PARAMETER ESTIMATION APPLIED TO PHYSIOLOGICAL SYSTEMS

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ABSTRACT. — Parameter estimation techniques are of ever-increasing interest in the fields of medicine and biology, as greater efforts are currently being made to describe physiological systems in explicit quantitative form. Although some of the techniques of parameter estimation as developed for use in other engineering and scientific problems may be carried over into physiology, it has nevertheless been necessary to re-examine the entire procedure of estimation, from model formulation to computer selection. The results of this re-examination, as set forth in this paper, give some guidance as to the selection of techniques for the estimation of the parameters of physiological systems.

RESUME. — Les techniques d'estimation de paramètres deviennent de plus en plus importantes dans les domaines de la médecine et de la biologie, puisqu'on s'intéresse actuellement de plus en plus à la description quantitative des phénomènes physiologiques. Bien que certaines techniques d'estimation, développées dans d'autres domaines scientifiques, puissent être employées pour des applications en physiologie, il est nécessaire de réexaminer les méthodes d'estimation à partir de l'élaboration du modèle jusqu'au choix du calculateur. Les résultats de cette étude sont discutés dans le présent article ; ils peuvent être utiles pour la sélection des procédés d'estimation des paramètres pour des applications physiologiques.

1. INTRODUCTION

In many medical and physiological investigations there is a need for quantitative or numerical information about the system that is being studied. This applies to . 1) Diagnosis in general, and, more particularly, computer-based classification of patients. 2) Therapy, to observe either immediate or the long term effects of both surgical and drug therapy. 3) Trend analysis, *i.e.*, detection of rather slow changes in the state of a patient for the purposes of diagnosis and therapy (this is particularly important when dealing with patients in intensive care units) 4) Screening with follow-up studies of large populations. 5) Physiological and pharmacological studies of sub-systems especially when intact animals are used which results in a limit in the number of variables that can be observed

In a recent survey [1], Bekey listed a number of reasons for the lack of acceptance in biomedicine of identification and estimation techniques. These reasons range from suspicion of the life scientist for not directly determining parameter values, to the cost of estimation procedures. He also referred to more typical problems encountered in the study of biological systems, such as the variability of measurement data and the fact that inputs and outputs of sub-systems are difficult to isolate. System identification is often very limited because of incomplete insight into the structure of the biological system. As a result of this, the subsequent parameter estimation is likely to be non-unique ; this problem is enhanced by the fact that most systems are non-linear.

Parameters are properties of the process or system, the specific values of which influence one or more variables ; they appear as constants or coefficients in equations. Examples are · dimensional quantities such as radii or volumes at zero distending pressure, vessel wall elasticity in the cardiovascular system, rate constants in chemical reactions, pressure-volume relations of ventricles or atria, and cardiac function curves. The time-dependent compliance used in some approximating descriptions of the heart action may also be considered as a set of parameters or as a parametric function. It must also be realized that some of these quantities are subject to change as a result of nervous or hormonal influence.

The more rapidly varying quantities in a system are in general considered to be variables ; these may include blood pressures and flows, the alveolar carbon dioxide partial pressure, rate of oxygen consumption, etc. For a given set of initial values, the variables are completely determined by a set of deterministic system equations and a complete set of parameters In the context of this paper the term *system* will ordinarily refer to a sub-system of the human or animal body which is under investigation. This could be, for example, the entire cardiovascular system, the respir-

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3. Available funding.
4. Available computer resources.

The selection is in general based on the need for a special service unique to a particular language. These special services may be summarized as follows:

MIMIC	– easy and inexpensive to use, easy to learn
DYNAMO	– language natural to non-engineering disciplines
CSMP/CSMP-III	– complete expression-oriented language with graphics
CSSL-3	– extensive set of MACRO directives
SL-1	– real-time, hybrid computer, and multiple derivative features
PROSE	– problem solving packages for optimization, nonlinear programming and parameter estimation
SALEM	– no longer supported
PDEL	– a PL/1 oriented system with considerable flexibility
LEANS	– handles elliptic, parabolic and hyperbolic equations
DSS	– will not handle hyperbolic equations
PDELAN	– structured for problems in meteorology
FORSIM	– a PDE interface to FORTRAN

The user is reminded of Hamming's statement that "The purpose of computation is insight not numbers". One uses simulation to gain insight into the behavior of systems. The models one uses are biased to a great extent by his choice of descriptive language. Therefore, the user should be familiar with constructive alternatives in order to make an intelligent selection as to which language is "best" suited for his class of problems.

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puts from corresponding outputs of the model to form error signals. Those parameters of the process which can be varied are then changed, with the aid of some optimization algorithm, to reduce some measure of the errors, such as the integral of the sum of their squares If this operation is successful, not only should the observable signals of model and system closely resemble one another, but also, if the model is adequate, other model output signals which may be unobservable in the system, should resemble those in the system, as should the parameter values.

It should also be noted that much attention is given in modern control literature to optimal control, in which the external inputs to a system are modified to cause the system to behave in some desired fashion, usually determined by minimization of some criterion. Although optimal control as it is ordinarily understood is beyond the scope of this paper, it may be important in connection with such problems as the design of artificial hearts or circulation assistance devices One approach to optimal control [5] falls within the scope of methods presented here.

It may not always be possible or necessary to force an input on the process being studied. This is the case, for example, when estimating parameters from the entire cardiovascular system ; it is a kind of self-contained system which needs no input signals to function (although it may have disturbance inputs). However, if the process is somewhat periodic in nature, then a signal may be used to synchronize the model, which facilitates the calculations of error signals e_j . When parameters of a part of some large system are to be estimated, some of its variables may be used as input signals to a partial model to determine the errors e_j .

As a simple example of how a parameter estimation method might be devised to determine some characteristics of a portion of the canine aorta consider the relations between pressures and flows in the lower thoracic aorta (p_1 , f_1) and upper abdominal aorta (p_3 , f_2) and the total blood volume of this segment, q_2 . A lumped « circuit » model of this arterial segment may be represented (see Fig. 2) using the same symbols as those used for the analogous electrical circuit described by the same equations [6, 7, 8] The mathematical representation is as follows :

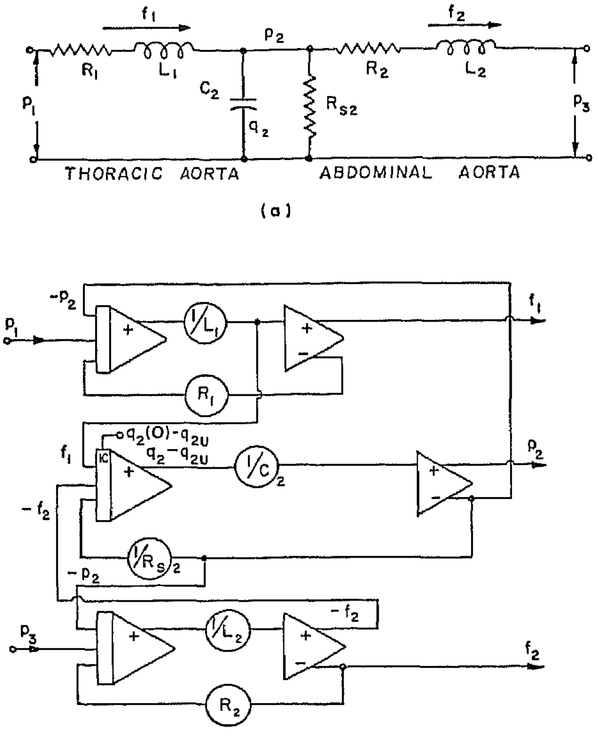
$$p_1 - p_2 = R_1 f_1 + L_1 \frac{df_1}{dt} \qquad (1')$$

$$p_2 = \frac{1}{C_2} (q_2 - q_{2u}) \qquad (2)$$

$$q_2 = q_2(0) + \int (f_1 - f_2 - p_2/R_{S2})\, dt \qquad (3)$$

$$p_2 - p_3 = R_2 f_2 + L_2 \frac{df_2}{dt} \qquad (4)$$

In each part of the segment, R_1 and R_2 are the symbols used for viscous resistance to flow, and L_1



(a)

(b)

Fig. 2.

and L_2 for the inertance of the blood. R_{S2} represents the resistance to flow of the combined renal, hepatic and upper mesentric branches (venous pressure assumed zero). The pressure-volume relation of the segment requires a sixth coefficient, the compliance C_2 used in Eq (2) ; here q_2 is the total volume and q_{2u} represents the unstressed volume of the segment, i.e , the volume when no distending pressure is present.

If we assume that it is possible to measure p_1 , p_3 , f_1 , f_2 , and the total length of the segment, and that we would like to know the elastic properties of the vessel, its dimensions and the value of the resistance

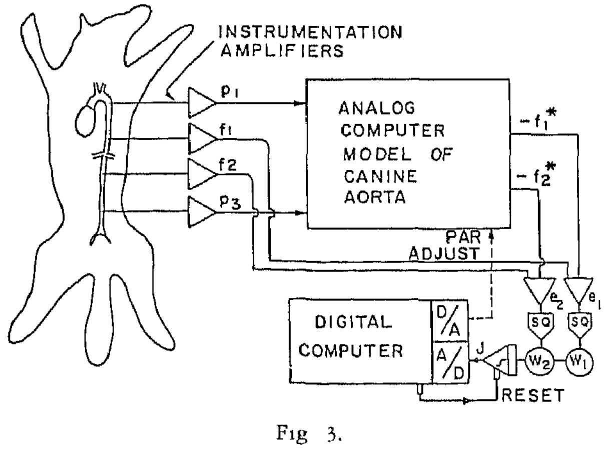


Fig 3.

R_{S2}, then the scheme shown in Fig 3 could be used. Here the analog computer part of a hybrid computer is used to model, in real time, the dynamics of the aortic segment of a dog (using the set-up of Fig. 2). In this example we choose to drive the model at each end by signals proportional to the corresponding dynamic pressures measured in the dog. The performance index is calculated from the difference between animal and model flow rate values ; here the differences are squared, multiplied by weighting factors, summed and integrated. This criterion is used in an algorithm set up in the digital computer for correction of the parameters of the unknown (or somewhat unknown) model, which in this case may be indicated as R_1^*, L_1^*, C_2^*, R^*, R_2^* and L_2^*.

If we neglect for a moment the presence of noise or error in the pressure and flow signals, it is relatively easy to see that these parameters are not independent of each other. Both resistance and inertance are functions of the length and the radius of the segment (see section 4). Thus, with R_1 and L_1 known, and if the density and viscosity of blood is also known, one can calculate the radius, r_1, and the length, l_1, of the left-hand half of the segment (of Fig. 2). Since it was assumed that the total length between the measuring points is known, the length l_2 of right-hand half of the segment can now be determined. This means that only one of R_2^* and L_2^* need to be determined to permit the value of the remaining parameter, r_2, to be calculated. Once the values of R_1^* and R_2^* are determined, the value of R^*_{S2} can be directly calculated using the average pressure and flow data from the dog. The remaining unknown parameter is C_2, and, once estimated, may be used together with the average radius to yield the product of Young's modulus and wall thickness [8]. Thus, in the case of noise-free data, and assuming this model is adequate, only four out of the six parameters need to be estimated and the remaining two can then be calculated

From this example, it may be seen that a number of factors must be considered in setting up a parameter estimation scheme.

These include :

— The determination of the model, or system identification.
— The selection of parameters to be estimated.
— The choice of system variables to be measured for comparison with model variables.
— The information content of the available signals in relation with noise, interdependence of data.
— The testing and selection of error criteria to indicate by their minimization when the best correspondence between system and model has been achieved.
— The selection of algorithms which will most effectively and efficiently reach the minima referred to above.
— The choice of a computer, together with the programming method and output presentation scheme best suited to the problem.

These various choices are closely interlinked, but will be examined one by one, with interrelationships indicated, where they are not obvious.

3. DETERMINATION OF MODEL FORM, AS A FIRST STEP IN PARAMETER ESTIMATION

The determination of the topology of network description of a system (as the part of system identification procedures preceding parameter estimation) may be achieved solely from input-output records by methods which are particularly well-understood for linear or slightly nonlinear systems [9]. But such methods do not make use of what is known about the form and physical relationship in the system, and do not yield parameters which are as likely to have physical significance. Physically determined models are, therefore, to be preferred whenever possible and the use of model-based parameter estimation schemes naturally follows.

Models of various biological systems have been designed, for many reasons ; these models include the respiratory system [10], the cardiovascular system [11], hormonal systems [12] and the interacting combination of the controlled respiratory and circulatory systems [13]. Besides the general considerations on the design of models [14, 15, 16], it is desirable for parameter estimation purposes that they have the minimum number of parameters to be determined. On the other hand, the model should be adequate to describe the process under study in enough detail so that the clinically or physiologically important parameters are included.

As an example of such trade-offs consider the arterial blood vessels, the mechanical properties of which are distributed quantities Descriptions are ordinarily based upon the lumped parameter technique. A large number of segments would result in many parameters probably with strong interdependency ; a small number of segments may not represent the vessels with sufficient detail.

Considerations of bandwidth of the segments in relation to the frequency content of the pressure and flow signals and the anatomical location of side branches have produced acceptable compromises [7, 17, 18]. Sims [19, 20] followed this approach and used a ten-segment model to describe the arterial system of a dog. This model was subsequently used by Sims in the estimation of ten compliances and three peripheral resistances, making use of three pressure and two flow signals obtained from a dog. Further work by Chang [21] using a similar model showed segments with insufficient bandwidth could lead to multiple minima and thus lack of uniqueness in parameter estimation. Wesseling [22], starting from a detailed 25-segment model of the arteries of a human arm, reduced this model to four segments, without materially degrading the pressure propagation characteristics of the model and with negligible change in its input impedance. It appeared that the pressure transfer characteristics as a function of frequency approximated by Chebychev polynomials also indicates that a four-segment arm arterial model furnishes sufficient detail [23].

Besides hemodynamic behavior of arteries, mass transport by the blood stream may have to be included in some studies. Beneken and Rideout [24] described the multiple model approach which can be used for that purpose. Tilanus [25] developed criteria for the optimal segment size in such models when very high accuracy is needed, as in the representation of indicator dilution behavior.

Although most of the models are primarily set up based on time domain equations, it must be kept in mind that under certain circumstances the system being studied can also be described in the frequency domain and that also in this domain parameter estimation is possible and sometimes advantageous [26, 27, 28].

Too much detail in models may not be advisable. Thus, in cardiovascular modeling, if individual lumped-parameter segments have bandwidths far beyond the frequency content of the signals related to these segments, a unique set of parameters may be difficult or impossible to find, and interdependence of the parameters may interfere with the estimation procedure. However, proper choice of parameters may make it possible to have an adequate number of segments without a large number of dependent parameters (see Sec. 4).

Another technique of modeling, useful in parameter estimation, is the inclusion of added detail in that part of the model which is of interest. This was done successfully by Aaslid [29] who incorporated much detail in the left ventricle and arterial system and, in order to maintain the closed system properties, represented the venous and pulmonary system and the right heart in a much simpler fashion. In another example in modeling Gianunzio [30] included great detail in the renal system, which was represented by more segments than all the rest of the circulatory system. Differentiation between various aspects of renal functions has led to two successfully applied parameter estimation schemes. Rothe and Nash [31] concentrated on renal arterial properties, while Wilson *et al.* [32] indirectly determined renal blood flow using a model that dealt with compartments of the kidney involved in exchange of radioactive material.

Because of the nonlinearities and distributed nature of the systems of the body, it will be clear that no generally applicable prescription can be given for the design of models for parameter estimation. It is important, though, to incorporate as much relevant *a priori* information as possible regarding both qualitative aspects of the system and permissible ranges of parameter values Preliminary studies with the model alone may yield useful insight into such matters as *sensitivities* of variables to changes in certain parameters. Such data should in turn aid in the assigning of weighting factors in the performance index. Another useful result of such preliminary studies may be the indication of which variables which are most useful for the determination of the wanted parameters, as well as those which are not important and which may not be necessary.

4. SELECTION OF PARAMETERS TO BE ESTIMATED

Studies involving parameter estimation should be preceded by a problem definition. It should be obvious that no adequate direct means of determining the unknown quantities is available. The model will subsequently be set up such that the quantities to be determined are incorporated as parameters (or sometimes as state variables). It often happens that the model adjustment, to make its behavior similar to that of the real system, involves a larger number of parameters than needed for the problem under study. In this case relations among them may be sought to reduce the number of parameters to be estimated [21, 33]. It is often possible to reduce the model by using another system variable as a driving function (as in the example of Fig. 3).

The errors e_j, indicating the difference between the system and the model, are functions of all parameters in the model. If the performance index, built up from all e_j's, varies greatly as a result of a certain percentage change in a parameter, the sensitivity for this parameter is said to be high. When sensitivity for any parameter is low it can be set anywhere over a large range of values without much altering the model behavior ; such a parameter will be difficult to estimate with any accuracy, and if the parameter is important a different criterion, sensitive to this parameter, may have to be sought.

Thus a satisfactory performance index is a function of practically all parameters, as is its minimum. When some of the parameters are kept at the values initially guessed and the remainder are adjusted to minimize the performance index, their values may differ widely from the values attained when all parameters are optimally adjusted. In other words, estimation of only a few parameters with insufficient attention to the values of other parameters may yield quite erroneous results.

As stated above, parameter estimation makes possible the determination of parameter values that cannot otherwise be measured. This points toward another reason for the preference we have to base models on physical relationships ; this leaves open a possibility for testing the entire procedure. If a parameter estimation method using non-invasive measurements is applied to a patient, then there is no way to test the result. However, by extensive testing in animal experiments the reliability of the entire procedure, including the adequacy of the model and the accuracy of the parameter values can be evaluated when the parameters have physical meaning and can be directly measured by some (usually invasive) technique.

In cardiovascular modeling, fluid resistance R, inertance L and vessel compliance C have been popularly used, according to the following expressions (8),

$$R = \frac{81}{8} \frac{\eta l}{r^4} \tag{6}$$

$$L = \frac{9}{4} \frac{\rho l}{\pi r^2} \tag{7}$$

$$C = \frac{3 r^3 \pi l}{2 E h} \tag{8}$$

where η is the blood viscosity and ρ the blood density. Under certain circumstances, however, effective cross-sectional area, πr^2, segment length, l, and the vessel wall elasticity-thickness product $E h$, may be better selections because they are more easily measurable in the physical system [21, 33, 49].

Physical or other considerations sometimes put *constraints* on parameter values. They may be removed by introducing a « slack variable ». In the case of an inequality constraint, the slack variable may convert this in an equality constraint [34]. A simple example illustrates this : If a parameter is subject to an inequality constraint, $p \geqslant C$, where C is a constant, then introduction of a slack variable s such that

$$p = C + s^2 \qquad \text{or} \qquad p = C + e^{s} \tag{9}$$

replaces the inequality constraint by an equality. It is now possible that an optimum value of s and thus of p may be obtained.

5. SELECTION OF VARIABLES FOR USE IN PARAMETER ESTIMATION

Variables measured from the system under study may be used either as input driving functions for the model, or in the determination of the performance index based on the difference between corresponding system and model variables as indicated in Sec. 4. Furthermore, the application of specific test signals may be considered [35]. The use of a system variable as a driving function, in general, tends to eliminate the necessity for incorporating into a model that part of the system which is beyond that variable. Thus, the use of the brachial arterial pulse as a driving function for a model of the arm arteries by Wesseling *et al.* [22] eliminated the need for modeling the heart and the central arterial system while estimating arm arterial parameters. A similar idea is behind the fact that in many studies of the arterial system, the outflow pressures are assumed to be constant, thus eliminating the venous system.

A number of practical factors governs, in general, the choice of the system variables which will be used in a parameter estimation scheme

1. The existence of instrumentation and of measuring techniques for those variables which might be of interest.

2. The fact whether a test signal can or should be applied Such a test signal can be a perturbation of the entire system (an exercise test or respiration according to a prescribed pattern for lung mechanical parameters) or a test signal of foreign nature, such as a sudden injection of a radio-active tracer [36, 37, 38]. Cohen [39] refers to theoretical studies to optimize the probing signal to provide maximum sensitivity for particular parameters. He states that, in biological applications, optimal test signals are often difficult to synthesize and apply.

3. The consideration of the desirability of using non-invasive methods of measurement. Difficult trade-offs are necessary, because non-invasive measurement is seldom as satisfactory as invasive measurement. A simple example of this is in the measurement of blood pressure, which may be most accurately determined with the aid of catheters, either with a fluid-filled or tip-manometer. Non-invasive methods may be used to determine the time course [22] but the off-set and calibration may not be known, which means that additional unknown parameters must be determined in the non-invasive case. The hope is, of course, that parameter estimation will permit the otherwise inferior non-invasive methods to be used.

Blood flow may be measured by an electromagnetic flow meter, a method which is severely invasive. Blood velocity may be measured externally using an ultrasonic flow meter ; but, this leaves the vessel cross-sectional area to be determined as an unknown parameter before flow can be determined as the product of velocity and effective area. Since effective cross-sectional area is also needed for the determination of hemodynamic quantities R, L and C (Eqs. 6, 7, 8, Sec. 4), parameter estimation may contribute to non-invasive measurements of blood flow. When gated ultra-sound techniques for the measuring of velocity profiles in the blood stream become practically useful [40], they will yield blood flow *and* cross-sectional area, which constitutes the essential information for the longitudinal impedance consisting of R and L. This will improve the possibility for accurate non-invasive pressure measurements, as indicated above.

The number of variables to be measured, and the positions within the system where these measurements are made may be of considerable importance because of their effect upon performance criteria (see Sec. 7). It would be expected, in general, that the more measurements that could be made, suitably distributed throughout the system and independent of each other, the better would be the accuracy of parameter estimation; but, such advantages must be balanced against the ethical limitations and the costs of making (and properly using) large numbers of measurements

Kuwahara *et al.* [38] used a counter for radioactivity placed over the heart-region to obtain the radiocardiogram. An additional counter was placed over the subclavian veins in order to adjust two parameters by which the input signal (time course of tracer concentration going to the right heart) could be optimally matched. As a result of this, a practically unique solution was found for the total of 10 parameters that were to be estimated

In some cases, separation of one variable into two by filtering may eliminate coupling between parameters For example, mean pressures and flows may be used to calculate resistance values, while the pulsatile parts of these signals tend to be more related to compliance and inertance values

The duration of the available measurement period is an important factor in selecting the variables. In order to assure stationarity of the system one would like to rely on short measurement periods [41]. However, the variability of biological systems tends to cause much noise which prevents accurate parameter estimations [42] When the system is stationary one may use various averaging techniques on the signals and estimate parameters on the basis of averaged variables. Certain high frequency components, however, may disappear.

Transformation of signals into the frequency domain followed by parameter optimization using error criteria in the frequency domain has been successfully performed [43, 44, 26].

6. INFORMATION LIMITATIONS IN PARAMETER ESTIMATION

Reduced to its simplest form, parameter estimation is a technique for determining one set of numbers (the unknown parameter values of the system) from another set of numbers (the sampled amplitudes of the measured system variables) It might be expected that some limitation in the number of parameters which could be estimated with a given precision might be related to the number of system variable samples and their precision. Considerations based on information theory serve to give an upper bound to such limitations

Suppose, for example, that data is available for a cardiovascular system in the form of pressure and flow signals measured over a single heart period of 0.8 seconds, and that the bandwidth of these signals are limited to 10 Hz, with an assumed signal-to-noise power ratio of 44, corresponding roughly to 15 % random error or noise into measured variable amplitudes. With these assumptions the maximum number of bits of information in one cycle (of pressure or flow waves) would be

$$\begin{aligned} H &= BT \log_2 (+ S/N) \\ &= 10 X . 8 \log_2 (1 + 44) \\ &= 44 \text{ bits} \end{aligned} \quad (10)$$

by the Shannon formula [45]. If three pressures and two flows were measured (as in the work by Sims [19, 20], then a maximum of 220 bits of information might be extracted from this data. This would assume that these waves were independent of one another and that they were coded in optimal fashion, which of course they are not. In the ideal case these 220 bits could be used to determine 55 parameters with four-bit precision — i.e., to within 1/16 of their maximum value or to about 7 %.

It might be expected that the actual number of parameters which might be so determined would be much less than 55 It is interesting to mention that Sims [20] and Katz [48] each attempted to determine 13 parameters; however, some interdependence certainly existed among their parameters, as well as among their system variables. The rough calculations of the kind made above are not of much practical use except to give some very approximate upper limits on estimation. More important is that these considerations reveal that the number of bits of information is finite with an upper limit which can be roughly calculated, and thus that a decision to determine the values of more parameters from the given information will mean that each is determined with reduced precision. Conversely, if more precision is desired, fewer parameters can be determined — in our ideal case, for example, a requirement of 5 bit precision would permit a maximum of only 44 parameters, rather than 55, to be determined.

The avoidance of noise of any kind (or measurement error, which may be treated as noise) is also seen to be important However, great reduction in noise and the consequent improvement in signal-to-noise ratio may not yield the sort of advantage indicated in the expression for H above, because the « coding » is fixed by nature and is not modified to take advantage of improved S/N. Bandwidth is also important. Our assumption that pressure and waveform pulses have a spectrum extending only to 10 Hz ignores the much higher frequency sounds and murmurs which originate in and near the heart. However, it is not easy to build the more detailed models which produce such high-frequency sounds in a correct manner, and for the same reason the information they contain would be difficult to use for parameter estimation.

In those cases where a system may be regarded as linear, the notion of observability may be useful. If a given state (in the state-variable representation of a linear system) does not affect the observed outputs, then complete parameter estimation is impossible Powerful matrix methods have been developed for use in the study of observability and identifiability in linear systems [46].

7. TESTING AND SELECTION OF PERFORMANCE CRITERIA

Performance measures commonly used are integrals, over some suitable time, of some weighted term of even functions of error*. A performance index I may take the form

$$I_n = \int_{t_1}^{t_2} \sum_{i=1}^{m} K_i \, |x_i - x_i^*|^n \, dt \quad (11)$$

* In discrete-time systems, definitions and notations are different. This does not influence the reasoning in the remainder of this section.

where x_i is one of the i variables of the system, and $x_i{}^*$ is the corresponding variable in the model. The period of integration, $t_2 - t_1$, in pulsatile systems such as the respiratory or cardiovascular, is usually selected to be some small whole number of periods.

The mean squared error is rather commonly used [$n = 2$ in Eq. (10)], because some commonly used parameter estimation algorithms are based on squared error, for mathematical convenience [19, 20, 22, 26, 47]. However, different values of n have been used. Thus Katz *et al.* [48] used the absolute value criterion ($n = 1$) successfully in their estimation of 13 parameters in the canine venous system. Loeve [49] also used the absolute value criterion as did Chang [21]. Both found that the use of the absolute value criterion gave better final convergence of model parameter values to system values, in model-to-model studies. This might be expected, since studies have shown that [50] the use of an absolute-value criterion is one of the simpler schemes for emphasizing small errors in the determination of a criterion.

The weighting factors K_i in Eq. (10) are set values, chosen to incorporate *a priori* knowledge about reliability of measurements into the criterion [51, 21], or to force parameters sequentially to their optimum values [52].

When a small number of parameters is of particular interest in a certain study, it may be possible by preliminary model studies to choose variables $x_j{}^*$ for use in the criterion to make it more sensitive to changes in these parameters. By giving the corresponding K_j factors higher values than the remaining factors, a relatively higher accuracy in the determination of the selected parameters may be obtained, when adequate degree of independence exists among the parameters.

When certain parameters are time-dependent and undergo large changes in value, the amplitude and timing of which have to be estimated, then it may be advantageous to separate the integration interval into smaller intervals (windows) with separation points which correspond grossly to the instants at which these changes are expected. This creates a number of performance indices each of which is likely to be highly sensitive to changes in a limited number of parameters. This window parameter optimization has successfully been applied in an estimation study of heart muscle parameters, among which the time course of the active state of the muscle must be estimated [51]. The choice of the estimation algorithm (see Sec. 8) depends to some degree on the nature of the criterion surface as a function of the parameter values. If long valleys or false minima are expected, then more sophisticated methods may have to be applied, as opposed to the use of simple straightforward methods when the surface is regular. Fast hybrid computers are able to calculate these surfaces and when two parameters are changed at one time, then a three-dimensional image of the error criterion surface can be generated [45, 21, 33]. When large numbers of parameters are to be estimated routinely, then a preliminary study of the shape of the error criterion surface may improve the efficiency of the estimation procedure. Chang [21, 33] in particular, used a detailed study of this kind to aid in the « design » of an effective parameter estimation criterion.

To improve the efficiency of parameter optimization procedures, it seems important to have sufficient insight into the system in order to take specific properties of both the system and its model into account when selecting the performance index.

8. THE CHOICE AND TESTING OF ALGORITHMS FOR CRITERION MINIMIZATION

Many papers, reviews [2, 3, 34, 52, 53, 54] and books [55, 56, 57, 58, 59] have appeared which deal with system identification and the problem of devising efficient algorithms for the minimization of criteria in parameter estimation or optimization problems. These methods are classified in almost as many ways as there are review papers and books on this subject. However it will be useful here to consider a division of algorithms into three principal types ; search, gradient and Gauss methods. Search algorithms in turn may be of random or pattern search varieties, while gradient methods include steepest descent and Newton-Raphson procedures. Search methods are in general straightforward procedures which require only evaluations of the performance index and some information about previous data points. *Random search* is illustrated for a two-parameter case in Fig. 4 (a). Here point 1 is located at the initial estimate (or guess), and increments in parameter values p_1, p_2 are chosen from a random number table or its equivalent. The criterion is re-determined and, if its value is less, a step is made using these increments to point 2. This procedure continues until a step which gives a lower criterion value cannot be made in a certain number of trials. When this happens the step-size may be reduced by using half the value of the numbers from the random table [as at point 5 in Fig. 4 (a)]. Termination of the procedure may be chosen to occur when the minimum ratio for any parameter value to the corresponding parameter correction exceeds some chosen value. This general kind of technique, which is called « creeping random search » has certain advantages when large numbers of parameters must be estimated, and can also be used when constraints are present. Although many steps may be needed to reach a minimum, few calculations (except for the re-determination of the criterion value) are needed. Random search has been applied to studies of the circulatory system [61], the respiratory system [62] and in neurophysiology [63, 64]. Donders *et al.* [51] used random search superimposed on other methods to avoid local minima. *Pattern search* is illustrated for a two-parameter case in Fig. 4 (b). Here steps are taken of some pre-chosen value of one parameter at a time from the initial estimate at 0 to determine points of reduced criterion at l' and l''. These two increments give the new point at 2 in the parameter space. This is followed by another

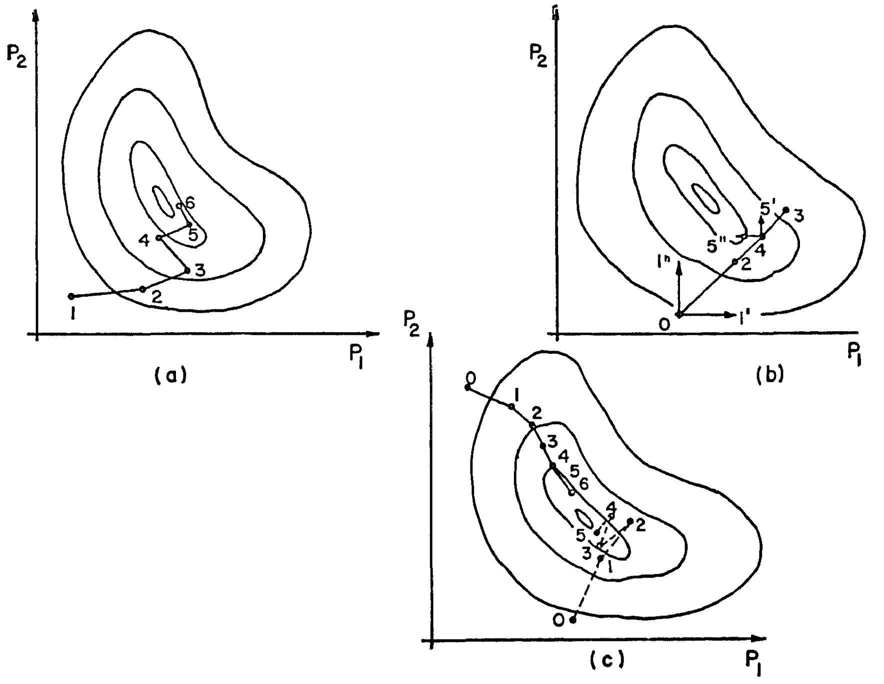


Fig. 4.

criterion determination (at 2) and a « pattern » step in the same direction to point 3. This step is kept if the criterion is further reduced, and new individual parameter tests made. If no improvement in criterion can be found, which will be the case here, step test size is halved and the same procedure followed, starting at 2, to go to point 4. Many variations of this kind of scheme have been suggested. It will in general require fewer steps than the creeping random search method described above, but for each step approximately 3 N/M times as many criterion evaluations are needed, when N is the number of parameters, and M is the average number of trials needed to achieve success in the random creep method (assuming pattern steps can be used in either case and are equally effective).

Pattern search has been used by Gatewood *et al.* [65] in blood-glucose studies and by Abbrecht *et al.* [66] in a dialysis investigation. The Hooke and Jeeves [67] pattern search strategy (see also Wilde and Beightler [55]) has been successfully applied by Loeve [49] and Chang [21, 33]. More efficient « conjugate direction » and simplex methods have been described [52].

Gradient methods require the determination of gradients, as well as the evaluation of the performance index values, in general. The gradients are expressed in terms of partial derivatives of the performance index functions with respect to the parameters. In multidimensional studies the set of first partial derivatives is called the Jacobian vector J, and that of second partial derivatives, the Hessian matrix H. *Steepest descent* methods require that the parameters be adjusted to move in a direction parallel to the local gradient vector in parameter space. Finite parameter adjustment steps ΔP may be determined using

$$\Delta P_i = -K \frac{\partial I}{\partial P_i} \qquad (12)$$

for all parameters where K is a constant. The result of using this scheme will be a smooth progression toward the optimum as shown in Fig. 4 (c), if K is not too large.

This scheme makes good progress initially, but near the optimum it proceeds slowly. More rapid optimization is possible if K is larger, up to values which result in erratice progress (as shown dotted in Fig. 4 (c)). Sophisticated schemes may be used to determine optimum values of K for use in steepest descent procedures [55].

The components $\partial I / \partial P_i$ of the gradient vector may be determined approximately by finite difference schemes in which the Δ I's corresponding to finite ΔP_i's are determined. Another scheme uses parameter influence coefficients (or sensitivity co-system) to determine the gradient vectors [3, 68]. This method may be illustrated by a simple one-parameter example in which the system is

$$\frac{dx}{dt} = \beta x + u \qquad (13)$$

and the model is

$$\frac{dy}{dt} = by + u \tag{14}$$

while the error criterion is

$$I = \int_0^T (y - x)^2 \, dt \tag{15}$$

If the error criterion is differntiated with respect to the model parameter b, there results

$$\frac{\partial I}{\partial b} = \int_0^T 2\,(y - x)\,\frac{\partial y}{\partial b}\,dt \tag{16}$$

This may be evaluated if we know the parameter influence or sensitivity coefficient $\partial y/\partial b$ This appears in the model equation (14) it is differentiated with respect to b, yielding

$$\frac{d}{dt}\left(\frac{\partial y}{\partial b}\right) = b\,\frac{\partial y}{\partial b} + y \tag{17}$$

(if an interchange of the order of integration is permissible on the left side of the equation)

Equation 17, however, is the same as the original model equation, with $\partial y/\partial b$ replacing y, and y replacing u. Thus the model, or another computer set-up identical to the model, may be used to determine influence coefficients and thus gradients. Unfortunately this scheme requires a sensitivity model for each parameter or sequential use of the same model (with some changes, particularly in nonlinear cases), and this may make it undesirable for use in cases where the number of parameters is large. The finite difference scheme may be preferable, therefore, and it may have further advantages if noise is present in the measured variables.

Newton-Raphson method. As mentioned above the steepest descent scheme has disadvantages near the minimum. A number of higher-order gradient schemes have been evolved which, directly or indirectly, make use of the curvature as well as the slope of the criterion contours. This will be illustrated by considering the Newton-Raphson procedure for a single parameter system. Assume that the criterion I is a parabolic function of b, or

$$I_n(b) = I_0 + k\,(b_n - b_0)^2 \tag{18}$$

Then

$$\frac{\partial I_n}{\partial b_n} = 2\,k\,(b_n - b_0) \tag{19}$$

and

$$\frac{\partial^2 I_n}{\partial b_n^2} = 2\,k \tag{20}$$

The correction $b_n - b_0$ to reach the minimum at I_0 in one step may now be calculated,

$$b_n - b_0 = \frac{\partial I_n/\partial X}{\partial^2 I_n/\partial X^2} \simeq \frac{(I_{n+1} - I_{n-1})\,2\,\Delta b}{(I_{n+1} + I_{n-1} - 2\,I_n)\,(\Delta b)^2} \tag{21}$$

This may be extended to the multi-parameter case by use of the Hessian matrix H of the second partial derivatives (which matrix should be positive definite, for convergence), together with the gradient vector $\nabla_b J$ The estimated stepsize then becomes :

$$\overline{b_n - b_0} = \overline{H\,(\nabla_b J)} \tag{22}$$

which becomes an iterative scheme if I is not quadratic.

Because the second partials require more work to determine than the first partials and are somewhat more affected by noise, the use of curvature methods involving second derivative determination has not been popular The advantage of such schemes that fewer steps are needed (or only a single step for quadratic functions) has led to the devising of methods which use curvature information to minimize a criterion in few steps. These include such methods as the Davidon-Fletcher-Powell method (DFP) which converge rapidly, but do not require inversion of the matrix of the second partials [52]. Although the DFP method (which is usually regarded as the best of the curvature schemes) avoids matrix inversion, it still requires matrix manipulation, and thus needs more calculations per step than simple gradient schemes.

Method of Gauss. The method of Gauss is quite different than the search and gradient techniques discussed above in that it is not based on a criterion scheme : it starts from the system and a corresponding model. The method may be explained in terms of the linear (or linearized) system

$$\frac{d\bar{x}}{dt} = \bar{B}\,\bar{x} + \bar{\mu} \tag{23}$$

and the model

$$\frac{d\bar{y}}{dt} = \overline{B^*\,y} + \bar{\mu} \tag{24}$$

Each of the m system variables x_i and m models variables y_i is sampled at r times, and it is assumed that the relationship among x_i's and y_i's is given by the first term of a Taylor's expansion in each case

$$x_i(t_j) = y_i(t_j) + \sum_{k=1}^{q} \frac{\partial y}{\partial b_k}\,\Delta b_k \tag{25}$$

where there are q parameters b_k in B These mr equations may be expressed in matrix form as

$$\begin{vmatrix} \frac{\partial y_1(t_0)}{\partial b_1} & \cdots & \frac{\partial y_1(t_0)}{\partial b_q} \\ \frac{\partial y_1(t_{r-1})}{\partial b_1} & \cdots & \frac{\partial y_1(t_{r-1})}{\partial b_q} \\ \frac{\partial y_2(t_0)}{\partial b_1} & \cdots & \frac{\partial y_2(t_0)}{\partial b_q} \\ \frac{\partial y_m(t_{r-1})}{\partial b_1} & \cdots & \frac{\partial y_m(t_{r-1})}{\partial b_q} \end{vmatrix} \cdot \begin{vmatrix} \Delta b_1 \\ \\ \Delta b_q \end{vmatrix} = \begin{vmatrix} x_1(t_0) - y_1(t_0) \\ \\ x_m(t_{r-1}) - y_m(t_{r-1}) \end{vmatrix} \tag{26}$$

or

$$\overline{B}\,\Delta\,\overline{b} = \overline{x - y} \tag{27}$$

This set, with mr equations and q unknowns may be multiplied by the transpose of B to reduce it to a set of q equations,

$$|\overline{B}^T\overline{B}|\;|\Delta b| = |\overline{B}^T|\;|\overline{x - y}| \tag{28}$$

Solution now requires inversion of a matrix of order q. This is somewhat more tedious than any of the preceding schemes, but it is a method which converges rapidly after the initial iterations which reduce the errors to a point where the Taylor series approximation is more correct. Criterion evaluation may be used as a check, and as a means to determine when iteration should cease The Marquardt [71] method uses a combination of the method of Gauss and steepest descent, the latter for starting and the former for its rapid convergence characteristics. This method is very effective and has seen much use [72, 19, 20] but requires a large digital computer for matrix inversion if the number of parameters is large.

The various criterion minimization schemes are difficult to compare, for any given application, because their speed depends upon criterion contour shapes and the level and character of noise in the data, as well as the number of parameters to be determined. Thus the matrix manipulation necessary in the use of such higher-order gradient methods as the Davidon-Fletcher-Powell method may so add to the total computer time necessary that these methods lose their advantage over simpler steepest descent methods if the number of parameters is large, particularly if the criterion has been chosen to have adequate sensitivity and no long valleys. The method of Gauss has the further disadvantage that it is tied to the use of a mean square criterion, whereas weighted absolute-value criteria, for example, may have important practical advantages.

If the data used contains noise, even the steepest descent methods may give trouble, and pattern search methods may be preferred as pointed out by Birta [53]. These methods have the advantage that since derivatives need not be determined, computer time per iteration is reduced, which may help to compensate for the larger number of iterations required.

Random creeping search [60] is a method which minimizes the computer time needed per iteration, and is proof against rather high noise levels in the data being used. These advantages, if the number of parameters to be determined is quite large, may make this method advantageous.

It is desirable that algorithms be tested and compared, as was suggested for criteria. Once again, the speed of the hybrid computer makes it desirable for such comparison, even though it might not be used for routine performance of the final parameter estimation.

9. CHOICE OF COMPUTER

Models of biological systems must be rather detailed if parameter estimation is to be used, and experience has shown that even rather simple simulations may involve long run-times on digital computers. The multiplicity of runs required in parameter estimation schemes makes this problem even more severe, and points to the analog computer as the preferred scheme for setting up a model. The digital computer is to be preferred for the implementation of parameter estimation algorithms, and thus the hybrid computer, which is a combination of analog, digital, and interface, is to be preferred over all-analog or all-digital schemes This is particularly true for the early stages of parameter estimation studies, especially if criterion surfaces must be examined. It is noteworthy that hybrid computers have been used in all large estimation studies so far reported [54, 48, 53, 19, 49, 51, 21].

Unfortunately, hybrid computers of the size needed for biological parameter estimation work are not widely available for such studies. Some efforts have been made to use all-digital methods [73, 74]. Such methods will no doubt be improved in the future, and are, of course, important because of the ubiquity of the digital type of machine Also it should be possible to use all-digital methods of parameter estimation in many cases after preliminary work has been done on a hybrid machine.

With the advent of the integrated circuit and its advantages in cost, size and reliability over older techniques, the parallel type of digital differential analyzer should become a real possibility for a machine which could be combined with an ordinary digital computer to provide an all-digital machine with the necessary speed and computing power to handle biological parameter estimation problems.

10. CONCLUSIONS

A wide range of factors, biological to computational — must be considered if large scale parameter estimation is to be successfully applied using physically-based models. The systems of concern are so complex that parameter estimation schemes cannot be as easily chosen or applied as in many engineering systems. In this paper we have stressed the point that many factors and methods must be considered, and that experimentation with these methods on both a model-to-model and an animal-to-model basis is essential. Fortunately the power of modern computers makes such an approach possible, and the great importance and constant recurrence of the systems evolved in the human body makes such approaches worthwhile. The present use of parameter estimation of the kind described here has been for research purposes. The hope for future application of these techniques to clinical uses is one which will require not only the further development of the techniques described in this paper, but also long periods of clinical testing.

LIST OF SYMBOLS

P_i, P_i^*, e_j, x_j, x_j^*

p_1, p_2, p_3, f_1, f_2, R_1, R_{s2}

L_1, L_2, C_2, R_2, q_2, q_{2u}

R_1^*, L_1^*, C_2^*, R^*, R_2^*, L_2^*, R_{s2}^*

r_1, r_2, l_1, l_2

η, l, ρ, E, h, π, p, C, s

H, B, T, S, N

I_n, m, n, K_i, x_i, x_i^*, t

N, M, β, b

J_n, J_{n+1}, b_n, b_0, I_0, H, $\nabla_b I$, $\nabla_b J$

B, B*, r

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