# AN EXPONENTIAL-PROCESS ANALYZER AND SYNTHESIZER

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## Summary

A five time-constant, electrical-analogue curve synthesizer and analyzer is described. The machine utilizes decade resistors and capacitors to simulate a biological system containing separate volumes between which tracer material diffuses. It is cycled with a 1.5-second period. At the beginning of the cycle, one of its time-constant capacitors is charged to an accurately known, adjustable voltage. During the cycle, the voltage from this or any other of the time-constant capacitors drives a galvanometer whose spot of light falls on a sheet of graph paper affixed to the machine. The galvanometer spot is swept across the graph paper by a synchronized sweep mirror, thus causing the voltage-time response to be plotted out on the graph paper where it may be compared with and adjusted to coincidence with an experimental curve obtained from the biological system. Curves made up of sums and differences of as many as five exponential terms may be rapidly synthesized or analyzed by adjustment of analogue parameter values to yield system interconnection and accurate values of the volumes of distribution and diffusion rate constants of the biological system.

## Introduction

The present instrument was designed to solve rapidly and accurately the problem of diffusion of a tracer substance from one fluid volume in a biological system into as many as four other volumes. As diffusion occurs from the volume into which a known amount of the tracer is initially injected, the tracer concentration in this volume decreases while those of the other volumes increase from zero. At the beginning of an experiment, all the volumes and diffusion rate constants between the volumes are unknown. These quantities must be extracted from measurements of the tracer concentration as a function of time in one or more of the accessible volumes of the system. When the system is linear and the volumes and diffusion rates constant during the experiment, these concentration curves are composed of sums and differences of exponentials.[1] If the volumes and diffusion rates are known, it is a simple matter to calculate the concentration curves. The reverse calculation is a different matter, however; and when three or more separate volumes are involved, it is virtually impossible in practical cases to calculate the system parameters from knowledge of the concentration curves. The present machine, by making use of an electrical analogy of the biological system, eliminates the need for such calculations. In electrical terms, it allows a circuit synthesis to be carried out so that system parameters are obtained from the transient response of the system to an impulse applied at $t = 0$. Although it was built specifically for a medical application, the same machine can solve similar diffusion problems occurring in many diverse fields of activity, of which chemical process studies, geophysics, and semiconductor physics may be mentioned.

The specific medical application for which the present instrument was designed is the diffusion of radioactive sulphate, $S^{35}O_4$, injected into the blood of human subjects. Since only a few micrograms of labelled sulphate is thus injected, the normal blood sulphate concentration remains essentially undisturbed. In well subjects, the tracer rapidly mixes with the blood and diffuses into the rest of the extra-cellular fluid (ECF) volume (the lymph system, etc). It is assumed that such mixing occurs in a time short compared with the volume-to-volume diffusion processes. Tracer is also removed from the blood by the kidneys and eventually appears in the urine. From the extracellular volume, a small amount of tracer diffuses into the cells. In patients sick with edema and/or ascites conditions, diffusion also occurs from the ECF volume into these additional fluid volumes as well.

The blood plasma compartment of the body represents a fairly well defined single volume. On the other hand, many of the other volumes with which we are concerned, such as the cell volume, represent the sum of a large number of separate elemental volumes. The lumping of such elements into a single "average" volume usually turns out to be an excellent approximation. The volume of a compartment in a tracer experiment is not necessarily its total physical volume but, by definition, is that part of such volume which is accessible to the tracer. Thus, at final equilibrium, the magnitude of the compartment as measured by the specific tracer used will be proportional to the amount of labelled material (proportional

to counting rate for a radioactive tracer) in the compartment. Strictly speaking, therefore, the volumes with which one is concerned in a tracer experiment should be designated "tracer spaces", e.g.,"radiosulphate space" in the present experiment. In many cases, a tracer material can be found whose corresponding volumes of distribution approximate quite closely to the physical volumes of interest in the biological system.

The above picture, and its corresponding translation to electrical terms, is only correct if it is assumed that uniform concentration of tracer within any compartment is achieved by mixing and internal diffusion in a time short compared to the time required for inter-compartmental diffusion. Although this condition is only approximately met in practice in some compartments, the good agreement often obtained between theory and experiment indicates that it is usually not of paramount importance.

## The Diffusion Analogue

The electrical analogy of diffusion between two volumes $v_a$ and $v_b$ with a diffusion rate constant $k_{ab}$ is a resistor connected between two capacitances.[2] The details of the analogy are readily derived from the corresponding differential equations, which are

$$\left.\begin{aligned} \frac{dm_a}{dt} \equiv v_a \frac{dc_a}{dt} &= -k_{ab}(c_a - c_b) \\ \frac{dm_b}{dt} \equiv v_b \frac{dc_b}{dt} &= -k_{ab}(c_b - c_a) \end{aligned}\right\}, \qquad (1)$$

$$\left.\begin{aligned} \frac{dQ_a}{dT} \equiv C_a \frac{dV_a}{dT} &= -\frac{1}{R_{ab}}(V_a - V_b) \\ \frac{dQ_b}{dT} \equiv C_b \frac{dV_b}{dT} &= -\frac{1}{R_{ab}}(V_b - V_a) \end{aligned}\right\}. \qquad (2)$$

The quantities m and c are tracer mass and concentration, while Q is electric charge, V voltage, C capacitance, and R resistance.

Comparison of the two sets of equations allows us to write the following transformation equations. Below each equation the units we shall use are also shown.

$$m = \delta \cdot Q \qquad (3)$$
$$[\text{counts/min}] = [\delta][\mu\text{coulombs}]$$

$$t = \epsilon T \qquad (4)$$
$$[\text{hours}] = [\epsilon][\text{seconds}]$$

$$v = (\delta/\lambda)C \qquad (5)$$
$$[\text{liters}] = [\delta/\lambda][\mu\text{farads}]$$

$$c = \lambda V \qquad (6)$$
$$[\text{counts/min-liter}] = [\lambda][\text{volts}]$$

$$k = (\delta/\epsilon\lambda)R^{-1} \qquad (7)$$
$$[\text{liters/hr}] = [\delta/\epsilon\lambda][\text{megohms}]^{-1}$$

The conversion factors, denoted by Greek letters, are chosen so that the relations $m = vc$ and $Q = CV$ both hold as they should.

The results of a biological experiment are the initial tracer charge, $m_o$, and one or more curves of concentration versus time. The essence of the use of an electrical analogue for analyzing such curves is to derive from it voltages V(T) which can, in some fashion, be compared with the experimental concentration curves. Then, the analogue elements, applied voltage, etc. are adjusted until V(T) versus T is of the same form as one of the concentration curves. The conversion factors may then be evaluated and used in conjunction with the final values of the electrical parameters to yield the desired volumes and rate constants of the biological system which led to the experimental curves. Since different concentration curves may often be obtained from simultaneous measurements in two or more separate volumes of the biological system, while analysis of the system can be carried out with only one such curve, a very valuable internal check of the correctness of the assumed biological model is available. When only one curve is used to obtain the system interconnection and parameters, the output of the analogue may be then switched to yield a voltage proportional to the concentration in another volume, and this curve then checked against the experimental result for this volume. Good agreement indicates that the model and parameter choice obtained from the analogue are good approximations for the actual system.

## Description of Apparatus

The possible interconnections of the five analogue capacitors and resistors are shown in Fig. 1a. There are six distinguishable

combinations, of which the three most important are shown in Fig. 1b, 1c, and 1d. The final combination is that which experimental evidence shows represents the edema-ascites condition most closely. The electrical elements of the analogue are labelled, for convenience, in terms of the corresponding volumes of this biological system. The initial amount of radioactive tracer, $m_o$, is usually injected into the blood and corresponds to an initial charge $Q_o$ on the blood capacitor $C_B$. Some of the charge flows out with the urine through the resistor $R_u$. In addition, equilibrium between the tracer in the blood and that in the remaining part of the ECF volume, represented by $C_D$, is rapidly attained. Also, tracer (or charge) diffuses from $C_D$ more slowly into the other volumes (or capacitances) of the system: the cell volume, the edema volume, and the ascites volume.

The analogue capacitances are each made up of one-percent mylar-dielectric decades covering a range from 11.11 $\mu$f to 0.001 $\mu$f. The resistors are each three-decade plug-in units (see Fig. 2) and have maximum values ranging in steps of ten from 9.99 megohms to 0.00999 megohms. The resistance tolerance on each plug-in unit is also one percent.

A simplified electrical block diagram of the system is shown in Fig. 3. An accurately known capacitor charging voltage $V_o$ (0-10 volts) is derived from a highly stabilized voltage source and a ten-turn helipot. In order to obtain repeated outputs from the analogue, it is cycled with a period of 1.5 seconds. At the beginning of each cycle, one capacitor of the analogue is charged to $V_o$ and then discharges for 1.0 second into the rest of the system, which is initially uncharged. During the remaining 0.5 second of each cycle, all of the remaining capacitors are shorted and the selected capacitor, usually $C_B$, is charged. This sequence of events is diagrammed in Fig. 4. The top curves show the decay of the voltage on the charged capacitor, while the bottom ones refer to one of the other analogue capacitances. To obtain precise and reproducible initiation of each cycle, the switching relays are energized electrically at the beginning of the cycle rather than at the end.

Figure 3 also shows that the voltage output of the analogue taken from any selected capacitor passes to a very-high-input-impedance feedback amplifier whose current output, which is accurately proportional to the input voltage, drives a galvanometer.[3] The circuit of this amplifier is presented in Fig. 5. Both negative and positive feedback are used, and it is flat to over $10^3$ cps. The floating-point adjustment in the cathode circuit of the first tube allows the input grid potential when floating disconnected to be adjusted to exactly ground potential. For incremental signals around ground potential, its input impedance is then infinite. For voltage swings as large as +10 volts, it is still more than 500 megohms using a 12BZ7 for the input tube. With this high an input impedance, the voltage across a given capacitance is left essentially unchanged during a cycle by connection of the amplifier input to the capacitance. After proper adjustment of the floating point, the input impedance for +5 volts applied is more than $10^3$ megohms and is even greater for smaller voltages. To improve the stability of the floating point, the heater voltage of the amplifier is regulated.

Comparison of the analogue output during a cycle and experimental concentration curves is accomplished using the galvanometer, as shown in the mechanical block diagram of Fig. 6. The galvanometer spot (0.06-inch in diameter) is focussed by a curved mirror at the galvanometer on a piece of graph paper upon which the experimental curves have been plotted. The y-axis deflection of the spot is proportional to the voltage on the capacitance of the analogue selected for study. In addition, there is an x-axis sweep so adjusted that the spot traverses the entire marked long axis of the graph paper in exactly a second. This sweep is derived from the sweep cam and mirror system shown. The cam follower tilts the sweep mirror so as to change the angle of reflection and moves the spot across the paper. The cam system is driven by a hysteresis synchronous motor and the sweep cam is accurately cut; thus, the sweep is highly linear. The cam incorporates a fast retrace section. The drawing shows the cam almost at the end of the sweep and about to begin the fast return.

Synchronism between the electrical charge-discharge cycle and the x-axis spot sweep is accomplished by turning on the charging and discharge relays by separate microswitches which, in turn, are actuated by cams rigidly connected to the sweep-cam shaft. The beginning of the cycle when the charged capacitor begins to discharge is made to occur by this means at exactly the time that the galvanometer spot reaches $x = 0$ and starts along the marked portion of the graph paper.

Also shown in Fig. 6 is a retrace blanking cam which eliminates the spot during the 0.5-second retrace time. The semi-transparent graph paper containing the experimental curve or curves is clamped at the corners over a transparent plastic surface, curved along the x-axis as shown to reduce optical errors. It is viewed from above.

The galvanometer is of low-mass and is rapid acting. It has a natural resonant frequency of several hundred cycles and is damped by the 0-500 ohm sensitivity rheostat of Fig. 5. With 500-ohms damping, it is somewhat underdamped, but overshoot is still not noticeable. Another sensitivity adjustment is afforded by the "scale" helipot of Fig. 5. This adjustment controls the magnitude of the total current which passes through the galvanometer and its

damping resistor for a given input voltage. It is found that with 500 ohms damping, the sensitivity of the system is such that for any applied voltage from 10 to 0.1 volts, more than seven times greater current may be applied to the galvanometer than is required to displace the spot the full length of the y-axis on the graph. When the sensitivity is further increased by decreasing the scale resistance even more, the linear relation between input voltage and output current suddenly fails as the amplifier is called on to deliver more current than it is capable of.

To operate the machine, the graph paper on which are plotted the experimental curves is positioned in the machine so that the cycle begins at x = 0, and so the spot follows the x axis with zero applied voltage. Then, analogue elements and applied voltage are adjusted until the spot follows one of the curves as closely as possible over its entire length. Finally, for checking purposes, the amplifier input may be switched to another of the analogue capacitors corresponding to one of the additional experimental curves on the graph, and the degree of fit observed between the spot motion and the selected curve.

In spite of the absence of spot persistence in the system, it is a simple matter to adjust the analogue elements to achieve correspondence between experiment and analogue. Further, the analogue output can be taken from one of the capacitors which represents an inaccessible volume in the biological system, such as the cell volume. Hence, valuable information is obtained concerning concentration changes in such volumes. Finally, after analogue adjustment the paths of the spot for all the different capacitances can be accurately drawn on the graph in a very short time, yielding a permanent record of the concentration curves for all the volumes of the system. Alternatively, a permanent record can be obtained using photographic paper in place of the graph paper. Since the tracer is not always injected into the blood, provision is made that any of the five analogue capacitors can be charged while all the others are shorted during retrace. In addition, the voltage across any one of the capacitors can be used to drive the galvanometer.

Figure 2 shows a front view of the machine. The graph-paper support is inset within the instrument somewhat to reduce the incident light level. For operation under very high ambient light level conditions, an additional metal shield swings out from the machine to shield the graph region even further. This shield is not clearly visible in Fig. 2.[4,5]

## Performance

The intrinsic linearity of the system may be first assessed by static methods. With no current through the galvanometer, the sweep motor may be turned by hand and the spot positions noted on the graph for each of the 30 full revolutions required for the spot to traverse the x axis completely. Such a test was carried out and the deviations from linearity evaluated. The deviations found were almost too small to observe and certainly amounted to less than 0.5 percent of the full sweep length anywhere in the sweep.

A static test of the y-axis linearity for various x values can be carried out by plotting $V_o$, as read off the helipot dial, versus y-axis spot position from full deflection to zero. Again, the maximum deviation was found to be extremely small and certainly amounted to no more than 0.5 percent of full deflection.

A dynamic test of the system as a whole is afforded by fitting to single exponential decay curves. A number of such theoretical curves having time constants varying over a range of several hundred were plotted on the same graph. Then, using a single analogue resistance and capacitance, the corresponding time constant was adjusted to make the spot follow one of the theoretical curves. It was found that this was possible for all the curves and that the degree of fit was equally good on all. Because the fit was so good, it was difficult to estimate the maximum error. As far as the eye could tell, it was possible to make the spot follow any of the curves exactly. Thus, the dynamic error is also of the order of 0.5 percent or less.

Although the intrinsic accuracy of the machine, including the analogue elements, is of the order of one percent, it is not always possible to derive the system parameters from a single experimental curve to this accuracy even in the absence of any error in the experimental data on which the curve is based. Even though the shape of any curve is determined by all the elements of the system and the element values are unique for a given system, the curve shape will be a more sensitive function of some elements than of others. Even though added accuracy can be obtained by carrying out the analysis in steps by plotting the data on two or three separate graphs with increasing time scales, analyzing that with the shortest scale first, then using the resulting analogue element values in fitting the next, and so on, there are some cases where element changes of as much as 10 percent produce no very appreciable change of the curve followed by the galvanometer spot. This will be particularly the case if the element changed is separated by several diffusion constants from the capacitance whose voltage is observed.

The situation is quite different when more than one concentration curve can be obtained. Then, the voltage across the capacitors corresponding to the volumes associated with these additional curves may be directly compared with the concentration curves and a much more sensitive adjustment of the parameter values is possible. Were curves available for all the volumes

of the system, all the parameters could be found to within approximately one percent. In practical cases, one curve is generally available when three volumes are present, two with four volumes, and three with five volumes. In these cases, the accuracy of the elements of the system derived from the analogue will generally range from one or two percent for the most sensitive elements to five to ten percent for those least sensitive whose concentration curves are unavailable.

These conclusions are illustrated in Figures 7 and 8 which show experimental points derived from a patient with ascites and solid curves drawn by recording the positions of the light spot on the graph after best adjustment of the analogue elements. Figure 7 shows the fit obtainable for the blood and ascites concentration curves plotted on a linear scale 12.5 hours long. It shows the details of the curves clearly from one hour on. The log-log presentation of Fig. 8 is included to show the curves in more detail for short times. To obtain the machine-produced curves shown in Fig.8, the medical data was plotted on a linear graph such as Fig. 7 three times, using scale lengths of 12.5, 2.5, and 0.625 hours. Keeping the capacitance settings constant, the analogue resistances were increased by factors of first five and then four to pass from the curves of 12.5 to 2.5 hour scale lengths and from those of 2.5 to 0.625 lengths. In this fashion, accurate adjustment of those parameters such as $C_C$ and $R_D$ of most influence at short times could be carried out. The analogue curves recorded on these graphs of different time scales were then replotted in Fig. 8.

Figure 8 shows machine derived curves for $c_D$ and $c_C$ as well as for $c_B$ and $c_a$. Most of the initial rise of the $c_D$ curve occurs in less than 0.05 hour. The fact that the machine curve for $c_a$ lies somewhat above the experimental points for short times may possibly indicate incomplete mixing in the ascites volume for times less than about an hour. The electrical and mechanical system data derived from the analogue are summarized below. $m_o$ was 58,470 counts/min.

| | |
|---|---|
| $C_B$ = 0.400 μf | $v_B$ = 3.43 liters |
| $C_D$ = 1.0 μf | $v_D$ = 8.6 liters |
| $C_a$ = 1.00 μf | $v_a$ = 8.59 liters |
| $C_c$ = 0.630 μf | $v_c$ = 5.40 liters |
| | |
| $R_u$ = 0.700 MΩ | $k_u$ = 0.982 liters/hr |
| $R_D$ = 8.0 KΩ | $k_D$ = 86 liters/hr |
| $R_a$ = 0.370 MΩ | $k_a$ = 1.85 liters/hr |
| $R_c$ = 36.0 KΩ | $k_c$ = 19.1 liters/hr. |


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## References


1. C. W. Sheppard and A. S. Householder, "The mathematical basis of the interpretation of tracer experiments in closed steady-state systems," J. Appl. Phys., Vol. 22, pp. 510-520; April, 1951.

2. We use lower-case letters throughout for the parameters of the biological system and upper-case letters for those of the corresponding electrical system.

3. The amplifier is an improved version of a circuit described by G. E. Valley and H. Wallman, "Vacuum Tube Amplifiers," McGraw-Hill Book Company, Inc., New York, 1948, p. 480.

4. Since the design of the present instrument was completed, an account of a somewhat similar analogue machine has been found in the literature (Ref. 5). This machine uses a much shorter time scale than the present instrument, and its method of comparing the analogue output with experiment is less convenient and accurate.

5. G. L. Brownell, R. V. Cavicchi, and K. E. Perry, "An electrical analog for analysis of compartmental biological systems," Rev. Sci. Inst., Vol. 24, pp. 704-710; August, 1953.