The Use of an Analog Computer for Analysis of Control Mechanisms in the Circulation

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Summary—Two approaches are presented to the study of regulation in the circulatory system. One consists of programming on an analog computer equations to represent part of the system and then, using suitable transducer, substituting the computer for the biological component. An example is presented in which a part of the mechanism which regulates arterial pressure (the carotid sinus) is simulated. The other approach involves simultaneous solution of equations derived to represent each system component. Simulation of a transient disturbance in blood distribution (Valsalva maneuver) is presented to illustrate the use of this approach in predicting the role of each component in determining over-all system behavior.

INTRODUCTION

The human heart and circulation are a complex closed-loop system consisting of distensible reservoirs, variable flow pumps and branched transmission lines. Not only is the performance of each component determined by the behavior of its immediately adjacent component, but through the medium of the nervous system, the characteristics of each component may vary as a function of events taking place in remote areas of the circulatory system and even outside the system itself. Because of these complexities, it is no wonder that to date a satisfactory analysis of the circulation as a self-regulated system has not been undertaken. The purpose of this paper is to present two approaches to this problem, each of which involves the use of an analog computer.

PART I

One approach consists of using the analog computer to simulate part of a control mechanism. In the experiment presented here, the organ being simulated by the computer is the carotid sinus, a small organ made up of stretch-sensitive nerve endings in the wall of a large artery in the neck. The variable controlled by this organ is arterial pressure.

From work done by others using an isolated carotid sinus preparation it is known that the frequency with which action potentials move along the carotid sinus nerve from the carotid sinus toward the brain is directly related to the pressure in the carotid artery (as long as the pressure exceeds a certain minimum value) and is also a direct function of the rate of change of arterial pressure. In the present study the transfer function used to represent the carotid sinus is

\[ \frac{n}{P - P_0} = k_1 + k_2 \]

where \( n \) is the frequency of impulses on the carotid sinus nerve, \( P \) is the pressure in the carotid artery, \( P_0 \) is the minimum static pressure capable of eliciting impulses on the carotid sinus nerve, \( s \) is the Laplace operator, and \( k_1 \) and \( k_2 \) are constants.

The operation of the system may be explained by referring to Fig. 1. A rise in arterial pressure results in a rise in \( e_s \), the input voltage to the computer. The output voltage, \( e_o \), will also rise according to the transfer function shown and result in an increased rate of stimulation of the carotid sinus nerve. The increased frequency of impulses on the carotid sinus nerve produces relaxation of the smooth muscles of small arteries and results in a fall of arterial pressure back toward the control level. By adjusting a bias voltage in the computer, the arterial pressure can be adjusted and maintained over quite a wide range.

Experiments were carried out to evaluate the dynamic behavior of this system. The artificial system, when attached in parallel with the dog’s own regulating mechanism, acts as an amplifier of carotid sinus function. Variations in pressure were induced by producing variation in flow. The variations in flow were achieved by stimulating a vagus nerve. The time-course of variation in the frequency of vagus nerve stimulation results in a pattern of heart rate and pressure variation of the same frequency but opposite phase. This can be seen in Fig. 2. Although the extremes of variations in amplitude of the forcing function (rate of stimulation of vagus nerve) remained constant, the resulting amplitude of the variation in pressure was frequency dependent. In the control records, the largest variations in pressure occurred when
Examination of (1) shows that the carotid sinus does have a mechanism for anticipating changes in pressure in that it is sensitive to the rate of change of pressure. This might in part compensate for the lag at the level of the artery smooth muscle were it not for the nature of the arterial pressure wave. Notice in Fig. 2 that with each heart cycle, large excursions in pressure occur. The rate of change of pressure with each heart beat is so rapid that it completely masks the slope of any variations in mean pressure. For this reason the "lead" in the carotid sinus mechanism is ineffective as a device for anticipating changes in mean pressure. That this is true is shown by the fact that \( k_1 \) of (1) could be varied from zero to large values without detectable effect on the dynamic response of the pressure regulating system.

**Part II**

The analog computer may be used in another way to study the regulation of the circulation. Through the simultaneous solution of a set of differential equations derived from current knowledge to represent each of the system's components, behavior of the system as an intact unit may be predicted. Verification of such predictions must then be made by comparing predicted with observed system behavior.

Fig. 4 is a block diagram of the circulation. The system is lumped as follows: the left atrium and pulmonary veins are treated as a single reservoir, the left ventricle is described as a system with two states, systole (contraction and emptying) and diastole (relaxation and filling), and the arterial bed is treated as a transmission line. The system is symmetrical, the equations of the two sides differing only in their coefficients. The analysis will involve the variables, volume, flow, pressure and time.

Fig. 5 shows the equations used to represent each of these circulatory components and a diagram of the way in which each of these equations is represented on the computer. Another set of equations identical to these except for their coefficients is used to represent the right side of the circulation. The first equation expresses the volume of the pulmonary vein-left atrial system as the sum of the initial volume and the integral of inflow.

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Fig. 4—This is a block diagram of the components into which the circulation is lumped for purposes of the present analysis.

Fig. 5—Equations used to represent the systemic half of the circulation using the variables volume (V), flow (f), pressure (p) and time. Laplace operator notation (s) is used where convenient. The delays which determine the systolic or diastolic state are controlled from a magnetic tape recording of left ventricular pressure, thus synchronizing the computer operation with the biological system.

minus outflow. Laplace operator notation “s” is used where more convenient. This summation and integration is carried out in the computer by feeding the voltages representing flow and minus flow 2 into an integrating amplifier. The output voltage then represents V1. Initial condition voltage on the amplifier is set to correspond to the initial condition. Eq. (2), in Fig. 5, expresses the relationship between pressure and volume in this component. The function is plotted for the desired values of the coefficients “a” and “n” and set up on a multidiode function generator.

Eq. (3) (Fig. 5) represents the flow into the left ventricle during diastole as a function of the pressure gradient across the valve and a time lag (T1) which depends on the inertia of this element. The pressure-volume curve for the ventricle is similar to that for the atrium but with different coefficients. The left ventricle during diastole will have a volume which is the integral of its inflow plus its volume at the end of the preceding systole. This is shown in (5) in Fig. 5. The volume of the left ventricle during systole is given by (6) in Fig. 5. For the derivation of this, refer to Fig. 6. During systole, the ventricle can be likened to a capacitor which has been charged up during diastole to a certain volume. The rate of discharge of this capacitor will depend upon three characteristics of the myocardium: 1) the static volume—pressure relationship represented here as C2; 2) the coefficient of frictional forces (R2), which limit the rate of emptying; and 3) an inertia coefficient (L2), which limits the rate at which a given rate of emptying can be achieved. In addition, the rate of ventricular emptying will depend upon certain factors on the other side of the aortic valve; namely, the distensibility (C3), and volume (Q3) of the aorta, the inertia of the column of blood in the aorta (L3), and the frictional resistance to flow in the arteries (R3). Eq. (6), in Fig. 5, is an explicit expression for left ventricular volume (V2) during systole based on this electrical analogy.

Flow into the aorta (F3) is zero during diastole and is given by the derivative of (6) in Fig. 5 during systole. The volume of the aorta (V3) at any time is the integral of the difference between inflow and outflow of the arterial bed. Flow out of the arterial bed into the vein (F4) is related to the aorta volume by a constant and a lag factor with a time constant of T2. A similar set of equations, but with different coefficients, is used to represent the right side of the circulation. In the computer the systolic and diastolic states are determined by two alternative positions of a set of relays. These relays are synchronized with systole and diastole of the experimental animal being studied. From a recording on magnetic tape of the subject's ventricular pressure pulse a signal is derived which allows the computer to trigger the relays at the proper time.

Fig. 7 shows examples of the type of systematic analysis that can be performed with this technic. Here the effect on the predicted time course of left ventricular volume and aortic inflow of changing certain equation coefficients is shown. Each record shows a control tracing together with the function obtained after increasing one of the system’s parameters by a factor of two. A decrease in stroke volume may result from increasing either the frictional coefficient (R2) or the capacitance (C2) of the ventricle. Ignoring inertia of the ventricle (L2) produces an unrealistic initial spike on the aortic inflow curve. Increasing peripheral resistance (R3) decreases stroke volume, while increasing arterial capacitance increases stroke volume. Increasing diastolic capacity of the ventricle (1/a4) increases both stroke volume and end systolic residual volume. Each of the system’s parameters may be systematically studied in this manner. It seems likely that the rapid progress being made in the development of transducers should soon make it possible to test the accuracy of these predictions in experimental animals.

Using the equations here presented, a prediction may be made of the response of the whole circulatory system to a transient disturbance. Since the system is a closed loop, such a prediction involves solving all the equations of the system simultaneously. One such solution is shown in Fig. 8. The physiologic situation being simulated is called a Valsalva maneuver and is performed by the subject attempting a forced expiration against a closed glottis. Such a maneuver increases intrathoracic pressure and thus prevents blood from returning to the heart. Because all the blood which leaves the lungs is not replaced, a redistribution of blood between the pulmonary veins and systemic veins occurs. Thus, to simulate the state of affairs at the end of a Valsalva maneuver the initial voltage on the pulmonary vein—left atrial integrator is made lower than its equilibrium value and the voltage on the right atrial-systemic vein integrator higher than its equilibrium value. Upon starting the problem, the predicted response of the system to release of the Valsalva can be observed.

The solution shown on the left in Fig. 8 was obtained with constant coefficients in all of the equations. This predicted time course of aortic volume is similar to the time course of aortic pressure obtained in an animal deprived of reflex activity by prior administration of blocking drugs. The response shown in the tracing on the right was obtained by allowing peripheral resistance \( R_3 \) to vary as a function of aortic volume and a time lag such as was demonstrated in the first part of this paper for the carotid sinus mechanism. An overshoot is now evident such as is seen in the arterial pressure curve of a normal subject with an intact reflex system following release of a Valsalva maneuver.

This set of equations predicts a rapid return to equilibrium for the circulatory system following transient disturbance of several types. This is true in the presence of a wide variety of values for each of the system’s parameters with one exception, the exception being the case of very high flow in which some overshoot may be observed even with constant coefficients.

The adequacy of the equations presented is currently being evaluated using the system shown in block diagram in Fig. 9. Up to seven variables may be recorded from the biological system during an experiment. These are recorded on multi-channel magnetic tape using frequency modulation. The tape recorder has two transports. Data are originally recorded using a reel-to-reel transport and then segments are copied onto a tape loop for analysis along with additional programming data. Thus, transient phenomena recorded on the tape may be reproduced over and over again for analysis. Some variables reproduced from the tape are displayed on a multichannel oscilloscope for comparison with values for the corresponding variables being predicted by the computer. The computer coefficients are varied until the best possible fit between predicted and recorded waveforms is obtained. If a solution is not found which accurately predicts the experimental observation, a new equation must be sought. On the other hand, when an equation is found whose solution conforms to the experimental data, the generality of this equation must be judged by its ability to predict system behavior under other experimental conditions.