DECUS
PROGRAM LIBRARY

DECUS NO.	8-524
TITLE	GRNDYE - A PROGRAM TO ESTIMATE CARDIAC OUTPUT OFF-LINE FROM AN INDICATOR DILUTION CURVE
AUTHOR	Jens G. Rosenkrantz, M. D. and John G. Parnevelas, M. S.
COMPANY	Children's Hospital of Los Angeles Los Angeles, California
DATE	January 15, 1972
SOURCE LANGUAGE	PAL 8 (or PAL III)

DECUS Program Library Write-up   DECUS NO. 8-524

INTRODUCTION

A popular technique of estimating cardiac output in laboratory
animals and humans has been the indicator dilution method. Although
its accuracy has been questioned[1,2], the Stewart-Hamilton method[3]
with indocyanine green as the indicator, has been most widely used.
Basically, a known amount of dye is delivered as a bolus into the pul-
monary artery, as aortic blood is sampled for dye concentration. The
concentration of the dye in the aortic blood is determined by a densi-
tometer and recorded, against time, by an electronic recorder. Cardiac
output is then calculated from the equation:

$$(1)....\dot{Q} = \frac{\text{Amt. injected}}{\int_0^\infty c(t)\, dt}$$

Where $\dot{Q}$ = cardiac output
$c(t)$ = concentration of dye

One of the chief problems in this method is the effect of recirc-
ulation. Equation (1) assumes that there is no recirculation, i.e.,
that no dye which has flowed past the sampling port is allowed to re-
circulate past the sampler. Such of course is not the case in the
intact animal or human, and recirculation does occur. Although the
effects of recirculation can be minimized by the use of catheter
densitometers with short time lags[4], most laboratories employ densitom-
eters which are not placed in the aortic blood stream and resulting

dye concentration curves show the effect of recirculation before concentration has dropped to a negligible level. The Stewart-Hamilton method fits a negative exponential function to the portion of the curve, c(t), from just past its maximum to infinity, in order to ignore mathematically the effects of recirculation.

This paper reports a program written in PAL-8 machine language which, given calibration data and measurements from an indicator dilution curve, computes cardiac output by the Stewart-Hamilton method.

REQUIREMENTS

PDP-8 with 4K; High Speed Reader.

METHODS

1. Obtaining the Dye Curve:

A catheter is positioned in the main pulmonary artery and a second catheter in a peripheral artery or in the aorta of the subject. A densitometer is used to measured arterial concentration of dye and is connected to a recorder. The densitometer should have a switch which gives a known signal to the recorder, as a check on the amplifier settings and should be proven to be linear in its response. This check deflection is measured before each curve (and called Curve Check) and before calibration (and called Calibration Check).

Dye curves are obtained by bolus injection of indocyanine green from a special volumetric syringe (0.75 to 1.5 ml) into the

2

pulmonary artery. The densitometer is balanced and zeroed immediately before the injection.

Calibration of the system is done as follows: The amount of dye injected at each dye curve (same volume, same batch) is mixed with 10 ml of the subject's blood. 0.4 ml of this mixture is diluted with 9.6 ml of the subject's blood. An additional 10 ml of the subject's blood is drawn through the cuvette, while the densitometer is zeroed and balanced. The diluted dye is then drawn through the cuvette and the resultant deflection (in mm) is called Calibration Factor.

Data are then obtained from each recording: i) from each subject, the Calibration Check and Calibration Factor (in mm) and ii) from each dye curve, the Curve Check and the deflection of the curve (in mm), every 0.5 sec. Curve measurements are taken from the time of departure of the curve from the baseline to its return near baseline (usually 6-10 secs. later--see Fig. 1). These data are presented to the program for computation.

In the event that no electronic check on the amplifier setting is provided by the densitometer, both Curve Check and Calibration Check can be called equal to 1.

2. Preparation of Data Tape:

EDITOR (DEC-08-ESAB) is used to prepare the data tape in ASC ††
format. For each set of curves the following are given as integers:

   i) Calibration Check (carriage-return-line-feed)

   ii) Calibration Factor (carriage-return-line-feed)

Then the data for each curve in the set are given seriatim in integer format:

   i) Curve Check (carriage-return-line-feed)

   ii) D1; D2; D3; D4;....: DN; (carriage-return-line-feed)

where the D's are deflections in mm, and semicolons are used as terminators for each deflection. These deflections must be on one line of the data tape, and there can be no more than 24 such deflections given. (The program ignores all deflections subsequent to the 24th).

When the set of curves is finished, the Curve Check for the next line is coded as zero ("0; carriage-return-line-feed").

If more sets are to be done, the process above is repeated, giving the Calibration Check, Calibration Factor and Data from each curve as above. The number of curves in a set must be less than 4096; the number of sets is limited only by the paper-tape available.

When the data tape is complete, two entries of "0; carriage-return-line-feed" are appended.

3. <u>Running the Program</u>:

The binary tape, GRNDYE 1970, is loaded <u>after</u> Floating Point Interpreter #4 (Digital-8-25-F), by use of the binary loader (DEC-08-LBAA). The data tape is placed in the High Speed Reader, and the program is started at Starting Address = 0200.

4

DESCRIPTION OF PROGRAM

I. <u>Data</u>:

The program accepts positive numbers less than 4096 on the high speed reader with ";" as the terminating character for each number. It stores them in buffer, with the octal number in the first of three locations and 0's in the succeeding two locations. The program does this in a subroutine, called Decrd, which is a modification of DIG-8-28-U-SYM. The terminating character, Carriage-return-line-feed, causes exit from this subroutine. Decrd counts entries as it reads them (and calls the number, N) and checks to make sure the number of entires does not exceed 24. If so, it ignores subsequent entries.

The program interprets the first number in buffer as "Calibration Check" on the first pass through Decrd; on the second pass, it interprets the first number in buffer as "Calibration Factor". For subsequent input, the program interprets the first number in buffer as "Curve Check"; deflection measurements are then read and counted on the next pass through Decrd. The program later recycles through the "Curve Check" and deflection readings until it encounters a Curve Check = $\emptyset$.

In the event that the program encounters a "Curve Check" equal to 0, it reinitializes; so that different "Calibration Check" and "Calibration Factor" can be read in on the same tape. Should it encounter a "Calibration Check" equal to 0, it terminates.

II. <u>Calculation of Area under the Dye Curve</u>:

1. <u>Recognition of "upswing" and "downswing"</u>:

The program compares each deflection with the preceding one until

the difference is negative, calling this deflection the maximum. It then compares subsequent deflections until it encounters a deflection more than 5 MM below the maximum. The ordinal number of this deflection is called Tmax (TMCTR). The data up to Tmax are considered to be in the "upswing" and subsequent data from the "downswing" of the dye curve.

2. <u>Calculation of area under upswing</u>:

This is done by Simpson's Rule, after the program recognizes Tmax as even or odd. The area is called A1.

3. <u>Calculation of area under downswing</u>:

The Stewart-Hamilton method calls for the fitting of a negative exponential curve from Tmax until recirculation occurs. Recirculation is recognized by the fact that all subsequent observed points lie above the fitted negative exponential curve.

The program finds the natural logarithm of each deflection from Tmax to N. It then fits a straight line by least squares to Tmax and the next two points. All subsequent points are checked against theoretic points of this semilogarithmic fit. If all lie above the corresponding theoretic points, it recognizes TMCTR + 3 as "recirculation" and calculates the answers. If one actual deflection is less than the theoretic deflection, the program recycles and fits to Tmax and the next three points. This process is continued until recirculation is recognized or until N-1 is reached. In the latter case, the program prints "NO RECIRC" and computes the answers.

Area is calculated by finding the integral from Tmax to infinity of the negative exponential fit, and is called A2.

6

III. Calculation of Cardiac Output:

The following formula is used to calculate cardiac output:

$$Q = 15 \cdot (\text{calib factor}) \cdot (\text{curve check/calib check})/(A1 + A2)$$

IV. Output:

The program prints calibration check and calibration factor and then for each curve types out the following: curve number, curve check, and all deflections given to program (up to maximum of 24). It then reports Tmax (in seconds), recirculation time (in seconds), the sum square (variance) of the semilog least square fit, and Q, the cardiac output (in L/min).

Two output programs are used: a subroutine, called Decprt (modified DIG-8-22-U-SYM) and the output controller of floating point interpreter #4. Both use the (wait for flag; JMP.-1) routine, as does Decrd, and must be modified if the interrupt is turned on.

V. Modifications Easily Accomplished:

1. To increase maximum number of deflections allowed:
    On source tape, change BUFFR = 717 to BUFFR = 1744; change MAXNUM = -31 to MAXNUM = -1211; and assemble source tape.

2. For paper tape system (program is presently geared to run off a disc or dectape system) toggle in a HLT (7402) in location 223, with the program in core.

3. To assemble the source tape with a PAL-III or PAL-D assembler, remove all "FIXMRI" pseudo-operations from source tape.

CHECK OF PROGRAM'S ACCURACY

Fifty-six indocyanine dye-dilution curves were obtained on 14 miniature pigs by the methods outlined above. For each curve, the area under the "non-recirculation" curve (A1 + A2) was obtained by hand-calculation by the Stewart-Hamilton method and from the program, GRNDYE. These areas are given in Table 1.

Results were then compared for agreement. If hand-calibrated data are considered as the independent variable and program-calculated areas as the dependent variable, then the least squares fitted straight-line[5] has the form:

$$y = 0.999x - 1.880$$
$$\text{with} \quad r = 0.9996 \ (P < .01)$$

Figure 2 shows the points of these experiments along with the line of identity and demonstrates graphically the excellent agreement between computed and hand-calculated results.

CONCLUSIONS

An off-line program is presented which calculates cardiac output on a PDP-8 computer. This program is written in PAL machine language and is usable in a paper tape or disc-monitor system. This program is sufficiently accurate, compared with hand calculations, to be useful to the laboratory measuring cardiac output by indicator dilution methods. It suffers from the limitations of the Stewart-Hamilton method itself.

8

REFERENCES

1. Sato, T. A critical study of Hamilton-Stewart's principle for the analysis of hemodynamics - a mathematical analysis. Japanese J. Physiol. 13:260, 1963.

2. Jacobs, R.R., Schmitz, U., Heyden, W.C., Roding, B., and Schenk, W.G.,Jr. Determination of the accuracies of the dye dilution and electromagnetic flowmeter methods of measuring blood flow. J. Thorac. & Cardiovasc. Surg. 58:601-608, 1969.

3. Hamilton, W.F., Moore, J.W., Kinsman, J.M., and Spurling, R.G. Simultaneous determination of the pulmonary and systemic circulation times in man and of a figure related to the cardiac output. Am. J. Physiol. 84:338-344, 1928.

4. Hugenholtz, P.G., Wagner, H.R., Gamble, W.J., and Polanyi, M.L. Direct read-out of cardiac output by means of the fiberoptic indicator dilution method. Am. Heart J. 77:178-186, 1969.

5. Snedecor, G.W., and Cochran, W.G. Statistical Methods, 6th ed., Ames, Iowa: Iowa State University Press, 1967, Chpt. 6.

****

Table I

HAND CALC. VS. GRNDYE - AREAS

| Hand Calc.	Comp.	Hand Calc.	Comp.	Hand Calc.	Comp.
436.3	431.8	358.4	367.8	299.5	297.1
442.6	443.7	380.9	362.3	370.1	355.0
226.0	226.5	383.3	365.1	339.4	326.9
178.6	178.1	243.9	233.6	194.6	188.0
185.9	190.0	242.0	239.4	231.1	243.3
239.4	246.4	316.2	314.1	192.0	178.6
126.6	126.7	439.4	437.3	240.7	239.6
409.3	447.0	291.8	289.1	290.2	288.0
434.8	472.0	398.5	391.0		
471.9	465.5	217.2	215.1		
314.9	315.2	210.2	210.5		
332.2	319.1	230.7	227.3		
330.5	334.5	450.9	448.4		
248.5	246.5	437.3	441.2		
212.7	211.1	218.8	214.6		
219.7	206.3	419.7	419.2		
470.0	463.5	402.6	398.9		
482.7	472.7	376.1	374.1		
399.7	394.6	379.3	378.1		
353.0	352.2	360.8	362.9		
375.0	368.7	516.4	522.1		
491.5	487.0	508.9	505.0		
485.0	471.0	540.3	535.0		
451.1	451.9	534.9	522.3		
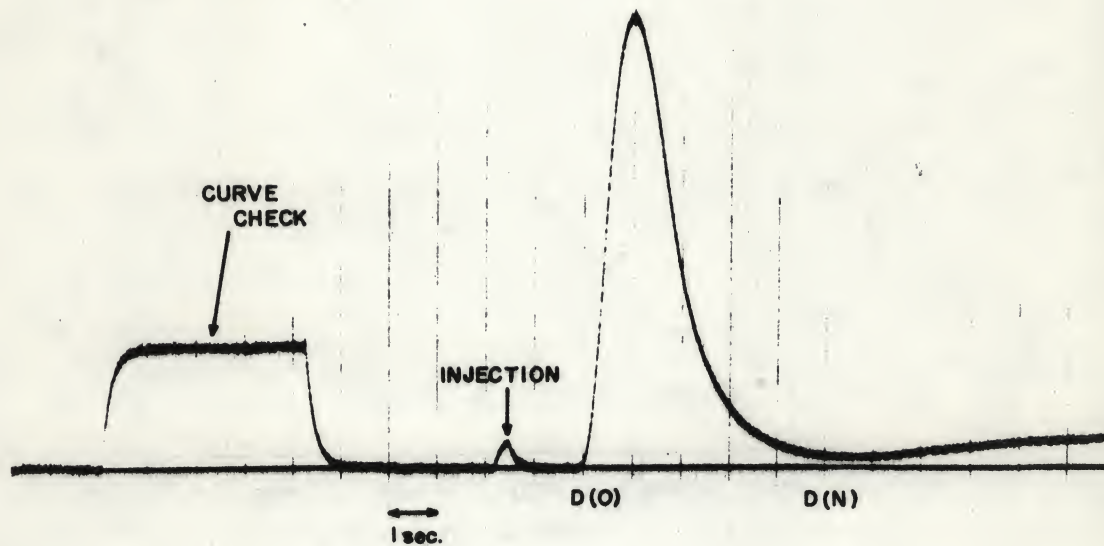
Fig. 1 Typical Dye Curve
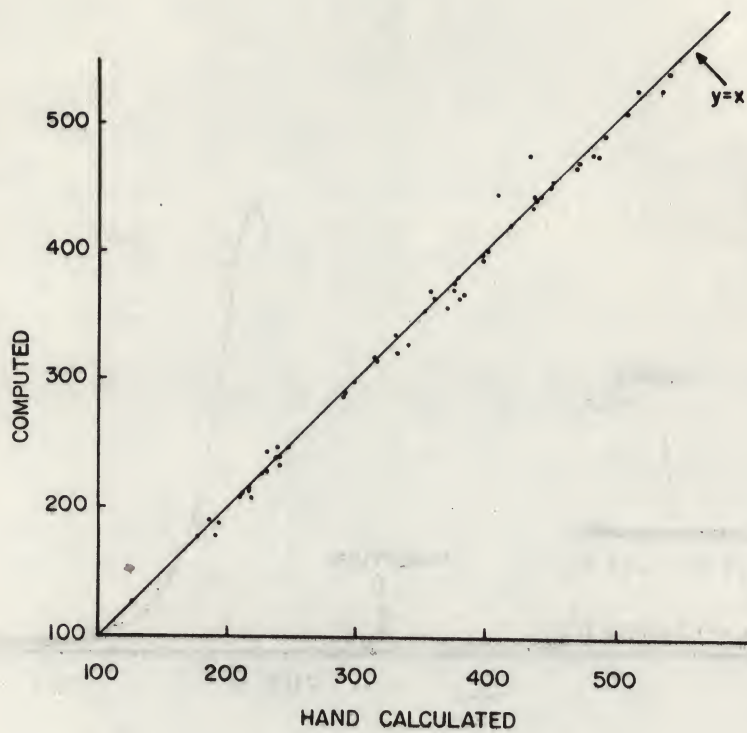
Fig. 2 Hand calculated areas versus areas calculated
by program. The straight line superimposed
on the data is the line of identity.

APPENDIX I: TYPICAL DATA TAPE

120;
123;
120;
9;22;47;70;79;73;60;45;35;27;22;19;18;
118;
9;27;51;63;57;46;34;25;18;15;13;12;11;10;9;
0;
0;

13

GRNDYE 1970

CAL CH= 120   CAL F= 123

CRV NO: 1   CH= 120
    9   22   47   70   79
    73   60   45   35   27
    22   19   18
TM=   3.0 SEC   TR=   5.0 SEC
     SUM SQ= 0.1704196E-02

    Q=   6.573   L/MIN

CRV NO: 2   CH= 118
    9   27   51   63   57
    46   34   25   18   15
    13   12   11   10   9
TM=   2.5 SEC   TR=   4.5 SEC
     SUM SQ= 0.4476360E-02

    Q=   9.441   L/MIN

GRNDYE 1970