SENSITIVITY ANALYSIS AND PARAMETER IDENTIFICATION
FOR A MODEL OF LEFT VENTRICULAR MECHANICS AND
THE SYSTEMIC ARTERIAL LOAD

by

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ABSTRACT

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An identification scheme for the determination of several parameters associated with a third-order lumped-parameter model of the systemic arterial system has been developed previously (1). In the present study, a parameter sensitivity analysis of this model is conducted in conjunction with the identification scheme. This analysis indicates that the state variables of this system are not unduly sensitive to changes in the model parameters or initial conditions. It also indicates the relative sensitivities of the individual model parameters and provides valuable insight into the behaviour of the arterial model. This insight resulted in a significant simplification of the identification scheme (1) that makes it more likely to be employed in practice.

The arterial model mentioned above is driven by aortic root flow $f_a(t)$, and this waveform is approximated by either of two methods, one involving the measurement of left ventricular pressure, the other a measurement of left ventricular volume. Adequate specification of the model driving waveform $f_a(t)$ is very important to the identification process and, therefore, the abilities of the aforementioned methods in approximating $f_a(t)$ under practical measurement conditions are investigated.

The left ventricular mechanics for an individual patient are specified by the elastance curve in this study. Two clinical approaches, the direct and the indirect, to the estimation of left ventricular elastance are presented. A multiple
measurement technique is used to solve for end-diastolic volume in the direct problem and an approximate method for the determination of the aortic valve resistance $R_A$ is suggested for the solution of the indirect problem. A sensitivity analysis of the left ventricular model proved useful in the analysis of both approaches.
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I. INTRODUCTION

1.0 Thesis Objective

One of the goals of mathematically modeling a physical system is to reduce the description of the system to a set of meaningful parameters. In the case of biological systems, knowledge of the anatomy and physiology may allow the modeler to easily determine an equivalent block diagram of the system and to write the system describing equations. The system equations contain parameters which may be unknown or measured with extreme difficulty. Through parameter estimation techniques, values for the system parameters may be obtained.

The sensitivity of a dynamic system to variations in its parameters is one of the basic aspects in the treatment of dynamic systems. The question of parameter sensitivity arises quite naturally in many fields of engineering where mathematical models are utilized. In order to present a unique formulation of the problem, the model usually is assumed to be known exactly. Such an assumption is unrealistic since there is always discrepancy between the actual system and its mathematical model. This is due to the following reasons: (1) a real system cannot be identified exactly due to the restricted accuracy of measuring devices; (2) a theoretical concept cannot be implemented exactly because of manufacturing tolerances; (3) the behavior of any physical system changes in time; (4) mathematical models are often simplified intentionally to make the problem mathematically tractable. Thus, the results of the mathematical model may be very poor as in the case where there are considerable parameter deviations between the real system and the model, and the solution is very sensitive to changes in parameters. Therefore, it is essential to know the parameter
sensitivities of a given model.

The purpose of this thesis is to mathematically model the mechanics of the left ventricle and the systemic arterial load and to develop a clinically oriented parameter identification scheme that will estimate certain model parameters for an individual patient. The structure of each of the models is explained as is a parameter identification scheme developed previously (1). A sensitivity analysis is performed on the systemic arterial load model and the modifications of the identification scheme suggested by the results of this analysis are discussed. These modifications make the identification scheme simpler and more clinically feasible.
1.1 **Background**

1.1.1 **The Arterial Model**

The arterial tree is a many-branched elastic conduit which carries blood from the heart to the body tissues. Each vascular segment of this system can be described by three fundamental physical properties: resistance, inertance, and compliance. Resistance \( R \) arises from the friction between shearing molecules of lamina of blood flowing at different velocities through the segment. This fluid resistance is analogous to electrical resistance and is defined as the pressure drop \( (\Delta P) \) across the segment divided by the flow \( (F) \) through the segment.

\[
R = \frac{\Delta P}{F} \quad (1.1)
\]

The vessel wall also has a small resistance opposing radial distention and collapse. Inertance \( L \) results primarily from the mass of blood in the vascular segment and secondarily from the mass of the arterial wall. Inertance is equivalent to electrical inductance and is defined as the pressure drop \( (\Delta P) \) across the segment divided by the time derivative of blood flow \( \left( \frac{dF}{dt} \right) \) through the segment.

\[
L = \frac{\Delta P}{\frac{dF}{dt}} \quad (1.2)
\]

Compliance \( C \) is a property of the arterial wall arising from its distensibility and due mainly to the elastic fibers in the vascular segment. Compliance is analogous to electrical capacitance and under normal physiologic conditions is defined as the blood volume \( (V) \) within the segment divided by the transmural pressure \( \Delta P_t \) (pressure difference across the vessel wall).

\[
C = \frac{V}{\Delta P_t} \quad (1.3)
\]

The last two properties, inertance and compliance, are associated with energy storage within the system and, because a differential equation describes each, the
number of compliant and inertial elements found in the model indicates the order of the model.

Any arrangement of these physical properties must be capable of mimicking two basic characteristics of the arterial circulation to be considered an adequate model of this system. The model must be able to produce the undulations present in the arterial waveform (e.g. the dichrotic notch). Secondly, the model must have an input impedance consistent with what has been measured in man. Impedance is a function of frequency determined as the ratio of the Fourier transform of pressure to the Fourier transform of the flow at the site the pressure was recorded. Nichols, et al. (2) measured aortic root pressure and flow to calculate the input impedance to the arterial tree in man. The input impedances they produced are characteristically very high at d.c., decrease rapidly and maintain a relatively constant level at higher frequencies. The constant value attained at higher frequencies is referred to as the characteristic impedance (Z_Q).

Figure 1.1 shows a typical diastolic peripheral arterial pressure waveform and a typical input impedance for man (2).

There has been much effort in the past to model the arterial tree. In 1753, Stephen Hales (3) suggested that the systemic arterial tree was similar to the reservoir system used in early fire engines and pipe organs, which maintained a steady output flow for an intermittent driving input. Otto Frank (4) employed Hale's idea, which became known as the "windkessel theory" in his attempts to model the systemic arterial circulation. In the windkessel theory, blood is pumped in at one end of the system during ventricular ejection and stored in a reservoir, while the output through the peripheral resistance is kept relatively constant. Thus, the windkessel model consists of a parallel arrangement of a hydraulic
Fig. 1.1 Two basic characteristics of the systemic arterial tree
a) undulations in the diastolic portion of an arterial pressure
b) input impedance which does not go to zero at high frequency
compliance and a hydraulic resistance. Figure 1.2a shows the electrical equivalent of a windkessel model. Since the model is a first order system (one compliance), the pressure falls exponentially as soon as ejection is complete and there is no hope of producing the undulations in the diastolic arterial waveform. There is no attempt to account for the changes in waveform shape as the pressure pulse moves to the periphery, since only a single reservoir is assumed. The input impedance of the windkessel model at high frequencies goes to zero, a clear deviation from figure 1.1b. Westerhof et al. (5) attempted to reconcile this input impedance discrepancy by the addition of a resistance ($R_Q$) equivalent to the characteristic impedance. This model, known as the westkessel model, is shown in figure 1.2b. Though the westkessel model is capable of mimicking the input characteristics, it can not produce the undulations seen in the diastolic waveform (fig. 1.1a).

Roston (6) added another chamber to the windkessel model to account for pressure waveform differences as the pressure pulse advances to the periphery. The two compliant chambers were connected by a resistance. This second order system has two roots and one of these roots is necessary to produce the dominant diastolic exponential discharge. Since only a complex conjugate pair of roots can produce oscillations, no second order model can produce the undulations and the exponential discharge in the diastolic arterial pressure waveforms. Furthermore, the input impedance of this model tends to zero as frequency increases. Spencer and Denison (7) also presented a two chamber model (see figure 1.2c). Unlike Roston, these investigators connected the chambers of their model by an inertance, describing the inertial properties of the column of blood between the two reservoirs. Radial resistance in each chamber is accounted for by placing a
Fig. 1.2 Arterial models
resistance in series with each chamber's compliance. In this model, there is blood flow through two peripheral resistance, $R_1$ associated with the proximal chamber, and $R_2$ associated with the distal chamber. The three energy storage elements ($C_1$, $L$, $C_2$) indicate a third order system. It is well known that for a nondegenerate third-order system there are three distinct normal modes. Thus, the solutions for the diastolic arterial pressures can have a dominant exponential decay (1 mode) with a superimposed sinusoid (remaining 2 modes) to fit the characteristic undulations. The model of Spencer and Denison is a low order approximation to the actual system and cannot produce the hump at 5-6 Hz in the input impedance shown in figure 1.1b but estimates $Z_0$ fairly accurately due to the radial resistances $R_3$ and $R_4$. Goldwyn and Watt (8) used a third order model similar to the Spencer and Denison model but reduced the number of resistances to one ($R_2$). Although the Goldwyn and Watt model can produce undulations, the input impedance tends to zero at higher frequencies.

The models discussed above are all lumped parameter models. They represent the arterial load in a general sense. More detailed models, characterizing the specialized circulations, have been developed. Sims (9) modeled each section of artery with the circuit shown in figure 1.2d. His model, developed for canine studies, contained three peripheral resistances, one for the vascular bed associated with each of the three major arteries in the dog. By reducing the number of major arteries at the bifurcation of the aorta from three to two, the model becomes valid for human studies. Rideout (10) used the same model for a segment of artery as Sims and developed an analog computer model designed as an aid in teaching cardiovascular dynamics.

The model chosen for this study is a lumped third-order model similar to
Electrical Equivalent of the Arterial Model

Fig. 1.3 The electrical equivalent of the arterial model chosen in this study.
that of Goldwyn and Watt and of Spencer and Denison (see figure 1.3). The addition of the resistance $R_T$ to the Goldwyn and Watt model is significant for two reasons. The upstream pressure $P_1$ in the Goldwyn and Watt model tends to be quite oscillatory for bad choices of parameter values and the resistance $R_T$ provides a dissipative influence that helps to damp such oscillation. The resistance $R_T$ also keeps the input impedance from going to zero at higher frequencies and, in fact, is the characteristic impedance $Z_0$. The model equations are simpler and contain fewer resistive parameters than the equations for the model of Spencer and Denison. In short, the arterial model in figure 1.3 seems to be the lowest order model with the fewest number of parameters which can adequately describe the systemic arterial tree.
1.1.2 Model of Left Ventricular Mechanics

Analysis of left ventricular mechanics has been approached from two basic viewpoints; the classical muscle mechanics approach, emphasizing length, tension, and shortening velocity in an idealized cardiac muscle fiber, and a functional approach, describing the ventricle, on the whole, as an active pump. The muscle mechanics approach stems from the work of Hill (11) who proposed a model to explain the mechanical activity of skeletal muscle. Hill noted that when an isometrically contracting muscle is suddenly allowed to shorten by abrupt reduction of its load, the muscle shortens first very rapidly (related to the amount the load is reduced) and then much slower (dependent on the amount of load remaining). The model Hill devised to account for these observations is shown in figure 1.4a. The series elastic element (SE) represents the undamped elastic component of the muscle fiber which recoiled rapidly when the load was reduced. The contractile element (CE) represents the actively contracting portion of the muscle which produced the slower shortening. At rest, the CE is thought to be freely extensible so the CE-SE complex cannot support resting tension. In skeletal muscle, resting tension is trivial or absent when developed tension is maximum, but in cardiac muscle, resting tension is relatively large and therefore, a third element must be added to Hill's model in order to represent this type of muscle. Two muscle models which incorporate this third element, called the parallel elastic element (PE), are shown in figure 1.4b and c. The PE plays no role in contraction. The resting tension is supported by the PE alone in the Maxwell model (fig. 1.4b), and by the PE and SE in the Voight model (fig. 1.4c).

Sonnenblick (12) performed afterloaded isotonic experiments on isolated cat papillary muscle to determine a family of force-velocity curves shown in
Fig. 1.4: a) Hill's model of skeletal muscle, b) The Maxwell model to represent cardiac muscle, c) The Voight model to represent cardiac muscle. SE = series elastic element; CE = contractile element; PE = parallel element.
figure 1.5. Parmley et al. (13) analyzed the three models in figure 1.4 based on results from afterloaded isotonic contractions and found the $V_{\text{max}}$ (maximum shortening velocity) in all three models was relatively constant for low preload but was significantly reduced at higher preload. For isometric contractions, they found similar results except that $V_{\text{max}}$ remained constant at higher preloads with the Maxwell model. Thus, modeling error is present in figures 1.4a-c. Although studies in isolated papillary muscle provide us with an understanding of the mechanisms of muscle contraction, the extension of these results to the intact heart must be considered with some caution. Isolated preparations deprived of blood supply and the responses of electrically stimulated papillary muscles do not necessarily reflect the behavior of the intact heart. Taylor et al. (14) performed a series of experiments on closed-chest sedated dogs to evaluate the applicability of force-velocity relations in the intact heart. Instantaneous contractile-element velocity was calculated from left ventricular pressure during isovolumic contractions produced by sudden balloon occlusion of the ascending aorta during diastole. Typical force-velocity relations obtained had an inverse curvilinear relation between force and velocity. Increasing end-diastolic pressure (increased preload) shifted these curves to the right but only at high end-diastolic pressures (greater than 15 mmHg) was there a shift in $V_{\text{max}}$. Thus, the principles of isolated muscle mechanics can be extended to the intact ventricle which also demonstrates an inverse relationship between the velocity of shortening and load.

The muscle mechanics models discussed up to this point are one dimensional models. Stress is considered in only one direction, circumferential, which is adequate for skeletal muscle. In cardiac muscle, however, the stresses are three dimensional. Figure 1.6 depicts an element within the wall of the
Fig 1.5 Force-Velocity results from Sonnenblick's studies with isolated cat papillary muscle.
Fig. 1.6 Stress analysis for a three dimensional model of cardiac muscle
ventricle. Three stresses are acting on this element. Ghista and Sandler (15) developed a three-dimensional model based on figure 1.6. The analysis of such a model is complex and highly dependent on the form chosen to express the geometry of the ventricle (i.e. spherical, ellipsoidal, etc.). The idealized myocardial wall element is generally assumed to be from an equatorial slice and stresses vary considerably in elements of other slices. Furthermore, techniques for direct atraumatic measurement of ventricular wall stress, myocardial fiber length and shortening length are not currently available and must be inferred from pressure-volume measurements.

The classical muscle mechanics approach is clearly at the microscopic level, centered about the problem of describing myocardial properties. The functional approach is a more macroscopic approach considering the collective properties of the ventricle. The functional models are in the class of one-dimensional left ventricular models. Elzinga and Westerhof (16) demonstrated that the isolated heart with constant filling pressure and a given arterial load does not behave like a pressure source or a flow source (fig. 1.7a). These authors decided to model the heart as a generator with a constant generator pressure, the so-called hydro motive pressure (HMP), and a constant internal impedance ($Z_s$). Left ventricular pressure is represented by the voltage just proximal to the diode (aortic valve) (17). Their model is shown in figure 1.7b. Previously, Buoncristiani et al. (18) used a similar model, using a pure resistance as the internal impedance. Elzinga and Westerhof (16) showed that the internal impedance cannot be purely resistive. Min et al. (19) described the pumping function of the ventricle based on a Thevenin equivalent model. Their model had the same elements as figure 1.7b except that the aortic valve was placed in the load block.
a) Ideal pressure and flow source models

b) The source generator concept of Elzinga and Westerhof

Fig. 1.7 Left ventricular models
The internal source pressure concept represents one way of characterizing the left ventricle as a functional unit. An alternate way is the elastance approach. Left ventricular elastance is defined as the instantaneous pressure volume ratio in the left heart (eq. 1.4)

\[ E_{LV}(t) = \frac{P_{LV}(t)}{V_{LV}(t)} \quad (1.4) \]

Suga (20-22) has shown that this pressure-volume ratio uniquely characterizes the ventricular contractile state. Numerous authors have employed the elastance concept in their models of the left ventricle. The model of Greene et al. (23) is shown in figure 1.8. The aortic valve is characterized as an ideal diode with a series resistance. It is assumed the valve operates with no leakage and that its opening and closing is instantaneous. Deswysen (24) used a similar model but included no aortic valve resistance. Noldus (25) defined a model for the ventricle during ejection. His model had the same form as figure 1.8, but he included an inertial term in the outflow tract. Since only the ejection time period was being considered, the aortic valve can be represented as a short circuit.

Demoment (26) took a rather novel approach to the elastance characterization of the ventricle. They claimed the canine isovolumic elastance curve could be described by a quadratic expression and that a loss term proportional to the ventricular outflow could be subtracted from the isovolumic elastance to produce the ejecting elastance curve.

The left ventricular model chosen in this study is the model shown in figure 1.8. No compelling evidence was found in this literature survey which would indicate that an inertial term, such as Noldus proposes, is necessary to model the left ventricle. Many authors (Buoncristiani (18), Sims (9), Greene (23)) have found that a resistance in series with a switch is adequate to model the
Electrical Equivalent of the Left Ventricular Model

Fig. 1.8 Left ventricular model chosen in this study
ventricular outflow tract.

1.1.3 Identification Methods in Cardiovascular Modeling

A. Arterial Model Parameter Identification

Several of the arterial models described in section 1.1.2 were developed so that parameter identification techniques could be applied to them. Laxminarayan et al. (27) analyzed the frequency-response vector plot for the westkessel model (shown in figure 1.2b) to calculate total arterial compliance. Goldwyn and Watt (8) attempted to identify the three energy storage elements of their model (discussed in section 1.1). They described the brachial artery pressure during diastole by equation (1.5).

\[ P_2(t) - \alpha_1 = \alpha_2 e^{-\alpha_3 t} + \alpha_4 e^{-\alpha_5 t} \cos (\alpha_6 t - \alpha_7) \]  

The \( \alpha \) parameters were obtained from a least squares fit of patient brachial artery pressures using equation (1.5). For any given value of peripheral resistance, the model parameters \( C_1, C_2 \) and \( L \) can be calculated in terms of the \( \alpha \) parameters. Using the same model, Burrus, Parks and Watt (28) identified the Z-transform coefficients for the diastolic portion of arterial blood pressures with a technique for designing digital filters known as the Prony method. Deswysen (24) also identified the parameters of this arterial model with only the diastolic portion of an arterial pressure but he used aortic arch pressure (\( P_1 \)) rather than a distal arterial pressure (\( P_2 \)). Aortic arch pressure and aortic flow were measured and input as data in this scheme. The peripheral resistance was calculated as the ratio of mean aortic pressure and mean aortic flow. The parameters \( L, C_1 \), and \( C_2 \) are estimated along with the state variables using a nonlinear filter algorithm derived by Jazwinski (29).

Identification of the parameters of larger models is more difficult and
certain parameters are usually assumed fixed in these models. Sims (9) recorded three pressures and two flows to serve as identifying waveforms for his model discussed in section 1.1.1. The six inertial terms and the fifteen radial wall resistance terms were fixed at values obtained from the literature. The nonlinear least squares Marquardt method (30) was employed to identify the ten compliance terms and the three peripheral resistances. Chang et al. (31) recorded four pressures and two flows to identify nine parameters associated with their model. A modified Hooke and Jeeves pattern search algorithm (32) was used for minimization in the parameter estimation scheme.

The identification scheme employed in this study is a two stage procedure which identifies the parameters of the model in figure 1.3 based on the entire cycle of two arterial pressures ($P_1$ and $P_2$). This method was presented by Clark et al. (1) and is outlined below. The first stage deals with determination of initial values for the parameters of the arterial load model based on a best-fit to the diastolic portion of the distal arterial pressure ($P_2$). The parameters identified are $C_L$ (proximal compliance), $C_R$ (distal compliance), $L$ (inertance), $R_T$ (radial wall resistance in the proximal chamber) and $f(o)$ (flow through the inertial element at the beginning of diastole). The second stage of the identification scheme is an iterative nonlinear least squares method applied to the entire $P_1$ and $P_2$ waveforms for accurate determination of the load parameters.

During diastole the arterial system is unforced and is a nondegenerate third order system. Any response of the system can be given as a linear combination of three distinct modes. Thus, $P_2$ can be written as

$$P_2(t) = q_1 e^{-q_2 t} + q_3 e^{-q_4 t} \cos(q_5 t + q_6) \quad (1.6)$$
during diastole. The Z transform of this system is written as:

$$Z\{P_2(t)\} = \frac{a_0 + a_1 z^{-1} + a_2 z^{-2}}{1 + b_1 z^{-1} + b_2 z^{-2} + b_3 z^{-3}}$$  \hspace{1cm} (1.7)

Application of the Prony method (28) to this problem results in a solution for the a and b coefficients in the Z-transform representation. Since the Z-transform of the impulse response of the sampled system is equal to the Z-transform of the impulse response of the continuous system, equation 1.7 can be equated to the Z-transform of equation 1.6 and the q coefficient can be solved for. The Laplace transform of this third order system can be written as

$$\mathcal{L}\{P_2(t)\} = \frac{N_1 S^2 + N_2 S + N_3}{S^3 + D_1 S^2 + D_2 S + D_3}$$  \hspace{1cm} (1.8)

By equating (1.8) and the Laplace transform of (1.7), the N and D coefficients can be determined. The Laplace transform of the system equations is given by

$$\begin{bmatrix} P_1(s) \\ P_2(s) \\ f(s) \end{bmatrix} = \begin{bmatrix} s + R_T/L & -R_T/L & 1/C_L \\ 0 & s + 1/R_R C_R & 1/C_R \\ -1/L & -1/L & s \end{bmatrix}^{-1} \begin{bmatrix} P_1(0) \\ P_2(0) \\ f(0) \end{bmatrix}$$ \hspace{1cm} (1.9)

From equation (1.9) an expression for \(P_2(s)\) is obtained and by equating powers of \(s\) in this expression and equation (1.8), a set of nonlinear equations can be formed. This set of equations can be solved for any value of \(R_T\). A Fibonacci search method (33) is used to find the value of \(R_T\) which gives the best set of parameter
values to fit the diastolic portion of the \( P_1 \) and \( P_2 \) pressure waveforms. This best set of parameters is then input to the second stage of the identification scheme, the application of the Marquardt method described in appendix A. The Marquardt method is applied to the entire cycle of the \( P_1 \) and \( P_2 \) waveforms to adjust the model parameters \( C_L, L, C_R, \) and \( R_T \). The parameter adjustments are assumed complete and the parameter values final when two error criterion are met: 1) the relative change of all the parameter is less than 0.1 and 2) the relative change in error is less than 0.05. A block diagram of the parameter identification scheme is shown in figure (1.9).

Thomasson (34) applied the Prony method and the Marquardt method to the analysis of multicomponent exponential decay curves. He found the Prony method to be quite sensitive to noise and the Marquardt method to give good results at low noise levels. Noise in the patient data used in this study was reduced by averaging over many cycles and by application of a smoothing cubic spline. The routine used was taken from the IBM: System/360 Scientific Subroutive Package. The analog curves, being much less noisy, were smoothed by an algorithm based on error detection (35).

The total peripheral resistance, \( R_T \), is estimated from the relation

\[
R_T = \frac{\overline{P}}{Q},
\]

where \( \overline{P} \) is the mean blood pressure in the proximal brachial artery and \( Q \) is the cardiac output. The value of \( R_T \) is not adjusted during the identification procedure. The aortic valve resistance is calculated as

\[
R_A = \frac{\Delta \overline{P}}{F_S},
\]

where \( \Delta \overline{P} \) is the mean pressure difference between the left ventricular pressure and the ascending aortic arch pressure during ejection and \( F_S \) is the mean flow through the aortic valve during ejection. \( F_S \) is obtained from

\[
F_S = \frac{SV}{T_S}
\]

and \( T_S \) is the time interval of ejection. The value of \( R_A \) is also not altered during
Fig. 1.9 Block diagram of the identification scheme to estimate the parameters of the arterial model.
the parameter identification.

The initial conditions of the three state variables, $P_1$, $P_2$, and $f$ must be specified in order to solve the system equations. The initial conditions for $P_1$ and $P_2$ are data (patient pressures at the beginning of diastole) and the initial conditions for flow is given as

$$f(o) = \frac{P_2(o)}{R} + C_R P_2(o)$$

All the derivatives are calculated by finite difference equations. The integrations necessary for the Fibonacci search and for the Marquardt method are performed by a fourth-order Runge-Kutta method. In the Marquardt method, the integrations are assumed to have reached a steady state when the first point of the pressure waveforms $P_1$ and $P_2$ are within 1.5 mmHg of their last points, respectively.

B. **Left Ventricular Parameter Identification**

Identification of ventricular parameters is inherently more difficult than identification of arterial parameters because of the difficulty in measuring ventricular data such as the HMP of Elzinga and Westerhof (17) and ventricular volume. However, Elzinga and Westerhof propose a method of calculating HMP (as a function of frequency) and the source impedance $Z_s$. Two measurements of left ventricular pressure ($P_{LV_1}$, $P_{LV_2}$) and two measurements of aortic flow ($I_1$, $I_2$) are taken at different arterial loading conditions and $Z_s$ is solved for as

$$Z_s(w) = \frac{P_{LV_1}(w) - P_{LV_2}(w)}{I_1(w) - I_2(w)}$$

Min et al. (19) identified their source impedance and source pressure in an identical fashion. They induced load changes in dogs by the inflation of a balloon.
in the ascending aorta. Buoncristiani et al. (18) also used this balloon method to identify their source resistance.

Deswysen (24) included estimation of the time varying capacitance C(t) which models the left ventricle along with identification of his arterial model. In order for the nonlinear filter of Jazwinski (29) to be applied, C(t) was approximated as a third order polynomial

\[ C(t) = a_o + a_1t + a_2t^2 + a_3t^3 \]  

with \( t = 0 \) at the beginning of systole (\( a_o \) must be chosen beforehand). The coefficients \( a_1 \), \( a_2 \), and \( a_3 \) are solved for along with the model state variables using the nonlinear filter. Noldus (25) attempted to work an optimization problem to determine left ventricular elastance. The performance index Noldus employs is

\[ J = \int_0^t (p^2(t) + \alpha p(t)i(t)) dt, \quad \alpha > 0 \]  

Equation 1.13 may be interpreted as a weighted sum of the integral square ventricular pressure, and the mechanical work generated by the ventricle, during ejection. Hence, the criterion tends to minimize the mechanical work required for blood flow ejection, while at the same time it penalizes the build up of high pressure peaks. DeMond (26) estimated end-diastolic volume along with left ventricular elastance in their ventricular identification scheme. Isovolumic (nonejecting) elastance was defined as

\[ E_{iso}(t) = a(t-t_o)^2 + b(t-t_o) \]  

where \( t_o \) is the origin of time and is to be identified. Left ventricular pressure was then calculated by

\[ p(t) = (E_{iso}(t)-cq(t)) (V_o-\int_0^t q(x)dx) \]  

where \( q(t) \) is aortic flow. Aortic flow and left ventricular pressure were necessary measurements for the identification with the error criterion being the
squared error between the measured pressure and that given by equation (1.15). The parameter identification method employed was a combination of two algorithms, a local and a global method. A second order algorithm, similar to the Newton-Raphson technique, called Bonnemay's method, was used as a local method to obtain parameter values within a certain predetermined error contour. The global method then searches out the confidence intervals for the parameter solutions.

Several approaches were used in this study. Application of the Marquardt method in a formulation similar to Demoment did not prove to be very successful. The best results were obtained from a multiple measurement technique similar to Elzinga and Westerhof.
There are two different modeling problems encompassed in this study, the systemic arterial load and the mechanics of the left heart. Throughout the following chapters, a separation of these two problems is maintained. Chapter two describes the sensitivity analysis applied to the arterial load, the generation of the analog data used in the sensitivity study and the results of the analysis. In chapter three the changes in the identification scheme brought about by the results of chapter two are explained. The results of the modified scheme are shown and the case of noise corrupted input data is considered. Chapter four returns to the discussion of the ventricular problem. The left ventricular model is considered in two different approaches, dependent on the information available. The results of these approaches (referred to as the direct and the indirect case) are given in chapter four. Chapter five summarizes and discusses the results obtained in the two previous chapters.
II. SENSITIVITY ANALYSIS OF THE SYSTEMIC ARTERIAL MODEL

2.0 Preamble

Parameter identification is widely applied to biological models but sensitivity analysis in such schemes is rarely mentioned. Bekey and Grove (37) have pointed out the importance of sensitivity analysis in parameter estimation. Final parameter values may be sensitive to a variety of errors, such as (1) the system in study may involve many parameters where values must be assumed known, (2) biological systems may have great variability, (3) limited data base, that they can not be trusted.

This chapter is concerned with the development and testing of the sensitivity equations for the arterial model of figure 1.3. The sensitivity analysis is performed as part of the iterative Marquardt parameter identification scheme, and the computational aspects of this analysis are discussed in section 2.2. The sensitivity analysis is tested on simulated blood pressure data that is presented as input to the identification scheme. The simulated data utilized in this study is generated by an analog computer program of the left heart and systemic arterial load (fig. 1.3), that is capable of accurately mimicing human arterial blood pressure waveforms. The computer program for generating the simulated patient data is given in section 2.2 and the results of the sensitivity analysis are discussed in section 2.3.
2.1 Development of the Sensitivity Equations

The system equations for the systemic arterial model are

\[
\begin{bmatrix}
\dot{P}_1(t) \\
\dot{P}_2(t) \\
\dot{f}(t)
\end{bmatrix}
= \begin{bmatrix}
-R_T/L & R_T/L & -1/C_L \\
0 & -1/R_RC_R & 1/C_R \\
1/L & -1/L & 0
\end{bmatrix}
\begin{bmatrix}
P_1(t) \\
P_2(t) \\
f(t)
\end{bmatrix}
\begin{bmatrix}
1/C_L & R_T \\
0 & 0
\end{bmatrix}
\begin{bmatrix}
f_a(t)
\end{bmatrix}
\] (2.1)

where \(f_a(t)\) is aortic root flow (1/min), \(\dot{f}_a(t)\) is its derivative with respect to time (1/min²), \(P_1(t)\) and \(P_2(t)\) are the aortic root and brachial artery pressures (mmHg) and \(f(t)\) is peripheral flow through the inductance \(L\) (liters). Referring to equation (2.1) let

\[
x(\alpha,t) = \begin{bmatrix}
P_1(\alpha,t) \\
P_2(\alpha,t) \\
f(\alpha,t)
\end{bmatrix}
\] (2.2)

define the state variable vector, where \(\alpha\) represents an \(m \times 1\) parameter vector. Equation (2.1) becomes

\[
\dot{x}(\alpha,t) = A(\alpha)x(\alpha,t) + B(\alpha)u(t) = f(x(\alpha),u,t)
\] (2.3)

where

\[
A(\alpha) = \begin{bmatrix}
-R_T/L & R_T/L & -1/C_L \\
0 & -1/R_RC_R & 0 \\
1/L & -1/L & 0
\end{bmatrix}
\] (2.4)
\[
B(\alpha) = \begin{bmatrix}
I/C_L & R_T \\
0 & 0 \\
0 & 0
\end{bmatrix}
\tag{2.5}
\]

and
\[
\mathbf{u}(t) = \begin{bmatrix}
f_a(t) \\
f_B(t)
\end{bmatrix}
\tag{2.6}
\]

The forcing function \( f_a(t) \) is assumed to be independent of the parameters \( \alpha \) and to be non-zero only during the ejection phase of the systole.

The parametric sensitivity of the state \( x \) with respect to the \( k^{th} \) parameter \( \alpha_k \) is determined by taking the partial derivative of equation (2.3) with respect to \( \alpha_k \). Specifically,
\[
\frac{\partial}{\partial \alpha_k} \frac{dx(\alpha,t)}{dt} = \frac{\partial}{\partial \alpha_k} f(x,\alpha,y,t) = J_x^f \frac{\partial x}{\partial \alpha_k} + \frac{\partial f}{\partial \alpha_k} \tag{2.7}
\]

where \( J_x^f \) is a Jacobian matrix defined as
\[
J_x^f = \left( \frac{\partial f_i}{\partial x_j} \right) \quad \text{for } i,j = 1, 2, ..., n \tag{2.8}
\]

An expression for the total derivative of \( x(\alpha,t) \) with respect to time is given as:
\[
\frac{dx(\alpha,t)}{dt} = J_x^a \frac{d\alpha(t)}{dt} + \frac{\partial x(\alpha,t)}{\partial t} \tag{2.9}
\]

where \( J_x^a = \left( \frac{\partial x_i}{\partial \alpha_j} \right) \quad i = 1, 2, ..., n \) and \( j = 1, 2, ..., m \) \tag{2.10}

Since the parameters in this case are time invariant, the term \( \frac{d\alpha(t)}{dt} \) is zero, and therefore, \( \frac{dx}{dt} \) may be replaced by \( \frac{\partial x}{\partial t} \) in the left hand side of (2.7). Changing the order of differentiation and rearranging terms one obtains
If the \( k \)-th state trajectory sensitivity vector is defined as

\[
\xi^k = \frac{\partial x}{\partial \alpha_k}
\]  

(2.12)

then (2.11) may be rewritten as

\[
\frac{\partial \xi^k}{\partial t} = J_x^f \xi^k + \frac{\partial f}{\partial \alpha_k}
\]  

(2.13)

In this case, \( J_x^f = A(\alpha) \) and

\[
\frac{\partial f}{\partial \alpha_k} = \frac{\partial A(\alpha)}{\partial \alpha_k} x + \frac{\partial B(\alpha)}{\partial \alpha_k} u
\]  

(2.14)

Substituting those expressions into (2.13) yields

\[
\dot{\xi} = A_x^\alpha \xi + \frac{\partial A}{\partial \alpha_k} x + \frac{\partial B}{\partial \alpha_k} u
\]  

(2.15)

For the problem at hand, let

\[
\alpha = \begin{bmatrix} C_L \\
C_R \\
L \\
R_T \\
R_R \end{bmatrix}
\]  

(2.16)

and therefore, the five trajectory sensitivity vectors \( \xi^k \) are:
\[
\dot{x}_1^{(1)} = A \dot{x}_1^{(1)} + \begin{bmatrix} 0 & 0 & 1/C_L^2 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} x + \begin{bmatrix} -1/C_L^2 & 0 \\ 0 & 0 \\ 0 & 0 \end{bmatrix} u \tag{2.17}
\]

\[
\dot{x}_2^{(2)} = A \dot{x}_2^{(2)} + \begin{bmatrix} 0 & 0 & 0 \\ 0 & 1/R_R C_R^2 & -1/C_R^2 \\ 0 & 0 & 0 \end{bmatrix} x \tag{2.18}
\]

\[
\dot{x}_3^{(3)} = A \dot{x}_3^{(3)} + \begin{bmatrix} R_T/L^2 & -R_T/L^2 & 0 \\ 0 & 0 & 0 \\ -1/L^2 & 1/L^2 & 0 \end{bmatrix} x \tag{2.19}
\]

\[
\dot{x}_4^{(4)} = A \dot{x}_4^{(4)} + \begin{bmatrix} -1/L & 1/L & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} x + \begin{bmatrix} 0 & 1 \\ 0 & 0 \\ 0 & 0 \end{bmatrix} u \tag{2.20}
\]

\[
\dot{x}_5^{(5)} = A \dot{x}_5^{(5)} + \begin{bmatrix} 0 & 0 & 0 \\ 0 & 1/R_R^2 C_R & 0 \\ 0 & 0 & 0 \end{bmatrix} x \tag{2.21}
\]

where the system matrix \( A \) is given by (2.4). Equations (2.17-2.21) are recognized as belonging to a system having the same system matrix \( A \) as the original system, but is forced by linear combinations of the state (\( x \)) and input (\( u \)) vectors. A signal flow diagram showing the simultaneous solution of all trajectory sensitivity functions is given in figure (2.1).
Fig. 2.1 Flow diagram of the calculation of the parameter sensitivities.
Equation (2.15) may also be used in the calculation of the state sensitivities to the initial conditions for the state variables. The parameter vector $\alpha$ can now be written as

$$
\alpha = \begin{bmatrix}
P_1(\alpha) \\
P_2(\alpha) \\
f(\alpha)
\end{bmatrix}
$$

(2.22)

Since $\frac{\partial A}{\partial \alpha_k}$ and $\frac{\partial B}{\partial \alpha_k}$ are zero in this case equation (2.15) reduces to

$$
\dot{\xi}(k) = A\xi(k)
$$

(2.23)

Thus, the state sensitivities to the initial conditions are of the same form as the original system equation unforced.
2.2 Computational Aspects of the Sensitivity Analysis

Numerically, the equations of state (equation 2.1) are solved first using a 4th order Runge-Kutta integration scheme. The resultant state vector \( \mathbf{x}(t) \) and the system input vector \( \mathbf{u}(t) \) are then supplied to the vector differential equations (2.17-2.21), which are solved sequentially using the same Runge-Kutta integration method to yield the five trajectory sensitivity vectors \( \xi^{(k)}(t) \), \( k = 1, 2, \ldots, 5 \). The initial conditions \( \xi^{(k)}(t_0) \) may be set equal to zero, and the solution iterated over several heart periods to obtain the steady state solution. Alternatively, more suitable initial conditions may be employed based on knowledge of the solution, to minimize the number of iterations required to achieve steady state. The initial condition sensitivities (equation 2.23) are solved using the following set of initial conditions:

- initial condition \( P_1(0) \): \( \xi^6(t_0) = (1 \ 0 \ 0)^T \) (2.24)
- initial condition \( P_2(0) \): \( \xi^7(t_0) = (0 \ 1 \ 0)^T \) (2.25)
- initial condition \( f(0) \): \( \xi^8(t_0) = (0 \ 0 \ 1)^T \) (2.26)

The system model, the sensitivity equations and the parameter estimation method discussed in section 1.1.3 were programmed on a Digital Equipment Corporation PDP 11-34 computer.

The sensitivity functions plotted in chapter three are actually relative sensitivities \( S \) defined according to the expression

\[
S \frac{\alpha_k}{\alpha_k} = \left( \frac{\alpha_k}{x_i(t)} \right) \frac{\partial^3 x_i(t)}{\partial \alpha_k \partial \alpha_j} \quad i = 1, 2, 3 \quad j = 1, \ldots, 5
\] (2.27)

where \( \alpha_k \) is the nominal value of the parameter and \( x_i(t) \) is the nominal solution for the \( i^{\text{th}} \) state variable. Such a definition allows one the opportunity to
compare easily the relative change in a given state variable in response to changes in the various model parameters. The average power sensitivity for the \( k^{th} \) parameter is defined as

\[
P_p = \frac{1}{T} \int_0^T \frac{\partial P_1(t)}{\partial a_k} f_a(t) \, dt
\]  

(2.28)

where \( T \) is the ejection time period.

Simulated patient data for use in the sensitivity analysis were generated by programming the left ventricular elastance model and the systemic arterial load model described in section 1.1.1 on an Electronic Association Incorporated (EAI) MINIAC analog computer. The circuit diagram for the analog computer is shown in figures 2.2a and 2.2b. A timer drives a variable diode function generator which was programmed to approximate the left ventricular elastance curve from patient G.M. (see (1) for patient data acquisition). The elastance curve multiplies the left ventricular volume curve to produce a left ventricular pressure curve (figure 2.2a). An atrial source pressure is set by a pot setting and a limiter (#1) is used to allow input flow only when the atrial pressure exceeds the ventricular pressure. Similarly, the output flow occurs only when left ventricular pressure exceeds the aortic arch pressure. Limiter #2 provides this condition. Left ventricular volume is the result of integrating the input and output flow difference. The output flow is used to drive the arterial model (figure 2.2b).

The resulting pressures, \((P_{LV}, P_1, P_2)\) are reasonable good fits to those of patient G.M. The analog waveforms of left ventricular pressure and volume, aortic root flow and the arterial pressures \( P_1 \) and \( P_2 \) were sampled at a rate of 1.25 KHz using the A/D channels of a Digital Equipment Corporation PDP 11-03 Minc computer and stored on disk for later analysis.
Fig. 2.2 a) Circuit diagram for the ventricular model
Analog Circuit

Arterial Load

Fig. 2.2 b) Circuit diagram for the arterial load
2.3 **Results of the Sensitivity Analysis**

In figure 2.3, the results of a sensitivity analysis performed in conjunction with the iterative two stage identification scheme described in chapter three are shown. The input pressure data to the identification scheme are obtained from digitized records of the data from the analog computer model discussed in section 2.2. The nominal solution for the distal pressure $P_2(t)$ is shown in figure 2.3a along with the relative sensitivity functions $S_{C_L}^P$, $S_{C_R}^P$, and $S_L^P$ (see equation 2.28). As the iterative identification proceeds, the sensitivity of $P_2$ with respect to $C_L$ remains essentially unchanged (e.g., figure 2.3b (after 9 iterations) and figure 2.3c (after 18 iterations)). The relative sensitivities $S_{C_L}^P$ and $S_L^P$, however, increase as a better fit is obtained to the measured distal pressure waveform $P_2(t)$ (see figures 2.3b and 2.3c). The increase in sensitivity is also reflected in the parameter identification where parameters $L$ and $C_R$ are varied to a greater extent than $C_L$. The conclusion is drawn that the Prony starter method discussed in section 1.1.3 provides a good nominal value for $C_L$, and that this proximal compliance is dominant during diastole. In figure 2.3d, the relative sensitivity of $P_2$ to changes in the resistance parameters $R_T$ and $R_R$ are shown at the final (18th) iteration of the Marquardt identification method. The scale changes should be noted in comparing figures 2.3 a-c with figure 2.3d. Clearly, the magnitude of $S_{R_R}^P$ has a relatively low value and is significant only during the systolic period of the cardiac cycle.

Similar plots of the relative sensitivities of central aortic pressures $P_1(t)$ to changes in the parameters are shown in figures 2.4a and 2.4b. In figure 2.4a, the relative sensitivities $S_{C_L}^{P_1}$, $S_{C_R}^{P_1}$, and $S_L^{P_1}$ are plotted for the final Marquardt iteration. Note that the sensitivities $S_{C_R}^{P_1}$ and $S_L^{P_1}$ are less than the corresponding
Figure 2.3 Sensitivity of $P_2$ to $C_L, C_R, L$ at iterations a) 1 b) 9 c) 18 and d) to $R_R$ and $R_T$ at iteration 18
Figure 2.4 Sensitivities of $P_1$ to a) $C_L, C_R, L$ b) $R_R, R_T$ and of $f$ to c) $C_L, C_R, L$ and d) $R_R, R_T$ at iteration 18
sensitivities for $P_2$, namely $S_{P_2}^{C_R}$ and $S_{P_2}^{L}$ given in figure 2.3c. In figure 2.4b, the sensitivities $S_{R_1}^{P_1}$ and $S_{R_1}^{P_1}$ are shown and may be seen to be quite similar in shape to the sensitivities $S_{R_2}^{P_2}$ and $S_{R_2}^{P_2}$ shown in figure 2.3d. Again, $S_{R_1}^{P_1}$ is significant only during diastole.

In figure 2.4c and 2.4d, the relative sensitivity of the peripheral flow $f(t)$ to changes in the various parameters are shown. The peripheral flow waveform is complicated and has strong oscillatory components; similarly the relative sensitivity function tend to be oscillatory. In a relative sense, the parameters $C_R$ and $L$ are shown to be sensitive parameters (figure 2.4c) while in figure 2.4d, $S_{R_T}^{f}$ appears to be more sensitive in the systolic portion of the cycle and $S_{R_T}^{f}$ has a much smaller mean value over the cycle than that calculated for the pressure sensitivities $S_{R_R}^{P_1}$ or $S_{R_R}^{P_2}$ (figures 2.3d and 2.4b).

Table 2.1 indicates the average power sensitivities of the five load parameters as defined by equation (2.25). As is expected, the resistive parameters $R_R$ and $R_T$ affect the power dissipated in the load much more than any of the energy storage elements. The peripheral resistance $R_R$ is the most sensitive parameter with respect to power calculation, as figure 2.4b indicates.

The sensitivities of the state variables to the initial conditions $P_1(o)$, $P_2(o)$ and $f(o)$ at iteration 18 are shown in figure 2.5a-c. It is evident that $P_2(t)$ is most sensitive to the choice of initial conditions. These results are consistent with the other state sensitivity plots in which $P_2(t)$ is the most sensitive state variable and $P_1(t)$ and $f(t)$ are rather insensitive.
Figure 2.5 Sensitivities of a) $P_1$, b) $P_2$ and c) $f$ to the initial conditions $P_1(0)$, $P_2(0)$ and $f(0)$
<table>
<thead>
<tr>
<th>Iteration</th>
<th>$C_L$</th>
<th>$R_T$</th>
<th>$L$</th>
<th>$C_R$</th>
<th>$R_R$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.232469</td>
<td>1.721720</td>
<td>0.018908</td>
<td>0.009963</td>
<td>18.359101</td>
</tr>
<tr>
<td>9</td>
<td>-0.005947</td>
<td>2.759660</td>
<td>0.106633</td>
<td>-0.066096</td>
<td>17.537403</td>
</tr>
<tr>
<td>18</td>
<td>0.243850</td>
<td>3.001480</td>
<td>0.142359</td>
<td>-0.156855</td>
<td>17.378810</td>
</tr>
</tbody>
</table>

Table 2.1 Average Power sensitivities
III. **MODIFIED IDENTIFICATION SCHEME AND ITS APPLICATION TO THE ARTERIAL LOAD MODEL**

3.0 **Preamble**

The results of the sensitivity analysis proved to be very useful in evaluating the parameter identification scheme discussed in section 1.1.3. Several possible modifications of this scheme became quite obvious after analyzing the results presented in chapter two. This chapter discusses the specific modifications in the identification algorithm and shows the results of applying the modified scheme to simulated and actual patient data.

The accuracy of the identification algorithm is quite dependent on adequate specification of the input driving function to the arterial load model. This problem is studied in some detail in this chapter where the input driving function is represented by two different mathematical expressions; one derived for the case when left ventricular pressure is used as data for the identification scheme, the other for the case when left ventricular volume is used. In this chapter, the results of utilizing the modified identification scheme are shown for each model input driving function, and practical considerations associated with specifications of these waveforms in a clinical setting are discussed.
3.1 Modifications of the Identification Scheme

In the identification scheme discussed in section 1.1.3, an iterative procedure (Fibonacci search) was used to obtain a nominal value of the parameter \( R_T \) to establish initial values for the parameters \( C_L, C_R, \) and \( L \) to be input to the Marquardt method. The results of the sensitivity analysis indicate that \( R_T \) is not a sensitive parameter during the diastolic phase of the cardiac period. Thus, the Fibonacci search (which operates on the diastolic portion of the arterial waveform) is meaningless. Upon investigation, it was found that any reasonably choice for \( R_T \) in the range of \( 0 < R_T < 2 \) mmHg min/1 will allow the Prony method to provide suitable nominal values for \( C_L, C_R, \) \( L \) and the initial condition for peripheral flow \( f(o) \). A value of \( R_T = 0.5 \) was used in the present study to provide a nominal value for \( R_T \).

The sensitivity analysis also indicates that changes in the model parameter values influenced the waveform of \( P_2(t) \) to a greater extent than that of \( P_1(t) \). This is reflected particularly in the relative sensitivity function \( S_{C_R}^{P_2}(t) \) and \( S_L^{P_2}(t) \) in figure 2.3c compared with similar sensitivity functions in figure 2.4a and in figure 2.5b where the initial condition sensitivities are quite oscillatory compared with figure 2.5a and c. Thus, \( P_2 \) is a better identifying waveform than \( P_1 \) for this system; this leads quite naturally to the question of whether or not a reasonably good approximation to the aortic arch pressure \( P_1 \) could be obtained by using only a single pressure measurement \( P_2(t) \) as input to a modified identifications scheme. The block diagram of such a scheme is shown in figure 3.1, and a modified identification scheme is discussed in greater detail below.

Figure 3.2 shows the fit to the simulated input data after 18 iterations of
Fig. 3.1 Block diagram of the modified identification scheme
Proximal Aortic Pressure (P1), Distal Arterial Pressure (P2)

2 Pressure Identification $P_LV$ Driven

Figure 3.2
2 Pressure Identification – fa Driven
<table>
<thead>
<tr>
<th>Input Pressures to Identification Scheme</th>
<th>Driving Function</th>
<th>Parameter</th>
<th>Values</th>
<th>RMS Reconstruction Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual Analog Settings</td>
<td>-----</td>
<td>$C_L$</td>
<td>$0.1250 \cdot 10^{-2}$</td>
<td>$0.7610 \cdot 10^{-4}$</td>
</tr>
<tr>
<td>$P_1$ and $P_2$</td>
<td>$P_{LV}$</td>
<td>$C_R$</td>
<td>$0.12477 \cdot 10^{-2}$</td>
<td>$0.68945 \cdot 10^{-4}$</td>
</tr>
<tr>
<td>$P_2$ only</td>
<td>$P_{LV}$</td>
<td>$L$</td>
<td>$0.12194 \cdot 10^{-2}$</td>
<td>$0.68934 \cdot 10^{-4}$</td>
</tr>
<tr>
<td>$P_1$ and $P_2$</td>
<td>$f_a$</td>
<td>$R_T$</td>
<td>$0.12451 \cdot 10^{-2}$</td>
<td>$0.78873 \cdot 10^{-4}$</td>
</tr>
<tr>
<td>$P_2$ only</td>
<td>$f_a$</td>
<td>$P_1$</td>
<td>$0.12846 \cdot 10^{-2}$</td>
<td>$0.72371 \cdot 10^{-4}$</td>
</tr>
<tr>
<td>$P_1$ and $P_2$</td>
<td>$\dot{v}_{LV}$</td>
<td>$P_2$</td>
<td>$0.12540 \cdot 10^{-2}$</td>
<td>$0.78361 \cdot 10^{-4}$</td>
</tr>
<tr>
<td>$P_2$ only</td>
<td>$\dot{v}_{LV}$</td>
<td>$P_2$</td>
<td>$0.12621 \cdot 10^{-2}$</td>
<td>$0.97508 \cdot 10^{-4}$</td>
</tr>
</tbody>
</table>

$R_R = 0.13769 \cdot 10^{+2}$ for all cases

Table 3.1 Parameter values from various identification runs
$L$ - mmHg.min.min/min
$C_R,C_L$ - 1/mmHg
$R_T$ - mmHg.min/min
the Marquardt identification method, using two input pressures $P_1$ and $P_2$; the model is driven by aortic root flow $f_a(t)$ approximated by the expression

$$f_a(t) = \frac{P_{LV}(t) - P_1(t)}{R_A}$$  \hspace{1cm} (3.1)$$

where $P_{LV}(t)$ is the left ventricular pressure, and $P_1(t)$ the aortic arch pressure. $R_A$ represents the aortic valve resistance. The identification runs using equation (3.1) as the expression for $f_a(t)$ are referred to as $P_{LV}$ driven, whereas those using the analog aortic root flow as input are termed $f_a$ driven. (It should be noted that in either the $P_{LV}$ driven or the $f_a$ driven case, the input vector $u$ is $(f_a(t), f_a(t))^T$ as given in equation 2.1). The fits are indeed very good as expected in this model to model check. Essentially the same results are obtained if the model is driven by the aortic root flow waveform $f_a(t)$ from the analog computer model data, and two pressures ($P_1$ and $P_2$) are used as input to the identification scheme (figure 3.3 and table 3.1). Furthermore, figure 3.4 shows the predictions to the $P_1$ and $P_2$ waveforms generated by the modified identification scheme (figure 3.1) where the model is driven by aortic root flow $f_a(t)$ (equation 3.1) and only $P_2$ is used as input to the identification scheme. In this last case, the value of $R_A$ was set to the actual value used in the analog simulation (0.667 m mHg min/l). Again, using the analog generated aortic root flow $f_a(t)$ and, this time, only $P_2$ as input to the identification good fits are obtained as shown in figure 3.5. Table 3.1 may be consulted for a comparison of the relative rms reconstruction errors encountered in using these various modifications to the identification scheme on simulated data. As might be expected, the fit obtained in figure 3.4 and 3.5 is not as good as that obtained using both pressures $P_1$ and $P_2$ as input to the identification
1 Pressure Identification - $P_{LV}$ Driven

Figure 3.4
1 Pressure Identification - fa Driven

Figure 3.5
scheme; nevertheless, a reasonably good prediction to $P_1$ is obtained. This statement holds true for prediction to actual patient data (patients G.M. and G.S.) shown in figures 3.6 and 3.7 wherein the model is driven by $f_a$ given by equation (3.1) and $P_2(t)$ is the only input to the identification scheme. These fits compare very well with the two pressure identification fits obtained in Clark et al. (1), (figs. 3 and 4) and thereby indicate the feasibility of the modified identification scheme in a clinical setting.
patient G.M.

1 Pressure Identification - $P_{LV}$ Driven

Figure 3.6
patient G.S.

1 Pressure Identification - $P_{LV}$ Driven

Figure 3.7
3.2 **Representation of the Model Driving Function**

In animal experiments, one may utilize an electromagnetic flow probe to obtain a reasonably accurate measurement of aortic root flow $f_a(t)$, which may subsequently be used as a driving waveform for the arterial model. The identification scheme may then be applied using either $P_2$ alone, or both $P_1$ and $P_2$, to estimate the parameters of the arterial model in figure 1.3. On the other hand, in human subjects undergoing cardiac catheterization for diagnostic purposes, this method is not feasible. An estimate of $f_a(t)$ may be obtained, however, by taking a time derivative of a left ventricular volume curve $V_{LV}(t)$, during the ejection phase of the systolic period, i.e.,

$$f_a(t) = -\frac{dV_{LV}(t)}{dt} \quad (3.2)$$

Here the left ventricular volume measurements may be obtained via x-ray cineventriculography (38), or by a composite left ventricular time-activity curve obtained with a scintillation camera or a cardiac probe after intravenous injection of technetium-99m albumin or labeled red blood cells (39). The latter technique is very desirable from the standpoint that it is truly noninvasive. Recently, interest has been expressed in employing the left ventricular time-activity curve to estimate other parameters associated with the left ventricle (40). There are however, practical problems that influence the accuracy of such a method. Since the noninvasive aspects of the nuclear medicine technique are so desirable, a modeling study of this problem was conducted to understand the limitations of using the time-derivative of left ventricular volume ($V_{LV}$) as a driving waveform for the arterial model in this identification scheme.

A major difficulty with the use of $V_{LV}$ is that the ventricular volume curve is corrupted to a significant degree by measurement noise. In the case of
radionuclide ventricular time-activity curves, the noises may be adequately characterized as a Poisson process (41). With $V_{LV}(t)$ corrupted with measurement noise, a numerical filtering scheme must be used in approximating the derivative relationship in equation (3.2) if the model is to have a reasonably noise-free input driving function. If the idealized noise-free case is considered first and the derivative of the left ventricular volume curve obtained from the analog simulation is used as a forcing function, very good results are obtained in predicting the arterial pressures $P_1$ and $P_2$, when either two pressures or only $P_2$ are used as input to the identification scheme. This is shown in figures 3.8 and 3.9 as well as in the last two rows of table 3.1 (note that in both the two pressure and the one pressure cases the rms reconstruction error is relatively small). The sampling frequency was 125 Hz in this case.

Figure 3.10a indicates a simulated left ventricular time-activity curve that has been corrupted by Poisson-distributed measurement noise. This simulated volume curve and the volume curves referred to in table 3.2 were generated by first sampling the analog volume curve at 24 msec intervals (41.7 Hz), and then corrupting the sampled data with a Poisson noise process (appendix B). The effective signal to noise ratio (S/N) of the corrupted waveform in figure 3.10a is 43.7. The derivative of this noisy signal is shown in figure 3.10b ($f_a(t)$ no filtering). Clearly, this nonfiltered waveform is not a good approximation to the noise-free $f_a(t)$ and will not produce good results if it is used as the forcing function in the identification scheme. Some form of filtering is necessary to obtain a better approximation to the noise-free $f_a(t)$ waveform.

In order to determine the characteristics of a low pass filter that can reduce the noise in the corrupted volume curve, a fast Fourier transform (41) was
2 Pressure Identification – $\dot{V}_{LV}$ Driven

Figure 3.8
1 Pressure Identification - $\dot{V}_{LV}$ Driven

Figure 3.9
used to obtain the frequency domain representation of the noise-free volume curve (figure 3.11 $V_{LV}(f)$ noise-free). Since there is not much frequency information above 10 Hz, this seems like a reasonable cutoff frequency for a low pass filter. A 31 point finite impulse response (FIR) digital filter was designed using the methods of McClellan and Parks (42). The passband for this filter was specified to be 0.0-7.2 Hz and the stopband region to be 16.00-80.00 Hz which straddles the desired 10 Hz cutoff frequency. The coefficients for the filter and other specifications in the design are given in appendix C. The frequency domain representation of the filter is shown in figure 3.11.

The filtered $f_a(t)$ waveform in figure 3.10b is a much better approximation to the ideal $f_a(t)$ waveform. After the filtered $f_a(t)$ is fit with a natural cubic spline (43) and sampled at 8 msec intervals (125 Hz), it is used to drive the arterial model. The analog $P_2(t)$ waveform is used as input data, and the unknown proximal aortic waveform $P_1(t)$ is estimated very well as seen in figure 3.10c. An even better fit would be expected if measurements of both pressures are employed in the identification scheme. When this identification process is repeated for ventricular volume waveforms having different noise content (indicated by different S/N ratios), the effect of measurement noise on the accuracy of the identification scheme becomes obvious. The trends are shown in table 3.2.

In practice, ventricular volume waveforms are not as noisy as depicted in this modeling study (fig. 3.10a), and in fact, the 31 point low-pass FIR filter may be adequate for most clinical cases. In these studies, the filter yielded a good $f_a(t)$ driving waveform for the identification scheme for S/N ratios above 27. This filter is by no means unique or optimal for the problem; however, it has a nearly flat passband and a relatively sharp transition to the reject band, so it could not be replaced by an arbitrary low pass filter.
Figure 3.10 a) Noise corrupted volume curve b) aortic root flow c) predicted $P_1$ pressure waveform
Fig. 3.11 Frequency domain analysis of the simulated volume curve and of the 31-point digital filter (see text)
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<th>RMS Reconstruction Error</th>
<th>Parameter Value (predictions from identification runs on noise corrupted volume waveforms)</th>
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\( R_r = 0.1379 \times 10^{-2} \) for all cases.
IV. Modeling the Mechanics of the Left Ventricle

4.0 Preamble

This chapter is concerned with the discussion of methods that attempt to characterize the mechanics of the left ventricle of individual patients undergoing clinical testing. In clinical practice, there are two commonly used approaches to the assessment of ventricular mechanics; a direct, invasive approach, and an indirect, noninvasive approach. The former utilizes the procedures and techniques common to the modern cardiac catheterization laboratory (37,42) and it will be discussed first.

In the previous study by Clark et al. (1), a data acquisition scheme was developed wherein pressure waveforms at three anatomical sites (brachial artery, ascending aorta and the left ventricle), left ventricular volume and electrocardiographic data could be obtained routinely from patients undergoing cardiac catheterization. From this type of data, systolic ventricular elastance, for example, can be determined directly. The aforementioned study (1) pointed to an intriguing possibility; namely that a reasonably accurate model prediction of the systolic portion of the left ventricular volume curve could be obtained using only pressure measurements and a measurement of cardiac output (C.O.). With regard to figure (1.8) this would mean that if \( P_{LV} \), \( P_1 \) and C.O. are measured a reasonably accurate approximation to aortic valve resistance \( R_A \) may be computed according to the expression

\[
R_A = \frac{\Delta P}{f_a}
\]

where \( \Delta P \) is the average pressure difference between \( P_{LV} \) and \( P_1 \) during systole.
and $f_a$ is the average aortic root flow during systole. In earlier studies, cardiac output was determined via x-ray cineventriculography while in the present study, it is assumed to be specified by available methods such as a separate venous catheter measurement that utilizes a thermodilution principle (43,44) or a non-invasive nuclear medicine study (45). Instantaneous aortic root flow ($f_a(t)$) during systole may be calculated according to

$$f_a(t) = \frac{P_{LV}(t) - P_1(t)}{R_A} \quad (4.2)$$

while left ventricular volume is given by

$$V_{LV} = V_{ed} - \int_{t_o}^{t} f_a(t) \, dt \quad (4.3)$$

Here $V_{ed}$ is the volume at end-diastole. Since the aortic valve resistance $R_A$ may be determined with reasonable accuracy from the measurements of $P_{LV}$, $P_1$ and C.O., the single unknown parameter in this direct approach is $V_{ed}$. If it is known, the mechanics of the left ventricle during systole may be characterized in terms of the ventricular elastance curve ($E_{LV}(t)$) given in equation (1.4).

The second approach is called the indirect case in that ideally, indirect noninvasive measurements are utilized to assess the mechanics of the left ventricle of an individual patient. The objective in this case is to determine left ventricular pressure ($P_{LV}(t)$) from indirect measurements of $V_{LV}(t)$ and $P_1(t)$. Aortic root flow $f_a(t)$ may be determined by differentiating the left ventricular volume curve, since from the model equations associated with figure 1.8.
Rearranging equation (4.2), the following expression is used to calculate $P_{LV}(t)$:

$$f_a(t) = -\frac{d}{dt}V_{LV}(t) \quad (4.4)$$

$$P_{LV}(t) = P_1(t) + R_A f_a(t) \quad (4.5)$$

Thus, in the indirect approach, $V_{ed}$ is specified in the measurement of $V_{LV}(t)$ and the single unknown parameter is $R_A$. If it can be accurately estimated, then, theoretically, a ventricular elastance curve $E_{LV}(t)$ may be generated to characterize the mechanics of the ventricle.

This approach, however, has severe practical difficulties that center about the accuracy of the indirect measurements of the primary hemodynamic variables $V_{LV}(t)$ and $P_1(t)$. Left ventricular volume may be obtained non-invasively using nuclear medicine techniques (section 3.2), but with an estimated accuracy of only $\pm 10-12\%$ (46). A peripheral arterial blood pressure waveform may be determined indirectly, for example, by using a Doppler ultrasonic method to measure brachial artery wall movements during deflation of a pneumatic cuff placed around the arm. By plotting cuff pressure versus the time between the R wave of the ECG and the artery opening signal, the rising phase of the arterial pulse is obtained; by plotting cuff pressure versus time between the R wave and the artery closing signal, the falling phase of the arterial waveform can be determined. Multiple inflations and deflations of the cuff are required to obtain a sufficient number of data points to reconstruct the entire pulse pressure waveform. Descriptions of the technique were presented by Ware and Laenger (47) and Kardon et al. (48).
The accuracy of this technique depends heavily on the constancy of heart period and minimization of body movement relative to the ultrasonic procedure. Furthermore, the pressure that is measured is the distal arterial pressure $P_2(t)$, rather than the central aortic pressure $P_1(t)$ required by the equation (4.5) for determining $P_{LV}(t)$. However, it was shown in section 3.2 that given accurate measurement of $V_{LV}(t)$ and $P_2(t)$, a good estimate of the aortic root pressure $P_1(t)$ can be produced by the parameter estimation algorithm. Significant measurement error would of course seriously degrade the model-generated prediction to $P_1(t)$.

In view of the current measurement limitations discussed above, the ideal indirect approach to the assessment of ventricular mechanics is considered non-feasible as a routine clinical testing procedure. If the objective of this approach is modified to allow a single pressure measurement via an arterial puncture, then this modified indirect approach becomes much more feasible. For example, if the tip of an arterial catheter is placed at the root of the aorta, $P_1(t)$ may be measured with very little error. If in addition, $V_{LV}(t)$ is measured by nuclear medicine techniques and $R_A$ estimated, a reasonable estimation of $P_{LV}(t)$ may be obtained via equation (4.5). If the arterial catheter is placed so as to record distal blood pressure $P_2(t)$, a reasonable estimate of $P_1$ may be obtained using the parameter estimation scheme (section 3.2) as was mentioned previously.

In this chapter, the direct and indirect approaches are explored in greater detail. Section 4.1 presents the method of Demoment and Hinglais which was briefly mentioned in section 1.1.3. A technique for solving the direct problem by making multiple measurements of the physiologic data is discussed in section 4.2. Finally, an approximate method for the solution of the indirect problem is presented in section 4.3.
4.1 The Method of Demoment and Hinglais

The method of solution for the direct problem proposed by Demoment and Hinglais (26) was discussed briefly in section 1.1.3. Their reasoning is based somewhat on anthropomorphic considerations: when the ventricle contracts it does not "know" if the aortic valve will open and therefore the shape of the elastance curve should be the same at least for the initial isovolumic period of contraction, whether ejection occurs or not. The shape of the non-ejecting elastance curve differs in the vicinity of its maximum from the elastance for a normal ejecting beat (Suga (20), (21)). This difference is due to the influence of the systemic load, and therefore, systolic elastance, as it is usually defined, is not an intrinsic quantity. Demoment and Hinglais claim that a good left ventricular model should present a structure independent of the inputs. They assume that the intrinsic quantity of the left ventricle is isovolumic elastance and that it can be represented by

$$\alpha(t) = A(t-t_0)^2 + B(t-t_0)$$  \hspace{1cm} (4.6)

where \(t_0\) is introduced to solve offset problems associated with data collection. This equation is then extended to the case of an ejecting ventricle by the addition of a loss term proportional to ventricular outflow. The equation for the model is therefore written as

$$P_{LV}(t) = (A(t-t_0)^2 + B(t-t_0) - C f_a(t))(V_{ed} - \int_o^t f_a(t)dt)$$  \hspace{1cm} (4.7)

Demoment and Hinglais recorded left ventricular pressure and aortic root
**Figure 4.1** Application of the method of Demoment and Hinglais to the simulated patient data
flow in dogs to serve as an input to an identification scheme used to estimate $A$, $B$, $C$, $V_{ed}$ and $t_0$. The performance index for this scheme was the squared difference between the recorded left ventricular pressure and the model-generated left ventricular pressure given by equation (4.4). The identification procedure consists of two algorithms; a local method (similar to the Newton-Raphson technique but without the calculations of second derivatives) called Bonnemay's which method, locates a point within an acceptable error contour, and a global method which probes the position and nature of the uncertainty domains to obtain confidence intervals for the parameters.

There are several problems that arise from this approach. The results Demoment and Hinglais report (26, Table 3) are somewhat puzzling. Table 4.1 shows the confidence intervals for the estimated parameters in five dogs. The values obtained for $V_{ed}$ are, in general, quite high for the 20-30 kilogram dogs used in the experiments. Furthermore, the confidence intervals for $V_{ed}$ are very large, sometimes over 30 mL. These results could not be considered adequate to specify the ventricular mechanics of dog with any certainty. Aside from the rather poor results in table 4.1, the particular form assumed for the ventricular elastance function (a quadratic function of time) is inadequate for the characterization of the elastance function for humans. For example, figure 4.1 shows the results of applying this form for the ventricular elastance to the simulated patient data discussed in section 2.2. The isovolumic portions of the analog elastance curve are fit in a least squares sense with a quadratic to generate the isovolumic elastance (Eiso). The best least squares fit to the ejecting portion of the elastance curve is calculated using equation (4.8).
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Table 4.1 Values shown in table 3 ref. (26) for the confidence intervals
D_o is the stopping error criterion for the local search, V_o is the end-diastolic volume
A bar above a parameter indicates the upper boundary of the confidence interval, a bar below indicates the lower boundary
\[ E_{LV}(t) = E_{iso} - C_{fa}(t) \]  \hspace{1cm} (4.8)

As can be seen in figure 4.1, the calculated elastance is a very poor fit to the true elastance. Demoment and Hinglais' figures are also in question. Figure 4.2a shows the isovolumic elastance curve and the ejecting elastance curve obtained by carefully digitizing the figures of Demoment (26, fig. 3, 4). The difference between the isovolumic elastance and the ejecting elastance is plotted in figure 4.2b along with the aortic root flow waveform. The dissimilar time courses of the two curves indicate that the loss term is not proportional to aortic root flow as assumed by Demoment.

The reasoning that the isovolumic elastance is the intrinsic quantity of the ventricle and that the ejecting elastance differs from isovolumic elastance by a loss term appears to be sound. However, characterizing the isovolumic elastance by a quadratic form is not adequate for human elastance curves. From figure 4.3 it can be seen that the isovolumic portions of the dog elastance curve can be fit by a quadratic but this is not the case in the human. Also, assuming that the loss term is proportional to the ventricular output flow has no physiologic basis and this is a point of concern. The shoulder in the ejecting portion of the human elastance curve cannot even be approximated with a loss term proportional to aortic root flow (fig. 4.1). Other nonphysiologic terms such as \( f_a(t)V_{LV}(t) \) and \( f_a(t)V^2_{LV}(t) \) were tested to try and specify the loss term but these were also unable to produce the shoulder in the human elastance curve.

Since an alternative loss term could not be specified appropriately, another approach was taken by modifying equation (4.7). In this case, the ejecting elastance curve is characterized by a sixth order polynomial. Thus, the new
Figure 4.2 a) Digitized isovolumic and ejecting elastance from (26, fig. 3, 4) b) comparison of measured aortic root flow and the differences in the curves in a)
Figure 4.3 Comparison of systolic elastance in dog and man
equation for $P_{LV}(t)$ was written as

$$P_{LV}(t) = (\sum_{i=0}^{6} a_i t^i) (V_{ed} - \int_0^t f_a(t) dt)$$

(4.9)

The Marquardt method described in appendix A was used in a parameter identification scheme to estimate the $a_i$ and $V_{ed}$. Since $a_0$ is given by $P_{LV}(t_0)/V_{ed}$, there are six $a$ parameters and $V_{ed}$ to solve for. This formulation leaves too much freedom to fit the left ventricular pressure $P_{LV}$. With a given set of initial parameter values, the algorithm adjusts the $a$ parameters to reduce the error between the model $P_{LV}$ and the data $P_{LV}$, leaving $V_{ed}$ virtually unchanged. This approach did not yield acceptable results and was also abandoned.
4.2 Multiple Measurement Technique

The method of Elzinga and Westerhof (17) used to determine the source impedance in their ventricular model (see section 1.1.2B) provides a simple procedure for determining ventricular mechanics. The idea behind this approach is to make two measurements of the physiologic data at different arterial load settings. Min et al. (19) inflated a balloon from a catheter in the ascending aorta to produce such load changes. A basic assumption in this technique is that the ventricular contractile state does not change with a change in the arterial load. With balloon inflation, this assumption is valid for only the first four or five heart cycles in the intact heart, before neural feedback to the heart influences ventricular contractility. Mathematically, the equations for the two measurements are written as

\[
E_{LV}(t) = \frac{P_{LV}(t)}{V_{LV}(t)} 
\]

\[
E'_{LV}(t) = \frac{P'_{LV}(t)}{V'_{LV}(t)} 
\]

where \( \cdot \) indicates the second measurement (elastance \( E_{LV}(t) \) is the same in equations (4.10) and (4.11) by the assumption).

This multiple measurement technique is not useful in the indirect case where ventricular volume is obtained from a nuclear medicine study. Nuclear medicine data collection requires several minutes to accumulate enough scintillation counts to generate an acceptable left ventricular volume curve. If data acquisition is begun upon inflation of a balloon in the aorta, ventricular contractility will change during the data collection and this violates the basic
assumption in the technique. Therefore, the multiple measurement method is limited to the calculation of $V_{ed}$ in the direct approach.

In the direct case, substitution of equation (4.3) and equating equations (4.10) and (4.11) produces

$$P_{LV}(t)(V_{ed} - S'(t)) = P'_{LV}(t)(V_{ed} - S(t)) \quad (4.12)$$

where $S(t) = \int_0^t f_a(t)dt$ and $S'(t) = \int_0^t f'_a(t)dt$. Solving for $V_{ed}$ results in

$$V_{ed} = \frac{P_{LV}(t)S'(t) - P'_{LV}(t)S(t)}{P_{LV}(t) - P'_{LV}(t)} \quad (4.13)$$

To test the two measurement method, a load change in the arterial model was simulated on the analog computer by increasing the peripheral resistance $R_R$ from the control setting (14.25 mmHg min/l) to a higher value (21.366 mmHg min/l). The measurements from the control setting ($P_{LV}, P_1$) were carefully time aligned with the measurements from the altered load setting ($P'_{LV}, P'_1$). Only one measurement of cardiac output is necessary since the aortic valve resistance $R_A$ is assumed constant (in equation 4.1). Equation (4.13) is valid for any time point during the ejection period under both load conditions and therefore it was solved at numerous time points with the final value for $V_{ed}$ taken to be the average of all the solutions. The value obtained for $V_{ed}$ was 152.1 ml which is in good agreement with the actual value of 148.654 ml. The resultant fit to the simulated elastance curve is shown in figure 4.4. Even though the estimation of $V_{ed}$ was fairly accurate, the calculated elastance deviated from the actual elastance curve indicating $V_{ed}$ must be a sensitive parameter in the calculation of elastance.
Figure 4.4 Fit to the simulated systolic elastance using $V_{ed}$ as calculated by the multiple measurement technique (eq. 4.13)
A sensitivity analysis of the left ventricular model was conducted to test the sensitivity of left ventricular elastance to the model parameters $V_{ed}$ and $R_A$. Elastance can be written as a function of both $R_A$ and $V_{ed}$:

$$E_{LV}(t) = \frac{P_1(t) + R_A f_a(t)}{V_{ed} - S(t)}$$

(4.14)

The sensitivities can be calculated directly from equation (4.14) by taking partial derivatives with respect to $V_{ed}$ and $R_A$. In figure 4.5a and b the relative sensitivities (equation 2.27) of left ventricular elastance to $V_{ed}$ and $R_A$ are plotted. The sensitivity of $V_{ed}$ is seen to be large in magnitude at the beginning of ejection and grows larger as time proceeds; whereas the sensitivity to $R_A$ is very small during the entire ejection period. The results of figure 4.5a are consistent with figure 4.4. The fit to the actual elastance curve grows progressively worse as ejection proceeds (due to the increased sensitivity to $V_{ed}$). The sensitivity analysis indicates that the multiple measurement method must be carried out carefully (i.e. data from both load conditions acquired without a change in ventricular contractility and accurate time alignment of the data records) to produce acceptable results in the calculation of $V_{ed}$ for the direct problem.
Figure 4.5 Sensitivity of ejecting elastance to a) $V_{ed}$ b) $R_A$
4.3 **Estimation of Aortic Valve Resistance**

In section 4.2, it is shown that left ventricular elastance is insensitive to the aortic valve resistance $R_A$. This result raises the question of how well a nominal guess of $R_A$ in the indirect problem would serve in fitting the elastance curve. Figure 4.6 shows a family of curves produced from the simulated patient data with different values for $R_A$. Elastance is calculated by equation (1.4) where $P(t)$ is given by equation (4.5) and $f_a(t)$ by equation (4.4). The control value is 0.667 mmHg min/l, the analog setting for $R_A$ and -50% (0.333 mmHg min/l), -75% (0.167 mmHg min/l), 50% (0.999 mmHg min/l) and 100% (1.333 mmHg min/l) variations were used. As can be seen in figure 4.6, even the elastance calculated with a 100% deviation from the actual $R_A$ value is a fairly good fit to the measured elastance. The same test was applied to patient data (G.S.) where the left ventricular volume curve was obtained from cineangiographic data and $P_1$ was obtained from catheterization data. Figure 4.7 displays these results. The actual value of $R_A$ as calculated by equation (4.1) is 0.4202 mmHg min/l and the deviations tried were -50% (0.210 mmHg min/l), -75% (0.105 mmHg min/l), 50% (0.630 mmHg min/l), 100% (0.840 mmHg min/l). Again the calculated elastance in all cases is a reasonable fit to the measured elastance.

The indirect approach to calculating left ventricular elastance requires a measurement of left ventricular volume which if obtained by nuclear medicine technique is corrupted by measurement noise (see section 3.2). To determine the influence on elastance of a noisy volume curve with different values of $R_A$, a filtered noise-corrupted volume curve discussed in section 3.2 ($S/N = 43.7$) is used to calculate left ventricular elastance. In figure 4.8, the resulting family of curves is shown. The $R_A$ variations are the same as those in figure 4.6. The
Figure 4.6 A family of elastance curves calculated from different values of $R_A$.
Figure 4.7 Elastance curves calculated with patient data and variations of the parameter $R_A$
calculated elastance curves have a rounded off peak but are still reasonable fits to the data. Finally, the case is considered where the ventricular volume curve is obtained by a simulated nuclear medicine study and $P_1(t)$ (in equation (4.5)) is the prediction to the aortic arch pressure produced using the parameter identification algorithm with only a peripheral arterial pressure as input (see section 3.2 figure 3.10c). Using the same noise-corrupted volume curve as in figure 4.8, a family of elastance curves with variations of $R_A$ is plotted in figure 4.9. The time courses of the calculated elastance curves differ from the time course of the actual data especially in the peak area but the fits are still reasonable. The results of this study indicate that a nominal choice of $R_A$ for the indirect approach to calculating left ventricular elastance is acceptable especially if the choice lies within a range of ± 50% of the actual $R_A$ value.
Figure 4.8 Elastance curves calculated from filtered noise-corrupted volume waveform using different variations of $R_A$.
Figure 4.9 Elastance curves calculated using predicted $P_l$ (from $l$ pressure identification) and filtered noise-corrupted volume curve with variations of $R_A$. 
V. DISCUSSION AND CONCLUSIONS

5.1 The Arterial Model

In this study, sensitivity analysis and parameter identification techniques were used in conjunction with a model of left ventricular mechanics and the systemic arterial circulation in order to estimate certain model parameters for an individual patient in a clinical setting. The research was divided into two modeling problems, the systemic arterial load and the left ventricular mechanics, and these were analyzed separately. The sensitivity analysis conducted on the modified "windkessel" model of the systemic arterial circulation demonstrated that the state variables of the system $P_1(t)$, $P_2(t)$ and $f(t)$ are not especially sensitive to changes in the model parameters, or to their initial conditions. In a relative sense, the state variables are found to be most sensitive to the peripheral resistance $R_P$, and the proximal compliance $C_L$ (e.g., note figure 2.3 c and d). It should be noted that these parameters yield the highest mean values for the computed relative sensitivities shown in these figures. These parameters ($R_P$, $C_L$) may also be seen to be the dominant parameters during the diastolic period. On the other hand, the inertance ($L$) and the peripheral compliance ($C_R$) were found to be most sensitive to the dynamic aspects of the waveform, particularly during systole and the time period coincident with the appearance of the dicrotic notch in the $P_1$ and $P_2$ waveforms (see figure 2.3 c). The proximal resistance $R_T$ yields a relative sensitivity that is significant only during the systolic period (e.g., figure 2.3 d). This latter result proved quite important for it allowed the search for an appropriate initial value of $R_T$ (Fibonacci search) utilized previously in reference (1) to be eliminated; this afforded a major simplification of the two-stage identification scheme.
A modified identification scheme that utilizes either two input arterial pressures \(P_1\) and \(P_2\), or only one \(P_2\), is also discussed in this study and is tested on simulated data via an appropriate analog computer model (figure 2.2 a and b). In this modified identification scheme the equivalent network model of the arterial system is driven by aortic root flow \(f_a(t)\) and its derivative \(f_a'(t)\). Aortic root flow can be specified in two ways, either with left ventricular pressure \(P_{LV}(t)\) as a given measurement in the form of equation (4.2) or with left ventricular volume as a given measurement in the form of equation (4.4).

Since \(P_{LV}(t)\) can be measured more accurately than \(V_{LV}(t)\), it would represent the best choice of a driving waveform for the network model. However, a catheter must be placed into the left ventricle for this measurement. Determining \(f_a(t)\) by taking the time derivative of a left ventricular time-activity curve is an attractive approach, since ventricular volume can be measured non-invasively in this manner. A radiopharmaceutical (e.g., Tc-99m) is administered intravenously and multiple time-gated blood pool images are formed. Available techniques for measuring left ventricular volume are inherently less accurate than those for measuring blood pressure due in part to the measurement noise that is added. Nevertheless, the modeling studies performed in chapter three indicate that with a sufficiently high S/N ratio, practical digital filters can be designed to yield a good approximation to the aortic flow waveform \(f_a(t)\). This waveform may in turn be used to drive the equivalent network of the arterial system. With a single distal arterial pressure waveform as input, the modified two-stage identification scheme may be used to obtain good fits to both the proximal and distal arterial pressures \(P_1\) and \(P_2\).
5.2 The Ventricular Mechanics Model

The ventricular mechanics for an individual patient was assumed to be specified by the elastance curve in this study. The derivation of a patient's left ventricular elastance was divided into two cases dependent on the type of data available. In the cardiac catheterization lab, accurate measurements of blood pressures and cardiac output can be made directly with the use of appropriate catheters. Given left ventricular \((P_{LV})\) and ascending aorta \((P_1)\) pressure recordings and cardiac output, elastance during ejection may be completely specified if end-diastolic volume \((V_{ed})\) is known. \(V_{ed}\) is a diagnostically significant parameter and x-ray cineangiography is a common technique used in the cath lab to obtain values for left ventricular volume (and hence \(V_{ed}\)). It is, however, a relatively inaccurate measurement technique and, since there is a well-recognized danger to the patient with multiple injections of radio-opaque dye, it is usually employed only once on an individual patient to determine \(V_{LV}(t)\).

In section 4.2, an alternate technique was proposed to calculate \(V_{ed}\) which employed only direct measurements, taken twice, each from different arterial load conditions. In the cath lab, a multiple catheter with two solid state pressure transducers (positioned on the catheter so \(P_{LV}\) and \(P_1\) can be recorded simultaneously) and a distal balloon port to alter resistive load conditions is placed in the patient. A venous catheter is placed so that cardiac output can be measured by a thermodilution technique. The balloon is then inflated in the lower aorta and \(P_{LV}\) and \(P_1\) are once again recorded. The end-diastolic volume can then be calculated by equation (4.13).

Although this method utilizes only direct measurements, exact specification of the elastance function is difficult due to the high sensitivity of
elastance to $V_{ed}$. This was demonstrated by figure 4.5 a. In order to ensure a good estimation of end-diastolic volume and thus elastance, the second set of measurements must be made immediately after balloon inflation to prevent any neural feedback effects on the ventricular mechanics (which render this technique useless) and the two sets of measurements must be carefully time aligned.

There are several advantages of calculating $V_{LV}(t)$ via a model prediction rather than by cine-ventriculography. The multiple measurement technique discussed in section 4.2 allows for rapid calculation of $V_{ed}$ (equation (4.13)) and, thus, $V_{LV}(t)$ (equations (4.2) and (4.3)) whereas processing of cine-ventriculograms is a very slow and tedious procedure. Also, numerous determinations of $V_{LV}(t)$ are possible with the multiple measurement technique and, as pointed out above, are not practical with cine-ventriculography. This would be beneficial, for example, in exercise testing of ventricular mechanics and for following changes in $V_{LV}(t)$ over time in intensive care unit patients who often have cardiac catheters indwelling for constant monitoring.

Cardiac catheterization is a useful procedure because direct measurements of some of the hemodynamic variables may be made, but it is unpleasant for the patient because of its invasive nature. Currently, there is a trend toward developing non-invasive measurement techniques for clinical diagnosis. The ideal non-invasive approach for identification of left ventricular mechanics requires an indirect measurement of both left ventricular volume and of a central arterial pressure measurement ($P_1$). The feasibility of this approach is discussed at length in section (4.0) and the conclusion is reached that, at the present time, indirect measurement of these hemodynamic variables cannot be made with sufficient accuracy to render the indirect approach a viable measurement technique.
It is of interest, however, to consider an intermediate method which would require an arterial puncture but may be useful in current clinical practice. For example, in the case where left ventricular volume is calculated from a nuclear medicine study and a peripheral arterial pressure is recorded from a catheter placed in a major peripheral artery (i.e. brachial or femoral), a patient's left ventricular mechanics can be specified if a value for aortic valve resistance $R_A$ is known. In section (4.3) it was shown that the sensitivity of elastance to $R_A$ is very small (figure 4.5 b) and that large deviations of $R_A$ from the actual value still produce acceptable elastance curves (figures 4.6 and 4.7). These results indicate that an average value might be used for $R_A$ to yield reasonable curves for $E_{LV}$ and $P_{LV}$. This suggests that a future study must be made wherein left ventricular pressure, ascending aortic pressure and cardiac output are recorded and $R_A$ calculated from equation (4.1) for patients assumed to have normal aortic valves (the ventricular model is valid only for individuals with good valves). The average value of $R_A$ would then be normalized to body surface area for the individual patient undergoing testing. The study in section 4.3 showed that even with a noise corrupted volume waveform and an approximation for $R_A$, this method produces adequate results. Clearly this method for the determination of ventricular mechanics via a quasi-indirect measurement technique is only an approximate method.

There are clinical situations which may require an indwelling arterial catheter and thus present an excellent opportunity to apply this quasi-indirect technique. Often, a patient will return from open-heart surgery with a peripheral arterial catheter in place to regularly measure mean arterial blood pressure. The management of such post-operative patients would be enhanced by the periodic determination of their ventricular mechanics by the approximate method described above.
VI. APPENDICES

Appendix A. The Marquardt Method

An important special case of objective functions to be minimized is the sum of the squares of a set of functions. Let \( y_m(\alpha, t) \) be the model output (a function of the model parameters \( \alpha \) and of time; \( \alpha = (\alpha_1, \alpha_2, \ldots, \alpha_m)^T \)). An error function can be specified as

\[
e(\alpha, t) = y^*(t) - y_m(\alpha, t) \quad (A.1)
\]

where \( y^*(t) \) is measured data. In discrete form, an error vector can be written as

\[
e(\alpha) = (e_1(\alpha, t_1), e_2(\alpha, t_2), \ldots, e_n(\alpha, t_n))^T \quad (A.2)
\]

The objective function is then

\[
E(\alpha) = \frac{1}{2} e^T e \quad (A.3)
\]

which is minimized by setting the partial derivatives of \( E(\alpha) \) with respect to \( \alpha \) to zero.

\[
\frac{\partial E(\alpha)}{\partial \alpha} = 0 \quad (A.4)
\]

\[
\frac{\partial E(\alpha)}{\partial \alpha} = \frac{\partial}{\partial \alpha} \left( \frac{1}{2} e^T(\alpha)e(\alpha) \right) = \left( \frac{\partial e(\alpha)}{\partial \alpha} \right)^T e(\alpha) \quad (A.5)
\]

Let \( J(\alpha) = \left( \frac{\partial e(\alpha)}{\partial \alpha} \right)^T \) (m x n Jacobian matrix) whose m rows are assumed to be linearly

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independent, then

\[ \frac{\partial E(\alpha)}{\partial \alpha} = J(\alpha)e(\alpha) \quad (A.6) \]

Gauss noticed that if \( e(\alpha) \) was a linear function of \( \alpha \) then the Jacobian matrix does not change from one point \( \alpha \) to the next \( \alpha + \Delta \alpha \). Thus, he suggested the gradient \( \frac{\partial E(\alpha)}{\partial \alpha} \) be approximated as

\[ \frac{\partial E(\alpha + \Delta \alpha)}{\partial \alpha} = J(\alpha)e(\alpha + \Delta \alpha) \quad (A.7) \]

Expressing \( e(\alpha + \Delta \alpha) \) with first order terms of the Taylor series expansion

\[ e(\alpha + \Delta \alpha) = e(\alpha) + \left( \frac{\partial e}{\partial \alpha} \right) \Delta \alpha \quad (A.8) \]

Combining equation (A.7) and equation (A.8)

\[ \frac{\partial E(\alpha + \Delta \alpha)}{\partial \alpha} = J(\alpha)(e(\alpha) + J^T(\alpha) \Delta \alpha) \quad (A.9) \]

To satisfy equation (A.4)

\[ J(\alpha)e(\alpha) + J(\alpha)J^T(\alpha) \Delta \alpha = 0 \quad (A.10) \]

Since the rows of \( J(\alpha) \) are assumed to be linearly independent and \( (J(\alpha)J^T(\alpha))^{-1} \) exists, the correction which drives all components of the gradient to zero is given by
\[ \Delta \alpha = -(J(\alpha)J^T(\alpha))^{-1}J(\alpha)e(\alpha) \] (A.11)

If Gauss' quadratic approximation is poor, the procedure will behave erratically because of the unwarranted extrapolation. Levenberg (49) proposed a modification which prevents steps far out of the region where the Gauss approximation is still reasonable. The strategem is to find where Gauss' approximation would predict a minimum on a hypersphere of radius \( r \), chosen small enough to prevent leaving the range of validity for the quadratic approximation. Thus, \( E(\alpha) \) is minimized subject to the constraint

\[ |\Delta \alpha|^2 = r^2 \] (A.12)

Utilizing the Lagrange multiplier technique, the augmented objective function for the problem is

\[ L(\alpha) = E(\alpha) - \frac{\lambda}{2}(|\Delta \alpha|^2 - r^2) \] (A.13)

where \( \lambda \) is a Lagrange multiplier.

\[ \frac{\partial L(\alpha)}{\partial \alpha} = \frac{\partial E(\alpha)}{\partial \alpha} - \lambda \Delta \alpha \] (A.14)

Thus, \( \Delta \alpha = -(J(\alpha)J^T(\alpha) - \lambda I)^{-1}J(\alpha)e(\alpha) \) (A.15)

In order to improve the numerical aspects of the computing procedure, scaling can be employed. Let
\[ A = (a_{ij}) = J(\alpha)J^T(\alpha) \quad (A.16) \]

and,
\[ b = (b_i) = J(\alpha)e(\alpha) \quad (A.17) \]

then,
\[ A^* = (a_{ij}^*) = \frac{\sqrt{a_{ij}}}{\sqrt{a_{ii}a_{jj}}} \quad (A.18) \]

and,
\[ b^* = \frac{b_i}{\sqrt{a_{ii}}} \quad (A.19) \]

Now,
\[ \Delta \alpha^* = (A^* + \lambda I)^{-1}b^* \quad (A.20) \]

so that,
\[ \Delta \alpha = \frac{\Delta \alpha^*}{\sqrt{a_{ii}}} \quad (A.21) \]

The variation of \[ \alpha \], which alters the method from a gradient (large \( \lambda \)) to a Gauss-Newton (small \( \lambda \)) method, is controlled as follows:

1) if \( E(\lambda_{i-1}/s) < E_{i-1} \) then \( \lambda_i = \lambda_{i-1}/s \)

2) if \( E(\lambda_{i-1}/s) > E_{i-1} \) and \( E(\lambda_{i-1}) < E_{i-1} \) then \( \lambda_i = \lambda_{i-1} \)

3) if \( E(\lambda_{i-1}/s) > E_{i-1} \) and \( E(\lambda_{i-1}) > E_{i-1} \) then \( \lambda_i = \lambda_{i-1}s \)

where \( s > 1 \)

A flow diagram of the Marquardt method is shown in figure (A.1) for the one pressure identification scheme.
Figure A.1 A flow diagram of the Marquardt method applied to the pressure identification problem.

- **E** is the previous error
- **E1** is the current error
- **α** is the parameter vector
- **P1, P2, f** are model solutions
- **P** is data
- **λ** is the Levenberg adjustment parameter

Initial guess α

$\text{INDEX } = T$

Solve Model Equations

$P_1 = F(\alpha, P_1, P_2, f, \alpha)$

$P_2 = F(\alpha, P_1, P_2, f, \alpha)$

$f = F(\alpha, P_1, P_2, f, \alpha)$

$e = (P_2 - P_1)$

$E_1 = e^2$

Calculate Jacobian

Solve:

$(JJ^T)\Delta \alpha = -JE_1$

$\alpha = \alpha + \Delta \alpha$

Solve Model Equations

$E = E_1$

$E_1 = e^2$

If $E_1 > E$

$\lambda = \lambda \times S$

$\alpha = \alpha - \Delta \alpha$

If $E_1 > E$

$\lambda = \lambda \times S$

$\alpha = \alpha - \Delta \alpha$

$\text{INDEX } = T$

If $E_1 > E$

Stop

If $E_1 \leq E$

$\lambda = \lambda / S$

$\alpha = \alpha - \Delta \alpha$

$\text{INDEX } = F$

If $\text{INDEX } = T$

Repeat

If $\text{INDEX } = F$

Stop

If $\text{final } \alpha$

Stop
Appendix B. Noise Considerations

The measurement noise in a ventricular volume curve obtained by radionuclide counting is characterized by a Poisson distribution (e.g., (40)). An expression for the probability \( P \) of obtaining \( n \) decays given that the mean number of decays is \( \lambda \), may be written as

\[
P(n; \lambda) = \frac{\lambda^n e^{-\lambda}}{n!}
\]  

(B.1)

If \( x_k = \ln \{u_1, u_2, ..., u_k\} \) where \( u_k \) is a random number uniformly distributed between 0 and 1, then the smallest \( k \) for which \( x_k > -\lambda \) will be a random variable having a Poisson distribution with mean \( \lambda \) (50). In the problem at hand, volume curves of different signal-to-noise ratios (S/N) were generated by arbitrarily scaling the analog volume curve to an appropriate number of counts, corrupting the scaled curve with Poisson distributed noise as described above, and then rescaling the noisy curve.

The signal-to-noise ratios were calculated as the rms value of the uncorrupted volume curve divided by the rms difference between the corrupted and uncorrupted volume curves.
Appendix C. Filter Specifications

FINITE IMPULSE RESPONSE (FIR)
LINEAR PHASE DIGITAL FILTER DESIGN
REMEZ EXCHANGE ALGORITHM

BANDPASS FILTER

FILTER LENGTH = 31

**** IMPULSE RESPONSE ****
H( 1) = 0.11592434E-02 = H( 31)
H( 2) = 0.54956129E-03 = H( 30)
H( 3) = -0.20108132E-02 = H( 29)
H( 4) = -0.52407002E-02 = H( 28)
H( 5) = -0.47554905E-02 = H( 27)
H( 6) = 0.27871081E-02 = H( 26)
H( 7) = 0.14016423E-01 = H( 25)
H( 8) = 0.17838469E-01 = H( 24)
H( 9) = 0.35020220E-02 = H( 23)
H(10) = -0.26315747E-01 = H( 22)
H(11) = -0.49279522E-01 = H( 21)
H(12) = -0.33776160E-01 = H( 20)
H(13) = 0.37494514E-01 = H( 19)
H(14) = 0.14797674E+00 = H( 18)
H(15) = 0.24987362E+00 = H( 17)
H(16) = 0.29128414E+00 = H( 16)

LOWER BAND EDGE 0.0000000 0.2000000
UPPER BAND EDGE 0.0900000 0.5000000
DESIRED VALUE 1.0000000 0.0000000
WEIGHTING 1.0000000 1.0000000
DEVIATION 0.0010773 0.0010773
DEVIATION IN DB 0.0093521 -59.3529701

EXTREMAL FREQUENCIES--MAXIMA OF THE ERROR CURVE
0.0000000 0.0332031 0.0625000 0.0820312 0.0900000
0.2000000 0.2078125 0.2253906 0.2507813 0.2800781
0.3093750 0.3406250 0.3718750 0.4031250 0.4363628
0.4677781 0.5000000
Appendix D. Fortran Programs

PROGRAM MARALL

MARALL PERFORMS A HARQARDT PARAMETER IDENTIFICATION ON THE
ENTIRE PRESSURE WAVEFORM

DIMENSION PARA(5),PARAM(6)
DIMENSION AA(4,4),DELST(4),AD(4),AST(4,4),B(4)
DOUBLE PRECISION ERROR(200)
COMMON/HLR/RV,CL,RT,L,CR
COMMON/TOTAL,PA1,FBA(200),FLOW(200)
COMMON/SENS/PA(5),200),FBAH(200)
COMMON/HOL/DFA(200),FPA(200)
COMMON/HOL/R,B/R
COMMON/AL MULT
COMMON/MARALL/ITER
COMMON/PLT/SCALE(6),6,DISP(6)
LOGICAL INDEX
DOUBLE PRECISION DF,DP1,G,AST,AD
REAL LAMBDA,INDEX
INDEX = .TRUE.

READ INFORMATION FROM MAIN STORED IN FORTRAN DATA FILE $99

THIS INFORMATION INCLUDES THE INPUT DATA (# OF PARAMETERS
# OF TOTAL POINTS, # OF DIABETIC POINTS, CARDIAC OUTPUT, SAMPLING
INTERVAL, STROKE VOLUME, FLY, FAA, PFA) AND THE INITIAL GUESSES
AT THE PARAMETER VALUES

OPEN (UNIT=99,TYPE='OLD')
READ(99,7) MULT
READ(99,1) ND,NDIA,T,STVOL,XAMDA,UMU,N
1 FORMAT(214,E10.4,3F10.5,14)
NFA = ND*MULT
READ(99,2) (PAI),I=1,NFA)
2 FORMAT(5F13.6)
READ(99,4) (FBAI),I=1,ND)
4 FORMAT(5F13.6)
READ(99,5) (PARAI),I=1,5)
5 FORMAT(5E15.8)
READ(99,6) PARAM(6)
6 FORMAT(F15.8)
7 FORMAT(15)
READ(99,8) FAA
8 FORMAT(F13.6)
CLOSE (UNIT=99)
WRITE(7,9)
9 FORMAT('FIRST SCALE & DISPLACEMENT FACTORS [F1,CL,RT,L,CR,RR]')
DO 15 I=1,6
READ(15,14) SCALE(I),DISP(I)
14 FORMAT(2E15.8)
15 CONTINUE
RI = PARAM(1)
CL = PARAM(2)
L = PARAM(3)
FLOW(1) = PARAM(4)

CR = PARAM(5)
RR = PARAM(6)
LAMDA = XAMDA
NSYS = ND - NDIA

CALCULATE THE CARDIAC OUTPUT DURING SYSTOLE ONLY
STROKE VOLUME * TIME

AFLLOW = STVOL/NSYS*T
TFD = 0.0
NDIA = NDIA + 1

CALCULATE THE PRESSURE DIFFERENCE BETWEEN THE LEFT VENTRICLE AND
THE AORTIC ARCH DURING SYSTOLE

IJ = 0
10 CONTINUE
IJ = 0

CALCULATE THE AVERAGE SYSTOLIC PRESSURE DIFFERENCE AND
USING THIS DIFFERENCE AND THE FLOW DURING SYSTOLE, THE AORTIC
VALUE RESISTANCE CAN BE DETERMINED

DELP = TFD/NSYS
RV = DELP/AFLLOW
WRITE(6,19)
19 FORMAT(40X,'OUTPUT RESULTS')
WRITE(6,20) AFLLOW
20 FORMAT('/','AVERAGE FLOW THROUGH THE AORTIC VALVE = ',E15.8, ' ML/

MIN')
WRITE(6,21) DELP
21 FORMAT('0', 'PRESSURE DIFFERENCE BETWEEN THE L.V. AND A.A. IN S

$STROKE = F12.3', ' MMHG')
PARA(1) = CL
PARA(2) = RI
PARA(3) = L
PARA(4) = CR
PARA(5) = RV

CALL DETS TO TAKE THE DERIVATIVE OF LEFT VENTRICULAR PRESSURE
SO THE SYSTEM EQUATIONS DURING THE WHOLE CARDIAC CYCLE CAN BE
INTEGRATED

T = T/MULT
CALL DERIV(T,ND)

CALL TOTAL TO PERFORM RUNGE-KUTTA INTEGRATION ON THE ENTIRE
CARDIAC CYCLE

CALL TOTAL(ND,PARA,T)
ND = ND*MULT
CALL SENSED(ND,T)
CALL SENSEND(ND,T)
CALL SENSESL(ND,T)
CALL SENSCK(ND+1)
CALL SENSER(ND+1)
ND = ND/MULT
CALL FSENS1(ND+HDIA)
CALL FSENS2(ND+HDIA)
J = 0
DO 25 1=1,1,1
FAAM(I) = FAAM(I)
FPAM(I) = FPAM(I)
25 CONTINUE
J = 0
DO 30 I=1,1,HD
ERROR(I) = FBA(I) - FPAM(I)
30 CONTINUE
IF (J.EQ.1) GO TO 120
DO 40 I=1,1,HD
IF (ERROR(I) .LT. UMAX) GO TO 35
40 DP = 1.0D0*ERROR(I)*ERROR(I)
35 CONTINUE
E = DP
ES1 = SORT(E/HD)
DP = 0.0
DO 40 I=1,1,HD
40 DP = DP + 1.0D0*ERROR(I)*ERROR(I)
E3 = DP
ES3 = SORT(E3/HD)
WRITE(6,50)
50 FORMAT('THE STARTING PARAMETER VALUES AND RMS ERROR')
WRITE(6,51) (FARA(I),I=1,5)
51 CL = 'E13.6+1X,RT = 'E13.6+1X,L = 'E13.6+1X,CR
WRITE(6,52) RR
52 FORMAT('RMS ERROR OF BOTH PRESSURES = 'E20.8)
WRITE(6,53) ES1
53 FORMAT('RMS ERROR OF B.A. PRESSURE = 'E20.8)
CALCULATE THE GREATEST DEVIATION OF THE MODEL GENERATED CURVES FROM
THE ACTUAL PRESSURE WAVEFORMS
VMAX1 = ABS(ERROR(I))
J = 1
DO 65 I=2,HD
IF (VMAX1 .LT. UMAX) GO TO 65
J = 1
VMAX1 = ABS(ERROR(I))
65 CONTINUE
C WRITE MAXIMUM DEVIATIONS
WRITE(6,70) VMAX1, IJK
70 FORMAT(0 THE MAX. DEVIATION OF B.A. = 'E15.8, AT',IS)
72 FORMAT('I',10X,'FLU',10X,'FBA',8X,'ERROR',8X,'RUA',9X,'ERROR',
8X,'FLOW',6X,'FLOWV',6X)',/)
75 CONTINUE
ITER = 0
BEGIN THE ITERATIVE LOOP I THE # OF ITERATIONS CANNOT EXCEED 30
80 ITER = 1 + ITER
IF (ITER.GT.30) GO TO 374
CALL JACX(ND+HD,PARA)
C FORM UP J=1
C FORM UP J=2
DO 85 J=1,N
DP = 0.0
DO 90 I=1,1
90 DP = DP + 1.0D0*ERROR(I)*F(J,I)
0(J) = DP
95 CONTINUE
C FORM J=3
C FORM J=4
DO 100 I=1,N
100 DP = DP + 1.0D0*F(I,M)*F(J,H)
C SET J=5 = AST(4,4) .J=6 = G
C THE SCALING TO MAKE THE SOLUTION VIABLE IS THEN:
C AST(I,J)/AST(4,4)*AST(4,4)
C G(I)/DSQRG(T/DP)
120 CONTINUE
G(I) = G(I)/AB(I)
DO 130 J=1,N
   AST(I,J) = AST(I,J) / (AD(I)*AD(J))
   THE DIAGONAL ELEMENTS HAVE LAMBDA ADDED TO THEM
   IF (I.EQ. J) AST(I,I) = AS(I,J) + LAMBDA
   CONTINUE
   IF (N.EQ. 1) GO TO 140
   GO TO 150
130 CONTINUE
   GO TO 140
140 DELST(I) = 6(I)/AA(I,1)
150 CONTINUE
C
C SOLVE THE LINEAR EQUATIONS FOR DELX
C
C CALL SIMO(AST,G,N,KS)
C WRITE(7,550) (G(I),I=1,4)
C500 FORMAT(/A15.9)
   IF (KS.EQ. 1) GO TO 410
   GO TO 150
140 CONTINUE

C SCALE DELX + DELX/AST(I,J)
C
C DO 160 I=1,N
160 CONTINUE
C WRITE(7,560) (DELST(I),I=1,4)
C560 FORMAT(4F15.6)
C
C INCREMENT PARAMETERS BY DELX
C
C DO 170 I=1,N
170 CONTINUE
C CALL TOTAL TO PERFORM THE RUNGUE-KUTTA INTEGRATION DURING THE
C ENTIRE CARDIAC CYCLE
C
C CALL TOTAL(ND,PARA,T)
   ND = NDMULT
   CALL SENS(ND,1)
   CALL SENS(ND,4)
   CALL SENS(ND,7)
   CALL SENS(ND,10)
   ND = ND/MULT
   CALL PSEN1(ND,NDIA)
   CALL PSEN0(0,NDIA)
170 CONTINUE
C
C CALL TOTAL(ND,PARA,T)
   ND = NDMULT
   CALL SENS(ND,1)
   CALL SENS(ND,4)
   CALL SENS(ND,7)
   CALL SENS(ND,10)
   ND = ND/MULT
   CALL PSEN1(ND,NDIA)
   CALL PSEN0(0,NDIA)
   J = 0
170 CONTINUE

C CALL TOTAL(ND,PARA,T)
   ND = NDMULT
   CALL SENS(ND,1)
   CALL SENS(ND,4)
   CALL SENS(ND,7)
   CALL SENS(ND,10)
   ND = ND/MULT
   CALL PSEN1(ND,NDIA)
   CALL PSEN0(0,NDIA)
   J = 0
170 CONTINUE

171 CONTINUE
J = 0
C
C FORM UP THE ERROR VECTORS
C
C DO 180 I=1,ND
180 CONTINUE
C
C CALCULATE THE RMS ERRORS
C
C DO 190 I=1,ND
190 CONTINUE
C
C WRITE THE RMS ERRORS
C
C WRITE(6,220) E
220 FORMAT(1X,'PREVIOUS ERROR =',E14.7)
   WRITE(6,230) E,ITER,LAMBDA
230 FORMAT('0 E1 =',F15.6,'ITER =',I4,5X,'LAMBDA =',E15.6)
   ES1 = SORT(E1/ND)
   ES3 = SORTE3(ND)
   WRITE(6,54) ES1
   WRITE(6,55) ES3
C
C CALCULATE THE MAXIMUM DEVIATION OF THE MODEL CURVES FROM THE
C ACTUAL PRESSURE CURVES
C
C VMAX1 = ABS(ERROR(I))
   IJK = 1
   DO 250 I=2,ND
      IF (ABS(ERROR(I)) .LT. VMAX1) GO TO 250
170 CONTINUE
C
C WRITE THE MAXIMUM DEVIATIONS
C
C WRITE(6,255) VMAX1, IJK
CALL PLSENS(0,ND,NDIA)
J = 0
DO 311 I=1,NFA,MULT
    J = J + 1
    PAAM(J) = PAAM(I)
    FRAH(J) = FRAH(I)
311 CONTINUE
J = 0
DO 320 I=1,ND
    ERROR(J) = FRA(I) - FRAH(I)
320 CONTINUE
GO TO 80
330 FCODE = (E - E1)/E
E = E1
IF (LAMDA > .0001) 340, 340, 345
340 LAMDA = 0.0
GO TO 350
345 LAMDA = LAMDA/VMU
350 CONTINUE
PMAX = 0.0
DO 360 I=1,N
    TRY = ABS(DELT(I)/PARA(I))
    IF (TRY > .01, PMAX) PMAX = TRY
360 CONTINUE
WRITE(6,370)
370 FORMAT('STOP CRITERION')
WRITE(A,371) PMAX
371 FORMAT('THE MAX. RELATIVE CHANGE OF PARAMETER =',E20.8)
WRITE(6,372) FCODE
372 FORMAT('THE RELATIVE CHANGE OF ERROR =',E20.8)
C CALL PLSENS(1,ND,NDIA)
C CALL PLSENS(0,ND,NDIA)
IF (PMAX > .01) GO TO 80
IF (FCODE > .005) GO TO 80
IF (IER > .LT. 20) GO TO 80
C THE END OF THE ITERATIVE LOOP
C 374 WRITE(6,375)
375 FORMAT('/// THE BEST FIT IS: ///')
WRITE(A,371) PARA(I),I=1,5
WRITE(A,372) PMAX
WRITE(A,373) FCODE
376 FORMAT///10X,'FRA-MODEL',9X,'FBA',8X
    '*'FRA-MODEL',5X,'ERROR',9X,'FLOW'
    DO 379 I=1,ND
        WRITE(A,377) I,PAAM(I),FBA(I),FRAH(I),ERROR(I),
            FLOW((MULT#1)-MULT#4)
377 FORMAT(15*E13.5)
379 CONTINUE
C WRITE(A,380)
C 380 FORMAT('/// 40X 'COMPARATIVE PLOTS')
C WRITE(A,381)
C 381 FORMAT(/// /// AORTIC ARCH PRESSURE--PREDICTED VS. RFORDER')

255 FORMAT(' THE MAX. DEVIATION FOR PA = ',E15.8, ' AT', I5)
WRITE(6,51) PARA(I),I=1,5
WRITE(6,52) RR
C WRITE(6,257)
C257 FORMAT('0',10X,'FLV',10X,'FBA',9X,'FRA',10X,'ERROR',
    40X,'FLOW',4X,'FLORV',2)
DO 260 I=1,ND
C WRITE(6,74) I,FLV(MULT#1-MULT#4),PAAM(I),FBAH(I),ERROR(J),
C $FLOW(MULT#1-MULT#4), FLORV((MULT#1)-MULT#4)
260 CONTINUE
C WRITE(6,265)
C265 FORMAT('1')
C INCREDENT OR DECREMENT LAMDA ACCORDING TO THE METHOD DESCRIBED
C BY LEVENBURG IN HIS PAPER ON THIS TECHNIQUE
C IF (E1 .LT. E) GO TO 330
270 LAMDA = LAMDA * VMU
DO 280 I=1,N
280 PARA(I) = PARA(I) - DELST(I)
    CALL TOTAL(ND,PARA,T)
    ND = ND*MULT
    CALL SENS(ND,T)
    CALL SENS(ND,T)
    CALL SENS(ND,T)
    CALL SENS(ND,T)
    CALL SENS(ND,T)
    ND = ND*MULT
    CALL PLSENS(1,ND,NDIA)
    CALL PLSENS(0,ND,NDIA)
J = 0
DO 281 I=1,NFA,MULT
    J = J + 1
    PAAM(J) = PAAM(I)
    FRAH(J) = FRAH(I)
281 CONTINUE
J = 0
DO 290 I=1,ND
    ERROR(J) = FRA(I) - FRAH(I)
290 CONTINUE
INDEX = .FALSE.
GO TO 80
300 LAMDA = LAMDA * VMU
DO 310 I=1,N
310 PARA(I) = PARA(I) - DELST(I)
    CALL TOTAL(ND,PARA,T)
    ND = ND*MULT
    CALL SENS(ND,T)
    CALL SENS(ND,T)
    CALL SENS(ND,T)
    CALL SENS(ND,T)
    CALL SENS(ND,T)
    ND = ND*MULT
    CALL PLSENS(1,ND,NDIA)
SUBROUTINE TOTAL(N,FARA,T)
C
C TOTAL PERFORMS NUMERICAL INTEGRATION OVER THE ENTIRE CARDIAC
C CYCLE BY MEANS OF A 4TH ORDER RUNGE-KUTTA INTEGRATION SCHEME.
C FA IS USED TO FORCE THE EQUATIONS DURING SYSTOLE
C
DIMENSION FARA(5)
COMMON/SENS/P(5,200),FAAM(200),FBAM(200)
REAL L
COMMON/TOTAL/FAA1,FBAM(200),FLOW(200)
COMMON/HOLD/FA(200),DFA(200)
COMMON/HOLD2/RV,CL,RT,L,CR
COMMON/HOLD6/RR
COMMON/ALL/MULT
COMMON/MARALL/IITER
ITER = 0
CL = FARA(1)
RT = FARA(2)
L = FARA(3)
CR = FARA(4)
RV = FARA(5)
FAAM(I) = FAA1
FBAM(I) = FBA1
WRITE(6,1) CL,RT,L,CR
C
1 FORMAT(2x,2x,'CL = ',E15.8,'2x',RT = ',E15.8,'2x',L = ',E15.8,'2x','CR = ',E15.8)
C
N = NMULT
NDT = (2*N) + 1
10 I = 0
DO 20 I=1,NDT
I = I + 1
A1 = EVAL(1,FAAM(I),FAAM(I),FLOW(I),FA(I),DFA(I))
A2 = EVAL(2,FAAM(I),FAAM(I),FLOW(I),FA(I),DFA(I))
C1 = EVAL(3,FAAM(I),FAAM(I),FLOW(I),FA(I),DFA(I))
T1 = FAAAM(I) + 0.5*A1
T2 = FBAM(I) + 0.5*B1
T3 = FLOW(I) + 0.5*C1
A2 = EVAL(1,T1,T2,T3,FA(I),DFA(I))
B2 = EVAL(2,T1,T2,T3,FA(I),DFA(I))
C2 = EVAL(3,T1,T2,T3,FA(I),DFA(I))
T1 = FAAAM(I) + 0.5*A2
T2 = FBAM(I) + 0.5*B2
T3 = FLOW(I) + 0.5*C2
A3 = EVAL(1,T1,T2,T3,FA(I),DFA(I))
B3 = EVAL(2,T1,T2,T3,FA(I),DFA(I))
C3 = EVAL(3,T1,T2,T3,FA(I),DFA(I))
T1 = FAAAM(I) + A3
T2 = FBAM(I) + B3
T3 = FLOW(I) + C3
A4 = EVAL(1,T1,T2,T3,FA(I),DFA(I))
B4 = EVAL(2,T1,T2,T3,FA(I),DFA(I))
C4 = EVAL(3,T1,T2,T3,FA(I),DFA(I))
A = (A1 + 2.0*A2 + 2.0*A3 + A4)/6.0
B = (B1 + 2.0*B2 + 2.0*B3 + B4)/6.0
FAAM(I+1) = FAAAM(I) + (A + B)
SUBROUTINE SENSCL(N, T)

C THIS ROUTINE CALCULATES THE SENSITIVITY COEFFICIENTS EXACTLY
C FOR THE PARAMETER CL, A FOURTH ORDER RUNGE KUTTA INTEGRATION
C SCHEME IS EMPLOYED TO SOLVE THE DIFF. EQ'S FOR SENSITIVITY TO CL, THE
C SENS. COEFFS. ARE THEN STORED IN THE 1ST ROW FO THE MATRIX P
C THE 1ST N BEING PI SENSITIVITIES AND THE NEXT N BEING SENSITIVITIES
C OF P2J THE P MATRIX IS THEN USED IN THE MARQUARDT METHOD.

C COMMON/HOLD/RV,CL,RT,LL,CLR
C COMMON/HOLD/RR
C COMMON/SENS/S,FAAM(200),FBAH(200)
C COMMON/TOBALFAAM,FBAM(200),FLOW(200)
C COMMON/HOLD/FA(200),DBA(200)
C COMMON/ALL/MULT
C REAL L
C E1 = 0.0
C E2 = 0.0
C E3 = 0.0
C J = 0
C I = 0
C DO 10 II=1,2*N
C I = I + 1
C IF (MOD(I-MULT) .NE. 0) GO TO 5
C J = J + 1
C P(I,NJ) = E1
C P(I,J) = E2
C 5 A1 = RT(IE-1)/L - E3/CL + (FLOW(I)-FA(I))/(CL*CL)
C B1 = E3/CR - E2/(CR*RR)
C C1 = (E1-E2)/L
C T1 = E1 + 0.5*AI
C T2 = E2 + 0.5*AI
C T3 = E3 + 0.5*C1
C A2 = RT(T2-T1)/L - T3/CL + (FLOW(I)-FA(I))/CL*CL
C B2 = T3/CR - T2/(CR*RR)
C C2 = (T1-T2)/L
C T1 = E1 + 0.5*AI
C T2 = E2 + 0.5*AI
C T3 = E3 + 0.5*C1
C A3 = RT((T1-T2)/L - T3/CL + (FLOW(I)-FA(I))/CL*CL
C B3 = T3/CR - T2/(CR*RR)
C C3 = (T1-T2)/L
C T1 = E1 + 0.5*AI
C T2 = E2 + 0.5*AI
C T3 = E3 + 0.5*C1
C A4 = RT((T1-T2)/L - T3/CL + (FLOW(I)-FA(I))/CL*CL
C B4 = T3/CR - T2/(CR*RR)
C C4 = (T1-T2)/L
C E1 = E1 + T*AI + 2.0*A2 + 2.0*A3 + A4)/6.0
C E2 = E2 + T*AI + 2.0*A2 + 2.0*A3 + B4)/6.0
C E3 = E3 + T*(AI + 2.0*A2 + 2.0*A3 + C4)/6.0
C IF (I .EQ. N) J=0
C IF (I .EQ. N) I=0
C 10 CONTINUE

C WRITE(7,20)
C FORMAT( ' CL SENS DONE')
C RETURN

END
SUBROUTINE SENSL(N,T)

C THIS ROUTINE CALCULATES THE SENSITIVITY COEFFICIENTS EXACTLY FOR
C THE PARAMETER L. A FORTH ORDER RUNGE-KUTTA INTEGRATION SCHEM IS
C EMPLOYED TO SOLVE THE DIFF. Eqs. FOR THE SENSITIVITIES TO RT.
C THE SENSITIVITIES (VS. TIME) ARE THEN STORED IN THE 2ND ROW OF
C THE MATRIX P THE 1ST N ARE SENSITIVITIES TO F1, THE NEXT N TO F2
C
COMMON/HOLD/1/RV,CL,RT1,CL,CR
COMMON/HOLD/6/RR
COMMON/SENS/L(5,200),FAA(200),PBAM(200)
COMMON/TOTAL/PAAL,PHA(200),FLOW(200)
COMMON/HOLD/TA(200),BFA(200)
COMMON/ALL/MULT
REAL L
E4 = 0.0
E5 = 0.0
E6 = 0.0
J = 0
D0 10 II=-1,2,M
I = I + 1
IF (MOD(I-1,MULT),NE.0) GO TO 5
J = J + 1
F(J,N+J) = E4
F(J+1,N+J) = E5
5 A1 = RT*(E4-E5)/L - E6/CL + (PBAM(I)-FAA(I))/L + DFA(I)
B1 = E4/CR - E5/(CR*CR)
C1 = (E4-E5)/L
T4 = E4 + 0.5*A41
T5 = E5 + 0.5*A51
T6 = E6 + 0.5*C1
A2 = RT*(T15-T4)/L - T4/CL + (PBAM(I)-FAA(I))/L + DFA(I)
B2 = T6/CR - T5/(CR*CR)
C2 = (T4-T5)/L
T4 = E4 + 0.5*A42
T5 = E5 + 0.5*A52
T6 = E6 + 0.5*C2
A3 = RT*(T15-T4)/L - T6/CL + (PBAM(I)-FAA(I))/L + DFA(I)
B3 = T6/CR - T5/(CR*CR)
C3 = (T4-T5)/L
T4 = E4 + 0.5*A43
T5 = E5 + 0.5*A53
T6 = E6 + 0.5*C3
A4 = RT*(T15-T4)/L - T6/CL + (PBAM(I)-FAA(I))/L + DFA(I)
B4 = T6/CR - T5/(CR*CR)
C4 = (T4-T5)/L
E4 = E4 + T4*A1 + 2.0*A2 + 2.0*A3 + A4/6.0
E5 = E5 + T5*A1 + 2.0*A2 + 2.0*A3 + A4/6.0
E6 = E6 + T6*A1 + 2.0*A2 + 2.0*A3 + A4/6.0
IF (II.EQ. N) J=0
IF (II.EQ. N) I=0
10 CONTINUE
WRITE(7,20)
20 FORMAT(' R1 SENS DONE')
RETURN
END

SUBROUTINE SENSL(N,T)

C THIS ROUTINE CALCULATES THE SENSITIVITY COEFFICIENTS EXACTLY FOR
C THE PARAMETER L. A FORTH ORDER RUNGE-KUTTA INTEGRATION SCHEM IS
C USED TO SOLVE THE DIFF. Eqs. ASSOCIATED WITH DX/DL. THE RESULTS ARE
C STORED IN THE 3RD ROW OF MATRIX P. THE 1ST N ARE SENSITIVITIES TO
C F1, THE NEXT N TO F2.
C
COMMON/HOLD/1/RV,CL,RT,CL,CR
COMMON/HOLD/6/RR
COMMON/SENS/L(5,200),FAA(200),PBAM(200)
COMMON/TOTAL/PAAL,PHA(200),FLOW(200)
COMMON/HOLD/TA(200),BFA(200)
COMMON/ALL/MULT
REAL L
E7 = 0.0
E8 = 0.0
E9 = 0.0
J = 0
D0 10 II=-1,2,M
I = I + 1
IF (MOD(I-1,MULT),NE.0) GO TO 5
J = J + 1
F(J,N+J) = E7
F(J+1,N+J) = E8
5 A1 = RT*(E7-E8)/L - E9/CL + RT*(PBAM(I)-FAA(I))/L
B1 = E7/CR - E8/(CR*CR)
C1 = (E7-E8)/L
T7 = E7 + 0.5*A71
T8 = E8 + 0.5*A81
T9 = E9 + 0.5*C1
A2 = RT*(T18-T7)/L - T9/CL + RT*(PBAM(I)-FAA(I))/L
B2 = T9/CR - T8/(CR*CR)
C2 = (T7-T8)/L + (PBAM(I)-FAA(I))/L
T7 = E7 + 0.5*A72
T8 = E8 + 0.5*A82
T9 = E9 + 0.5*C2
A3 = RT*(T18-T7)/L - T9/CL + RT*(PBAM(I)-FAA(I))/L
B3 = T9/CR - T8/(CR*CR)
C3 = (T7-T8)/L + (PBAM(I)-FAA(I))/L
T7 = E7 + 0.5*A73
T8 = E8 + 0.5*A83
T9 = E9 + 0.5*C3
A4 = RT*(T18-T7)/L - T9/CL + RT*(PBAM(I)-FAA(I))/L
B4 = T9/CR - T8/(CR*CR)
C4 = (T7-T8)/L + (PBAM(I)-FAA(I))/L
E7 = E7 + T8*A1 + 2.0*A2 + 2.0*A3 + A4/6.0
E8 = E8 + T8*A1 + 2.0*A2 + 2.0*A3 + A4/6.0
E9 = E9 + T8*C1 + 2.0*A2 + 2.0*A3 + C4/6.0
IF (II.EQ. N) J=0
IF (II.EQ. N) I=0
10 CONTINUE
WRITE(7,20)
20 FORMAT(' R1 SENS DONE')
RETURN
END
SUBROUTINE SENSFR(N,T)


COMMON/HOLI1/RV+CL+RT+L+CR
COMMON/HOLI6/RER
COMMON/SENS)/(5+200)+PBAH/(200)+PBAH/(200)
COMMON/3AA/(200)+PBAH/(200)
COMMON/HELP/FA/(200)+PBAH/(200)
COMMON/ALL/MULT
REAL L
E10 = 0.0
E11 = 0.0
E12 = 0.0
J = 0
DO 10 II=1,2N
I = I + 1
IF (MOD(I-1,MULT) .NE. 0) GO TO 5
J = J + 1
F(A,N,J) = E10
F(A,J) = E11
A = RT/(A1-E10)/L - E12/L
C = (E10 - E11)/L
T10 = E10 + 0.5A1#1
T11 = E11 + 0.5B1#1
T12 = E12 + 0.5C1#1
A2 = RT/(T11-T10)/L - T12/L
C2 = (T10 - T11)/L
T10 = E10 + 0.5A2#1
T11 = E11 + 0.5B2#1
T12 = E12 + 0.5C2#1
A3 = RT/(T11-T10)/L - T12/L
B3 = T12/CR - T11/(CR+RR) + PBAH/(I)/(RR+CR) - FLOW/(I)/(CR+CR)
C3 = (T10-T11)/L
T10 = E10 + 0.5A3#1
T11 = E11 + B3#1
T12 = E12 + C3#1
A4 = RT/(T11-T10)/L - T12/L
B4 = T12/CR - T11/(CR+RR) + PBAH/(I)/(RR+CR) - FLOW/(I)/(CR+CR)
C4 = (T10-T11)/L
E10 = E10 + TR(A1 + 2.0A2 + 2.0A3 + A4)/6.0
E11 = E11 + TR(B1 + 2.0B2 + 2.0B3 + B4)/6.0
E12 = E12 + TR(C1 + 2.0C2 + 2.0C3 + C4)/6.0
IF (II .EQ. N) J = 0
IF (II .EQ. N) I = 0
CONTINUE
WRITE(7,20)
FORMAT(' CR SENS I N N F )
RETURN
END

SUBROUTINE SENSFR(RR,T)

THIS ROUTINE CALCULATES THE SENSITIVITIES TO THE PARAMETER RR. A FOURTH ORDER RUNGKUTA INTEGRATION SCHEME IS USED TO SOLVE THE DIFF. EN'S ASSOCIATED WITH DX/DRR. THE RESULTS ARE STORED IN THE 5TH ROW OF THE MATRIX P (THE FIRST N POINTS ARE THE SENSITIVITIES OF P1 AND THE NEXT N POINTS ARE THOSE OF P2).

COMMON/HOLI1/RV+CL+RT+L+CR
COMMON/HOLI6/RER
COMMON/SENS)/(5+200)+PBAH/(200)+PBAH/(200)
COMMON/3AA/(200)+PBAH/(200)
COMMON/HELP/FA/(200)+PBAH/(200)
COMMON/ALL/MULT
REAL L
E13 = 0.0
E14 = 0.0
E15 = 0.0
J = 0
DO 10 II=1,2N
I = I + 1
IF (MOD(I-1,MULT) .NE. 0) GO TO 5
J = J + 1
F(A,N,J) = E13
F(A,J) = E14
A = RT/(A1-E13)/L - E15/L
B = E15/CR - E14/(CR+RR) + PBAH/(I)/(CR+RR)
C = (E13-E14)/L
T13 = E13 + 0.5A1#1
T14 = E14 + 0.5B1#1
T15 = E15 + 0.5C1#1
A2 = RT/(T11-T10)/L - T15/L
B2 = T15/CR - T14/(CR+RR) + PBAH/(I)/(CR+RR)
C2 = (T13-T14)/L
T13 = E13 + 0.5A2#1
T14 = E14 + 0.5B2#1
T15 = E15 + 0.5C2#1
A3 = RT/(T11-T10)/L - T15/L
B3 = T15/CR - T14/(CR+RR) + PBAH/(I)/(CR+RR)
C3 = (T13-T14)/L
T13 = E13 + A3#1
T14 = E14 + B3#1
T15 = E15 + C3#1
A4 = RT/(T11-T10)/L - T15/L
B4 = T15/CR - T14/(CR+RR) + PBAH/(I)/(CR+RR)
C4 = (T13-T14)/L
E13 = E13 + TR(A1 + 2.0A2 + 2.0A3 + A4)/6.0
E14 = E14 + TR(B1 + 2.0B2 + 2.0B3 + B4)/6.0
E15 = E15 + TR(C1 + 2.0C2 + 2.0C3 + C4)/6.0
IF (II .EQ. N) J = 0
IF (II .EQ. N) I = 0
CONTINUE
WRITE(7,20)
FORMAT(' RR SENS I N N F )
RETURN
END
REFERENCES


