On-line Computation of Cardiac Output from Dye Dilution Curves

By Hiroshi H. Hara, M.S., and J. Weldon Bellville, M.D.

Calculation of cardiac output from dye dilution curves as described by Hamilton has been well verified. The technique of calculating the cardiac output with the use of a planimeter or replotting on log paper is tedious and often inexact. Furthermore, the necessary long delay between the dye injection and the availability of the result has limited the use of this technique in medical research.

In order to circumvent these difficulties, a new technique has been developed in which a general purpose analog computer is used for automatic computation of cardiac output and the mean transit time. Removal of the recirculation hump as well as the correction for baseline offset are accomplished automatically, and the results are obtained within 20 seconds after the presentation of the dye curve to the computer. The computer circuitry and its operation are fully described and computer results compared to those obtained by the usual Stewart-Hamilton method.

Reshaping of Dye Curve

A cuvette densitometer yields a voltage which is proportional to dye concentration in the blood. A typical plot of the voltage as a function of time is shown in figure 1. It is known that in the neighborhood of \( t_i < t < t_o \), the curve is characterized by an exponential decay, and it is desirable that the portion of the curve for \( t > t_o \) be completely decayed out, thereby removing the undesirable recirculation hump.

Let us designate the original curve by \( c(t) \) and the desired curve by \( c'(t) \) as shown in figure 2. Note that \( c(t) = c'(t) \) for \( t \geq t_o \).

In order to generate \( c'(t) \) for \( t \leq t_i \), it is necessary that the slope of \( c(t) \) at \( t = t_i \), as well as \( c_o \), be known. Since \( c'(t) \) for \( t \geq t_i \) is of the form

\[
c'(t) = c_o e^{-\beta(t - t_i)}
\]

the constants \( c_o \) and \( \beta \) must be such that the two curves are continuous at \( t = t_i \). Clearly,

\[
c_o = c(t) \quad t = t_i
\]

Differentiating both sides of equation (1)

\[
\frac{dc'}{dt} = -\beta c_o e^{-\beta(t - t_i)}
\]

Hence,

\[
\frac{dc'}{dt} \bigg|_{t = t_i} = -\beta c_o
\]

Since \( c'(t) \) must be continuous to \( c(t) \) at \( t = t_i \) and

\[
\frac{dc'}{dt} \bigg|_{t = t_i} = \frac{de}{dt} \bigg|_{t = t_i}
\]

\[
\beta = \frac{de}{dt} \bigg|_{t = t_i} = \frac{c(t) - e(t)}{t - t_i}
\]

The generation of \( c'(t) \) is implemented by the circuit shown in figure 3. When an integrator is in the I.C. (initial condition) mode of operation, it merely tracks the negative of the input voltage applied to the I.C. terminal. (Time constant of the I.C. circuit must be short enough for adequate tracking of the input voltage.) At \( t = t_i \), the integrator is suddenly placed in the COMP (compute) mode, and this is the mode in which the actual integration is carried out. That is, the voltage appearing at the output of the multiplier is integrated with respect to time. The
Typical dye dilution curve.

Dye dilution curve and generated desired exponential decay (dashed line).

The integrator output voltage at the start of the COMP mode is always the same as the voltage at the end of the preceding I. C. mode. Note that in COMP mode the integrator completely ignores the voltage applied to the I. C. terminal. For $t = t_i$, therefore, the circuit in figure 3 solves the differential equation

$$\frac{de_0}{dt} + \beta e_0 = 0$$

with the initial condition

$$e_0 \bigg|_{t = t_i} = c(t_i) \bigg|_{t = t_i} = c(t_i).$$

The solution of this equation is

$$e_0 = c(t_i) \bigg|_{t = t_i} e^{-\beta(t - t_i)}$$

and since $e_0 = c(t)$ for $t < t_i$, $e_0 = c'(t)$ provided that $\beta$ is obtained according to equation 2.

Detailed Description of Analog Computer Program for Cardiac Output

(Figs. 4, 5 and 6.) The output of the Colson Cuvette Densitometer* can be received directly by amplifier 00 or indirectly via magnetic tape. Potentiometer 00 in the feedback of amplifier 00 is used to amplify the input

*Colson Corporation, Elyria, Ohio.
voltage sufficiently high to be processed by the following computer circuitry. Amplifier 01 is used as an inverter. The modes of all the integrators with exception of integrators 10, 14, and 15 are controlled by computer control bus lines. At the time of dye injection, the computer goes into the COMP mode from the I. C. mode. Integrator 02, a track and hold integrator, holds the negative output voltage of inverter 01 at the time of injection, and will hold this value until the end of computation. Note that this integrator cannot distinguish between the COMP and the HOLD mode because its only input is the I. C. input. Since the output of integrator 02 is summed with the output of inverter 01 by summer 04, the summer output is always the dye concentration voltage less the baseline voltage, and thus automatic baseline correction is achieved.

To implement the reshaping of the dye curve as described in the previous section, it is necessary to calculate $\beta$ according to equation 3 and to determine switching time $t_1$ for the generation of the decay curve. A differentiator is provided to determine the slope of the dye curve and also to detect the time at which the highest dye concentration is reached. The differentiator consists of integrator 06, summer 07, and inverter 08 together with potentiometer 07. Since the bandwidth of the differentiator need not be high due to the low frequency characteristics of the dye curve, potentiometer 07 is set to a low value to avoid possible differentiation of noise. As the dye concentration begins to decrease from its peak value, the output of inverter 08 becomes negative to energize operational relay K01. An operational relay is energized when the sum of input voltages is negative and is deenergized when the sum is positive. Note that a set of relay contacts K010 is in the energized position during computation since K00 is deenergized only when the computer is in the I. C. mode of operation. When K01 is energized, through a set of its own contacts, a 100 volts is applied to keep it locked in the energized state until the computer is placed in the I. C. mode before the computation of the next cardiac output. Relay K02 which parallels the operation of K01 is used to control the mode of integrator 10. By way of potentiometer 02, a small positive offset voltage is provided to ensure that these relays do not energize until the peak concentration is reached. In the meantime, integrator 10 has been tracking the output voltage of integrator 14 through potentiometer 10. When relay K02 energizes, integrator 10 effectively goes into the HOLD mode thereby holding the peak concentration multiplied by constant $\delta$. Thus, $c_0$ is obtained as a predetermined fraction, $\delta$ ($\delta = 0.4$ was chosen), of the maximum dye concentration. As the output of integrator 14 decreases and becomes less than $c_0$, operational relay K03 is energized. Operational relay K04, which has been energized until this time, now becomes.
**TABLE 1**

Comparison of Analog Computer Results with Stewart-Hamilton Method

<table>
<thead>
<tr>
<th>Time</th>
<th>Determination</th>
<th>Computer*</th>
<th>Difference between pairs</th>
<th>S-H method</th>
<th>Difference between pairs</th>
<th>Recalculated S-H method</th>
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<td>1.65</td>
<td>1.65</td>
<td>+0.01</td>
<td>1.65</td>
</tr>
</tbody>
</table>

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*Regular type represents answer obtained when tape recorded dye dilution curve was fed into computer the first time. Italic type represents answer obtained the second time same tape was fed into the computer.

Shift in baseline of dye curve.

desensitized to place integrators 14 and 15 in the COMP mode. Since integrator 15 has been tracking the output of divider 00 which equals \( \frac{dc}{dt} \), its output is now held to the desired value of \( \beta \) for the generation of holding.
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The decay curve. The reshaped dye curve is now used to calculate cardiac output and mean transit time.

Cardiac output and mean transit time are computed according to the following equations:

\[
\text{CARDIAC OUTPUT} = \frac{60 \cdot I \cdot a}{\int c'(t) \, dt} \text{ in liters/min}
\]

where \( I \) = Amount of dye injected in mg
\( a \) = Calibration factor volt/(mg/l)
\( t \) = Time in sec

\[
\text{MEAN TRANSIT TIME} = \frac{\int tc'(t) \, dt}{\int c'(t) \, dt} - t_{0d}
\]

where \( t_{0d} \) = Dead space correction in sec

Integrator 18 integrates \( c'(t) \) with respect to time, while integrator 03 is used as time base generator. The product of constant \( I \) and \( a \) is entered with potentiometer 05 while constant \( t_{0d} \), is entered by way of potentiometer 09. Potentiometers 03, 18, and 19 are provided for scaling purposes. Cardiac output and mean transit time appear as output of divider 04 and summer 09, respectively.

A test circuit is provided to generate a curve resembling a dye curve with the recirculation hump. The test circuit is useful in checking the reshaping and final computation circuitries.

Results

The results of the cardiac output determination computed by analog techniques and conventional techniques2 are shown in table 1. To obtain these, the output of the cuvette densitometer was recorded on magnetic tape.* Later the output of the tape recorder served as an input to the analog computer† that was programmed as described herein.

Run 1 was unsatisfactory since the recorder gain was too low. All subsequent determinations were done in duplicate, one shortly following the other, during the course of the experiment. There was generally close agreement between any pair of determinations. Differences between methods greater than 10 liters per minute were evaluated and computational errors were found for Stewart-Hamilton determinations 8 and 18. The large difference for determination 11 remains unexplained. The analog computer calculation for determination 12 is inaccurate because there was a shift in the baseline after the computer was placed in the COMP mode and before the dye curve appeared, so that the whole corrected dye curve was displaced downward. The tape was rewound and the computations again repeated. The close agreement between these answers (italic type fig. 1) and those obtained previously is apparent.

These results indicate that the system presented in figures 4, 5 and 6 and herein described is feasible. Figure 7 represents some of the data recorded during computation. Readout of these parameters is helpful in the evaluation of computer performance. Relay duty cycles (not shown) for relays K01 and K04 were also recorded.

The point at which tracking ceases and the ideal exponential decay curve is generated can be varied by the setting of different values of \( \delta \) on potentiometer 10. If the setting on this potentiometer is too low, it would not commence generating the ideal curve, \( c'(t) \), before recirculation occurred. If too high, it would generate the ideal decay curve before the exponential decay slope was well defined. To examine these effects, the setting on potentiometer 10 was varied from 0.2 to 0.8 and the dye dilution curve recorded on magnetic tape for run 21 which was processed repeatedly through the computer (table 2). It appears

*Circulation Research, Volume XII, April 1963.
Multiple recordings obtained during computation. Recordings shown are: the one second marker, the dye curve (amplifier 01 output), the corrected dye curve (amplifier 14 output), cardiac output (divider 04 output), mean transit time (amplifier 09 output), and dye injection switch (relay K00). That values between 0.2 and 0.6 gave consistent results and that therefore the arbitrary choice of 0.4 was reasonable.

Although precision components have been used in the construction of this analog computer (e.g. the accuracy of an operational amplifier is .01%), it is difficult to state the over-all accuracy of the system. Repeated determinations of cardiac output from a dye dilution curve recorded on magnetic tape varied usually by only a few hundredths of a liter per minute. The most expeditious and accurate method of checking the over-all function of the system was to employ the simulated dye curve generated by the test circuit (fig. 4) and observe that the readout varied by no more than 0.1%. Repeat determinations of cardiac output from recorded dye dilution curves usually did not vary by more than 1%.

Discussion

At the 4th International Conference on Medical Electronics (New York City, July 17-21, 1961), Moody et al. presented a description of a cardiac output computer. Their approach is different from ours in that they take the recorded dye concentration curve and place it in an optical system where it can be compared to an ideal curve (no recirculation peaks) generated by a function generator and visualized on a cathode ray tube. The parameters of the function generator are varied until a good curve fit is obtained. These parameters from the oscillator and sawtooth generator feed into a computer into which is also entered the quantity of indicator dye injected and blood-indicator calibration factor, a. The output of the calculator yields cardiac output and mean transit time. Although a good approximation between the dilution curve and the generated sinusoidal segment terminated by an exponential decay is usually obtained, in some instances it was difficult to fit the curve. The added step of trying to match two curves is, in our opinion, unnecessary and undesirable. It introduces a source of human error, it may be affected by recorded characteristics, and it takes time.

Skinner and Gehmlich described the use of an analog computer circuit for computing cardiac output from the dye dilution curve. Instead of generating the exponential decay as we do, they employed a logarithmic function generator to linearize the curve before differentiating. Differentiating increases noise to signal ratio. It might have been better if they had placed the log function generator following amplifier 7 rather than amplifier 1 because integrator 6 will act as an additional filter of noise. If the differentiator is too sensitive, any small fluctuation in dye concentration slope will be reflected by a change in differentiator output. It is essential to control the time constant of the differentiator, so that small fluctuations in dye concentration...
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are not immediately magnified. We were able to control the time constant of the differentiator adequately with potentiometer 07. It should also be pointed out that Skinner and Gehlrich selected the point at which to generate the ideal exponential decay as a function of time after the slope of the dye concentration curve became negative, rather than selecting a fraction of the peak dye concentration value as we do. We believe the latter procedure is better.

For the proper operation of our computer, it is essential that operational relays K01 and K02 do not energize until the peak value of the dye curve is obtained. In case of presence of severe noise between the time of dye injection and the time at which the maximum value is obtained, it is possible that these relays may be triggered when the differentiator output becomes sufficiently negative. The difficulty can be circumvented by setting the potentiometer 02 sufficiently high so that the relays will not be triggered until that portion of the dye curve beyond the peak is reached. This will only result in integrator 10 learning the product of 8 and a value which is slightly less than the peak dye concentration, and this will not affect the accuracy of computation.

The system will not operate properly if the shape of the dye curve is such that the slope of the over-all dye curve (not including that of noise) changed sign before the arrival of the peak value. In addition, if the base line shifts after the time of injection when the computer has entered the “compute” mode, the accuracy of computation will be affected.

It must be remembered that this method employs the actual dye concentration curve until t₀, as well as the new curve c'(t) generated after t₀. Thus, it involves no new assumptions about the shape of the initial part of the dye curve, but does assume an exponential decay after time t₀.

Summary

An analog computer circuit for calculating cardiac output and mean transit time has been described which receives as its input the output of a cuvette densitometer. The results obtained with the computer have been compared with those obtained by the usual method.

References

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