STUDY REPORT

THE APPLICATION OF SENSITIVITY ANALYSIS TO MODELS OF LARGE SCALE PHYSIOLOGICAL SYSTEMS

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TABLE 1

GLOSSARY OF TERMS

e	error between unperturbed and perturbed model output or error between model output and corresponding experimental results
E	error criterion
F	function representing a second-order system
q_i	denotes the ith parameter in a system
S	differential sensitivity coefficient
$\bar{S}$	logarithmic sensitivity coefficient
ΔS	incremental sensitivity coefficient
t	time
U	fractional perturbation of a parameter
y	dependent variable

Superscripts

o	corresponds to the unperturbed state of the model
*	corresponds to the model output

Notation of Thermoregulatory Model (Chapter 5)

CLOV	clothing resistance
PCAB	barometric pressure
MUSCLE BF	muscle blood flow
QBASAL	basal metabolic rate
QEVAP	heat loss due to sweat evaporation
QSENS	sensible heat loss
QSHIV	heat generated due to shivering
QSTOR	heat stored in body relative to a reference state
RM	metabolic rate due to exercise
SKIN BF	skin blood flow
TCAB	ambient temperature

TABLE 1 (Continued)

TDEWC	ambient dewpoint temperature
THEAD	head core temperature
TSKIN	mean skin temperature
TW	ambient wall temperature
UEFF	efficiency of exercise
VCAB	free air velocity

1.0 INTRODUCTION

The analysis of dynamic systems usually involves obtaining the solution of a model as functions of certain independent variables (i.e., forcing functions and initial conditions). However, it is often very desirable to have a knowledge of the variations of the solutions with respect to the parameters of the model. This need arises because parameter values are never known with complete accuracy in any real dynamic system and, therefore, there always exists an uncertainty in the output behavior of a model representing that system. Since this is the case, the influence which parameter variations have on the system's behavior can be important information in predicting errors in model output, in determining operating characteristics in the synthesis of yet-to-be designed technnological control systems and in understanding the importance of specific parameters in the analysis of already designed biological systems.

Definitions

Sensitivity analysis is a method to study the response of a system due to variations in parameters. Parameters may be defined as properties of a system whose values are arbitrary rather than absolute, but are constant over a finite and specified time interval. Parameters may be under no control in which case they are a passive property of the system or they may be themselves part of a feedback loop and are time-variant in which case they may be better defined as dependent variables. However, although most physiological parameters are time varying to some extent, they may be considered constant if their values change slowly compared to the transient response of the system. Sensitivity analysis can be applied to the study of all types of parameters; initial conditions, time-invarient coefficients, time-varient coefficients, integration time steps, etc.

The conceptual basis of sensitivity analysis is extremely simple; small variations are made in the values of the system parameters of a model and the effects of these changes are observed in the solution of the dependent variables.

Sensitivity functions are computed which describe the observed effects and these are interpreted to extract information about the dynamic system that could not be obtained from simply finding solutions to a particular set of input conditions. (Techniques are also available which can generate sensitivity functions without resorting to physically perturbing the parameters). This procedure can be compared with the typical method of simulating dynamic systems, which in essense is to determine solutions of the model by changing independent forcing functions and initial conditions rather than system parameters. Sensitivity analysis may include the variation of forcing functions and initial conditions and in this sense this type of analysis may appear to overlap typical simulation experiments. However, there are several important differences between these two procedures. In sensitivity analysis the perturbations are much smaller, they are often performed by varying one parameter at a time, the end result is to obtain sensitivity functions rather than solutions of the dependent variable, and comparisons are usually made between two or more simulation runs rather than between model results and experimental data.

Usefulness of Sensitivity Analysis

Although sensitivity analysis is conceptually simple, it is capable of producing much useful information. In this report we shall show that sensitivity analysis provides:

a) a quantitative means of comparing the relative influence of different parameters on any system variable,

b) a means of assessing the relative linearity that exists between any parameter and any variable,

c) a means of determining interactive effects of two or more parameters on model behavior,

d) a method of predicting the influence of perturbing any combination of parameters simultaneously on any of the system variables using simple linear models and avoiding the use of additional time-consuming simulation experiments,

e) a tool to help assess the validity of a particular model without the need to collect and utilize extensive measurements from the real system,

f) information in the form that can easily be interpreted by those familiar with the subject matter of the model, but not necessarily knowledgeable with simulation techniques,

g) a systematic method of evaluating all parametric effects on overall model behavior and as such is capable of revealing unexpected behavior that might not otherwise come to light if the model was used only to simulate particular sets of experiments,

h) a means of assigning relative importance to all parameters which can be valuable both to the simulationist in performing parameter estimation or stability analysis and to the experimentalist in allocating resources for data collections,

i) a means of utilizing uncertainty in input data to produce an estimate of uncertainty in model prediction, and

j) a practical method of analyzing and comparing two different models purporting to represent the same physical system.

Purpose and Scope of Report

The main purpose of this report is to explore the applicability of sensitivity analysis in studying large scale models of physiological systems. Although there has not been much previous work in this regard this investigation has revealed that sensitivity analysis is not restricted to a single area of application, but many as the list above indicates. Therefore, a large part of this report deals with these varied applications.

There are two main problems encountered during a sensitivity analysis: a) determining the sensitivity functions and b) analyzing these functions to obtain meaningful information about the system. In this report, both of these factors are discussed. Inasmuch as there are few examples in the literature of physiological systems illustrating methods and application of sensitivity analysis, the suitability of these techniques are suggested by way of some original examples. However, the full potential of sensitivity analysis in analyzing complex physiological systems must await further study.

Certain elementary methods in sensitivity analysis that may not prove suitable for large scale systems are described. This will be done to provide a basis for describing more applicable empirical methods and to suggest tools that could be used with less complex models. A detailed example will be presented illustrating some of the techniques of sensitivity analysis as it applies to a complex model of the human thermoregulatory system. Finally, the application of sensitivity analysis to related areas in the study of dynamic systems will be discussed: error and noise analysis, stability analysis, parameter estimation analysis, and inverse sensitivity.

Literature Review and Background

Although at the present time sensitivity analysis is applied to numerous fields, there are few books devoted exclusively to this subject (5, 20, 21). The application of sensitivity analysis to physiological control systems may be about 30 years old, sensitivity analysis first received important attention about 15 years later and the first papers on biological application of sensitivity analysis did not appear until about five years ago (10)*. A review of several major symposiums and journals concerned with physiological regulation and control over the past several years reveals only about a dozen papers that have utilized formal sensitivity theory and few that deal with larger scale physiological systems.

While the biological field has received scant attention, the theory of sensitivity analysis has advanced considerably although application is devoted almost entirely to technological control systems (2, 5, 10, 16, 20, 21) where the trend is toward the design of adaptive systems, that is, self-correcting systems that change

* Sensitivity analysis is used here in the formal sense whereby the computation of sensitivity coefficients occurs somewhere in the analysis. Other methods in which parameter variation effects are studied will be discussed separately. Of these parameter estimation analysis is the only related area to receive considerable attention in the biological field (8).

parameters to optimize certain system functions. (This trend has some obvious implications and future applications in physiological control systems in which certain parameters such as set points and gains are thought to be under some type of control). Unfortunately, the emphasis of technological system theory is to compute optimum operating characteristics and synthesize or design systems rather than to measure control parameters and analyze function as is the case in physiological systems. Thus fundamental difference, and the fact that technological control systems are often much less complex than physiological systems, severely restrict the interchange between these two fields.

Recently however, sensitivity analysis has been finding increased use in the analysis of such diverse systems as ecological , behavioral, economical, societal, and management systems (e. g. , 7, 11, 13, 14, 15). Like physiological systems, but unlike technological systems, these are models of systems that are not completely man-made, their component interractions are highly complex and not well understood and they contain parameters that are difficult to measure. Thus, many of the references used in this report come from these areas as well as from the technological and physiological literature.

2.0 THEORETICAL BACKGROUND

Consider the following linear or nonlinear mathematical model of a second-order system (e.g., a two-compartment system) with dependent variable y and parameter q:

$$F(\ddot{y}, \dot{y}, y, t, q) = 0 \tag{2-1}$$

The solution will be a function of time, t, in the form:

$$y^{o} = y(t, q) \tag{2-2}$$

We can solve (2-1) successively using various values for the parameter. For example, let q be changed by an incremental amount Δq. Then the solution becomes:

$$y = y(t, q + \Delta q) \tag{2-3}$$

Comparing (2-2) and (2-3) we obtain an indication of the sensitivity of the system which we can express by means of the fraction

$$\Delta S = \frac{\text{change of output variable}}{\text{change of parameter}} = \frac{\Delta y}{\Delta q}$$

$$= \frac{y(t, q + \Delta q) - y^{o}(t, q)}{\Delta q} \tag{2-4}$$

If ΔS has a limiting value as Δq approaches zero, we get the partial differential

$$\lim_{\Delta q \to 0} \Delta S = S(t, q) = \frac{\partial y(t, q)}{\partial q} \tag{2-5}$$

Nomenclature

S is known as the differential sensitivity coefficient* of the dynamic system and can be obtained by differentiating (2-1) with respect to q. ΔS is sometimes

*We shall also use the term sensitivity function to emphasize that S is not always constant but is dependent both on time and the value of q.

called the incremental sensitivity coefficient. The distinction between these two different sensitivities resides in the fact that the incremental value applies to changes in parameter variations of any size whereas the differential sensitivity strictly applies to infinitesimally small changes. We shall see that the differential sensitivity coefficient is a more useful indicator of trends of a system's behavior since it allows the derivation of general relations not connected with the actual form of the variation. In practice values for S or ΔS may be computed by several methods, both analytically and numerically (on analog or digital computers). In this report, the interest will be primarily in methods suitable for computer solution.

Equation (2-2) is said to represent the fundamental behavior of the system while (2-3) corresponds to the varied behavior. The difference between the two,

$$\Delta y = y(t,\ q + \Delta q) - y^{o}(t,\ q) \tag{2-6}$$

is said to define the supplementary behavior. The simulation of any model is usually concerned with determining the supplementary motion due to a parametric disturbance (including changes in initial conditions or forcing functions). Sensitivity analysis can provide a convenient method for determining supplementary behavior. Equation (2-6) can be represented by a Taylor series,

$$\Delta y(t,\ \Delta q) = \left(\frac{\partial y}{\partial q}\right) \Delta q + \left(\frac{\partial^2 y}{\partial q^2}\right) \frac{\Delta q^2}{2} + \cdots\cdots \tag{2-7}$$

Neglecting higher order terms and substituting (2-5) we get

$$\Delta y = S(t, q)\ \Delta q \tag{2-8}$$

This very important relationship allows us to predict the behavior of a system following a parametric variation using simple algebra and without the necessity of performing a simulation run. A knowledge of the sensitivity function is required however. In many cases this method of analyzing supplementary behavior is often more convenient than a direct simulation of the varied system.

The value of the differential sensitivity coefficient is determined to a large extent by two factors as indicated by Equation (2-5):

1) the time or time period during which the sensitivity coefficient is computed, and

2) The absolute value that is assigned to the parameter or parameters.

In addition to these factors, the incremental sensitivity coefficient depends on the total deviation of the parameter (Δq) from some nominal value. If the system is in a steady-state the sensitivity coefficient depends only on the absolute value of the parameter, S(q). The fact that the sensitivity coefficient depends on the absolute value of the parameter represents an additional difficulty in the sensitivity analysis of dynamic systems, especially when the value of q may vary within broad limits (as is true in adaptive control systems). When the dynamic system has many parameters, $(q_1, q_2, \ldots, q_m)$ whose values are not known to a high degree of accuracy, the problem will be compounded since sensitivity may depend on the particular values of all of them. In the general case the sensitivity coefficient, $S(t, q_1, q_2, \ldots, q_m)$, is a quantity associated with every point of parametric space (i.e., the operating point) and changes with the position of the point. Thus, it is essential to carefully define and specify the time and parameter limits which are of primary interest.

The Sensitivity Equations

Assuming that the equations describing the dynamic system are known and are easily differentiable we can calculate the sensitivity coefficient on the basis of the definition given by (2-5). For the system given in Equation (2-1), the partial derivative of the function F with respect to q yields the following:

$$\frac{dF}{dq} = \frac{\partial F}{\partial \ddot{y}} \frac{\partial \ddot{y}}{\partial q} + \frac{\partial F}{\partial \dot{y}} \frac{\partial \dot{y}}{\partial q} + \frac{\partial F}{\partial y} \frac{\partial y}{\partial q} + \frac{\partial F}{\partial q} = 0 \qquad (2\text{-}9)$$

and noting that

$$\frac{\partial \dot{y}}{\partial q} = \frac{\partial}{\partial t}\left[\frac{\partial y}{\partial q}\right] = \frac{\partial S}{\partial t} = \dot{S} \quad \text{and} \quad \frac{\partial \ddot{y}}{\partial q} = \frac{\partial^2}{\partial t^2}\left[\frac{\partial y}{\partial q}\right] = \ddot{S}$$

Equation (2-9) becomes

$$\frac{\partial F}{\partial \ddot{y}} \ddot{S} + \frac{\partial F}{\partial \dot{y}} \dot{S} + \frac{\partial F}{\partial y} S = - \frac{\partial F}{\partial q} ; \quad S(0) = 0 \qquad (2\text{-}10)$$

Equation (2-10) is called the sensitivity equation of the dynamic system and its solution will yield the sensitivity coefficient, S(t, q). In practice the system equation (2-1) and the sensitivity equation (2-10) are solved simultaneously on an analog or digital computer. The sensitivity equations are generally linear even if the original system is nonlinear.

Multivariable, Multiparameter Systems

While the above discussion was concerned with a simple system with one parameter the methods are applicable to more complicated systems. For a system with n variables and m parameters, there are n x m sensitivity coefficients:

$$S_{ij}(t) = \frac{\partial y_i(t)}{\partial q_j} , \quad (i=1,\ldots,n; \; j=1,\ldots,m) \qquad (2\text{-}11)$$

which are obtained from a solution of m sensitivity equations similar to (2-10) except for the right hand, non-homogenous term which is differentiated with respect to a different parameter for each equation. We shall see that for large scale systems the derivation and solution of the sensitivity equations become somewhat impractical and we shall resort to more straightforward numerical methods to obtain the sensitivity functions.

Equations (2-6) through (2-8), which have been derived for a single parameter system, can be easily extended to describe supplementary behavior for multiparameter systems. For example, the Taylor series expansion for a two parameter system, p and q , is given by:

$$\Delta y\,(\Delta p,\ \Delta q) = y(p + \Delta p,\ q + \Delta q) - y(p,\ q)$$

$$= \left(\frac{\partial y}{\partial p}\right)\Delta p + \left(\frac{\partial y}{\partial q}\right)\Delta q + \left(\frac{\partial^2 y}{\partial p_2}\right)\frac{\Delta p^2}{2}$$

$$+ \left(\frac{\partial^2 y}{\partial q_2}\right)\frac{\Delta q^2}{2} + \left(\frac{\partial^2 y}{\partial p\,\partial_q}\right)\Delta p\ \Delta q + \ldots\ldots$$

$$= S_p \Delta p + S_q \Delta q + \dot{S}_p \frac{\Delta p^2}{2} + \dot{S}_q \frac{\Delta q^2}{2}$$

$$+ \dot{S}_{pq} \Delta p\ \Delta q + \ldots\ldots \qquad (2\text{-}12)$$

The coefficients, $\dot{S}$, are called second-order sensitivity functions and there are methods available to compute these either analytically or empirically (20). As a rule these and higher order terms are neglected since the values of p, q, or $\dot{S}$ are sufficiently small.* In that case, the general expression for supplementary behavior for a system with m parameter variations becomes,

$$\Delta y(\Delta q_1, \ldots\ldots, \Delta q_m) = \sum_i^m \left(\frac{\partial y}{\partial q_i}\right)\Delta q_i$$

$$= \sum_i^m S_i\,\Delta q_i \qquad (2\text{-}13)$$

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* The mixed partial derivative term in (2-12), $\partial^2 y / \partial p\,\partial q$, represents the mutual influence of q and p on y and there are cases when this interraction term becomes significant.

3.0 METHODS FOR DETERMINING THE SENSITIVITY COEFFICIENTS

In this section we shall use a simple mathematical model to illustrate several methods for determining the sensitivity coefficients for dynamic systems as well as discussing their application in a systems analysis.

Population Growth Model (23)

A population of bacteria growing in a finite space with an unlimited food supply can be described by the following differential equation showing the net rate of growth:

$$\dot{y} = P y - D y^2 \quad ; \quad W = P/D$$

$$= (P - \frac{P}{W} y)\, y \, ; \quad y(0) = A \tag{3-1}$$

where $y(t)$ = the number of bacteria present at any time

$P y$ = the absolute rate of growth proportional to the present population,

$D y^2$ = the absolute rate of destruction proportional to the present population squared,

A = the initial population

Figure 1 shows the solution to this equation for $A^o = 1$, $W^o = 2$, and $P^o = 1$. (The superscript o designates this as a nominal base condition from which we shall study parameter perturbations).

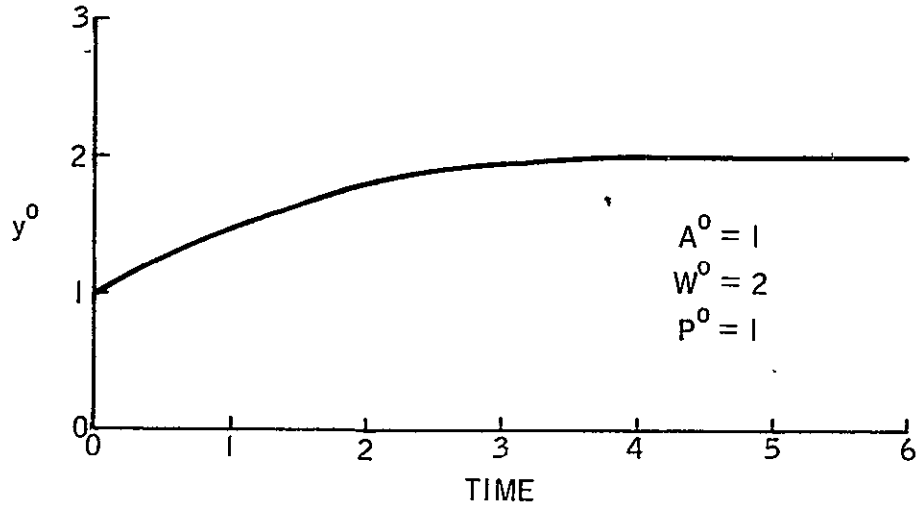

Figure 1: Growth Curve of Population Model

The effects of changing the three parameters of the system on the growth curve are shown in Figure 2. One of the primary purposes of sensitivity analysis is to provide an alternate and more informative method of presenting the type of information contained in Figure 2. The first step in such an analysis entails computing the sensitivity coefficients of the system. Three methods for accomplishing this will be illustrated.

Method I: Sensitivity Coefficients from the Analytic Solution

If the analytic solution to a system is known the sensitivity coefficients can be computed in a very straightforward manner. The analytic solution to (3-1) has been found to be:

$$y = \frac{W}{1 + \left(\frac{W}{A} - 1\right) e^{-Pt}} \tag{3-2}$$

Taking the partial derivatives of y with respect to each parameter yields the sensitivity coefficients:

$$S_A = \frac{\delta y}{\delta A} = \left[\frac{y}{A}\right]^2 e^{-Pt}$$

$$S_W = \frac{\delta y}{\delta W} = \left[\frac{y}{W}\right]^2 (1 - e^{-Pt})$$

$$S_P = \frac{\delta y}{\delta P} = \frac{y^2}{W}\left[\frac{W}{A} - 1\right] t\, e^{-Pt} \tag{3-3}$$

Since the sensitivity coefficients are functions of y Equations (3-2) and (3-3) must be solved simultaneously. The results of such a solution will be presented later in this section.

Method II: Sensitivity Coefficients from the Sensitivity Differential Equation

If the analytic solution of the original differential equation is not known explicitly, the sensitivity coefficients can be obtained by deriving the sensitivity

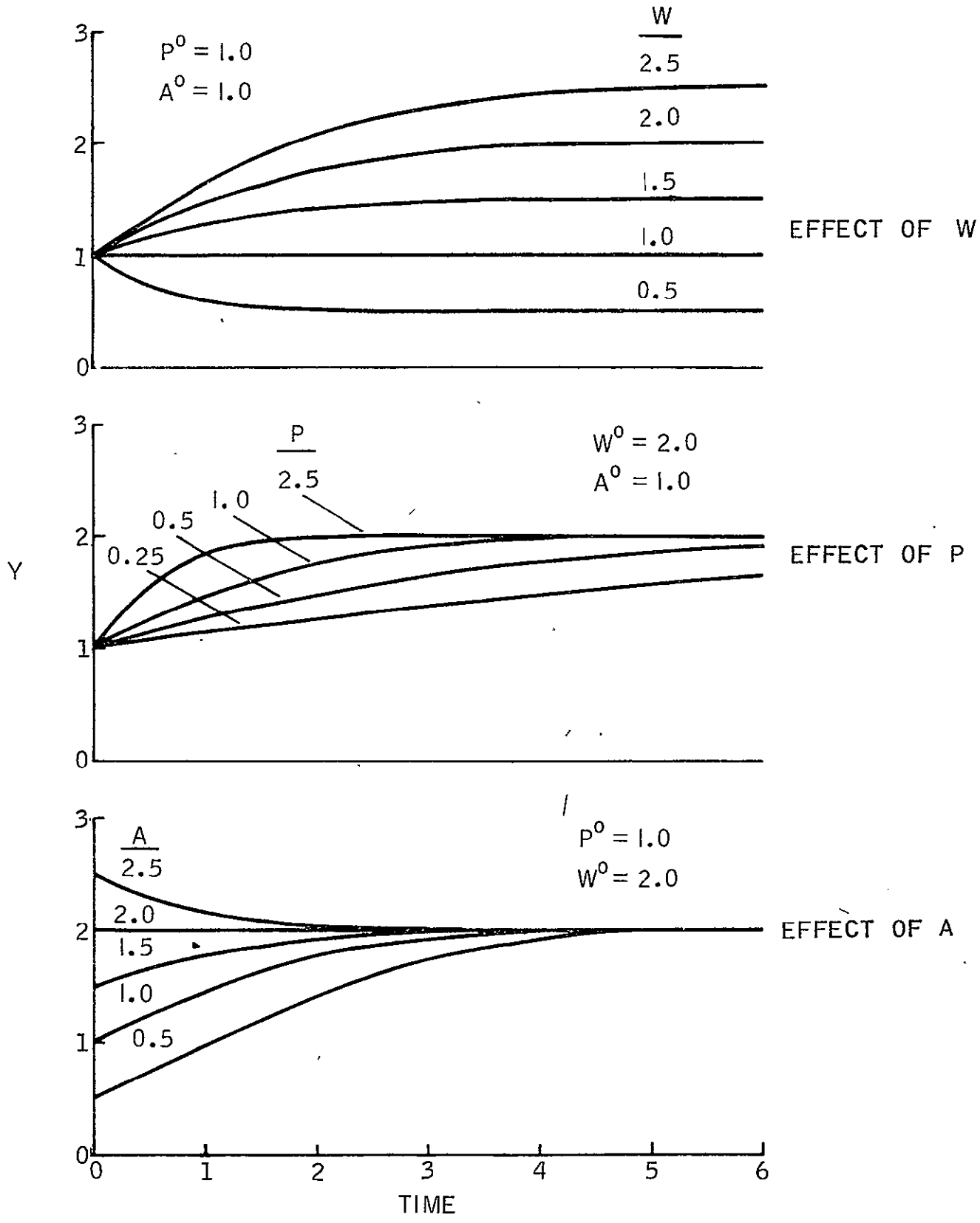

Figure 2: Effect of Parameters on Population Model Output

differential equations from the system equation and solving these equations for S_A, S_W, and S_P. For example, the sensitivity equation for S_A is found by taking the partial derivative, $\partial y/\partial A$, of each term in (3-1) and rearranging terms. Similarly the equations for S_W and S_P are found by taking partials $\partial y/\partial W$ and $\partial y/\partial P$, respectively. This yields the following:

$$\dot{S}_A = \left(P - \frac{2P}{W}\, y\right) S_A \quad ; \qquad S_A(0) = 1$$

$$\dot{S}_W = \left(P - \frac{2P}{W}\, y\right) S_W + \frac{P}{W^2}\, y^2 \quad ; \qquad S_W(0) = 0$$

$$\dot{S}_P = \left(P - \frac{2P}{W}\, y\right) S_P + y - \frac{1}{W}\, y^2 \quad ; \qquad S_P(0) = 0 \qquad (3\text{-}4)$$

These sensitivity equations are linear with respect to S even though the original system equation (3-1) is nonlinear. Also observe that values of y are necessary to solve equations (3-4). In practice Equations (3-1) and (3-4) are solved simultaneously on either analog or digital computer. Computation and programming is facilitated by the fact that, except for the rightmost non-homogenous terms in (3-4), the system differential equation and the sensitivity equations are all structurally similar; thus, the sensitivity coefficients can be computed without changing the system's block diagram or its numerical method of solution. This is a particularly useful feature when dealing with large scale systems (6).

The structural similarity of this system and the construction of a sensitivity model are illustrated in Figure 3. The analog diagram is presented for obtaining the solution to Equations (3-1) and (3-4) (the model for S_A was omitted for convenience). The top section is the model of the original system while the bottom two sections are the sensitivity models. The connecting links between the two are the non-homogenous terms of (3-4) and are functions of y. A single simulation run of these three almost identical models will generate y(t), $S_P(t)$ and $S_W(t)$. This method of obtaining the sensitivity coefficients is most suitable

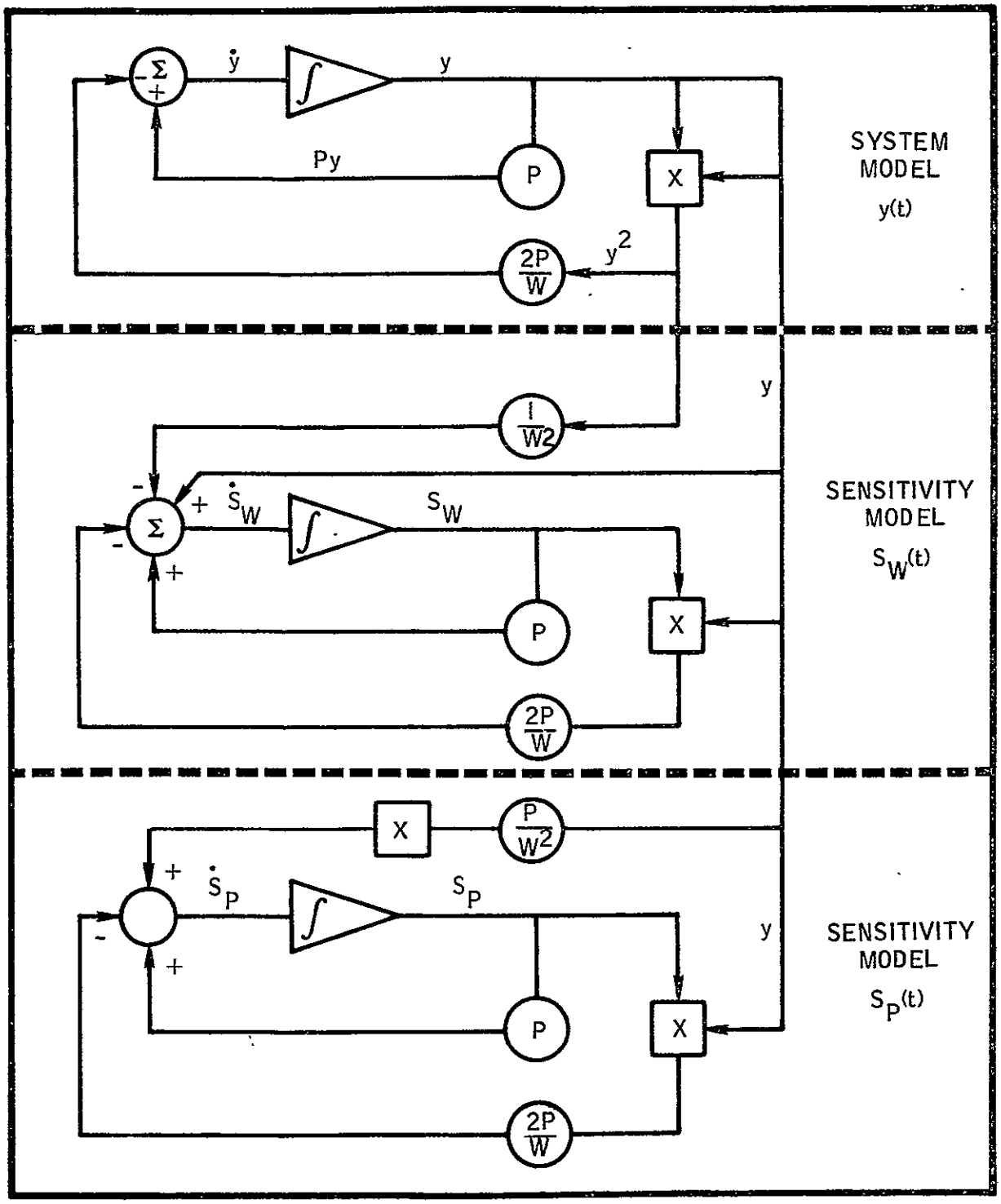

Figure 3: Analog Diagram of System Model and Sensitivity Models

Notice the same structural similarity of all models except for connecting links which are functions of y.

for any system whose differential equations have been explicitly formulated, but whose analytic solution is not known. The disadvantage of this method is that a separate model is required for each sensitivity function as well as for the original system.

Method III: Sensitivity Coefficients from a Single Sensitivity Model

There is a class of models that are amenable to a method of determining all of the sensitivity functions simultaneously, using a single sensitivity model that is essentially a replica of the original system model. This approach is called the "sensitivity points" method and appears to be applicable only to a certain small class of linear systems (2, 10, 16, 20, 21). This may be a severe restriction if one is concerned with large scale, nonlinear systems operating over a wide range. However, if the operating point of interest is in a linear region, this method may have some applicability. Because the practical application of the method has not been described in sufficient detail in the literature, no attempt will be made to apply the sensitivity points technique to the example in this section. Nevertheless, an additional simple example of the technique is presented in the Appendix so that it's attractiveness may be appreciated. Further study may be warranted to evaluate it's usefulness to large scale nonlinear models.

Method IV: Sensitivity Coefficients from Parameter Variation

In those cases where neither the analytic solution nor the explicit formulation of the sensitivity equations are readily obtainable, an empirical method is available. This technique involves varying a single parameter by a small increment about its nominal value and performing a single simulation. The sensitivity coefficient is obtained by comparing the value of the output variable from this run with its value during a run in which none of the parameters are perturbed.

Consider a general case in which there are m parameters, so that the solution for the unperturbed system may be written as:

$$y^{o} = f(t, q_i^{o}), \qquad (i=1, \ldots, j, \ldots, m) \tag{3-5}$$

The corresponding solution for the perturbed case where a single parameter, q_j^o, is varied an incremental amount is given by:

$$y = f(t, q_i^o, q_j^o + \Delta q_j) \quad , \quad (i=1,\ldots,m-1) \tag{3-6}$$

The incremental sensitivity function that describes the change in y^o due to the variation Δq_j is given by Equation (2-4):

$$\Delta S_j(t, q_i^o, \Delta q_j) = \frac{y(t, q_i^o, q_j^o + \Delta q_j) - y^o(t, q_i^o)}{\Delta q_j} \tag{3-7}$$

Note from Equation (2-5) that ΔS_j approaches the differential sensitivity coefficient, $S_j(t, q_i^o)$, as Δq_j approaches zero. Thus, if a parameter is perturbed by a very small amount (say 1%) the value of ΔS_j determined from (3-7) will be approximately equal to the true sensitivity coefficient. This method requires that each sensitivity function, S_i (i=1,...,m) be determined by a separate simulation during which only a single parameter is perturbed. It should be observed that in Methods I and II parameter sensitivity is determined by solving the system in the unperturbed case and that only in this empirical method are actual parameter perturbations used explicitly. The number of computations required in this method is nearly identical to that required by Method II. The later method requires one simulation with multiple models while the former requires multiple simulations with only the system model.

Logarithmic Sensitivity Coefficients

A more meaningful and widespread definition of the sensitivity function is:

$$\bar{S}_j = \frac{\delta \ln y}{\delta \ln q_j} = \frac{\delta y/y^o}{\delta q_j/q_j^o} = S_j\left[\frac{q_j^o}{y^o}\right] \approx \frac{\Delta y/y^o}{\Delta q_j/q_j^o} \tag{3-8}$$

where $\bar{S}_j$ is called the logarithmic sensitivity coefficient and is defined as the fractional change in dependent variable due to the unity fractional change in

parameter value (i.e., doubling the parameter value). If $\bar{S}_j$ is known then the percent change in the output variable, y , is given by $\bar{S}_j$ multiplied by the percent change in parameter q_j. Equations (3-3) have been converted to logarithmic functions ($\bar{S}_A$, $\bar{S}_W$, $\bar{S}_P$) in the example to follow by multiplying them by A/y, W/y, and P/y, respectively, as the fourth term in Equation (3-8) suggests.

Predicting Supplementary Behavior

Once the sensitivity functions are determined for each of the parameters it is possible to estimate the variation of y^o for any combination of parametric changes. In order to derive the expression for predicting the supplementary motion of the population model we shall define U_i as the fractional perturbation of a parameter about its nominal values:

$$U_i = \frac{\Delta q_i}{q_i^o} = \frac{q_i - q_i^o}{q_i^o} \qquad (3\text{-}9)$$

Equation (2-13) can be rewritten for the output of the population model using the definitions given in (3-8) and (3-9):

$$\Delta y/y^o = \sum_{i=1}^{q} \bar{S}_i \, (\Delta q_i/q_i^o) = \bar{S}_W \, U_W + \bar{S}_P U_P + \bar{S}_A \, U_A \qquad (3\text{-}10)$$

where, $\bar{S}_W = \frac{\Delta y/y^o}{\Delta W/W^o}$, $\bar{S}_P = \frac{\Delta y/y^o}{\Delta P/P^o}$, $\bar{S}_A = \frac{\Delta y/y^o}{\Delta A/A^o}$ (3-11)

Results of Sensitivity Analysis on Population Model

The techniques discussed above will be illustrated using the population growth model. In Table II, values for y^o , $\bar{S}_A$, $\bar{S}_W$, and $\bar{S}_P$ have been computed for the case where $A^o = 1$, $W^o = 2$, and $P^o = 1$ which we shall define as the nominal, unperturbed state of the system. Values for the sensitivity coefficients have been obtained both by Method I ($\bar{S}_i$(theoretical)) using the analytic expressions (3-3) and by Method IV ($\bar{S}_i$(estimated)). In the latter case, the incremental sensitivity coefficients were computed from Equation (3-7) by varying one parameter at

TABLE II

SENSITIVITY COEFFICIENTS OF POPULATION GROWTH MODEL

- THEORETICAL VS. ESTIMATED VALUES - *

TIME	Y^o	$\bar{S}_A$			$\bar{S}_W$			$\bar{S}_P$		
		THEOR.	ESTIMATED		THEOR.	ESTIMATED		THEOR.	ESTIMATED	
			$\Delta = 1\%$	$\Delta = 20\%$		$\Delta = 1\%$	$\Delta = 20\%$		$\Delta = 1\%$	$\Delta = 20\%$
0	1.000	1.000	1.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000
0.5	1.245	0.755	0.753	0.720	0.245	0.243	0.213	0.189	0.189	0.186
1.0	1.462	0.538	0.535	0.492	0.462	0.460	0.417	0.269	0.268	0.256
1.5	1.635	0.365	0.363	0.354	0.635	0.633	0.592	0.274	0.272	0.248
2.0	1.762	0.238	0.237	0.207	0.762	0.760	0.727	0.238	0.237	0.205
2.5	1.848	0.152	0.150	0.130	0.848	0.847	0.823	0.190	0.188	0.154
3.0	1.905	0.095	0.094	0.080	0.905	0.904	0.888	0.142	0.140	0.109
3.5	1.941	0.059	0.058	0.049	0.941	0.941	0.931	0.103	0.101	0.075
4.0	1.964	0.036	0.035	0.030	0.964	0.964	0.957	0.072	0.071	0.050
4.5	1.978	0.022	0.022	0.018	0.978	0.978	0.974	0.049	0.048	0.033
5.0	1.987	0.013	0.013	0.011	0.987	0.987	0.984	0.034	0.033	0.021
5.5	1.992	0.008	0.008	0.007	0.992	0.992	0.990	0.022	0.022	0.014
6.0	1.995	0.005	0.005	0.004	0.995	0.995	0.994	0.015	0.014	0.009

*Nominal Parameter Values Used: $A^o = 1$, $W^o = 2$, $P^o = 1$

a time by either 1% or 20% from its nominal value. There is excellent agreement between the two methods over the entire time range when the variance is 1%. Agreement is worse for the larger variance of 20%. Figure 4 shows more clearly the relationship between the differential sensitivity coefficient and the incremental sensitivity coefficient with respect to the parameter W (at t=3) where ΔS_W has been computed for very large perturbations. This analysis suggests that the numerical procedure for estimating the sensitivity functions (Method IV) can be very accurate if the parameter perturbations are allowed to be small.

The sensitivity functions of Table II ($\bar{S}_i$ (theoretical)) have been plotted in Figure 5. The influence of the three parameters on the system's behavior are seen to be not only different from each other, but just as importantly, the relative differences change with time. Thus, the behavior of the growth curve of Figure 1 is influenced almost entirely by the initial condition A at the outset of growth and by the production/destruction rate constant ratio W at steady states, while the influence of the production rate constant, P, has an important influence only in the midrange period.

Figures 2 and 5 contain the same type of information. However, the perturbations required to generate the curves in Figure 2 were much larger than those implied in Figure 5 and a larger number of simulations were required as well. In large scale multivariable, multiparameter systems, the number of computer runs and the volume of data resulting from an analysis typified by Figure 2 could easily be prohibitively large and difficult to interpret. In addition, the sensitivity functions appear to produce a more coherent and easily interpretable picture of parameter sensitivity than is possible with variations in the output function.

If this model were an accurate representation of a physical system under investigation, the sensitivity functions could provide valuable information to guide experimentation. For example, if only steady-state conditions were desired, the ratio W = P/D would have to be measured very accurately as compared to the values of P and A. Conversely, if the model were being used to predict growth and if W were the only parameter known accurately, it could be stated that the model's ability

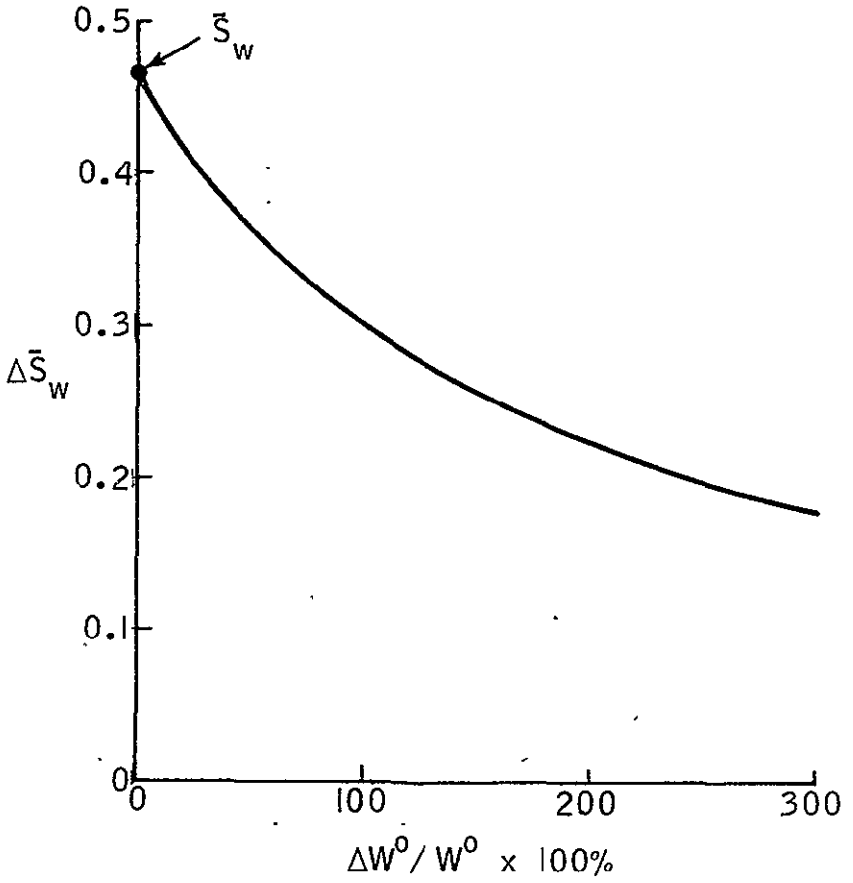

Figure 4: Effect of Changing the Parameter W_o on the Incremental Sensitivity Coefficient, ΔS_w

The corresponding differential sensitivity coefficient, $\bar{S}_w$, is shown.

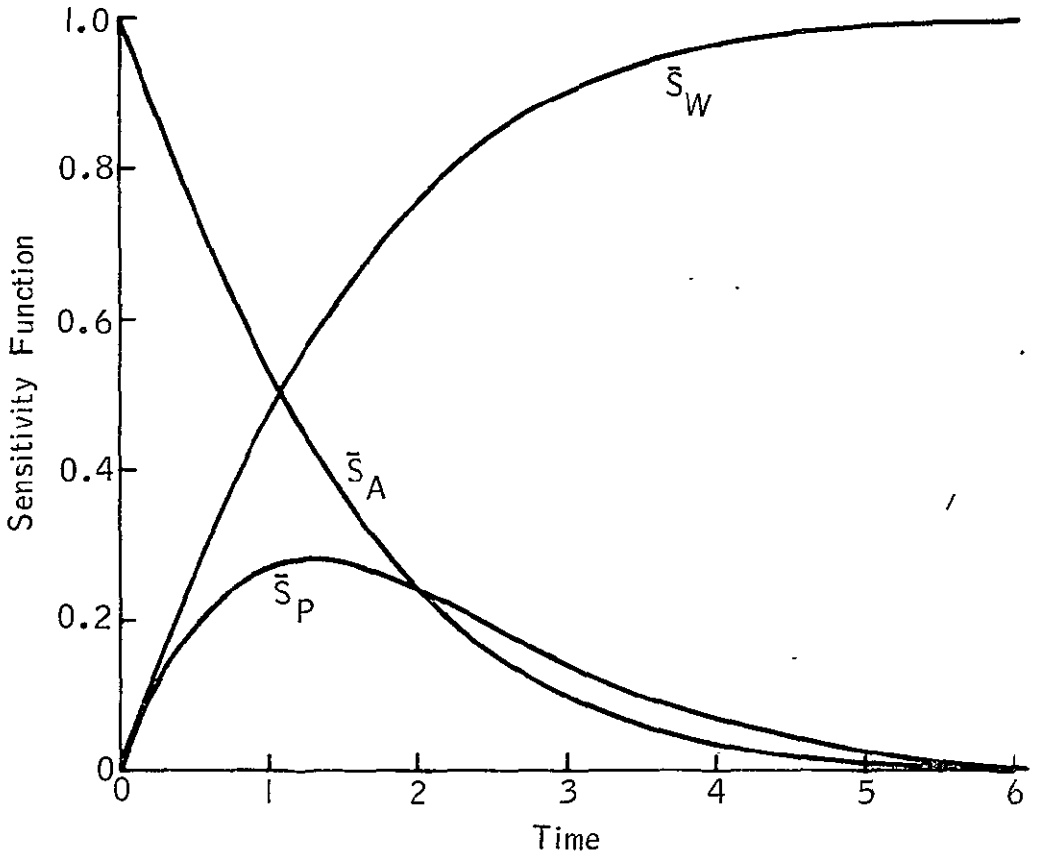

Figure 5: Sensitivity Functions of Population Growth Model

to predict is poorest in the transient time periods. Perhaps this particular model is simple enough to have made these insights without resorting to computing sensitivity functions. However, in more complex models, the relationships are far from obvious and an analysis in this fashion might benefit both modeler and experimenter.

Sensitivity studies can be a valuable adjunct to a systems analysis with regard to determining model validity. A person familiar with the subject matter of the model (but not necessarily familiar with simulation techniques) can make a judgement concerning the validity of the model based on the reasonableness of the sensitivity relations. It is true that the behavior of the dependent variables in response to a specific stress (such as in Figure 1) also can provide valuable clues about model validity. However, it is worth pointing out that a variety of "black box" models could have generated the output curve shown in Figure 1 while only a deterministic model bearing a good likeness to the real system could produce parameter sensitivity functions that are reasonable. In addition, sensitivity functions of system parameters (such as W and P) are independent of any particular environmental stress so that a picture of model validity can be obtained without resorting to comparison with a particular data set.

An important application of the sensitivity function is in predicting the supplementary motion of a system. Equation (3-10) may be rewritten as

$$y(t, \Delta A, \Delta W, \Delta P) = y^{o}(1 + \sum_{i=1}^{3} \bar{S}_i U_i) \qquad (3\text{-}12)$$

Thus, we have the capability to predict the value of y for parameter values that are different from but centered about the nominal values. An illustration of the accuracy of this equation is given in Table III. The solution to the population growth model has been found for four different sets of parameter values: 1) one-half the nominal values used in Table II, 2) twice the nominal values, 3) 0.8 x nominal value, and 4) 1.1 x nominal value. The true solution to the model given by Equation (3-2) is listed under y_{TRUE} and the predicted solution from Equation (3-12) is given under y_{PRED}. The values for $\bar{S}_i$ used in (3-12) were obtained from

TABLE III

BEHAVIOR OF POPULATION MODEL FOR SIMULTANEOUS VARIATION OF ALL PARAMETERS

ACTUAL VS. PREDICTED BEHAVIOR

PARAMETER	NOMINAL VALUE	RUN 1		RUN 2		RUN 3		RUN 4	
A	1.0	0.5		2.0		0.8		1.1	
W	2.0	1.0		4.0		1.6		2.2	
P	1.0	0.5		2.0		0.8		1.1	
TIME		Y_{true}	Y_{pred}	Y_{true}	Y_{pred}	Y_{true}	Y_{pred}	Y_{true}	Y_{pred}
0		0.50	0.50	2.00	2.00	0.80	0.80	1.10	1.10
1		0.62	0.53	3.52	3.32	1.10	1.09	1.65	1.65
2		0.73	0.67	3.93	3.94	1.33	1.33	1.98	1.98
3		0.82	0.82	3.99	4.08	1.47	1.47	2.12	2.12
4		0.88	0.91	4.00	4.07	1.54	1.54	2.17	2.18
5		0.92	0.96	4.00	4.04	1.57	1.58	2.19	2.19
6		0.95	0.98	4.00	4.02	1.59	1.59	2.20	2.20
7		0.97	0.99	4.00	4.01	1.59	1.60	2.20	2.20

Table II. The actual parameter values used for each run are shown at the top of each column. There is almost perfect agreement between the true and predicted solution for Runs 3 and 4 which are operating close to the nominal condition. For Runs 1 and 2, which are separated by a four-fold difference in parameter values, the agreement is still very good. The deviation becomes worse as the operating point moves further from the nominal value because Equation (3-12) has neglected the higher order terms shown in Equation (2-12). These terms become increasingly significant for larger perturbations.

The usefulness of predicting model behavior with simple algebraic equations rather than by direct simulation of the original analog system (which involves solutions of differential equations) is, of course, obvious. Fundamentally, this procedure is not new since it is really based on linearization of a system using Taylor series expansion. However, the coefficients of the Taylor series in this case are the sensitivity functions which have intrinsic meaning by themselves. In addition, the results are expressed in terms of linear algebraic equations rather than linear differential equations. The technique illustrated in this example appears to be applicable to most nonlinear, multivariable, multiparameter models. However, the disadvantages have also become apparent: a) all the sensitivity coefficients must be computed in the desired time period, b) the degree of accuracy of the method around the operating point should be established by some independent check, c) in highly nonlinear systems higher order sensitivity functions may have to be computed or alternatively, d) a series of first-order sensitivity functions may have to be computed at closely spaced operating points. In addition, the equations for this procedure no longer describe a deterministic system even though the coefficients were generated from one. There is a danger that persons not familiar with the use of this method may extend it beyond its limitations. Notwithstanding these restrictions the method appears to be powerful enough to be suitable for certain types of application even with complex models, especially where high speed, large core computers are not available.

Summary

This section has illustrated several methods for obtaining sensitivity functions and described some of the applications of a sensitivity analysis. Several methods are available for easily obtaining all the sensitivity functions simultaneously for linear or simple nonlinear systems (Methods I, II, III). Method I involved the formulation of sensitivity equations which were obtained by differentiating the analytic solution of the system with respect to the system parameters. If the analytic solution cannot be easily formulated, differential sensitivity equations may be generated from the system equations according to Method II. The solution of these sensitivity equations in terms of using sensitivity models were described which structurally resemble the original system and can be obtained by simple manipulation of the original system's block diagram. If the systems are complex, (i.e., no analytic solution attainable), nonlinear, and large scale (i.e., many parameters), Method II is still applicable and the sensitivity functions may be generated simultaneously. However, a considerable amount of preliminary analysis and additional programming is required. Essentially, this involves programming a number of sensitivity models (equal to the number of parameters) and determining the connecting links between the models. An empirical method was described and illustrated (Method IV) that overcomes this limitation in that it requires working only with the original system (i.e. additional models are not necessary) and involves approximately the same computation time as the sensitivity model method (Method II). However, this technique does not permit simultaneous determination of the sensitivity functions, but rather only one function can be obtained during a single simulation run in which a single parameter is varied. In addition the method suffers from the same inaccuracies that are inherent in any finite difference method. Nevertheless, these restrictions are not severe and it appears that Method IV may be quite suitable for large scale models. In Section 5.0, the numerical estimation procedure for a relatively complex thermoregulatory model is illustrated.

4.0 THE PERFORMANCE CRITERION

The basic question to be answered in a sensitivity analysis is "how does parameter variation effect the behavior or performance of the system under study?" If the concern is the the effect on a particular variable, such as skin temperature or sweat rate in a thermoregulatory model, the solution can be relatively straightforward and has already been discussed (e.g., see Equation 2-13)). However, in many cases when dealing with a model with many dependent variables it is desirable to define a single measure of overall system performance. Such a measure, which is called the performance criterion would be extremely useful in performing both sensitivity analysis and parameter estimation since the effects of multiple parameter variations can be related to changes in this single variable rather than an arbitrarily large number of dependent variables. However, the definition of a performance criterion is difficult and cannot always be accomplished since it depends on the purpose for which the simulation was carried out and on an assessment of subjective features. The use of a performance criterion (also called performance index, evaluation criterion, measure of deviance, error criterion, criterion function, and goodness of fit criterion) is more widespread in parameter estimation (or identification) problems than in sensitivity analysis, but in either case, little information is available to guide a user in its formulation. It is the purpose of this section to discuss some possible guidelines.

Some examples may help clarify the concept and usefulness of a performance criterion:

1) In parameter estimation analysis the parameters of a simulated model are fitted to experimental data according to a specified criterion of goodness of fit. Carson and Finkelstein (3) measured the plasma disappearance of labelled albumin after intravenous injection and fitted it to a simple three term model,

$$y_j^* = \sum_{i=1}^{3} A_i e^{-a_i t_j} \qquad (4\text{-}1)$$

where y_j^* is the predicted albumin concentration at time t_j. Estimates of the six parameters A_i, a_i (i=1,2,3) were obtained when an error criterion

$$E = \sum_{j=1}^{n} (y_{exp} - y_j^*)^2 \qquad (4\text{-}2)$$

had been minimized where y_{exp} is the value of sampled plasma concentrations at time t_j. The summation is taken for points within a given time interval.

2) In a more complex model of predicting plasma concentration changes during hemodialysis, Abbrecht and Prodany (1) estimated the mass transfer parameters for urea and creatinine by minimizing the error criterion summed over the number of consecutive sample points

$$E = \frac{\sum (y_{1exp} - y_1^*)^2}{\sum (y_{1exp})^2} + \frac{\sum (y_{2exp} - y_2^*)^2}{\sum (y_{2exp})^2} \qquad (4\text{-}3)$$

where y_{iexp} and y_i^* are the experimental and model predicted concentrations, respectively, for urea (i=1) and creatinine (i=2).

3) Donders, et al (6) have used a more complex error criterion to estimate five parameters in a heart function model. The error criterion function was constructed from the left ventricular pressure P(t) and left ventricular volume V(t), resulting from experiments and those resulting from the model, $P^*(t)$ and $V^*(t)$.

$$E = \int_0^T \left\{ w_1 \left| P - P^* \right| + w_2 \left| V - V^* \right| + w_3 (P - P^*)^2 + w_4 (V - V^*)^2 \right\} dt \qquad (4\text{-}4)$$

where weighting coefficients w_i are used to give more weight to either the volume data or the pressure data depending on the accuracy of measurements.

In all these examples the minimum of E equals zero if model and experimental results perfectly match. In the first two examples the error criteria are functions of the error squared while in the latter case the absolute error is also incorporated; this results in positive values for E.

Compared to the work on parameter estimation there has been almost no effort to use overall performance criteria in sensitivity analysis of physiological systems. While in parameter estimation, the difference between experimental and model responses is crucial there is no need to utilize these types of experimental measurements in sensitivity analysis. Rather the performance criterion is a measure of difference between the response of the model at some nominal base condition and the model's response when one or all of the parameters are perturbed. The error criterion equations in the examples given above can be used for sensitivity analysis by simply replacing the experimental response with the model response for the perturbed case and letting the starred (*) variable represent the model's unperturbed case. Thus, parameter estimation may be described as a model-to-experiment study while sensitivity analysis is a model-to-model study. Since a model-to-model analysis is really not a measure of error but of deviance it is more appropriate to replace the term "error criteria" by "performance criteria" or "measure of deviance."

Miller (14) has described the use of the measure of deviance, D, in sensitivity analysis of ecological systems. The sensitivity coefficients are formed by the partial derivatives, $S_i = \partial D / \partial q_i$, where q_i (i=1,..,m) are the m parameters of the system. Values of S_i can be found as previously described by the method of parameter variation; parameters are deviated on either side of their normal value by a fixed small percentage of their normal values and the resulting performance criteria are computed. Then,

$$S_i = \frac{\partial D}{\partial q_i} \approx \frac{D(q_i + \Delta q_i) - D(q_i)}{\Delta q_i} = \frac{D(q_i + \Delta q_i)}{\Delta q_i} \qquad (4\text{-}5)$$

Note that the value of $D(q_i)$ is computed for the unperturbed case and is zero by definition. The number of sensitivity coefficients of a large scale system of n dependent variables and m parameters is reduced from m x n to m when a performance criterion is used as a measure of overall system behavior since S_i is computed only for the variable D.

While the choice of an overall performance criterion of a model is somewhat arbitrary, experience has provided certain guidelines in its formulation. These are discussed below:

1) An overall performance criterion is a function of one or more of the systems dependent variables. This function is usually (but not necessarily) of one of the following forms or a combination of them:

$$D = \sum^{n} |e_j| \quad , \qquad D = \sum^{n} (e_j)^2$$

$$D = \frac{\sum^{n} |e_j|}{\sum^{n} |y_j^*|} \quad , \qquad D = \frac{\sum^{n} (e_j)^2}{\sum^{n} (y_j^*)^2} \tag{4-6}$$

where y_j^* = the model response of the jth variable for the unperturbed case, y_j = the corresponding variable for the perturbed case, $e_j = y_j - y_j^*$ and n is the number of samples taken over a finite time interval.

2) The choice of variables used in forming the performance criterion should be related to the most important variables of the system or a combination of variables that are representative of some index of overall behavior. This choice could, of course, change as the objectives of the simulation study change. For example, the Guyton model of circulatory regulation has been extremely valuable in elucidating the mechanisms that control long term fluid volumes and blood pressure changes. Although it contains over 300 dependent variables it is conceivable that a meaningful performance criterion can be formulated from only two variables, arterial blood pressure and extracellular fluid volume since all the other variables are known to exert some influence on these two. It would be possible and often desirable to construct a performance criterion that gives more weight to one variable than another as well as giving different weights to the

transient and steady-state responses. Miller (14) has shown that a number of reasonable, but different choices for the performance criterion all produce very similar results in a particular example. He states "generally a balanced measure of all the output variables is more successful, and it is unwise to use one single output variable as a 'general indication of model behavior' ".

3) The value of D should be zero when there is no perturbation of parameters and be positive otherwise.

4) The performance criterion chosen should correlate well with other possible performance measures and with intuitive estimates of model change.

5) The variables chosen to formulate D should be capable of easy and accurate measurement in the laboratory even though these experimental measurements are not used in sensitivity analysis. There are two reasons for this requirement: a) the results can be judged more valid and can be more easily interpreted if the behavior of these variables in the real system are known for certain situations and b) sensitivity analysis can be a very powerful tool to select those parameters for parameter estimation and this latter method does depend very heavily on experimental measurements. The formulation of D used in sensitivity analysis can be used in the same form as the error criterion for parameter estimation analysis.

6) The variables chosen to formulate D should be related in some direct way to the parameters of primary concern. Thus, if a mass transfer parameter of species $\underline{i}$ is an important parameter, the concentration of species $\underline{i}$ would be a likely candidate to use in developing a performance criterion.

In the next section the usefulness of the performance criterion in sensitivity analysis will be developed by applying these techniques to a complex human thermoregulatory model.

5.0 APPLICATION OF SENSITIVITY ANALYSIS TO A MODEL OF THE HUMAN THERMOREGULATORY SYSTEM

In this section we will apply some of the techniques of sensitivity analysis to a fairly complex model of the thermoregulatory system which as been described elsewhere (12). For simplicity, the steady-state version of the model will be used exclusively, which means we shall be determining static sensitivity coefficients and ignoring parametric sensitivity during transient states. The following presentation is not meant to be a complete sensitivity analysis of the system under study, but is rather suggestive of the type of analysis that might be performed.

Typical Parameter Analysis

A traditional analysis of parametric variation is illustrated in Figure 6 in which the effects of metabolic rate (exercise) on certain important variables have been plotted.* Similar graphs using other parameters on the abscissa such as TCAB, TW, PCAB, and VCAB could be prepared.**

The sensitivity coefficients, $S_i = \partial y_i / \partial RM$ (where y represents any variable), could be generated by computing the slope of the curves shown. Since the slopes are somewhat steeper at the lowest values of RM it would be expected that the sensitivity coefficients would be different at either end of the abscissa. This is the reason that sensitivity coefficients are usually related to a perturbation about a specific operating point. We shall be considering two operating points in this example, characterized by the input parameters shown in Table IV. The first case represents a moderately relaxed, supine subject and the other an exercising, standing subject both in comfortable environments.

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*Table 1 presents the definitions of the symbolic notation used in this model.

**In a strict sense these should be described as independent variables, input parameters or forcing functions rather than system parameters. However, sensitivity analysis is suitable for studying the effects of these factors if the range of their values about an operating point is not excessive.

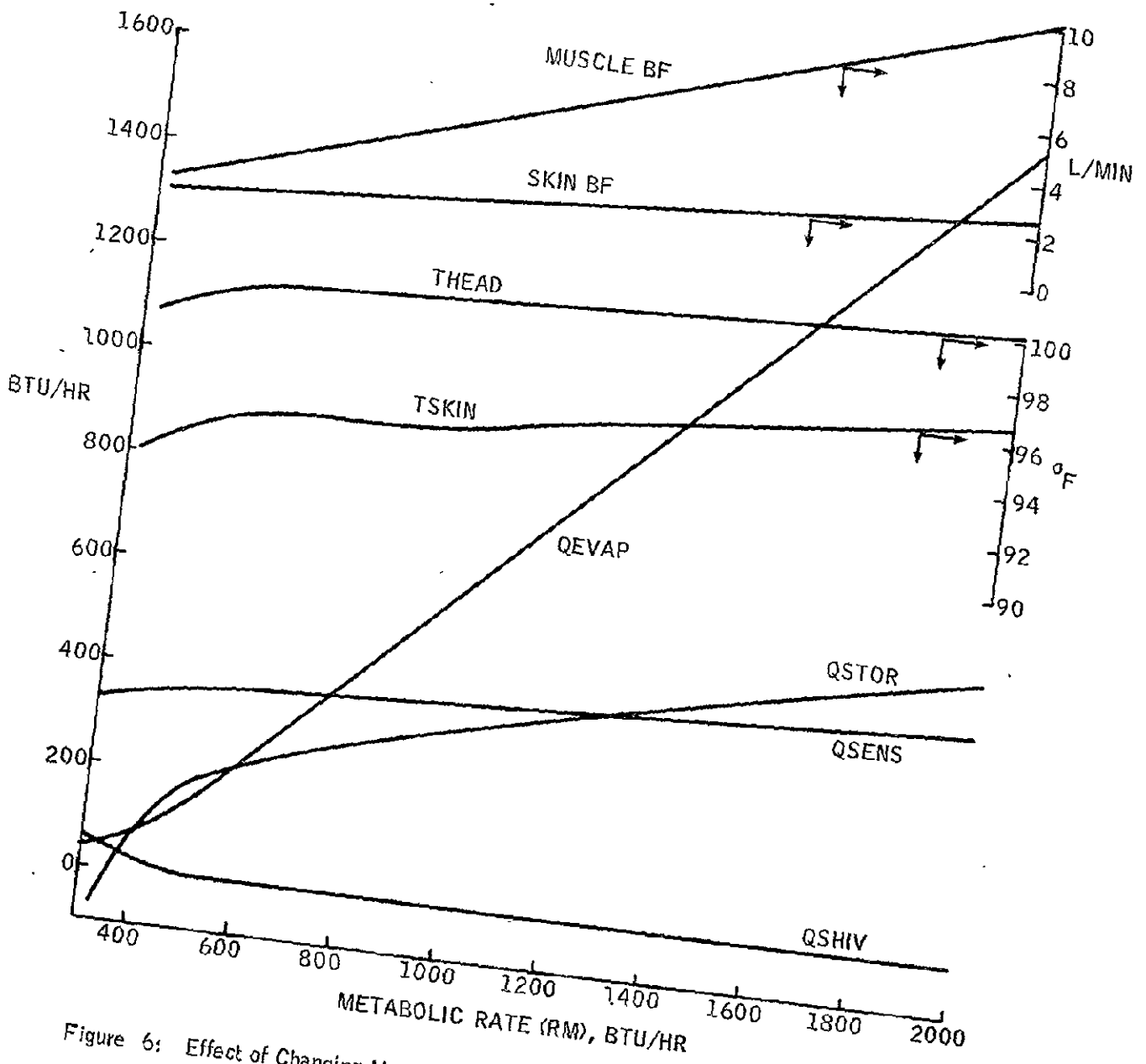

Figure 6: Effect of Changing Metabolic Rate on Selected Thermoregulatory Variables

TABLE IV

INPUT PARAMETERS FOR TWO OPERATING POINTS

INPUT PARAMETER	CASE 1: MODERATELY RELAXED	CASE 2: MEDIUM EXERCISE
RM (BTU/hr)	330	1165
QBASAL(BTU/hr)	283	283
UEFF	0	13.5
TCAB(^{o}F)	68	75
TW (^{o}F)	68	75
TDEWC (^{o}F)	50	55
VCAB (f/m)	30	30
PCAB (psi)	14.7	14.7
CLOV	0.35	0.5

The sensitivity coefficients have been computed for a selected variety of parameters and variables for each of the two operating points. Shown in Table V, each value has been computed by varying a single parameter, listed on the left, by +10% away from the operating point and determining the change in the particular variable shown across the top of the table using computer simulation of the model. The relative sensitivity coefficients were determined by Equation (3-8).

There is a large variation of values among the coefficients shown in Table V; the higher the value the greater the effect of a given parameter on the designated variable. The skin and head temperatures are relatively insensitive to any parameter, which is expected since negative feedback temperature regulation is an important feature of the model. Similarly, exercising muscle blood flow (Case 2) is insensitive to all the parameters studied except for metabolic rate, while perhaps surprisingly the model predicts a generally higher sensivity of the resting muscle flow (Case 1) to all the input parameters. Other differences in sensitivity between the two cases shown can be easily noted from this

TABLE V

SENSITIVITY COEFFICIENTS FOR 10% CHANGE IN PARAMETER VALUES

(THERMOREGULATORY MODEL)

CASE 1: REST

PARAMETER	QSTOR	QEVAP	QSENS	QSHIV	SKIN BF	MUSCLE BF	THEAD	TSKIN
RM	5.18	0.56	.0.08	-6.77	0.10	0.37	0.00	0.02
TCAB	2.57	0.26	-1.16	-9.03	0.26	-3.15	0.00	0.05
TW	2.94	0.25	-1.23	-9.64	0.10	-3.36	0.00	0.05
TDEWC	-0.03	-0.81	0.00	-0.70	0.09	-0.29	0.00	0.00
VCAB	0.49	0.04	0.15	0.66	0.06	0.18	0.00	-0.01
CLOV	0.69	-0.07	-0.18	-1.56	0.10	-0.59	0.00	0.01

CASE 2: EXERCISE

PARAMETER	QSTOR	QEVAP	QSENS	QSHIV	SKIN BF	MUSCLE BF	THEAD	TSKIN
RM	.62	1.51	0.11	0	1.35	1.28	0.01	0.01
TCAB	.42	1.04	-1.62	0	1.04	0.01	0.01	0.04
TW	.53	1.13	-1.77	0	1.11	0.01	0.01	0.04
TDEWC	-.06	0.00	-0.01	0	0.18	0.01	0.01	0.00
VCAB	-.03	-0.09	0.14	0	-0.03	0.01	0.00	0.00
CLOV	0.11	0.14	-0.21	0	0.21	0.01	0.02	0.01

table (especially the effects on QSHIV, QEVAP and QSTOR). This analysis allows one to observe quite easily which sections of the model are most and least sensitive to a particular parameter. For example, both the free air velocity (VCAB) and clothing resistance (CLOV) are seen to have their greatest influence on shivering in the relaxed state and on sensible heat loss in the exercising state. Also, it appears that many of the variables studied are more sensitive to wall temperature than to air temperature. In general, it appears that RM, TCAB, and TWALL exert a more profound influence on the model than do TDEWC, VCAB and CLOV.

Use of the Performance Criterion

As mentioned in the previous section, the formulation of a single performance criterion representing overall model behavior is a desirable objective. In the case of the thermoregulatory model the variable, QSTOR, representing the amount of heat stored in the body relative to reference state, appears to satisfy the requirements for a performance criterion outline in Section 4.0. QSTOR is defined in the 41-node model as:

$$QSTOR = \sum_{i=1}^{41} C_i(T_i - TSET_i) \qquad (5\text{-}1)$$

where T_i = temperature of the ith body node, $TSET_i$ is the reference set point (corresponding to the temperature in a neutral thermal environment) and C_i is the heat capacity (BTU/^{o}F) of the ith node. When the subject is in a neutral environment $T_i = TSET_i$ and QSTOR = 0. Inasmuch as the individual body segment temperatures are the net result of all the thermal forces acting on the body QSTOR is a good indicator of overall model performance. (A similar but related criterion might be mean body temperature). QSTOR has already been successfully used to define the limits of thermal comfort for manned space flight (22). The outside tolerance limits have been set at QSTOR = $\pm$ 300 BTU.

(These limits would be exceeded by slightly more than a one degree change in mean body temperature indicating that QSTOR is very sensitive to changes in heat balance).

The sensitivity coefficients for QSTOR relative to several input parameters has already been presented in Table V. As can be noted, QSTOR is many times more sensitive to the parameters studied near the resting operating point than in the exercising state. One interpretation of this observation is that the absolute values of the input parameters should be known to a higher degree of accuracy during the resting state as opposed to the exercising state to achieve the same degree of model accuracy.

The degree of linearity of QSTOR about the exercise operating point has been tested and the results summarized in Table VI. The values in this table have been obtained in exactly the same way as for those already described in Table V except that now QSTOR is the only variable studied and each parameter has been varied over a $\pm$ 60% range from the operating point. The results suggest that the sensitivities are extremely constant over a wide range.

The parameters studied thus far have been input parameters to the model which are usually known to a fairly high degree of accuracy. However, the model contains many other parameters, called system parameters, that are properties of the controlled or controlling systems and do not vary from run-to-run as do the input parameters. Also, their values are not known with great certainty. Examples of these parameters are: the skin-air interface heat transfer coefficients, tissue thermal conductivities, basal blood flow rates and thermoregulatory control parameters.

We have investigated the sensitivity coefficients of the seven thermoregulatory control parameters with respect to overall model performance as measured by QSTOR (see Table VII) to illustrate several points.

TABLE VI

VALUES OF THE OVERALL PERFORMANCE SENSITIVITY COEFFICIENT*

FOR ONE-AT-A-TIME PARAMETER CHANGES ABOUT THE NOMINAL

OPERATING POINT FOR EXERCISE**

PARAMETER INCREASE	0.5%	1%	10%	20%	40%	60%
RM	.626	.627	.619	.738	.696	.668
TCAB	.345	.346	.416	.420	.276	.169
TW	.530	.532	.527	.464	.291	.242
TDEWC	-.055	-.054	-.058	.063	.059	.019
UCAB	-.028	-.028	-.026	-.025	-.024	-.023
CLOV	.109	.109	.106	.102	.095	.093
UEFF	-.065	-.065	-.064	-.064	-.064	-.064

PARAMETER DECREASE	-0.5%	-1%	-10%	-20%	-40%	-60%
RM	.630	.630	.640	.663	.721	1.61
TCAB	.348	.348	.368	.388	.450	.653
TW	.534	.535	.559	.579	.632	.744
TDEWC	-.051	-.051	-.047	-.043	-.036	-.030
UCAB	-.026	-.027	-.028	-.029	-.032	-.028
CLOV	.113	.111	.115	.120	.131	.145
UEFF	-.061	-.063	-.063	-.063	-.063	-.063

*** See Text for explanation of brackets

* $\bar{S}_i = \frac{\Delta QSTOR}{QSTOR^o} \times \frac{q_i^o}{\Delta q_i}$, $QSTOR^o = 332$ ** See Table IV for absolute values of parameters at operating point.

TABLE VII

SENSITIVITY COEFFICIENTS FOR THERMOREGULATORY CONTROL PARAMETERS WITH RESPECT TO OVERALL PERFORMANCE

(Vary each parameter separately by 10%)

SYSTEM PARAMETER	NORMAL VALUE	SENSITIVITY COEFFICIENT = $\frac{\Delta QSTOR/QSTOR^{o}}{\Delta qi/q_{i}^{o}}$	
		Rest	Exercise
CSW	705	.040	.407
SSW	63.9	.091	.068
CDIL	143	.115	.174
SDIL	9.2	.025	.019
CCON	2.78	.001	.000
SCON	2.78	.000	.000
PCHIL	25.7	2.1	.000

First, the sensitivities are seen to vary from a highly significant to a negligible level. Secondly, the sensitivities can have widely different effects during either exercise or rest, stressing the importance of studying these effects at different operating points. If experiments were to be performed to measure these parameters the level of accuracy required would be approximately proportional to the relative values of the sensitivity coefficients. In some cases (i.e., CCON, SCON) it would be of little benefit to expend resources except to make the coarsest of measurements. Also, if parameter estimation analysis were to be used (instead of direct laboratory measurements) to determine a more accurate fit of model performance to existing data the parameters that would appear to be the best candidates to select for estimation would be CSW, SSW, CDIL, and PCHIL (in the resting state).

Prediction of QSTOR From a Sensitivity Model

It has been shown that it is possible to predict the value of a particular variable of a complex model from simple algebraic equations that are functions of the sensitivity coefficients with the need to perform simulations of the entire model on high speed computers (see Equations 2-13 and 3-12). Previously a simple example of this technique was illustrated. Here, the attempt is to predict values of QSTOR for a wide range of simultaneous parameter variations.

Let D be a measure of deviance from some operating point,

$$D = \frac{QSTOR - QSTOR^{o}}{QSTOR^{o}} \tag{5-2}$$

The relative sensitivity coefficients, $\bar{S}_i$, in Table VI have been determined by varying one parameter at a time:

$$\bar{S}_i = \frac{\partial D}{\partial q_i/q_i^{o}} \approx \frac{(QSTOR - QSTOR^{o})/QSTOR^{o}}{(q_i - q_i^{o})/q_i^{o}} \tag{5-3}$$

where q_i = the value of any parameter and (o) refers to the value at the operating point. Rewriting Equation (3-10) for n parameters and substituting QSTOR for y results in a formula for predicting D:

$$D_{PREDICT} = \sum_{i=1}^{n} \bar{S}_i U_i \tag{5-4}$$

where U_i is defined in Equation (3-9). In this example, the concern is with varying only those parameters listed in Table VI and the use of the value for $\bar{S}_i$ listed in the +1% column. Furthermore, a restriction to making changes in the parameters about operating points for Case 2 will be considered only within the ranges shown below.

TABLE VIII

VALUES OF PARAMETERS AND SENSITIVITY COEFFICIENTS

USED FOR PREDICTING CHANGES IN QSTOR

PARAMETER	NOMINAL VALUE	MINIMUM VALUE	MAXIMUM VALUE	$\bar{S}_i$
RM	1165	330	2000	.627
UEFF	13.5	5	22	-.0647
TCAB	75	55	75	.346
TW	75	55	75	.532
TDEWC	55	45	65	-.0536
VCAB	30	10	50	-.028
CLOV	0.5	0.1	0.9	.109

The brackets in Table VI represent the minimum and maximum values corresponding to the above table. A series of 24 runs were simulated with the thermoregulatory model. Each run consisted of changing all seven of the parameters simultaneously. The actual values for the parameters for a given run were obtained by choosing values within the limits given above at random assuming that all values have the same probability of being chosen. For each run a value of D was computed ($D_{COMPUTED}$) from Equation (5-2) and compared to the value of $D_{PREDICT}$ determined from Equation (5-4). The values of $\bar{S}_i$ used in Equation (5-4) are shown in Table VIII while values for U_i were determined from the random perturbations for each parameter. It should be emphasized that Equation (5-4) uses the sensitivity coefficients obtained from simulations varying one parameter at a time by 1% to predict values for D in which all parameters are varied over a much wider range simultaneously.

Figure 7 shows the results of this study. The dashed line represents perfect agreement between $D_{PREDICT}$ and $D_{COMPUTE}$. The origin represents the operating point. While the agreement becomes very poor for negative deviations from the operating point it is encouraging to see a reasonable correlation

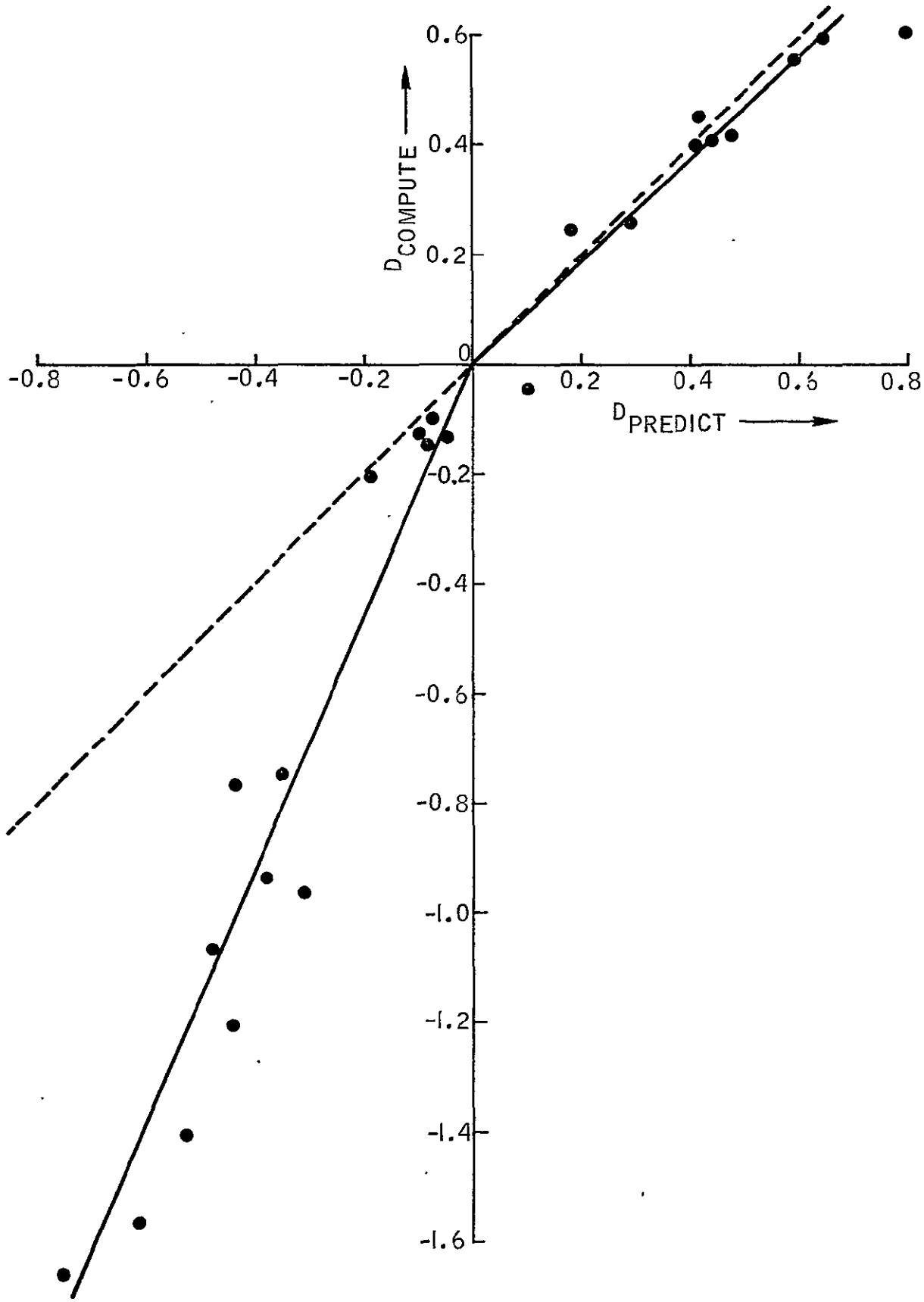

Figure 7: Overall Measure of Deviance of Thermoregulatory Model Due to Variation of all Input Parameters Simultaneously: Comparison of Computed vs. Predicted Results

of all the runs that can be described by two straight lines intersecting the origin. This is in spite of the very wide range of random parameter variations. Thus $D_{PREDICT}$ allows a good estimate of D (and therefore QSTOR) between the range of $-0.2 < D_{PREDICT} < +0.7$. For example, assume that it is desired to estimate the value of QSTOR for the following conditions: RM = 1300 BTU/hr; TCAB TCAB = TW = 80°F, and all other input parameters identical to those given in Table IV, Case 2. Then Equation (5-4) can be solved using only three terms, those describing the perturbations of RM, TCAB and TW from the operating point:

$$D_{PREDICT} = 0.627\left[\frac{1300 - 1165}{1165}\right] + 0.346\left[\frac{80 - 75}{75}\right] + 0.532\left[\frac{80 - 75}{75}\right]$$

$$= 0.131$$

This value can be used to estimate $D_{COMPUTE} = 0.125$ from Figure 7 which corresponds to QSTOR = 374 BTU. The value actually obtained during simulation of this particular condition is QSTOR = 379. Values of D outside the range mentioned above can also be predicted once the correlation between $D_{PREDICT}$ and $D_{COMPUTE}$ has been established (Figure 7), although the errors will be larger. The reasons for the deviation from the theoretical line in Figure 7 is probably due to two factors: 1) the assumption of constant sensitivity (especially for RM) over a range for which it is not really constant (see Table VI), and 2) neglect of higher order sensitivity coefficients (see Equation (2-12)).

It would be possible to prepare a family of curves similar to Figure 7 for a series of important operating points. Once this has been done, QSTOR could be reasonably well predicted over a wide range in the manner just illustrated. Other variables besides QSTOR could be handled in the same way. The relative values of each term in Equation (5-4) will also provide a quantitative measure of the importance of each parameter.

Another important application of sensitivity analysis is to investigate the interdependence of parameters. In Figure 8 the metabolic rate and ambient temperature have been varied simultaneously over a wide range and QSTOR contour lines were drawn. The convergence of contour lines towards the lower left shows that QSTOR becomes more sensitive to simultaneous changes of TCAB and RM as these parameters decrease in value. Also, there appears to be a region of very high sensitivity in the region of 550 Btu/hr and 80^{o}F, a commonly encountered environment. Further analysis of these and other parameters would be suitable for obtaining human tolerance limits and may reveal minimum or maximum points of sensitivity. An analysis of second-order sensitivity coefficients of the type, $\partial y/\partial q_1 \, \partial q_2$ would also help to reveal mutual interraction effects of parameters.

These results have been illustrated for the steady-state case. For models that are capable of predicting time-dependent behavior such as is shown in Figure 2 the quantitative relationships of sensitivity coefficients is more obscure than for the simpler steady-state relationships shown in Figure 6. Thus, the computation of sensitivity coefficients becomes even more relevant for studying transient behavior. It is important, however, to define the time limits of interest since it has been shown that sensitivity coefficients may be time-dependent.

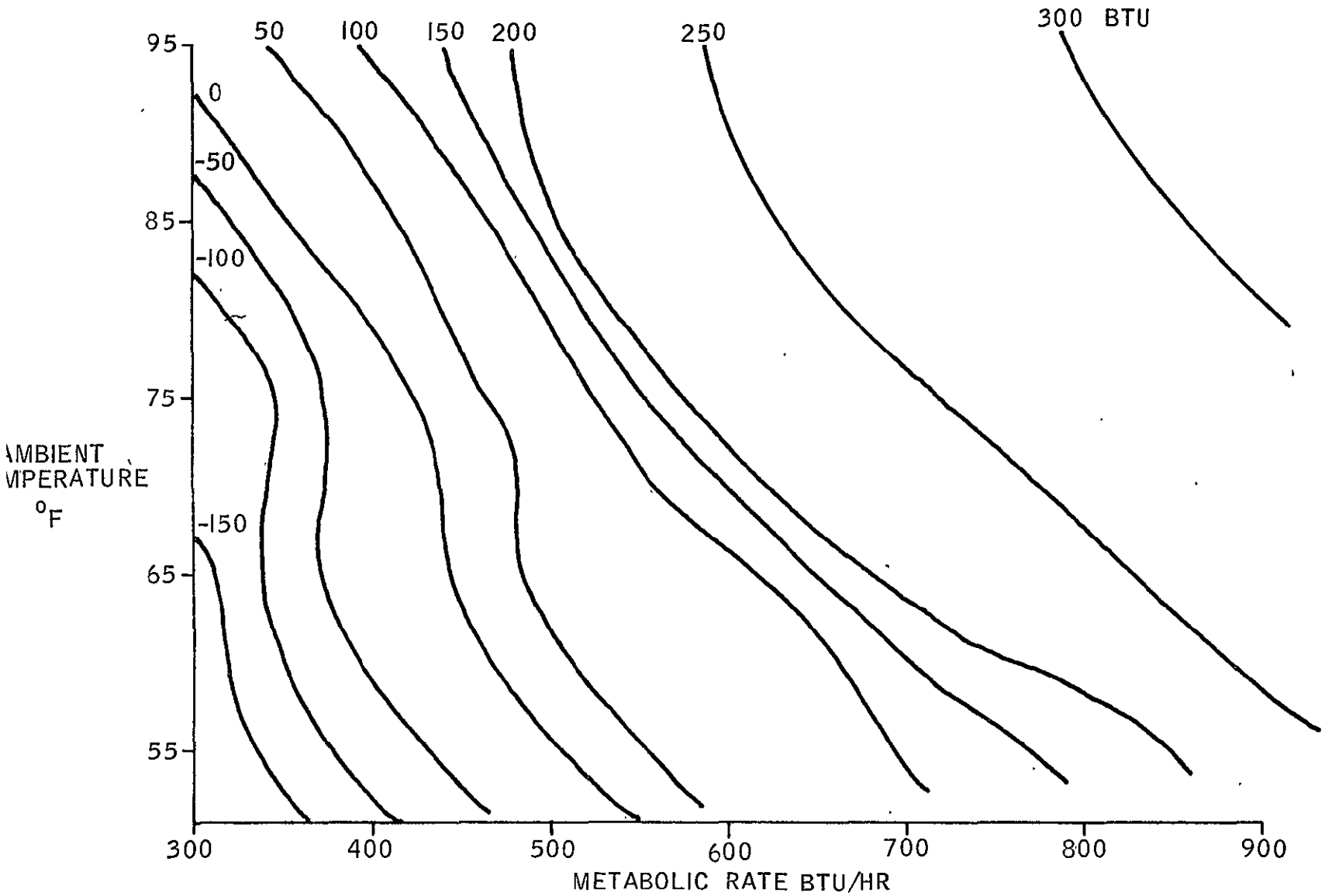

Figure 8: QSTOR Contour Lines for Simultaneous Changes in Ambient Temperature and Metabolic Rate

6.0 OTHER APPLICATIONS

Error and Noise Analysis

The possibility of using sensitivity analysis for predicting errors and uncertainty in model results based on uncertainty of input data has been suggested. Approaches to achieve this end have been discussed in References 7, 11, 13, 14, and 19. They are based on assuming nominal values for parameters and some distribution of experimental error for each of these values. For example, a predicted variance for a particular variable may be obtained directly from Equation (5-4) by letting U_i have a mean value of zero and a variance $(\delta_i/q_i^o)^2$ so that the variance of D (representing any variable) is:

$$VAR(D) = \sum_{i=1}^{n} \bar{S}_i^{\,2} (\delta_i/q_i^o)^2 \qquad (6\text{-}1)$$

The limitations of the use of this equation are the same as for those of using $D_{PREDICT}$ to estimate D described in the last section; higher order sensitivity coefficients may be neglected and the principle of linear superposition must be valid in the range studied. When these restrictions are met and numeric values are substituted into (6-1), the contribution to the overall uncertainty of each of the input parameters can be immediately identified. Then the sensitivity coefficient establishes an analytical connection between component errors and the performance of dynamic systems.

Parameter values are never known with 100% accuracy. If the standard deviation around the mean value can be estimated for each parameter it would be possible to place statistical confidence limits on a model's behavior (7) as well as identifying the experimental limits of accuracy needed in any parameter in order to reduce these confidence limits. This becomes especially desirable in large scale systems where the large number of parameters promulgate errors through the simulation (15) and in certain nonlinear systems where the interactive effects

of the parameters might lead to amplification of individual errors. Unfortunately, even though the techniques to accomplish this are rather straightforward, there are few, if any, examples to point to in the literature of physiological systems.

A related problem that has application to error and sensitivity analysis is the effect of noise on the behavior of the system. Noise can be described as a statistical disturbance of a particular variable and is characterized by statistical properties such as a mean value, probability distribution, spectral density, etc. The variation of model output due to noise can be found by including a distribution function with each parameter or variable that exhibits noisy behavior. This problem becomes extremely relevant in parameter estimation analysis when model output is compared to data that has a significant noise level (17, 18).

Stability Analysis

It is appropriate to mention stability analysis of dynamic systems because of the inverse relationship between sensitivity and stability in negative feedback systems. In general sensitivity to disturbing factors can be reduced by an increase in feedback gain (in technological systems at least). On the other hand, the onset of instability occurs as a consequence of this gain increase. Thus, systems with high gain may have low sensitivity to external perturbations, but may also be operating on the borderline of instability. Most biological systems are normally stable and they do exhibit low sensitivity. Whether or not they are working somewhere near the stability limit via high gain factors is not known, but should be studied on a case by case basis (9). An analysis of stability can become an important measure of the competence of a model in that if both model and actual system can be thrown into instability by the same parametric changes there is reason for having greater confidence in the mathematical representation.

Little work has been done on stability analysis of complex physiological system of a practical nature. Formal techniques for investigating stability in linear systems and for simple nonlinear systems have been reported (9, 18, 20, 21), but for the most part, studying large scale nonlinear models is a trial and

error experience. Systems that exhibit oscillatory or periodic behavior in normal operation (i.e., eye movement, respiration) can often be made unstable more easily than systems that behave monotonically. Inherent instability is dependent upon the properties of the system and is normally not a function of the specific disturbance. If the system is inherently stable, all transients will ultimately disappear regardless of the disturbance causing them. On the other hand any disturbance to an unstable system will initiate oscillations that increase in amplitude with time.

Stability can arise from either inherent features of the real system or from structural features of the mathematical model (such as a long integration interval). The techniques of sensitivity analysis can reveal both types although it is not always possible to distinguish between the two. Tomovic (20, 21) has suggested that it may be easier to study the stability of a system by observing solutions of the sensitivity equations rather than the system equations themselves. At least one of the sensitivity coefficients in an unstable system will show divergent characteristics with increases in time. Like sensitivity, stability is a function of the operating point so that it becomes necessary to test all possible operating points for stability. Thus, a careful, systematic sensitivity analysis may often reveal not only points of instability but their causes as well.

Parameter Estimation

The object of parameter estimation (or identification) analysis is to determine the value of one or more parameters in a model. The parameters selected for estimation are usually impossible or difficult to measure directly in the real system. In practice, the technique involves repetitive adjustment of the parameter values until some subjective judgement of goodness of fit between model output and corresponding measurements in the system prototype has been satisfied. There is a large body of literature on parameter estimation in physiological systems and algorithms for optimizing parameters automatically have been the object of considerable attention (e.g. 8). It is the purpose of this section to discuss parameter estimation in terms of sensitivity analysis, a relationship that is not often mentioned.

Some of the error criterion used in parameter estimation have already been discussed (see Section 4.0). They all contain a difference function of the form

$$e(t) = y(t) - y^*(t) \tag{6-2}$$

where y is a dependent variable that has been measured in the real system and y^* is the corresponding model variable. The error criterion, E, is a function of e, usually $|e|$ or e^2, integrated over a specified time interval, e.g.,

$$E = \int_0^T |e| \, dt \tag{6-3}$$

Since y is dependent on the system parameters, q_i, e can be expressed as $e(t) = e(t, q_1, q_2, \ldots, q_m)$. The criterion for the best fit between data and model is achieved when E reaches a minimum value, hopefully zero. This can also be expressed as

$$\frac{\delta E}{\delta q_1} = 0, \quad \frac{\delta E}{\delta q_2} = 0, \ldots\ldots, \quad \frac{\delta E}{\delta q_m} = 0 \tag{6-4}$$

where $\delta E / \delta q_i$ is nothing more than the sensitivity coefficient of E with respect to the parameter q_i. Thus, many of the techniques of sensitivity analysis can be used to evaluate the error criterion for parameter estimation.

A more powerful use of sensitivity analysis (but one which has been used infrequently) is in determining which paramerers could most accurately be estimated by the curve fitting procedure discussed above. Parameter estimation is used most effectively on parameters exerting a strong influence on a particular model variable which can be easily measured in the real system. If sensitivity analysis is used prior to parameter estimation it is possible to select those parameters with the highest sensitivity coefficients as the best candidates for parameter estimation analysis. When the parameter sensitivity of a given error

criterion is low, then that parameter value cannot be estimated with certainty using that criterion; that parameter should be set at a reasonable constant value determined from other sources. Chang (4) has used this procedure to good advantage in investigating a complex circulation model. A similar example has been given in Section 5.0.

Inverse Sensitivity

If the problem of sensitivity analysis is expressed as determining the behavior of a model given all the parameter variations, then the inverse problem would be to determine (or identify) the parameter variations capable of producing a given behavior of the real system. The problem of direct sensitivity can be solved satisfactorily if the sensitivity coefficients of the dynamic system are known. The method for finding inverse sensitivity is also based on a knowledge of the sensitivity coefficients. Unlike direct sensitivity analysis, both parameter estimation and inverse sensitivity analysis requires data measurements from the real system. It is the purpose here to merely point out the existence of the inverse technique, its relationship to sensitivity analysis and its practical significance.

In essense solving the inverse sensitivity problem is not unlike parameter estimation analysis. Analytic methods have been worked out for linear system (20) while empirical methods must be used for nonlinear systems. With inverse sensitivity we start from the known perturbation of the transient state and seek the set of parameter perturbations capable of causing them. For example, in Equation (2-13), the value of Δy and the values of S_i would be given and it would be required to determine Δq_i. This inverse problem may not have a unique solution. Uniqueness is dependent primarily on the number of parameters vs. the number of variables measure and the number of points in time at which measurements are made. Nevertheless, it would be valuable to know the various solutions possible since this would be a great aid in hypothesis testing. If several

different parameter perturbations could produce similar model results it may be possible to accept the most reasonable based on physiological plausibility or alternatively this information could provide the basis for further experimental testing.

7.0 CONCLUSIONS

General Applicability of Sensitivity Analysis

Having discussed sensitivity analysis at some length, it is appropriate to consider its usefulness at various stages of model building and testing. The history of a simulation model may be conveniently broken into five stages: 1) thorough analysis of the system under study in order to ascertain its most important elements and to formulate their interactions and behavior mechanisms in mathematical terms, 2) construction of the mathematical model, translation to computer language, preliminary assignment of the required data base, implementation on the computer and program debugging, 3) model verification by ensuring that a simulation model behaves as the experimenter/model-builder intended for one or two special cases, 4) model validation by comparing model and real system responses for several other specific stresses, 5) advanced simulation tests of the models for the purposes of parameter estimation, validating the model over a wider data base, and making inferences from the model for the purposes of pure prediction or to guide laboratory experimental design. With this framework in mind it is possible to conclude that sensitivity analysis can find equal usefulness in the last three stages of model construction.

A review of the literature of physiological systems analysis reveals that sensitivity analysis has either been neglected entirely or else has been used to provide merely supplementary information to the reader well after model validation (Stage 5). Even in other fields it is only recently that this technique has been used as a tool in its own right as a stepping stone to verify and validate models (Stages 3 and 4) and to provide information about the relative importance of parameters for the purposes of parameter estimation or deciding on the allocation of resources for data collection. In this regard the physiological systems analyst can learn much from his counterpart who simulates ecological, behavioral, and management systems. In all fairness however, it should be pointed out that parameter variation studies of some type are usually carried out on an informal

basis in almost all modeling endeavors even though they usually do not extend to formulating, computing, and interpreting sensitivity coefficients which are the basis of a systematic sensitivity analysis.

Miller (13) has presented some compelling arguments that suggest sensitivity analysis can be extremely useful quite early in the development process. He has shown that identification of the relative importance of parameters can be made even in models that are somewhat inaccurate. The possibility of identifying those parameters and the accuracy needed in their measurement would mean that one could predict how much effort would be required in order to produce a valid model before massive resources were committed. The problem is to decide how much confidence to place in the sensitivity analysis of a simulation system before proper validation has taken place. In attempting to answer this question Miller (14) has shown that sensitivity analysis on certain classes of systems can be used to partially validate models by implicating experimentalists in interpreting results. One of the most important advantages of sensitivity analysis during these early stages of development is that it does not require extensive data collection to determine qualitative model validation.

Once the model has become validated and its credibility ascertained the techniques of sensitivity analysis can still be used to good advantage. Several examples have illustrated the capability of using sensitivity coefficients to form simple predictive linear models of complex systems. Some of the more advanced procedures of noise analysis, parameter estimation, stability analysis, and inverse sensitivity problems have been discussed. In addition there will usually always be other areas of the system under study that need strengthening by introducing new elements or improved parameter values. A sensitivity analysis on a validated model could provide the motivation, direction and support for this effort. Finally, when a model is used for making inferences regarding untested situations, it has been shown that sensitivity analysis is useful for predicting uncertainty in model behavior based on measurement errors of input data.

Application to Large Scale Physiological Systems

This report is part of an overall study of physiological models that are as advanced in complexity as any in existence; they may be characterized as large scale, multivariate, multiparametric, nonlinear, homeostatic, dynamic models. As a result any simulation technique (i.e., parameter estimation, sensitivity analysis, stability analysis, etc.) is challenged to its theoretical and practical limits.

If the sensitivity of a single parameter on such a system is desired, the problem is straightforward. But, if one wishes to observe sensitivity to the simultaneous variation of several parameters the problem is more difficult as has been shown. In this case the change of a specific parameter must be studied with various combinations of the other parameters. That is, one is dealing with a poly-parametric sensitivity coefficient in a multi-dimensional parametric space. In this problem it is essential to scan a much larger parametric space than previously and one is obliged to determine interaction effects of parameters in this space (e.g., compute higher order sensitivity functions). The techniques we have discussed to measure all the sensitivity coefficients simultaneously are less practical for these systems.

Large scale models also suffer from potential large scale errors because as more parameters are added to the model the errors in their assigned value may be promulgated through a simulation and contribute to uncertainty in the models prediction. In these models, especially when they are in an advanced stage of development, a combined sensitivity-error analysis becomes highly desirable.

This study has dwelled at some length on the value of overall performance criteria. The formulation of such a function would be more difficult with a large scale system, but it often requires a thoughtful and worthwhile re-evaluation of many aspects of the model, its goals and general usefulness.

Certain problems in sensitivity analysis (i.e., error and noise analysis, parameter estimation, inverse sensitivity) require measurements from the real system, including measurement errors and behavior of specific dependent variables. As the data base of the system and its handling capability improves

these aspects of sensitivity analysis become more manageable and provide a tool with which to integrate the data with model performance.

Thus, even though the problem is definitely tractable, a complete and systematic sensitivity analysis of a large system can take considerable time. This requirement can be greatly reduced by carefully selecting a smaller subset of parameters and dependent variables which are of interest and making certain assumptions regarding linearization about specific operating points. Sensitivity analysis itself can help to define these subsets by eliminating insensitive parameters in a systematic way from the area of concern.

Whether or not the gains derived will always be commensurate with the time necessary for performing these analyses is difficult to judge. The decision is hampered by the fact that application to biological problems has lagged far behind theoretical developments. The literature reviewed does not report a single case where an extensive sensitivity analysis has been performed on physiological systems of the scale concerned with here. Nevertheless, the techniques discussed in this report have revealed that sensitivity analysis can be a useful tool in the hands of a competent systems analyst at nearly every stage of model development. Thus, the need to begin applying some of the methods described in this report is clearly indicated.

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APPENDIX

OBTAINING ALL THE SENSITIVITY FUNCTIONS SIMULTANEOUSLY FROM A SINGLE MODEL

The method described here called the "sensitivity points" method, is suitable primarily for linear systems of a certain type as described in References 2, 10, 20, and 21. Its applicability to large scale nonlinear models is uncertain and it is included here for completeness.

Consider the simple linear negative feedback system shown in Figure A-1 with input x, output y, gain K_1 in the forward path and gain K_2 in the feedback loop.

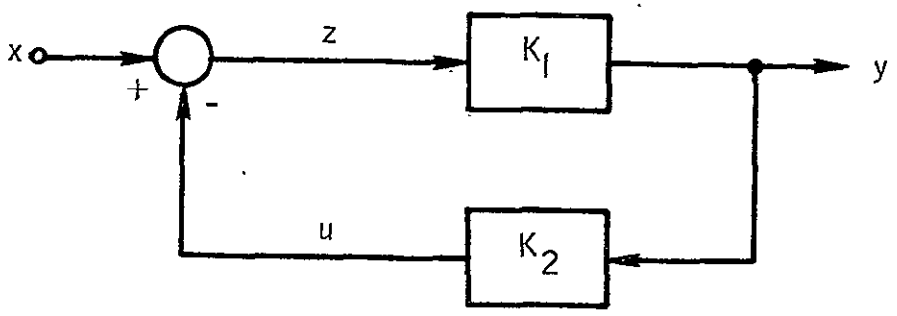


Figure A-1

The following relationships are easily formulated:

$$y = K_1 z \tag{A-1}$$

$$u = K_2 y \tag{A-2}$$

$$z = x - u \tag{A-3}$$

$$y = K_1(x - K_2 y) \tag{A-4}$$

$$\text{Open Loop Gain} = u/z = K_1 K_2 \tag{A-5}$$

$$\text{Closed Loop Gain} = y/z = K_1/(1 + K_1 K_2) \tag{A-6}$$

The sensitivity functions may be obtained by solving (A-6) for y and seeking the partial derivatives:

$$S_1 = \frac{\delta y}{\delta K_1/K_1} = \left[\frac{1}{1 + K_1 K_2}\right] y \qquad \text{(A-7)}$$

$$S_2 = \frac{\delta y}{\delta K_2/K_2} = \left[\frac{-K_1 K_2}{1 + K_1 K_2}\right] y \qquad \text{(A-8)}$$

The sensitivity coefficients can also be generated from an analog sensitivity model equivalent to the original model using the output from the original model as input:

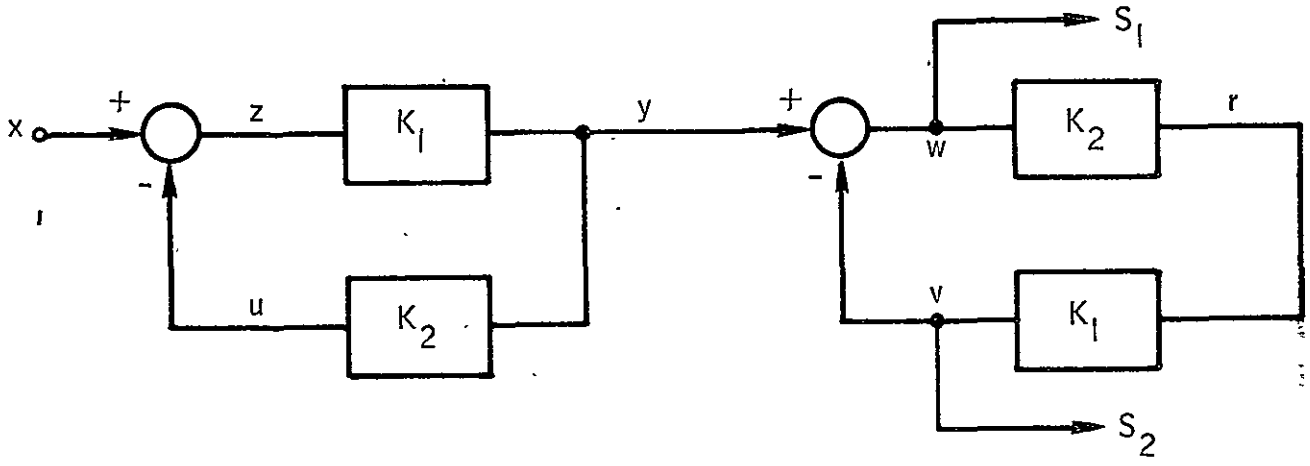


Figure A-2

It can be easily shown that $\underline{w}$ and $\underline{v}$ in Figure A-2 are identical to the sensitivity coefficients S_1 and S_2. Noting the correspondence between $\underline{x}$ and $\underline{y}$, $\underline{z}$ and $\underline{w}$, $\underline{y}$ and $\underline{r}$ and $\underline{u}$ and $\underline{v}$ we obtain from Equations (A-1) to (A-5):

$$w = y - v = y - K_1 K_2 w = \left[\frac{1}{1 + K_1 K_2}\right] y = S_1 \qquad \text{(A-9)}$$

and

$$v = K_1K_2w = \left[\frac{K_1K_2}{1 + K_1K_2}\right]y = -S_2 \qquad \text{(A-10)}$$

Thus, the sensitivity functions can be obtained at points $\underline{w}$ and $\underline{v}$ (called sensitivity points) by solving the original and sensitivity models simultaneously as indicated in Figure A-2. In like manner the output of the sensitivity model can be used as input into a third identical model to obtain second-order sensitivity coefficients if desired.

The transfer functions K_1 and K_2 can represent Laplace operators describing an nth order linear system. Tomovic (20) has shown that the sensitivity functions for an nth order system can be generated in a similar fashion. For example, Figure A-3 represents the analog solution to a third-order system:

$$\frac{d^3x}{dt^3} + \frac{d^2x}{dt^2} + a_1\frac{dx}{dt} + a_o = y(t)$$

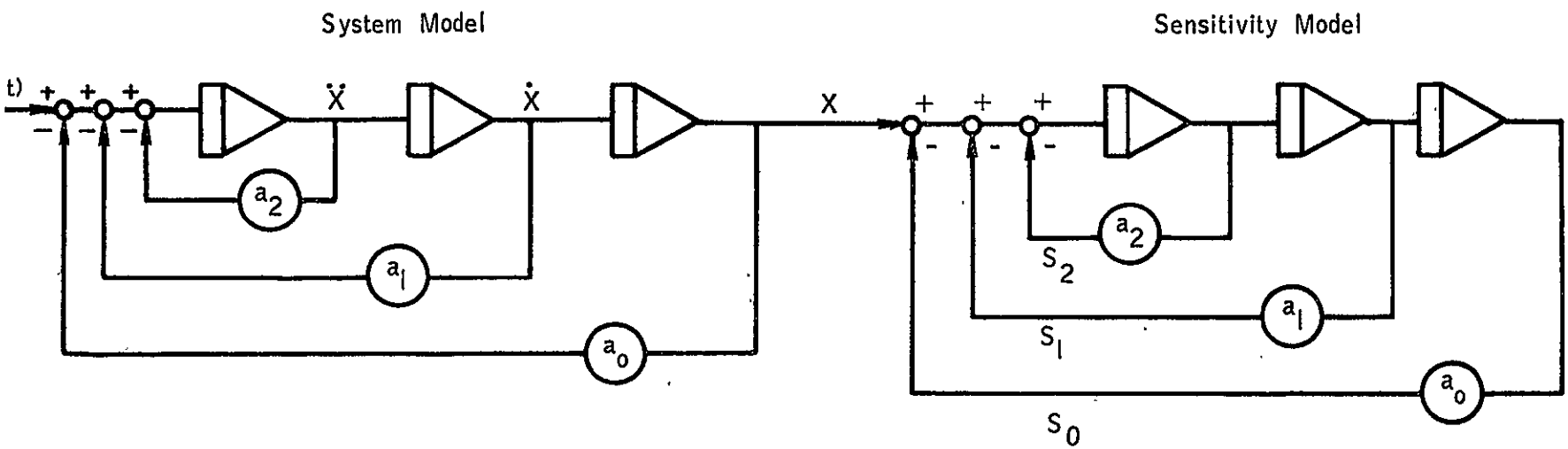
The model on the left of Figure A-3 represents the original system whose solution is x while the identically structured model on the right is the sensitivity model. S_o, S_1, and S_2 are the sensitivity points, where

$$S_i = \frac{\partial x(t)}{\partial \ln a_i}$$

The following general conclusions can be drawn from this example:

a) If the response x(t) of the system is introduced at the input of an identical system, then points S_i (i=1, 2, . . . , m) will exist on the sensitivity model block diagram.

b) All the sensitivity coefficients can therefore be determined by solving the sensitivity model simultaneously with the system model.



$$\frac{d^3X}{dt^3} + a_2\frac{d^2X}{dt^2} + a_1\frac{dX}{dt} + a_0 = Y(t)$$

Figure A-3: Block Diagram for Simultaneous Measurement of the Sensitivity Coefficients