). A theorem by Frobenius (1912) for irreducible nonnegative matrices provides insight into the nature of the matrices of compartment models (Emanuel, 1978).

Definition 4.1 (Gantmacher, 1959)

The $n \times n$ matrix $\underline{A} = (a_{ij})$ is said to be reducible if and only if there is a permutation of the indices which reduces it to the form

$$\underline{A} = \begin{bmatrix} \underline{B} & \underline{O} \\ \underline{C} & \underline{D} \end{bmatrix} \tag{4.7}$$

where $\underline{B}$ and $\underline{D}$ are square matrices of order less than n. Otherwise the matrix $\underline{A}$ is called irreducible.

Definition 4.2 (Lancaster, 1969)

A matrix $\underline{A}$ is said to be nonnegative if and only if no element of $\underline{A}$ is negative.

Theorem 4.1 (Frobenius, 1912)

An irreducible nonnegative matrix $\underline{A} = (a_{ij})$ always has a positive characteristic number r, which is a simple root of the characteristic equation. The moduli of all the other characteristic numbers are at most r. A characteristic vector $\underline{z}$ with positive coordinates corresponds to the "dominant" characteristic number r.

In order to apply the above theorem to matrices of ecological systems, define an $n \times n$ matrix $\underline{D}$ as follows

$$\underline{D} = \underline{A} + \zeta \underline{I} \tag{4.8}$$

where $\underline{I}$ is an n-th order identity matrix and

$$\zeta = \max |a_{ii}|, \quad i = 1, \ldots, n. \tag{4.9}$$

Then $\underline{D}$ is nonnegative, $\underline{D}$ is reducible if and only if $\underline{A}$ is reducible, and the eigenvalues u_i of $\underline{D}$ are related to those of $\underline{A}$ by

$$u_i - \zeta = \lambda_i, \quad i = 1, \ldots, n. \tag{4.10}$$

Hence, from (4.10) and Gerschgorin's theorem, if $\underline{A}$ is irreducible, then there is at least one real, simple, least-negative eigenvalue which is dominant. The other roots may or may not be real. Sufficient conditions for the eigenvalues of $\underline{A}$ to be real have been presented by Goldberg (1956) and Hearon (1963) and are discussed in detail by Thron (1972), Smith (1971), and Funderlic (1971).

Theorem 4.2 (Hearon)

If an $n \times n$ matrix $\underline{A} = (a_{ij})$ is sign-symmetric and satisfies any one of the following properties, then it is similar to a symmetric matrix and hence all its roots are real:

(a) There exist positive numbers $s_1, s_2, \ldots, s_n$ such that

$$a_{ij} s_j = a_{ji} s_i.$$

(b) The graph of $\underline{A}$ has no cycles involving three or more nodes.

(c) For each subset $\{i_1, i_2, \ldots, i_k\}$ of $\{1, \ldots, n\}$, $k \leq n$,

$$a_{i_1 i_2} a_{i_2 i_3} \cdots a_{i_{k-1} i_k} a_{i_k i_1} = a_{i_1 i_k} a_{i_k i_{k-1}} \cdots a_{i_2 i_1}.$$

Theorem 4.3 (Goldberg)

If a matrix $\underline{A} = (a_{ij})$ is such that $a_{ij} a_{ji} \geq 0$ and property (c) of Theorem 4.2 is satisfied, then all roots are real.

A discussion of the physical meaning of these properties applied to compartmental models is provided by Funderlic (1971). Property (a) states that fluxes in the two directions between compartments are equal. No indirect feedback may exist in order to satisfy property (b), and property (c) implies that for each cycle in the graph of the system the reverse cycle exists and has the same product.

Shipley and Clark (1972) and Atkins (1969) along with many other authors of books on the tracer method accept the conditions for real eigenvalues as not being unusual.

The $\underline{A}$ matrices of ecosystems described by (2.2) are column diagonally dominant, that is, $a_{jj} > 0$ and

$$|a_{jj}| \geq \sum_{i=1}^{n}{}' |a_{ij}| = r_j \quad (j = 1, \ldots, n). \tag{4.11a}$$

Let

$$\delta_j = |a_{jj}| - r_j \quad (j = 1, \ldots, n). \tag{4.11b}$$

Then, $\delta_j \geq 0$ defines the distance between the j-th Gerschgorin circle and the Im $\{\lambda\}$ axis of the λ-plane as shown in Figure 3. These circles lie in the left-half of the λ-plane. This follows from the fact that $-a_{jj}$ (the center of the circle) is a negative real number which is in magnitude greater than or equal to the radius r_j.

If $\delta_j = 0$, for all $j = 1, \ldots, n$, then the ecosystem is closed with respect to the material flows defined. Under this condition, all Gerschgorin circles intersect $\lambda = 0$, the A-matrix is singular, and hence the set of eigenvalues includes zero. Very few model ecosystems, even laboratory microcosms, are truly closed. Therefore, at least one of the terms δ_j will be assumed to be nonzero, which implies the

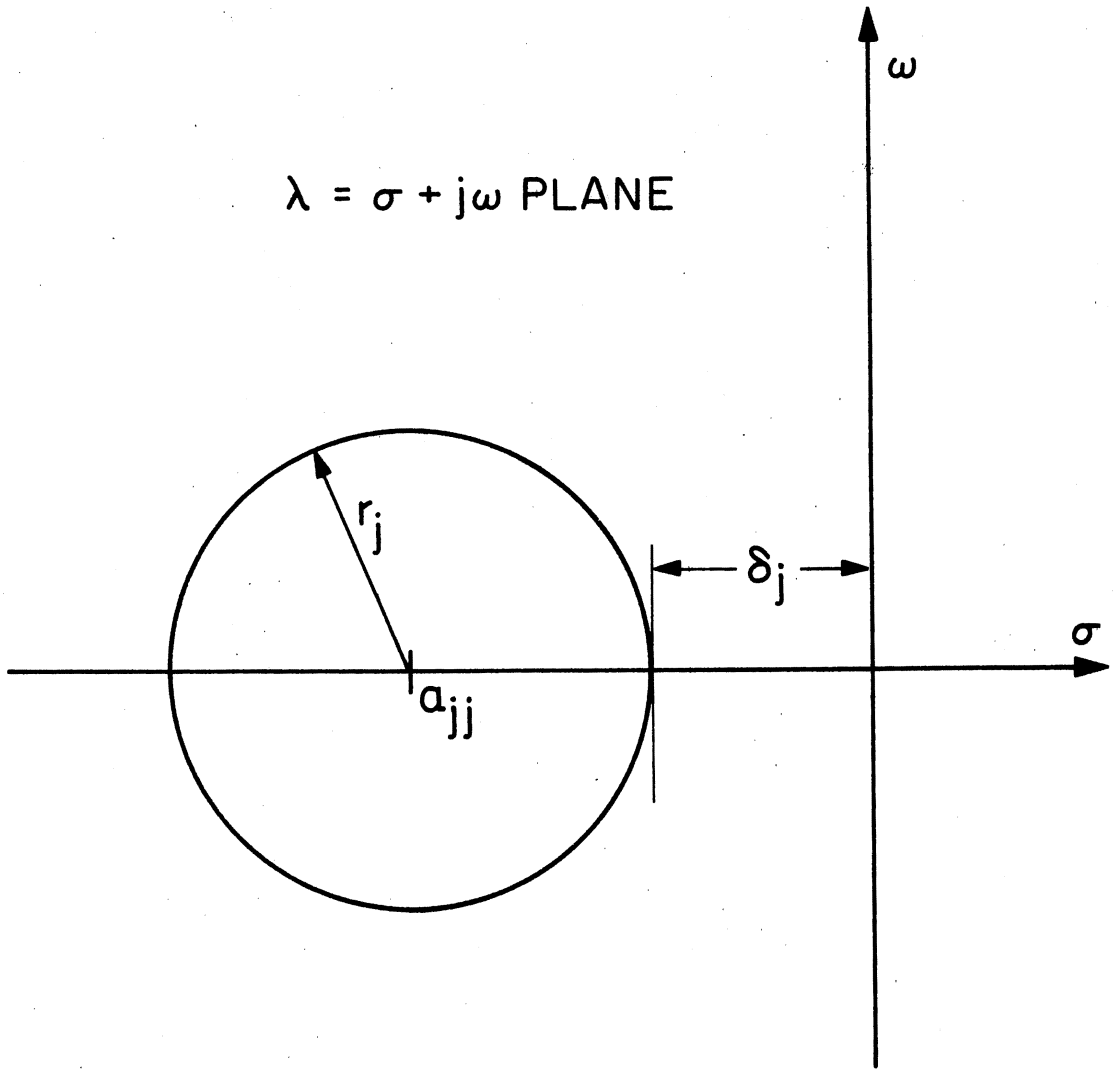


Figure 3. The j-th Gerschgorin Circle Plotted in the Complex Plane

solution of (3.26) is a bounded function of time and $\underline{x}(t) \to \underline{0}$, as $t \to \infty$, because all the eigenvalues of $\underline{A}$ are negative real numbers (Hearon, 1963). That is, Equation (3.26) is asymptotically stable. This enables the set of distinct eigenvalues of $\underline{A}$ to be ordered and bounded as follows:

$$-\alpha < \lambda_1 < \lambda_2 < \ldots < \lambda_n < -\delta. \tag{4.11c}$$

The eigenvalue bounds are

$$\alpha = \max_{1 \le j \le n} [r_j + |a_{jj}|] \tag{4.11d}$$

and

$$\delta = \min_{1 \le j \le n} [\delta_j \neq 0], \tag{4.11e}$$

which are clear from Figure 3.

Definition 4.1

The Taxi-cab norm of the vector $\underline{x}$, as denoted by $1\ \underline{x}\ 1$, measures the distance between the origin and any point in n-dimensional state-space by computing

$$1\ \underline{x}\ 1 = \sum_{k=1}^{n} |x_k|. \tag{4.12}$$

Theorem 4.1 (Mulholland and Keener, 1974)

Consider the system (2.2) written as

$$\dot{x}_i(t) = -a_{ii}x_i(t) + \sum_{j=1}^{n}{}' a_{ij}x_j(t) + u_i(t), \tag{4.13}$$

for $i = 1, \ldots, n$, where

$$a_{ii} = a_{oi} + \sum_{j=1}^{n}{}' a_{ji}, \tag{4.14}$$

and $a_{ij} \geq 0$ and $u_i \geq 0$ for all i and j. If $x_i(t)$ is a solution of this system with $x_i(0) > 0$ for each $i = 1, \ldots, n$, then $x_i(t) > 0$ for all $t > 0$.

Proof

Suppose for some $i = 1, \ldots, n$ and $t > 0$, $x_i(t) = 0$. Then there exists a point $t_o > 0$ such that for all $i = 1, \ldots, n$ $x_i(t) > 0$ on the interval $[0,t_o)$ and

$$x_i(t_o) = 0 \tag{4.15}$$

for some $i = 1, 2, \ldots, n$. Then for each i and t in $[0,t_o)$,

$$\dot{x}(t) + a_{ii}\, x_i(t) \geq 0. \tag{4.16}$$

Then, on the interval $[0,t_o)$, for each i,

$$d/dt[e^{a_{ii}t}\, x_i(t)] \geq 0 \tag{4.17}$$

and

$$x_i(t) \geq x_i(0)\, e^{-a_{ii}t}. \tag{4.18}$$

By the continuity of $x_i(t)$,

$$x_i(t_o) \geq x_i(0)\, e^{-a_{ii}t_o} > 0 \tag{4.19}$$

thus contradicting (4.15). This contradiction completes the proof of the theorem.

It should be noted that Theorem 4.1 with $x_i(0) < 0$ implies

$x_i(t) < 0$ for $i = 1, \ldots, n$ and all $t \geq 0$. The more ecologically realistic case of positive solutions of (4.13) means the Taxi-cab norm is easily computed by summing the state components:

$$|\underline{x}| = \sum_{k=1}^{n} x_k \tag{4.20}$$

It is useful to be able to denote vectors with all nonnegative (or non-positive) entries.

Definition 4.2

A vector with nonnegative (nonpositive) components will be denoted by $\underline{x} \geq 0$ ($\underline{x} \leq 0$), while positive (negative) vectors will be given by $\underline{x} > 0$ ($\underline{x} < 0$).

Theorem 4.2 (Thron, 1972)

When a compartment model initially in a steady-state $\underline{x}_{s1} > 0$ with an input $\underline{u}_1 \geq 0$ responds to a negative step function perturbation, which leads to a new input $\underline{u}_2 \geq 0$ ($\underline{u}_1 - \underline{u}_2 > 0$) and new steady-state $x_{s2} \geq 0$, then the transition to the final steady-state is monotonic.

Proof

Assume the negative step perturbation occurs at $t = T_o$ as shown in Figure 2. For $t \geq T_o$ (4.13) can be written as

$$\dot{\underline{x}} = \underline{A}\,\underline{x} + \underline{u}_2 \tag{4.21}$$

with initial condition

$$\underline{x}(T_o) = \underline{x}_{s1}. \tag{4.22}$$

The stability of (4.21) (Mulholland and Keener, 1974) implies

$$\underline{x} \to \underline{x}_{s2} = -\underline{A}^{-1}\underline{u}_2 \tag{4.23}$$

as $t \to \infty$. Now, differentiate (4.21) to give

$$\dot{\underline{y}} = \underline{A}\,\underline{y} \tag{4.24}$$

where $\underline{y} = \dot{\underline{x}}$. The initial condition for (4.24) is given by (4.21):

$$\underline{y}(T_o) = \underline{A}\,\underline{x}(T_o) + \underline{u}_2 = -\underline{u}_1 + \underline{u}_2 \tag{4.25}$$

Since the step perturbation is negative with $\underline{u}_2 - \underline{u}_1 < 0$, the initial condition is negative: $\underline{y}(T_o) < 0$. Thus, by Theorem 4.1, the solution of (4.24) is negative $\left(y(t) < 0 \text{ for all } t \geq T_o\right)$; and since $\underline{A}$ is a stable matrix, $\underline{y} \to \underline{0}$. Thus, the vector $\underline{x}$ decreases monotonically from $\underline{x}_{s1}$ to $\underline{x}_{s2}$. See Figure 2.

Theorem 4.3

Starting at an initial steady-state determined by the input $\underline{u}_1$, the solution of (4.13) is bounded in norm by

$$e^{-\alpha t}\,|\underline{x}(0)| \leq |\underline{x}(t)| \leq e^{-\delta t}\,|\underline{x}(0)| \tag{4.26}$$

when the input is removed.

Proof

Let the input be removed at $t = 0$ and note that the solution of (4.13) starting at

$$\underline{x}(0) = \underline{x}_{s1} = -\underline{A}^{-1}\underline{u}_1 > 0 \tag{4.27}$$

converges monotonically to the zero steady-state. Summing the index i in (4.18) for i = 1, . . . , n yields

$$|\underline{x}(t)| \geq e^{-a_{ii}t}\, x_1(0) + \ldots + e^{-a_{nn}t}\, x_n(0) \tag{4.28}$$

and since $\underline{x}(0) > 0$,

$$|\underline{x}(t)| \geq e^{-\alpha t}\, |\underline{x}(0)|, \tag{4.29}$$

which gives the lower bound in terms of the maximum compartmental turnover. Now, sum equations represented by (4.13) for i = 1, . . . , n:

$$\dot{x}_1 + \ldots + \dot{x}_n = -a_{01}x_1 - \ldots - a_{0n}x_n. \tag{4.30}$$

Equations (4.11) and (4.30) give

$$\sum_{k=1}^{n} \dot{x}_k \leq -\delta \sum_{k=1}^{n} x_k \tag{4.31}$$

and by repeating the steps in the proof of Theorem 4.1, there results

$$|\underline{x}(t)| \leq e^{-\delta t}\, |\underline{x}(0)|, \tag{4.32}$$

which gives the upper bound on the state in terms of the minimum exogenous turnover. This completes the proof of the theorem.

Direct and Indirect Methods

The collection of time series data for each compartment in the ecosystem takes place in two distinct steps, in which first time and then amplitude are quantized. The samples of the state are obtained only at discrete times. These samples are periodically spaced apart by τ time units giving a data base defined by $\{\underline{x}(0), \underline{x}(\tau), \ldots, \underline{x}[(k+1)\tau]\}$. It has been shown the minimum data base for solution of

the identification problem is (n + 1) state samples or k = n. Next, the finite precision with which the measurements of state are made must be accounted for in terms of a mathematical relationship. The assumption is that $\underline{x}(t)$ and its samples are fixed point numbers which are less than or equal to one. These samples, arising from radiological measurement equipment, are data with no more than a fixed number of digits to the right of the decimal point. Let 10^{-d}, where d is a positive integer, be the smallest number in the data set. Then, the quantizing operation on the samples is described by the function y = f(x) as plotted in Figure 4, or by the relations:

$$y = 0 \qquad \text{for } 0 \leq x < 10^{-d}$$

$$y = 10^{-d} \qquad \text{for } 10^{-d} \leq x < 2\text{x}10^{-d}$$

$$y = 2\text{x}10^{-d} \qquad \text{for } 2\text{x}10^{-d} \leq x < 3\text{x}10^{-d}$$

etc.

These quantized samples assume a pure truncation scheme for the finite precision arithmetic. Depending upon the measurement equipment used, other arithmetic schemes may be necessary. For example, it is common to round 0.478554 to either 0.4786 or 0.4785 as a four-place number depending upon whether or not the last digit is even (or odd). The roundoff error for such a scheme is $|E| \leq 0.5 \times 10^{-d}$, while the proposed truncation scheme gives an error of $0 \leq |E| < 10^{-d}$. Since the samples are positive numbers, the pure truncation scheme was selected for reasons of symmetry to represent the quantizer.

The relationship between the sample period, the quantization of the samples, and eigenvalue bounds is of interest. As has been pointed out,

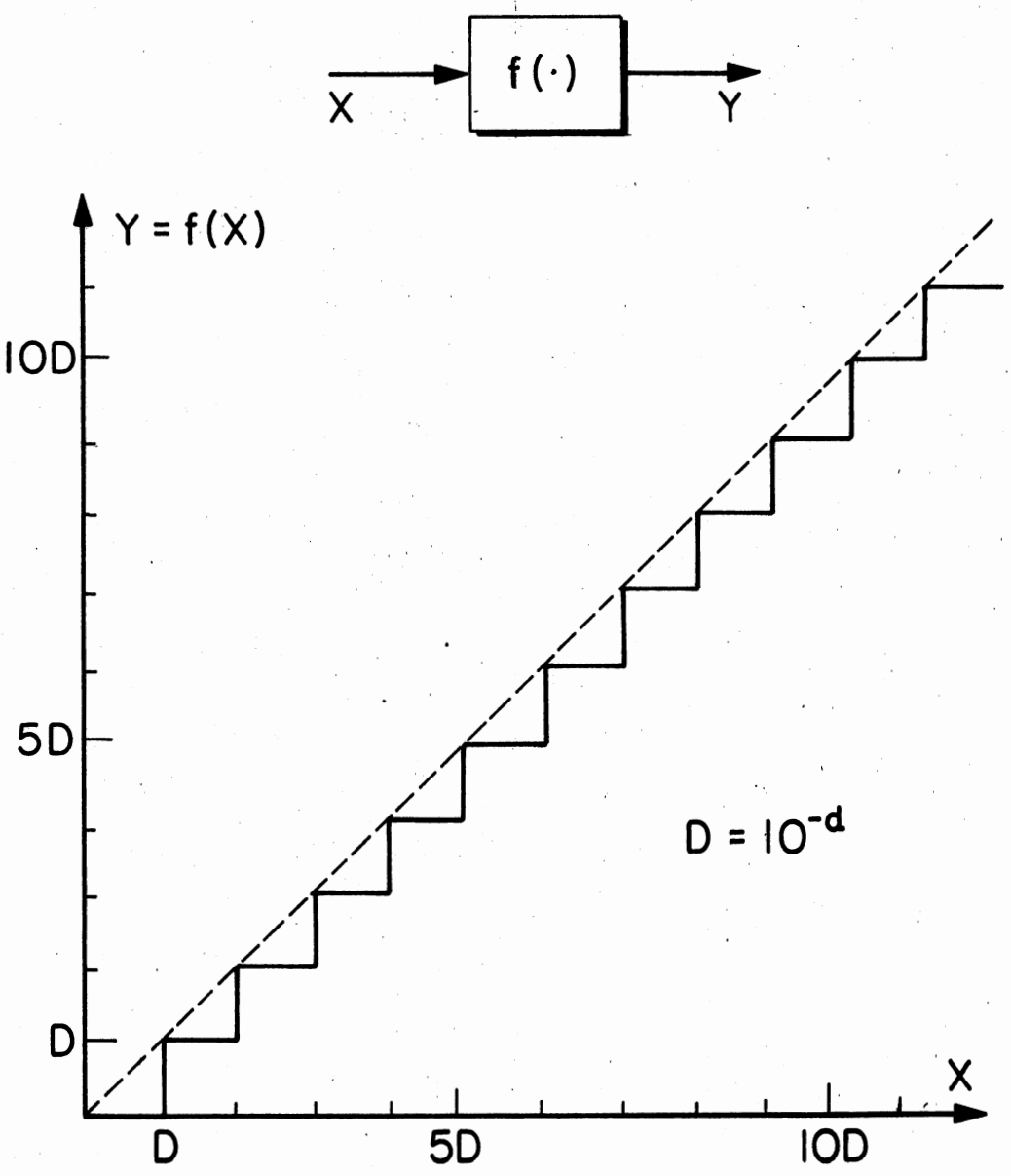


Figure 4. Functional Relationship for a Quantizer Which Truncates

it is possible for the sample period to be too small. This results in $\underline{x}(t)$ and $\underline{x}(t + \tau)$ having the same numerical value when both are truncated to d digits. Since (4.32) gives an upper bound for $\underline{x}(t)$, a measure of the minimum sampling time, denoted by τ^-, is given by

$$1 - 10^{-d} = e^{-\delta\tau^-} \geq |\underline{x}(\tau^-)| \tag{4.33}$$

or solving for the minimum sampling period yields

$$\tau^- = (-1/\delta)\ \ell n\ (1 - 10^{-d}). \tag{4.34}$$

The state samples are therefore independent if $\tau > \tau^-$, but an upper bound on τ also exists. If τ is chosen large enough that the last sample(s) in the data set are truncated to zero by the quantizer, then the data set is incomplete and the identification problem cannot be solved. Thus, the maximum sample period, denoted by τ^+, must be such that the (n + 1)-th sample is at least equal to the smallest number in the finite precision arithmetic, that is,

$$|x(n\tau^+)| \geq 10^{-d}. \tag{4.35}$$

Equation (4.29) gives a lower bound for $\underline{x}(t)$; thus, the maximum sample period is easily computed from

$$10^{-d} = e^{-\alpha n\tau^+} \leq |x(n\tau^+)| \tag{4.36}$$

which results in

$$\tau^+ = (-1/\alpha n)\ \ell n\ (10^{-d}). \tag{4.37}$$

As an example of the application of these equations, consider a three-compartment system with eigenvalue bounds of $\alpha = 190$ and $\delta = 2$.

Suppose samples of the state of this system can be made with four-place precision, so d = 4. Then, from (4.34) and (4.37) $\tau^- = 5 \times 10^{-5}$ and $\tau^+ = 0.012$ are obtained.

A reasonable choice for τ is the geometric mean of τ^+ and τ^-, or

$$\tau = (\tau^+\tau^-)^{1/2}, \tag{4.38}$$

which for this example gives $\tau = 0.00089$. A more practical choice is obtained by rounding τ to 0.001.

Equation (4.38) gives a relationship for choosing the sampling period for the identification problem which is valid as long as $\tau^- < \tau^+$, or

$$\delta/\alpha n > \ell n(1 - 10^{-d})/\ell n(10^{-d}). \tag{4.39}$$

The eigenvalue bounds (δ and α) and the number of ecosystem compartments (n) are fixed constants, hence a computation yielding $\tau^- > \tau^+$ implies the precision of the measurements is too low to solve the identification problem. This computation can be made prior to the collection of data, thus validating the sampling program. For the example under consideration, (4.39) holds for all integers $d \geq 3$. Therefore, radiological measurement equipment with at least three-place accuracy for fixed-point numbers is required for sampling the state of this example system.

In order to compute the bounds τ^+ and τ^- for the sample period τ, it is necessary to know the eigenvalue bounds α and δ. However, computations of these bounds using (4.10) and (4.11) requires knowledge of the entries in $\underline{A}$, which are unknown.

Based upon intuition, experience, or isolated laboratory experiments, ecologists tend to know the turnovers for the species present in

an ecosystem. Such knowledge is at least accurate to an order of magnitude. Thus, a relationship between the turnovers and the eigenvalues would enable the computation of the eigenvalue bounds, and in turn determine τ^+ and τ^-.

Consider again the compartment model defined by (4.13) where the turnover time T_i, given by (2.4) is written as

$$T_i = 1/a_{ii} \quad (i = 1, \ldots, n), \tag{4.40}$$

from the ecologically unrealistic assumption that no coupling exists between the n compartments of the ecosystem, the eigenvalues can be shown to equal the compartment turnovers. Let the solution of (4.13) under these conditions be written as

$$x_i(t) = x_i(0)\, e^{-t/T_i}. \tag{4.41}$$

The eigenvalues are $\lambda_i = T_i^{-1}$ for $i = 1, \ldots, n$. For this case the Gerschgorin circles are degenerate, with all radii equal zero, consisting of the n points given by T_i^{-1} for $i = 1, \ldots, n$.

From (4.6) the Gerschgorin circle radii ware clearly determined by the pattern and amount of coupling between ecosystem compartments. The Gerschgorin circle centers are equal to the diagonal elements of $\underline{A}$, which regardless of intercompartmental coupling equal the turnovers as defined by (4.40). Since all the Gerschgorin circles are known to lie in the left-half of the λ-plane, the center magnitude must be greater than or equal the center radius:

$$T_j^{-1} = |a_{jj}| \geq r_j \tag{4.42}$$

For each circle $j = 1, \ldots, n$. Let T_o^{-1} be the maximum turnover,

then it is clear that all eigenvalues of the system lie in the circle of center and radius T_o^{-1}. Hence $2T_o^{-1} \geq \alpha$ and $-2T_o^{-1} \geq \lambda_1 < \lambda_2 < \cdots < \lambda_n < 0$. Using T_o^{-1} as an estimate for α in (4.37) yields

$$\tau^+ = (-1/2nT_o^{-1}) \ln (10^{-d}). \tag{4.43}$$

Given the number of compartments in the ecosystem, the maximum turnover, and the precision with which the measurements of the system state are to be made, (4.43) prescribes the maximum sample period.

The minimum sample period is not easily computed without the eigenvalue bound of (4.11). Fortunately, it is the maximum sample period bound which is the more important extremal. Assuming sufficient arithmetic precision of the state samples to prescribe $\tau^- < \tau^+$, it is merely necessary to choose $\tau \leq \tau^+$ in order to solve the identification problem. Exact knowledge of τ^- is of little use when d is large enough.

Earlier the solution of the identification problem was explained to begin with an experiment which initially places the ecosystem in steady-state. The observation of this steady-state is obtained by noting $\dot{x}_i = 0$ for all $i = 1, \ldots, n$, or by the condition

$$\underline{0} = \underline{A}\,\underline{x}_s + \underline{B}\,\underline{u}. \tag{4.44}$$

If both observations are made, sufficient data exist to determine the steady-state condition and δ_j for each compartment. In other words, these data determine the compartmental losses f_{oj} and steady levels $\bar{x}_j$, so that $\delta_j = f_{oj}/\bar{x}_j$ for $j = 1, \ldots, n$. The value δ is then determined by (4.10) which in turn prescribes τ^- through (4.34). The measurement of x_j in steady-state is required to determine $x_j(0)$, the first sample for compartment j, thus the additional measurement of f_{oj}

enables the computation of τ^{-}, which may be worth the additional effort in certain cases.

Approximation Method

The approximation method of identification is based upon the convergence of the exponential series (3.57) for which τ is chosen small enough to eliminate terms of k that are greater than or equal to some positive integer m within the finite precision arithmetic.

Definition 4.3

The norm of a vector $\underline{x}$ is equal to zero within the finite precision arithmetic, denoted by

$$|x| \stackrel{\circ}{=} 0 \tag{4.45}$$

if and only if

$$|x| < 10^{-d} \tag{4.46}$$

where 10^{-d} is the smallest number of arithmetic accuracy.

Consider the series (3.57) written as

$$\underline{\Phi} = \underline{I} + \underline{A}\tau + \underline{R}_k \tag{4.47}$$

where $\underline{R}_k$ is the remainder term defined by

$$\underline{R}_k = e^{\underline{A}\tau'} \underline{A}^k \tau^k / k!, \quad 0 \leq \tau' \leq \tau \tag{4.48}$$

and k is some positive integer greater than one. It is desired to find the value of d such that

$$|\underline{R}_k| \stackrel{\circ}{=} 0. \tag{4.49}$$

Equating the remainder term to zero within the finite precision arithmetic will result in an approximation of Equation (4.47).

Definition 4.4

If the elements of an n-th order matrix $\underline{A}$ are real numbers, the norm of $\underline{A}$ is denoted by $|\underline{A}|$ and is defined by the sum of the Taxi-cab norms $\alpha_j = r_j + |a_{jj}|$ of the column vectors of $\underline{A}$, $j = 1, \ldots, n$.

Setting

$$|\underline{R}_k| < 10^{-d} \tag{4.50}$$

and letting $\tau = \tau^-$, defined by (4.34) as

$$\tau^- = -(1/\delta)\ \ell n\ (1 - 10^{-d}), \tag{4.51}$$

one obtains

$$e^{|\underline{A}|\tau'}|\underline{A}|^k\ 1 - (1/\delta)\ \ell n\ (1 - 10^{-d})1^k/k! < 10^{-d} \tag{4.52}$$

Now from Definition 4.1, the norms of column vectors of $\underline{A}$ may be computed by

$$\alpha_j = \sum_{i=1}^{n}{}' a_{ij},\ j = 1, \ldots, n \tag{4.53}$$

the maximum α_j being the lower eigenvalue bound α of the matrix $\underline{A}$ (see Equation 4.10)). The norm of $\underline{A}$ may therefore be represented by

$$|\underline{A}| = n\alpha. \tag{4.54}$$

Then (4.52) may be written as

$$e^{\alpha n\tau'}(n\alpha)^k[-\ell n(1 - 10^{-d})]^k/\delta^k k! < 10^{-d} \tag{4.55}$$

and using the fact that

$$-\ell n(1 - 10^{-d}) > 10^{-d}, \tag{4.56}$$

Equation (4.55) becomes

$$e^{\alpha n\tau'}(n\alpha)^k \, 10^{-d(k-1)}/\delta^k k! < 1 \tag{4.57}$$

Letting $\tau' = \tau = \tau^-$, and solving for d, one obtains

$$d > -\ell og_{10}[k!\delta^k/(n\alpha)^k]e^{n\alpha\delta 10^{-d}}/(k - 1). \tag{4.58}$$

But the value of $(n\alpha\delta 10^{-d})$ is sufficiently large for the exponential term to be approximated by unity, resulting in

$$d > -\ell og_{10}[k!\delta^k/(n\alpha)^k]/(k - 1). \tag{4.59}$$

For k = 2, this result gives a bound on the arithmetic precision required for approximating (4.47) by

$$\underline{\Phi} \doteq \underline{I} + \underline{A}\tau, \tag{4.60}$$

where Equation (4.60) prescribes the approximation (3.59) of the exact relationship between the matrix of coefficients $\underline{A}$, the state transition matrix Φ, and the sample period τ.

For the preceding example, with n = 3, α = 190, and δ = 2, the inequality of (4.59) yields d > 4.6 (or d = 5) in order to approximate the state transition matrix by two terms in the exponential series as in (4.60).

Summary

The use of the algorithm for the single-dose method of

identification has been based upon the new deterministic theory of sampling presented in this chapter. Bounds were given on the sample period for data collection which depend upon the arithmetic precision of the data, the dimension of the ecosystem, and its maximum turnover. The application of the sampling theory is primarily intended for laboratory ecosystems, although the results may be extended to natural systems.

CHAPTER V

IDENTIFIABILITY

Introduction

Before implementation of the identification algorithm, conditions should be investigated that will ensure the uniqueness of a numerical estimation of the associated parameters. A priori knowledge of which and/or how many parameters of the flow matrix A can be determined by means of the chosen input-output experiment is termed identifiability (Cobelli, 1976). If the internal couplings cannot be uniquely determined, changes in the mathematical model structure or the experiment itself must be modified. Therefore, an identifiability analysis may be considered as a necessary step preceding identification.

Often, identification is derived from numerical values of a few known parameters and is reduced to a problem of state estimation in which it is natural to deal with identifiability in a probabilistic manner. Identifiability in such stochastic systems may be defined by the existence of an estimator (Tse, 1973, 1978) or by the uniqueness of the probability distribution function (Bowden, 1973). A survey of similar investigations is provided by Reid (1977). In the study of biological systems, identification often depends upon a priori knowledge of the model structure (at least order); and it is appropriate to use a deterministic canonical system approach to the determination of model

parameters. Other approaches to the problem include parametrization (Glover, 1974) and parameter sensitivity analysis (Reid, 1977), which are both closely related to transfer function methods.

An explicit discussion of the problem of structural identifiability in the frequency domain is given by Bellman and Astrom (1970) where they propose the use of the transfer function to investigate identifiability. Consider the system

$$\dot{\underline{x}}(t) = \underline{A}\,\underline{x}(t) + \underline{B}\,\underline{u}(t) \tag{5.1a}$$

$$\underline{y}(t) = \underline{C}\,\underline{x}(t) \tag{5.1b}$$

which is the linear compartment model defined by (3.1) with a single-dose input $\underline{u}(t)$, where $\underline{y}(t)$ is an m-vector of measurements of the state $\underline{x}$, and $\underline{C}$ is a $p \times n$ connectivity matrix of the form

$$C_{ij} = \begin{cases} 1 \\ 0 \end{cases} \tag{5.2}$$

and

$$\sum_{j=1}^{n} C_{ij} = 1$$

for all $i = 1, \ldots, p$. Let $\underline{Y}(s)$ be the Laplace transform of $\underline{y}(t)$ and $\underline{U}(s)$ that of $\underline{u}(t)$. Then

$$\underline{Y}(s) = \underline{G}(s)\,\underline{U}(s) \tag{5.3}$$

where $\underline{G}(s)$ is the transfer matrix given by

$$\underline{G}(s) = \underline{C}(s\underline{I} - \underline{A})^{-1}\,\underline{B} \tag{5.4}$$

and $\underline{I}$ is the n-th order identity matrix. The problem of identifying the

flow matrix $\underline{A}$ from the experimental data may be reduced to that of identifying the coefficients of the transfer matrix, each coefficient being a combination of the elements of $\underline{A}$. Therefore, the $\underline{A}$ matrix is identifiable when this nonlinear system of equations has a unique solution.

Lin and Yu (1977) considered the single input and single output special case of (5.1) in canonical form, where $\underline{A}$ is the companion matrix associated with the characteristic polynomial

$$s^m + a_{m-1} s^{m-1} + \cdots + a_1 s + a_0 = 0 \tag{5.5}$$

and

$$\underline{C} = [c_1 c_2 \cdots c_n] \tag{5.6}$$

$$\underline{B}^T = [0\ 0 \cdots 1] \tag{5.7}$$

This leads to a scalar input/output formulation for (5.3) in which G(s) contains 2n unknown parameters (n poles, n-1 zeros, and a gain factor). The identification of these parameters is demonstrated by a time series analysis of the output variable given by

$$y(t) = \gamma_1 e^{\lambda_1 t} + \cdots + \gamma_n e^{\lambda_n t}.$$

A numerical algorithm called Prony's method (Hildebrand, 1974) is applied to y(t) in order to resolve the parameters λ_i and γ_i of the exponential curve fit. The λ_i and γ_i parameters are then shown to uniquely determine the 2n unknown parameters of G(s).

The precise definition of identifiability provided by Bellman and Astrom (1970) is equivalent to saying that the parameters of $\underline{A}$ are

identifiable only if any change in the values of the coefficients causes a change in the measured quantities $\underline{y}(t)$. Thus, a necessary condition for identifiability is that a system be controllable and observable in the sense of Kalman (1963).

Definition 5.1

A linear system is said to be completely state controllable if for any initial state at t_o it can be driven to any other state in the state space at $t = T$.

Definition 5.2

A linear system is said to be completely output controllable if it is possible to drive any initial output at t_o to any final output in a finite time interval.

Definition 5.3

A linear system is said to be completely observable if for every initial time t_o and some finite time T_1, $t_o \leq t \leq T_1$ every initial state at t_o can be determined from the knowledge of the output on $t_o \leq t \leq T$.

Rigorous treatments on the properties of controllability and observability can be found in system theory literature (Kalman, 1963; Luenberger, 1963; Lee, 1964; Ogata, 1967; and Chen, 1970). In the following, these properties will be considered as they apply to the previously discussed methods of identification for compartmental models.

Direct Method

Assume that a single dose of tracer may be directly inserted via special routes into system compartments and that tracer behavior can be experimentally monitored in specified compartments when the system is switched to a tracer-free environment. The controllability and observability of such a system has been explicitly discussed by Bellman and Astrom (1970) and Johnson (1976).

A system described by (5.1) is controllable if and only if the column vectors of the n × nm test matrix

$$\underline{P}_c = [\underline{B} \vdots \underline{AB} \vdots \underline{A^2B} \vdots \cdots \vdots \underline{A^{n-1}B}] \tag{5.8}$$

span the n-dimensional space on which $\underline{x}(t)$ is defined. In other words, $\underline{P}_c$ must be of rank n if the system is to be controllable (Kalman, 1963).

Definition 5.4

A system is open (closed) when there is some (no) exchange of material from the system either to the environment or to another subsystem.

Using the properties of the controllability matrix $\underline{P}_c$, Johnson (1976) shows that closed systems are uncontrollable regardless of their structure. Open systems are also examined and are found to be controllable, in general, if the matrix flow matrix $\underline{A}$ is of rank n or (n - 1) and at least one flow between the system and its environment is controlled. Necessary conditions for complete controllability can also be derived from physical reasoning. Cobelli and Romanin-Jacur (1976) adopt a structural point of view by relating controllability and

observability of compartmental systems to their experimental design. A system is shown to be completely controllable only if there exists at least one path from some input to every compartment. In addition, it should be noted that the specification of bounds on the controlled elements implies that a system otherwise completely controllable must now have a restricted range of controllability in state space.

The concept of observability of a dynamic system is associated with the processing of data obtained from measurements on the system. Analagous to the test for controllability, Kalman (1963) has shown that a linear, time-invariant system defined by (5.1) is observable if and only if the n × np matrix

$$\underline{P}_o = [\underline{C}^T \vdots \underline{A}^T\underline{C}^T \vdots (A^T)^2\,\underline{C}^T \vdots \cdots \vdots (\underline{A}^T)^{n-1}\underline{C}^T] \qquad (5.9)$$

is of rank n. If there is only one output (p = 1), then a necessary and sufficient condition for observability is that $\underline{P}_o$ be non-singular. The test for observability may be applied to compartmental models by utilizing techniques that were employed when discussing controllability. Upon inspection of the definition of observability, it is clear that observability does not depend upon the controlled input matrix, but rather on the output matrix. A linear compartment model, in the structural sense, is completely observable if at least one output is reachable from every compartment. It is also necessary that no outputs be associated with only the state variables which form one or more traps, all influencing the same outputs (Cobelli and Romanin-Jacur, 1976).

Definition 5.5

A subsystem of compartments which receives input from the remainder

of the system, but has no transfers out of the subsystem from any of its compartments, is called a trap. A trap may also be called a closed subsystem.

It is important to mention that the conditions given for controllability and observability are not sufficient; that is, the preceding conditions neither guarantee the identifiability of $\underline{A}$, nor are the elements of $\underline{A}$ in the uncontrollable and unobservable part of the system necessarily unidentifiable. Counter-examples which clarify these points are considered by Distefano (1977). Bellman and Astrom (1970) emphasize the difficulty of the problem of identifiability; and since that time, only necessary conditions have been related in the literature. Cobelli and Romanin-Jacur (1976) give criteria for sufficient conditions, but a close study (Delforge, 1977) shows by counter-example that the proposed criteria are necessary, but not sufficient. The problem reduces to a recurring mathematical question which asks how many solutions a set of nonlinear equations has.

Let $\underline{A}$ be unidentifiable. Then it may be possible to formulate an experiment to show that a subset of compartmental levels can be controllable even when the system fails to meet controllability and observability requirements (Johnson, 1976). For example, consider a system in which certain states are, for biological reasons, not accessible and their evaluation, according to the structural identifiability tests, not possible. If a feasible experimental condition can be obtained by adding a new input, thereby yielding necessary conditions, the system may be considered identifiable (Milanese, 1976). Also, it has been suggested that the simplest way to deal with a multicompartment system is to ignore closed subsystems if possible, because any or all of the

traps can be deleted without altering the behavior of the rest of the system (Thron, 1972). In general, this is possible with regard to measurements on compartments of completely open subsystems; and most systems utilizing the direct method for identification of the $\underline{A}$ matrix would fall into this category. However, certain observations, such as the kinetics of urinary excretion, require the use of an indirect measurement; and hence the accumulation pools may not be excluded. Necessary conditions for identifiability are therefore derived for the indirect algorithm.

Indirect Method

The necessary conditions given for controllability and observability of a system for the direct identification algorithm imply that any modeling of a real system with one or more compartments acting as stores for the system may not be identifiable. With the indirect scheme, the observer states $\underline{y}$ form a set of flows disjoint from the internal couplings, each accumulation compartment being a singular trap. In this section, criteria are investigated for controllability and observability related to compartmental structure of a system having ℓ accumulation pools ($\ell \leq n$) from which all observations are to be made. The local model of (3.1) is again incorporated along with the linear observer of (3.40). By rewriting the system as

$$\begin{bmatrix} \dot{\underline{x}} \\ \dot{\underline{y}} \end{bmatrix} = \begin{bmatrix} \underline{A} & \underline{0} \\ \underline{K} & \underline{0} \end{bmatrix} \begin{bmatrix} \underline{x} \\ \underline{y} \end{bmatrix} + \begin{bmatrix} \underline{B} \\ \underline{0} \end{bmatrix} \underline{u} \qquad (5.10a)$$

the total system behavior may be explored. Now define the measurement vector $\underline{z}$ as follows:

$$\underline{z} = [\underline{0} \quad \underline{I}] \begin{bmatrix} \underline{x} \\ \underline{y} \end{bmatrix} . \tag{5.10b}$$

Measurements are to be taken from each of the ℓ observer states. The system described by (5.10) is controllable if and only if the partitioned matrix

$$\underline{P}_{ic} = \begin{bmatrix} \underline{P}_1 \\ \underline{P}_2 \end{bmatrix} = \left[\begin{bmatrix} \underline{B} \\ \underline{0} \end{bmatrix} \vdots \begin{bmatrix} \underline{AB} \\ \underline{KB} \end{bmatrix} \vdots \begin{bmatrix} \underline{A^2B} \\ \underline{KAB} \end{bmatrix} \vdots \begin{bmatrix} \underline{A^3B} \\ \underline{KA^2B} \end{bmatrix} \vdots \cdots \vdots \begin{bmatrix} \underline{A^{n-1}B} \\ \underline{KA^{n-2}B} \end{bmatrix} \right] \tag{5.11}$$

spans the $(\ell + n)$ state space on which the system is defined, where the two $\ell \times nm$ submatrices $\underline{P}_1$ and $\underline{P}_2$ are called the upper and lower partitions, respectively, of the controllability matrix. Now if $\underline{P}_{ic}$ is of rank $\ell + n$, then $\underline{P}_1$ and $\underline{P}_2$ must both be of full rank. Note that the upper partition of the controllability matrix is the same test matrix as that for the direct method (see (5.8)). Thus, as with the direct method, if there is no path from any input to compartment i, then the i-th row of the controllability matrix is identically null, as no input enters compartment i. Next consider the lower partition of the matrix $\underline{P}_{ic}$. If, in addition to the aforementioned condition, there is no accumulation compartment that can be reached from a given compartment i, then every element of the i-th row of the controllability matrix is null as no pool is influenced by the state variable associated with the i-th compartment.

For a clearer understanding of the observer portion of the controllability matrix, consider the dynamic states $\underline{y}$ to be continuous observations rather than accumulation pools. Then from Kalman (1963)

and the definition of output controllability, the system is said to be completely output controllable if and only if the composite matrix

$$\underline{P}_{oc} = [\underline{KB} \vdots \underline{KAB} \vdots \underline{KA^2B} \vdots \cdots \vdots \underline{KA^{n-1}B} \vdots \underline{D}] \qquad (5.12)$$

is of the same rank as the row order of $\underline{K}$, where $\underline{D}$ is the connectivity matrix which constitutes direct transmission from $\underline{u}$ to $\underline{y}$ in Equation (5.10). The existence of a direct input into any accumulation pool is not assumed to exist, that is, $\underline{D} = \underline{0}$. In fact, if the same compartment is available for insertion and observation of tracer, identification requires that the associated flow matrix be irreducible (Smith, 1976); whereas the flow matrix for the indirect identification scheme is reducible. Thus, tracer must be injected into the internal system $\underline{x}$ and not into the observer $\underline{y}$. If the rank of the $\ell \times nm$ matrix

$$\underline{P}_2 = [\underline{0} \vdots \underline{KB} \vdots \underline{KAB} \vdots \underline{KA^2B} \vdots \cdots \vdots \underline{KA^{n-2}B}] \qquad (5.13)$$

is of rank ℓ, then the rank of the $\ell \times nm$ matrix $\underline{P}_{oc}$ given by (5.12) is necessarily ℓ. Notice that state controllability is neither necessary nor sufficient for output controllability.

The discussion of indirect controllability to this point has relied upon the knowledge of the rank of $\underline{P}_{ic}$ which is not customarily known when discussing identifiability. Conditions must be placed upon the submatrices $\underline{P}_1$ and $\underline{P}_2$ such that the indirect controllability matrix will be of rank $\ell + n$, giving a necessary condition for identifiability.

Definition 5.6

A system is said to be reduced controllable if and only if the rank of the matrix $\underline{P}_k$ where

$$\underline{P}_k = [\underline{B} \vdots \underline{AB} \vdots \underline{A^2B} \vdots \cdots \vdots \underline{A^{k-1}B}] \qquad (5.14)$$

is n for $k < n$. The smallest possible integer k for which $\underline{P}_k$ is of rank n will be called the reduced order. Sufficient conditions for the controllability matrix $\underline{P}_{ic}$ to be of the desired rank follow.

Definition 5.7

Two $m \times n$ matrices are defined to be equivalent if and only if one may be transformed into the other by non-singular elementary row and column transformations. If $\underline{A}$ and $\underline{B}$ are equivalent, we write

$$\underline{A} \overset{E}{=} \underline{B}. \qquad (5.15)$$

Theorem 5.1

A system given by (5.1) in which measurements are obtained from ℓ accumulation pools is controllable if the test matrix $\underline{P}_{ic}$ (5.11) of the system is such that

(i) The upper partition $\underline{P}_1$ is a reduced controllability matrix $\underline{P}_k$ with $2k < n - 1$, where n is the rank of $\underline{A}$ and k is the reduced order of the controllability matrix; and

(ii) $\underline{KA}^k\underline{P}_k$ is of rank ℓ.

Proof: Rewrite the indirect controllability matrix as

$$\underline{P}_{ic} = \begin{bmatrix} \underline{P}_1 \\ \underline{P}_2 \end{bmatrix} = \begin{bmatrix} \underline{B} & \underline{AB} & \cdots & \underline{A^kB} & \underline{A^{k+1}B} & \cdots & \underline{A^{n-1}B} \\ \underline{0} & \underline{KB} & \cdots & \underline{KA^{k-1}B} & \underline{KA^kB} & \cdots & \underline{KA^{n-2}B} \end{bmatrix} \qquad (5.16)$$

Now if the matrix $\underline{P}_1$ is reduced controllable, then $\underline{P}_k$ is of rank n where

$$\underline{P}_k = [\underline{B} \vdots \underline{AB} \vdots \cdots \vdots \underline{A}^k\underline{B}]. \tag{5.17}$$

Since $\underline{P}_k$ is of rank n, then $\underline{P}_1$ is of rank n and

$$\underline{P}_1 \overset{E}{=} [\underline{I} \vdots \underline{0}] \tag{5.18}$$

where $\underline{I}$ is the n-th order identity matrix. Next multiply the matrix $\underline{P}_k$ by $\underline{KA}^k$, yielding

$$\underline{P}_k' = [\underline{KA}^k\underline{B} \vdots \underline{KA}^{k+1}\underline{B} \vdots \cdots \vdots \underline{KA}^{2k}\underline{B}]. \tag{5.19}$$

If $2k < n - 1$, then $2k$ is at most $n - 2$ so that if $\underline{P}_k'$ is of rank ℓ, then

$$\underline{P}_k'' = [\underline{KA}^k\underline{B} \vdots \underline{KA}^{k+1}\underline{B} \vdots \cdots \vdots \underline{KA}^{n-2}\underline{B}] \tag{5.20}$$

is of rank ℓ. (Recall that the rank of a product is less than or equal to the rank of either matrix. Therefore, the matrix $\underline{P}_k''$ is at most of rank ℓ.) Notice that $\underline{P}_2$ can be rewritten as

$$\underline{P}_2 = [\underline{0} \vdots \underline{KB} \vdots \cdots \vdots \underline{KA}^{k-1}\underline{B} \vdots \cdots \vdots \underline{P}_k''] \tag{5.21}$$

and if $\underline{P}_k'$ is of rank n, then

$$\underline{P}_2 \overset{E}{=} [\underline{0} \vdots \underline{I}'] \tag{5.22}$$

where $\underline{I}'$ is the ℓ-th order identity matrix. Therefore,

$$\underline{P}_{ic} = \begin{bmatrix} \underline{P}_1 \\ \underline{P}_2 \end{bmatrix} \overset{E}{=} \begin{bmatrix} \underline{I} & \underline{0} \\ \underline{0} & \underline{I}' \end{bmatrix} = \underline{I}'' \tag{5.23}$$

where $\underline{I}''$ is an $(n + \ell) \times (n + \ell)$ identity matrix. Thus, the indirect controllability matrix $\underline{P}_{ic}$ is of rank $(n + \ell)$ which is a necessary and sufficient condition for controllability.

Two special cases of the indirect controllability matrix are to be investigated.

Case 1. If $\underline{B}$ and $\underline{KB}$ are non-singular, then the matrix $\underline{P}_{ic}$ is of rank $\ell + n$. This result follows because $\underline{P}_{ic}$ can be regularly partitioned into a triangular block matrix

$$\underline{P}_{ic} \stackrel{E}{=} \begin{bmatrix} \underline{B} & \underline{O} \\ \underline{O} & \underline{KB} \end{bmatrix} \tag{5.24}$$

which is non-singular if and only if each diagonal box is non-singular (Parker and Eaves, 1960).

Case 2. If $\underline{K}$ is the $n \times n$ accumulative flow matrix of (5.10) which is used in the indirect algorithm, $\underline{K}$ is non-singular because all flows are on the diagonal. Now if the matrix $\underline{A}$ is multiplied on either side by a non-singular matrix, the product has the same rank of $\underline{A}$. That is, the rank of $\underline{KA}$ is n. It follows that the rank of $\underline{KA}^k$ is n and if $\underline{P}_k$ is of rank n, then $\underline{KA}^k\underline{P}_k$ is of rank n. In Theorem (5.1), the matrix $\underline{KA}^k\underline{P}_k$ had to be of the rank of $\underline{K}$. Therefore, in the special case where there is an accumulation pool for each compartment, this condition is automatically satisfied.

Theorem 5.2

For indirect identification, there must be at least two inputs to the compartmental system.

Proof: The number of accumulation pools within a system is assumed to be less than or equal to the number of compartments in the

system. That is, $\ell \leq n$. In addition, the number of rows in $\underline{P}_{1c}$ must be at most equal to the number of compartments n times the number of inputs m, or

$$\ell + n \leq nm. \tag{5.25}$$

Now divide both sides of (5.19) by n, yielding

$$\frac{\ell}{n} + 1 \leq m, \tag{5.26}$$

but since $\ell \leq n$, then $\frac{\ell}{n} \leq 1$ and unless $\ell = 0$ (which is the direct method), $m \leq 2$ because there can be no partial inputs.

Measurements of the accumulation pools are to be obtained for identification of the system of equations (5.10). In order for the system to be observable in the sense of Kalman (1963), it is necessary and sufficient that the test matrix

$$\underline{P}_{1o} = \begin{bmatrix} \underline{P}_3 \\ \underline{P}_4 \end{bmatrix} = \begin{bmatrix} \underline{0} & \underline{K}^T & \underline{A}^T\underline{K}^T & \cdots & \underline{A}^{T^{n-2}}\underline{K}^T \\ \underline{I}' & \underline{0} & \underline{0} & \cdots & \underline{0} \end{bmatrix} \tag{5.27}$$

is of rank $n + \ell$ where $\underline{I}'$ is the ℓ-th order identity matrix. Note that if the submatrix $\underline{P}_3$ is of rank n, then

$$\underline{P}_3 \quad [\underline{0} \quad \underline{I}] \tag{5.28}$$

where $\underline{I}$ is the n-th order identity matrix and hence,

$$\underline{P}_{1o} = \begin{bmatrix} \underline{P}_3 \\ \underline{P}_4 \end{bmatrix} \underline{E} \begin{bmatrix} \underline{0} & \underline{I} \\ \underline{I}' & \underline{0} \end{bmatrix} = \begin{bmatrix} \underline{I} & \underline{0} \\ \underline{0} & \underline{I}' \end{bmatrix} \tag{5.29}$$

giving an equivalent $(n + \ell) \times (n + \ell)$ identity matrix. Thus, for $\underline{P}_{1o}$ to be of the desired rank, $\underline{P}_3$ must be of rank n. By considering the

states $\underline{y}$ as continuous observations of the internal states $\underline{x}$, the necessary conditions presented by Cobelli and Romanin-Jacur (1976) for observability for the direct algorithm may be applied to the indirect scheme. In the structural sense, the indirect model is completely observable if at least one flow to an accumulation compartment is reachable from every internal compartment. In addition, no accumulative flows may be associated with only the internal state variables which form one or more traps, all influencing the same pool.

Combined Direct-Indirect

Applications of the direct and indirect algorithms may tend to overlap in certain systems. An introduced (labeled) substance may metabolize and accumulate, along with its metabolites, in one or more pools and also be directly measurable as an output from compartments within the system itself. In another system, the outputs available for data collection might be the sum of observations from a compartment and its accumulation pool.

The method in which the observations are made is not involved in controllability which is concerned with the flow of the inputs, so the indirect controllability conditions suffice for the combined measurement technique.

Observability of the two types of combined systems will be discussed in this section. Requirements for observability are straightforward. First consider the system of (5.10) where the measurement vector is of the form

$$\underline{z} = \begin{bmatrix} \underline{C} & \underline{0} \\ \underline{0} & \underline{I} \end{bmatrix} \begin{bmatrix} \underline{x} \\ \underline{y} \end{bmatrix} . \qquad (5.30)$$

Measurements are to be collected from both system compartments and accumulation pools. The system is observable if and only if the test matrix

$$\underline{P}_{di} = \left[\begin{array}{c|c|c|c|c|c|c} \underline{0} & \underline{C}^T & \underline{A}^T\underline{C}^T & \cdots & (\underline{A}^T)^{n-1}\underline{C}^T & \underline{0} & \underline{K}^T & \underline{A}^T\underline{K}^T & \cdots & (\underline{A}^T)^{n-2}\underline{K}^T \\ \underline{I} & & & \underline{0} & & & & & \underline{0} & \end{array}\right] \tag{5.31}$$

is of rank p + ℓ where I is an ℓ-th order identity matrix. Define the upper partition to be

$$\underline{P}'_{di} = [\underline{0} \vdots \underline{P}_5 \vdots \underline{P}_6] \tag{5.32}$$

and notice that $\underline{P}_5$ is the observability matrix $\underline{P}_o$ for the direct algorithm, while $\underline{P}_6$ is the observability matrix $\underline{P}_{io}$ for the indirect scheme for identification. The system is completely observable if the conditions for direct observability are satisfied because $\underline{P}_5$ would be of rank p, making the system

$$\underline{P}_{di} \overset{E}{=} \left[\begin{array}{ccc} \underline{I}' & \underline{0} & \underline{P}_6 \\ \underline{0} & \underline{I} & \underline{0} \end{array}\right] \tag{5.33}$$

of rank p where $\underline{I}'$ and $\underline{I}$ are p-th order and ℓ-th order identity matrices, respectively. Also, if there are as many (or more) accumulation pools as directly measurable states (p), and the conditions for indirect observability hold, then the system is of the form

$$\underline{P}_{di} \overset{E}{=} \left[\begin{array}{ccc} \underline{I}' & \underline{0} & \underline{P}_5 \\ \underline{0} & \underline{I} & \underline{0} \end{array}\right] \tag{5.34}$$

and the desired rank is obtained. In addition, if the two test matrices

(direct and indirect) combine to form a matrix $\underline{P}_7$ of rank p, the system becomes

$$\underline{P}_{di} = \begin{bmatrix} \underline{0} & \underline{P}_6 \\ \underline{I} & \underline{0} \end{bmatrix} \underline{\underline{E}} \begin{bmatrix} \underline{I}' & \underline{0} \\ \underline{0} & \underline{I} \end{bmatrix} \tag{5.35}$$

and the necessary and sufficient conditions for identifiability are fulfilled.

Consider next a system which has as its output the sum of observations. In this combined case, the measurement vector for the system is

$$\underline{z} = [\underline{C} \quad \underline{I}] \begin{bmatrix} \underline{x} \\ \underline{y} \end{bmatrix} \tag{5.36}$$

and the system is said to be observable in the sense of Kalman (1963) only if the test matrix

$$\underline{P}s = [\underline{C}^T \vdots \underline{A}^T\underline{C}^T \vdots \ldots \vdots (\underline{A}^T)^{n-1}\underline{C}^T] + [\underline{0} \vdots \underline{K}^T \vdots \underline{A}^T\underline{K}^T \vdots \ldots \vdots (\underline{A}^T)^{n-2}\underline{K}^T] \tag{5.37}$$

is of rank p. Thus, system is observable if the sum of observability matrices for the direct and indirect algorithms is of rank p. However, two matrices of different orders cannot be added, so in order for the test matrix $\underline{P}s$ to be defined, the number of direct observations, p, must equal the number of accumulation pools, ℓ.

Summary

This chapter has shown how the concepts of observability and controllability can be used as necessary conditions for the structural identifiability of a system. For the direct method of identification

discussed in Chapter III, closed systems are uncontrollable for any system. Observability and controllability conditions for open systems as discussed by Cobelli and Romanin-Jacur (1976) have been reviewed. The necessary conditions for direct identifiability have also been shown to be applicable to the indirect identification scheme of Chapter III. By formulating the problem of controllability of the accumulation pools as one of output controllability, additional conditions for indirect controllability have been derived by using the Kalman test matrix. Finally, structural identifiability conditions have been considered for systems in which the indirect and direct schemes overlap.

CHAPTER VI

CONSTANT INFUSION

Introduction

A constant infusion input has occasionally been used in order to label compartments to a high specific activity. The constant influx of tracer was probably first incorporated by Hevesey and Hahn (1940) to obtain high concentrations of ^{32}P-phosphate in plasma. Hevesey and Hahn, however, were not interested in analyzing the data to determine model parameters. Constant infusion is also used when there are problems with incomplete and non-instantaneous mixing within compartments, usually due to spacial heterogeneities. Shipley and Clark (1972) present textbook cases in which the method and its usage are discussed. Assuming that the chronic infusion of tracer does not disturb the behavior of the recipient compartments, then the constant input level of Table I, part (b), gives rise to a steady-state defined by $\underline{x}_s$.

The constant infusion method as discussed in Chapter III is based upon the compartment model defined by (3.1) as

$$\dot{\underline{x}} + \underline{A}\underline{x} + \underline{B}\underline{u}. \qquad (6.1)$$

Linearly independent inputs generate an ensemble of linearly independent steady-state samples of the system state $\underline{x}$ from which the coefficients of the matrix of rate coefficients may be determined.

Constant Infusion Identifiability

When in steady-state, the system of (6.1) can be described by

$$\underline{0} = \underline{A}\underline{x} + \underline{B}\underline{u}. \tag{6.2}$$

Recall that $\underline{x}$ is an n-vector of compartmental states, $\underline{u}$ is an m-vector of specified inputs, and $\underline{B}$ is an $n \times m$ matrix where

$$b_{ij} = \begin{cases} 1 \\ 0 \end{cases}$$

and

$$\sum_{i=1}^{n} b_{ij} = 1.$$

Let $\underline{u}_1, \underline{u}_2, \ldots, \underline{u}_m$ span R^m. Assuming that the compartmental system is open so that $\underline{A}^{-1}$ exists, then $\underline{x}_1, \underline{x}_2, \ldots, \underline{x}_m$ span at most an m-dimensional subspace of R^n where

$$\underline{A}\,\underline{x}_k = -\underline{B}\,\underline{u}_k \quad k = 1, \ldots, m. \tag{6.3}$$

Now set

$$-\underline{B}\,\underline{u}_k = \underline{w}_k \quad k = 1, \ldots, m \tag{6.4}$$

which results in

$$\underline{A}\,\underline{X} = \underline{W} \tag{6.5}$$

where the $n \times m$ matrices

$$\underline{X} = [\underline{x}_1, \underline{x}_2, \ldots, \underline{x}_m] \tag{6.6}$$

and

$$\underline{W} = [\underline{w}_1, \underline{w}_2, \ldots, \underline{w}_m] \tag{6.7}$$

are both of rank m. Taking the transpose of each side of Equation (6.5) gives

$$\underline{X}^T \underline{A}^T = \underline{W}^T. \tag{6.8}$$

Next define the n-vector $\underline{a}_k$ to be the k-th column of $\underline{A}^T$ such that

$$\underline{A}^T = [\underline{a}_1, \underline{a}_2, \ldots, \underline{a}_n]. \tag{6.9}$$

The vectors $\underline{a}_k$ define the unknown system parameters, i.e., the rate coefficients of the compartment model. Thus,

$$\underline{X}^T \underline{a}_k = \underline{z}_k \quad k = 1, \ldots, n \tag{6.10}$$

where $\underline{z}_k$ is the m-vector of the k-th column of

$$\underline{Z} = \underline{W}^T \tag{6.11}$$

where

$$\underline{Z} = [\underline{z}_1, \underline{z}_2, \ldots, \underline{z}_n] \tag{6.12}$$

and rank $(\underline{Z})$ = m. It should be noted that the vectors $\underline{a}_k$ and $\underline{z}_k$ of (6.10) are completely determined by the compartmental inputs. That is, $\underline{a}_k$ represents the k-th row of $\underline{A}$ giving endogenous inputs to the compartment, and $\underline{z}_k$ defines the possibility of an exogenous input to compartment k.

Identifiability related to the system structure for a multi-input/multi-output system where all states can be measured directly is to be considered first. The system is structurally identifiable when the number of parameters that can be estimated is not smaller than the number of unknown system parameters in the algebraic equation (6.5).

Only compartment models which are open to their environment are considered in this chapter because closed systems with constant rate inputs accumulate material at a constant rate, never reaching steady-state. This condition does not prohibit the closure of an individual compartment or groups of compartments as long as they do not form a decoupled subsystem. The $\underline{A}$-matrix for an open system is characterized by a nonzero determinant. This result implies that in the special case when the inputs $\underline{u}_k$ ($k = 1, \ldots, n$) span R^n, the resultant steady-states $\underline{x}_k$ ($k = 1, \ldots, n$) also span R^n and $\underline{X}^{-1}$ exists. Hence, the matrix equation (6.5) can be solved by multiplying on the right by $\underline{X}^{-1}$, giving $\underline{A} = \underline{W}\underline{X}^{-1}$. Input access to every compartment in the system and the ability to measure all compartmental steady-states then imply structural identifiability. These sufficient conditions are only rarely met in practice, requiring for biochemical systems the organic synthesis of tracer material for all chemical species present in the system. For ecological systems, only a few natural input pathways to the system exist with many compartments being essentially inaccessible. Therefore, the remainder of this chapter concerns the development of conditions which relate identifiability to system structure with restricted compartmental access.

Theorem 6.1

A compartmental system is identifiable only if there exists at least one path from some constant input to every compartment.

Proof: By contradiction, if there is no path from any input to one or more compartments, then for all k, Equation (6.3) can be

partitioned as

$$\begin{bmatrix} \underline{A}_1 & \underline{A}_2 \\ \underline{0} & \underline{A}_3 \end{bmatrix} \begin{bmatrix} \underline{x}_{k_1} \\ \underline{x}_{k_2} \end{bmatrix} = \begin{bmatrix} \underline{w}_k \\ \underline{0} \end{bmatrix} . \tag{6.13}$$

Hence, the following relationships arise:

$$\underline{A}_1 \underline{x}_{k_1} + \underline{A}_2 \underline{x}_{k_2} = \underline{w}_k \tag{6.14}$$

and

$$\underline{A}_3 \underline{x}_{k_2} = \underline{0}. \tag{6.15}$$

But $\underline{A}_3^{-1}$ exists, that is, there are no closed subsystems; and the vector $\underline{x}_{k_2}$ is identically null. Thus, regardless of the values of the elements comprising $\underline{A}_3$, the model parameters contained in $\underline{A}_3$ and $\underline{A}_2$ cannot be identified by solving equations of the form (6.10). Thus, structural identifiability depends on the ability inputs to reach every compartment.

Theorem 6.2

A system is identifiable by the constant infusion method only if at least one outlet to the environment is reachable from every compartment along any path.

Proof: By contradiction, if no system outlets can be reached from compartment m, then this compartment and all compartments coupled to it continuously accumulate material without reaching a steady-state. This, of course, prohibits identification using (6.5).

The preceding concepts of structural identifiability based upon the data derived from constant infusion experiments parallel those already known for the single-dose method (see Chapter V). However, the solution

of the identification problem of a constant input applied to a system is further constrained by the static nature of the resultant steady-state. Indeed, as will be shown, the dynamic systems concept of observability plays no role in solving this algebraic problem.

Theorem 6.3

For m exogenous inputs $\underline{u}$ to an identifiable compartmental system, there can be at most (m-1) endogenous inputs to any single compartment k.

Proof: For m inputs into a system, Equation (6.10) produces m independent equations in the n unknown parameters of $\underline{a}_k$. But at most m unknowns can be determined from the solution of m independent equations. Recall that the k-th entry in the n-vector $\underline{a}_k$ represents the turnover of the k-th compartment. If the compartment turnover is to be estimated, then at most m - 1 of the endogenous inputs to the k-th compartment (the remaining entries in $\underline{a}_k$) can be identified. Thus, for m inputs to a system, there can be at most m - 1 endogenous inputs to a single compartment.

The (n - m) compartments κ without exogenous inputs produce m dependent equations of the form

$$\underline{X}^T \underline{a}_\kappa = \underline{0} \tag{6.16}$$

where $\underline{a}_\kappa$ is defined as in (6.10). Therefore, (n - m) additional equations are needed for the solution of (6.5). The necessary equations may be obtained from each of the (n - m) compartments $\underline{a}_\kappa$ in one of the following ways:

1. Turnover of x_κ must be known from an independent measurement

of *a priori* knowledge of the compartmental turnover, giving the κ-th entry in $\underline{a}_\kappa$.

2. Flow out of the compartment to the environment must be determined for an open compartment.

3. A closed compartment offers an additional independent equation given by the null column sum

$$\sum_{i=1}^{n} a_{i\kappa} = 0 \tag{6.17}$$

where $a_{i\kappa}$ $(i = 1, \ldots, n)$ define the components of $\underline{a}_\kappa$.

Consider the three-compartment system of Figure 5 which gives an $\underline{A}$-matrix of unknown system parameters of the form

$$\underline{A} = \begin{bmatrix} a_{11} & 0 & a_{13} \\ a_{21} & a_{22} & 0 \\ 0 & a_{32} & a_{33} \end{bmatrix} \tag{6.18}$$

Assume the two exogenous inputs u_1 and u_2 drive the system to a steady-state, resulting in the following equation of the form of (6.12):

$$\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix} = \begin{bmatrix} a_{11} & 0 & a_{13} \\ a_{21} & a_{22} & 0 \\ 0 & a_{32} & a_{33} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} + \begin{bmatrix} 1 & 0 \\ 0 & 1 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \end{bmatrix} \tag{6.19}$$

Performing $m = 2$ experiments with two linearly independent constant inputs generates the ensemble of steady-states given by (6.5) as

$$\begin{bmatrix} a_{11} & 0 & a_{13} \\ a_{21} & a_{22} & 0 \\ 0 & a_{32} & a_{33} \end{bmatrix} \begin{bmatrix} x_{11} & x_{12} \\ x_{21} & x_{22} \\ x_{31} & x_{32} \end{bmatrix} = - \begin{bmatrix} u_{11} & u_{12} \\ u_{21} & u_{22} \\ 0 & 0 \end{bmatrix} . \tag{6.20}$$

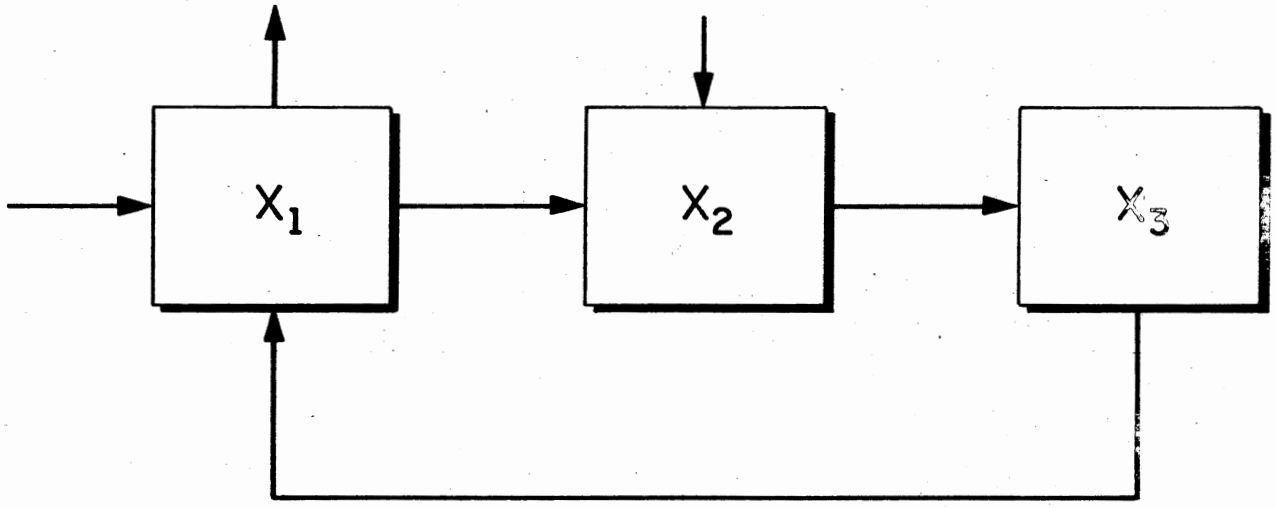


Figure 5. Hypothetical Three-Compartment System

Taking the transpose of each side yields

$$\begin{bmatrix} x_{11} & x_{21} & x_{31} \\ x_{12} & x_{22} & x_{32} \end{bmatrix} \begin{bmatrix} a_{11} & a_{21} & 0 \\ 0 & a_{22} & a_{32} \\ a_{13} & 0 & a_{33} \end{bmatrix} = - \begin{bmatrix} u_{11} & u_{21} & 0 \\ u_{12} & u_{22} & 0 \end{bmatrix} \tag{6.21}$$

which is the matrix form of the following three sets of equations in the six unknown rate coefficients:

$$\left.\begin{aligned} x_{11}\ a_{11} + x_{31}\ a_{13} &= -u_{11} \\ x_{12}\ a_{11} + x_{32}\ a_{13} &= -u_{12} \end{aligned}\right\} \tag{6.22}$$

for the first column of $\underline{A}$,

$$\left.\begin{aligned} x_{11}\ a_{21} + x_{21}\ a_{22} &= -u_{21} \\ x_{12}\ a_{21} + x_{22}\ a_{22} &= -u_{22} \end{aligned}\right\} \tag{6.23}$$

for the second column, and

$$\left.\begin{aligned} x_{21}\ a_{32} + x_{31}\ a_{33} &= 0 \\ x_{22}\ a_{32} + x_{32}\ a_{33} &= 0 \end{aligned}\right\} \tag{6.24}$$

for the third column. The system may be tested for identifiability by inspecting the necessary conditions provided in this section. There is a path from some input to every compartment; and one outlet to the environment is reachable from every compartment, thus satisfying Theorems 6.1 and 6.2. The system has two exogenous inputs and at most one (m - 1) endogenous input to a single compartment. Notice that the sets of equations (6.22) and (6.23) have a unique solution if and only if

$$\begin{vmatrix} x_{11} & x_{31} \\ x_{12} & x_{32} \end{vmatrix} \neq 0 \qquad \text{and} \qquad \begin{vmatrix} x_{11} & x_{21} \\ x_{12} & x_{22} \end{vmatrix} \neq 0. \tag{6.25}$$

Furthermore, Equation (6.24) has a nontrivial solution if and only if

$$\begin{vmatrix} x_{21} & x_{31} \\ x_{22} & x_{32} \end{vmatrix} = 0. \tag{6.26}$$

These conditions are required for identifiability and are obtained when the $\underline{X}$-matrix of steady-states has row rank of $m = 2$, and the individual state vectors can lie anywhere in the m-dimensional subspace of the state space R^n. A sufficient condition for these constraints on the $\underline{X}$-matrix of steady-states is provided by the controllability of $(\underline{A}, \underline{B})$.

Equations (6.22), (6.23), and (6.24) can provide five independent equations in the six unknown entries in the $\underline{A}$-matrix. Thus, with this example, it is clear that knowledge of the turnover a_{33} of compartment 3, or the exogenous flow $(a_{33} + a_{13})x_3$ from compartment 3, provide the identification of the systems model. It is also clear that closure of compartment 3 gives

$$a_{13} + a_{33} = 0, \tag{6.27}$$

which along with (6.22) and (6.23) and one equation drawn from (6.24), defines six independent equations in the six unknown entries in $\underline{A}$.

If the compartment(s) without an exogenous input is (are) not closed, it may be difficult, if not impossible, to identify the compartment model from steady-state measurements alone. In such cases, it may be useful to define the maximum identifiable sub-model of the system. The identifiable sub-model parameter matrix $\underline{A}_{max}$ consists of all

transfers associated only with compartments which are either closed or have exogenous inputs. The dimension of the sub-model being (m + c) where c is equal to the number of compartments without an input or a flow to the environment. For example, consider the system of Figure 5 with an additional flow from compartment 3 to the environment. The matrix of rate, coefficients for maximum identifiable sub-model is

$$\underline{A}_{max} = \begin{bmatrix} a_{11} & 0 \\ a_{21} & a_{22} \end{bmatrix} . \tag{6.28}$$

The identifiability of this sub-model depends only on the measurement of steady-states. In order to identify the full system model, an experimental design which incorporates material flow measurements must be implemented.

As a practical matter, it is often true that the closure of a compartment indicates its inaccessibility with respect to exogenous inputs. Thus, the case when (m + c) = n is important in the applications of the theory of structural identifiability. For this case the following theorem gives sufficient conditions for identifiability.

Theorem 6.4

An open compartment model with m inputs is identifiable provided:

1. The pair ($\underline{A}$, $\underline{B}$) is controllable.
2. A maximum of (m - 1) endogenous inputs enter each of the m compartments.
3. The (n - m) compartments without exogenous inputs are closed.

Proof: Because ($\underline{A}$, $\underline{B}$) is controllable, the row rank of $\underline{X}^T$ is m,

and

$$\underline{X}^T \underline{a}_k = \underline{z}_k \quad k = 1, 2, \ldots, m \tag{6.29}$$

has a unique solution for the m^2 unknowns in the n-vectors $\underline{a}_k$. Also, the controllability of $(\underline{A}, \underline{B})$ along with the fact that $\underline{A}$ is open implies that

$$\underline{X}^T \underline{a}_{k+m} = \underline{0} \quad k = 1, 2, \ldots, c \tag{6.30}$$

where $c = n - m$, gives $c(m - 1)$ equations in cm unknowns. These results follow from the fact that controllability implies an input to (6.1) can produce an arbitrary steady-state which is not constrained to lie in a proper sub-space of R^n. Also, since $\underline{A}$ is open without closed proper subsystems, the resultant coefficient matrix (see (6.24)) of (6.30) is of rank $(m - 1)$. So, Equations (6.29) and (6.30) give

$$m^2 + c(m - 1) = mn - c \tag{6.31}$$

independent equations in nm unknowns. However, c compartments are closed, yielding c independent equations for the columns of $\underline{A}$. Thus, the solution of the resultant set of mn linearly independent equations gives the desired nm rate coefficients comprising the $\underline{A}$-matrix.

Now consider the case in which some states cannot be measured directly. It will be shown by example that it is impossible to identify all unknown parameters unless there is access to every compartment. Assume that measurements can be taken only from compartments 1 and 2 of Figure 5. The ensemble measurement matrix $\underline{Y}$ may be given by

$$\underline{Y} = \underline{C}\,\underline{X} \tag{6.32}$$

where $\underline{C}$ is defined by (5.2), resulting in

$$\begin{bmatrix} y_{11} & y_{12} \\ y_{21} & y_{22} \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \end{bmatrix} \begin{bmatrix} x_{11} & x_{12} \\ x_{21} & x_{22} \\ x_{31} & x_{32} \end{bmatrix} . \tag{6.33}$$

substituting the measured values $\underline{Y}$ into the system of (6.20) gives the system

$$\begin{aligned} y_{11}\ a_{11} + x_{31}\ a_{13} &= -u_{11} \\ y_{11}\ a_{21} + y_{21}\ a_{22} &= -u_{21} \\ y_{21}\ a_{32} + x_{31}\ a_{33} &= 0 \\ y_{12}\ a_{11} + x_{32}\ a_{13} &= -u_{12} \\ y_{12}\ a_{21} + y_{22}\ a_{22} &= -u_{22} \end{aligned} \tag{6.34}$$

with the additional equation $a_{13} + a_{33} = 0$ provided by (6.24). Notice that the result is a set of six linearly independent equations with eight unknowns since the values of x_{31} and x_{32} cannot be measured.

Although the parameters associated with compartments which are immeasurable cannot be estimated, again, a maximum sub-model can be identified. The identifiable sub-model flow matrix is composed of those parameters associated <u>only</u> with those compartments which can be measured directly and satisfy conditions given when all states are measurable. Thus, for Figure 5, the maximum identifiable sub-model flow matrix $\underline{A}_{max}$ is that of (6.25).

Summary

Controllability of the system (6.1) allows the exogenous inputs to produce arbitrary steady-state values anywhere in state space resulting in sufficient, but not necessary, conditions for the structural

identifiability of the system when direct measurements can be obtained from every compartment. There is, however, no need to investigate the observability of the system as this concept plays no role in solving the problems of constant infusion identifiability.

Although the conclusions on identifiability for the constant-infusion method are somewhat limited by system structure and the lack of necessary conditions, it should be pointed out that the prevalent notion that "identification of dynamic parameters on the basis of measurements is only possible if the measurements are taken when the system is in a transient state" (Graupe, 1976, p. 7) is erroneous; because indeed, complete sets of parameters can be identified when the system is in steady-state under conditions which are often met in practice.

CHAPTER VII

EXAMPLES

Introduction

The identification algorithm and its associated sampling strategy are suited to a wide variety of identification problems in biological and ecological systems. In order to illustrate the use of the identification scheme, its implementation as a computer algorithm, the developed sampling theory, and the concepts of identifiability, several elementary examples of both laboratory and natural ecosystems are considered. Some sample problems are from the literature and others have been specially selected to exhibit the variety of forms in which the problems may be posed and the capabilities of the material given in the foregoing chapters.

Direct Method

Serving as a first example is the analysis by Rescigno and Segre (1962) of the work by Barnum and Huseby (1950) on the kinetics of inorganic phosphorus and pentose nucleic phosphorus in the liver nuclei of mice injected with radiophosphorus. Figure 6 indicates transfer (a_{21}) between inorganic phosphorus (x_1) and pentose nucleic phosphorus (x_2) which Rescigno and Segre compute as 0.1 per hr. They also compute the turnover a_{22} to be 0.5 per hr. Using the published time series

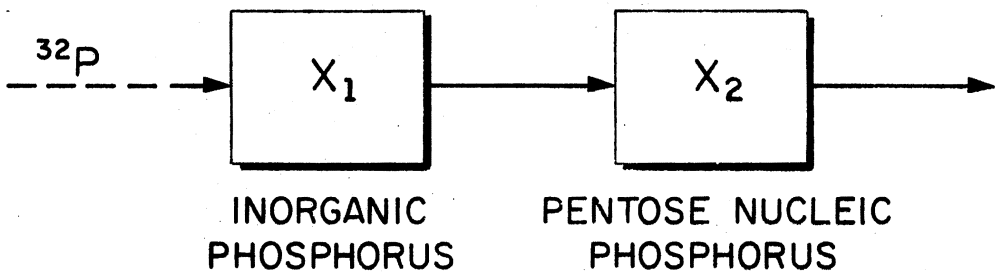


Figure 6. Specific Activity of Inorganic Phosphorus and of Pentose Nucleic Phosphorus in Liver Nuclei of Mice Injected With ^{32}P

specific activity data in the identification scheme of Equation (3.37), values of a_{21} = 0.11 per hr. and a_{22} = 0.33 per hr. are obtained. These calculations represent differences of 10 percent between transfers (a_{21}) and 34 percent for the turnovers (a_{22}). The rather large discrepancy is probably due to a precursor compartment missing from the experimental data (Barnum and Huseby, 1950). It may be that identification with (3.37) is more sensitive to the missing precursor, which is probably extracellular inorganic phosphorus, than the scheme employed by Rescigno and Segre. The missing precursor would have little effect on the transfer a_{21} as indicated.

For another example which provides a better agreement between identification schemes, recall the work of Welch, Adatepe, and Potchen (1965) on technetium kinetics in humans. Figure 7 gives the compartmental model under consideration. Welch and his colleagues produce a_{12} = 1.7 per hr., a_{21} = 1.47 per hr., and a_{01} = 0.9 per hr. for the model rate coefficients, while Equation (3.37) gives the $\underline{A}$ matrix of the following system:

$$\begin{aligned} \dot{x}_1 &= 1.66x_1 + 1.46x_2 \\ \dot{x}_2 &= 1.63x_1 - 1.62x_1 \end{aligned} \tag{7.1}$$

which gives a_{12} = 1.66 per hr., a_{21} = 1.46 per hr., and a_{01} = 0.16 per hr. for a maximum difference of under 16 percent. Actually, with this example, the two turnovers a_{11} and a_{22} exhibit discrepancies of under five percent.

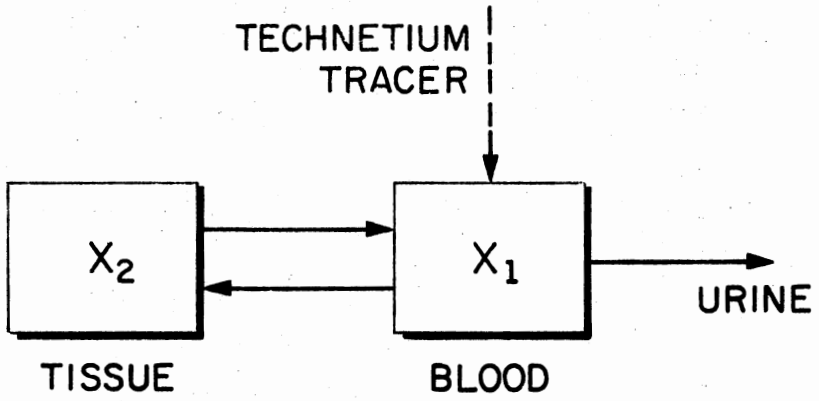


Figure 7. Analysis of Technetium Kinetics

Indirect Method

Next consider the study of Nelson and O'Reilly (1960) on the kinetics of sulfisoxazole acetylation and excretion in humans. This research provides an example of the utility of the indirect method of transfer rate identification by studying the urinary excretion of the sulfa-drug (x_1) and its metabolite (x_2) following the administration of a single dose to man. Using observer time series data of the accumulated free drug (Y_1) and the collected acetylated drug (Y_2), the identification algorithm of (3.55) produced the compartment model of Figure 8, the behavior of which is determined by a system with the following $\underline{A}$ matrix:

$$\underline{A} = \begin{bmatrix} -0.13 & -0.003 \\ 0.05 & -0.8 \end{bmatrix} \tag{7.2}$$

Nelson and O'Reilly determined the rate coefficients by graphical analyses and obtained comparative values of $a_{11} = -0.108$ per hr., $a_{21} = 0.21$ per hr., and $a_{22} = -0.76$ per hr. which are in relative agreement with the rate coefficients calculated from (3.55). Note that based upon theoretical grounds $a_{12} = 0$, which is verified by the corresponding (identified) transfer coefficient -0.003.

Sampling Theory

As an elementary illustration of the identification algorithm with emphasis on the sampling theory, consider the recent study of phosphorus kinetics in freshwater microcosms provided by Sebetich (1975). This research concerns the transfer of radiophosphorus among lake water,

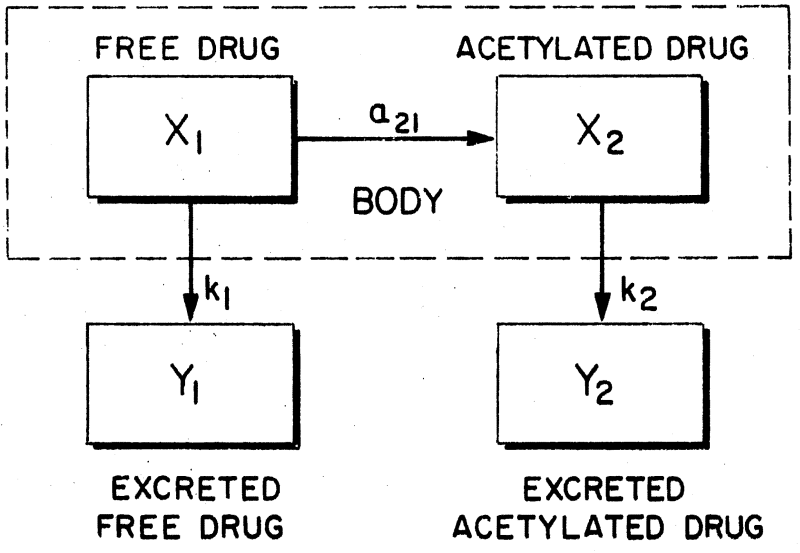


Figure 8. Metabolism and Excretion of a Sulfa Drug

diatom, snail and sand compartments. Using a standard technique pioneered by Patten and Witkamp (1967), the analog computer is employed to identify the transfer rates and to simulate the dynamic behavior of microcosms of varying complexity. The single and combined effects of diatoms, snails, and sand on the movement of radiophosphorus through the system are noted.

Sebetich presents time series data of radiophosphorus concentrations within each compartment of the microcosm system. These data are compared with analog computer simulations of a mathematical model of fixed structure and free parameters corresponding to the transfer rates of radiophosphorus. By manipulating the free model parameters, a fit between the computer simulations and the time series data is obtained by trial and error. It is this approximate identification scheme which the results of this paper propose to replace.

Table II gives the maximum turnover, the corresponding turnover time, and the maximum sample period, assuming precision $d = 3$, for the seven microcosm systems considered by Sebetich. Because the microcosms are presumed to be closed systems, no minimum sample period is computed. Consider the system in which diatoms (Nitzschia palea) take up phosphorus from lake water. Three samples spaced at intervals of twenty-five hours (maximum) are sufficient to prescribe the compartment model for the system. Data presented by Sebetich (1975) is variously spaced from one hour to twenty-five hour intervals. On a time scale of fifty hours with a sample period (τ) of ten hours, samples were extracted from these data; and several associated compartment models were constructed using (3.37). The best of these three-point models indicated a mean square error of 0.0574 when used to reproduce the entire fifty-

TABLE II

COMPUTED SAMPLING TIMES FOR THE COMPARTMENTAL RADIOPHOSPHORUS IN MICROCOSMS OF VARYING COMPLEXITY (SEBETICH, 1975)

Compartments	T_o^{-1} (hr.$^{-1}$)	T_o (hr.)	τ^+ (hr.)
Water-diatom	0.0689	14.5	25.06
Water-snail	0.0043	233	401.61
Water-sand	0.0633	15.8	27.28
Water-diatom-snail	0.0379	26.4	30.38
Water-diatom-sand	0.1000	10.0	11.51
Water-snail-sand	0.0611	16.4	18.84
Water-diatom-snail-sand	0.1035	9.66	8.34

hour data set. The Gaussian least squares algorithm of (3.39) was used next to construct a compartment model from all six data points on the fifty-hour time scale. The mean square error incurred by this model in reproducing the data base was 0.0043, a significant, but expected, improvement in accuracy.

The identification algorithm of (3.39) produced the following six-point compartment model:

$$\begin{aligned} \dot{x}_1 &= -0.063x_1 + 0.0054x_2 \\ \dot{x}_2 &= 0.052x_1 - 0.016x_2 \end{aligned} \tag{7.3}$$

Sebetich (1975) does not present details of the transfers produced by the analog computer identification scheme, but he does give values for the turnovers of 0.069 and 0.018 for the diatoms and water, respectively, which should be compared with 0.063 and 0.016 as obtained from (7.3). It is interesting to note that the model of (7.3) is not closed with respect to the phosphorus transfers. This is not unexpected mainly because a more accurate model for the uptake of phosphorus by algae includes dissolved inorganic, organic, and dissolved organic phosphorus compartments (e.g., Watt and Hayes, 1963), as shown in Figure 9. Because the model of (7.3) is not closed with respect to material transfers, it is clear that the algorithm of (3.39) has again identified a missing compartment. With reference to Figure 9, dissolved organic phosphorus is probably the missing compartment, thus indicating that an essential transfer from algae back to water has not been modeled.

In order to illustrate the sensitivity of the identification scheme with respect to the sample period, a hypothetical ecosystem, first

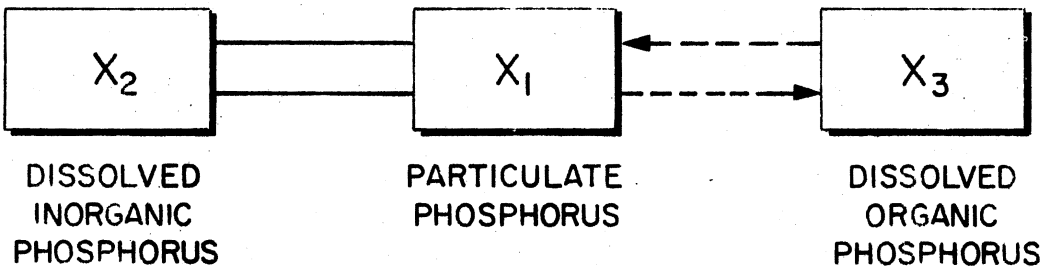


Figure 9. Aquatic Phosphorus Cycle

described by Smith (1970), is considered. The system consists of three compartments: water (x_1), an aquatic plant population (x_2), and an herbivore population (x_3). Figure 10 shows these compartments along with the material balance, assumed to be phosphorus. The only input (u_1) is the phosphorus contained in the water flowing through the system. The outputs are phosphorus from the water and herbivore compartments. The compartment model describes the steady-state model resulting from an input of $u_1 = 100$ mg. P/day. From the data presented by Smith, the rate coefficients can be computed, resulting in

$$\begin{aligned} \dot{x}_1 &= 5x_2 + 5x_3 - 16x_1 + 100 \\ \dot{x}_2 &= 14x_1 - 95x_2 \\ \dot{x}_3 &= 90x_2 - 14x_3 \end{aligned} \tag{7.4}$$

as a characterization of the ecosystem. The $\underline{A}$-matrix is thus given by

$$\underline{A} = \begin{bmatrix} -16 & 5 & 5 \\ 14 & -95 & 0 \\ 0 & 90 & -14 \end{bmatrix} \tag{7.5}$$

which has eigenvalues

$$\begin{aligned} \lambda_1 &= -6.1630 \\ \lambda_2 &= -23.9367 \\ \lambda_3 &= -94.9002. \end{aligned} \tag{7.6}$$

The following simulation experiment is performed. Starting from the steady-state given by $x_1 = 95$, $x_2 = 1.4$, and $x_3 = 9$, the model of

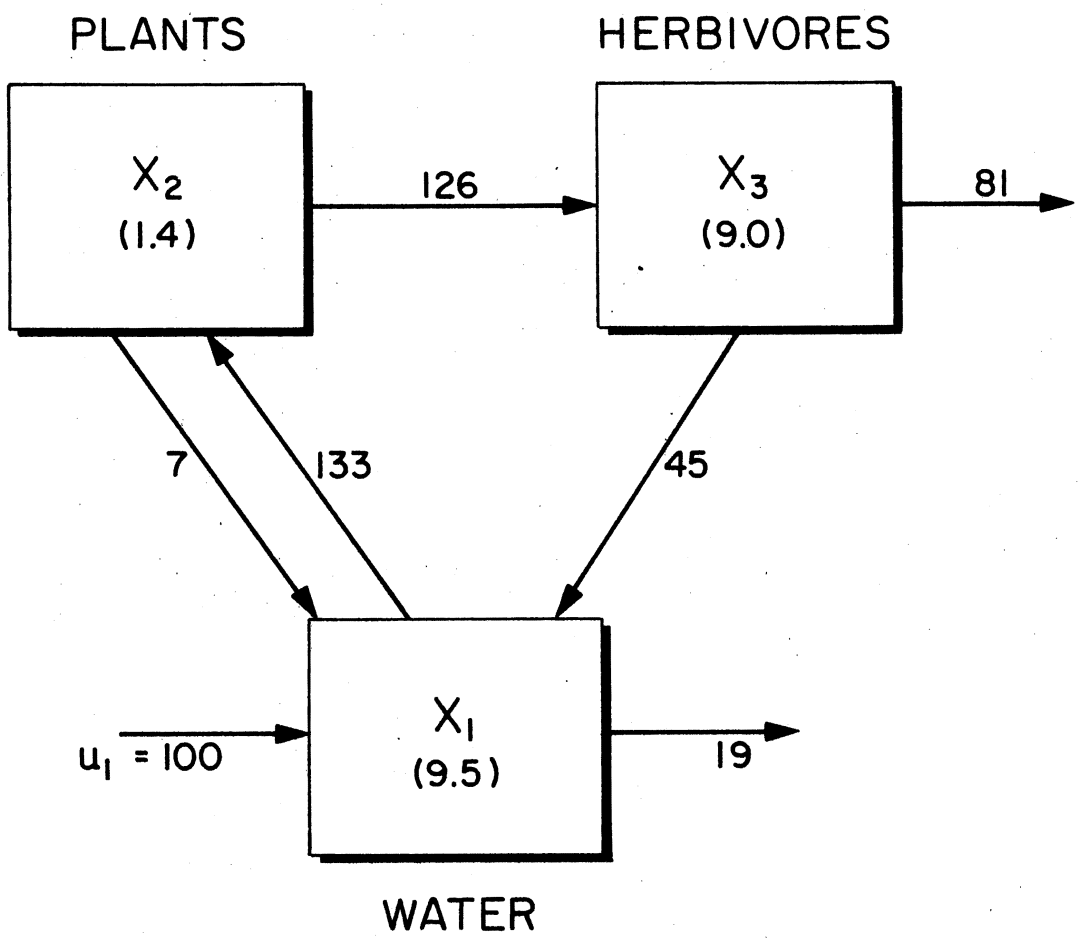


Figure 10. Phosphorus Balance for a Hypothetical Ecosystem Model*

* The numbers on the directed line segments indicate flows of phosphorus in mg./day units and the numbers in the boxes are the stored quantities of phosphorus in mg.

(7.4) is solved with zero input using the IBM simulation language CSMP. From the simulation output, samples of the state are gathered with four-place accuracy. The measurements may then be used to reconstruct the model of (7.4) using the computer program in the Appendix.

From (7.4), the Gerschgorin circle can be plotted and $\alpha = 190$ and $\delta = 2$ is computed. Thus, $\tau^- = 5 \times 10^{-5}$ and $\tau^+ = 0.012$ are obtained from (4.34) and (4.37), respectively. From simulation results with a sample period on the time scale $0.005 \leq \tau \leq 0.02$. the eigenvalues of the model are predicted to well within one percent accuracy. However, a model on the time scale $\tau \geq 0.03$ is in significant error. For a sample period less than 0.005, the model errors are suddenly very large, indicating that the identification algorithm is very sensitive to the lower bound. In fact, in this case, the lower bound is somewhat inaccurate and should be refined. A reasonable choice for the sample period is obtained by rounding τ close to the upper bound τ^+.

Table III provides a survey of computed sampling times for various aquatic and terrestrial microcosms based upon an assumed three-place decimal precision for measured data. It should be noted that with the exception of Azotobacter the maximum sample period τ^+ is less than the reciprocal of the maximum turnover T_o^{-1}. Thus, without the detailed information necessary to employ (4.43) for the computation of τ^+, a rough estimate for the sample period is provided by T_o.

The sampling theory developed for implementing the identification algorithm presented in this paper is based upon the analysis of laboratory ecosystems. The basic idea is that such systems are isolated from the cyclic environmental inputs present in nature. As a first step in ecosystem modeling, the cyclic behavior of environmental parameters is

TABLE III

COMPUTED SAMPLING TIMES FOR ELEMENTAL DYNAMICS WITHIN SELECTED LABORATORY ECOSYSTEMS

Ecosystem (type)	Element Transferred	T_o^{-1} (hours^{-1})	T_o (hours)	τ^+ (hours)	Reference
Artificial pond	$^{32}_{P}$	0.091	10.99	4.74	Whittaker (1961)
Aquarium	$^{32}_{P}$	0.200	5.00	3.45	Whittaker (1961)
Aquarium	$^{32}_{P}$	0.104	9.66	8.34	Sebetich (1975)
Sea water	$^{32}_{P}$	0.17	5.87	6.76	Watt and Hayes (1963)
Lake water	$^{32}_{P}$	0.24	4.17	3.60	Lean (1973)
Azotobacter cultures	$^{15}_{N}$	0.0128	77.9	89.9	Visser et al. (1973)
Terrestrial microcosm	$^{134}_{Cs}$	0.0313	31.9	22.1	Patten and Witkamp (1967)
Liriodendron forest	$^{137}_{Cs}$	0.00185	540	311	Olson (1965)
Terrestrial microcosm	$^{137}_{Cs}$	0.00967	103	71.5	Witkamp and Frank (1970)

often ignored in favor of analysis with average inputs. This results in open systems with time invariant relationships between structure and function which have as linear approximations models of the form considered in (3.1). For such systems the sampling theory developed in this paper has application to the design of field experiments. Table IV provides a comparison of sample periods for terrestrial (old fields and forests) and aquatic (lakes and springs) natural systems. From the maximum turnovers, number of compartments, and an arithmetic precision of three decimal places, the maximum sample period for each system is presented. Also, except for the Frains Lake and Liriodendron forest studies, which represent closed material cycles, the minimum sample periods are computed. The sample period τ of Table IV is taken as the geometric mean of τ^+ and τ^- according to (4.38). The rain forest data provided by H. T. Odum (1970) presents a problem with $d = 3$, in that $\tau^+ < \tau^-$. This problem arises because the model includes a microbe compartment with an extremely high turnover typical of tropical rain forests. This is a severe limitation on the experimental procedure requiring four-place data precision ($d = 4$) for which a sample period of $\tau = 0.002$ yr. results. Table IV is based in part upon data provided by O'Neill (1971).

Because of the interactive nature of ecosystems, the turnover of species within a system differs from the observed for isolated species. Observations of ecological systems depend upon these interactions; however, the system dynamics can be estimated from the isolated species behavior. Referring to (4.43), which estimates the sample period, the term T_o^{-1} defines the turnover of the fastest species (with respect to turnover time) in the system, n is a measure of the ecosystem size and

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TABLE IV

COMPUTED SAMPLING TIMES FOR ECOSYSTEM ENERGY OR BIOMASS DYNAMICS

Ecosystem (type)	T_o^{-1} (1/yr.)	τ^+ (yr.)	τ^- (yr.)	τ (yr.)	Reference
OLD FIELD					
Grazing food chain					
a	0.131E3	0.879E-2	0.848E-3	0.273E-2	Golley (1960)
b	0.215E3	0.321E-2	0.556E-4	0.422E-3	Pearson (1964)
Arthropod food chain					
a	0.220E3	0.523E-2	0.217E-3	0.107E-2	Menhinich (1967)
b	0.155E3	0.742E-2	0.256E-4	0.436E-3	Van Hook et al. (1970)
Vegetation					
a	0.902E1	0.957E-1	0.391E-2	0.193E-1	Golley (1960)
b	0.416E1	0.207E0	0.391E-2	0.285E-1	Kelly et al. (1969
AQUATIC					
Cedar Bog Lake	0.138E1	0.834E0	0.269E-2	0.474E-1	Lindeman (1942)
Lake Mendota	0.167E1	0.517E0	0.142E-2	0.377E-1	Lindeman (1942)
Lago Pond	0.370E3	0.104E-2	0.100E-2	0.102E-2	Emanuel and Mulholland (1975)
Frains Lake	0.130E4	0.440E-3	--	0.440E-3	Saunders (1971)
Silver Springs	0.210E3	0.329E-2	0.48E-3	0.125E-2	Odum (1957)
Cone Spring	0.351E3	0.620E-3	0.550E-3	0.580E-3	Tilly (1968)
Root Spring	0.138E3	0.250E-2	0.580E-3	0.120E-2	Teal (1957)
FOREST					
Post oak-blackjack	0.302E2	0.143E-1	0.100E-1	0.120E-1	Johnson and Risser (1974)
Mixed deciduous	0.811E2	0.266E-2	0.200E-2	0.230E-2	Satchell (1971)
Oak-pine	0.437E0	0.263E1	0.127E-1	0.183E0	Woodwell (1970)
Rain Forest	0.380E3	0.130E-2	0.210E-1	--	Odum (1970)
Liriodendron forest	0.646E2	0.200E-2	--	0.200E-2	Shugart et al. (1976)

hence all its possible interactions, and d gives the precision with which measurements can be made. Since the sample period is inversely proportional to n, the interactive nature of the ecosystem is clear. The problem of extremely small sample periods required for very large ecosystems can be to a certain extent compensated for by increasing the precision of the measuring instruments; but fundamental limits on the precision exist, necessitating simultaneous measurement and analysis within subsystems of lower dimension. It should be noted that Smith (1975), using similar concepts including the characterization of fast and slow turnovers, argues for theoretical relationships between evolution and ecosystem science. Thus, the sampling theory presented provides a potential tie between theory and experiment at the ecosystem level.

The application of the sampling theory developed in this paper to natural systems as depicted in Table IV may shed new light on the study of ecosystem development. The value for the sample period provides a single number as a measure for the dynamics of the structure and function relationship at a particular stage of ecological succession. Some knowledge of the successional stage for each system in Table IV is required for such comparison. This represents a study unto itself beyond the intent of this thesis. However, it should be noted that the sample period depends upon the maximum turnover which is believed to be correlated with the stages of ecosystem development (Odum, 1971, p. 252). This correlation is evident in the experimental data produced by Whittaker (1961) on the transfer of radiophosphorus within aquaria. Table V summarized Whittaker's data to show that in the developmental stages ecosystems require more rapid sampling techniques, while in the

mature stage the system structure and function are such that a longer sample period will suffice.

TABLE V

COMPUTED SAMPLING TIMES FOR THE COMPARTMENTAL RADIOPHOSPHORUS TRANSFER IN AQUARIA (WHITTAKER, 1961)

Time Period Following Inoculation	T_o^{-1} (hrs.$^{-1}$)	T_o (hrs.)	τ^+ (hrs.)
Initial (0-7 hrs.)	0.313	3.19	2.21
Intermediate (7-63 hrs.)	0.0855	11.7	8.08
Final (5-46 days)	0.0091	109.9	75.9

Single Dose Identifiability

The controllability, observability, and structural identifiability properties provided by Cobelli and Romanin-Jacur (1976) may be analyzed by studying the Bilirubin compartment model of Figure 11.

The compartments are tissue unconjugated (x_1) and conjugated (x_2) bilirubin; plasma unconjugated (x_3) and conjugated (x_4) bilirubin; liver unconjugated (x_5) and conjugated (x_6) bilirubin; and bile conjugated bilirubin (x_7). The tracer experiment consists of the injection of tracer into the plasma compartment, x_3. Thus, the necessary condition for controllability is satisfied because the input can be traced

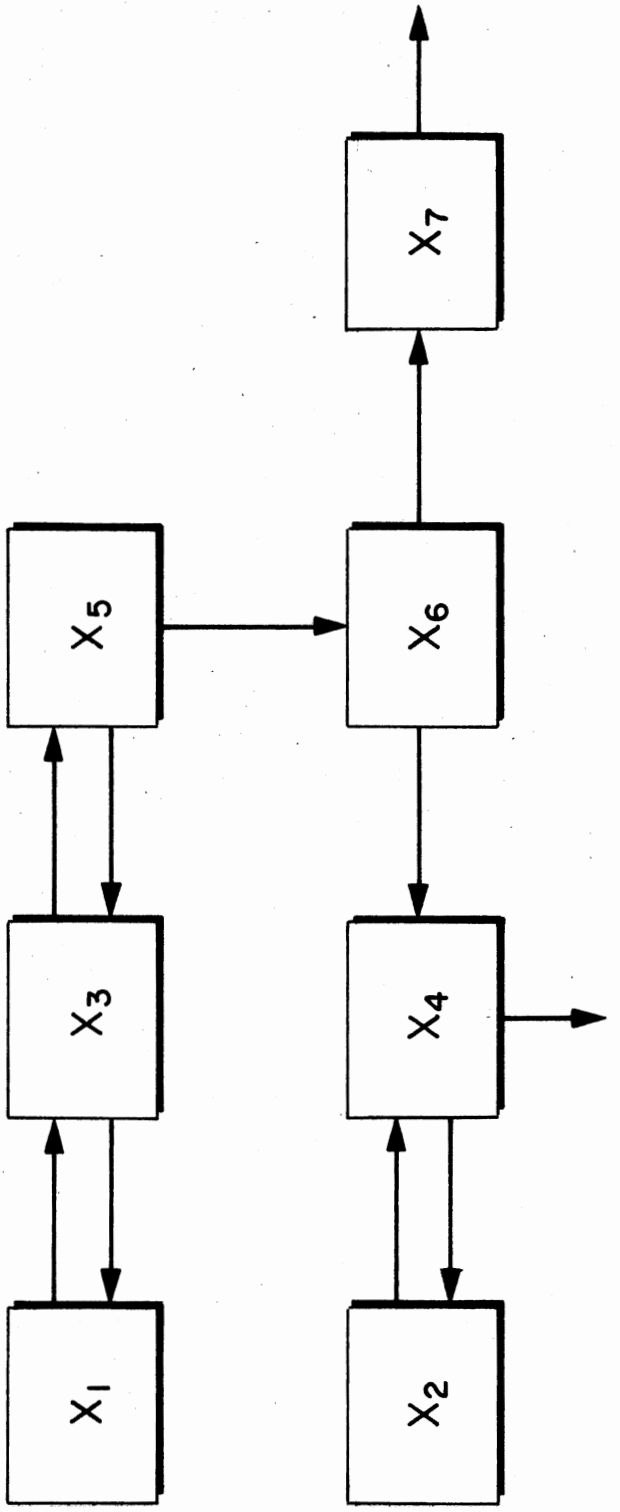

Figure 11. Bilirubin Metabolism

to every compartment. For the system to satisfy the necessary conditions for observability, however, one must have access to at least the bile (x_7) and either tissue or plasma conjugated (x_2 or x_4) bilirubin. Otherwise, a new model structure should be adopted assuring at least one output reachable from every compartment. Again note that the conditions for controllability and observability are not sufficient for identifiability.

Constant Infusion Identifiability

The need for identification of flow rate parameters of a steady-state system arose from an evaluation of models describing volatile fatty acid (VFA) interconversion and production in the rumen of steers (Sharp, 1977). Due to non-instantaneous and incomplete mixing within the rumen, the constant-infusion method of tracer administration was the method of choice. The compartment diagram of ruminal VFA metabolism is presented in Figure 12. The VFA isotopes, ^{14}C acetate, butyrate, and propionate were to be infused into the rumen with samples being available from each of the system compartments. Sharp was unable to identify the flow from the valerate compartment to the propionate compartment by conventional biochemical methods due to the design of the experiments.

Notice that there are three inputs and at most two endogenous flows to each compartment, and at least one outlet is reachable from every compartment. Also, measurements are available from every compartment. Hence, if the system is controllable, it is structurally identifiable; and all VFA flows may be estimated using the proposed constant-infusion method of parameter identification.

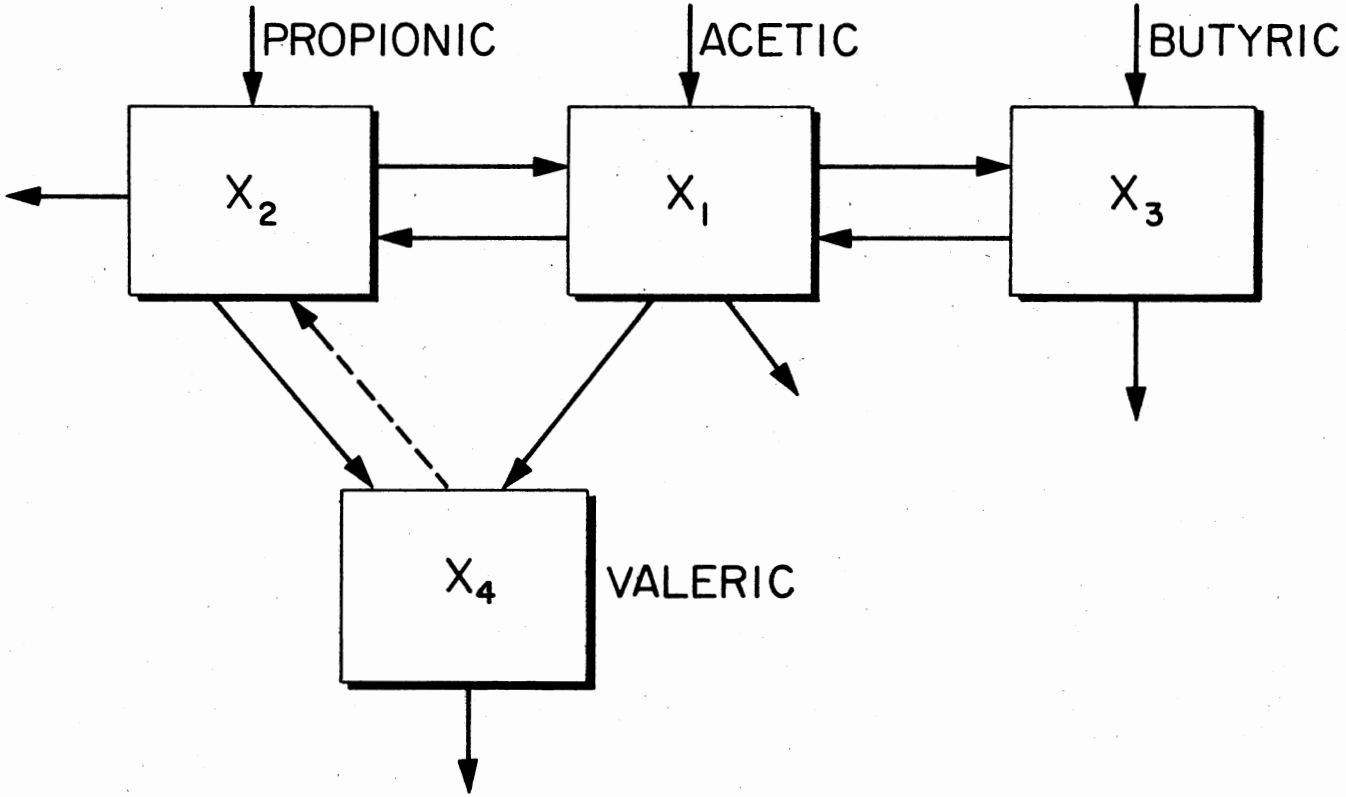

Figure 12. Ruminal VFA Metabolism

Summary

Numerous applications were chosen to exemplify the potential use of the developed identification and sampling schemes. The examples presented were of the simplest possible types. It should be emphasized that the proposed strategies not only apply to these examples, but to problems with greater complexity.

CHAPTER VIII

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

An algorithm for the measurement of ecosystem structure designed for the purpose of computing ecosystem function has been described and implemented in this thesis. The general methodology and capabilities of the strategies discussed were exhibited by solving several laboratory problems.

The problem of determining the ecosystem function from observations of the compartmental states has become known as system identification. Using inputs familiar to the method of tracer analysis, basic experiments were suggested for ease in the laboratory. An identification algorithm, first proposed by Lee (1964), has been derived for systems in which spatial homogeneity may be assumed. A modification of the technique was then applied to systems with accumulation pools. For systems with spatial inhomogeneities, a continuous input of tracer is shown to result in an ensemble of steady-states from which the system parameters may be identified.

Application of the single-dose identification scheme was shown to be dependent upon the sampling period used in data collection. This sampling period which may be calculated before experiments are begun depends upon the arithmetic precision of the data, the dimension of the ecosystem, and its maximum turnover.

One of the fundamental questions of identification is whether or not the parameters in the system model can be uniquely estimated. Conditions for structural identifiability for single-dose tracer experiments have been evaluated in Chapter V, and constant-infusion identifiability is considered in Chapter VI.

Finally, the general methodology and capabilities of the proposed identification and sampling strategies are exhibited by solving several elementary example problems.

It is felt that the identification algorithms and sampling theory discussed have considerable unexploited potential for use in a variety of environmental problems. Although the experiments have been designed primarily for laboratory systems, extension of these results to natural ecosystems may be considered. Several topics for further research will be discussed in the next section.

Recommendations for Further Research

Within the analytical framework established by this thesis, several additional areas of research arise for the application of the proposed identification and sampling schemes to the study of laboratory ecosystem structure and function. The problems are for the most part concerned with statistical error analysis, the central theme being clearly aimed at discovering how the sample period effects the errors in the $\underline{A}$-matrix of (3.1).

The sampling theory has been based upon deterministic concepts of system theory, and the development of the identification algorithm for modeling ecosystem structure and function assumes the existence of error-free samples. The bounds produced for the sample period result

from the finite precision with which measurements can be made on an ecosystem, with no consideration given to the arithmetic errors which result from roundoff or truncation. Therefore, the successful application of the proposed theory to experimental design critically depends upon the statistical analysis of the measurement and arithmetic errors which are inherent in the analysis. It is suggested that the linear compartment model of (3.1) be modified to include the effects of these errors treated as a stochastic process. The inclusion of measurement errors and their simultaneous propagation in the identification algorithm define an error analysis for determining the entries in the $\underline{A}$-matrix of (3.1).

An analysis of the errors which come about as the result of quantizing the state samples would be useful in establishing bounds on the accuracy of the identification scheme. This error analysis could be based upon the upper and lower amplitude bounds derived in Chapter IV where the exponential terms are assumed to be fixed-point numbers, each with an error assumed to be a uniformly distributed random variable according to the bounds. Thus, the truncation errors of the samples could be related to quantization errors for each exponential mode.

Finally, when all measurement and arithmetic errors have been accounted for, bounds on the deviation of the assumed linear model from the true nonlinear system behavior may be obtained.

The linear donor controlled model of (3.1) is presented as a local representation which describes the relationship between ecosystem structure and function. As discussed by Patten (1975), such linear models are valid for small perturbations lying within a neighborhood of the steady-state. The responses forced by largely different inputs

lead to gross changes in system behavior. That is, global models of ecosystem structure and function are nonlinear. This fact has been pointed out by Mulholland and Keener (1974) and Thornton and Mulholland (1974). Smith (1970) gives an example of the construction of nonlinear models as an attempt at a global representation. Smith runs a hypothetical ecosystem at different rates of phosphorus inflow (u_1 = 25, 100, 200, and 400 mg./day) and observes the six compartmental transfers and three storages after steady-state is achieved. All quantities are noted to increase with increasing inflow, but not linearly. The next step is a study of the acquired data leading to hypotheses for the construction of the dependence of compartmental transfers upon storages. The resultant correlations provide a nonlinear model for ecosystem structure and function. Presumably the compartmental transfers observed by Smith are to be directly measured under the varying inflow conditions. The following scheme for measuring these transfers and obtaining a global (nonlinear) model is proposed for study. For each ecosystem inflow condition, assume that a linear model holds in some local neighborhood of steady-state. Identify this linear model using the techniques discussed in this thesis. This allows the determination of ecosystem function from measurements of structure for the specific inflow condition. By repeating this process for each system input, a table of compartmental transfers and storages can be constructed from varying input data. Smith's method for deriving ecosystem hypotheses can then be applied to the development of a global (nonlinear) ecosystem model.

Because of the interactive nature of ecosystems, the turnover of species within a system differs from that observed for isolated species. Observations of ecological systems depend on these interactions;

however, the system dynamics can be estimated from the isolated species behavior. Since the sample period is inversely proportional to the measure of ecosystem size, the interactive nature of the ecosystem is clear. The problem of extremely small sample periods required for large systems can be to a certain extent compensated for by increasing the precision of the measuring instruments. However, fundamental limits on precision exist, necessitating simultaneous measurement and analysis within subsystems of lower dimension.

Finally, it has been shown that upper and lower bounds on the sample period can be expressed which provide a means for determining a periodic data collection before system identification begins. The measurement scheme was conceived to operate on a fixed commensurate time scale. For ecological systems in which the precalculated minimum and maximum sampling periods are widely separated, however, it may be possible to utilize incommensurate sampling by interlacing multiple fixed sample periods, the ratio of the different periods being non-integers. This strategy would be equivalent to the familiar engineering sampling technique of sampling rapidly at the beginning and more slowly near the end of the transient response.

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APPENDIX

COMPUTER ALGORITHM

COMPUTER ALGORITHM

A digital computer user package implementing the foregoing single-dose identification algorithm has been developed. Programmed in standard Fortran, the code which implements the identification algorithm is available in two forms, batch and interactive, both of which run efficiently on a standard IBM 370 operating system. The code is independent of any special library routines, and as such is completely transportable to any IBM System/360 or System/370 series computer. The interactive program can be implemented on any IBM System/370 time share operating system.

The software consists of a main program and one subroutine, EIVECT, the flow diagrams of which are shown in Figures 13 and 14.

The program begins by reading the number N of compartments in the biological system being analyzed, the number K of measurements obtained from a single experiment, and the pre-calculated sample period T. Two flags are then set which indicate row or column data input and printing options, respectively. The program then moves immediately to a loop that reads and stores the sample data array in matrix form, i.e., $\underline{X}(t)$. Since N + 1 discrete measurements of the state are necessary and sufficient for the determination of the state transition matrix $\underline{\Phi}$, the program terminates for $K < N + 1$. If $K = N + 1$, two matrices of coefficients, $\underline{X}_1$ and $\underline{X}_2$, are formed from the N + 1 state samples as described by (3.35) and (3.36). The solution for the state transition matrix $\underline{\Phi}$ is acquired by inverting matrix $\underline{X}_1$ of (3.35). Gaussian elimination with partial pivoting on a matrix scale is used. Upon computing the N × N matrix subroutine EIVECT is called for the

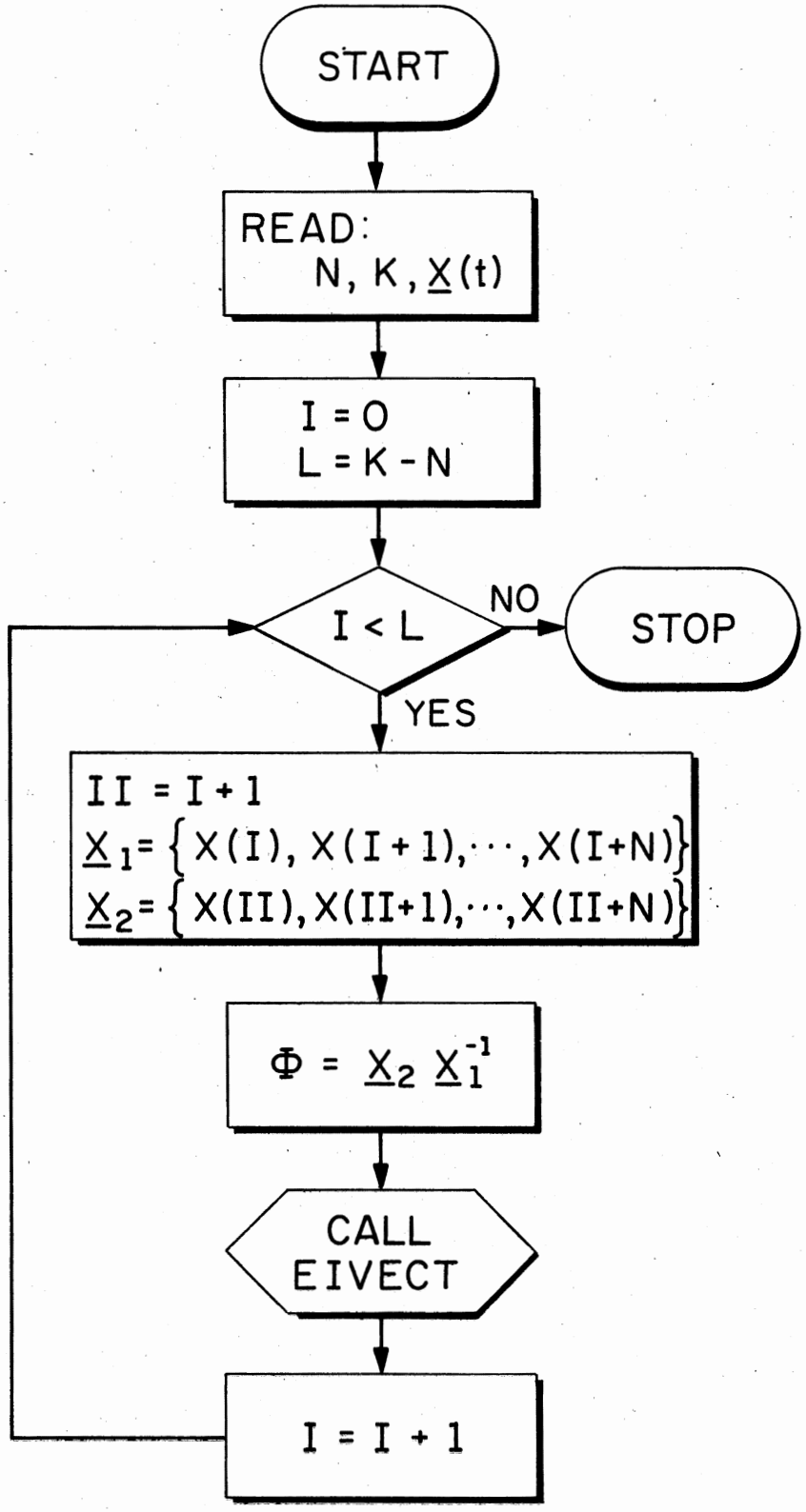

Figure 13. Flow Diagram for Main Program of the Identification Algorithm

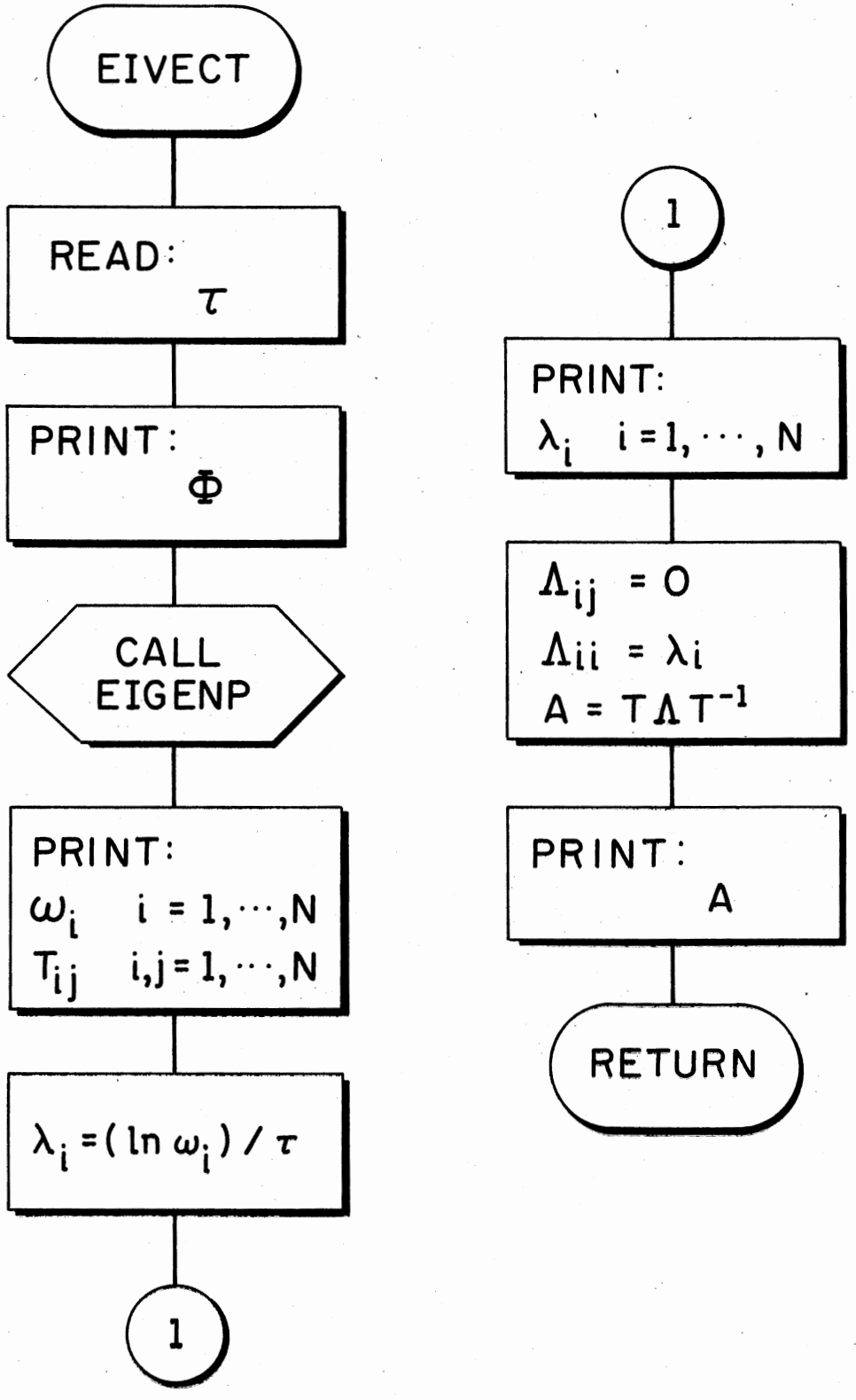

Figure 14. Flow Diagram for Subroutine EIVECT

identification of the matrix of rate coefficients $\underline{A}$. The indices I and L of the main flow diagram are utilized in the formation of a loop in which several $\underline{A}$ matrices may be computed for a comparative analysis if $K > N + 1$.

Subroutine EIVECT solves (3.37) for the matrix of transfer constants $\underline{A}$. The EISPACK [IBM/360 version (Smith et al., 1976)] is utilized to obtain the eigenvalues ω_i ($i = 1, \ldots, N$) and the eigenvectors of $\underline{\Phi}$. The EISPACK uses QR transformation and decomposition, an explanation of which is given by Wilkinson (1965) and Wilkinson and Reinsch (1971).

The matrix $\underline{\Phi}$ can be reduced to a diagonal matrix $\underline{\Omega}$ in which the eigenvalues ω_i ($i = 1, \ldots, N$) of $\underline{\Phi}$ appear on the diagonal. The eigenvalues λ_i ($i = 1, \ldots, N$) of $\underline{A}$ are determined by

$$\lambda_i = (1/T) \ln \omega_i, \tag{A.1}$$

and the reduced diagonal form $\underline{\Lambda}$ of the matrix of transfers $\underline{A}$ is formed. The matrix of rate coefficients is readily identified by

$$\underline{T}^T \underline{A}^T = [\underline{T}\ \underline{\Lambda}]^T \tag{A.2}$$

where $\underline{T}$ is a similarity transformation having the eigenvalues of $\underline{\Phi}$ as its column vectors. Equation (A.2) is solved successively for the columns of $\underline{A}^T$, again using Gaussian elimination. Note that the column vectors must be linearly independent for the existence of $\underline{T}^{-1}$. This follows from the assumption that the eigenvalues of $\underline{\Phi}$ are distinct.

It should be mentioned that EIVECT derives the complex matrix $\underline{A}$ for a real matrix $\underline{\Phi}$ using the complex principal value natural logarithm in (A.1). Also, all manipulations are in double precision.

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