A Nonlinear Least Squares Program, MULTI(FILT), Based on Fast Inverse Laplace Transform for Microcomputers

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A nonlinear curve fitting program MULTI(FILT) into which the fast inverse Laplace transform (FILT) is incorporated was developed on a microcomputer. FILT is an algorithm for the numerical inversion of Laplace-transformed equations (image equations) to generate the corresponding real time courses. The pharmacokinetic models can be defined in the form of Laplace-transformed equations as a subroutine in MULTI(FILT). MULTI(FILT) achieves the numerical inversion of the defined image equations according to FILT and the subsequent curve-fitting of the inverse-transformed time courses to the experimental data points to estimate the pharmacokinetic parameters by the nonlinear least-squares method. MULTI(FILT) has a function to impose constraints on the pharmacokinetic parameters. In order to verify the reliability of MULTI(FILT), the pharmacokinetic parameters estimated by MULTI(FILT) were compared with those by MULTI using 100 time courses which were artificially generated according to the Monte Carlo method, based on data for theophylline and bishydroxycoumarin. The estimated pharmacokinetic parameters by MULTI(FILT) agreed with those by MULTI. Thus, it is suggested that FILT, developed in the field of electronic technology, is also useful in the pharmacokinetic field.

Keywords pharmacokinetics; MULTI; FILT; MULTI(FILT); curve fitting; Laplace transform; least square; microcomputer

Introduction

A nonlinear curve fitting technique is indispensable to evaluate the pharmacokinetic properties of drugs. The pharmacokinetic models which form the basis for the curve-fitting are usually constructed from differential equations based on the mass balance of drugs in the body, in the organ *etc.* Some simple ordinary differential equations can be solved in an analytical way, and some ordinary nonlinear differential equations can be solved only be a numerical technique such as the Runge–Kutta–Gill method.[1] When drug disposition processes are assumed to be linear, the corresponding differential equations are often solved by means of the Laplace transform. The Laplace-transformed solutions (image solutions) are obtained in the routine process, but the inversion of the image equations into the real time course equations is often difficult or impossible. Even if the real equation may be analytically obtained, the solution is often given in the form of an infinite series or a complicated integral which is difficult to handle. The liver perfusion system[2] is well represented by partial differential equations which are also solved by Laplace transform, and the transformed solutions alone are obtainable. The blood recirculatory system[3] is simply represented in the form of a Laplace-transformed equation which is a combination of some transfer functions.

Considering the difficulty in the analytical inversion of the Laplace transform, we have developed the nonlinear regression program MULTI (FILT) in which the fast inverse Laplace transform (FILT)[4,5] is combined with the least squares program MULTI.[6] FILT is an algorithm for the numerical inversion of Laplace-transformed model equations (image equations) to generate the corresponding real time courses. MULTI (FILT) numerically converts the image model equations into the real time courses and subsequently performs the curve-fitting to the observed time course data. As FILT was developed in the field of electronic technology and is new in the pharmacokinetic field, the usefulness and the reliability of FILT in pharmacokinetic analysis are unknown.

The purposes of the present report are to present MULTI (FILT), to describe the usage of MULTI (FILT), and to compare the pharmacokinetic parameters estimated by MULTI (FILT) with those by MULTI to confirm the reliability of MULTI (FILT) as well as FILT. In order to compare MULTI (FILT) with MULTI, 100 time courses were generated by adding the normal random errors not only to pharmacokinetic parameters but also to the time course data points, and the generated time courses were used for the curve fitting both by MULTI (FILT) and by MULTI. The advantages and limitations of MULTI (FILT) are discussed.

Method

A. Hardware MULTI (FILT) is written in FORTRAN77 which allows the use of complex numbers, since FILT is intimately related to the arithmetics of complex variables.[4] MULTI (FILT) was developed in Microsoft FORTRAN (Ver. 3.2) on a personal computer (PC9801F, NEC, Japan), and can be compiled with other FORTRAN77 compilers on a personal computer or on a mainframe computer without any modification. The source program occupies about 21 Kilobytes.

B. Algorithms and Constraints Four algorithms, the Gauss–Newton method, the damping Gauss–Newton method, the modified Marquadt method, and the simplex method are provided for the nonlinear curve fitting, which are the same as in MULTI.[6] The purpose of ordinary least squares (OLS) is to evaluate the parameter vector $\boldsymbol{P}=(P_1, P_2, \cdots, P_m)$ which gives the smallest residual sum of squares (SS) in Eq. 1:

$$SS=\sum_{i=1}^{n} W_i(C_i-f(t_i, \boldsymbol{P}))^2 \quad (1)$$

where m is number of parameters, n is number of data points, W_i is data weight, C_i is a dependent variable, t is time, and $f(t_i, \boldsymbol{P})$ is a model equation which is the inverse form of an image equation. MULTI (FILT) estimates $\boldsymbol{P}$ in the image equations $\tilde{f}(s, \boldsymbol{P})$ defined by the user. The data weights of 1, $1/C_i$, and $1/C_i^2$ can be selected, where C_i is the measured value. In estimating pharmacokinetic parameters, MULTI (FILT) allows us to impose constraints on parameters according to the following four transformations[7]: (1) no constraints, (2) $P_i=Q_i^2$, (3) $P_i=B+(A-B)\cdot\sin^2(Q_i)$, and (4) $P_i=B+(A-B)\cdot\exp(Q_1)/(1+\exp(Q_i))$, where P_i is the pharmacokinetic parameter, Q_i is an intermediate parameter, and A and B are lower and upper limits of constraints, respectively. At the end of calculation, MULTI (FILT) gives the final parameter values, final SS value, Akaike's information criterion (AIC)[8] for the selection of the most proper model, and a graphic representation of the observed data and predicted time courses.

C. Example Run of MULTI (FILT) Before the execution of MULTI (FILT), the pharmacokinetic model equations must be defined in the form

of image equations in the subroutine FFUNC. Table I presents the plasma concentrations of cefotiam (one of the cephalosporin antibiotics) after intravenous (i.v.) and intramuscular (i.m.) administration to a rat. These data were obtained in our laboratory, but the details of the experimental procedures are not given here. The one-compartment model with i.v. administration, and one-compartment model with first-order absorption are adopted here (Fig. 1). The corresponding image equations are given by Eqs. 2 and 3, respectively:

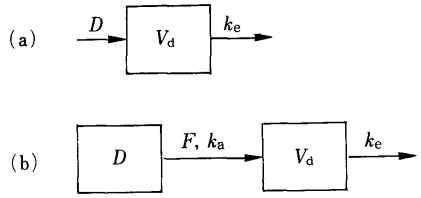

Fig. 1. One-Compartment Models

(a) The one-compartment model with i.v. administration, (b) the one-compartment model with first-order absorption.

```
C  =====  FUNCTION FOR MULTI(FILT)  ======
      SUBROUTINE FFUNC(J,M,P,NC,Q,PL,PU,S,T,CCP)
      DIMENSION P(20),Q(20),PL(20),PU(20)
      COMPLEX S,CCP
      DO 10 IS=1,M
         CALL CONST2(IS,NC,P,Q,PL,PU)
   10 CONTINUE
C  --------- COMMON EQUATIONS --------
C  --  DEFINE MODEL EQUATIONS BELOW --
      GO TO (100,200,300,400,500) J
  100 CCP=P(1)/(S+P(3))
      RETURN
  200 CCP=P(1)*P(2)*P(4)/(S+P(3))/(S+P(4))
      RETURN
  300 CONTINUE
      RETURN
  400 CONTINUE
      RETURN
  500 CONTINUE
      RETURN
      STOP
      END
```

Fig. 2. The Definition of Model Equations in the Subroutine FFUNC for the Example Run of MULTI(FILT)

```
=====================================
          MULTI LINES FITTING
   BY FAST INVERSE LAPLACE TRANSFORM
=====================================
  (0)GAUSS NEWTON          METHOD
  (1)DAMPING GAUSS NEWTON METHOD
  (2)MODIFIED MARQUARDT    METHOD
  (3)SIMPLEX               METHOD

   WHICH ALGORITHM DO YOU SELECT ?      .....selection of algorithm for
1                                          non-linear least-squares method
   SUBJECT NAME ?
EX.1
   NUMBER OF LINES (1-5)  ?
2
   WEIGHT OF DATA (0,1,2) ?
0
   NUMBER OF PARAMETERS   ?
4
   NUMBER OF POINTS ( 1)  ?
6
   NUMBER OF POINTS ( 2)  ?
7
    T 1( 1)  , CP 1( 1) ?                ..... input data
0.0833,102.0
    T 1( 2)  , CP 1( 2) ?                      i.v. data
0.1667,56.0
    T 1( 3)  , CP 1( 3) ?
0.25,24.8
    T 1( 4)  , CP 1( 4) ?
0.3333,22.0
    T 1( 5)  , CP 1( 5) ?
0.6667,8.04
    T 1( 6)  , CP 1( 6) ?
1.0,3.10
    T 2( 1)  , CP 2( 1) ?                      i.m. data
0.0833,6.03
    T 2( 2)  , CP 2( 2) ?
0.1667,9.73
    T 2( 3)  , CP 2( 3) ?
0.25,13.4
    T 2( 4)  , CP 2( 4) ?
0.3333,11.8
    T 2( 5)  , CP 2( 5) ?
0.6667,10.8
    T 2( 6)  , CP 2( 6) ?
1.0,8.97
    T 2( 7)  , CP 2( 7) ?
1.5,6.31

 --- CONSTRAINT ON P(I) ---
  (1) NO CONSTRAINT
  (2) P(I)=Q(I)*Q(I)
  (3) P(I)=B+(A-B)*SIN^2(Q(I))
  (4) P(I)=B+(A-B)*(EXP(Q(I))/(1+EXP(Q(I))))
  WHICH CONSTRAINT DO YOU SELECT (1,2,3,4)  ?
3
  INITIAL P( 1) = ?                      ..... selection of constraint
180
  LOWER , UPPER LIMIT OF P( 1) = ?       ..... input initial parameters
100,300                                        and lower, and upper limits
  INITIAL P( 2) = ?
0.9
  LOWER , UPPER LIMIT OF P( 2) = ?
0.1,1
  INITIAL P( 3) = ?
7.2
  LOWER , UPPER LIMIT OF P( 3) = ?
1.0,20.0
  INITIAL P( 4) = ?
0.6
  LOWER , UPPER LIMIT OF P( 4) = ?
0.1,50.0
  DP FOR JACOBIAN (0.1-0.0001) ?
0.001
  INITIAL SS=  .13574E+03

LOOP=   1
  DAMP= 1
 P( 1)=  184.478200
 P( 2)=     .910398
 P( 3)=    7.185228
 P( 4)=     .678226
 SS=  .11598E+03

  **** EX.1                  ****      ..... result of the calculation
  BY DAMPING GAUSS NEWTON METHOD
   WEIGHT =1/CP (0)
    - CONSTRAINT ON P(I) -
      P(I)=B+(A-B)*SIN^2(Q(I))
   LOOP =    3
   AIC =     69.791340
   DP FOR JACOBIAN=     .001000

  FINAL P( 1)=  184.405100   S.D.=   12.241890 ..... obtained final
  FINAL P( 2)=     .917766   S.D.=     .431440
  FINAL P( 3)=    7.182499   S.D.=     .507642            parameters
  FINAL P( 4)=     .678005   S.D.=     .397908
  SS=  .11595E+03


  DO YOU CONTINUE (Y/N) ?
Y
```

```
T 1=     .083300 ,CP 1 =    101.375700(   102.000000)..... result of line 1 (i.v. data)
T 1=     .166700 ,CP 1 =     55.692700(    56.000000) time , predicted conc. (observed conc.)
T 1=     .250000 ,CP 1 =     30.614250(    24.800000)
T 1=     .333300 ,CP 1 =     16.829490(    22.000000)
T 1=     .666700 ,CP 1 =      1.536279(     8.040000)
T 1=    1.000000 ,CP 1 =       .139404(     3.100000)

 GRAPH  ON(1),OFF(0) ?
1
MINIMUM , AND MAXIMUM OF T-AXIS  ?
0,1.5
  MINIMUM OF CP-AXIS ?
0
  MAXIMUM OF CP-AXIS ? IF [0] THEN        184.3907000
150
  NAME OF  T-AXIS ?
TIME (HR)
  NAME OF CP-AXIS ?
CP
     CP
 150.000+ *
          I
          I
          I  *
 112.500+
          I   O
          I   *
          I
  75.000+    *
          I    *
          I    O
          I     *
  37.500+      *
          I     O*
          I       *O
          I         *****     O
    .000+                  ***************O****************
       +---------+---------+---------+---------+---------+
        .00       .30       .60       .90      1.20      1.50
                                    TIME (HR)

 DO YOU CONTINUE (Y/N) ?
Y

T 2=     .083300 ,CP 2 =      6.868060(     6.030000)..... result of line 2 (i.m. data)
T 2=     .166700 ,CP 2 =     10.275100(     9.730000) time , predicted conc. (observed conc.)
T 2=     .250000 ,CP 2 =     11.793640(    13.400000)
T 2=     .333300 ,CP 2 =     12.296140(    11.800000)
T 2=     .666700 ,CP 2 =     10.965540(    10.800000)
T 2=    1.000000 ,CP 2 =      8.881234(     8.970000)
T 2=    1.500000 ,CP 2 =      6.370610(     6.310000)

 GRAPH  ON(1),OFF(0) ?
1
MINIMUM , AND MAXIMUM OF T-AXIS  ?
0,1.5
  MINIMUM OF CP-AXIS ?
0
  MAXIMUM OF CP-AXIS ? IF [0] THEN        13.4000000
15
  NAME OF  T-AXIS ?
TIME (HR)
  NAME OF CP-AXIS ?
CP
     CP
  15.000+
          I
          I        O
          I       ***O******
  11.250+        *          ****O
          I     **                *****
          I     O                      *****O
          I    *                            ******
   7.500+    *                                    ******
          I                                            ****O
          I  *O
          I
   3.750+
          I *
          I
          I
    .000+
       +---------+---------+---------+---------+---------+
        .00       .30       .60       .90      1.20      1.50
                                    TIME (HR)

 DO YOU CONTINUE (Y/N) ?
Y
(  0) GAUSS NEWTON          METHOD
(  1) DAMPING GAUSS NEWTON METHOD
(  2) MODIFIED MARQUARDT    METHOD
(  3) SIMPLEX               METHOD
( -1) END

 WHICH ALGORITHM DO YOU SELECT (0-3, OR -1) ?
-1
Stop - Program terminated.
```

Fig. 3. An Example Run of MULTI(FILT)

TABLE I. Plasma Concentration of Cefotiam after i.v. and i.m. Administration to Rat (50 mg/kg)

Time (h)	$C_P^{i.v.}$ (μg/ml)	$C_P^{i.m.}$ (μg/ml)
0.0833	102.0	6.03
0.1667	56.0	9.73
0.25	24.8	13.4
0.3333	22.0	11.8
0.6667	8.04	10.8
1.0	3.10	8.97
1.5	—	6.31

$$\tilde{C}_p^{i.v.}(s) = D/V_d/(s+k_e) \quad (2)$$

$$\tilde{C}_p^{i.m.}(s) = FDk_a/V_d/(s+k_a)/(s+k_e) \quad (3)$$

where $\tilde{C}_p(s)$ is the Laplace transform of the plasma concentration profile $C_p(t)$, D is dose, F is fraction of drug absorbed, V_d is volume of distribution, k_a is first-order absorption rate constant, and k_e is first-order elimination rate constant. Figure 2 shows the definition of the image models in the subroutine FFUNC where S is the Laplace variable, CCP is transformed concentration, and $P(1)$, $P(2)\cdots$ are the pharmacokinetic parameters to be estimated. It should be noted that S and CCP are complex variables, while $P(1)$, $P(2)\cdots$ are real variables. $P(1)$ represents D/V_d, $P(2)$ F, $P(3)$ k_e, and $P(4)$ k_a. Figure 3 shows an example run of MULTI (FILT). The underlines in Fig. 3 specify the input into the computer through the keyboard and the lines without underline are the responses on the CRT from MULTI (FILT). The data are given weightings of unity (weight $= C_P^0$). The constraint (3) is imposed on parameters in this example (Fig. 3). The computing time was about 15 min on a personal computer (PC9801F). It is confirmed that the same parameters are obtained without constraint (constraint (1)). The estimated parameters by MULTI (FILT) coincided with those by MULTI[6] ($P_1 = 180$, $P_2 = 0.918$, $P_3 = 7.18$, and $P_4 = 0.667$).

D. Comparison of Parameters by MULTI (FILT) and MULTI by Monte Carlo Simulation To confirm the reliability of MULTI (FILT), the pharmacokinetic parameters estimated by MULTI (FILT) were compared with those by MULTI, using a one-compartment model with first-order absorption (model I) and a two-compartment model with instantaneous administration (model II). These two models have been frequently adopted in the pharmacokinetic field. Fifty time courses for each model (100 time courses in total) were generated by adding the normal random errors both to pharmacokinetic parameters and to the time course data points. The former error corresponds to the interindividual variation, and the latter to the intraindividual variation in the population pharmacokinetics.[9] The normal random errors were generated from the RND function of BASIC according to the Box-Muller formula.[10] All pharmacokinetic parameters and plasma concentrations were generated under the restriction to take positive values, by excluding zero or negative values. Constraint (1) (no constraint) was selected in the execution.

The image equation for model I is given by Eq. 3, and the real equation is given by Eq. 4.

$$C_p(t) = \frac{FDk_a}{V_d(k_a - k_e)}\{\exp(-k_e \cdot t) - \exp(-k_a \cdot t)\} \quad (4)$$

The population parameters of theophylline (500 mg dose) reported by Kelman *et al.*[11] were adopted here as those of model I [$V_d = 361$ (C.V. = 0.2), $k_a = 0.35\,h^{-1}$ (C.V. = 0.5), and $k_e = 0.13\,h^{-1}$ (C.V. = 0.5)], where C.V. means the coefficient of variation. The drug was assumed to be completely absorbed ($F = 100\%$). The C. V. for each data point (intraindividual deviation) was assumed to be 0.15 according to the literature.[11] Based on these population parameters, five data points at $t = 0.5$, 1, 2, 4, and 8 h were generated per time course. Figure 4 shows the correlation of the estimated pharmacokinetic parameters by MULTI (FILT) and by MULTI. The obtained values by MULTI (FILT) are close to the estimates by MULTI. There are some cases where the final k_e takes a negative value. The negative k_e results from the fact that the generated time course is always ascending in the interval from 0 to 8 h. The computing time by MULTI (FILT) was about 5 min, using the damping Gauss–Newton method with no constraint.

The image equation and the real equation for model II are given by Eqs. 5 and 6, respectively.

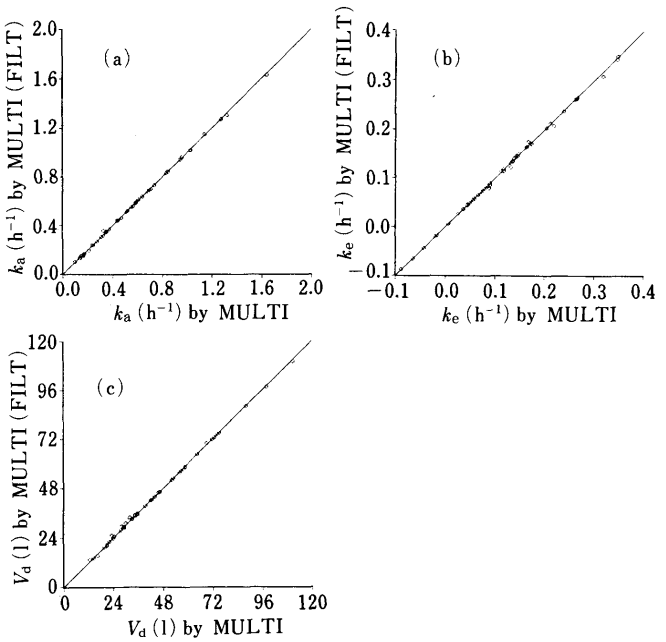

Fig. 4. The Correlations of the Estimated Parameters by MULTI (Abscissa) and MULTI(FILT) (Ordinate) for Model I

(a) k_a, (b) k_e and (c) V_d. The solid line represents the identity of the values on the abscissa and ordinate.

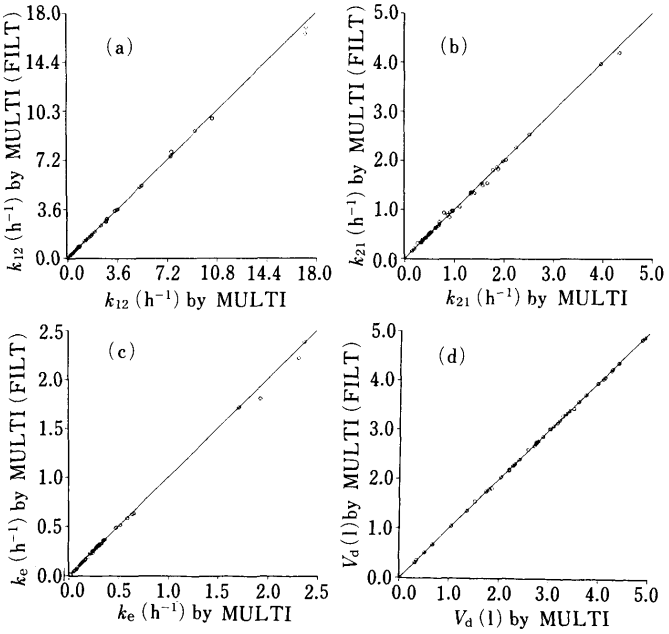

Fig. 5. The Correlations of the Estimated Parameters by MULTI (Abscissa) and MULTI(FILT) (Ordinate) for Model II

(a) k_{12}, (b) k_{21}, (c) k_e and (d) V_d. The solid line represents the identity of the values on the abscissa and ordinate.

$$\tilde{C}_p(s) = A/(s+\alpha) + B/(s+\beta) \quad (5)$$

$$C_p(t) = A\exp(-\alpha \cdot t) + B\exp(-\beta \cdot t) \quad (6)$$

where A, B, α, β are hybrid parameters and given by;

$$A = \frac{D(\alpha - k_{21})}{V_d(\alpha - \beta)}$$

$$B = \frac{D(k_{21} - \beta)}{V_d(\alpha - \beta)}$$

$$\alpha + \beta = k_{12} + k_{21} + k_e$$

$$\alpha \cdot \beta = k_{21} \cdot k_e$$

where k_{12} and k_{21} are reversible transfer rate constants between two compartments, V_d is volume of distribution of the central compartment, and k_e is elimination rate constant from the central compartment. The pharmacokinetic parameters of bishydroxycoumarin (150 mg dose)[12] were adopted as those of model II. The interindividual variations for all rate constants were assumed to be 0.5 as C. V. and that for V_d 0.2. The intra-individual variation for each time course point was assumed to be 0.15 as C. V. Eight points on each time course were generated according to the sampling schedule of the original report.[12] The hybrid parameters A, B, α, β were estimated by the curve fitting and the phamacokinetic parameters were calculated from the estimated hybrid parameters. Figure 5 shows the correlations of pharmacokinetic parameters estimated by MULTI (FILT) with those by MULTI. A good correlation was found between the parameters by MULTI (FILT) and by MULTI. The computing time for each time course was about 15 min when the damping Gauss–Newton method with no constraint was adopted.

Discussion

In this report, the reliability of MULTI (FILT) was examined by comparing the pharmacokinetic parameters estimated by MULTI (FILT) with those by MULTI. No remarkable difference was found between the estimated parameters in the adopted models mentioned above, and it appears that MULTI (FILT) can work well in the adopted pharmacokinetic models. Although the reliability of MULTI (FILT) was only confirmed for some restricted models, for which the explicit analytical solutions are available, MULTI (FILT) as well as FILT should also be applicable to parameter estimation in complicated pharmacokinetic models for which explicit analytical solutions are difficult or impossible to obtain. Simulation programs according to FILT were developed in BASIC by Hosono.[5] However, the programs in BASIC need some complicated modifications in defining the image equations because BASIC does not support complex variables. This is one of the reasons why MULTI (FILT) is written in FORTRAN77. In MULTI (FILT), the user has only to define the model equations in Laplace-transformed form, and this should be especially useful and effective when the convolution or the deconvolution of time courses is required.

Despite the advantages mentioned above, there are some limitations in the manipulation of MULTI (FILT). The Laplace transform can be applied only to linear pharmacokinetic models. Thus FILT is not applicable to nonlinear pharmacokinetic processes. FILT is defined for $t>0$. When the concentration at $t=0$ is measured, MULTI (FILT) substitutes the concentration at $t=1\times10^{-5}$ for it. As FILT is new in the pharmacokinetic field, care might the required when FILT is adopted to analyze a linear pharmacokinetic phenomenon.

References

1) K. Yamaoka and T. Nakagawa, *J. Pharmacobio-Dyn.*, **6**, 595 (1983).
2) M. S. Roberts and M. Rowland, *J. Pharmacokinet. Biopharm.*, **14**, 227 (1986).
3) M. Weiss, *J. Math. Biology*, **15**, 305 (1982).
4) T. Hosono, *Radio Sci.*, **16**, 1015 (1981).
5) T. Hosono, "Fast Inverse Laplace Transform in BASIC," Kyo-ritsu Syuppan Co., Ltd., Tokyo, 1984.
6) K. Yamaoka, Y. Tanigawara, T. Nakagawa, and T. Uno, *J. Pharmacobio-Dyn.*, **4**, 879 (1981).
7) K. Yamaoka and H. Tanaka, *J. Pharmacobio-Dyn.*, **10**, 26 (1987).
8) K. Yamaoka, T. Nakagawa, and T. Uno, *J. Pharmacokinet. Biopharm.*, **6**, 165 (1978).
9) L. B. Sheiner, B. Rosenberg, and V. V. Marathe, *J. Pharmacokinet. Biopharm.*, **5**, 445 (1977).
10) G. E. P. Box and M. E. Muller, *Ann. Math. Stat.*, **29**, 610 (1958).
11) A. W. Kelman, B. Whiting, and S. M. Bryson, *Br. J. Clin. Pharmac.*, **14**, 247 (1982).
12) R. Nagashima, G. Levy, and R. A. O'Reilly, *J. Pharm. Sci.*, **57**, 1888 (1968).