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ANALOG SIMULATION OF LEFT VENTRICULAR
BYPASS MODE CONTROL

by

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ABSTRACT

Analog Simulation of Left Ventricular Bypass Mode Control

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The subject of this study is optimal mode control for the left ventricular bypass pump used to assist the failing heart. A mathematical model has been formulated for the overall cardiovascular system, both with and without bypass assistance. The closed-loop, uncontrolled model of the unassisted circulation has been implemented on an analog computer, and has been demonstrated capable of simulating normal as well as abnormal physiological behavior. Implementation of the bypass pump model has been shown to produce the general expected hemodynamic effects of decreasing pressure in the left atrium, while increasing that in the systemic arterial load. Four logical modes of pump control have been described and compared on the basis of their effect upon a scalar performance index used to reflect the basic goals of cardiac assistance.

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TABLE OF CONTENTS

CHAPTER I: INTRODUCTION.	.1
CHAPTER II: THEORETICAL DEVELOPMENT OF THE UNASSISTED CIRCULATORY MODEL.	.4
Section A. The Representation of Heart Function	
Part 1. The Elastance Concept	
Part 2. The Left Heart Model	
Part 3. The Right Heart Model	
Section B. Vascular Model Development	
Part 1. The Systemic Arterial Model	
Part 2. The Systemic Venous Model	
Part 3. The Pulmonary Load Model	
CHAPTER III: COMPUTATIONAL ASPECTS OF THE UNASSISTED CIRCULATORY MODEL.	.21
Section A. Parameter Development for the Unassisted Circulation	
Part 1. Heart Parameters	
Part 2. Systemic Load Parameters	
Part 3. Pulmonary Load Parameters	
Section B. Model Results for the Unassisted Circulation	
Part 1. Simulation of Normal Conditions	
Part 2. Simulation of Abnormal Conditions and Physiological Manipulations	
CHAPTER IV: THE ASSISTED CIRCULATION.	.51
Section A. Theoretical Aspects of the Pump Model	
Part 1. The Analog Model	
Part 2. Asynchronous, Time-Triggered Control	
Part 3. Synchronous, Time-Triggered Control	
Part 4. Asynchronous, Volume-Triggered Control	
Part 5. Synchronous, Time-and-Volume-Triggered Control	
Section B. Performance Index Development	
Section C. Computational Aspects of the Pump Model	
Part 1. The Analog Model	
Part 2. Implementation of Logical Pump Control	
Section D. Model Results for the Assisted Circulation	

Part 1. Assistance of the Normal Heart with Fixed Control Parameters	
Part 2. The Assisted Normal: Changes in Performance due to Control Parameter Variation	
Part 3. The Assistance of the Asynergistic Left Ventricle	

CHAPTER V: CONCLUSIONS.	.87
APPENDIX A: NOMENCLATURE.	.93
APPENDIX B: ANALOG COMPUTER DIAGRAMS.	.97
REFERENCES.	.109

CHAPTER I: INTRODUCTION

The left ventricular bypass pump is a parallel type of cardiac assist device. It has been used experimentally [Ross et al, 1971], and has also been shown to have clinical application in cases where open-chest surgery has been performed [DeBakey, 1971]. The question of how to control this device without the need of constant operator attention and in a manner which optimizes the assistance of the failing heart is an important problem. The purpose of this study is to analyze in detail different modes of pump control and to compare their performance. An analog computer simulation approach is used for the following reasons: In an experimental environment, results are dependent upon many factors, and it is therefore difficult to isolate the problem of control from those of surgical procedure, biomaterials, pump geometry, and so on. By developing a mathematical model capable of simulating general hemodynamic behavior, one can concentrate on the effects that changes in bypass pump mode control have on the overall circulation. Furthermore, by modelling such a complex biological process as the cardiovascular system, one can hope to better understand its physiology.

The system to be simulated is shown in Figure 1.1 in block diagram form. The bypass assist device is connected to the circulatory system in such a way that blood is drawn out of the left atrium to fill the pump and subsequently reinjected into the systemic arterial load. Because of the nature of its operation this pump affects both the pre-load and after-load on the left ventricle. For this reason, the cardiovascular system must be characterized in closed-loop form. The overall circulatory model used in this study therefore includes both left and

Figure 1.1. Block Diagram of the Circulatory System as Assisted by the Left Ventricular Bypass Pump.

right heart, systemic arterial and venous compartments, and pulmonary load. Note also from Figure 1.1 that neural effects on the cardiovascular system are not modelled. Thus, the representation of the circulation is a closed-loop, uncontrolled one.

This thesis is organized as follows: Theoretical development of the circulatory model is discussed in Chapter II. The formulation is based upon selecting specific models from the literature and combining them together in order to obtain a fairly simple characterization of the overall circulation. A system of equations to mathematically describe the composite model is then specified. In Chapter III, the computational aspects of the problem are considered, and the results of the analog computer implementation are presented. The unassisted circulatory model is verified by demonstrating its ability to simulate both normal and abnormal physiological behavior. Characterization of the left ventricular bypass pump is described in Chapter IV, and output of the assisted circulatory model is discussed in detail. Finally, in Chapter IV, the results of the simulation of both the assisted and unassisted circulation are briefly summarized, and their implications considered.

CHAPTER II: THEORETICAL DEVELOPMENT OF THE UNASSISTED CIRCULATORY MODEL

Before the effects of left ventricular bypass pumping can be analyzed, the unassisted circulatory system must first be characterized. The purpose of this chapter is to discuss the theoretical development of an uncontrolled, closed-loop cardiovascular model. The overall model is a composite of those found in the literature which are based upon the analogy of electrical and hydraulic quantities. The properties of the heart itself are considered in Section A., and then in Sections B. and C., models for the systemic and pulmonary vasculature are described.

Section A. The Representation of Heart Function

Central to the problem of quantitating the dynamic behavior of the overall circulatory system is an adequate characterization of the cardiac pump. Of the four contractile chambers of the heart, the ventricles perform the majority of the pumping function, and their mathematical description is therefore considered first.

Part 1. The Elastance Concept

Three basic types of approach to the problem of characterizing ventricular pump properties are common in the literature: 1) input-output analysis, 2) muscle mechanics modelling, and 3) the elastance concept. Starling's law relating cardiac output to mean atrial pressure is an example of describing the ventricle in terms of its hydraulic

input-output properties. More recent characterizations of this type include the ventricular function curve used by Sarnoff [1962] to relate external mechanical work to end-diastolic pressure, and the cardiac output surface described by Sagawa to relate cardiac flow to arterial and venous pressures. The main problem with this type of approach is the failure to isolate the intrinsic properties of the ventricle from the effects of pre-load and after-load. Moreover, time dependence is not specified, and therefore applicability to dynamic simulation is severely restricted.

A far more fundamental modelling approach is one based upon the attempt to relate the periodic contraction and relaxation of myocardial fibers to the changes in pressure and volume in the ventricle. In order to characterize ventricular pumping at this level, however, one must have knowledge of the passive length-tension relationships in the muscle, the temporal course of the spread of electrical activation through the tissue, and the active muscle properties such as the relationship of developed force to velocity of shortening under given loading conditions. Furthermore, in order to relate muscular tension to ventricular pressure and volume, the geometry of fiber orientation must also be specified. Thus, although it would certainly be satisfying, characterization of ventricular mechanics at this microscopic level is not feasible.

A third approach to ventricular mechanics is to consider the contractile chamber as a whole in terms of the instantaneous ratio of intraventricular pressure to volume. This elastance, the reciprocal of hydraulic compliance, has a small value during filling when the ventricle is relaxed. Then, in systole, wall stiffness increases greatly, causing first the elevation of intraventricular pressure at constant

volume and subsequently the ejection of blood into the arterial load. The concept of the time-varying elastance function to characterize periodic ventricular contraction has been shown to be a bridge between the empirically derived input-output models and the very fundamental muscle mechanics models discussed earlier [Suga and Sagawa, 1972]. Furthermore, Suga has demonstrated experimentally that the elastance function during systole uniquely characterizes ventricular contractile state, and is nearly unchanged by alterations in pre-load and after-load.* This ability to isolate the intrinsic properties of the ventricle from those of the load is valuable for two reasons: 1) It simplifies the formulation of the overall circulatory model, and 2) It offers a promising clinical tool for categorizing different cardiovascular disease states.

Baldrige [1973] has shown how elastance data obtained from human patients can be used to separate them into clinical categories. Those with normal ventricular function are found to have similar elastance curves, while those with severe coronary artery disease or abnormal movement of the ventricular wall exhibit both diminishment in peak systolic elastance and increases in the time required to attain it, in general.

*Although other investigators have supported the contention that the elastance function is independent of after-loading conditions, there has been some disagreement regarding the importance of pre-load. In particular, studies by Green and Clark [1973] have shown that ventricular elastance is a function of end-diastolic volume. Rather than using a family of elastance curves, however, the linear, single-curve representation is used throughout this study.

Part 2. The Left Heart Model

As discussed in Chapter III of this thesis, the elastance function used to characterize left ventricular contraction is that analyzed by Balldridge. However, for simplicity, elastance is here assumed to be a function of time only. The left ventricular model shown in Figure 2.2 at the end of this chapter, depends solely on the periodic time function $E_{LV}(t)$ and the resistances of the inlet and outlet valves, R_{MT} and R_{AO} . Flow through the mitral valve is unidirectional, and is determined by the following relationship of left atrial and left ventricular pressures:

$$F_{MT}(t) = \begin{cases} [P_{LA}(t) - P_{LV}(t)]/R_{MT} & P_{LA} > P_{LV} \\ 0 & \text{otherwise} \end{cases} \quad (2.1)$$

Similarly, blood is allowed to flow only outward through the aortic valve into the systemic arterial load, where the pressure is P_{SA1} :

$$F_{AO}(t) = \begin{cases} [P_{LV}(t) - P_{SA1}(t)]/R_{AO} & P_{LV} > P_{SA1} \\ 0 & \text{otherwise} \end{cases} \quad (2.2)$$

Ventricular volume is found by integrating the net flow into the chamber:

$$V_{LV}(t) = \int [F_{MT}(t) - F_{AO}(t)] dt \quad (2.3)$$

The instantaneous relationship between this volume and ventricular pressure is determined by the elastance function:

$$P_{LV}(t) = E_{LV}(t) V_{LV}(t) \quad (2.4)$$

The above four equations describe the mathematical model of the left ventricle.

As noted in Equation 2.1, ventricular filling is dependent upon atrial pressure. A simple elastance function is therefore assumed for the left atrium (See Chapter III), in order that P_{LA} can be determined as follows:

$$P_{LA}(t) = E_{LA}(t) V_{LA}(t) \quad (2.5)$$

Left atrial volume is determined by integrating flow in through the pulmonary vein minus that leaving the chamber through the mitral valve:

$$V_{LA}(t) = \int [F_{PV}(t) - F_{MT}(t)] dt \quad (2.6)$$

The model of the left heart is completely described by Equations 2.1-2.6.

Part 2. The Right Heart Model

One observes from Figure 2.2 that the right heart, like the left, is represented by two time-varying elastance functions and two uni-directional valves. The development of the right heart model is based upon the same approach as that just discussed for the left heart.

As pointed out in Chapter III, the elastance function used to characterize right ventricular function is derived from that actually measured for the left ventricle. Right ventricular pressure is determined

by:

$$P_{RV}(t) = E_{RV}(t) V_{RV}(t) \quad (2.7)$$

The instantaneous volume in the right ventricle is computed by integrating flow inward through the tricuspid valve minus that which leaves through the pulmonic valve:

$$V_{RV}(t) = \int [F_{TC}(t) - F_{PM}(t)] dt \quad (2.8)$$

Flow through the pulmonic valve is dependent upon the pressure difference between the ventricle and the pulmonary artery:

$$F_{PM}(t) = \begin{cases} [P_{RV}(t) - P_{PA}(t)]/R_{PM} & P_{RV} > P_{PA} \\ 0 & \text{otherwise} \end{cases} \quad (2.9)$$

Flow through the tricuspid valve is also ideally limited:

$$F_{TC}(t) = \begin{cases} [P_{RA}(t) - P_{RV}(t)]/R_{TC} & P_{RA} > P_{RV} \\ 0 & \text{otherwise} \end{cases} \quad (2.10)$$

Equations describing the right atrial variables are exactly analogous to Equations 2.5-2.6 which apply to the left atrium. Pressure is again determined from the assumption of a simple elastance function:

$$P_{RA}(t) = E_{RA}(t) V_{RA}(t) \quad (2.11)$$

And, volume is computed by integrating net flow into the chamber, which is that entering from the proximal systemic vein, F_{SV1} , minus that exiting into the right ventricle:

$$V_{RA}(t) = \int [F_{SV1}(t) - F_{TC}(t)] dt \quad (2.12)$$

Having thus characterized both left and right heart function, the next section is devoted to the development of models to describe the systemic and pulmonary vasculature.

Section B. Vascular Model Development

The human vasculature is made up of a highly-branched system of elastic tubular segments ranging in diameter from many millimeters down to a few microns. Due to the extreme complexity and irregularity of this physical system, previous investigators have made many simplifying assumptions in order to formulate models which mathematically describe general hemodynamic behavior [Noordergraaf, 1969]. The particular assumptions used in this thesis include the following: First, blood is assumed to be a homogeneous, Newtonian fluid whose flow is laminar throughout the system. Second, the net transfer of fluid across capillary membranes is neglected, and the amount of blood in the overall system is assumed constant. Third, neural control of vascular caliber is ignored, and all vessels are assumed passive. Fourth, the distributed physiological system is approximated by a lumped-parameter model based on the grouping of vascular segments.

All blood vessels exhibit resistance, compliance, and inertance

properties. By considering pressure analogous to voltage, flow analogous to current, and volume analogous to charge, these hydraulic characteristics can be described in terms of electrical quantities as follows: The frictional forces acting on fluid flowing through a vascular segment result in a drop in pressure which is proportional to volume flow rate. This fluid resistance is analogous to electrical resistance which relates voltage drop to the flow of current, and it is linear if laminar flow is assumed. Because of the distensibility of blood vessels, radial as well as axial (real) flow can occur and thereby change the volume of fluid stored in a segment. The ratio of fluid volume to transmural pressure, the hydraulic compliance, is analogous to electrical capacitance relating charge to voltage. If flow through a segment is not constant, inertance effects must also be considered because the acceleration of a mass of fluid is associated with a change in pressure. The ratio of pressure change to the time derivative of flow is analogous to electrical inductance relating voltage to the time derivative of current.

Using the above analogies, the electrical model for a generalized vascular segment shown in Figure 2.1 is obtained. The parameters which characterize such a segment are: 1) blood inertance, L , 2) resistance to axial flow, R , 3) vessel compliance, C , and 4) resistance to radial wall movement, RW .

Figure 2.1. Electrical Model for a Generalized Vascular Segment.

Although more elaborate characterizations such as that of Spencer [1963] including radial inertance and axial compliance have been proposed, the simple model shown in the foregoing figure suffices to describe the general behavior of a vascular segment. Segmental models of this type are used as building blocks in the forthcoming development of mathematical characterizations for both the systemic and pulmonary circulations.

Part 1. The Systemic Arterial Model

Because the systemic arterial load constitutes the immediate after-load on the left ventricle, its representation is of primary interest in the study of assist pumping. Models such as those of Snyder and Rideout [1968], which divide the arterial circulation into many specialized compartments, give good agreement with physiological behavior, but they are very complicated and require the specification of a large number of parameters. On the other hand, there is a model formulated by Spencer [1963], which is much simpler, but still offers some degree of physiological realism. In it, the entire systemic arterial system is divided into two parts: 1) a proximal segment roughly representative of the ascending aorta, the brachiocephalic and subclavian arteries and their branches, and 2) a distal portion consisting of the descending aorta and its subsequent branches. With such a gross lumping, one certainly cannot expect correlation of model variables with precise anatomical sites. However, Spencer has shown that fairly realistic simulation of proximal pressures such as that in the aortic arch and distal pressures such as that in the femoral artery can be obtained by driving this linear seven-parameter model with a current source representing the flow output of the left ventricle. More recently, Heithecker [1972] demonstrated the utility

of the model in analyzing ventricular assistance by intra-aortic balloon pumping. The Spencer model of the systemic arterial load is selected for application to the current study of left ventricular bypass assistance because, while simple, it does divide the arterial compartment into proximal and distal segments. This separation facilitates the simulation of the attachment of the mechanical pump's outlet connector to the descending aorta or axillary artery [Ross et al, 1971; DeBakey, 1971]. (For further discussion of the bypass pump model, the reader is referred to Chapter IV.)

The actual systemic arterial load model used in this thesis is shown in Figure 2.2. Note that the proximal and distal segments, SA1 and SA2, are each modelled by a circuit similar to that shown in Figure 2.1 for a generalized vascular segment, except that the inertance effects of both are lumped into the single parameter, L_{SA} . The proximal segment is represented by the axial resistance R_{SA1} , the compliance, C_{SA1} , and the radial resistance, RW_{SA1} , while the distal segment is similarly characterized by the parameters R_{SA2} , C_{SA2} , and RW_{SA2} . The circuit shown in Figure 2.2 is actually a modified form of the open-loop Spencer model: Axial flows through the proximal and distal arterial segments continue into veins rather than ground. This difference is reflected in the development of the following seven equations which describe the systemic arterial model.

Proximal arterial pressure is the sum of that across the compliance C_{SA1} , and the radial resistance RW_{SA1} :

$$P_{SA1}(t) = 1/C_{SA1} \int F_{SA1}(t) dt + RW_{SA1} F_{SA1}(t) \quad (2.13)$$

The radial flow into the proximal segment, FW_{SA1} , is in turn computed as the algebraic sum of flow from the left ventricle through the aortic valve, axial flow into the proximal systemic vein, and that through the inertance:

$$FW_{SA1}(t) = F_{AO}(t) - F_{SA1}(t) - F_{SL}(t) \quad (2.14)$$

Longitudinal flow through the axial resistance R_{SA1} is dependent upon the pressure gradient across it:

$$F_{SA1}(t) = [P_{SA1}(t) - P_{SV1}(t)]/R_{SA1} \quad (2.15)$$

Meanwhile, flow through the inertance L_{SA} , is determined by the following integral relation:

$$F_{SL}(t) = 1/L_{SA} \int [P_{SA1}(t) - P_{SA2}(t)] dt \quad (2.16)$$

Equations describing the behavior of variables in the distal arterial segment are similar to those for the proximal segment. Total pressure depends both upon radial flow and its integral:

$$P_{SA2}(t) = 1/C_{SA2} \int FW_{SA2}(t) dt + RW_{SA2} FW_{SA2}(t) \quad (2.17)$$

Radial flow is found by summing currents into the node:

$$FW_{SA2}(t) = F_{SL}(t) - F_{SA2}(t) \quad (2.18)$$

And finally, real flow in the segment is again computed from the arterial-venous pressure gradient:

$$F_{SA2}(t) = [P_{SA2}(t) - P_{SV2}(t)]/R_{SA2} \quad (2.19)$$

The venous pressure P_{SV2} , as well as that for the proximal segment referred to in Equation 2.15, are outputs of the systemic venous model whose description follows.

Part 2. The Systemic Venous Model

In order to have a closed-loop representation of the cardiovascular system, some provision must be made for blood flowing out of the left ventricle to return to the right heart. It is only for this reason that a venous compartment is added to the systemic load model. Unlike such studies as that of Snyder [1969], it is not the intent of this thesis to analyze venous behavior in detail, and therefore collapse phenomena, valves, and hydrostatic pressure sources are not included here. As seen in Figure 2.2, this systemic venous model consists of two resistive-compliant segments, SV1 and SV2, which are similar to those used by Guyton [1955].

Note that the overall model of the systemic vasculature offers two parallel paths for real flow out of the left ventricle. First, consider the case in which blood follows a "lower" circulatory route through the distal segments SA2 and SV2 before entering SA1 and returning to the right heart. Pressure in SV2 is determined by the volume stored in the distal systemic venous compliance:

$$P_{SV2}(t) = 1/C_{SV2} \int [F_{SA2}(t) - F_{SV2}(t)] dt \quad (2.20)$$

Flow through the axial resistance R_{SV2} depends upon this pressure as well as that in SA1:

$$F_{SV2}(t) = [P_{SV2}(t) - P_{SV1}(t)]/R_{SV2} \quad (2.21)$$

There is also a direct flow into the proximal systemic vein through an "upper" circulatory route from SA1. By integrating net flow into C_{SV1} , proximal venous pressure is computed:

$$P_{SV1}(t) = 1/C_{SV1} \int [F_{SV2}(t) + F_{SA1}(t) - F_{SV1}(t)] dt \quad (2.22)$$

All flow through the systemic load model returns to the right atrium through the axial resistance R_{SV1} :

$$F_{SV1}(t) = [P_{SV1}(t) - P_{RA}(t)]/R_{SV1} \quad (2.23)$$

The above four equations specify hemodynamic relationships in the four-parameter model of the systemic venous compartment. Only the pulmonary model remains to be described.

Part 3. The Pulmonary Load Model

Like the systemic vasculature, the pulmonary circulation consists of a complicated arrangement of visco-elastic tubular segments. Once again motivated by the need for a simple model to simulate general hemodynamic behavior, a series of simplifying assumptions have been made.

First, since this study is not directly concerned with pulmonary diseases which may create perfusion imbalances in the two lungs, they are assumed identical and lumped into one compartment. Furthermore, inertance effects are neglected because of their relatively small contribution [Shaw, 1963] in comparison to that in the higher pressure systemic circulation.

Resistance effects in the pulmonary circulation are modelled as follows: Consistent with other models such as that of Rideout and Katra [1969], wall resistance throughout the pulmonary bed is assumed negligible. Resistance to axial flow is represented by the series connection of vessels classified into the following three functional groups: 1) large arteries, 2) large veins, and 3) small vessels including capillaries, arterioles, and venules. Although this is not intended to be a precise anatomical grouping, these segments are represented in the model shown in Figure 2.2 by the resistance parameters R_{PA} , R_{PV} , and R_{PC} , respectively. (In general, pulmonary capillary resistance is dependent upon the volume of air in the alveoli, but in this thesis, ventilatory effects on the pulmonary circulation are not considered, and R_{PC} is assumed constant.)

As pointed out by Fishman [1963], the pulmonary vessels are more distensible than those comprising the systemic circulation. In addition, unlike vessels in solid viscera, they are subject to extravascular pressure changes which occur during respiration. However, again for simplicity, transmural pressures in the pulmonary model shown in Figure 2.2 are referenced to atmospheric rather than pleural pressure. Note that the compliance of the entire pulmonary circulation is lumped into two parameters: C_{PA} represents the compliance of the pre-capillary vessels,

while that of the post-capillary ones is characterized by C_{PV} .

The equations describing the pulmonary load are easily written by inspection of the circuit model in Figure 2.2. Blood flows out of the right ventricle through the pulmonic valve (F_{PM}) into the pulmonary artery:

$$P_{PA}(t) = P_{PC}(t) + R_{PA} F_{PM}(t) \quad (2.24)$$

Pulmonary capillary pressure is computed by integrating the net flow into the pre-capillary compliance, C_{PA} :

$$P_{PC}(t) = 1/C_{PA} \int [F_{PM}(t) - F_{PC}(t)] dt \quad (2.25)$$

Axial flow through R_{PC} , the pulmonary capillary resistance, is found by the following relation:

$$F_{PC}(t) = [P_{PC}(t) - P_{PV}(t)]/R_{PC} \quad (2.26)$$

Net radial flow into the post-capillary compliance, C_{PV} , determines pulmonary venous pressure:

$$P_{PV}(t) = 1/C_{PV} \int [F_{PC}(t) - F_{PV}(t)] dt \quad (2.27)$$

Finally, flow through the pulmonary vein into the left atrium is dependent upon the pressure gradient across its axial resistance:

$$F_{PV}(t) = [P_{PV}(t) - P_{LA}(t)]/R_{PV} \quad (2.28)$$

Equations 2.24-2.28 describe the dynamic relationship of pulmonary load variables in terms of the five parameters R_{PA} , C_{PA} , R_{PC} , C_{PV} , and R_{PV} . Together with Equations 2.1-2.23, they complete the theoretical description of a closed-loop mathematical model of the uncontrolled cardiovascular system. Computational aspects of this model of the unassisted circulation are considered in the next chapter.

Figure 2.2. Schematic Diagram of the Overall Cardiovascular Model.

CHAPTER III: COMPUTATIONAL ASPECTS OF THE UNASSISTED CIRCULATORY MODEL

Having established a theoretical model of the uncontrolled cardiovascular system, the purpose of this chapter is to treat the computational aspects of the problem. In Section A., the method of solution of model equations and the procedure of parameter development are discussed. Then, results of simulations under normal as well as various abnormal conditions are presented in Section B.

Section A. Parameter Development for the Unassisted Circulation

The system of differential equations which were developed in the previous chapter to describe the composite cardiovascular model are solved using an EAI Model 680 analog computer. Advantages of analog simulation include the following: First, non-linear equations such as those resulting from rectifying characteristics of heart valves can be solved with relative ease. Second, real-time and faster than real-time solutions are possible. Finally, steady state, as well as transient behavior of the system can be studied, because many cycles of the solution can be determined without the expense of digital computation. Analog computer diagrams for the solution of model equations are given in Appendix B.

Part 1. Heart Parameters

In order to develop a set of model parameters which result in reasonable simulation of physiological behavior, the characteristics of the ventricular contraction must first be determined. Since the

major work load is carried by the left ventricle, its elastance function is derived from clinical measurement. Balldridge obtained such data by using left ventricular pressure recordings in combination with sampled values of left ventricular volume determined from single-plane cine-angiography.* By computing the ratio of pressure over volume at each sample point, the value of elastance is found at discrete times in the cardiac cycle. For use in the analog model, this discrete function is plotted by hand to determine break points. Then, an analog approximation of the systolic elastance function is obtained by using a ten-segment diode function generator. Diastolic elastance, assumed constant in the model, is computed by averaging over all data points taken in this interval of the cardiac period.

The first case of interest is the normal. Although the left ventricular elastance curve selected is that of a particular patient who exhibited no clinical signs of cardiac disease, it is typical of the class of normals studied. Figure 3.1 gives a summary of the clinical data available for this patient. Model parameters are chosen so as to produce pressures and volumes which are comparable to those indicated. Using the approach of Beneken [1965], atrial elastance is described in the model by a constant value for the majority of the cardiac cycle, and a half-sine wave during the relatively brief period of atrial systole. Considering first the left atrium, diastolic elastance is chosen so as to yield a mean atrial volume of about 100 ml. The strength of atrial contraction, represented by the amplitude of the half-sine wave, is adjusted so as to contribute approximately 20% to left ventricular

*Measurements were taken by Dr. J.S. Cole, Cardiac Catheterization Laboratory, Baylor College of Medicine.

Clinical Classification	Normal
Left Ventricular Pressure	120/0/6 mm Hg
Systemic Arterial Pressure	120/80 mm Hg
Heart Rate	74 beats/min
Ventricular Stroke Volume	84 ml
Cardiac Output	6.2 l/min
Left Ventricular End-Diastolic Volume	120 ml
Left Ventricular Ejection Fraction	.70

Figure 3.1. Summary of Clinical Data Available for Patient with Normal Ventricular Function.

filling [Scher, 1965]. The timing of atrial systole relative to that of the ventricle is shown graphically in Figure 3.2. Note that for the left atrium, diastolic elastance is .06 mm Hg/ml, peak systolic elastance is .17 mm Hg/ml, and the duration of systole is approximately .1 sec. The delay between the end of atrial contraction and the onset of ventricular systole, although not obvious in the figure, is about .01 sec. The elastance of the left ventricle is .025 mm Hg/ml during diastole, and reaches a peak systolic value of approximately 3 mm Hg/ml. The total time required for the single heart period shown in the figure is .81 sec.

Contractile properties of the right heart are characterized by magnitude scaling elastance functions determined for the left heart. Such an assumption of cardiac synchrony is necessitated primarily by the lack

Figure 3.2. Atrial and Ventricular Elastance Functions for the Left Heart.

of clinical data for right ventricular elastance. Using the reasoning that for a comparable volume, the right ventricle generates pressures only about 20% as great as those in the left ventricle, the elastance of the right ventricle is assumed equal to $E_{LV}/5$ ($K_V=.2$). Similarly, a constant fraction times E_{IA} (K_A) is used to simulate right atrial behavior.

Having established time-varying elastance functions for all four contractile chambers, only the specification of valve parameters remains to complete the description of both the right and left heart models. All four of the cardiac valves are assumed to permit no regurgitant flow. Such ideal zero limiting can be easily simulated on the 680 analog computer by the use of limit summers whose circuits include

diodes in the feedback path of the amplifier. Resistance to flow forward through the heart valves is normally quite small, and pressure drops across them are usually only a few mm Hg. For simplicity, the valvular resistance parameters R_{MT} , R_{AO} , R_{TC} , and R_{PM} are assumed equal and are implemented using pot feedback.

Part 2. Systemic Load Parameters

The first set of load parameters established are those which represent the systemic arterial compartment. Because the proximal and distal segments are separated only by an inertance (See Figure 2.2), the mean values of pressures P_{SA1} and P_{SA2} are equal. Knowing the cardiac output and choosing an arbitrary division of mean flow between the two segments, one can determine values for the axial resistance parameters, R_{SA1} and R_{SA2} . For the normal case summarized in Figure 3.1, the mean systemic arterial pressure is about 100 mm Hg, and the cardiac output is 6.2 l/min. Assuming that flow through the upper circulation constitutes one-third of the total cardiac output, R_{SA1} and R_{SA2} are determined to be 2.6 mm Hg-sec/ml and 1.3 mm Hg-sec/ml, respectively. Because no attempt is made to relate model segments to specific anatomical sites, the compliance parameters C_{SA1} and C_{SA2} are chosen so as to produce realistic aortic pressure waveforms rather than by computing the ratio of mean volume to mean pressure in each segment. Also, the parameter values RW_{SA1} , RW_{SA2} , and L_{SA} cannot be determined from physiological measurements and therefore their selection is also based upon waveforms P_{SA1} , P_{SA2} , and left ventricular volume variation. The particular values used in this study are listed in Figure 3.3.

As noted in Figure 2.2, the systemic venous model consists of four

Left Heart Model	R_{MT}	.01 mm Hg-sec/ml
	R_{AO}	.01 mm Hg-sec/ml
Right Heart Model	R_{TC}	.01 mm Hg-sec/ml
	R_{PM}	.01 mm Hg-sec/ml
	K_V	.2 (dimensionless)
	K_A	.4 (dimensionless)
Systemic Arterial Model	R_{SA1}	2.6 mm Hg-sec/ml
	R_{SA2}	1.3 mm Hg-sec/ml
	C_{SA1}	.5 ml/mm Hg
	C_{SA2}	1.3 ml/mm Hg
	RW_{SA1}	.07 mm Hg-sec/ml
	RW_{SA2}	.10 mm Hg-sec/ml
	L_{SA}	.00667 mm Hg-sec ² /ml
Systemic Venous Model	R_{SV1}	.03 mm Hg-sec/ml
	R_{SV2}	.09 mm Hg-sec/ml
	C_{SV1}	200 ml/mm Hg
	C_{SV2}	170 ml/mm Hg
Pulmonary Load Model	R_{PA}	.04 mm Hg-sec/ml
	R_{PC}	.02 mm Hg-sec/ml
	R_{PV}	.03 mm Hg-sec/ml
	C_{PA}	12.5 ml/mm Hg
	C_{PV}	16.7 ml/mm Hg

Figure 3.3. Summary of Model Parameters for the Normal Simulation.

parameters. The resistances R_{SV1} and R_{SV2} are quite small relative to arterial resistances, while venous compliances C_{SV1} and C_{SV2} are chosen sufficiently large to store a total of about 5 liters of blood at a very low pressure. For such parameter values, this venous compartment does not appreciably affect the loading of the left ventricle, and therefore very little change in cardiac output or arterial pulse pressure is noted when this compartment is added. The particular parameter values for the venous compartment are also listed in Figure 3.3.

Part 3. Pulmonary Load Parameters

Having specified parameters for the heart model and the systemic circulation, only those for the pulmonary compartment remain to be determined. (See Figure 2.2). Lacking pulmonary data on the particular patient under discussion, resistances R_{PA} , R_{PC} , and R_{PV} are adjusted to yield pulmonary pressures expected in the normal case [Folkow and Neil, 1971]. The compliance parameters C_{PA} and C_{PV} are chosen so as to store comparable volumes in the pre-capillary and post-capillary segments. The five pulmonary parameters complete the list of those given in Figure 3.3.

Once a set of normal parameters for the complete unassisted cardiovascular model have been specified, the effect of specific changes such as those discussed in the following section can be made. Of particular interest is the effect of abnormal ventricular performance on the overall circulation. For this reason, elastance data for a patient with ventricular asynergy (abnormal wall movement) has been obtained from the same cardiac catheterization laboratory which supplied measurements for the normal. To reproduce this abnormal elastance curve on the analog computer, a variable diode function generator is again used. Model

output in the next section relating to the case of ventricular asynergy can be compared with the clinical data summarized in Figure 3.4.

Clinical Classification	Asynergistic
Left Ventricular Pressure	120/4/10 mm Hg
Systemic Arterial Pressure	120/80 mm Hg
Heart Rate	70 beats/min
Ventricular Stroke Volume	83 ml
Cardiac Output	5.8 l/min
Left Ventricular End-Diastolic Volume	230 ml
Left Ventricular Ejection Fraction	.37

Figure 3.4. Summary of Clinical Data for Patient with Abnormal Ventricular Function.

Section B. Model Results for the Unassisted Circulation

Verification of the composite model of the unassisted circulatory system is dependent upon its ability to simulate both normal and abnormal physiological behavior. In this section, the results of a few such simulations are presented and discussed. First, some of the basic properties of the model are pointed out by consideration of the normal case in some detail. Then, various abnormal conditions are simulated by increasing valvular resistance, elevating systemic arterial resistance, changing overall blood volume, and finally altering ventricular elastance.

Part 1. Simulation of Normal Conditions

Results for the normal case are produced by using the normal elastance curve and the parameter development procedure discussed in the previous section. Figure 3.5 emphasizes the importance of the time-dependent elastance functions in determining the relationship between instantaneous pressure and volume within the heart's contractile chambers. Tracings a. and b. of this figure demonstrate how the left atrial and ventricular elastance functions discussed earlier are periodically repeated to allow simulation of the dynamic system in the steady state. Upon examination of left ventricular volume V_{LV} , shown in tracing c., one can see that the contribution of left atrial contraction to the filling of the left ventricle is about 20 ml in the model. The simulation indicates an end-diastolic volume of 115 ml and a stroke volume of 85 ml for the left ventricle. Both of these values are comparable to actual measurements from the patient whose elastance curve was used to drive the model. (See Figure 3.1). The heart rate is 74 beats/min, resulting in a cardiac output of about 6.3 l/min. Tracing d. of Figure 3.5 shows the time course of left ventricular pressure, P_{LV} . Note that this pressure is near zero during early diastole, increases to about 6 mm Hg following atrial contraction, and reaches its maximal value of 128 mm Hg approximately 150 msec before the peak in E_{LV} . These values as well as the general shape of the P_{LV} waveform are in close agreement with clinical measurement. Behavior of right ventricular variables is also recorded in Figure 3.5. Because the elastance functions used in the model for the right atrium and ventricle are simply those of the left side scaled down in magnitude, they are not shown explicitly. Tracing e. illustrates that right ventricular volume, V_{RV} , is comparable

Figure 3.5. The Effect of Atrial and Ventricular Elastance on Pressure and Volume in the Right and Left Ventricles.

to V_{IV} both in terms of end-diastolic volume and stroke volume. The pressure in the right ventricle (P_{RV}) shown in tracing f. is similar to P_{IV} in shape, but the peak value of 30 mm Hg is considerably less than that on the left side.

Figure 3.6 illustrates the relationship between flow through ventricular outlet valves and load pressures on both sides of the heart. Recall that both aortic and pulmonic valves were modelled as ideal diodes, and note from tracings a. and e. that indeed no backflow occurs through either one. The notching apparent in tracing c., which depicts pressure proximal to the left heart (P_{SA1}), is due to the inclusion of the inertance term in the systemic arterial load model. As shown in tracing b., the flow through this inductive element, F_{SL} , becomes negative after the closing of the aortic valve, and thus causes the appearance of a dicrotic notch in the P_{SA1} waveform similar to that commonly observed in physiological measurements. Such high-frequency variations are filtered out by the resistive-compliant segment representing the distal systemic arterial load, and therefore no notching is evident in the second arterial pressure waveform, P_{SA2} , recorded in tracing d. Due to phase shift caused by the inertance, the peak in pressure in the distal segment is delayed relative to that for the proximal segment. However, both P_{SA1} and P_{SA2} show a maximum value of 125 mm Hg and a minimum value of about 75 mm Hg, which correspond to realistic systolic and diastolic arterial pressures for the normal. Pulmonary arterial pressure P_{PA} , recorded in tracing f. exhibits no notching because no inertance term is included in the pulmonary load model. Note that P_{PA} is about 30 mm Hg/10 mm Hg, and although E_{LV} and E_{RV} have the same timing, the pulmonic valve remains open longer than the aortic, and peak flow through it is not as

Figure 3.6. The Relationship Between Flow Through Ventricular Outlet Valves and Load Pressures on Both Sides of the Heart. (For explanation see text).

great. (The area under the flow curves corresponds to ventricular stroke volume and is, of course, equal for the two sides of the heart in the steady state.)

Figure 3.7 gives a summary of model results for the unassisted normal circulation. The particular format used offers the following important information for the analysis of essential behavior of the overall model: Tracing a. of E_{LV} gives an indication of the strength of ventricular contraction as well as showing heart rate. End-diastolic volume, stroke volume, and ejection fraction of the left ventricle can be determined by examination of V_{LV} in tracing b. The recording of P_{LV} in tracing c. shows end-diastolic as well as peak pressure in the left ventricle. Tracings d. and e. of P_{SA1} and P_{SA2} illustrate systemic arterial load pressure variations at sites proximal and distal to the heart. Right ventricular end-diastolic volume and stroke volume can be noted from tracing f. of V_{RV} . The values of P_{PA} recorded in tracing g. give an indication of the after-load on the right ventricle. Under these normal conditions, P_{PA} is 26 mm Hg/9 mm Hg. Tracing h. shows pulmonary venous pressure P_{PV} , and is included in order to demonstrate any tendency toward accumulation of fluid in the pulmonary bed under pathological conditions. Note that for the normal, the mean value of P_{PV} is about 8.5 mm Hg.

Part 2. Simulation of Abnormal Conditions and Physiological Manipulations.

Case a. Mitral Stenosis

The first abnormal condition simulated is mitral stenosis, and the results, recorded in the same format as those for the normal, appear in

Figure 3.7. Summary of Model Output for the Normal Case.

Figure 3.8. The only change made from the normal case is that R_{MT} , the resistance of the mitral valve in the open position, is increased by a factor of 10. Ventricular function is normal, as indicated by the fact that tracing a. of the elastance function remains unchanged. The left ventricular volume recorded in tracing b. is 95/25 ml. Although the ejection fraction of .75 is high, ventricular filling is impaired and the stroke volume is reduced from 85 ml to 70 ml. Because the heart rate is fixed, this constitutes about an 18% decrease in cardiac output. Tracing c. shows that peak left ventricular pressure is reduced, and tracings d. and e. indicate that arterial pulse pressure has dropped to about 105/65 mm Hg. As seen in tracing f., the right ventricle fills to near normal 125 ml volume, but like the left ventricle, ejects only 70 ml per heart beat. Pulmonary artery pressure in tracing g. has increased to 37/20 mm Hg. Tracing h. illustrates that pulmonary venous pressure is up by more than 100% to a mean value of about 20 mm Hg. Also note that the peak in P_{PV} due to left atrial contraction is more evident, as increased mitral resistance causes more blood to flow back into the pulmonary vein rather than forward through the stenotic valve into the ventricle. In summary, the above observations from the simulation of mitral stenosis indicate that although circulation is decreased (assuming that compensatory changes in load parameters, heart rate, etc. do not occur), the most dramatic effect is on pulmonary variables. The elevation of pulmonary pressures is accompanied by an increase in the volume stored in these highly-compliant vessels as blood tends to accumulate behind the abnormal valve.

Case b. Aortic Stenosis

Figure 3.9 shows the results for the simulation of aortic stenosis.

Figure 3.8. Summary of Model Output for the Case of Mitral Stenosis ($R_{MT} = 10$ times normal).

In this case, all parameters are normal except R_{AO} , the forward resistance of the aortic valve, which has been increased by a factor of 10. Again, tracing a. shows normal ventricular elastance. The variation in left ventricular volume in tracing b. of approximately 120/35 ml indicates that both stroke volume and ejection fraction are near normal. Comparison of the maximum left ventricular pressure of 160 mm Hg recorded in tracing c. with the peak aortic pressure of 120 observed in d. demonstrates that the pressure drop across the aortic valve has increased appreciably. However, tracings e., f., g., and h. of P_{SA2} , V_{RV} , P_{PA} and P_{PV} all exhibit normal behavior. Thus, the effect of this degree of aortic stenosis is merely the elevation of left ventricular pressure during systole.

In order to effect a greater change in overall system behavior, a more severe aortic stenosis condition is imposed. Figure 3.10 shows the results of such a simulation in which R_{AO} is 20 times its normal value. Ventricular elastance in tracing a. is again unchanged. Tracing b. of V_{LV} indicates that end-diastolic volume is up to 130 ml, stroke volume is 80 ml, and the resultant decrease in ejection fraction to a value of about .6 is not severe. Peak P_{LV} from tracing c. is almost 200 mm Hg, while P_{SA1} and P_{SA2} in d. and e. are near normal. Tracing f. of V_{RV} is normal, and P_{PA} and P_{PV} in g. and h. show increases of only about 1 mm Hg. Thus, the model predicts that even for a pressure drop of almost 80 mm Hg across the aortic valve, circulation is not severely impaired. (One should keep in mind, however, that the need to generate such high pressure within the left ventricle may appreciably increase myocardial oxygen demand and coronary flow requirements.)

Figure 3.9. Summary of Model Output in the Case of Aortic Stenosis ($R_{A0} = 10$ times normal).

Figure 3.10. Summary of Model Output in the Case of Severe Aortic Stenosis ($R_{AO} = 20$ times normal).

Case c. Systemic Arteriolar Constriction

One of the most important factors in the regulation of blood pressure in the body is the ability of the arteriolar constriction vessels to effect changes in systemic load resistance. This physiological mechanism can be crudely represented in the model by manipulation of the parameter R_{SA2} . When this parameter is increased by a factor of 3 from its normal value, the model output shown in Figure 3.11 is the result. Note that ventricular elastance depicted in tracing a. remains unchanged, again indicating that the heart itself is normal. From tracing b. of V_{LV} , end-diastolic volume is seen to increase to 150 ml, stroke volume is up to 90 ml, and the ejection fraction is reduced to .60. The P_{LV} waveform shown in c. is dramatically affected, in that not only is peak systolic pressure up to 215 mm Hg, but end-diastolic pressure is also elevated. Systemic arterial pulse pressures of 210/155 mm Hg recorded in tracings d. and e. are also considerably greater than normal. Right ventricular volume in f. indicates only a slight increase in filling, while tracings g. and h. show somewhat elevated pulmonary arterial and venous pressures of 38/10 mm Hg and 10 mm Hg, respectively. Overall, the model suggests that the main effect of increasing systemic arterial resistance is an elevation of systemic pressures, and to a lesser extent, an increase in cardiac output for the normal heart.

Case d. Hemorrhage

In addition to being affected by load resistance changes, blood pressure is, of course, also dependent upon the total amount of fluid in the overall system. The simulation whose results are recorded in

Figure 3.11. Summary of Model Output in the Case of Increased Systemic Arterial Resistance ($R_{SA2} = 10$ times normal).

Figure 3.12 is performed by decreasing the initial conditions of the system (the volume in the systemic veins) by 50%. Such results emphasize the advantage of the closed-loop analog model by demonstrating the ability to simulate the effect of blood loss on overall circulatory performance. Tracing a. of Figure 3.12 shows that again E_{LV} is normal. The recording of V_{LV} in b. indicates that even though the left ventricular ejection fraction is normal, end-diastolic volume is reduced to 55 ml, and stroke volume is down to 40 ml. Peak P_{LV} shown in c. is only 65 mm Hg, and systemic arterial pulse pressures in d. and e. have decreased to 65/40 mm Hg. Tracing f. demonstrates that V_{RV} variations are quite similar to those occurring in the left ventricle. The pulmonary arterial and venous pressures of 13/4 mm Hg and 4 mm Hg shown in g. and h. are also considerably less than normal. In summary, the simulation of blood loss produces a diminishment in pressures and volumes in all segments of the circulatory model. Although heart and load parameters are all normal, cardiac output has been reduced by more than 50%.

Case e. Ventricular Asynergy

A most important effect yet to be considered in this section is that resulting from abnormalities in ventricular contraction. Such changes are simulated in the model by using an elastance curve such as that of the patient discussed in Section A, whose left ventricle is clinically classified as asynergistic. The results which follow demonstrate the effect of abnormal elastance first for both ventricles simultaneously, and then for either one singly. In an effort to isolate the effect of elastance changes, the circulatory loads, atria, and initial conditions are the same as for the normal case.

Figure 3.12. Summary of Model Output in the Case of Decreased Overall Fluid Volume.

Figure 3.13 shows the results of simulating abnormal contraction of both ventricles. The left ventricular elastance function is that obtained from patient data, and E_{RV} is assumed proportional to it. Examination of tracing a. reveals that the peak value of E_{LV} is diminished from over 3 for the normal down to about .65 in this asynergistic case. Also note that the time to peak is increased, and ventricular systole occupies a greater fraction of the cardiac cycle than for the normal. Heart rate changes only slightly to a new value of 70 beats/min. A most dramatic effect is noted in tracing b. of V_{LV} which indicates that end-diastolic volume is up to 160 ml, stroke volume is reduced to 50 ml, the ejection fraction is down to .31, and cardiac output is only 3.5 l/min. The waveform in c. of P_{LV} shows a decrease in left ventricular peak pressure to 95 mm Hg, as well as an elevation in diastolic pressure. Systemic arterial pressures in d. and e. are approximately 90/55 mm Hg. Tracing f. demonstrates dilatation of the right ventricle, which is to be expected in light of the assumption that its elastance function is also abnormal. Pulmonary artery pressure recorded in g. is 25/11 mm Hg, and mean P_{PV} in h. has increased to about 10.5 mm Hg. Overall, the above observations indicate that from this case of abnormal elastances for both sides of the heart, ventricular volumes are increased, while both cardiac output and systemic arterial pressures are reduced, and pulmonary venous pressure is somewhat elevated.

Given the abnormal elastance function for both ventricles, some form of compensation will have to be provided in the model if near normal cardiac output and arterial pressures such as those indicated in Figure 3.4 are to be achieved. Such an adjustment can easily be made without having to change load parameters, if the overall blood volume in the

Figure 3.13. Summary of Model Output in the Case of Abnormal Left and Right Ventricular Elastances (Uncompensated).

system is increased. Figure 3.14 gives the results of a simulation in which the model, again driven by asynergistic left and right ventricular elastance functions, is so compensated. Tracing a. shows the abnormal E_{LV} . From b., left ventricular end-diastolic volume is up to 215 ml, resulting in an increased stroke volume. Peak P_{LV} is now 120 mm Hg, and arterial pressures in d. and e. are approximately 120/75 mm Hg. Recording f. shows that right ventricular volume is even greater than V_{LV} . Pulmonary pressures in g. and h. of 31/14 mm Hg and 13.5 mm Hg indicate a further increase in P_{PV} as a result of volume compensation. Overall, this simulation demonstrates that, even with severely abnormal ventricular function of both sides of the heart, near normal systemic arterial pressures can be generated, at the expense of ventricular dilatation and elevation of pulmonary venous pressure. Note that actual measurement of the patient's left ventricular volume given in Figure 3.4 corroborates this tendency toward ventricular hypertrophy in the abnormal case.

Although the patient from whom the abnormal elastance data is taken was clinically diagnosed as having an asynergistic left ventricle, there is no real reason to assume right ventricular disfunction as well. Figure 3.15 shows the results of a simulation in which the elastance of the left ventricle is abnormal, while E_{RV} is that used to characterize the normal. Tracing a. shows the asynergistic E_{LV} . Left ventricular volume recorded in b. is approximately 245/170 ml, which indicates a stroke volume of 75 ml and an ejection fraction of only .32. Tracings b., c., and d. of P_{LV} , P_{SA1} , and P_{SA2} demonstrate that unlike the previous case, no volume compensation is necessary for the achievement of normal systemic arterial pressures. Note from tracing f. of V_{RV} that

Figure 3.14. Summary of Model Output in the Case of Abnormal Left and Right Ventricular Elastances (Volume Compensated).

Figure 3.15. Summary of Model Output in the Case of Abnormal Left Ventricular Elastance.

the right ventricle also exhibits normal behavior. Pulmonary artery pressure in g. is approximately 30/13 mm Hg, while mean pulmonary venous pressure in h. is about 13 mm Hg. In general, these results are similar to those produced previously under conditions of bilateral asynergy, except that here the right ventricle is normal, and therefore it does not become dilated.

If, on the other hand, it is the left ventricle which is normal while the right one is asynergistic, the model results shown in Figure 3.16 are produced. The function E_{LV} recorded in tracing a. is normal, and tracing b. of V_{LV} indicates that left ventricular end-diastolic volume is approximately 30 ml less than normal. Its stroke volume is also reduced, and pressures shown in tracings c., d., and e. are only about 85% of their normal values. As observed in f., the right ventricle is severely dilated due to its decreased elastance. Unlike the previous cases in which left ventricular elastance was abnormal, the pulmonary pressures observed in tracings g. and h. are actually less than normal.

The above cases serve to demonstrate the flexibility of the closed-loop analog model of the unassisted circulation. The simulation of left ventricular bypass assistance is the subject of the following chapter.

Figure 3.16. Summary of Model Output in the Case of Abnormal Right Ventricular Elastance.

CHAPTER IV: THE ASSISTED CIRCULATION

Having simulated the unassisted circulation, the purpose of this chapter is to discuss the model of the left ventricular bypass assist pump and its effect on hemodynamics. In Section A., the basic modeling approach is presented and four modes of pump control are described. Then, in order to facilitate quantitative comparison of these control modes, a scalar performance index is developed in Section B. Section C. treats the computational aspects of model implementation and parameter specification. Finally, results of simulations of the assisted circulation are presented and discussed in Section D.

Section A. Theoretical Aspects of the Pump Model

The left ventricular bypass pump which has been used at Baylor in animal experiments, as well as for a limited number of human patients, is a pneumatically-driven diaphragm pump with unidirectional valves at both the inlet and outlet of the fluid chamber. In this study, the pump is assumed to be connected so that blood can be drawn out of the left atrium and pumped into the arterial circulation by switching the pneumatic drive pressure between low and high pressure. Possible logical schemes used to control the timing of this switching are discussed in some detail later in this chapter.

Part 1. The Analog Model

A schematic of the electrical model of the bypass pump is shown in Figure 4.1. The lines leading to and from the pump are modelled as

Figure 4.1. Schematic of the Electrical Equivalent of the Analog Pump Model.

purely resistive, and the inlet and outlet valves are assumed ideal. Therefore, only when P_P , the pressure in the fluid chamber of the pump, is less than left atrial pressure can blood flow through R_{PI} , the lumped resistance of the inlet connector and valve:

$$F_{PI}(t) = \begin{cases} [P_{LA}(t) - P_P(t)]/R_{PI} & P_{LA} > P_P \\ 0 & \text{otherwise} \end{cases} \quad (4.1)$$

Similarly, flow out of the pump can occur only when P_P exceeds load pressure, P_{SA2} :

$$F_{PO}(t) = \begin{cases} [P_P(t) - P_{SA2}(t)]/R_{PO} & P_P > P_{SA2} \\ 0 & \text{otherwise} \end{cases} \quad (4.2)$$

Instantaneous volume in the fluid chamber is computed by integrating net flow into the pump:

$$V_P = \int [F_{PI}(t) - F_{PO}(t)] dt \quad (4.3)$$

The pressure source P_P shown in Figure 4.1 is, in general, a function of both the pneumatic pressure P_D driving the diaphragm, and V_P , the volume of fluid in the pump chamber. However, if V_P is kept within a prescribed range, P_P can be assumed to depend only upon P_D , as illustrated below in Figure 4.2:

Figure 4.2. The Relationship of Pump Fluid Pressure, P_P , to Pneumatic Drive Pressure, P_D , and Pump Volume, V_P .

Such a relationship can be described by the following equation:

$$P_P(t) = P_D(t) \quad V_{\min} < V_P < V_{\max} \quad (4.4)$$

If the diaphragm is overdriven by attempting to fill the pump when it has already reached its maximum value or to eject when the fluid volume is less than the prescribed minimum, then the assumption of volume-independence is violated. Rather than using a complicated function to reflect the dependence of P_P on both P_D and V_P , the following reasoning is used for modelling: During the time period in which the diaphragm is overdriven, the pump is rendered incapable of responding to the pneumatic driving pressure, and therefore no flow through the pump can occur. Thus, when filling is attempted with an already full pump (or ejection

is attempted with an empty one), the pump is forced into a "hold" state where it is essentially switched out of the circuit until the condition is relieved by permitting ejection (or filling) to resume. This reasoning is used in the development of the four modes of pump control whose descriptions follow.

Part 2. Asynchronous, Time-Triggered Control

The electropneumatic power unit which has been used at Baylor to drive the left ventricular bypass pump can be triggered either internally or externally by the subject's EKG signal. The first form of triggering results in a free-running mode of operation where assist pumping is not synchronized with the natural cardiac cycle. To implement such an asynchronous mode of pump control, one must specify the rate of pumping and the duration of the systolic gas pulse delivered to the diaphragm.

In order to model this time-triggered, asynchronous mode of control, a periodic logic signal, $P(t)$, of the form indicated in Figure 4.3 is generated. The parameters which specify this signal are the pump period, T_p , which is the reciprocal of pump rate, and T_s , the duration of pump systole. The logic signal $U(t)$ shown in the figure changes from 0 to 1 when the pump is turned on, and returns to 0 when a pumping episode is terminated. Taking into account the previous argument regarding attempts to overdrive the diaphragm, the logical decision criteria listed in b. are used to determine which one of the three possible states the pump is in at any particular point in time. The ejection state, E, means that P_p equals P_{max} , and therefore fluid is being forced out of the pump chamber. The fill state, F, occurs when P_p equals P_{min} , and flow is into the pump. When the pump is not on, or the diaphragm is being over-

driven, no flow is allowed through the chamber and the pump is in the hold state, H.

Figure 4.3. Asynchronous, Time-Triggered Pump Control. (a. Logical Timing Signals. b. Logical Decision Criteria.)

Part 3. Synchronous, Time-Triggered Control

If the EKG is used as an external trigger to the pneumatic driving unit, pump ejection can be constrained to occur only during a prescribed interval of the cardiac cycle. One way to implement such synchronous pumping is to specify the timing parameters T_D and T_S . The time between the occurrence of the subject's R wave and the time at which pump systole begins is T_D , the pump delay, and T_S is again the duration of pump systole. Using these parameters, a synchronized timing signal $S(t)$ of the form shown in Figure 4.4 can be generated. Pump ejection is timed to occur only during that time interval $T_D < t < T_D + T_S$ when $S(t)$ equals 1, and filling can take place for any t outside this interval where $S(t)$

equals 0. Due to the fact that only timing criteria are used to control pump state, the possibility of overdriving the diaphragm exists, and the model may therefore be forced into a hold state during pumping. The decision criteria for determination of pump state for this time-triggered synchronous mode of control are given in Figure 4.4.

Figure 4.4. Synchronous, Time-Triggered Pump Control. (a. Logical Timing Signal. b. Logical Decision Criteria)

Part 4. Asynchronous, Volume-Triggered Control

Another form of pump control which has been used in animal experiments is one in which volume criteria are used in place of a timing signal to determine the pump state. Norman et al [1973] have been able to determine the instantaneous volume of blood in the pump by using a capacitance technique: A metal film coated on the air dome of the pump, together with the blood in the chamber, constitute two conducting plates separated by a distance which varies as the volume of blood in the pump

chamber changes. Triggering pump ejection by noting that pump volume has achieved its maximum value and then commencing filling again as soon as the pump is empty, one hopes to maximize flow through the pump by keeping the diaphragm in constant motion, and thereby help to minimize the formation of thrombi due to stasis. In the model, this is equivalent to reducing the time spent in the hold state to zero once a pumping episode is begun.

Generation of logical control signals is as follows: The output of a flip-flop Q is set (becomes logical 1) by the condition $V_p > V_{\max}$, reset (changed to logical 0) by the condition $V_p < V_{\min}$, and maintains a constant state when neither of these two conditions is detected. Using the output of Q , the decision criteria shown in Figure 4.5 provide logical pump control for the asynchronous volume-triggered mode of operation.

Eject	$E = U \cap Q$
Fill	$F = U \cap \bar{Q}$
Hold	$H = \bar{E} \cap \bar{F} = \bar{U}$

Figure 4.5. Logical Decision Criteria for Asynchronous, Volume-Triggered Pump Control.

Part 5. Synchronous, Time-and-Volume-Triggered Control

By utilizing the EKG signal in addition to the volume information just discussed, synchronization can be achieved without restricting pump filling. Synchronizing constraints, presented in Part 3. of the current section, prohibit pump ejection when the logical signal $S(t)$ equals 0.

Therefore, if the volume in the pump chamber reaches its maximum value before the delay period T_D has elapsed, then the pump must hold until $t = T_D$. However, in the time-triggered mode described in Part 3, the pump is forced into the hold state not only for this condition, but also for the one in which the pump is empty, but the ejection period is not over. This problem can be avoided by using a flip-flop R, which is set by the leading edge of the synchronizing signal $S(t)$ and reset when V_P becomes less than $V_{\min}$. In this way, filling is allowed to commence when the pump becomes empty instead of having to wait for $S(t)$ to return to zero. Explicit decision criteria used for this synchronous, time-and-volume-triggered mode of pump control are summarized below in Figure 4.6.

Eject	$E = U \cap R$
Fill	$F = U \cap \bar{R} \cap (V_P < V_{\max})$
Hold	$H = \bar{E} \cap \bar{F}$

Figure 4.6. Logical Decision Criteria for Synchronous, Volume-Triggered Pump Control.

Section B. Performance Index Development

Part 1. Theoretical Considerations

In order to quantitatively compare the four proposed modes of pump control, one must specify a mathematical performance index which reflects the two main goals of assist pumping: 1) improvement of the circulation,

and 2) provision of a degree of "rest" to the failing ventricle. This latter goal implies the reduction of heart work, and is facilitated in bypass pumping by removing blood from the left atrium, and thus serving to reduce left atrial and ventricular end-diastolic pressures characteristically elevated in heart failure. By subsequent pumping of this blood into the systemic arterial load, cardiac output is augmented by pump output, and overall circulation can thus be improved.

Employing an approach similar to that utilized by Kane et al [1971] to assess the effect of intra-aortic balloon pumping, the performance index used in this study is a scalar functional which is the weighted sum of three terms, each of which is related to a particular goal of assist pumping.

The first term in the performance index reflects the goal of improving the circulation. Of primary interest in ventricular assistance is the enhancement of blood flow in the vital areas, such as those perfused by the coronary and carotid circulations. However, the lumped arterial model used in this study does not characterize such compartments specifically, nor does it include load parameter changes which can result in effects such as autoregulation of flow in specialized regions. Therefore, maximization of mean systemic arterial pressure is assumed to indicate optimal enhancement of overall circulation. Hence, the first term in the performance index is obtained by computing the mean value of P_{SA1} , the model variable which represents the arterial pressure at a site proximal to the left heart.

The second and third terms of the proposed performance index reflect the attempt to minimize heart work. The area enclosed by the pressure-volume loop traced out by the left ventricle in the course of

one cardiac cycle represents the actual external work it does in moving blood from a low-pressure source to a high-pressure load. This area can be computed by integrating the product of ventricular pressure and flow out through the aortic valve over the systolic interval, and then subtracting the integral of ventricular pressure times mitral flow. However, since the work done by the ventricle during systole far exceeds that done on it during diastole, the latter is neglected in the calculation of the second term of the performance index. The third term of the proposed index is used to reflect the fact that ventricular efficiency, the ratio of external work done to energy expended, is not constant. Many investigators have emphasized the importance of the development of isovolumic tension in determining myocardial oxygen consumption [Sarnoff et al, 1958; Sonnenblick et al, 1965; Burns and Covell, 1972]. In accordance with Laplace's law [Ruch and Patton, 1965], tension is dependent upon volume and geometry as well as pressure, and therefore the dilated ventricle works under a mechanical disadvantage. By attempting to reduce mean left atrial pressure, one hopes to minimize left ventricular end-diastolic volume and thereby remove the mechanical disadvantage, improve myocardial efficiency, and decrease oxygen requirement.

In accordance with the foregoing discussion, the performance index for a particular cardiac cycle ($0 < t < T$), is computed as follows:

$$\begin{aligned}
 P.I. &= k_1 \frac{1}{T} \int_0^T P_{SA1}(t) dt + k_2 \int_0^T P_{LV}(t) F_{AO}(t) dt + k_3 \frac{1}{T} \int_0^T P_{LA}(t) dt \\
 &= k_1 \overline{P_{SA1}} + k_2 V.W. + k_3 \overline{P_{LA}}
 \end{aligned} \tag{4.5}$$

To achieve the "best" performance, one attempts to maximize circulation, while minimizing heart work. Therefore, the first weighting coefficient

in the foregoing equation, k_1 , is positive, while the other two are negative.

The circuitry used to calculate the performance index on the analog computer is given in Appendix B. For computation of each of the three terms, an integrator is used in combination with a track/store summer. Then, weightings are performed by potentiometers, and the final addition is made.

Section C. Computational Aspects of the Pump Model

Part 1. The Analog Model

The analog implementation of Equations 4.1-4.4, which were developed in Section A to describe pump behavior, is shown in Appendix B. Aside from those related to control of pump timing, there are six parameters whose values must be specified before simulation of the assisted circulation can be carried out. Of these six physical parameters, two relate to volume, two to resistance, and two to pressure.

The volume parameters $V_{\min}$ and $V_{\max}$ specify the limits between which P_p can be assumed equal to pneumatic pressure driving the diaphragm, and are dependent on pump geometry. In the simulations discussed in the following section, the pump is assumed capable of holding a maximum of 50 ml and ejecting to a minimum of about 2 ml.

The parameters R_{PI} and R_{PO} represent the combined resistances of inlet and outlet lines and valves in the open position. Like those used in the heart model, pump valves are assumed ideal, and therefore implemented by limit summers in the analog model. The inlet and outlet resistance are assumed identical, and the values used are listed in Figure

4.8.

Selection of the pressure parameters $P_{\max}$ and $P_{\min}$ is at the discretion of the operator of the bypass pump. In the simulations which follow, they are held fixed in order to facilitate comparison of the different modes of controlling pump timing. Maximum pressure must be greater than that of the arterial load to guarantee ejection, and a value of 150 mm Hg is used in the model. The lower the minimum pressure, the more easily the pump can fill, but excessive vacuum can lead to atrial collapse. With these considerations in mind, the parameter $P_{\min}$ is chosen to be -10 mm Hg.

Values selected for the six physical parameters are summarized below in Figure 4.7:

$V_{\min}$	2 ml
$V_{\max}$	50 ml
R_{PI}	0.4 mm Hg-sec/ml
R_{PO}	0.4 mm Hg-sec/ml
$P_{\min}$	-10 mm Hg
$P_{\max}$	150 mm Hg

Figure 4.7. Summary of Physical Parameters used in the Analog Implementation of the Bypass Pump Model.

Note from the schematic in Appendix B, that switching of analog variables in the pump model is under logical control. One function relay is used to implement the switching of pump pressure between $P_{\max}$ and $P_{\min}$, while a second one can force the pump into the hold state by interrupting both inlet and outlet flow. Generation of the logical

signals which control the positioning of both of these electronic switches is discussed in Part 2 of this section.

Part 2. Implementation of Logical Pump Control

The explicit decision criteria outlined in Figures 4.3-4.6 of the previous section make implementation of mode control logic fairly straightforward. From the patching diagrams which are included in Appendix B., note that the logic signal U, described in Section A as denoting the duration of a pumping episode, is implemented by a manual pushbutton. The volume conditions, $V_P > V_{\max}$ and $V_P < V_{\min}$, are determined by comparators.

Recall from Figures 4.3-4.6 that generation of the logic signals P, Q, S, and R is also required in order to implement all of the four modes of control described. The signal P, which is needed for asynchronous, time-triggered pumping, is obtained by using a periodic timing integrator whose output is referred to as τ , in conjunction with one comparator to detect the condition $\tau > T_S$, and another to reset τ to zero when $\tau > T_P$. Similarly, the synchronizing signal S(t) is generated by comparison of the output t of the timing integrator which drives the cardiac model against specified control parameters T_D and $T_D + T_S$.* The asynchronous, volume-triggered mode of control is easily implemented with a single flip-flop Q, which is set and reset by volume criteria. Finally, the flip-flop R, whose output is required for synchronized,

*All values specified for T_D in this thesis are relative to the onset of atrial systole rather than the R wave of the EKG because it is more convenient in the model to reference time within the cardiac cycle in this manner. In fact, only mechanical events are characterized in this study, and their temporal relationships to electrical excitation are not considered.

volume-triggered control, is set with a pulse obtained by differentiation of $S(t)$ and reset by the volume condition $V_P < V_{\min}$.

To facilitate mode selection, each of the four control schemes is assigned a two-bit binary code. If a particular mode uses volume information for triggering pump ejection or filling, the higher-order, "V" bit of its code is 1. For the two modes in which pump systole is synchronized with the cardiac cycle, the lower-order "X" bit is set. The selection code is summarized as follows in Figure 4.8:

Control Mode	Code
Asynchronous, Time-Triggered	00
Synchronous, Time-Triggered	01
Asynchronous, Volume-Triggered	10
Synchronous, Volume-Triggered	11

Figure 4.8. Two-bit Binary Code used in Selection of Pump Control Modes.

By specifying the two code bits via manual pushbutton and using the gating circuitry shown in Appendix B., one of the four modes of pump control can be easily selected at any time during the course of a simulation experiment such as those whose results are presented in the following section.

Section D. Model Results for the Assisted Circulation

In this section, sample model results of the assisted circulation are presented and discussed. The effects of bypass pumping on the normal

heart are considered in the first two parts. In Part 1, fixed control parameters are used for each of the four control modes, and comparisons are made on the basis of the performance index developed in the previous section. Then, in Part 2, the sensitivity of overall performance to variations in these parameters is demonstrated for each control mode. Model results concerning bypass assistance of an abnormal left ventricle are presented in Part 3.

Part 1. Assistance of the Normal Heart with Fixed Control Parameters.

The results which follow pertain to the simulation of left ventricular bypass assistance of the normal circulation. For each mode of pump control, fixed parameters are specified and the following model variables monitored: 1) left ventricular volume, V_{LV} , 2) proximal systemic arterial pressure, P_{SA1} , 3) distal systemic arterial pressure, P_{SA2} , and 4) the volume of blood in the bypass pump, V_p . In addition, the total scalar performance index, as well as its component terms, is displayed. These terms have been weighted so as to be comparable in magnitude with one another and consistent with an assumption of approximately equal importance of circulatory enhancement and heart work relief. The weighting coefficients used are as follows: 1) $k_1 = 0.5$, 2) $k_2 = -0.5$, and 3) $k_3 = -5.0$. Since relative changes in the overall performance index are the main concern, both the origin and the units for the recording of P.I. are arbitrary. For convenience, the performance index in the unassisted case is taken as the zero reference level in the following simulations.

Figure 4.9 shows the model results of assistance with the pump operating in mode 00, the asynchronous, time-triggered mode of control.

For this particular simulation, pump period, T_p is set to 1 second, and T_s is fixed at 300 msec. Tracing a. of V_{LV} shows an approximate 15% reduction in left ventricular end-diastolic volume during assistance as compared to that before and after the pumping episode. Also note that ventricular stroke volume is decreased to about 65 ml during assistance. The recordings of P_{SA1} and P_{SA2} in b. and c. demonstrate the effect of pump systole on arterial pulse pressure. Recalling that the output of the bypass pump is connected directly to the distal arterial segment in the model, one observes that the very abrupt disturbances evident in the P_{SA2} waveform appear more damped in the pressure P_{SA1} recorded at the upstream site. Also note the lack of synchrony between ventricular systole and pump ejection which is apparent from these pressure recordings. Tracing d. depicting instantaneous pump volume, V_p , demonstrates that pump filling requires a much greater amount of time than does ejection. (Such a result is to be expected, considering that while the resistances R_{PI} and R_{PO} are assumed equal, the inlet pressure gradient is less than 15 mm Hg, while that at the outlet is approximately 50 mm Hg). Note that because ejection takes less than the allotted 300 msec, the pump is cyclically forced into the hold state in the empty position by this time-triggered mode of control. The pump fills to 26 ml and its flow output is slightly less than one-third that of the left ventricle. Changes in total flow output are related to mean systemic arterial pressure shown in tracing e. Although transient increases and decreases are observed in this recording just after the pump is turned on and off, steady-state changes in $\overline{P_{SA1}}$ appear to be very slight. Because assist pumping is not in synchrony with the cardiac cycle, all three component terms of the performance index show beat-to-beat variation. On the average, mean left atrial pressure

Figure 4.9. Assistance of the Normal Left Ventricle with Mode 00 Pump Control. ($T_p = 1$ sec, $T_g = .3$ sec)

recorded in tracing f. is decreased by approximately 1 mm Hg from its unassisted level. Similarly, the external work term in tracing g. is reduced by slightly less than 20%. The overall performance index recorded in h. appears to be increased approximately 6 units over the unassisted case, but cycle-to-cycle variations are considerable.

The results of the implementation of mode 01, the synchronous, time-triggered mode of pump control, are shown in Figure 4.10. For this particular simulation, pump ejection is triggered .5 sec after the beginning of atrial contraction, and the specified duration of pump systole is again 300 msec. Tracing a. shows a decrease in left ventricular end-diastolic volume during pumping which is comparable to that observed for mode 00. The recordings of P_{SA1} and P_{SA2} in b. and d. demonstrate that as a result of synchronization, pump systole occurs at the same time during ventricular diastole for every cardiac cycle. Note from tracing d. of V_p that the bypass pump fills to only 20 ml, and as in the synchronous, time-triggered case, the diaphragm is overdriven for a considerable portion of the pump cycle. Although the stroke volume of the pump is less than that for mode 00, the rate is faster, and the resultant pump flow outputs are approximately the same for the two time-triggered modes. Tracings e.-h. show that changes in performance terms are also comparable for the two modes. However, because of the synchronous nature of control in mode 01, performance is constant from cycle to cycle once the steady state is reached.

Model results for the case of asynchronous, volume-triggered pump control, mode 10, are recorded in Figure 4.11. Tracing a. indicates an even greater reduction in left ventricular end-diastolic volume during assistance than that resulting from either of the time-triggered modes just discussed. Note that the V_{LV} waveform, as well as that of

Figure 4.10. Assistance of the Normal Left Ventricle with Mode 01 Pump Control. ($T_D = .5$ sec, $T_S = .3$ sec)

P_{SA1} and P_{SA2} in tracings b. and c., shows tremendous beat-to-beat variation. This is due to the fact that pumping is asynchronous, and as evidenced in tracing d. of V_p , the stroke volume of the pump is now up to its 50 ml maximum. Pump period is concomitantly increased to about 1.5 seconds per cycle. The resultant flow output of the pump is approximately 2 l/min, as compared to only 1.5 l/min achieved with either of the time-triggered modes of control. Although different for each cardiac cycle, performance terms in tracings e.-h. seem to corroborate a general improvement in assistance over modes 00 and 01. Note in particular that the overall performance index shown in h. exhibits variations anywhere from about 6 units for those cardiac cycles in which no pump systole occurs, to approximately 10 units for those in which the pump ejects a full 50 ml into the load at an optimal time in the cardiac period.

Figure 4.12 shows the results of the synchronous, volume-triggered pump control, mode 11. The value of the parameter T_D used for this simulation is again .5 seconds. Tracing a. indicates that left ventricular end-diastolic volume is reduced to 90 ml every cardiac cycle during assistance once the steady-state is reached. The relationship between ventricular and pump systoles which is demonstrated in systemic arterial pressure waveforms in b. and c., is also constant for this synchronized mode of control. Tracing d. of V_p indicates that the bypass pump fills to 27 ml. Its flow output is approximately equal to that resulting from asynchronous, volume-triggered control. Unlike those recorded for mode 10, however, performance terms in tracings e.-h. show no cyc-to-cycle variation. Note from the comparison of mode 11 with the other synchronized mode that mean systemic arterial pressure is further increased, and mean left atrial pressure as well as

Figure 4.11. Assistance of the Normal Left Ventricle with Mode 10 Pump Control. ($SV_p = 50 \text{ ml}$)

Figure 4.12. Assistances of the Normal Left Ventricle with Mode 11 Pump Control. ($T_D \approx .5$ sec)

ventricular work show greater reduction due to increased bypass pump output. The overall performance index for synchronous, volume-triggered pumping is approximately 8 units above its unassisted level. This value is comparable to the mean performance index resulting from mode 10 pumping, and approximately 30% greater than that achieved in either mode 00 or 01 where only time-triggering is used to control pump ejection and filling.

Part 2. The Assisted Normal: Changes in Performance due to Control Parameter Variation.

The foregoing model results were obtained using arbitrary, fixed control parameters (T_P , T_S , T_D) for each mode. In order to make a more complete comparison of the four control schemes, changes in pump performance resulting from control parameter variation are now considered. The following results again refer to the case of bypass assistance of the normal heart.

The case of synchronous, volume-triggered pumping is considered first because performance is expected to depend only upon the single control parameter, T_D . Furthermore, for any particular value of pump delay, the performance index is constant once the steady-state is reached. To obtain the results shown in Figure 4.13, the parameter sweep circuit given in Appendix B. is used to make incremental changes in T_D every 20 cardiac cycles. (The strip chart output duplicated in the figure is recorded at a very slow paper speed in order to emphasize steady-state effects). Recalling that the heart period for the normal case is constant and equal to about .8 seconds, pump delay is varied from zero to slightly greater than this value in approximately 50 msec

Figure 4.13. The Assisted Normal: The Effect of Pump Delay on Overall Performance in Mode 11 Control.

increments, and these step changes are recorded in tracing d. Tracing a. shows that left ventricular volume excursions exhibit little dependence upon T_D , until this delay becomes so large that pump ejection is no longer triggered at all, and the cardiovascular system returns to unassisted conditions. Peak systemic arterial pressure in tracing b. is greatest when T_D is in the range of 150-200 msec. Referring to Figure 3.5, which depicts the time course of the normal cardiac elastance functions, one observes that such a delay means that pump ejection is superimposed on ventricular systole. The pump volume recorded in tracing c. reaches a value of 27 ml, and filling is essentially unaffected by changes in the timing of ejection (again, provided T_D does not exceed the total heart period). Tracing e. of the overall performance index exhibits a rather shallow minimum and an even less-pronounced maximum in the steady state. For T_D equal to 150 msec, performance is most seriously degraded because pump ejection occurs immediately following the ventricular isovolumic contraction period. A delay of approximately 400 msec, on the other hand, results in pump ejection during isovolumic relaxation. Optimal performance is thus achieved for this latter value of T_D because mean systemic arterial pressure is enhanced without increasing the after-load of the left ventricle.

In the other synchronous mode of control (01), pump filling is triggered by timing criteria rather than volume information, and therefore performance is expected to depend upon not only T_D , but also T_S . The results recorded in Figure 4.14 are obtained by setting pump delay to 400 msec, the value found optimal for mode 11 pumping, and then varying the duration of pump systole from zero to 400 msec in 10 msec steps. Tracing a. demonstrates that left ventricular end-diastolic

Figure 4.14. The Assisted Normal: The Effect of Pump Systolic Duration on Overall Performance in Mode 01 Control. ($T_D = .4$ sec)

volume is reduced to a greater extent as pump systolic duration is increased from zero, but it gradually increases again for T_S in excess of about 70 msec. The recording of V_P in tracing c. indicates that while very brief systolic durations are not adequate for complete pump ejection, much longer T_S intervals result in impairment of filling. Tracing e., which reflects the sensitivity of overall performance to the choice of T_S , rises very rapidly to a maximum for T_S equal to 70 msec, and then decreases more gradually for further increases in the duration of pump systole. Note that rather small perturbations in the parameter T_S to either side of the optimum value result in greater performance degradation than that suffered for almost any choice of T_D in the case of synchronous, volume-triggered control. In addition, peak P.I. for mode 01 pumping is slightly less than that achieved using mode 11 control.

In the remaining time-triggered control scheme, mode 00, performance is dependent upon the selection of T_P as well as T_S . Figure 4.15 shows the results of a simulation in which pump systolic duration is fixed at 70 msec, the value just found to be optimal for mode 01, and pump period is varied from .4 sec to 2.2 sec. Because pumping is asynchronous in this case, the performance index is not constant from one cardiac cycle to the next, and therefore results cannot be directly compared with those observed for the synchronous modes just considered. For this reason, the parameter sweep circuit shown in Appendix B. includes an averaging option. Following each incremental increase in T_P , 20 cardiac cycles are allowed to elapse in order to permit any transient effects to die out, and then the average performance index is computed over the next 100 cycles by using an analog accumulator technique. Step changes in pump period are indicated in tracing d. of Figure 4.15.

Figure 4.15. The Assisted Normal: The Effect of Changes in Pump Period of Overall Performance in Mode 00 Control. ($T_s = 70$ msec)

Tracings a. and b. of V_{LV} and P_{SA1} exhibit no clear-cut dependence on T_p . The recording of V_p in tracing c. shows that pump filling increases gradually as pump period lengthens, until finally the 70 msec interval allotted for pump systole is no longer adequate for complete ejection. The beat-to-beat performance index in tracing e. exhibits considerable variation. The average P.I. computed for each value of T_p is indicated by the peaks observed in tracing f. For pump periods in the range of 600 to 800 msec, a maximum value of this mean performance index is recorded which is comparable to optimal constant P.I. achieved in either of the synchronous modes of control.

Having performed the simulation of mode 00 control for what is expected to be an optimal choice of the parameter T_s , it is interesting to repeat the experiment for a different fixed value of pump systolic duration. The results recorded in Figure 4.16 are observed for T_s equal to 200 msec. Note from tracing c. of V_p that when this longer interval is allotted for pump systole, ejection is always complete. It is also observed that $\overline{P.I.}$ shown in tracing f. exhibits a maximum for T_p equal to 1.4 sec, approximately twice that obtained in the previous case. Furthermore, the optimal mean performance detected in the case of $T_s = 200$ msec is considerably less than that for $T_s = 70$ msec.

In asynchronous, volume-triggered pump control, no timing parameters have to be selected. However, with the technique used by Norman et al 1973, the stroke volume of the pump can be set to any desired value less than the maximum pump volume. Figure 4.17 shows the results of varying SV_p , the volume at which pump ejection is triggered. Tracing a. shows that, as expected, left ventricular volume is reduced from the unassisted level for all values of SV_p less than V_{max} . Tracings d. and c. show that the set value, as well as the actual stroke volume, increase

Figure 4.16. The Assisted Normal: The Effect of Changes in Pump Period on Overall Performance in Mode 00 Control. ($T_S = 200$ msec)

Figure 4.17. The Assisted Normal: The Effect of Changes in Preset Stroke Volume on Overall Performance in Mode 10 Control.

in approximately 5 ml increments starting at about 5 ml. The performance index displayed in tracing e. again shows considerable cycle-to-cycle variation for this asynchronous mode of pumping. Using the same averaging technique employed previously for assessment of mode 00 control, the $\overline{\text{P.I.}}$ indicated in tracing f. is obtained. Most notable is the observation that this mean performance index shows almost no variation resulting from changes in the control parameter, SV_p . In addition, the $\overline{\text{P.I.}}$ consistently achieved is comparable to the optimal performance index found for the other three modes of pump control.

Part 3. The Assistance of the Asynergistic Left Ventricle

Having discussed the effects of different modes of bypass pump control on the normal heart, assistance in the case of abnormal left ventricular function is now considered. In the simulations whose results follow, the systemic and pulmonary loads, the right heart, the left atrium, and the total blood volume in the system are all unchanged from the normal. The elastance function, E_{LV} , is that obtained from the patient referred to in Figure 3.4 as having an asynergistic left ventricle. Without assistance, this system produces a mean systemic arterial pressure of slightly less than 90 mm Hg and a mean left atrial pressure of about 10 mm Hg. The performance index in this case is computed using the same weighting coefficients k_1 , k_2 , and k_3 as for the normal, and again the unassisted value of P.I. is taken as the zero reference level.

Figure 4.18 shows a summary of the results of assistance of the asynergistic left ventricle using synchronous, volume-triggered control. The value of pump delay is again varied from zero to a value slightly

Figure 4.18. The Assisted Asynergistic Left Ventricle: The Effect of Pump Delay on Overall Performance in Mode 11 Control.

Figure 4.19. The Assisted Asynergistic Left Ventricle: Performance as a function of T_S in Mode 01 Control. ($T_D = 400$ msec)

longer than the total heart period in approximately 50 msec increments. Tracing a. shows that left ventricular volume, while always considerably more than for the normal, is reduced to a greater or lesser extent depending upon the choice of the control parameter T_D . As indicated in tracing b. of V_P , the pump fills to 34 ml. (This increase in filling over the normal case is facilitated by the increased left atrial pressure.). The overall P.I. recorded in tracing c. exhibits the same type of dependence on pump delay as that observed for this mode of control in the case of the assisted normal. This performance index is least when pump ejection falls at the beginning of the ventricular ejection period, and maximal when it occurs during early ventricular diastole. The peak P.I. observed in mode 11 assistance of the abnormal heart is almost 9 units above the unassisted level.

Mode 01 bypass assistance is simulated by again fixing T_D at its optimal value, and then varying the duration of pump systole. The results summarized in Figure 4.19 are similar to those produced when a like experiment was performed on the assisted normal. Tracing a. shows maximal reduction in V_{LV} for T_S sufficiently long to permit complete pump ejection, but not so long as to impair pump filling. This limitation of ejection and filling is demonstrated in tracing b. of V_P . The maximization of the overall performance index recorded in tracing c. is observed to occur for T_S equal to 180 msec. (This optimal value for pump systolic duration is greater than that determined for mode 01 assistance of the normal because the pump volume to be ejected is increased). Note from comparison of Figures 4.18 and 4.19 that while the maximum P.I.'s are comparable for modes 11 and 01, the latter is sensitive to changes in the additional control parameter, T_S .

Figure 4.20 shows the results of fixing T_s at 180 msec and varying pump period during asynchronous, time-triggered assistance. Tracing a. indicates that left ventricular volume reduction is, in general, not as great in this case as for the synchronous pump control modes. As T_p is incremented from .4 sec to 1 sec, note from tracing b. of V_p that pump filling is improved. Variation in the values of P.I. recorded in tracing c. again demonstrates the result of the lack of synchronization of assistance with ventricular pumping. Tracing d. of the mean performance index exhibits a maximum for pump period in the range of 1.0 to 1.2 sec. Note that this optimum mean performance index of approximately 8 units is less than that achieved in assistance of the abnormal by either mode 11 or 01 control.

Consider finally the results of asynchronous, volume-triggered pumping which are recorded in Figure 4.21. Tracing a. shows fairly consistent reduction in V_{LV} . As indicated in tracing b. of V_p , the pump fills to the level determined by the parameter SV_p . The performance index recorded in tracing c. again shows considerable variation, particularly as the stroke volume of the pump increases. However, the mean performance index indicated in tracing d., as in the case of the assisted normal, is independent of SV_p . This mean value of performance is somewhat less than that achieved in either synchronous mode of assistance.

Figure 4.21. The Assisted Asynergistic: Changes in SV_P in Mode 10 Control.

Figure 4.20. The Assisted Asynergistic: Changes in T_P in Mode 00 Control. (T_S = 180 msec)

CHAPTER V: CONCLUSIONS

In this thesis, a mathematical model has been developed to simulate the effects of left ventricular bypass assistance on the circulatory system. The analog computer implementation of this model, as well as results it has produced, have been discussed in considerable detail in previous chapters. The purpose of this final chapter is to briefly summarize these results and consider their implications. Realizing that the model is, after all, an abstraction of the physical process under study, some effort is made to point out its limitations as well as its strengths. Discussion of the model's strong points is important because it is through this process that one can gain insight into the physical system. On the other hand, consideration of the limitations of the simulation is necessary in order to prevent oversimplification and also to help define areas for future investigation. In this chapter, the strengths and weaknesses of both the unassisted and assisted circulatory models are summarized.

The flexibility of the analog simulation of the uncontrolled, closed-loop cardiovascular system is demonstrated in Chapter III. First, a left ventricular elastance curve is obtained from instantaneous pressure-volume data taken on a patient previously classified as being typical of a group of subjects free of cardiac disease. Assuming right ventricular elastance to be simply an attenuated version of that measured for the left ventricle, a set of model parameters is then determined for which normal hemodynamic behavior is simulated. It is observed that the model produces values for left ventricular end-diastolic volume, cardiac output, and systemic arterial pressures which are all comparable to

clinical data available for the patient whose elastance curve was used. To further verify the model, a series of isolated parameter manipulations is performed. The simulation of mitral stenosis, for example, results in the expected increases in left atrial and pulmonary venous pressures. In addition, the importance of changes in systemic arterial resistance and hemorrhage on blood pressure are demonstrated by the model. The effect of both bilateral and unilateral ventricular asynergy is also considered. As in the normal case, the simulation of abnormal ventricular function produces results which are comparable to actual patient data.

To indicate the limitations of the unassisted circulatory model, one need only recall some of the simplifying assumptions which were made in its formulation. Specifically, the complex, highly-distributed systemic and pulmonary vasculatures are represented by simple, lumped-parameter models. Linearity is assumed in all vascular compartments, and no specialized circulations are described. Furthermore, load parameters are held constant, thus ignoring all dependence on respiration, body position, or variations in vasomotor tone. Neural control effects on the heart are likewise neglected, as indicated by the use of a single periodic elastance function which implies the assumption of fixed heart rate and ventricular inotropic state. Keeping these basic assumptions in mind, the analog model is applicable to problems relating to the general behavior of the unassisted cardiovascular system.

In Chapter IV, a model for the left ventricular bypass pump is developed and the analog simulation of the assisted circulation is discussed. The diaphragm pump is represented by an idealized pressure source for fluid volumes within a specific range, and it is assumed

completely ineffective otherwise. Inlet and outlet valves are assumed ideal, and connectors to the left atrium and systemic arterial load are modelled as purely resistive. As expected, the operation of the bypass pump model demonstrates that shunting blood around the left ventricle has the general effect of lowering left atrial and left ventricular end-diastolic pressures, while augmenting cardiac output and mean systemic arterial pressures. These qualitative results are in keeping with the two basic goals of cardiac assistance, which are to provide a degree of rest to the failing ventricle while improving the circulation. Quantitative assessment of simulated assistance is based upon a scalar functional chosen to reflect these goals. This performance index is a weighted sum of mean systemic arterial pressure, the area enclosed by the pressure-volume loop traced out by the left ventricle during the course of each cardiac cycle, and the mean left atrial pressure.

Four modes of controlling the bypass pump are described, simulated, and compared on the basis of their effect on the performance index, which is computed for every heart beat. The four control schemes each use different logical criteria to trigger pump filling and ejection, which is forced by periodically switching the pneumatic pressure driving the diaphragm between minimum and maximum values. Each mode of control is designated by a unique two-bit binary code whose higher-order bit specifies whether volume information is used for triggering, and whose lower-order bit reflects whether there is synchronization with the natural cardiac cycle. Simulation of the assistance of the normal as well as the asynergistic left ventricle indicates that although all modes are capable of comparable performance for an optimal choice of control parameters, this selection is simpler and less critical in some cases

than in others. The performance index computed for mode 00 varies from one cardiac cycle to the next, and its average value is sensitive to the choice of two control parameters: 1) the pump period, T_p , and 2) the duration of pump systole, T_s . The addition of synchronization constraints results in mode 01 control, for which performance is constant from beat to beat and depends upon T_s as well as T_D , the time in the cardiac cycle at which ejection is triggered. The choice of T_s , while quite critical in both of these two time-triggered modes, need not be made if volume information is used for control. In mode 11 for example, so long as the time allotted for ejection is not inordinately brief, performance is dependent on the single parameter T_D , and it is not severely degraded if a suboptimal choice is made. No timing parameters at all need be specified for mode 10, in which control is determined by simply setting pump stroke volume, SV_p . The performance index resulting from this asynchronous form of assistance shows considerable beat-to-beat variation, but its mean value is comparable to the optimum achieved for the other three modes of control.

Again, conclusions drawn from the above results must be tempered with recollection of the assumptions used in the formulation of the bypass pump model. For example, if the inertance of the fluid in the connectors leading to and from the pump were considered in the model, one might expect performance to be degraded in the case of very low stroke volume, high frequency mode 10 assistance. (Also, recall that inertance of pneumatic lines and that of the diaphragm are neglected). In addition, the mechanical valves actually used in the physical pump are by no means ideal, and the allowance of regurgitant flow in the model could therefore alter pump performance. Such refinements of the pump model would be interesting for future study.

Conclusions regarding the optimal mode of pump control must also be weighed in light of the limitations of the uncontrolled, lumped-parameter circulatory model which were cited earlier. First, consider the possible complications introduced by neural control of the cardiovascular system. Ignoring all such control, the model implies that synchronization does not significantly improve assistance because mean performance for asynchronous pumping is comparable to that achieved for each beat during synchronous assistance. However, in the actual physiological system, large irregular disturbances in the pulse pressure waveforms such as those caused by asynchronous pump ejection, could produce deleterious results due to changes in baroreceptor feedback on the heart. Questions relating to possible effects on ventricular inotropic and chronotropic state are, of course, beyond the scope of the uncontrolled model. Moreover, because of the gross lumping used in the characterization of the vasculature, the model cannot address questions regarding flow in specific anatomical regions. In particular, improvement in coronary, cerebral, and renal perfusion cannot be guaranteed by simply increasing mean systemic arterial pressure.

Recall that maximization of this pressure, along with minimization of two terms relating to ventricular energy expenditure, is used to define optimal bypass assistance in this study. Recognizing that as in any optimal control problem, this particular choice for a performance index is not unique, an interesting subject for future investigation might be an analysis of the dependence of pump mode selection upon the specific quantitative measure used for comparison. Even if the performance index were based upon the same component terms, the effect of changing their relative weights might be considered. In particular, if

k_2 were set to zero, the resultant index would depend only upon left atrial and aortic pressures. Since both of these variables can be easily and accurately measured, the determination of optimal performance could thus be made feasible in the clinical environment.

APPENDIX A: NOMENCLATURE

Below is an alphabetized list of terms referred to in this thesis. The units consistently used are as follows: 1) time in sec, 2) pressure in mm Hg, 3) volume in ml, 4) resistance in mm Hg-sec/ml, 5) compliance in ml/mm Hg (elastance the reciprocal), and 6) inertance in mm Hg-sec²/ml.

Term	Meaning
C_{PA}	compliance of the precapillary pulmonary vessels
C_{PV}	compliance of the postcapillary pulmonary vessels
C_{SA1}	compliance of the proximal systemic arterial vessels
C_{SA2}	compliance of the distal systemic arterial vessels
C_{SV1}	compliance of the proximal systemic venous vessels
C_{SV2}	compliance of the distal systemic venous vessels
E	logical signal denoting pump ejection state
$E_{LA}(t)$	periodic left atrial elastance function
$E_{LV}(t)$	periodic left ventricular elastance function
$E_{RA}(t)$	periodic right atrial elastance function
$E_{RV}(t)$	periodic right ventricular elastance function
F	logical signal denoting pump filling state
$F_{AO}(t)$	instantaneous flow through the aortic valve
$F_{MT}(t)$	instantaneous flow through the mitral valve
$F_{PC}(t)$	instantaneous flow through the pulmonary capillary resistance
$F_{PI}(t)$	instantaneous flow through the inlet pump connector
$F_{PM}(t)$	instantaneous flow through the pulmonic valve
$F_{PO}(t)$	instantaneous flow through the outlet pump connector

$F_{PV}(t)$	instantaneous flow through the pulmonary venous resistance
$F_{SA1}(t)$	instantaneous flow through the proximal systemic arteries
$F_{SA2}(t)$	instantaneous flow through the distal systemic arteries
$F_{SL}(t)$	instantaneous flow through the systemic arterial inertance
$F_{SV1}(t)$	instantaneous flow through the proximal systemic vein
$F_{SV2}(t)$	instantaneous flow through the distal systemic vein
$F_{TC}(t)$	instantaneous flow through the tricuspid valve
$FW_{SA1}(t)$	instantaneous radial flow into the proximal systemic arteries
$FW_{SA2}(t)$	instantaneous radial flow into the distal systemic arteries
H	logical signal denoting pump hold state
K_A	ratio of right to left atrial elastances
K_V	ratio of right to left ventricular elastances
k_1	weighting coefficient for first term of performance index
k_2	weighting coefficient for second term of performance index
k_3	weighting coefficient for third term of performance index
L_{SA}	systemic arterial inertance
P	logical signal triggering pump ejection in mode 00
$P_D(t)$	instantaneous pneumatic pressure driving the pump diaphragm
$P_{LA}(t)$	instantaneous left atrial pressure
$\overline{P_{LA}}$	mean left atrial pressure
$P_{LV}(t)$	instantaneous left ventricular pressure
P_{max}	pump ejection pressure
P_{min}	pump filling pressure
$P_P(t)$	instantaneous pressure in the fluid chamber of the pump
$P_{PA}(t)$	instantaneous pulmonary artery pressure
$P_{PC}(t)$	instantaneous pulmonary capillary pressure
$P_{PV}(t)$	instantaneous pulmonary venous pressure

$P_{RA}(t)$	instantaneous right atrial pressure
$P_{RV}(t)$	instantaneous right ventricular pressure
$P_{SA1}(t)$	instantaneous proximal systemic arterial pressure
$\overline{P_{SA1}}$	mean proximal systemic arterial pressure
$P_{SA2}(t)$	instantaneous distal systemic arterial pressure
$P_{SV1}(t)$	instantaneous proximal systemic venous pressure
$P_{SV2}(t)$	instantaneous distal systemic venous pressure
P.I.	performance index for a single cardiac cycle
$\overline{P.I.}$	mean performance index over 100 cardiac cycles
Q	logical signal to trigger pump ejection in mode 10
R	logical signal to trigger pump ejection in mode 11
R_{AO}	forward resistance of the aortic valve
R_{MT}	forward resistance of the mitral valve
R_{PA}	axial resistance of the pulmonary artery
R_{PC}	axial resistance of the pulmonary capillary
R_{PI}	forward resistance of the pump inlet connector and valve
R_{PO}	forward resistance of the pump outlet connector and valve
R_{PV}	axial resistance of the pulmonary vein
R_{SA1}	axial resistance of the proximal systemic artery
R_{SA2}	axial resistance of the distal systemic artery
R_{SV1}	axial resistance of the proximal systemic vein
R_{SV2}	axial resistance of the distal systemic vein
R_{TC}	forward resistance of the tricuspid valve
R_{SA1}^W	radial resistance of the proximal systemic artery
R_{SA2}^W	radial resistance of the distal systemic artery
S	logical signal to trigger pump ejection in mode 01
SV_P	preset stroke volume in mode 10 pumping
T_D	pump delay used in modes 01 & 11 pumping

T_P	pump period specified in mode 00 pump control
T_S	pump systolic duration specified in modes 00 & 01
U	logical signal denoting duration of pumping episode
V	high-order bit of pump mode control code denoting volume triggering
V.W.	work done by the left ventricle in a single cardiac cycle
X	low-order bit of pump mode control code denoting synchronization with the natural cardiac cycle

APPENDIX B: ANALOG COMPUTER DIAGRAMS

The following pages show the analog and logic patching used to implement the mathematical model in this thesis. Most all symbols used in these diagrams are those referred to in the EAI Model 680 Reference Handbook. Note the additional shorthand for pot feedback and ten-fold amplification of inputs:

Figure B.2. The Right Heart Model

Figure B.3. The Systemic Arterial Load Model

Figure B.4. The Systemic Venous Model

Figure B.5. The Pulmonary Load Model

Figure B.6. The Bypass Pump Model1 (Analog Aspects)

Figure B.7. Generation of Logical Control Signals for all Control Modes

Figure B.8. Gating Circuitry for Pump Mode Selection

Figure B.9. Periodic Ramp Generation and Performance Index Computation

REFERENCES

1. Baldrige, D.L., An Elastance Characterization of the Normal and Failing Heart, Master's Thesis, Rice University, Houston, Texas, 1973.
2. Beneken, J.E.W., "A mathematical approach to cardiovascular function: The uncontrolled human system," Report #2-4-5/6, Institute of Medical Physics, Utrecht, Netherlands, 1965.
3. Burns, J.W. and Covell, J.W., "Myocardial oxygen consumption during isovolumic and isotonic contractions in the intact heart," Amer. J. Physiol. 223(6): 1491-1497, 1972.
4. Coleman, H.M., Sonnenblick, E.H., Braunwald, E., "Myocardial oxygen consumption associated with external work: The Fenn effect", Amer. J. Physiol. 217(1): 291-296, 1969.
5. DeBakey, M.E., "Left ventricular bypass pump for cardiac assistance", Amer. J. Cardiol. 27: 12, 1971.
6. Fishman, A.P., in Handbook of Physiology, Vol. 2, W.F. Hamilton and P. Dow, eds., Washington D.C.: Am. Physiol. Soc., 1963.
7. Folkow, B., and Neil, E., Circulation, Oxford Univ. Press, 1971.
8. Goldberg, H.S., "Assisting the Heart and Kidney" in Biomed. Engr. Systems, Inter-Univ. Electronic Series, Vol. 10, M. Clynes and J. Milsum, eds., New York: McGraw-Hill, 1970.
9. Greene, M.E. and Clark, J.W., "The innervated left ventricle: A mathematical model", Medical and Biological Engineering, July: 465-468, 1973.
10. Guyton, A.C., "Determination of cardiac output by equating venous return with cardiac response curves", Physiol. Rev. 35: 123, 1955.
11. Heithecker, T.E., An Adaptive Model of the Left Heart Function, Master's Thesis, Rice University, Houston, Texas, 1972.
12. Kane, G.R., Clark, J.W., Bourland, H.M., and Hartley, C.J. "Automatic control of intra-aortic balloon pumping", Trans. Amer. Soc. Artif. Int. Organs XVII: 148-152, 1971.
13. Noordergraaf, A., "Hemodynamics," in Biological Engineering, H.P. Schwan, ed., pp.391-545, 1969.
14. Norman, N.A., DeBakey, M.E., Noon, G.P., Ross, J.N., "Monitoring and closed-loop control of pneumatic blood pumps", Cardio. Res. Cntr. Bull. Baylor College of Medicine 12(1): 3-12, 1973.

15. Pollack, G.H., Reddy, R.V., Noordergraaf, "Input impedance, wave travel, and reflections in the human pulmonary arterial tree: Studies using an electrical analog", IEEE Trans. BME 15(3): 151-164, 1968.
16. Rideout, V.C., "Cardiovascular System simulation in biomedical engineering education", IEEE Trans. BME 19(2): 101-107, 1972.
17. Rideout, V.C. and Katra, J.A., "Computer simulation study of the pulmonary circulation", Simulation 12: 239-245, 1969.
18. Ross, J.N., Wieting, D.W., Hall, C.W., Kennedy, J.H., Garner, H.E., DeBaakey, M.E., "Use of a paracorporeal left ventricular bypass pump in experimental heart failure", Amer. J. Cardiol. 27: 12, 1971.
19. Ruch, T.C. and Patton, H.D., Physiology and Biophysics, W.B. Saunders, Philadelphia, 1965
20. Sarnoff, S.J., Braunwald, E., Welch, G.H., Case, R.B., Stainsky, W.N., Macrutz, R., "Hemodynamic determinants of oxygen consumption of the heart with special reference to the time-tension index", Amer. J. Physiol. 192: 148, 1958.
21. Snyder, M.F., A Study of the Human Venous System Using Hybrid Computer Modelling, PHD Thesis, Madison, University of Wisconsin, 1969.
22. Snyder, M.F., Rideout, V.C., and Hillestad, R.J., "Computer modelling of the human systemic arterial tree", J. Biomech. 1: 341-353, 1968.
23. Sonnenblick, E.J., Ross, J., Covell, J.W., Kaiser, G.A., Braunwald, E., "Velocity of contraction as a determinant of myocardial oxygen consumption", Am. J. Physiol. 209(5): 919-927, 1965.
24. Spencer, M.P. and Denison, A.B., "Pulsatile blood flow in the vascular system", Handbook of Physiology, Sec. 2, Vol. II: 839-864, 1963.
25. Spyker, D.A. and Bernstein, E.F., "An optimal controller for a left ventricular assist blood pump", 21st ACEMB, Houston, Texas, 1968.
26. Suga, H., "Theoretic analysis of a left ventricular pumping model based on the systolic time-varying pressure/volume ratio", IEEE Trans. BME 18(1): 47-55, 1971.
27. Suga, H. and Sagawa, K., "Mathematical interrelationship between instantaneous ventricular pressure-volume ratio and myocardial force-velocity relation", Ann Bio-Engr. 1: 160-181, 1972.