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The Efficient Use of NONLIN For Unbalanced Multiple Dose Data

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One of the uses of pharmacokinetic modeling is the fitting and prediction of blood levels after multiple dosing. The equations that govern this process are readily available for the case of equally spaced dosing intervals. For unequally spaced intervals, some rather inefficient methods have been suggested for use with NONLIN (1). This article shows how to implement parameter estimation and fitting of such data by means of NONLIN by summing the appropriate single-dose equations.

KEY WORDS: nonlinear estimation; multiple dose; NONLIN.

INTRODUCTION

The fitting of data from single-dose blood level studies to linear compartmental models has been made relatively convenient with the implementation of a general-purpose nonlinear estimation computer program such as our NONLIN (1). It is often of interest to fit or predict blood levels for the case of multiple-dose studies. The equations that govern the concentrations after dosing at equal time intervals are easily derived, and implementation in NONLIN is straightforward.

In practice, it often makes sense to dose at unequally spaced time intervals, possibly with unequal doses as well. In recent publications, approaches to this problem have been discussed with reference to NONLIN (2, 3). It is suggested there that the way to attack this problem is by writing the model in differential equation form and then use the NONLIN numerical integrator to solve for theoretical concentrations. Although this approach is certainly legitimate and feasible, it has at least two serious

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drawbacks. First, it requires extensive changes in the internal NONLIN source code, especially in its numerical integrator routine. An even more important consideration is that numerical integration by nature results in the use of large amounts of computer time and hence is expensive.

THEORY

In some detail, we will now show how to implement a solution to this problem without the use of differential equations and without the need to make changes in the internal NONLIN source code. Use is made of the rather obvious fact that the multiple dose equation can be considered to be a sum of single dose equations. To illustrate this method, we chose the simple one compartment model with instantaneous input. However, once the method is understood, it can easily be adapted to any model for which the single dose equations can be written in explicit form.

The model used is illustrated in Fig. 1. Let us assume that we are dosing a times $T_1, T_2, \ldots, T_n$, with doses of size $D_1, D_2, \ldots, D_n$, respectively. The serum concentration, $C_1(t)$, due to the first dosing D_1 given at time T_1 (T_1 is usually zero) is given by

$$C_1(t) = \frac{D_1}{V} e^{-k(t-T_1)} \tag{1}$$

Here V represents the volume of the compartment, and k the rate constant for excretion from the compartment. In general, the serum concentration due to the mth dosing, D_m, given at time T_m, can be written similarly:

$$C_m(t) = \frac{D_m}{V} e^{-k(t-T_m)} \tag{2}$$

In order to obtain the serum concentration due to repeated dosing, $C(t)$, all that is needed is to add the contribution at t of each of the single dose concentration curves resulting from the s dosings at or prior to time t. Mathematically,

$$C(t) = \sum_{r=1}^{s} \frac{D_r}{V} e^{-k(t-T_r)} \tag{3}$$

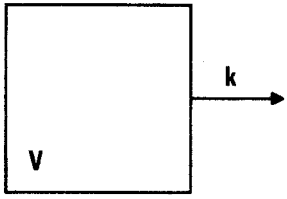

Fig. 1. The one-compartment model with instantaneous input.

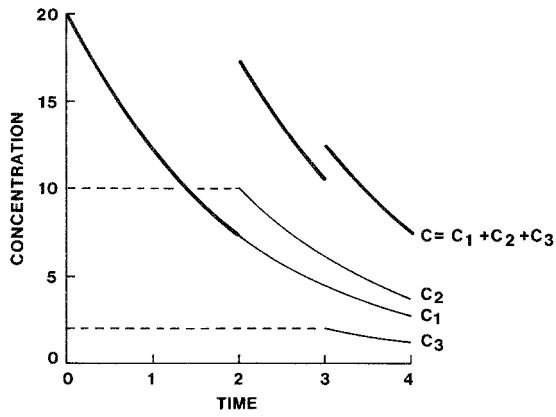

Fig. 2. Graphic illustration of method.

or, in general:

$$C(t) = \sum_{r=1}^{s} C_r(t - T_r) \tag{4}$$

In Fig. 2, this method is illustrated for the case of three dosings of size 20, 10, and 2 at times 0, 2, and 3, respectively. The concentration at time 3.5, for example, is the sum of the concentrations from each of the single-dose curves at that time.

IMPLEMENTATION IN NONLIN

Next we will show how to implement this approach in the DFUNC subroutine, which NONLIN uses to introduce the model to the program. First, we need to enter, by some means, the number of dosings, the dosing times, and the size of the doses administered. In the sample DFUNC of Fig. 3, this is done by means of the DATA statement, for ease of illustration purposes. Other methods such as reading in this information at the end of the data set by means of READ statements in DFUNC, or by introducing them via the array of constants, CON, are also possible and are often more flexible.

A DIMENSION statement was added (line 13), which gives the arrays DOSING (time of dosing) and DOSES (size of doses), their proper size, at least equal to NDOSE (the number of dosings). In the DATA statements (lines 20–22), the actual values of these parameters are introduced.

```
C ..... ONE-COMPARTMENT MODEL, INSTANTANEOUS INPUT–MULTIPLE DOSES          LINE  1
C ..... LINE  2
      SUBROUTINE DFUNC(F, P, CON, VAL, X, I, J, ISPEC, XCLC, Y, W, NOBS)   LINE  3
      IMPLICIT REAL * 8 (A-H, O-Z)                                         LINE  4
      DIMENSION ISPEC(1), NOBS(1)                                          LINE  5
      DOUBLE PRECISION P(1), VAL(1), F, CON(1), Y(1), W(1), X, XVEC(1)     LINE  6
C ..... LINE  7
C ..... NDOSE  = # OF DOSES ..... LINE  8
C ..... DOSES  = VECTOR OF NDOSE DOSE LEVELS ..... LINE  9
C ..... DOSING  = VECTOR OF NDOSE DOSING TIMES ..... LINE 10
C ..... DIMENSION OF DOSES AND DOSING MUST BE AT LEAST NDOSE ..... LINE 11
C ..... LINE 12
      DIMENSION DOSING (5), DOSES(50)                                      LINE 13
C ..... LINE 14
C ..... INDEX KEEPS TRACK OF TO WHICH DOSE THE OBSERVATION BELONGS ..... LINE 15
C ..... DIMENSION OF INDEX MUST BE AT LEAST EQUAL TO # OF OBSERVATIONS ... LINE 16
C ..... LINE 17
      DIMENSION INDEX (100)                                                LINE 18
C ..... LINE 19
      DATA NDOSE /3/                                                       LINE 20
      DATA DOSING /0., 2., 3./                                             LINE 21
      DATA DOSES /20., 10., 2./                                            LINE 22
C ..... LINE 23
C ..... THE NEXT STATEMENT IS NOT REQUIRED IF NO PLOTS ARE WANTED ..... LINE 24
C ..... LINE 25
      IF (ISPEC(8).EQ.10)GO TO 30                                          LINE 26
      IF (ISPEC(8).NE. - 1)GO TO 10                                        LINE 27
C ..... LINE 28
C ..... INDEX ARRAY IS COMPUTED HERE ONCE AND FOR ALL                      LINE 29
C ..... LINE 30
      NX = ISPEC(2)                                                        LINE 31
      DO 1 K = 1, NX                                                       LINE 32
          INDEX(K) = NDOSE                                                 LINE 33
              DO 2 L = 1, NDOSE                                            LINE 34
                  IF (XVEC(K).GE.DOSING(L))GO TO 2                         LINE 35
                  INDEX(K) = L - 1                                         LINE 36
                  GO TO 1                                                  LINE 37
2             CONTINUE                                                     LINE 38
1   CONTINUE                                                               LINE 39
C ..... LINE 40
C ..... V  = P(1) = VOLUME ..... LINE 41
C ..... RE  = P(2) = ELIMINATION RATE ..... LINE 42
C ..... LINE 43
10    V = P(1)                                                             LINE 44
      RE = P(2)                                                            LINE 45
      L = INDEX(I)                                                         LINE 46
      GO TO 20                                                             LINE 47
C ..... LINE 48
C ..... THIS SECTION IS USED ONLY IF PLOT OPTION IS SPECIFIED ..... LINE 49
C ..... LINE 50
30    L = NDOSE                                                            LINE 51
      DO 40 K = 1, NDOSE                                                   LINE 52
          IF(X . GE . DOSING(K)) GO TO 40                                  LINE 53
          L = K - 1                                                        LINE 54
          GO TO 20                                                         LINE 55
40    CONTINUE                                                             LINE 56
C ..... LINE 57
C ..... F IS COMPUTED BY SUMMING THE CONCENTRATIONS FROM EACH OF THE .... LINE 58
C ..... L = INDEX(1) DOSINGS PRIOR TO OR AT X ..... LINE 59
C ..... LINE 60
20    SUM = 0.                                                             LINE 61
        DO 4 K = 1, L                                                      LINE 62
            T = X - DOSING(K)                                              LINE 63
            SUM = SUM + DOSES(K)/V * DEXP(-RE * T)                         LINE 64
 4    CONTINUE                                                             LINE 65
        F = SUM                                                            LINE 66
        RETURN                                                             LINE 67
        END                                                                LINE 68
```

Since it is necessary to know how many dosings have preceded a given point in time, this information is computed once for each time at which an observation was taken and stored in an array, INDEX. This array is given a size at least as large as the number of observations in the data set in line 18 of DFUNC. The actual values for INDEX are computed in lines 27–39. Finally, the summing process, which computes the theoretical concentrations at a given time (Eq. 3) is implemented in lines 44–46 and 57–66. To duplicate this method for any other model, all that is necessary is to change 44–45 and 64 by replacing them with the single-dose equation for the chosen model. For more complicated models, this may require several additional lines of code.

One final point should be made about this sample DFUNC. In order to use the plotting facilities of NONLIN, the theoretical concentrations must be computed at a series of 101 time points. For this reason, the code in lines 26 and 48–56 is included. If no plots are desired, these lines may be omitted.

CONCLUSIONS

This method should save those NONLIN users who previously have tried to approach this problem via differential equations a considerable amount of time and expense. It can, of course, be used for the equally spaced, equal-dose situation as well, but for this it is certainly not the optimal approach. It is likely that with some modifications, the material in this article would also be useful to users of other nonlinear estimation programs.

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Fig. 3. Sample DFUNC subroutine.