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Editorial

Computers and Experimental Medicine

Because of their ability to perform a wide range of complex computations at a high rate of speed, electronic computers can be powerful tools for studying the complex systems found in the biological sciences. Technical and industrial advances in the past few years have made available computers which can fit the technical and financial capabilities of almost any laboratory. For these reasons, it is worthwhile to consider the place of computers in the experimental study of biological systems, the types of instruments available, and the manner in which some of them are used.

The strengths and weaknesses of computers as experimental aids are best considered in relationship to the general methodology of experimentation. The experimental study of any system involves collection of data, formulation of hypotheses to explain the data, and examination of these hypotheses to find areas which may be tested experimentally. Hypotheses are usually examined by using them to predict the behavior of specific parts of the system. These predictions can then be tested experimentally and the hypothesis modified to fit the new experimental findings. It is often difficult to make such predictions from hypotheses which concern biological systems, because of the complexity of the operations performed by individual units of the system (e.g., nephrons, alveoli, etc.), the large number of units involved, and the complexity of the interrelationships between units. Since they can perform numerous, interrelated, complex operations very rapidly, computers can often make such predictions quickly enough to be practical. Herein lie both the strengths and the limitations of the computer. It may increase the productiveness of a hypothesis by increasing its yield of experiments and may help to choose experiments best suited to the methods at hand. In doing so, however, it is entirely dependent upon the quality of the hypothesis and the quality of the data used in making the prediction. It is not a substitute for the creative imagination of the investigator or for careful collection of data.

Computers available for such purposes fall into two broad categories, analogue and digital. They differ from each other in principle of operation, accuracy, complexity and cost. Analogue computers accept and manipulate quantities as physical counterparts (length, voltage, and the like), a simple form being the slide rule. The accuracy of any single operation performed by an analogue computer rarely exceeds 0.1 per cent and the over-all accuracy of a long series of operations may be much less. However, these computers are relatively simple and inexpensive and can be purchased and operated much as any other laboratory instrument.

Digital computers accept and manipulate quantities as numbers, a simple form being the desk adding machine. The accuracy of single operations and of series of operations is much greater than that of analogue computers; and the great flexibility of these computers permits them to handle problems which analogue computers cannot. They are, however, very expensive to purchase or rent, and require of the operator a high order of mathematical and technical capability.

Since analogue computers fall within the

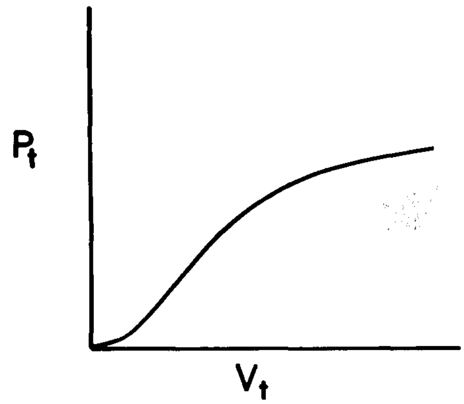


FIG. 1. Relationship between volume of the compartment (V_t) and the pressure difference across its wall (P_t).

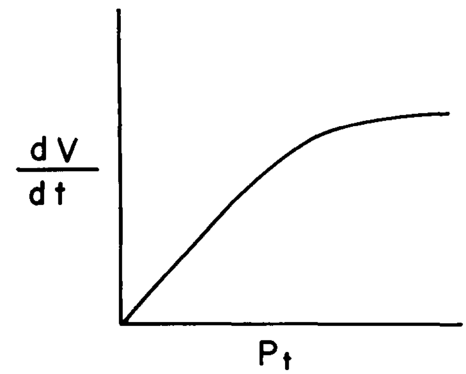


FIG. 2. Relationship between pressure-difference across the channel of exit (P_t) and volume flow through it (dV/dt).

range of financial and technical capability of most laboratories, we will consider their characteristics and mode of operation in some detail.

Analogue computers of the types which are now readily available perform operations on voltages. A voltage is made numerically equal to a variable in the problem (e.g., 1 volt = 5 ml./minute oxygen uptake) and the components in a portion of the computer are so arranged that the desired operation (e.g., subtraction, integration) is performed on the voltage.

The computer can be made to perform a number of operations, among them the following: (1) addition and subtraction, (2) multiplication or division by a constant, (3) integration, (4) multiplication or division of two variable quantities, (5) non-linear functional transformation. This last operation can be performed if a graph of the function is available even though the equation is not known. For example, if one component of the computer is arranged to represent the oxyhemoglobin dissociation curve and a voltage proportional to the partial pressure of oxygen is fed into it, its output is a voltage proportional to oxygen content.

Programming the computer to solve a problem simply amounts to deciding which operations must be performed in which sequence. The procedure is quite simple although it may appear a bit difficult because of its unfamiliarity. It is best illustrated by devising a program to solve a relatively simple problem which would be quite laborious to solve without the computer.

Consider the case of an elastic compartment whose pressure-volume diagram is non-linear and which is emptied through a channel in which the relationship between driving force and flow is non-linear. This system might represent a lung, a vascular compartment, or any one of a number of other components of a biological system. The first step is to identify the variables in the problem and to describe them in terms of constants and other variables. In this problem the variables are the pressure-difference between the inside and outside of the compartment at any time (P_t), the volume of material in the compartment at any time (V_t), and the rate at which material leaves the compartment (dV/dt). The relationship between the volume of the compartment (V_t) and the pressure difference across its wall (P_t) (which may have been established experimentally) can be expressed graphically as shown in Figure 1. The relation between flow through the channel of exit (dV/dt) and the driving force (P_t) (which may also have been determined experimentally) can also be expressed graphically. (Fig. 2.) Furthermore, the volume in the compartment after any interval of time equals the volume in the compartment at the beginning minus the quantity which has left in the interval. These relationships may be restated in symbols in the following equations:

$$P_t = f(V_t) \qquad (1)$$

$$dV/dt = \phi(P_t) \qquad (2)$$

$$V_t = V_0 - \int_0^t (dV/dt)\, dt \qquad (3)$$

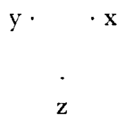
where V_0 = the volume in the compartment at the start of the experiment

f( ) = the relationship between volume and pressure shown in Figure 1

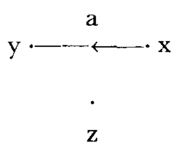
ϕ( ) = the relationship between driving force and flow described in Figure 2.

Several methods are available for converting this set of equations to a wiring diagram for the computer. One of the most easily and generally applicable of these methods is the signal-flow diagram [1,2]. Such a diagram is constructed by representing variables as points and operations on variables as lines with arrows. For example, the equation y = ax − bz is diagrammed as follows:

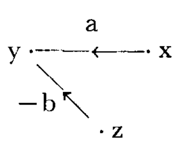
Three points, one for each variable, are placed in any convenient arrangement



A line drawn to indicate the fact that y comes from x through the operation a



A second line is drawn to indicate the fact that y also comes from z through the operation −b.



By following this scheme, equations 1, 2 and 3 lead to the diagram shown in Figure 3. This diagram can now serve as the guide for wiring the computer. Each point in the diagram represents a terminal in the computer. Each line in the diagram is a connection through a set of components which perform the operation written beside the line. The components are chosen in accordance with the instructions in the manual furnished with the computer. Solutions may be read out, on any of the recorders commonly used in the laboratory, as graphs of any of the variables (V_t, P_t, dV/dt) with respect to time.

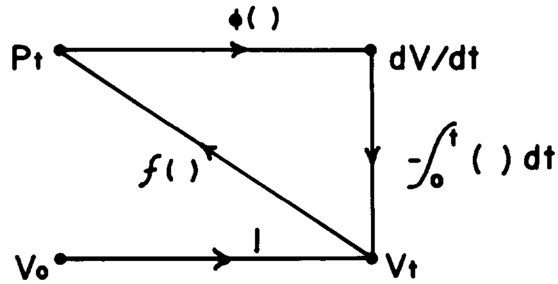


FIG. 3. Signal-flow diagram representing equations 1, 2, and 3 in text.

Several things should be noted about the programming procedure: (1) Little knowledge of electronics is required to solve the problem. Certain combinations of components perform certain operations. The operator need not know why. (2) Virtually no knowledge of operational mathematics is required. The equations are simple descriptions of relationships and are not subjected to any manipulation. For example, the operator need not know how to integrate an expression, only that the expression requires integration. (3) The intellectual labor lies where it belongs, in writing the equations and in interpreting the solutions. The steps between are purely mechanical and governed by a strict but easily applicable set of rules (those governing construction of the signal-flow diagram and those in the instruction manual of the computer).

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[1] MASON, S. J. Feedback theory: some properties of signal-flow graphs. *Proc. I.R.E.*, 41: 1144–1156, 1953.

[2] MASON, S. J. Feedback theory: further properties of signal-flow graphs. *Proc. I.R.E.*, 44: 920–926, 1956.