Use of analogue computers in the study of control mechanisms in the circulation[1]

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AN APPROACH TO THE STUDY of regulation and control of the circulation centered around the use of an analogue computer is the theme of this paper. The problem will be discussed in four parts: *1*) analysis of the circulation as a complex, closed-loop system; *2*) the use of the computer as an aid in performing experiments; *3*) the computer as a tool for reducing data to the desired form for analysis; and, *4*) the use of an analogue computer in testing an hypothesis or mathematical model.

The block diagram in Fig. 1 represents the circulation as a closed loop with two symmetrical halves. Each half consists of a distensible reservoir (the large veins and atrium); a pump which has two states, diastole and systole; a transmission line which is the large arteries; and a source of resistance to run-off from the large arteries, which is located at the level of the small arteries and arterioles. These elements are connected to the other half of the circuit to form a complete closed loop. Not only is each element affected by the element just ahead and just behind, but its performance is also influenced by events taking place at remote parts of the circulation. For instance, information regarding pressure in the large arteries is sent to the central nervous system which, in turn, modifies flow and resistance to flow. However, the circulatory system, even when deprived of this nervous control, has the ability to return to an equilibrium state following a transient disturbance. This we might call the "auto-regulation" of the circulation. It is important to first understand this phenomenon, since any nervous control of the circulation must be simply superimposed upon this basic auto-regulation phenomenon.

A set of eight equations is used to describe each half of the circulation. The two halves differ only in the values of the parameters.

$$V_1 = V_{1(t=0)} + \int (F_1 - F_2)\, dt \qquad (1)$$

Equation 1 states that the volume of the atrium and large veins is equal to its initial volume plus the difference between flow into the atrium (F_1) and flow out of the atrium (F_2) integrated with respect to time. The pressure (P_1) in the left atrium and pulmonary veins is treated as a power function of the volume divided by the capacitance of that chamber, in order to account for the well-known convexity toward the volume axis of the volume pressure curve of veins. This is expressed in *equation 2*:

$$P_1 = \frac{V_1^n}{C_1} \qquad (2)$$

Flow (F_2) out of the left atrium and into the left ventricle is zero during ventricular systole, and during diastole is equal to the pressure gradient across the valve divided by the resistance to flow (R_1), minus an inertia term which depends on the rate of change of flow as shown in *equation 3*.

$$F_2 = \frac{(P_1 - P_2)}{R_1} - L_1 \frac{dF_2}{dt} \quad \text{(diastole)}$$
$$F_2 = 0 \quad \text{(systole)} \qquad (3)$$

Pressure in the left ventricle (P_{2d}) during diastole is again expressed as a power function of volume divided by the diastolic capacitance of the ventricle C_{2d}.

$$P_{2d} = \frac{V_2^m}{C_{2d}} \qquad (4)$$

The volume of the ventricle (V_2) may be expressed as some initial volume plus the integral of flow in minus flow out as shown in *equation 5*.

$$V_2 = V_{2(t=0)} + \int (F_2 - F_3)\, dt \qquad (5)$$

Flow out of the ventricle (F_3) is zero during diastole and during systole depends upon the volume of the ventricle divided by its systolic capacitance (C_{2s}), on R_2, the frictional forces which limit the rate of contraction and also on the pressure in the aorta which will depend on the volume of the aorta (V_3) and the aortic capaci-

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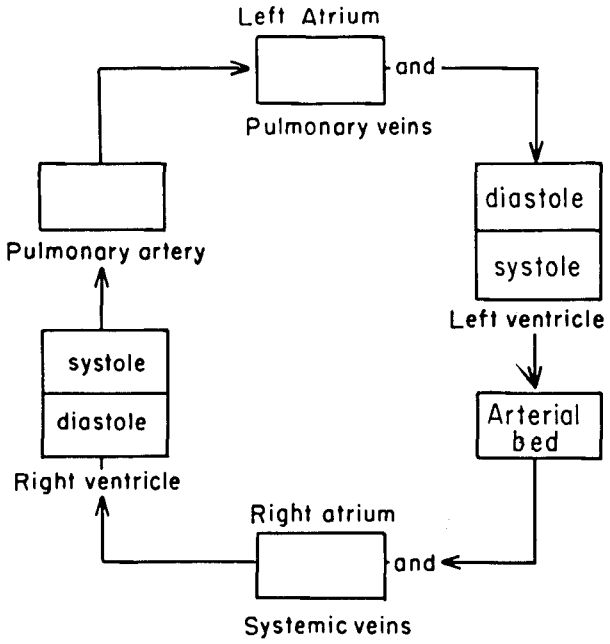

FIG. 1. Schematic block diagram of the circulation described mathematically by the equations in the text.

tance (C_3), and on an inertia term proportional to the rate of change of flow. This is expressed in *equation 6*.

$$F_3 = \frac{V_2}{R_2C_{2s}} - \frac{L_2}{R_2}\frac{dF_2}{dt} - \frac{V_3}{R_2C_3} \quad \text{(systole)} \qquad (6)$$

$$F_3 = 0 \quad \text{(diastole)}$$

The volume of the aorta depends on the integral of the flow in, minus the flow out, as shown in *equation 7*.

$$V_3 = V_{3(t=0)} + \int (F_3 - F_4)\, dt \qquad (7)$$

And, finally, *equation 8* expresses the flow out of the aorta (F_4) as a function of aortic volume, aortic capacitance, and the resistance to flow out of the arterial bed. The inertia term (L_3) is small but must be included in order to account for the experimental observations (1).

$$F_4 = \frac{V_3}{R_3C_3} - \frac{L_3}{R_3}\frac{dF_4}{dt} - \frac{V_4}{R_3C_4} \qquad (8)$$

V_3 and C_4 are volume and capacity of the systemic veins and right atrium.

To complete the loop, eight more equations must be written to describe the properties of the large systemic veins and right atrium, the right ventricle, and the pulmonary arterial bed. These equations have the same form as the ones just written.

The most important assumption made in the derivation of these equations is that the pumping action of the ventricles results from a triggering by the electrical event of the ventricular muscle from one passive state to another, represented here as a change from diastolic to systolic capacitance, and that the ejection of blood during systole is determined by the volume to which the ventricle filled during the previous diastole, the passive resistive and capacitive properties of the ventricle during systole and the impedance to flow into the aorta. These properties are not time dependent but remain constant during the course of systole. In support of this concept is the finding that wave forms generated by the model compare favorably with flow curves recorded with an electromagnetic flowmeter on the ascending aorta of a dog as shown in Fig. 2.

It is possible with this mathematical model to examine the response of this system to a transient disturbance from its equilibrium state and to compare this response to the response of its biological counterpart, which in this case is the circulatory system of a dog deprived pharmacologically of his autonomic nervous system. Simultaneous solution of this set of equations predicts a rapid return to equilibrium with no overshoot except at high flows following such a disturbance as a Valsalva maneuver in which blood is displaced from the pulmonary circuit into the systemic circuit. This is in agreement with the response observed in the biological preparation.

Once the investigator is satisfied that the equations will represent the observed dynamic inter-relationships in the circulation, he may proceed with a systematic investigation of the role played by each component in determining overall system performance. A new solution may be obtained with each sweep of the oscilloscope and a parameter change is accomplished by simple adjustment of a potentiometer in the analogue computer. The ease with which such an analysis of parameter changes may be performed is a distinct advantage of the analogue computer for this kind of work.

It is essential that this model, representing only the interrelationships among the physical properties of the circulation, be expanded to include the nervous reflex elements which play such an important role in controlling these physical properties in the intact animal. The analogue computer has also proved valuable in approaching this problem. The remainder of this paper will be a presentation of examples to illustrate the role an analogue computer may play in acquiring data from the experimental animal, in reducing the data to a meaningful form for analysis, and finally in simulation of the biological system under study as a means for testing an hypothesis regarding its dynamic characteristics. First, consider the role of an analogue computer as an integral part of data acquisition equipment for studying a reflex pathway.

In attempting a quantitative description of the effect of a particular nervous element in the control system, the exact form of the input function must be known. For instance, if a sinusoidal variation in the frequency of stimulation of a particular nerve is desired, a sine wave is generated by a function generator. This is fed to the computer, where it is scaled and biased to the desired level. The output voltage is then fed in parallel to a tape recorder to represent the input to the animal and to an analogue-to-frequency converter. Such de-

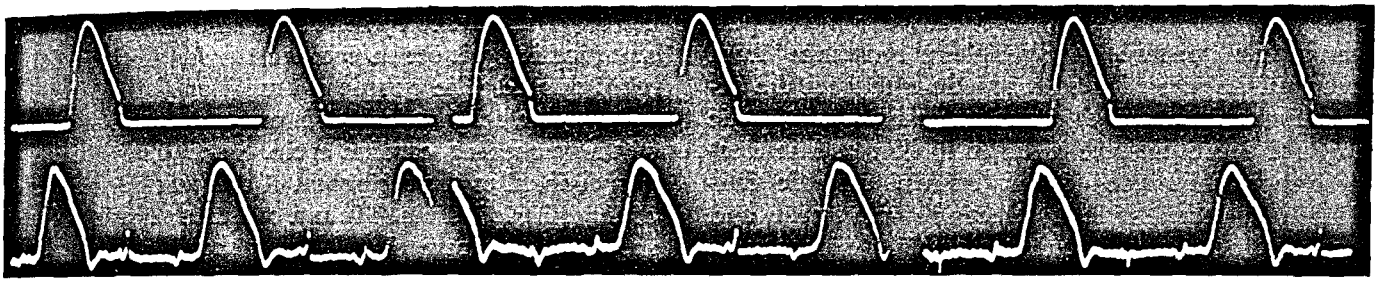

FIG. 2. Comparison of the time-course of flow in the ascending aorta predicted by the equations (smooth line) and the flow recorded from the ascending aorta of the dog. The theory does not account for the small reversal of flow at the end of systole seen on the recorded flow curve.

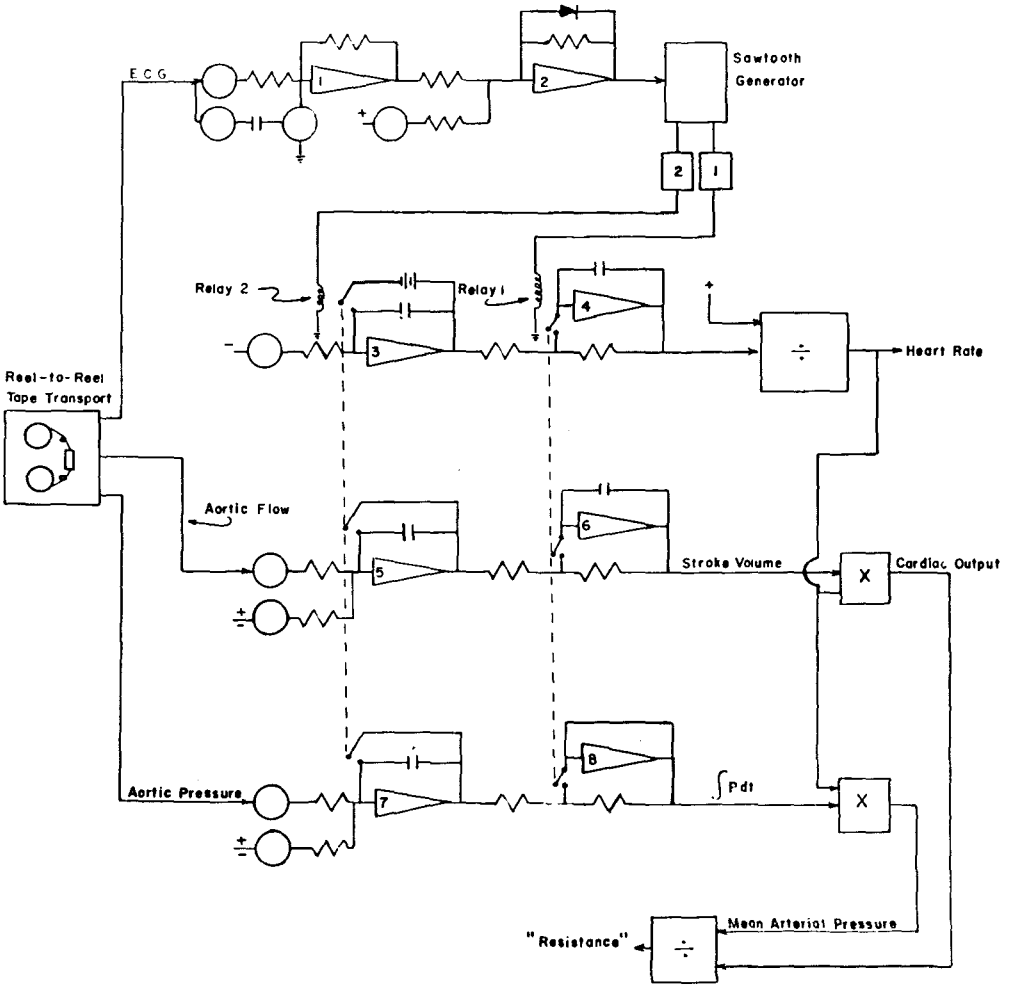

FIG. 3. Diagram illustrating the analogue computer program for deriving heart rate, stroke volume, cardiac output, mean arterial pressure, and resistance beat-by-beat from a tape recording of the electrocardiogram, flow in the ascending aorta, and aortic pressure.

vices are designed to operate at high frequencies. In order to increase the accuracy at low frequencies, pulses from the converter are fed to a counter where the output of the second decade is sampled. This divides the frequency by 100 and thus increases the accuracy of the analogue-to-frequency conversion near zero frequency by a factor of 100. The pulse out of the counter then drives the stimulator which, in turn, is connected to the stimulating electrodes in the animal.

If the input to the animal is to be a function of some variable elsewhere in the animal, this may be accomplished as follows: the variable is sensed with a transducer and the voltage from the transducer is fed to the computer, where the operations are performed in accordance with the known characteristics of the biological transducer or sense organ being simulated. This system, then, when placed in parallel with the dog's own biological transducer (for instance, the carotid sinus) acts to amplify any particular characteristic of this organ and may be used to study the effects of changing this organ's parameters on the performance of the whole circulatory system. Such a study has been carried out in the case of the carotid sinus (2).

Once the experiment has been performed and the output of the transducers recorded on magnetic tape, a computer may be used to convert this raw data into a more meaningful form for analysis. As an example of this, the analogue computer program used to obtain

beat-by-beat stroke volume, heart rate, cardiac output, mean arterial pressure, and "peripheral resistance" from three variables recorded on magnetic tape from the experimental animal, namely, the electrocardiogram, aortic flow, and aortic pressure is shown in Fig. 3. The electrocardiogram recorded during exercise may be considerably distorted, due to electrode movement and muscle artifact. Thus, in order to obtain a trigger pulse at the time of each R wave, the electrocardiogram is differentiated, then rectified and biased, in order to obtain a single spike from the R wave and zero voltage during the rest of the heart cycle. This spike triggers a sawtooth generator which, in turn, triggers two pulse generators in sequence. Each pulse generator operates a relay coil. Following each R wave, relay 1 closes first and allows amplifier 4 to charge up to the voltage existing on the output of amplifier 3. This relay then opens, and relay 2 closes, setting amplifier 3 back to its initial conditions. Each relay is closed for only 2 msec. Amplifier 3 then begins integrating the constant voltage generating a sawtooth whose final height is proportional to the period of the heart cycle. The initial condition voltage on amplifier 3 is set to compensate for the time lost in relay closure. The output of amplifier 4, then, is a step voltage, the height of which is proportional to the period of the preceding cardiac cycle. Since the heart rate is proportional to the reciprocal of this voltage, the output of amplifier 4 is divided into a constant voltage to generate the heart rate signal. Also shown are essentially identical circuits used to derive voltages proportional to the integral of arterial pressure, with respect to time over one heart cycle and a voltage proportional to stroke volume. Then, with multiplier and divider circuits, we may obtain beat-by-beat heart rate, stroke volume, cardiac output, mean arterial pressure, and the ratio of mean arterial pressure to cardiac output, the so-called peripheral resistance. Once the data has been reduced to this form, and beat-by-beat values for each of these variables recorded simultaneously, the interrelationships among them may become evident from the time sequence of events following a step or sine wave variation in speed of the treadmill on which the dog is exercising.

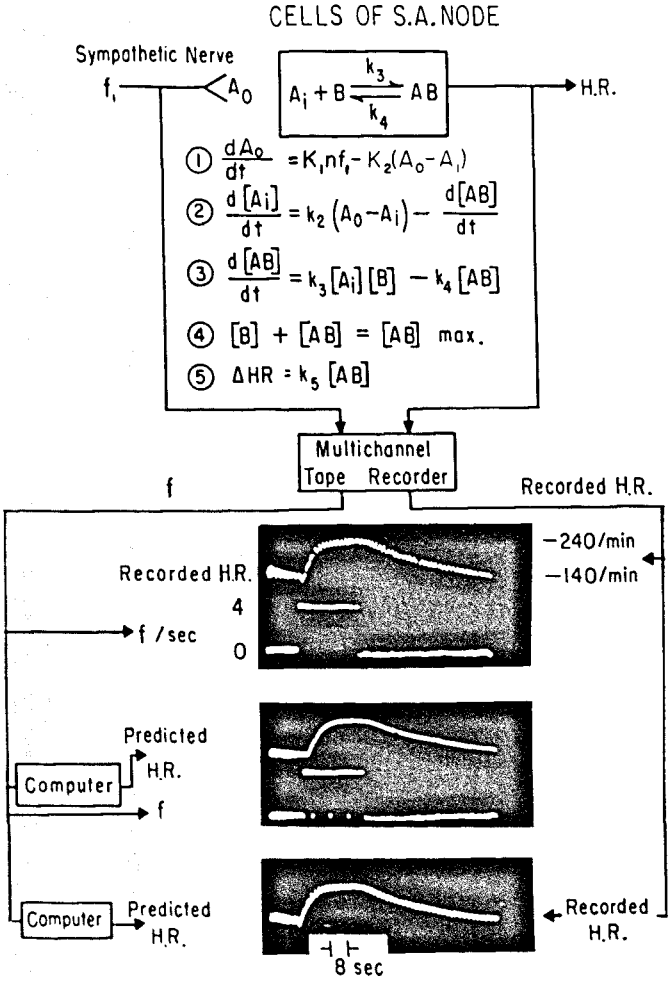

FIG. 4. Mathematical model representing the relationship between f_1, the frequency of stimulation of the sympathetic efferent nerves to the heart, and heart rate. The time-course of heart rate predicted from a solution of these equations is compared to the recorded heart rate from an experimental animal.

The final and perhaps the most useful role of the analogue computer is in testing hypotheses derived to represent the inter-relationships among the component parts of a circulatory reflex loop. As an example, a study of the relationship between heart rate and the frequency of efferent action potentials on the sympathetic nerves going to the heart will be presented. This system is just one link in the heart rate control system, but it is essential that each link be characterized in this fashion before the overall control mechanisms can be understood. In this study the computer was used to generate an analogue voltage proportional to the input which here is the frequency (f_1) of stimulation of the right preganglionic efferent sympathetic nerves to the heart of a dog anesthetized with Nembutal. Both cardiac sympathetic and both vagus nerves are severed. The electrocardiogram and a voltage proportional to f_1 are recorded on magnetic tape using a reel-to-reel transport. Later, the recorded data is reproduced and selected portions of the experimental data re-recorded on a continuous loop of tape along with the heart rate calculated by the computer from the electrocardiogram, as described above. Once this modified data is on a continuous loop, it is reproduced over and over again at eight times the original recording speed. The heart rate (or output) is displayed on the oscilloscope and the input (f_1) is fed into the computer on which is programmed the equations representing the hypothetical relationship between heart rate and f_1. The measured and predicted heart rates then are compared on a dual beam oscilloscope or X-Y plotter. The parameters of the equations are adjusted to obtain the best possible fit of the two curves. The block diagram and set of equations used to predict heart rate from frequency (f_1) of sympathetic nerve stimulation are shown in Fig. 4. *Equation 1* states that the rate at which noradrenalin concentration (A_0)

changes just beyond the sympathetic nerve endings is proportional to the frequency of sympathetic nerve stimulation (f_1) and the number of fibers responding to this stimulus (n), and that this noradrenalin diffuses to the active site on the S.A. node at a rate proportional to the concentration gradient ($A_0 - A_1$). A_1 reacts with a substance B in a reversible fashion to form compound AB and the resulting change in heart rate is proportional to AB concentration. Since the substance B is present in limited quantity it establishes the maximum heart rate which can be obtained.

These phenomena are represented by these five equations and are programmed on an analogue computer. In the top recording in Fig. 4 is shown the heart rate recorded in response to a step input in frequency (f_1) of sympathetic nerve stimulation. Below this is shown the predicted heart rate in response to the same step input, and at the bottom the predicted and recorded heart rate are superimposed. The equation parameters were manipulated to obtain the best possible fit with the experimental curve. The rate of increase in heart rate depends upon the frequency of stimulation. In many dogs, the response to a stimulus of 2/sec is approximately ¾ the response of a stimulus of 20/sec. Once the optimal equation parameters have been determined for two such step inputs in f_1, the equations will accurately predict the time-course of heart rate resulting from sinusoidal variations in f_1.

This example illustrates the way in which an analogue computer may be used to analyze the dynamic relationship between input and output for one component of a reflex arc. Such studies must be performed on each element of a nervous control loop or reflex before it can be integrated into the general model of the circulation.

Two points in regard to this approach should be emphasized. First, when an equation is found which will describe a system, its value must be judged on the basis of its ability to describe the system under all circumstances. The equation should have a minimum number of parameters and each of the parameters should be sensitive to changes in a particular system characteristic. If these two criteria are satisfied, the question of uniqueness of the equation is of no concern. The second point deserving emphasis is the fact that valuable information may be obtained each time an equation fails to predict the behavior of a system. Such a failure means that existing concepts regarding this system's performance are inadequate to account for the observed facts since the equation being tested was derived from these concepts. Thus, a modification of the prevailing concepts is necessary and new concepts must be sought. This negative information may be the most useful.

The very nature of the analogue computer lends itself to this sort of theoretical physiology. Often when a mathematical model fails to simulate its biological counterpart, valuable insight into the type of modification of the theory necessary to improve its correspondence to the biological system will be gained by careful consideration based on knowledge of the electrical analogue system. In other words, the electrical system provides just one more physical realm from which to derive insight regarding the dynamic characteristics of the biological system under study.

The examples presented illustrate the way in which an analogue computer may be used as an integral part of a laboratory engaged in the study of physiologic control, emphasizing its role in initial analysis of the overall system, as a tool for obtaining experimental data, and for reducing this data to the desired form for analysis, and as a means for solving sets of equations set up to represent hypotheses regarding input-output relationships. The accuracy with which an analogue computer will perform these tasks will vary from 0.1 to 2%, depending upon the nature and complexity of the system being studied. It is apparent, however, that the accuracy of the analogue computer does not determine the limits of accuracy of solution for most problems encountered in physiology today. Instead, these limits are set by the accuracy with which the original measurements are made and the necessity of simplifying assumptions incorporated into any mathematical model derived to represent a physiological system at the level at which measurement of system variables is now possible.

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