THE USE OF AN ANALOG COMPUTER FOR ANALYSIS OF PHYSIOLOGICAL SYSTEMS

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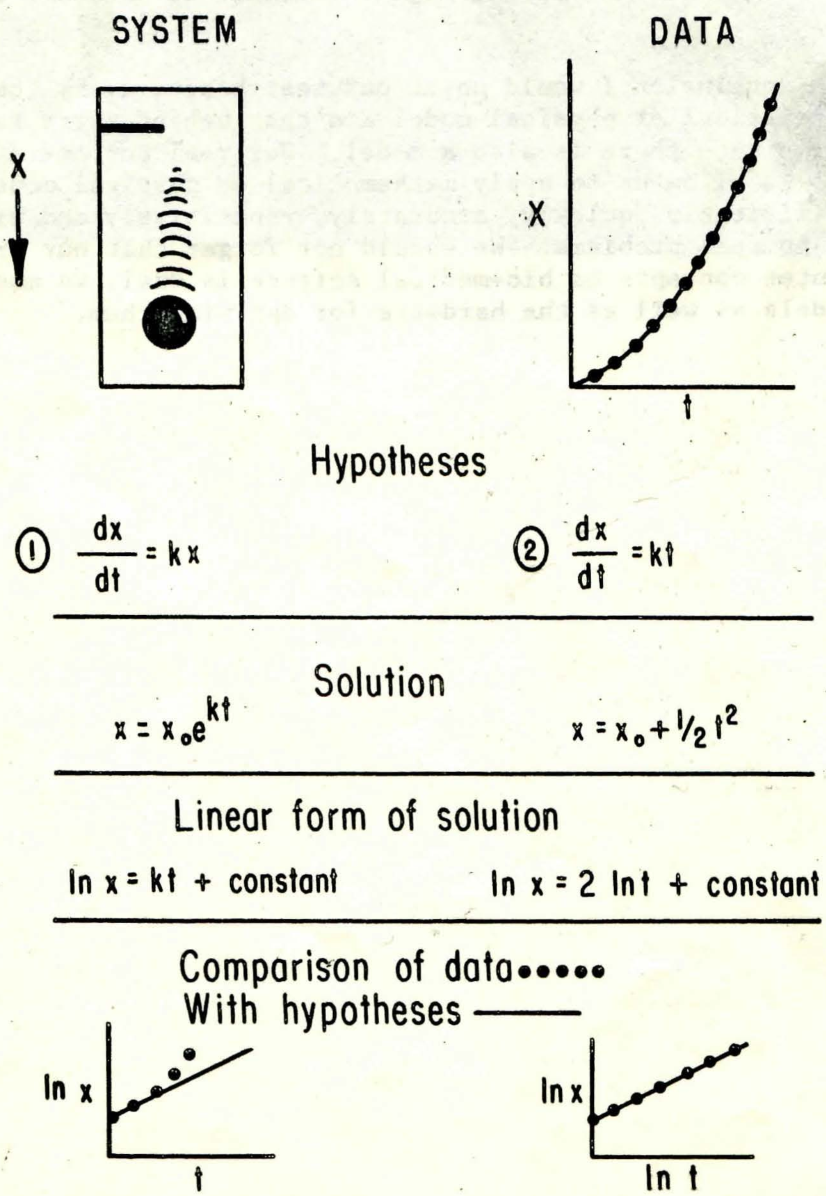
The subject of this discussion is the analog computer. Since this is basically a mathematical tool, it seems appropriate to begin with a simple example of a mathematical approach to a physical problem Figure 1.



Let us look at a system which consists of a free falling object in a vacuum. In this system we can determine the position of the object at any time. A plot of the distance traveled (x) against time (t) shows that the velocity (which is the slope of this plotted line) increases with distance and increases with time. Two hypotheses that seem worthy of testing are (1) that the velocity (dx/dt) is proportional to the distance traveled (x), and (2) that the velocity is proportional to the time elapsed (t) since the object was released. Each of these hypotheses is expressed in the form of a differential equation; that is, an equation which expresses the rate of change of one variable with respect to another, in this case, distance with respect to time. These equations must then be solved. Solving a differential equation such as these two consists of converting it to a form in which one variable is expressed directly as a function of the other. Here, each solution expresses x, the position of the object, as a function of time (t). In this form, however, it is difficult to determine the particular values for the constants or parameters of the equations that should be used in order to make a valid comparison between the observed distance and the predicted distance traveled by the object at any time. Fortunately both of these equations can be reduced to a linear form making this comparison easy. A plot of the logarithm of the measured distance against time fails to fit a straight line as would be predicted from hypothesis #1. However, a straight line does fit the data when the logarithm of x is plotted against the logarithm of time as predicted by our second hypothesis. Having thus established equation #2 as describing the data, we may then, by a further manipulation of the original equation; namely, differentiation, arrive at the fundamental conclusion that in this system acceleration is constant.

The steps involved in this analysis are common to the analysis of many systems. These steps are reviewed in Figure 2.

Step 1 Quantitative observations

Step 2 Observations suggest hypothesis

Step 3 Hypothesis expressed as differential equation

Step 4 Solution of differential equation

Step 5 Comparison of solution with data

Step 6 Deduction and prediction from equation

First, quantitative observations are made of the relationship of one or more variables in the system to other variables including time.

(2) These observations may suggest an hypothesis or generalization regarding the system being studied.

(3) This hypothesis is expressed mathematically, usually in the form of a differential equation. A differential equation again is an equation which includes one or more derivatives; that is, terms which express the rate of change of one variable with respect to another.

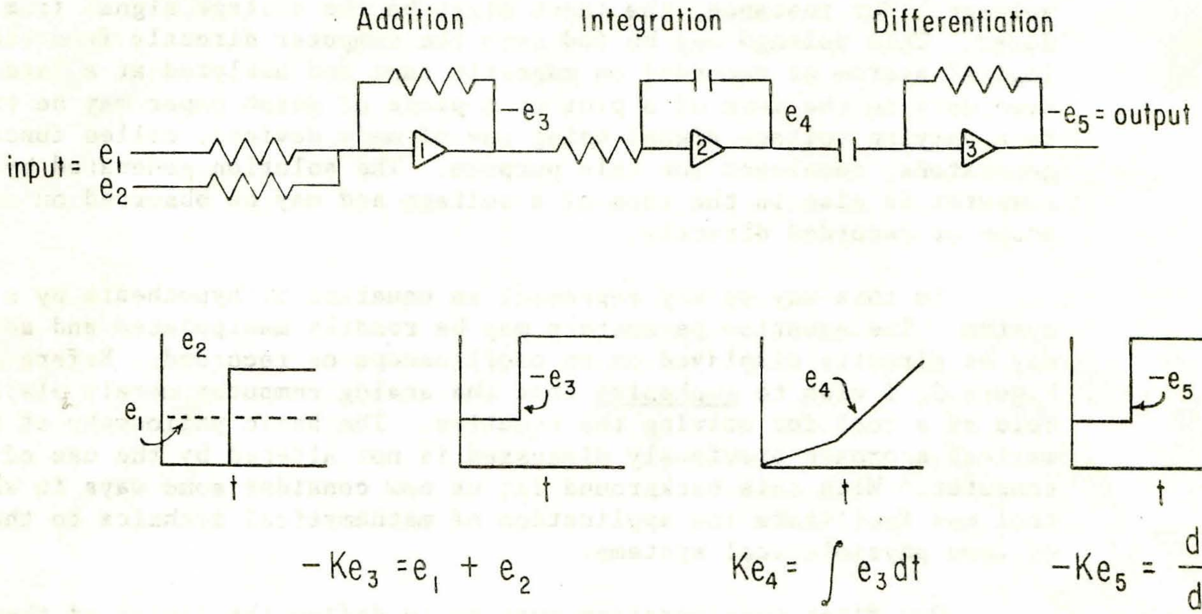
(4) The differential equations are solved in order to obtain an expression in which the equation variables are in the same form as the experimental data they are to represent. This usually means elimination of the derivative terms by integration.

(5) The solution is compared with the experimental data. This involves finding the optimal set of equation parameters. In the illustration just shown this was done by reducing the solutions to linear forms and then comparing the data to these straight lines. In more complex systems it is necessary to obtain repeated solutions, each time varying the parameters until the set of parameters is found that allows best prediction of the data by the equation.

(6) And finally, through examination and further manipulation of the equation, general properties of the system may be <u>deduced</u> which might not have been apparent except through this formal expression of the hypothesis. Also the equation may suggest directions in which future studies should be aimed in order to further test the hypothesis.

This type of mathematical approach has not been widely used in physiology in the past for several reasons. The biological scientist has been, and to some extent still is, limited in his ability to measure some variables with the accuracy necessary for an adequate analysis. In addition, the mathematical expressions of hypotheses devised to explain physiological systems are often non-linear simultaneous differential equations which may be difficult or impossible even for the most able mathematician to solve analytically. It is in overcoming this second obstacle that the analog computer can be of valuable assistance to the physiologist.

What is an analog computer? In the example just presented we considered the concept of describing a physical system by an abstract or mathematical expression. Since this is possible, it is conceivable that a physical system might be devised to represent any particular mathematical expression. Devising such a system might be of value if (1) the components of the physical system which represent the parameters of the equation could be easily manipulated and (2) if the relationship among the variables in the physical system could be directly observed. Of the physical systems which have been devised for this purpose electronic analog computer has been the most useful. To provide some insight into how such a computer operates let us look at the diagram shown in Figure 3.



The heart of an analog computer is the operational amplifier, three of which are represented here as triangles. To be an effective element in a computer such an amplifier must have certain characteristics, among which high gain and low drift are particularly important. The input end of the amplifier is represented by the blunt end of the triangle and the output by the other. By selecting the elements in the input and feedback circuits, the amplifier can be made to perform several different types of mathematical operations such as addition, integration, and differentiation. For instance, if voltages e_1 and e_2, having the time-course shown, were fed into amplifier number 1, its output e_3 would equal the sum of these voltages. Notice that a change of sign occurs at each amplifier. If e_3 is now fed into amplifier #2, which has a capacitor in the feedback circuit, its output e_4 would be the integral of e_3 with respect to time. The presence of a capacitor in the input circuit of amplifier 3 results in its output being the derivative of its input.

Thus the process of programing an analog computer consists of first reducing the equation to be solved to a form in which it can be represented on the computer in building-block fashion and then selecting the proper combination of computer components to perform the mathematical operations called for by each term in the equation. The only requirement of the input variable is that it be reduced to the form of a varying D.C. voltage. For instance, the input might be the voltage signal from a transducer. This voltage may be fed into the computer directly from the biological system or recorded on magnetic tape and analyzed at a later time. Even data in the form of a plot on a piece of graph paper may be translated to a varying voltage signal using one of many devices, called function generators, developed for this purpose. The solution generated by the computer is also in the form of a voltage and may be observed on an oscilloscope or recorded directly.

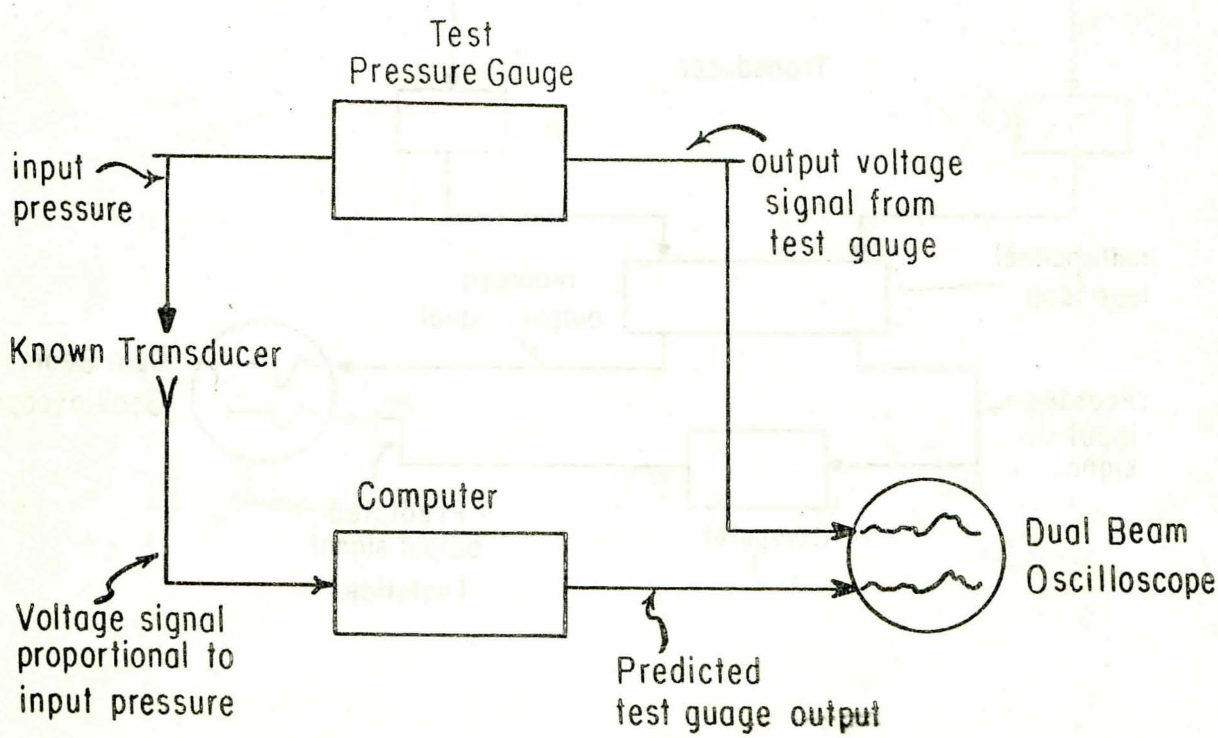
In this way we may represent an equation or hypothesis by a physical system. The equation parameters may be readily manipulated and solutions may be directly displayed on an oscilloscope or recorded. Before leaving Figure 3, I wish to emphasize that the analog computer merely plays the role of a tool for solving the equation. The basic philosophy of the mathematical approach previously discussed is not altered by the use of the computer. With this background let us now consider some ways in which this tool may facilitate the application of mathematical technics to the analysis of some physiological systems.

Our first consideration must be to define the limits of the system we wish to analyze. Since in most cases this system will be something less than the whole organism there are several alternatives. The usual approach of isolating the system anatomically from the rest of the organism allows the experimenter to control the input to the system and hold certain factors in its environment constant. However, it imposes the difficult task upon the experimenter of maintaining these variables as close as possible to the values existing in the intact animal if his analysis is to reveal the particular characteristics of this system which are important in determining its performance in the intact organism.

Another approach, which I will call the transfer function or input-output approach, may also be applied to the analysis of a biological system. In this approach the system is defined as consisting of all components of the organism which play a role in determining the transition from input to output. The transfer function is the ratio of system output to system input expressed in a form which takes into account not only the amplitude changes but the temporal relations as well. As physiologists we are familiar with this approach as a method of describing the characteristics of a linear transducer, for instance a pressure gauge. We know that if sine wave variations in pressure of constant amplitude are applied to a pressure gauge the amplitude of the excursions in signal output voltage will depend upon the frequency of the sine wave.

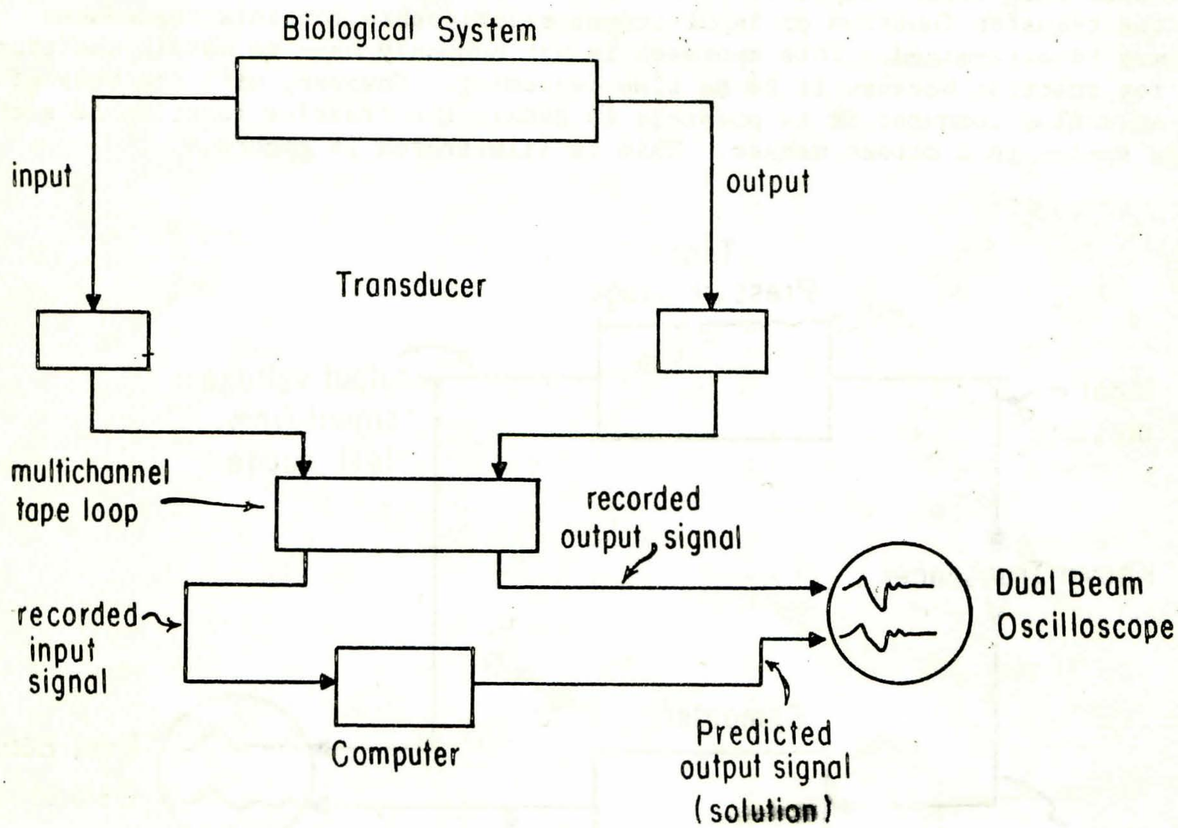
In testing the response of a pressure gauge to sinusoidal variations in pressure we realize, of course, that the gauge is not going to be subjected to pure sinusoidal variations in pressure when it is used to measure pressure in an artery. However, since any complex wave form may be expressed as the sum of sine waves whose frequencies are integral multiples of a fundamental frequency, our testing of the instrument's response to pure sine waves <u>will</u> reveal the information we need in order to evaluate the instrument's response to any input. Also having once determined the instrument's transfer function it is a simple matter to write the differential equation which describes its performance.

Now, in testing the response of a pressure transducer it is not necessary to use as an input pure sine waves of constant amplitude and varying frequency. Actually any wave form might be used for the input. Then by resolving this waveform and the output waveform from the transducer into their component sine waves (a procedure called Fourier analysis) the transfer function or input-output relationship for this transducer may be determined. This approach is not commonly used to obtain the transfer function because it is so time consuming. However, with the help of an analog computer it is possible to obtain the transfer function of such a system in a direct manner. This is illustrated in Figure 4.



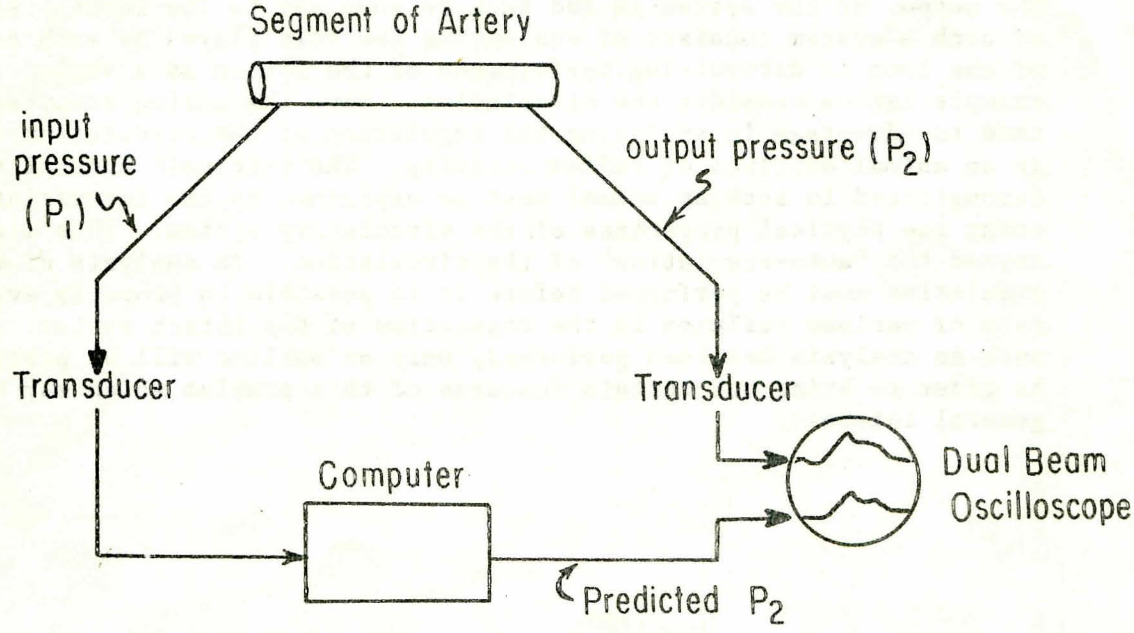
Here is shown a block diagram to illustrate the transfer function approach to the study of a system, in this case a pressure gauge. On the computer a differential equation is programmed which represents our hypothesis to explain the way in which the signal voltage from the test gauge will relate to a variation in the pressure which the gauge sees. A second transducer whose characteristics are known to be adequate to faithfully generate a signal proportional to this pressure is used to supply the input to the computer. The parameters of the equation are then adjusted empirically until the solution being generated by the computer matches the output signal from the gauge being tested. If the hypothesis is correct a match between the two waveforms will be obtained. When this has been accomplished the parameters of the equation may be read directly from the computer. In this manner the transfer function of the test gauge can be obtained.

Now we will apply this same approach to a biological system. In Figure 5 is shown a segment of the arterial bed. P_1 is the pressure wave-



form entering this segment and P_2 the pressure at the other end--the output. Using high fidelity transducers these pressures are converted to voltages without distortion. The hypothesis used to explain the change in contour of a pressure wave traveling down a segment of artery is based on the fact that the wall of the artery has inertia and is distensible and that some of the pressure is dissipated as friction. These three properties are treated as parameters of a 2nd order differential equation shown here and this equation programmed on the computer. It was found that this equation will predict P_2 from P_1 in many segments of the arterial bed with an accuracy that is surprising considering the fact that the model of the segment of artery is such a simple one. Determination of the particular transfer function of any given segment of artery permits characterization of that segment in terms of a resonant frequency and a damping coefficient.

Two features of this approach deserve emphasis. First, an analysis of a system within the organism was performed without having to either add an artificial input to the system or remove the system from its normal relationship with the rest of the organism. And second, this approach is not limited to systems whose input is periodic. In Figure 6 is illustrated one technic for reproducing a transient phenomenon many times making it subject to the type of analysis just described. The input and output data



Equation

$$a\frac{d^2P_2}{dt^2} + b\frac{dP_2}{dt} + cP_2 = P_1$$

from the biological system are converted to electrical form by transducers and recorded on a continuous loop of multichannel magnetic tape. The data may then be reproduced over and over again. The input signal is fed to the computer where the computer modifies this function in accordance with the equation being tested and generates an output which can be compared on an oscilloscope with the recorded output signal from the tape. This allows a solution to be obtained with each revolution of the tape loop, permitting emperical adjustment of the equation parameters to finally achieve the best possible match between the solution and the observed output. As an example, this particular approach has been successfully applied to the analysis of the time-course of the specific activity of circulating gramulocytes following the injection of a radioactive label.

Now let us turn our attention to another type of physiological problem which an analog computer may assist in solving. This is the problem of understanding the means by which a biological system regulates its output within certain well-defined limits despite large variations in input to the system. Although physiologists have long been concerned with this problem few quantitative studies have been undertaken. Since World War II the science of control engineering has made rapid strides in the development of technics for analysis and design of control systems. Many of these technics might be applied with advantage to the study of control in biological systems.

Any control system is a closed loop; that is, information regarding the output of the system is fed back in some way to the input. An analysis of such a system consists of evaluating the role played by each component of the loop in determining performance of the system as a whole. As an example let us consider the circulation. Here the analog computer has been used to advantage in analysing the regulation of the circulation that occurs in an animal deprived of reflex activity. The intrinsic control readily demonstrated in such an animal must be explained by the interrelationships among the physical properties of the circulatory system. This might be termed the "auto-regulation" of the circulation. An analysis of this auto-regulation must be performed before it is possible to properly evaluate the role of various reflexes in the regulation of the intact system. Although such an analysis has been performed, only an outline will be presented here in order to bring out certain features of this problem which may be of general interest.

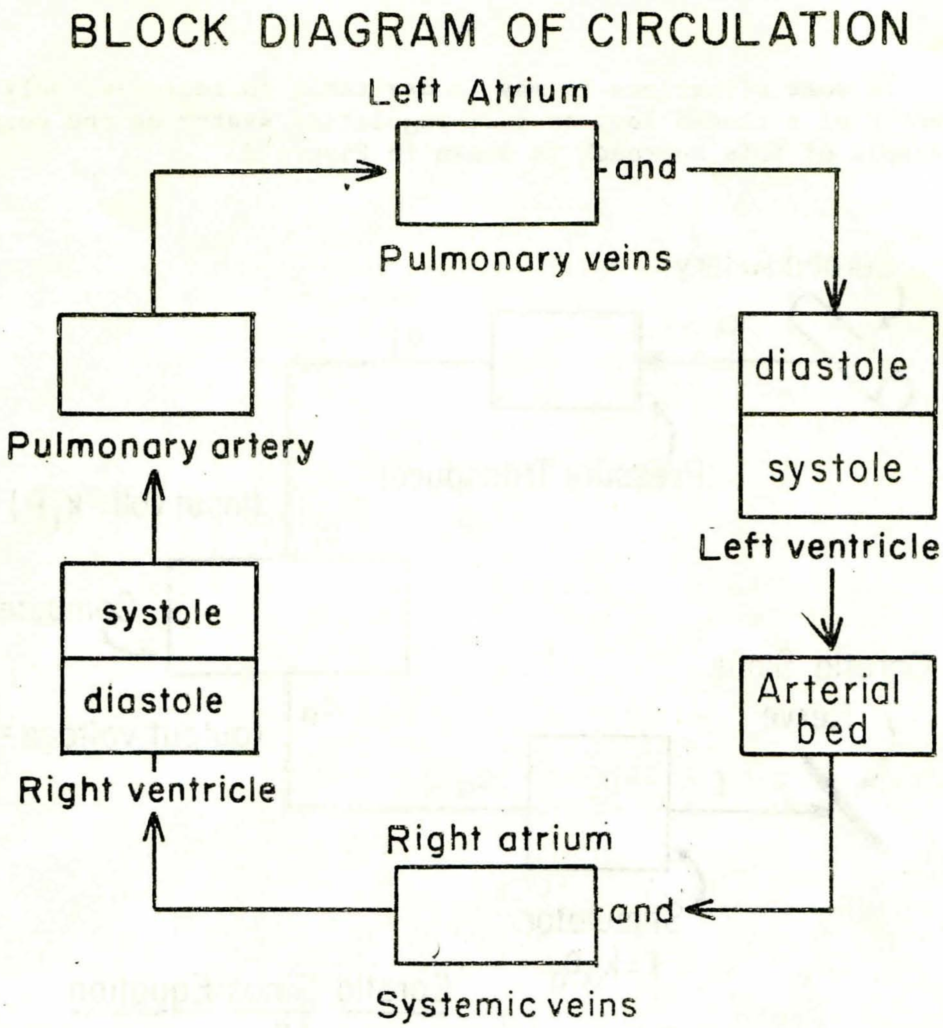
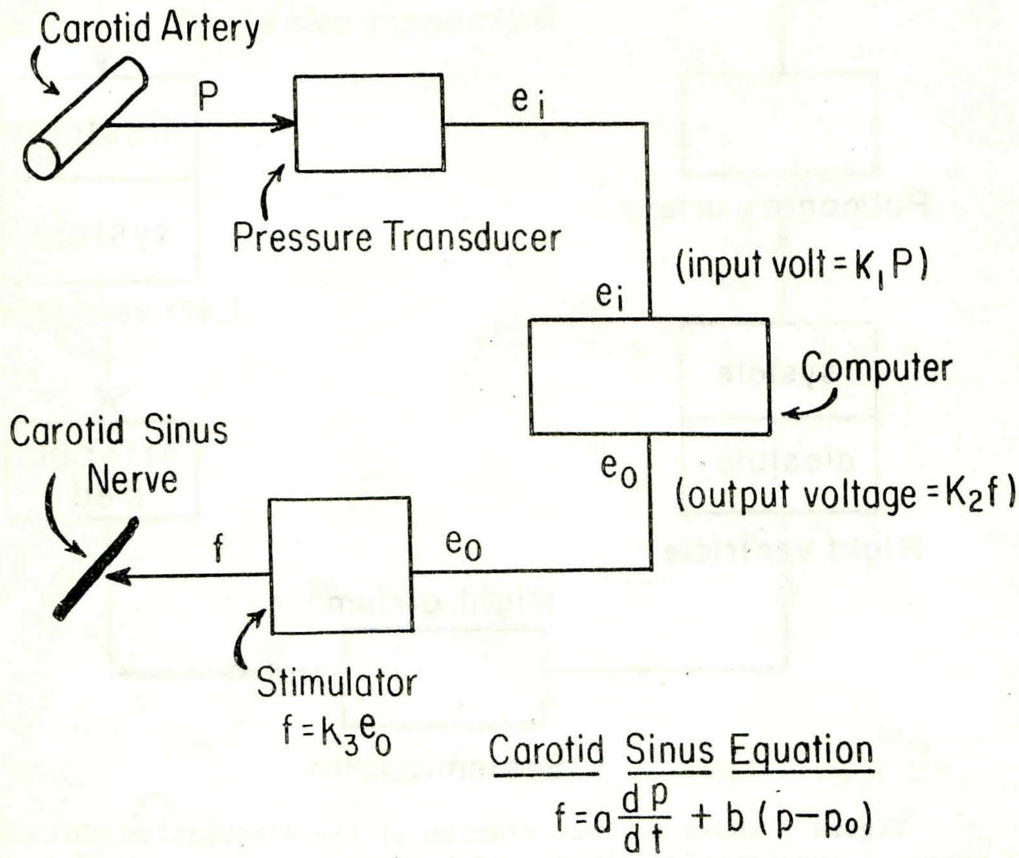


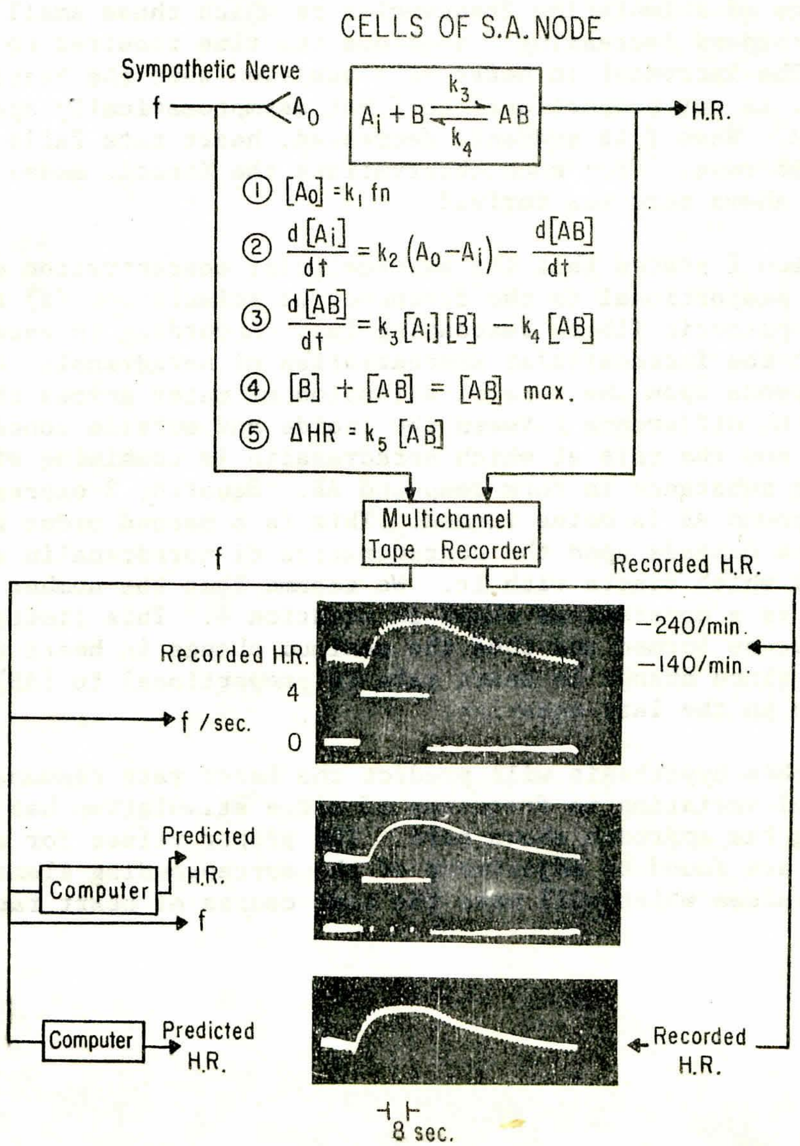
Figure 7 shows a block diagram of the circulation which consists of 2 pumps, 2 transmission lines, and 2 reservoirs in a closed loop. Much information is available concerning the characteristics of each component part of this system. From this information a set of 16 equations were derived to represent the interrelationship of volume, pressure, flow and time in each part of the system. Simultaneous solution of these equations allows prediction of the behavior of the whole system. If the system is disturbed from its state of equilibrium (for instance by displacing blood from the pulmonary circulation into the systemic circulation as occurs during a Valsalva maneuver) the time course of each variable may be observed as the system returns to equilibrium and this response compared to the response observed in the dog deprived of reflex activity. The parameters of the equation are adjusted until the solutions obtained accurately duplicate the biological observations. Manipulation of the equation parameters allows quantative assessment of the role of each component part in determining the performance of the system as a whole. In this way a framework is established upon which an analysis of the role of various reflexes in cardiovascular control may be undertaken.

In some situations it may be desirable to represent only one component of a closed loop or self-regulating system on the computer. An example of this approach is shown in Figure 8.



In this example the computer is substituted for part of a control system. The equation shown here is derived from available data concerning the relationship between input and output of the carotid sinus and is programed on the computer. The equation states that the frequency of action potentials (f) traveling up the carotid sinus nerve is proportional to the rate of change of pressure in the carotid sinus and to the pressure itself when it is above a certain threshold pressure (P_o). The input to the computer is a voltage signal (e_i) from a strain gauge sensing arterial pressure in a carotid artery. The output from the computer (e_o) drives a stimulator whose frequency is proportional to this voltage. The output of the stimulator is connected to electrodes on the afferent end of a previously severed carotid sinus nerve. Thus a rise in arterial pressure results in an increased rate of carotid sinus nerve stimulation just as would occur with the carotid sinus itself. With the computer, however, it is now possible to alter at will any one of the equation parameters (a,b, or P_o) and study the effect of this change on the behavior of the circulatory system. It was found that increasing the steady state gain (b) resulted in oscillations in arterial pressure similar to the so-called Traube-Hering waves. These oscillations are attributed to a phase change resulting from lags in the response of arterial smooth muscle to changing sympathetic efferent activity. Thus, this example illustrates that substitution of the computer for a component part of a control system will allow quantitative evaluation of the role of this component and may bring out certain characteristics of the rest of the system that might be difficult to detect otherwise.

<u>Finally</u> let us consider the use of a computer to gain insight into the kinetics of physical and chemical processes occuring at the cellular level from data obtained from a relatively intact gross preparation. As an example we consider the regulation of heart rate by efferent sympathetic action potentials (Figure 9).



The heart rate is determined by the frequency of action potentials in one or more cells in the region of the S.A. node in the right atrium. Modification of this rate may be effected by variation in efferent activity of the sympathetic nerves which end in this region. Our problem is to find an hypothesis or equation which will predict heart rate (HR) from the frequency (f) of action potentials on cardiac sympathetic nerves in the absence of vagal activity. Both vagus and sympathetic nerves to the heart were severed. (f) was varied by varying the rate of stimulation of the cardiac sympathetic nerves. The heart rate with each cycle was calculated by the computer from the interval between R waves of the electrocardiogram. Voltages proportional to input (f) and the output (heart rate) were recorded on magnetic tape.

In the top recording is shown the observed heart rate response to a step increase and decrease in frequency of stimulation of sympathetic efferents to the heart. The following characteristics of the response of this system were observed. No change in heart rate occurs for 1.5 seconds following a step increase in f. Heart rate then rises to a new level. Over the range of stimulation frequencies in which these small sympathetic fibers will respond increasing f shortens the time required to reach this new level. The increment in heart rate achieved when the heart rate reaches its new level is not proportional to f but asymptomatically approaches some maximum value. When f is suddenly decreased, heart rate falls much more slowly than it rose. From such observations the Kinetic model and system of equations shown here was derived.

Equation 1 states that the extracellular concentration of noradrenaline (A_0) is proportional to the frequency of stimulation (f) times the number of sympathetic fibers responding (n). According to equation 2, the rate at which the intracellular concentration of noradrenalin (A_1) changes with time depends upon the rate of diffusion of water across the cell membrane (k_2), the difference between the inside and outside concentration of noradrenalin and the rate at which noradrenalin is combining with some intracellular substance to form compound AB. Equation 3 expresses the rate at which compound AB is being formed. This is a second order reaction in which the rate depends upon the concentration of noradrenalin and another substance (B) which reacts with it. We assume that the number of molecules of B present is a constant as shown in equation 4. This limits the amount of AB that can be formed and thus the maximum change in heart rate that can be achieved, since change in heart rate is proportional to (AB) concentration as shown in the last equation.

That this hypothesis will predict the heart rate response to a variety of patterns of variation in frequency of nerve stimulation has been demonstrated using the approach shown here. The proper values for the equation coefficients are found by adjustment of the corresponding elements in the computer to values which will make the time course of heart rate predicted by the equations correspond to the recorded heart rate response. The predicted heart rate in response to this step increase in f is shown in the middle frame, and in the bottom frame the recorded and predicted response are superimposed. To establish the constants of these equations one must match the heart rate response to two step inputs of different magnitude. Once this is accomplished for a given dog, these equations will predict the time-course of heart rate resulting from any subsequent input pattern of variation in f.

I would like to point out that in deriving an equation for a system such as this, the system is not treated strictly as an unknown entity or black box. All known facts from any source are used. This is as it should be since the equation or hypothesis must account for these facts as well as those being observed in the present experiment. The important point is that the kinetics of this physical-chemical process observed in a relatively intact gross preparation may be evaluated in a quantitative manner with the help of the computer.

Finally, two other 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 be 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 the 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. It is my opinion that this "negative information" may be the most valuable type of answer that the computer can give us.

To summarize, a simple physical problem was first presented as a means for outlining the steps involved in the application of mathematics to the analysis of experimental data. The concept of a transfer function or input-output relationship was introduced, first through an example of its use in the evaluation of a pressure transducer and then by applying this approach to the study of pressure wave transmission by a segment of the arterial bed. The role of the computer in the analysis of closed-loop or self-regulating systems was illustrated by 2 approaches--one in which the performance of the whole system was expressed on the computer by the simultaneous solution of a set of differential equations and the other in which the computer was substituted in a biological system for one element of this system. Finally, an example was presented to illustrate the use of the computer in deriving information from a relatively intact gross preparation regarding the kinetics of physical and chemical processes

at the cellular level. The analog computer is a useful tool for the physiologist who would apply mathematical technics to the analysis of the systems he studies.

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... we should not forget that our problem in applying computer concepts to bio-medical science is dual; we must develop the basic models as well as the hardware for applying them.