Comput. Biol. Med. Vol. 19, No. 5, pp. 361–366, 1989
Printed in Great Britain

0010-4825/89 $3.00 + .00
Pergamon Press plc

# CARDIO—A LOTUS 1-2-3 BASED COMPUTER PROGRAM FOR RAPID CALCULATION OF CARDIAC OUTPUT FROM DYE OR THERMAL DILUTION CURVES*

R. W. BRILL† and P. G. BUSHNELL‡

†Southwest Fisheries Center Honolulu Laboratory, National Marine Fisheries Service, NOAA, 2570 Dole Street, Honolulu, HI 96822-2396, U.S.A.; and ‡John A. Burns School of Medicine, Department of Physiology, University of Hawaii, 1960 East-West Road, Honolulu, HI 96822, U.S.A.

(*Received* 15 *November* 1988; *received for publication* 22 *March* 1989)

**Abstract**—We have developed a menu-driven computer program (CARDIO), based on a Lotus 1-2-3 template and a series of macrocommands, that rapidly and semiautomatically calculates cardiac output from dye or thermal dilution curves. CARDIO works with any dye or thermal dilution recorder with an analog output, any analog to digital (A-to-D) conversion system, and any computer capable of running Lotus 1-2-3 version 2. No prior experience with Lotus 1-2-3 is needed to operate CARDIO, but experienced users can take full advantage of Lotus 1-2-3's graphics, data manipulation, and data retrieval capabilities.

Cardiac output  Indicator dilution  Dye dilution  Thermal dilution

## INTRODUCTION

The use of dye dilution curves to measure cardiac output has become a common practice since the technique (using cardiogreen dye) was first introduced in 1929 [1]. Thermal dilution also has gained wide popularity in research and clinical settings, especially the latter, since the introduction of the Swan-Ganz† catheter [2]. Calculation of cardiac output from indicator dilution curves can be time consuming, however. If data analysis is done manually, dye dilution curves must be replotted on a semilogarithmic scale, and the downslope of the curve extrapolated to baseline because of recirculation of the dye. Thermal dilution curves must be similarly treated [3].

Analog computers have been developed for both dye and thermal dilution systems, but these instruments are expensive and have a single purpose [4]. Techniques have been published for more rapid or automatic calculation of cardiac output from dye dilution curves [5–7], but all require either specialized equipment or manual measurement of curve heights. The computer program (CARDIO) described here is based on a Lotus 1-2-3 template and a series of Lotus 1-2-3 macrocommands. It is more rapid and accurate and less subject to human error than are previously published techniques.

## THEORY OF OPERATION

CARDIO uses a data set consisting of elapsed time and the corresponding voltage output from the dye or thermal dilution recording instrument. Once imported into the Lotus 1-2-3 template, the voltage data are converted to natural logarithms, and a linear regression is performed on the downslope of the indicator curve. This is equivalent to

*A copy of CARDIO and a sample dye dilution curve data set will be provided either on a 5 1/4 or 3 1/2 inch DS DD floppy disk. Instructions for program execution and modification also will be included.

† Reference to trade names does not imply endorsement by the National Marine Fisheries Service, NOAA.

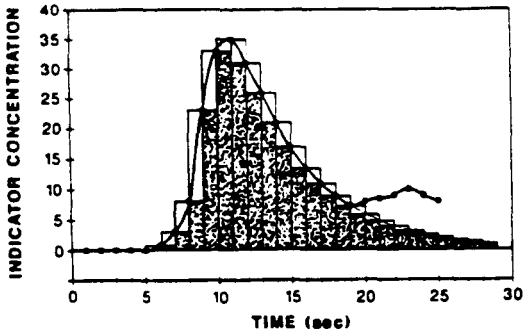


Fig. 1. Graphical representation of summation procedure used to estimate areas under indicator dilution curves. Shaded rectangles are summed to calculate minimum curve areas. Maximum area is calculated from the shaded plus clear rectangles. Data are from [5].

fitting an exponential decay curve

$$C = C_0 \cdot e^{-k \cdot t}; \tag{1}$$

where $C$ = indicator concentration, $C_0$ = indicator concentration at time zero, $k$ = rate constant of indicator decay, $t$ = elapsed time, and e = base of the natural logarithm [8]. The downslope of the indicator curve is extrapolated, based on this regression, until the curve falls below a user-selectable value (baseline).

Maximum ($Area_{max}$) and minimum ($Area_{min}$) areas under the curve are calculated by numerical integration (trapezoidal rule) over $n - 1$ time intervals:

$$Area_{max} = \sum_{i=1}^{n-1} (V_{i+1})(t_{i+1} - t_i) \tag{2}$$

and

$$Area_{min} = \sum_{i=1}^{n-1} (V_i)(t_{i+1} - t_i); \tag{3}$$

where $V_i$ = voltage at time $t_i$, $V_{i+1}$ and $t_{i+1}$ = the next recorded time–voltage data pair, and $n$ = the total number of time–voltage data pairs. The area under the curve ($Area_{avg}$) used for cardiac output calculations is taken as the average of $Area_{max}$ and $Area_{min}$. This technique is shown graphically in Fig. 1.

Cardiac output ($Q$) is calculated using the amount of indicator injected ($I$) and a calibration factor ($F$) that converts recorder voltage output to dye concentration.

$$Q = \frac{I \cdot F}{Area_{avg}}. \tag{4}$$

## METHOD OF OPERATION

Any A-to-D system is usable, and satisfactory, single-channel A-to-D systems are currently available for less than US$200. Only a simple program to create and record an ASCII data file of the recorder's voltage output and elapsed time is needed. Figure 2 is a BASIC language program that may be used as a guide. The only requirements are that the file name have the extension ".PRN" required by Lotus 1–2–3 for importing data files, that the first line be a string, and that the data be separated by commas or blank spaces.

Our BASIC program example stores a unique identifier string at the beginning of each data file, which is the same as the file name. However, any other identifier is acceptable. Used as a title for all graphs produced by CARDIO, this identifier is also printed with the cardiac output data summary (Fig. 3). Our program example stores the data in memory before writing it to disk and contains a loop (line 110) that slows data collection to avoid computer memory or buffer overflow. The delay loop may be modified or eliminated to suit data collection needs. Data may also be written directly to disk, but this may make

```
10 DIM V(600), ET(600)              'dimension voltage and elapsed time
20 KEY(1) ON                        'set up function key F1
30 INPUT "ENTER FILE NAME ", FILE$  'user prompted for the file name
40 FILE$ = FILE$ + ".PRN"           'add file name extension required by
                                     Lotus 1-2-3 for importing data files
50 START! = TIMER                   'read internal real time clock and
                                     define time zero
60 ON KEY(1) GOTO 130               'use function key F1 to halt data
                                     collection and write data to disk
70 ETIME! = TIMER                   'read internal real time clock
80 I=I+1                            'counter for writing stored data to
                                     disk
90 'Program lines to read analog to
    digital converter placed here.

100 ET = ETIME! - START!            'calculate elapsed time
110 FOR Z = 1 TO 500: NEXT I        'slow operation of data collection loop
120 GOTO 70                         'repeat data collection loop
130 OPEN FILE$ FOR OUTPUT AS #1     'set up disk file name
140 WRITE #1, FILE$                 'store file name (string) beginning of
                                     the data file
150 FOR J = 1 TO I                  'repeat until all voltage-elapsed time
                                     pairs have been written to disk
160 WRITE #1, J, V(J), ET(J)        'write voltage (V) and elapsed time
                                    (ET) data to disk
170 NEXT J: CLOSE                   'when completed, close the file
```

Fig. 2. BASIC language program for digitizing indicator dilution curves and storing the data on disk. The program will produce a data set suitable for use with CARDIO.

```
**************************************************
*           CARDIAC OUTPUT CALCULATIONS          *
*  .........     A:SJ1230-8.PRN     .........     *
*                                                *
*  DYE CONCENTRATION=          1.96 mg/ml        *
*  AMOUNT INJECTED=            0.1 ml            *
*  CALIBRATION FACTOR=        46.2 v/mg/ml       *
*                                                *
*  CURVE AREA=                 4.700 v-s         *
*  REGRESS COEFF=              0.998             *
*                                                *
*  ANIMAL WEIGHT=              1.411 kg          *
*  - - - - - -- - -- - - - - - - - - -- - - - -   *
*  CARDIAC OUTPUT=           115.7ml/min         *
*                             81.9 ml/min/kg     *
**************************************************
```

Fig. 3. Example of data summary produced by CARDIO. Curve area and regression coefficient (based on indicator dilution curve's downslope) are automatically produced by the program. The user then enters the dye concentration, amount of dye injected, and a calibration factor for the dye measurement instrument; whole animal and weight-specific cardiac output are then calculated by the program.

data collection unacceptably slow in some systems. Note that in line 160 a sequence number also is stored along with voltage and elapsed time. Sequence numbers are required because they are used as a means of identifying the curve's baseline in CARDIO.

After the indicator dilution curve is stored, Lotus 1-2-3 is loaded, and the template "CARDIO.WK1" retrieved. Instructions for running CARDIO and an operations menu are automatically presented. The items on the operations menu are selected and executed, as are other Lotus 1-2-3 commands, either by pointing or by typing their first letter. The indicator dilution data file must first be "imported" into the template by executing "Import". This macrocommand retrieves the data file from disk and automatically creates and graphs a semilogarithmic plot of the elapsed time–voltage data, as shown in Fig. 4a. From this plot, the operator selects the voltage to be used for the baseline (or steady state portion) of the curve and the data points on the downward slope to be used for the semilogarithmic linear regression and eventual extrapolation. Next, a series of macrocommands are executed that extrapolate the downslope of the curve to the end of the collected elapsed time–

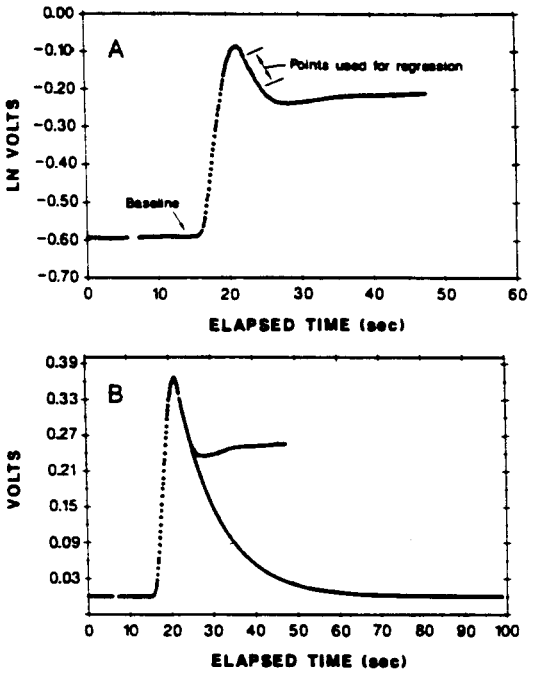


Fig. 4. An example of the semilogarithmic plot (a) and the extrapolated and extended curve (b) produced by CARDIO. The data are from a dye dilution curve from a skipjack tuna (*Katsuwonus pelamis*). Data were recorded approximately every 0.1 s. The linear portion of the curve's downslope, to be used for curve extrapolation, can be easily recognized. The data for these plots were produced by CARDIO and then replotted using Sigmaplot, a commercial plotting program, and a Hewlett-Packard 7475A pen plotter.

voltage data. If the extrapolated curve has reached or gone below the baseline at this time, the area under the curve is calculated, and the operator presented with a summary form (Fig. 3) in which values for dye concentration, amount of dye injected, calibration factor for recording instrument, and animal weight are entered. Once these data are entered, a final macrocommand is executed, and cardiac output automatically calculated.

The program also has two additional capabilities. One, if the curve does not reach baseline by the end of the collected data, the curve will automatically be extended until it falls below baseline. The time increments used for curve extension can be set by the operator. A curve extended in this manner, using 1 s increments, is shown in Fig. 4b. Two, a second macrocommand is available to correct for a linearly drifting baseline. The operator selects a portion of the baseline to be used for the linear regression, and the program automatically corrects the entire curve by subtracting or adding a value proportional to the elapsed time.

## PROGRAM PERFORMANCE AND TESTING

To verify CARDIO's performance, we calculated the cardiac output from a digitized dye dilution curve published by Lin [5] and shown in Fig. 1. Using the same points on the downslope to perform the regression for curve extrapolation, CARDIO calculated a curve area of 268.3 unit seconds (indicator concentration was given in arbitrary units) and a cardiac output of 1.490 l/min (for a 19.6 kg dog). Lin [5] calculated a curve area of 263.2 unit seconds and cardiac output of 1.519 l/min. The small differences are most likely the result of Lin's [5] apparently extrapolating the curve's downslope until it fell below 0.9

Table 1. Effect of baseline value on execution* time, mean calculated curve area, and final size of the worksheet for the dye dilution curve in Figs 4 and 5

| Baseline | Execution time (s) | Mean curve area (volt·s) | Final size of worksheet (lines) |
|---|---|---|---|
| $1 \times 10^{-3}$ | 77 | 4.628 | 454 |
| $1 \times 10^{-4}$ | 88 | 4.692 | 476 |
| $1 \times 10^{-5}$ | 101 | 4.700 | 498 |
| $1 \times 10^{-6}$ | 112 | 4.701 | 421 |
| $1 \times 10^{-7}$ | 125 | 4.702 | 643 |
| $1 \times 10^{-10}$ | 164 | 4.702 | 609 |
| $1 \times 10^{-13}$ | 205 | 4.702 | 675 |

* Time required to extrapolate and extend curve to below baseline and calculate area under the curve.

Table 2. Effect of sampling rate on mean calculated curve area. Data are from dye dilution curve shown in Fig. 4. The original sampling interval was approximately 0.1 s

| Approximate sampling interval (s) | Mean curve area (volt·s) |
|---|---|
| 1.0 | 5.178 |
| 0.5 | 4.701 |
| 0.2 | 4.676 |
| 0.1 | 4.702 |

units. CARDIO extrapolated the downslope until the curve fell below 0.0001 units and, therefore, produced a larger estimate of curve area and a smaller estimate of cardiac output. The difference in cardiac output estimates is $<2\%$.

Equation (1) shows that systems exhibiting exponential decay will only approach zero concentrations as elapsed time approaches infinity. An arbitrary baseline value, insignificantly different from zero, must be chosen as a cutoff point to terminate curve extrapolation. This baseline value may be adjusted for the range of the dye or thermal recorder's output (e.g. volts or millivolts). The value chosen will affect the accuracy of the curve area estimate, the final size of the worksheet (and the amount of computer memory required), and the execution time of the program. Using the data shown in Fig. 4, CARDIO was tested with various baseline values. The results (Table 1) indicate that curve area estimates are asymptotic and that choosing too small a baseline value will significantly increase execution time and the amount of computer memory required.

The effect of sampling rate (i.e. rate of A-to-D conversion of the indicator dilution curve) also was tested using the data from the curve in Fig. 4. Decreased data sampling rates were simulated by repeatedly removing every other data point from the original data set. Results are shown in Table 2. Higher sampling rates necessarily result in better estimates of curve area, but sampling rates are constrained by the computer memory available for use with CARDIO. CARDIO is currently designed to accept up to 600 elapsed time–voltage data pairs. This requires an available memory of 155 Kbytes after Lotus 1–2–3 is loaded. In other words, a minimum total available memory of approximately 412 Kbytes is needed. Template size may be easily increased if a larger number (i.e. $>600$) of elapsed time–voltage data pairs must be accommodated. The amount of data that can be handled is limited only by the amount of total (base plus expanded) computer memory and the maximum size of Lotus 1–2–3 worksheets (8,192 lines).

## ADVANTAGES OF CARDIO

Our program has distinct advantages over other techniques currently available. First, it requires only hardware and software (an IBM personal computer or equivalent, Lotus 1–2–3 version 2, any single or multichannel analog to digital (A-to-D) conversion system, and any dye or thermal dilution recording system with an analog output)—all of which

are already available in many laboratories. Second, because no manual data manipulation is performed, high rates of data collection can be handled, and inaccuracies due to manual measurement of curve heights or areas can be avoided. Nevertheless, the user is able to select the data points to be used for extrapolation of the downslope of the curve from a semilogarithmic curve presented on the computer screen and to edit the data as required. Third, use of the program can be easily learned because it is totally menu driven and requires no familiarity with Lotus 1-2-3 itself. Experienced Lotus 1-2-3 users, however, can take full advantage of this package's graphics, data manipulation, and data storage and retrieval capabilities. Fourth, because of the flexibility of Lotus 1-2-3, the template can be easily customized for use with either dye or thermal dilution curves, to fit available computer memory and to optimize execution time and the required accuracy. Fifth, CARDIO allows the rapid calculation of cardiac output. Using an IBM AT computer, we found that the average time to calculate cardiac output from dye dilution curves that include approximately 400-600 data points (dye dilution measurements recorded at approximately 10 times per second) was $<4$ min.

## SUMMARY

The estimation of cardiac output from indicator dilution curves can be time consuming if done manually, because of the replotting required to determine the curve's downslope in the face of indicator recirculation and the manual measurement of area under the indicator concentration curve. Although analog computers are available to automate the process, they are expensive and have a single purpose. We have developed a program, based on a series of Lotus 1-2-3 macrocommands, that automatically extrapolates the curve's downslope and then calculates area under the curve and cardiac output. Our program has the advantages of working with any dye or thermal dilution recorder with an analog output, any A-to-D conversion system, and any computer capable of running Lotus 1-2-3. Our program, therefore, takes advantage of equipment already common in many laboratories to make a semiautomatic cardiac output measurement system. Because of the flexibility of Lotus 1-2-3, the program may be easily customized to fit available computer memory, meet the required degree of accuracy, and work with thermal or dye dilution systems.

## REFERENCES

1. J. M. Kinsman, J. W. Moore and W. F. Hamilton, Studies on the circulation. I. Injection method: physical and mathematical considerations, *Am. J. physiol.* **89**, 322-339 (1929).
2. K. C. Ehlers, K. C. Mylrea, C. K. Waterson and J. M. Calkins, Cardiac output measurements. A review of current techniques and research, *Ann. Biomed. Engng.* **14**, 219-239 (1986).
3. D. J. Warren and J. G. G. Ledingham, Cardiac output in the conscious rabbit: an analysis of the thermodilution technique, *J. appl. Physiol.* **36**, 246-251 (1974).
4. T. G. Coleman and F. J. Criddle Jr, Computerized analysis of indicator-dilution curves, *J. appl. Physiol.* **28**, 358-360 (1970).
5. Y. C. Lin, A programmable calculator program for rapid logarithmic extrapolation, and calculation of mean transit time from an indicator-dilution curve, *Comput. Program. Biomed.* **9**, 135-140 (1979).
6. P. M. Olley, B. S. L. Kidd and S. Zelin, Cardiac output: rapid estimation form indicator dilution curves using a new nomogram, *Can. J. Physiol. Pharmacol.* **48**, 147-149 (1970).
7. J. C. P. Williams, T. P. B. O'Donovan and E. H. Wood, A method for the calculation of areas under indicator-dilution curves, *J. appl. Physiol.* **21**, 695-699 (1966).
8. D. S. Riggs, *The Mathematical Approach to Physiological Problems*, p. 445. MIT Press, Cambridge, MA (1963).

**About the Author**—RICHARD W. BRILL received a B.A. in biology from Lafayette College in 1970, a Masters in biology from Northeastern University in 1974, and a Ph.D. in biomedical sciences from the Physiology Department, John A. Burns School of Medicine, University of Hawaii in 1979. Following a one-year postdoctoral fellowship at the University of British Columbia, Dr Brill returned to Hawaii as Director of the Pacific Gamefish Research Foundation. He joined the staff of the National Marine Fisheries Service (Southwest Fisheries Center Honolulu Laboratory) in 1983 and is currently a member of the Pelagic Ecosystem Program.

**About the Author**—PETER G. BUSHNELL received a B.S. in biology from the University of Maryland in 1976, a Masters in marine biology from the University of Miami in 1982, and a Ph.D. in biomedical sciences from the Physiology Department, John A. Burns School of Medicine, University of Hawaii in 1989. Dr Bushnell is currently a postdoctoral fellow in the Department of Zoology, University of British Columbia.