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Abstract

This program is used in conjunction with FOCAL to make the best two parameter least square fit to the equation:

$$Y = \frac{A}{1 + \frac{B}{X}}$$

This equation is a very common equation in pharmacological work as it represents the dose response curve where A is the asymptotic level for maximal response and B is the response where Y is equal to $\frac{A}{2}$ i e ED50.

Storage

The number of data points must satisfy the relation a where N_X is the number of X-levels and N_Y is the number of observations. After having read in the program and started with a GO the computer will ask for the number of levels i,e, the number of X-values. For each X-value the computer will then ask for a) the dosage (i, e, the X-value), b) the number of observations i. e, values at this X-value and after that c) for the Y-values. The computer asks for AG and BG (the initial values of the constants for the iteration, see below). The output will depend on whether convergence can be obtained with the criterions in the program or not (see the mathamatical explanation below). If convergence can be obtained the program will output the found values for A and B, their standard deviations and their standard error of means. It will output total standard deviation and the co-variance of the material and the degrees of freedom for the T-test after which it stops. If convergence can not be obtained this may be due to two causes:

a/ N in equation number 7 may be 0 due to rounding errors in which case the computer will type DIVERGES N = 0 and ask you if want to try new initial values for A and B. An answer YES to this question will produce the question AG BG again and a new attempt. If you answer NO to this question the computer will stop.

b/ The other case which might produce a non convergent result is if the computer does not reach the criteria for convergence within ten iterations. In this case the computer will type TEN VALUES, it will output the values for AG and BG last found and the question SHALL I CONTINUE. Answer YES to this question will let the computer do 10 further iterations and answer NO to this question will put you in the same position as in case a. The computer will ask DO YOU WANT TO TRY AGAIN and you can make the necessary answers. Note that a restart with a GO will remove all variables. If you have input values and by mistake answered the question DO YOU WANT TO TRY AGAIN wrongly and wish to restart without re-inputting the values this can be done by starting the program with a GOTO 1.2. This will produce the question AG BG again.

Method

As the equation can not be solved through standard straight forward methods it is necessary to use an iterative procedure. The procedure is as follows: We are given equation 1 as us a fixed prechosen value we can assume that all the error is concentrated to Y. Calling the error in Y(i) δ(i) we get equation 2. We attempt to put in values of A and B, that is we guessed from previous knowledge of the material a reasonable value for A and B (in most cases the actual guessing is not critical). Out guessed values of A and B will not be correct so we will have equation 3, please note the signs. Inserting these values in equation 2 we get equation 4. We introduce the new variables

P, Q and R defined according to equation 5. Introducing these into equation 4 and rearranging we get equation 6. We are looking for the minimum of F = sum δi^2. Derivating this on the parameters $\alpha 1$ $\alpha 2$ and putting the derivates = 0 we get a system of linear equations which solv to give equation 7. Using this three values as criteria on convergence we have

a/ that N must not equal 0 which it might do due to rounding errors if the originally guessed values of A and B are two far from the correct.

b/ that AA resp. AB should be small in comparison to the actual values ie AG BG. The program is at present set such that AA and AB at the same time must be less than one promille of AG resp. BG before the computer considers the values to have converged. There is also a criterium in the program that no more than ten iterations should be attempted. It has been found through experimentation that convergence is very rapid, only in extreme cases does the computer try more than three or four values. If convergence has not been reached in ten tries it is better to start with new values for AG and BG than to let the computer iterate a further ten tries. When the calculations are acceptabel the computer goes on to calculate the variance of the material. The total variance S^2 is equation 8 where NU is the number of observations (note: not the same as N in equation 7). The variances for the α's are as givenin equation 8 and the same goes for the covariance. As divisor for the standard error of mean is used NU-1.

Comment

The question of accuracy in originally guessed values. In the cases we have tried the values of AG and BG have not been very critical.

It has been possible to guess values which are 25 to 50 % above or below the true values but it has been found that convergence is easier and more rapid if the values are guessed close to and below the true values. If the values are guessed extremely wrong eg both AG and BG are 100 % to large it can sometimes happen that the program converges on a root which isnnot the true solution. This might giwe reasonable values for the variances but it is easy through an inspection of the means to see that the result is not the wanted solution. It might for example converge on a negative dose value for ED50 in a dose response curve which of course is a rediculous answer. If this happens and the machine stops after having writtwn out the answer type: GOTO 1.2 and try with new values for AG and BG. Note: Do not restart the program with GO; as this erases all the variables in the computer.

$$Y = \frac{A}{1 + \frac{B}{X}}$$

$$(2N_X + N_Y) < 30 \qquad a$$

$$Y = \frac{A}{1 + \frac{B}{X}} \qquad 1$$

$$yi + \delta i = \frac{A}{1 + \frac{B}{X_i}} \qquad 2$$

$$A = AG - AA$$
$$B = BG + AB \qquad 3$$

$$y(i) + \delta(i) = \frac{AG - AA}{1 + \frac{BG + AB}{X(i)}} \qquad 4$$

$$P(i) = \frac{AG}{1 + \frac{BG}{X(i)}}$$

$$Q(i) = \frac{AG}{\left(1 + \frac{BG}{X(i)}\right)(B + X(i))} \qquad 5$$

$$R(i) = \frac{AG}{\left(1 + \frac{BG}{X(i)}\right)} - Y(i)$$

$$\delta_i = R(i) - AA \times P(i) - \alpha_2 \times Q(i) \qquad 6$$

$$AA = \frac{\bar{Z}\,Q\,Q\,\bar{Z}\,P\,R - \bar{Z}\,p\,Q\,\bar{Z}\,Q\,R}{N}$$

$$AB = \frac{\bar{Z}\,P\,P\,\bar{Z}\,Q\,R - \bar{Z}\,P\,Q\,\bar{Z}\,P\,R}{N} \qquad 7$$

$$N = \bar{Z}\,P\,P\,\bar{Z}\,Q\,Q - \bar{Z}\,P\,Q\,\bar{Z}\,P\,Q$$

$$S^2 = \frac{\bar{Z}\,\delta_i^2}{NU - 2} \quad i \qquad \delta_2 = S^2\,\frac{\bar{Z}\,QQ}{N} \qquad 8$$

$$\delta_{\alpha_2} = \frac{S^2\,\bar{Z}\,PP}{N} \qquad COV = \frac{\delta^2\,\bar{Z}\,PQ}{N}$$

$\bar{Z}$ stands for $\sum_{i=1}^{n}$

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C-FOCAL, 1969

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01.05 E
01.10 A "NUMBER OF ",?LEVELS?; F A=1,1,LE;D 5.0
01.20 T !; A ?AG?; A ?BG?;S B=10;G 1.3
01.26 S B=B-1; IF (B) 3.1,3.1,1.3
01.30 S QQ=0;S PR=0;S PQ=0;S QR=0;S PP=0;S DD=0;S NU=0
0 1.40 F A=1,1,LE; F C=1,1,OB(A); D 10.0
01.50 S N= PP*QQ-PQ*PQ
01.52 IF (N) 1.6,1.54,1.6
01.54 T " DIVERGES, N=0",; G 3.4
01.60 S AA=(QQ*PR-PQ*QR)/N
01.70 S AB=(PP*QR-PQ*PR)/N
01.80 S BG=BG+AB; S AG=AG-AA
01.90 IF (FABS<(AA)/AG>-0.001) 1.94,1.26,1.26
01.94 IF (FABS<(AB)/BG>-0.001)2.2,1.26,1.26

02.20 S NU=0; F A=1,1,LE; F C=1,1,OB(A);D 10.0; D 6.2
0 2.30 T !!,"VARIABLE    MEAN          S.D.           S.E.M.
0 2.32 T %8.04
02.35 S Q=DD/(NU-2)
02.40 T !,,"A      ",AG,FSQT(Q*QQ/N),FSQT(Q*QQ/(N*(NU-1)))
0  .50 T !, "B      ",BG, FSQT(Q*PP/N),FSQT(Q*PP/(N*(NU-1)))
0 2.70 T !!,"TOTAL -----------   ",FSQT(Q)
02.75 T !, "COV.     ", Q*PQ/N
02.80 T !!," D.F.", %2.00,NU-2
02.85 Q

03.10 T !," 10 VALUES
03.15 T %,
03.20 T !,"A",AG,!,"B",BG,!,"SHALL I CONTINUE ?"
03.30 A B; IF (B-155)1.2,3.4,1.2
03.40 T "DO YOU WANT TO TRY AGAIN ?"; A B
03.50 IF (B-155)1.2,2.85,1.2
03.60 Q

05.10 T !, %2.00, " LEVEL NO",A,"  DOSAGE"
05.20 A X(A); T "OBSERVATIONS"; A OB(A),!;F B=1,1,OB(A);D 6.1

06.10 S NU=NU+1; A Y(NU)
06.20 S DD=DD+(R-AB*Q-AA*P)↑2

10.05 S NU=NU+1
10.10 S P=1/(1+BG/X(A)); S Q=AG/((1+BG/X(A))*(BG+X(A)))
1 0.20 S R= AG/(1+BG/X(A))-Y(NU)
10.30 S QQ=QQ+Q*Q; S PR=PR+P*R;S PQ=PQ+P*Q; S PP=PP+P*P
1 0.40 S QR=QR+R*Q;
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NUMBER OF LEVELS:2
 LEVEL NO=  1  DOSAGE:0.003 OBSERVATIONS:4
:-70.5 :-68.5 :-69.5 :-61.83
 LEVEL NO=  2  DOSAGE:0.01 OBSERVATIONS:5
:-53.7 :-80 :-67.7 :-86.5 :-84.2
AG:-85 BG:0.001

VARIABLE    MEAN          S.D.          S.E.M.
A     =-  77.7931=   11.3462=     4.0115
B     =    0.0005=    0.0007=     0.0003

TOTAL ----------   =    10.6457
COV.    =-    0.0074

 D.F.=  7*
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