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Estimation of Parameters in Nonlinear Regression Models with Unequally Spaced Observations

Trijya Singh
Le Moyne College, 1419 Salt Springs Road, Syracuse, NY, USA

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SUMMARY

In nonlinear regression models, the least squares estimates of parameters are obtained using non-linear optimization algorithms. These algorithms need good initial estimates as seed values to start iterations. Usually graphical methods or a combination of graphical and transformation methods is used for the purpose. But in some ill conditioned situations with these estimates as initial seed values, convergence may be slow or to a local minimum. It is also possible that convergence may not occur at all. Therefore we not only need a good set of estimates close to the true least squares estimates but we also need another set of estimates to ensure convergence to a global minima. For unequally spaced observations, there is no procedure in literature to find the initial estimates. In this paper, we have developed a procedure which provides good initial estimates for parameters of nonlinear regression models. The method could be applied to both equally as well as unequally spaced observations. We have applied the procedure to some published data sets to demonstrate that it procedures good initial estimates for optimization algorithms.

Keywords: Non-linear Regression, Method of Least Squares, Asymptotic Regression, Growth Curves, Optimization Algorithms.

1. INTRODUCTION

Scientists in agricultural research, biology, medicine, engineering and many other applied disciplines quite often model the relationship between a response variable y with some control or predictor variable x as $E(y_t) = g(x_t, \theta)$, where $\theta = (\theta_1, \theta_2, ..., \theta_p)$ is a vector of unknown parameters and $g(x_t, \theta)$ is a known smooth function of x_t and θ in which $\theta_1, \theta_2, ..., \theta_p$ occur non-linearly. A model in which $g(x_t, \theta)$ cannot be made linear in parameters by any variable or parameter transformation is known as intrinsically nonlinear. Let $\{x_t, y_t\}$, $t = 1, 2, ..., n$ be a random sample in which x_t are deterministic, that is, without any measurement error. Considering the measurement errors in y, we can express the model as

$$y_t = g(x_t, \theta) + \in_t \quad t = 1, 2, ..., n \tag{1.1}$$

where the additive errors $\in_t$'s are assumed to be independently distributed with $E(\in_t) = 0$ and $\mathrm{Var}(\in_t) = \sigma^2$ for all t. For inference purposes, we often assume that these errors are normally distributed. The method of least squares is commonly used to obtain estimates of parameters in non-linear regression models. For a given sample we choose the values of parameters which minimizes the sum of squares of errors (SSE) given by

$$\mathrm{SSE}(\theta) = \sum_{t=1}^{n} \in_t^2 = \sum_{t=1}^{n} \left[y_t - g(x_t, \theta) \right]^2 \tag{1.2}$$

With easy access to fast computers and availability of optimization programs like Marquardt–Levenberg and 'nls' of R, the practice nowadays is to minimize objective function SSE(θ) directly using a suitable optimization algorithm. But all algorithms require good initial estimates as seed values. If many parameters are involved, the surface of SSE(θ) could be very rough and a poor choice of initial estimates may pose many

E-mail address: singht@lemoyne.edu

problems. The algorithm may converge to a local minima or convergence may be very slow and may need a lot of iterations and computing time. It may also be possible in some ill conditioned situations that convergence does not occur at all. In view of these problems, we need good initial estimates as close to the true least squares estimates as possible. Moreover, we need at least one more set of parameter estimates to check that the convergence occurs to the same values.

In earlier days, researchers used the graphical method of stripping (c.f. Wagner 1975) or a combination of graphical and transformation methods, well discussed in the book by Ratkowsky (1983). In the latter case, in the first stage one of the parameters is estimated graphically and then the data is transformed using this estimate. At the second stage, the model is transformed and available methods are used to estimate the remaining parameters. For intrinsically nonlinear regression models, an entire chapter is devoted to these methods in the aforementioned book. However, initial estimates obtained by these methods are not always precise enough to give desired convergence. Ratkowsky, therefore, proposes iterative procedures even to determine better initial estimates if a set of estimates fails to give convergence.

Some ingenious methods other than the graphical method were developed by illustrious statisticians like Fisher, Hotelling, Yule and Hartley for the logistic growth model. These methods are well explained by Nair (1953). Cornell (1962) proposed a method based on partial sums to estimate the parameters of a bi-exponential non-linear regression model $y_t = Ae^{-\alpha t} + Be^{-\beta t} + \in_t$. Shah (1973) proposed a difference–regression equation method for this model. But both methods require equally spaced observations. That is $x_{t+1} - x_t$ should be same for all t. Since in practice, the observations are often unequally spaced, these methods have a little scope of applicability. Foss (1969) proposed a method based on the area under $y(t)$ curve for the above model. However, this method fails if the regression line passes through origin or two consecutive observations are equal, that is $y_t = y_{t+1}$ for one or more t. Recently, Singh *et al.* (2016) proposed a method based on finite differences for the models which could be put under asymptotic regression category discussed by Stevens (1951). Because of the assumption of equally spaced observations the above methods have limited scope and the graphical methods have convergence problems in some situations. [cf. Wagner (1963), Steyn and Van Wyk (1977)]. Therefore, there is need of a procedure which could be applied to a large class of models with equally or unequally spaced observations. To meet this requirement we have proposed a procedure in section 2 of this paper which could be applied in some widely used intrinsically non-linear regression models. The procedure works well, whether the observations are equally or unequally spaced. In section 3, we have demonstrated the application of the procedure to several published data sets.

2. THE PROPOSED PROCEDURE

Foss (1965) developed a method which uses the estimated areas under $y(t)$ curve up to points x_t, $t = 1, 2, ..., n$ and linear multiple regression to estimate parameters of bi-exponential regression model. For estimating area under the $y(t)$ curve he used a quadrature formula of numerical integration. But the numerical integration procedure which he used fails if the regression line passes through the origin, that is, $y_t = 0$ for $x_1 = 0$ or $y_t = y_{t+1}$ for some t. Therefore the method works only for decay type data where $y(t)$ decreases monotonically. We shall follow a modified strategy with a different quadrature formula to ensure that the procedure works in all situations. In what follows, we shall develop the estimating procedures for some important non-linear regression models.

2.1 Asymptotic Regression Model

The asymptotic regression model is given by

$$y(t) = \alpha + \beta\rho^t + \in_t \tag{2.1}$$

where $y(t) \geq 0$, t ≥ 0 and $0 < \rho < 1$. Note that $y(t) \to \alpha$ as $t \to \infty$. Many important intrinsically non-linear models including Mitscherlish model and Gompertz model belong to this category (see Singh *et al.* 2016).

Now, though a process of differentiation and integration, we shall manipulate (2.1) to write it as a linear multiple regression model. Ignoring the error term $\in_t$ we obtain

$$\frac{d}{dt}y(t)=\ln(\rho)\,y(t)-\alpha\ln(\rho) \tag{2.2}$$

where ln(.) is the natural logarithm $\log_e$ (.) The initial condition is $y(0) = \alpha + \beta$. Now, replacing t by z in (2.2) and then taking integral with respect to z from $z = 0$ to t, we have

$$\int_o^t \frac{d}{dz}y(z)\,dz=\ln(\rho)\int_o^t y(z)\,dz-\alpha\ln(\rho)\int_o^t y(z)\,dz \tag{2.3}$$

Therefore, from the Fundamental Theorem of Calculus, we have

$$y(t) - y(0) = \ln(\rho).\ F(t) - \alpha\ln(\rho).t$$

or $y(t) = (\alpha + \beta) - \alpha\ln(\rho)t + \ln(\rho).\ F(t)$ (2.4)

where $F(t)=\int_o^t y(z)\,dz$. Thus the model (2.1) could be written as

$$y(t) = a + bt + cF(t) + \in_t \tag{2.5}$$

where $a = \alpha + \beta$, $b = -\alpha\ln(\rho)$ and $c = \ln(\rho)$. For a given sample $\{t_i, y(t_i)\}$, $i = 1, 2, ..., n$, we can obtain the estimates of $F(t_i)$, $i = 1, 2, ..., n$. We estimate $F(t_i)=\int_o^t y(z)\,dz$ using the given data and a simple trapezoidal quadrature formula of numerical integration. Thus, $F(t_i)$ could be estimated by

$$\hat{F}(t_i)=\sum_{k=1}^{i-1}(t_{k+1}-t_k)\cdot\frac{y(t_{k+1})+y(t_k)}{2},\ i = 1, 2, ..., n \tag{2.6}$$

Now, we have the data $\{t_i, y(t_i), \hat{F}(t_i)\}$, $i = 1, 2, ..., n$ at hand. With this data, we regress $y(t)$ on t and $F(t)$ and obtain the estimates of a, b and c using the theory of least squares. From these estimates the estimates of asymptotic regression model (2.1) could be obtained as

$$\hat{\rho}=\exp(\hat{c}),\ \hat{\alpha}=-\hat{b}/\hat{c}\ \text{and}\ \hat{\beta}=a-\hat{\alpha} \tag{2.7}$$

2.2 Logistic Regression Model

The logistic regression model can be written as

$$y(t)=\frac{k}{1+be^{-at}}+\in_t \tag{2.8}$$

For this model, we can use two approaches as follows.

Approach 1: By using the reciprocal transformation we can write (2.8) as

$$z(t_i) = \alpha + \beta\rho^{t_i} + e_{t_i},\ i = 1, 2, ..., n \tag{2.9}$$

where $z(t_i)=1/y(t_i)$, $\alpha=1/k$, $\beta=\frac{b}{k}$ and $\rho = e^{-a}$. The error e_{t_i} is different from $\in_t$ but we still assume that $E(e_{t_i})=0$ and $\text{Var}(e_{t_i})=\sigma^2$ for all t. Since $y(0) \neq 0$, we shall not face any technical difficulty. We can now use the procedure developed for asymptotic regression model to obtain the estimates of parameters of model (2.8).

Approach 2: In this approach, we directly deal with $y(t)$. Ignoring the error term, we obtain

$$\frac{d}{dt}y(t)=\frac{k}{1+be^{-at}}\cdot\frac{abe^{-at}}{1+be^{-at}}$$

with $y(0)=\frac{k}{1+b}$ it could easily shown that

$$\frac{d}{dt}y(t)=ay(t)\left[1-\frac{y(t)}{k}\right]$$

or $$\frac{d}{dt}y(t)=\alpha y(t)+\beta y^2(t) \tag{2.10}$$

where $\alpha = a$ and $\beta = -a/k$.

Now proceeding along the same lines as followed for the asymptotic regression model, we obtain

$$y(t)=\frac{k}{1+b}+\alpha\int_o^t \boldsymbol{y}(z)\,\boldsymbol{dz}+\beta\int_o^t \boldsymbol{y}^2(z)\,\boldsymbol{dz}$$

Thus, the model (2.8) could alternatively be written as

$$y(t) = \gamma + \alpha U(t) + \beta W(t) + \in_t \tag{2.11}$$

where $\gamma=\frac{k}{1+b}$, $\alpha = a$, $\beta = -a/k$ (2.12)

Also, $U(t)=\int_o^t y(z)\,dz$ and $W(t)=\int_o^t y^2(z)\,dz$

These integrals could be estimated using the given data and trapezoidal formula (2.6) for $t = t_1$,

t_2, ..., t_n. For $W(t)$ we shall use $y^2(t)$ instead of $y(t)$ in (2.6). Now using the data $\{t_i, y(t_i), \hat{U}(t_i), \hat{W}(t_i)\}$ $i = 1, 2, ..., n$ we regress $y(t)$ on t, $U(t)$ and $W(t)$. Applying the method of least squares, we obtain the estimates γ, α and β. From these estimates we obtain the estimates of original parameters as

$$\hat{a} = \hat{\alpha}, \hat{k} = -\hat{\alpha}/\hat{\beta}, \hat{b} = -\left[1 + \frac{\hat{\hat{\alpha}}}{\hat{\beta}\hat{y}}\right] \quad (2.13)$$

2.2 Gompertz Model

This model is given by

$$y(t) = a\, exp[-b\, exp(-ct)] + \in_t \quad (2.14)$$

Using a logarithmic transformation, we can put this model in asymptotic regression form as

$$z(t) = \alpha + \beta\rho^t + e_t \quad (2.15)$$

where $z(t) = \ln[y(t)]$, $\alpha = \ln(a)$, $\beta = -b$ and $\rho = e^{-c}$

Using the method developed for asymptotic regression model, we estimate α, β and ρ. From these estimates, we obtain the estimates of *a, b* and *c* by using an inverse transformation.

3. APPLICATIONS

A few points need to be mentioned before discussing the application of the proposed methods. The first and foremost issue in nonlinear regression models is that normal equations, unlike in linear regression models, do not produce the estimates of parameters in close form. Therefore iterative procedures are used to obtain the estimates. Nowadays, researchers directly minimize the sum of squares of errors, SSE(θ), given at (1.2) for the choice of θ and use the non-linear optimization algorithms for the purpose. But all available algorithms need good initial estimates as seed values to start the iterations. Since the surface of SSE(θ) is quite often rough they need at least two sets of initial estimates to ensure the convergence to a global minimum.

The second important point is that nice properties like unbiasedness and minimum variance available for estimators of parameters of linear regression models are not achievable in the case of nonlinear models. We have only asymptotic properties of least squares estimators [c.f. Seber and Wild (1989)]. Therefore, we can calculate only asymptotic standard errors of estimates after convergence is achieved. For the details of the procedure one may refer to Ratkowsky (1983, pp 15-17). In finite samples, however, the performance of the estimators or procedures could be judged by measures like the residual sum of squares (RSS) given by

$$\text{RSS} = \sum_{t=1}^{n}\left[y_t - g\left(x_t, \hat{\theta}\right)\right]^2 \quad (3.1)$$

or the mean squared error MSE = RSS/n. One can also use the mean absolute percent error (MAPE) which is defined as

$$\text{MAPE} = \frac{1}{n}\sum_{t'}^{n}\frac{[y_t - \hat{y}_t]}{y_t}100\% \quad (3.2)$$

where $\hat{y}_t$ is the predicted value.

We shall now apply the methods developed in previous section to some published data sets. For asymptotic regression model, we shall use three data sets.

Data Set 1: Stevens (1951)

A thermometer lowered into a refrigerated hold, gave the following six consecutive readings (°F) at half minute intervals:

Time	0	1	2	3	4	5
Temperature Readings (°F)	57.7	45.7	38.7	35.3	32.2	32.2

Data Set 2: Gomes (1953)

The mean yield of potatoes per plot of $\frac{1}{65}^{\text{th}}$ of an acre in an experiment with 5 levels (0, 40, 80, 120 and 160 pounds per acre) of superphosphate is given in the following table.

Fertilizer Level (x)	0	1	2	3	4
Yield (y)	229.1	231.8	254.2	250.6	249.6

Data Set 3: (Ratkowsky (1983), page 102)

The leaf production, number of leaves per tiller per day (y) versus light irradiance (x) in watts per square meter at 20°C is given in the following table.

x	12	23	40	92	156	215
y	0.094	0.119	0.199	0.260	0.309	0.331

Since the observations are unequally spaced in data set 3, we shall use this set to illustrate the application of the method developed in section 2. The areas $F(t_i)$ for t = 23, 40, ..…, 215 could estimated using, formula (2.6) and given the data and $F(12) = \int_0^{12} y(z)\,dz$ is extrapolated assuming $y(0) = 0$ in this case. Thus, by adding this area to areas obtained by (2.6), we get estimates of $F(12)$, $F(23)$, …, $F(215)$. The values are given in following table.

t	12	23	40	92	156	215
$y(t)$	.094	.119	.199	.260	.309	.331
$\hat{F}(t_i)$	.564	1.7355	4.4385	16.3725	34.5805	53.4605

Now, regressing $y(t)$ on t and $F(t)$ and using 'lm' program of R-3.2.2, we obtain

Intercept	Coefficients of t	$F(t)$
0.039134 $(\hat{\alpha})$	0.005257 $(\hat{\beta})$	–.015754 $(\hat{c})$

Using equations at (2.7), we get $\hat{\rho}$ = 0.98437, $\hat{\alpha}$ = 0.33369 and $\hat{\beta}$ = – 0.29456 which are quite close to the true least squares estimates reported by Ratkowsky (1983) in Table 5.1 on page 96. Note that true least squares estimates were obtained by Ratkowsky using his initial estimates in the optimization algorithm. For the above estimates we have RSS = 0.0006758, MSE = 0.0001126 and MAPE = 4.6298%. If we use above estimates in 'nls' program of R–3.2.2, we obtain convergence in 6 iterations and least squares estimates are $\hat{\alpha}$ = .335021 (standard error = .01736), $\hat{\beta}$ = – 0.29457 (standard error = .019564) and $\hat{\rho}$ = .98383 (standard error = .003702). For these least squares estimates we have RSS = 0.0006056, MSE = 0.00010 and MAPE = 4.63772%. It is evident from the values of these performance measures for the proposed method that initial estimates are quite close to corresponding values given above.

If we use a combination of the graphical and transformation method suggested by Ratkowsky to obtain initial estimates, we get $\hat{\alpha}$ = 0.34, $\hat{\beta}$ = 0.30521 and $\hat{\rho}$ = 0.98439 for which RSS = 0.000678, MSE = 0.000113 and MAPE = 5.04034l%. These values are obviously greater than the corresponding values of the proposed method.

The initial estimates of the parameters of proposed method, RSS, MSE and MAPE and number of iteration needed for the convergence for data sets of Stevens and Gomes are given in Table 1. Corresponding least square estimates obtained by 'nls' program of R-3.2.2 and their standard errors are also given. Comparison of the estimates and performance measures RSS, MSE and MAPE indicates that the proposed method performs well in both decay type data as well as in growth type data.

Now, to demonstrate the application of the proposed method in logistic growth model, we have considered pasture yield (y) versus growing time (x) data reported by Ratkowsky (1983) on page 88. The data is as follows:

x	9	14	21	28	42	57	63	70	79
y	8.93	10.80	18.59	22.33	39.35	56.11	61.73	64.62	67.08

Let us write $x = t$ and $y = y(t)$. If t starts from zero, values of $U(0)$ and $W(0)$ are taken to be zero. If it is not so then the values of $U(t_1)$ and $W(t_1)$ are to be extrapolated. For this we should have some idea about $y(0)$. We would have this idea from the graph of the data. We could easily guess at what height the curve will hit the y-axis if extended towards the left. Using this value of $y(0)$ and $y(t_1)$ we estimate the values of $U(t_1)$ and $W(t_1)$. These figures are added to values of $U(t_i)$ and $W(t_i)$ obtained by using the quadrature formula and the

Table 1. Estimates of parameters, their RSS, MSE and MAPE for the proposed method and nonlinear optimization (NLS) method

Data Set	Method	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\rho}$	RSS	MSE	MAPE (%)	I
Stevens	Proposed NLS	30.7252 30.7239 (.2310)	26.8414 26.8211 (.2577)	.5609 .5518 (.0085)	.3349	.0558 .0162	.4748 .3015	4
Gomes	Proposed NLS	256.2454 255.5306 (17.2375)	–29.4616 –28.3072 (17.0841)	.5952 .5744 (.4739)	132.5460 131.7859	26.5092 26.3572	1.7401 1.7015	17

Note: Figures within parentheses represent standard errors of the estimates and I is the total number of iterations needed for convergence.

given data. For the given data set, the values of $U(t_i)$ and $W(t_i)$ are obtained as follows:

$\hat{U}(t)$: 58.185, 107.510, 210.375, 353.595, 785.355, 1501.305, 1854.825, 2297.50, 2889.700

$\hat{W}(t)$: 430.852, 921.814, 2539.613, 5494.372, 19823.732, 55049.392, 75926.162, 103878.352, 142917.952

Now, we regress $y(t)$ on $U(t)$ and $W(t)$. Using 'lm' program of R–3.2.2, we obtain

Intercept	Coefficient of $U(t)$	Coefficient of $W(t)$
$\hat{\gamma} = 4.7612732$	$\hat{\alpha} = 0.0694327$	$\hat{\beta} = -0.0009623$

Using the relationships given at (2.13), we obtain the estimates of parameters as $\hat{a} = 0.0694$, $\hat{k} = 72.1529$ and $\hat{b} = 14.1541$. For the form of logistic model given in Ratkowsky, that is, $y(t) = y(t) = \dfrac{\alpha^*}{1+\exp[\beta^* - \gamma^* t]}$ we obtain estimates of parameters from above estimates as $\propto^* = 72.1529$, $\beta^* = 2.650$ and $\hat{\gamma}^* = 0.0694$. These estimates are quite close to non-linear optimization estimates reported by Ratkowsky in Table 4.1 on page 65. The parameter estimates, predicted values, RSS, MSE and MAPE for the proposed method (Approach 2 for logistic model) and non-linear optimization method are given in Table 2. Fig. 1 shows the closeness of predicted values by the proposed method to the observed and those predicted by the nonlinear method.

Table 2. Parameter estimates, RSS, MSE, MAPE and predicted values for logistic model

x	y	Proposed Method (Approach 2)	Non-linear Optimization
9	8.93	8.4125	8.5480
14	10.80	11.3546	11.4310
21	18.59	16.8056	16.7277
28	22.33	23.8472	23.5322
42	39.35	40.8496	40.0395
57	56.11	56.7931	55.9632
63	61.73	61.2345	60.5464
70	64.62	65.0220	64.5361
79	67.08	68.1518	67.9131
Parameters			
α^*		72.1529	72.4622 (1.7340)
β^*		2.6500	2.6181 (0.0883)
γ^*		0.06943	0.0674 (0.00344)
RSS		10.3325	8.0565
MSE		1.1481	0.8952
MAPE		3.9305%	3.4251%
Iterations		6	

Note: Figures within parentheses represent the standard errors of the estimates.

We have also obtained initial estimates using the reciprocal transformation discussed in Section 2. The estimates are $\hat{\alpha}^* = 71.0056$, $\hat{\beta}^* = 2.5604$ and $\hat{\gamma}^* = 0.0643$. For these estimates RSS = 38.4358, MSE = 4.2706 and MAPE = 4.7738%. Looking at the performance measures, this method is slightly inferior to the direct method.

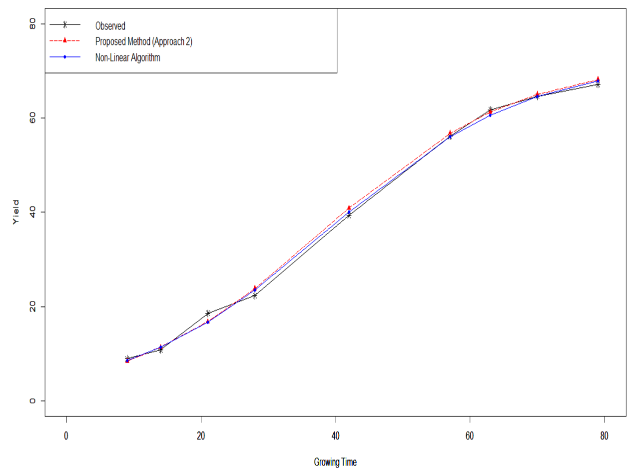

Fig. 1. Observed and Predicted Values Obtained from Proposed and Nonlinear Methods for Logistic Model

Lastly, we applied the proposed method for Gompertz model to the date set 3 reported on page 88 of Ratkowsky. The data set contains 9 unequally spaced observations regarding the area of cucumber cotyledous (y) versus growing time (x). The initial estimates are obtained as $\hat{a} = 9.8597$, $\hat{b} = 1.6426$ and $\hat{c} = 0.8185$. For these estimates the values of RSS, MSE and MAPE are given by 109.5340, 12.1705 and 89.158% respectively. If we use these initial estimates in 'nls' optimization algorithm of R-3.2.2. We get convergence in 8 iterations. The final least squares estimates are given by $\hat{a} = 6.9249$ (standard error = 0.2184), $\hat{b} = 2.1556$ (standard error = 0.1989) and $\hat{c} = 0.4933$ (standard error = 0.0516) which are same as those reported in Table 4.1 on page 65 of Ratkowsky (1983).

Thus, from the above examples it is evident that the proposed method provides good initial estimates of parameters in all situations whether the observations are equally or unequally spaced and whether the response variable represents a decay or a growth phenomenon.

REFERENCES

Cornell, R.G. (1962). A method of fitting a linear combination of two exponentials. *Biometrics*, **18**, 104-113.

Foss, S.D. (1969). A method of obtaining initial estimates of the parameters in exponential curve fitting. *Biometrics*, **25**, 580-584.

Gomes, F.P. (1953). The use of Mitscherlich's regression law in the analysis of experiments with fertilizers. *Biometrics*, **9**, 498-516.

Nair, K.R. (1954). *The Fitting of Growth Curves, Statistics and Mathematics in Biology*, Edited by Kempthorne, Lush and Bancroft.

Ratkowsky, D.A. (1983). *Nonlinear Regression Modeling-A Unified Practical Approach*. Marcel Dekker Inc., New York.

Seber, G.A.F. and Wild, C.J. (1989). *Non-linear Regression*. John Wiley and Sons, New York.

Shah, B.K. (1973). Obtaining preliminary estimates to the two term exponential model to blood concentration data. *J. Pharma. Sci*., **62**, 1208-1209.

Singh, Trijya, Mandal, S.K. and Kumar, Rajesh (2015). Parameter estimation in non-linear regression models. *J. Ind. Soc. Agril. Statist*. **70**(1), 51-61.

Steyn, H.S. and Van Wyk, J.W.J. (1977). Some Methods for Fitting Compartment Models to Data, Weteukskaplike by trees, Vandie, PU VIY CHO Reeks B. Natuur Wetenskappe Nr 91, Potchefstroom, South Africa.

Stevens, W.L. (1951). Asymptotic regression. *Biometrics*, **7**, 247-267.

Wagner, J.G. (1963). Some possible errors in plotting and interpretation of semi-logarithmic plotsof blood level and uninary excretion data. *J. Pharma. Sci*., **25**, 1092-1101.

Wagner, J.G. (1975). *Fundamentals of Clinical Pharmacokinetics*. Hamilton, Illinois:Drug Intelligence Publications.