Journal of Mathematical Biology 1, 241—257 (1975)
© by Springer-Verlag 1975

Discussion of Parameter Estimation in Biological Modelling: Algorithms for Estimation and Evaluation of the Estimates*

J. Swartz and H. Bremermann, Berkeley

Received June 13, 1974

Summary

This paper is concerned with the estimation of parameters when mathematical models are fitted to data. Two new algorithms are presented. The first is fast (economical in computation time), requires no initial estimates, but is not so accurate. The second requires more computation time, and fairly accurate initial estimates, but achieves high accuracy. The models discussed consist of sets of coupled, non-linear differential equations, but the second algorithm is applicable to wider classes of models as well.

The accuracy of the computed values of the parameters depends on the number of data points, and the errors in the data. The sensitivity of the different parameters to errors may differ by orders of magnitude. A method of calculating the expected errors in the parameters is described, and the results of some applications of the method are presented.

An important part of the construction of mathematical models in biology is their verification. This involves a comparison with experimental data. Often a model contains parameters that must be adjusted to obtain a best fit to the data. Many models have been described which have not been compared with the data, and these must stand alone on the reasonableness of their assumptions.

The problems considered in this paper are:

1. *The Parameter Estimation Problem*: When a model has been chosen, it may contain parameters which must be adjusted to obtain the best fit to the observed data.

Although there is a great deal of literature on this subject, there is a shortage of effective algorithms, especially for cases in which the systems cannot be easily linearized. In this paper two new algorithms are described. They may be used together. One is fast, and may be used to find initial estimates of the parameters, while the second which is slower can be used for maximum accuracy (after the first algorithm has provided good starting values).

* This investigation was supported in part by USPHS Training Grant No. 2-T01-GM 00829 from the National Institute of General Medical Sciences.

2. *Accuracy of Parameter Estimates*: It is important for several reasons that the accuracy of the parameter estimates be known. This information is useful in planning experiments, and evaluating parameter estimation techniques. Also, in some instances the prime reason for constructing a model is to determine the rate of the process, so it is important to know the accuracy of this determination.

The accuracy of the parameter estimate depends on the nature of the data, the noise in the data, and the structure of the model. In some circumstances a small error in the data will cause a vastly magnified error in the parameters. The technique of Rosenbrock and Storey [1] for estimating the accuracy of the parameter evaluations is described and the results of applying the technique to several test systems are presented.

Type of Model Treated

The model systems we have treated are described by sets of coupled, first order differential equations. Systems described by both linear and non-linear equations have been considered. Biological systems to which these models have been applied include biochemical kinetic systems, ecological systems, and physiological systems. Most of our techniques are applicable to a more general class of model than described by first order differential equations, but our applications have been limited to models of this type.

In general, the systems treated in this paper are described by sets of differential equations of the form:

$$\frac{dX_m}{dt} = \sum_i k_i^m X_i + \sum_{i,j} k_{ij}^m X_i X_j, \quad m = 1, \ldots, n. \tag{1}$$

The X_i are the state variables, and the k_i and the k_{ij} are the system parameters. The parameter estimation problem is solved by finding the values of the parameters that make the predictions of the model agree most closely with the experimental data. Agreement between model and data is measured in different ways by the functions F^A and F^B which are defined by equations 2 and 3 respectively. The subscript l indexes the time of measurement of each data point. Thus $X_{m,l}$ is the l-th measurement of the variable m:

$$F_A = \sum_m F_m^A, \tag{2}$$

$$F_m^A = \sum_l W_{m,l}^2 \left(\dot{X}_{m,l} - \sum_i k_i^m X_{i,l} - \sum_{i,j} k_{ij}^m X_{i,l} X_{j,l}\right)^2,$$

$$F^B = \sum_m F_m^B,$$

$$F_m^B = \sum_l W_{m,l}^2 (X_{m,l} - X_{m,l}^*)^2. \tag{3}$$

The $X_{m,l}^*$ are the values of the state variables calculated by integrating equations (1). The weighting factors $W_{m,l}$ may be chosen in accordance with the accuracy of the

corresponding data point. In general, we have used the weighting factors $W_{m,l}=\frac{1}{\sigma_{m,l}}$, where $\sigma^2_{m,l}$ is the variance of the measurement of $X_{m,l}$. This weighting function is suggested by the maximum likelihood principle.

Description of Parameter Estimation Techniques

The literature contains many techniques for parameter estimation, and for some systems some of them perform excellently. There are, however, many systems for which no technique performs well. For these systems the existing techniques are either too slow, fail to converge to the correct values, require starting guesses better than those available, or simply are not accurate enough. For a survey of parameter estimation techniques used in biological systems the reader is referred to papers by Davis and Ottaway [2], Swann [3], and Himmelblau [4], and the thesis by Swartz [5]. The paper by Davis and Ottaway presents the results of tests with several important methods, and discusses their usefulness and limitations. The limitations of other methods in current use are discussed in the thesis by Swartz, the paper by Himmelblau, and in papers by Chandler [6], et al, and Squire [7].

Our method 1 is straightforward, requiring no initial parameter estimates and little computer time. We minimize the function F^A (equation (2)) by applying the conditions.

$$\frac{\partial F^A}{\partial k_i}=0 \text{ or } \frac{\partial F^A}{\partial k_{ij}}=0 \tag{4}$$

for each parameter. Since the $X_{i,l}$ are linear functions of the parameters, F^A is a quadratic function of the parameters. That is, the highest order terms in F^A will contain the square of a parameter, or the product of two parameters. Hence, the equations formed by setting the partial deviatives of F^A with respect to the parameters equal to 0 will be linear. There will be one such equation for each parameter. Thus the equations constitute a set of exactly determined linear equations which can be solved by a technique for solving the matrix equation $A\,X=b$. Equations (4) are called the normal equations.

Smoothing the Data

The greatest problem in using this method is the difficulty of making accurate evaluations of the derivatives from the experimental data. Small errors in the measured values of the state variables can produce large errors in numerical differentiation.

Calculations of the derivatives will be greatly improved by fitting a curve to the data. The fitted curve will have much of the random error averaged out of it, and so will give a better approximation to the function and its derivatives. The techniques

of Squire [7] and Himmelblau [4] are similar to our method 1, but they do not involve smoothing the data, and hence are less accurate.

We have performed smoothing by fitting polynomials to the data. Over a small region most functions can be reasonably well approximated by polynomials. We have fitted a polynomial locally to a number of data points. For example, the first polynomial would be fitted to the points 1 to 9, and be used to calculate the derivative at point 5. The second polynomial would be fitted to points 2 through 10, and used to calculate the derivative at point 6, etc. For our purposes it is not necessary to fit a polynomial to the entire set of data. The only purpose of the polynomial approximation is to calculate the local derivatives.

To fit a polynomial we use M points, with $M > N+1$, where N is the degree of the polynomial, and we minimize F. The polynomial is: $Y = f(x) = \sum_{i=0}^{N} k_i X^i$ and F is defined:

$$F = \sum_{l=1}^{M} \left(Y_l - \sum_{i=0}^{N} k_i X_l^i \right)^2. \tag{5}$$

In other words we make a least squares fit.

The minimization of equation (5) can be accomplished by the standard technique of setting the partial derivatives to 0.

$$\frac{\partial F}{\partial k_i} = 0 \tag{6}$$

and solving the resulting normal equations by matrix inversion.

To test the smoothing technique we have run some trials in which the derivatives were calculated by least square polynomials (as described above), Lagrange polynomials (using Lagrange interpolation formulas where $M = N+1$), and the tangent method (i.e., using two neighboring points to calculate the slope). The

Table 1. *Comparison of Derivatives Computed by Different Methods with 1% Noise*

Variable	Point	Exact derivative	Tangent method	Lagrange method	Least squares polynomial method
1	10	−.227	.281	−.338	−.237
	26	.00399	.0604	.0192	.0090
	42	.193	.178	.200	.189
	58	.0188	.0439	.0606	.026
	74	−.221	−.183	−.160	−.221
	90	0.185	.0341	.0339	.0122
2	10	.00228	.0328	.601	−.0137
	26	−.196	−.237	−.257	−.175
	42	.0148	−.0721	−.120	−.0221
	58	.222	.284	.282	.214
	74	−.0221	.0628	.0113	−.021
	90	−.191	−.115	−.0776	−.198

curve used was one generated from the following system of Volterra-Lotka equations.

$$\dot{X}_1 = X_1 - X_1 X_2, \qquad \dot{X}_2 = X_1 X_2 - X_2. \tag{7}$$

Table 1 presents a comparison of some derivatives computed by different methods. The error in each data point was chosen at random from a uniform distribution which varied between 1% and −1% of the Y value at that data point. The results in Table 1 indicate that the least squares polynomial method of computing derivatives is consistently and significantly superior to the other methods. A more detailed discussion of the procedure can be found in reference [5]. The reader is also referred to a discussion of the problem by Ralston [8].

Method Two

Our second method consists of minimizing the function F^B (equation 3)

$$F^B = \sum_m F_m,$$

$$F_m^B = \sum_l W_{m,l}^2 (X_{m,l} - X_{m,l}^*)^2.$$

The $X_{m,l}^*$ are the values calculated by integrating the system equations 1.

The procedure used is as follows:

1. Initial estimates for the parameters are provided. In most cases the initial estimates were the values calculated by method one.
2. The system equations 1 are integrated numerically, using a fourth order Runge-Kutta technique, and F^B is calculated.
3. The global optimization technique of Bremermann [9] is used to improve the estimates.
4. The process is iterated. It is terminated either after a predetermined number of iterations, or after F^B remains approximately constant for several iterations.

The global optimization technique works as follows:

1. F^B is evaluated at the initial estimates for the parameters K.
2. A random direction r, in parameter space is chosen. The probability distribution for each element of r, r_i, is chosen to be Gaussian. In practice it may be desirable to choose the direction in normalized parameter space, that is let the r_i define a percentage change, rather than an absolute change in the parameters. Another possibility is that the logarithms of the parameters be used in place of the parameters.
3. F^B is computed at the values $K^0 + 2r$, $K^0 + r$, K^0, $K^0 - r$, $K^0 - 2r$. These five points define a fourth degree polynomial in a parameter λ. The polynomial is a Lagrangian 5 point approximation of the function F^B on the line $K^0 + \lambda r$.
4. The value of λ, λ_m which gives the minimum of the polynomial is calculated, and the new approximation for the parameter becomes $K = K^0 + \lambda_m r$.

The global optimization method has the advantage over many standard techniques of being able to extricate itself from a local minimum. For a discussion of the convergence properties, the reader is referred to reference [9].

It is shown in references [9] and [5] that the optimization technique performs best when all the unknown parameters are equally well determined. This suggests that an improvement in the efficiency of method two could be made by transforming the parameter values so that the expected error in each is the same. The transformation was performed by weighting the parameters by the reciprocal of the error expected in their evaluations. This latter quantity was calculated by the technique described below. This variation on method two will be referred to as method two B, and the results of a trial with this method are presented in the section on test systems.

Technique for Calculating the Accuracy of the Parameter Estimates

We have utilized the technique of Rosenbrock and Storey [1] for evaluating the accuracy of the parameter estimates.

The method works as follows: Let the system be denoted by $\dot{X}=f(X, K, t)$ where X is the vector of state variables, K is the vector of the parameters, $K=(k_1, k_2, \ldots)$.

Let the function F^B be minimized, and assume that the errors in the parameter estimates are reasonably small so that if $\dot{X}$ is expanded in a Taylor series around K, and only the first order terms are retained, a good approximation is obtained.

The details of the derivation and the method of calculation are presented in reference [1]. Here we state only the results.

Let a matrix $D(t_l)$ be defined for the time of each measurement t_l by

$$D_{ij}(t_l)=\frac{\partial X_i}{\partial k_j}(K, t_l) \tag{8}$$

and let the matrix H be defined by

$$H=\sum_{l=1}^{m} D_l^T W_l D_l \quad \text{and} \quad P=H^{-1} \tag{9}$$

where W_l is the weighting function for each data point. Then σ_i^2, the expected variance for the i-th parameter is

$$\sigma_i^2=P_{ii}. \tag{10}$$

The errors predicted by equation (10) are the errors expected if the optimal parameters are actually found, that is if the exact minimum of F_B is located. The proximity of the actual errors to the predicted errors gives an indication of the efficacy of the parameter estimation technique.

In studying the effectiveness of a parameter estimation technique, it is necessary to compare the actual errors with the expected errors. An effective technique will

find parameter values with errors in the neighborhood of the predicted errors, while for an ineffective technique the errors will be significantly larger. Moreover, the effectiveness of a technique may depend strongly on the errors in the data. For example, several of the techniques similar to method one performed well when there was little or no noise in the data, but performed very poorly when there was a slight increase in the noise. For all our studies on test systems both the actual and predicted errors are included.

Results of Experiments with Test Systems

To test our algorithms and the error prediction technique it is necessary to know the true values of the parameters. This is not possible with actual experimental systems. Therefore, we have constructed test systems from which artificial data points were generated and perturbed to include noise in the data.

First, a system of differential equation is chosen, which we then integrate numerically, using a fourth order Runge-Kutta technique. Noise, simulating experimental errors, was added to the data, according to the formula

$$X_{m,l} = X^0_{m,l}\left(1+(R-.5)\frac{2E}{100}\right) \tag{11}$$

where $X^0_{m,l}$ is the exact data point, $X_{m,l}$ is the data point perturbed by noise, R is generated by an algorithm that generates random numbers between 0 and 1 with a uniform distribution.

Thus if the maximum percentage error in the data for a particular experiment is E, then the error at each data point will be between $E/100$ times the value of the data point and $-E/100$ times the value of the data point. The distribution between extremes is uniform. The amount of noise in the data will be referred to by E, i.e., a system with $E\%$ noise is one which the error varies between $\frac{E}{100}$ and $\frac{-E}{100}$ of the value of the data point.

Test System 1 Volterra-Lotka System

The first system studied is a Volterra-Lotka system. It is described in a paper by Bellman et al. [10] in which the authors detail the results of using the quasi-linearization technique to estimate the parameters. The equations for the system are

$$\begin{aligned}\dot{X}_1 &= k_1 X_1 - k_2 X_1 X_2\\ \dot{X}_2 &= k_3 X_1 X_2 - k_4 X_2.\end{aligned} \tag{12}$$

The initial conditions are $X_1(0)=1.2$, $X_2(0)=1.1$. The time interval was from 0 to 10 time units, with 100 observations made at equally spaced intervals. A graph of the system appears in Fig. 1.

In Table 2 we present the results of using method one to evaluate the parameters for noise values of 1% and 10% (Fig. 1).

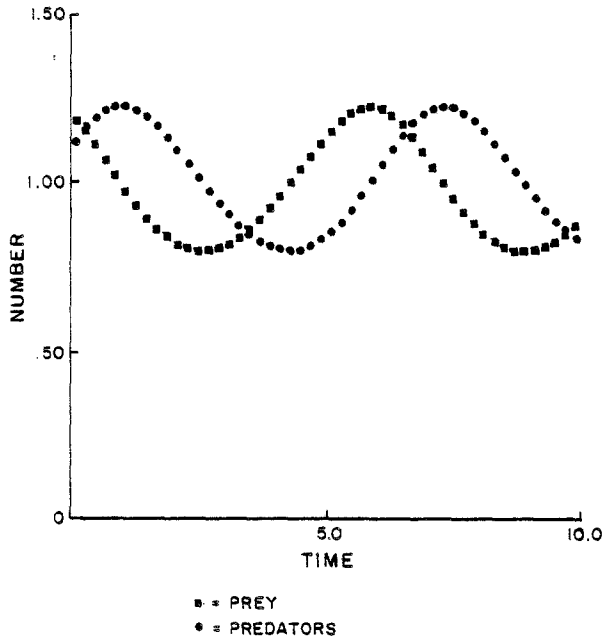

Fig. 1. Prey and predator for Volterra system

Table 2. *Results of Using Method One to Evaluate Parameters for Volterra-Lotka System (Test System 1). In Each Case the Exact Value for Parameters is 1.0*

Parameter	Value of error using method 1	Data Noise
1	5.6×10^{-4}	0%
2	5.6×10^{-4}	
3	3.0×10^{-4}	
4	3.0×10^{-4}	
1	7.9×10^{-3}	1%
2	8.5×10^{-3}	
3	-7.6×10^{-3}	
4	-7.1×10^{-3}	
1	−.12	10%
2	−.10	
3	−.22	
4	−.21	

We note that the results are, in general, good, and that the accuracy decreases with increasing noise. The total time required on the C.D.C. 6400 computer for method one was 5.5 seconds.

We then used method two to improve the results found by method one in the case with 10% noise. Forty five iterations were used requiring 32 seconds

computer time. The iteration process was terminated in this case (and for the other systems investigated) when F^B remained approximately constant over several iterations. In Table 3 the results of this computation are displayed along with the expected error values, and the values determined by Bellman et al., using the quasi-linearization method [10].

Table 3. *Results of Using Method Two on the Volterra-Lotka System (Test System 1). Noise = 10%. 45 Iterations Were Used. The Exact Value for Each Parameter = 1.0. A Comparison with the Results Obtained by Quasi-Linearization Is Included*

Parameter	Starting value	Found by method 2	Error with method 2	Error with quasi-lin.	Expected error
1	0.885	1.016	.016	−.018	.035
2	0.899	0.967	−.033	.026	.034
3	0.782	0.963	−.037	.065	.038
4	0.790	0.993	−.007	.019	.038

Our results using method two show a significant improvement over those obtained by method one, and compare favorably with those obtained by quasi-linearization. The errors are equal to or less than the errors predicted by the Rosenbrock and Storey technique.

The total time required on the C.D.C. 6400 to produce these results, using no initial guesses, was about 37 seconds. Results with similar accuracy were produced with the quasi-linearization technique in about two minutes on the I.B.M. 7044. The quasi-linearization technique requires reasonably accurate initial estimates for the parameters, and the authors do not report the initial estimates they used.

Test System 2; Linear, Chemical System

The next system studied is a linear system of coupled chemical reactions taken from a paper by Himmelblau et al. [11]. The equations describing the system are

$$\begin{aligned} \dot{X}_1 &= k_2 X_2 - k_1 X_1 \\ \dot{X}_2 &= k_1 X_1 - k_4 X_3 - (k_2 + k_3) X_2 \\ \dot{X}_3 &= k_3 X_2 - k_4 X_3 . \end{aligned} \tag{13}$$

31 data points were used, spaced at intervals of .1 time units. The initial conditions were $X_1(0) = 1$, $X_2(0) = X_3(0) = 0$. Fig. 2 shows variables 1 and 2 as a function of time.

In Table 4 we present the results of using our identification methods on this system for 5 percent noise. The table includes the results using method one, the results using method two starting with the values found by method one, and the expected errors. Thirty interations of the second method were used requiring a total time of 14.2 seconds (Fig. 2).

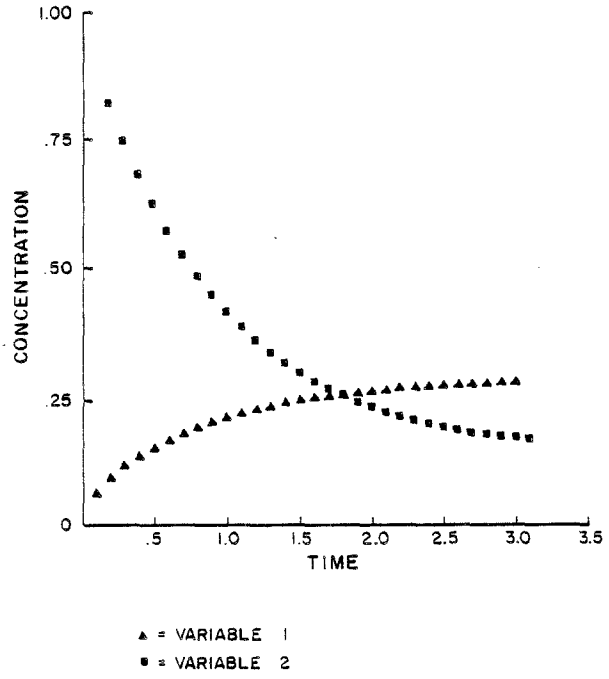

Fig. 2. Test system 2

Table 4. *Results of Using Parameter Estimation Techniques on Test System 2: Linear, Chemical System*

Parameter	Exact value	Error using method one	Error using method two	Expected error
1	1.0	−.041	.012	.0095
2	0.5	−.040	.021	.014
3	10.0	−.61	−.17	.31
4	5.0	−.39	.07	.18

The results show that our methods of parameter estimation used in conjunction have produced parameter values with good accuracy (the errors are in the same range as the expected errors) in a small amount of time. It is also worthwhile to note that this system is linear. Although there are special techniques available to handle linear systems, these frequently do not work well. The results from this system demonstrate that our methods can be effective on linear systems.

Another test system studied is taken from a paper by Garfinkel [11] on simulations of ecosystems. It is a model of a two trophic level ecosystem with one herbivore (X_3) eating two types of grass (X_1 and X_2). The equations for the system are

$$\begin{aligned} \dot{X}_1 &= k_1 X_1 - k_2 X_1 X_3 - k_3 X_1^2, \\ \dot{X}_2 &= k_4 X_2 - k_5 X_2 X_3 - k_6 X_2^2, \\ \dot{X}_3 &= \tfrac{1}{20} k_2 X_1 X_3 + \tfrac{1}{30} k_5 X_2 X_3 - k_7 X_3 - k_8 X_3^2. \end{aligned} \tag{14}$$

100 data points, spaced at intervals of .036, were used. The starting values were $X_1(0)=5\times10^4$, $X_2(0)=5\times10^4$, $X_3(0)=2.5\times10^3$. Fig. 3 shows X_1 and X_2 as a function of time. The exact parameter values are: $k_1=1.0$, $k_2=1.0\times10^{-3}$, $k_3=1.0\times10^{-5}$, $k_4=1.2$, $k_5=1.0\times10^{-3}$, $k_6=1.2\times10^{-5}$, $k_7=1.0$, $k_8=8.0\times10^{-5}$. For this system both method two and the variation of method two (method two *B*) in which the parameters are weighted inversely by the expected error, were used to improve the values found with method one. Method two *B* was tried because the percentage errors found with method one for two of the parameters were unexpectedly large, and the use of method two was unable to improve these values. The results for 9% maximum noise are presented in Fig. 4. For each version of method two, 18 iterations were used, requiring 79 seconds on the C. D. C. 6400 (Figs. 3 and 4).

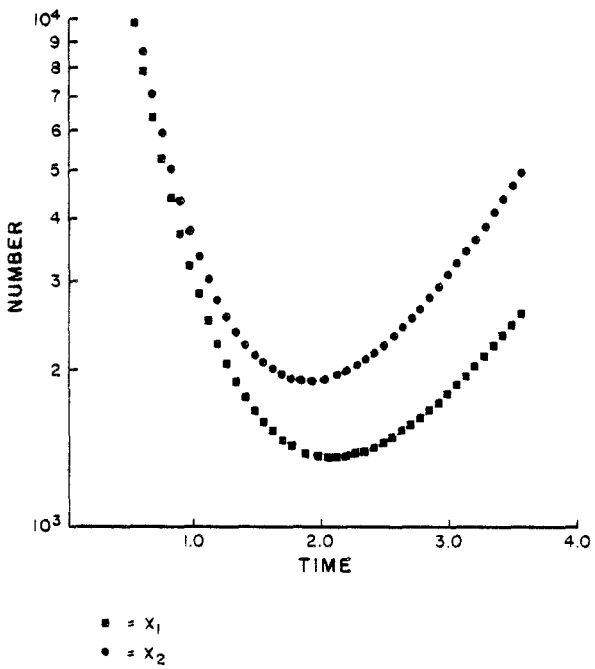

Fig. 3. Variables 1 and 2 for Grasseater system

The results were generally good, with the error in the final value, in most cases being in the neighborhood of the predicted error. In the cases of parameters 3 and 6, for which the errors with method one were large, method two *B* was able to improve the accuracy of the values significantly, whereas method two was unable to produce improvement. These results indicate that weighting the probe step in the optimizing technique by the expected error does in fact improve its effectiveness.

A final test system studied is a model for inducible enzyme synthesis discussed in a paper by Roth and Roth [12]. In reference [12] Roth and Roth discuss the results of using the quasi-linearization algorithm to identify the parameters for the system.

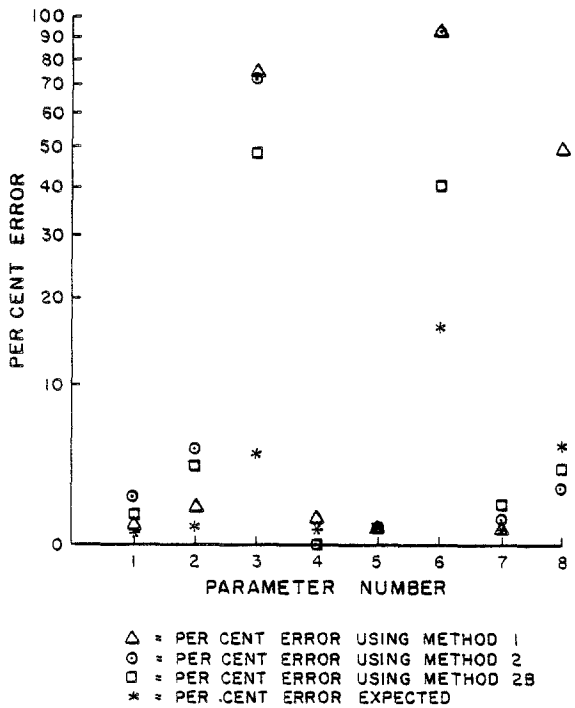

Fig. 4. Results of parameter evaluations on Grasseater system (test system 3). 100 date points used. Noise = 9%

Their calculations, in general, were unsuccessful, even when exact data was used. Using our methods, we were able to identify the parameters when there was no noise in the system, but had poor results when even a small amount of noise was added to the data. The difficulty in this case apparently stems from the fact that the system is extremely ill-conditioned. It is possible that the parameters could be determined if the initial conditions were changed.

Accucary of Parameter Estimates for Sums of Exponentials

Compartment analysis and numerous chemical, biological, and biomedical problems require the fitting of sums of exponentials to data. Unfortunately this task is highly ill conditioned if the exponents are of the same order of magnitude. Lanczos [13] (among others) has analysed this problem exemplified by the following example:

$$X(t) = k_1 e^{-k_4 t} + k_2 e^{-k_5 t} + k_3 e^{-k_6 t} \tag{15}$$

$k_1 = .0951$ $\quad k_4 = 1.0$
$k_2 = .8607$ $\quad k_5 = 3.0$
$k_3 = 1.5576$ $\quad k_6 = 5.0$

Following Lanczos we have simulated this system over 1.2 time units with 24 equally spaced data points, with a random error at each data point uniformly distributed between -0.005 and 0.005. The values at the data points ranged from 2.5 to 0.6, thus the maximum error at each point ranged from .2% to .83%, an accuracy rarely met under experimental conditions. We calculated the expected errors for the parameter estimates with the method of Rosenbrock and Storey and obtained predicted errors between 120% and 3000%. Calculations with our algorithms bore out these error estimates. This enormous amplification of small errors in the data is intrinsic to the problem and does not depend upon the specific computational method used. Inspite of this fact new computational algorithms for fitting sums of exponentials keep on being published while the effect of noisy data on parameter accuracy is often completely neglected. Since experimental errors are rarely as small as our simulated errors, results based on exponential fits may be so much in error as to be meaningless.

Paramecia System

We applied some of our techniques to a system of competing species of paramecia. Vandermeer [14] studied the growth of four species, individually, in pairwise competition, and in four way competition, and attempted to fit the logistic equation to the data. For one species growing alone the equation is

$$\frac{dN}{dt} = \frac{r N (K-N)}{K} \tag{16}$$

N is the number of organisms, r is the growth constant, K is the saturation constant.

In order to put the equation in a form in which $\frac{dN}{dt}$ is linear in the parameters, we have written equation 16 as

$$\frac{dN}{dt} = k_1 N - k_2 N^2. \tag{17}$$

When there are m competing special equation (17) becomes

$$\frac{dN_i}{dt} = r_i N_i - s_i N_i^2 - \sum_{j=1}^{m} k_{ij} N_i N_j. \tag{18}$$

Vandermeer used the technique described by Gause [15] to estimate the parameters. Since this procedure requires drawing a smooth curve through the data by eye, and the separate estimation of the parameters rather than using all the data together to determine the best fit, it is likely to be somewhat inaccurate. We used our method two to calculate the parameters for the system under several conditions.

In Table 5 the values of the parameters calculated by the Gause method and method two are compared for individual growth*. In Table 6 interaction

* In Fig. 5 a comparison between the number observed and the number predicted by the model for species PB growing alone is presented. The curves for the other species are similar, and this one is presented as a representative example.

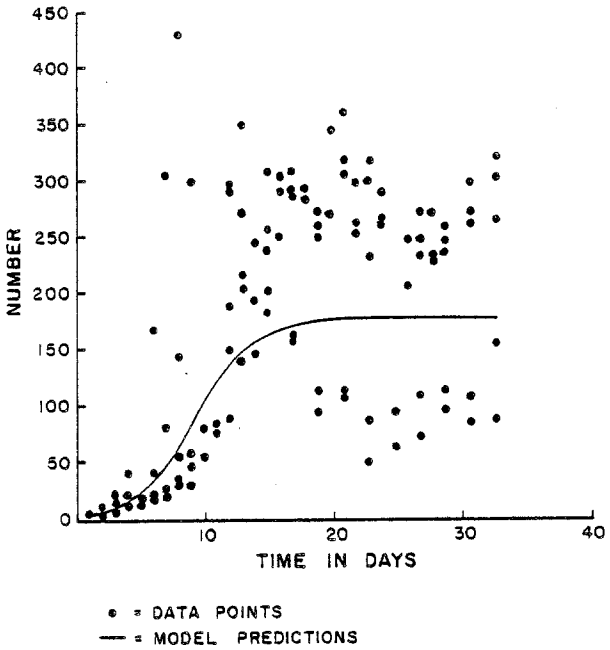

Fig. 5. Species PB alone

coefficients calculated by each method are presented. k_{ij} is the interaction coefficient measuring the effect of the j-th species on the i-th species. The expected errors are given in the cases in which they were calculated. Twenty-six iterations were used in each case, with the values found using the Gause method as the starting values.

1 represents species PA, 2 represents species PB,
3 represents species PC, 4 represents species BL.

Table 5. *Results of Using Method Two to Calculate Parameters of Logistic Equation for Individual Growth for Paramecia System*

	Parameter	Found by Gause method	Found by method two	Expected error
1. Species PA	1	1.05	.809	.008
	2	1.51×10^{-3}	1.068×10^{-3}	$.0028 \times 10^{-3}$
2. Species PB	1	0.470	0.546	
	2	2.04×10^{-2}	2.58×10^{-3}	
3. Species PC	1	1.07	1.27	.02
	2	2.90×10^{-3}	3.41×10^{-3}	$.16 \times 10^{-3}$
4. Species BL	1	0.91	0.95	
	2	4.7×10^{-3}	5.2×10^{-3}	

Table 6. *Results of Using Method Two to Calculate Interaction Coefficients for Paramecia System. k_{ij} is the Interaction Coefficient Measuring the Effect of the J th Species on the I th Species*

Parameter	Value X 10^{-3} found by Gause method	Value X 10^{-3} found by method two
k_{12}	−2.13	−2.12
k_{13}	1.86	1.64
k_{14}	6.71	7.44
k_{21}	1.27	1.23
k_{23}	22.0	2.12
k_{24}	1.29	1.46
k_{31}	1.03	−.065
k_{32}	1.70	1.41
k_{34}	2.04	−8.58
k_{41}	1.25	1.19
k_{42}	−2.50	3.29
k_{43}	3.00	2.60

In some cases there is good agreement between the parameters found by the two methods, while in others the parameters differ greatly. Twentysix iterations were used in each case to calculate the interaction coefficients.

The parameters computed above were used to simulate 4 way competition between all the species. The simulations do predict the general trend of the data, i.e., that species *PB* and *BL* become extinct while species *PA* and *PC* survive. The actual fits are, however, poor, indicating the inadequacy of the model.

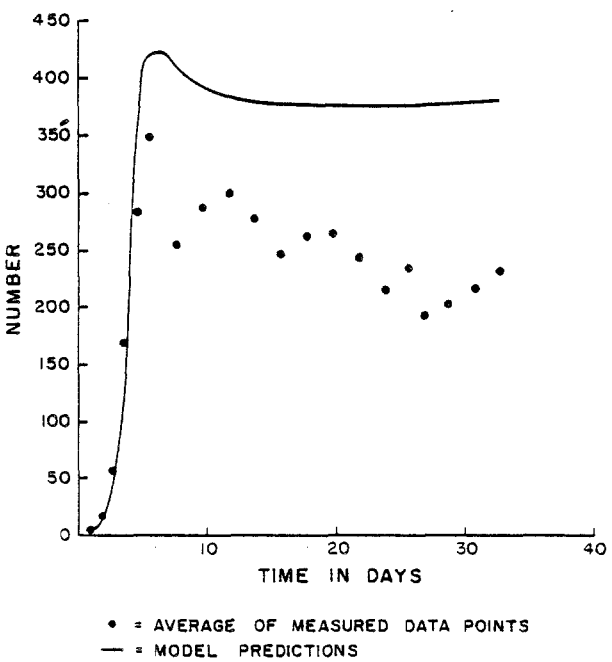

Fig. 6. Species PC in 4-way competition

The results of the simulation for species *PC* and *BL* are presented in Figs. 6 and 7. These are the best fits, one for a case in which the species persists, and one for a case in which it becomes extinct (Figs. 6 and 7).

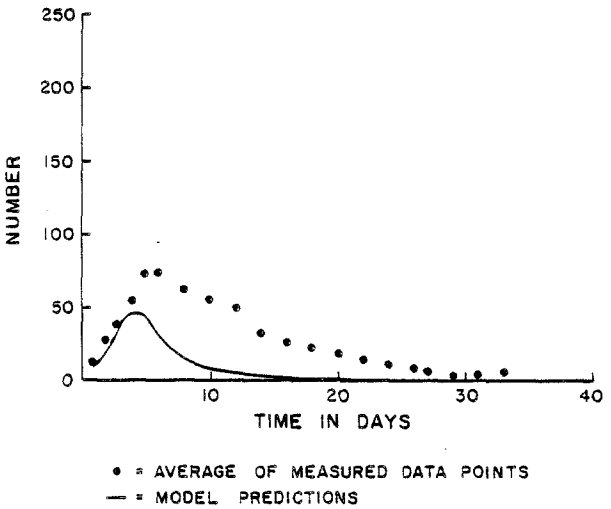

Fig. 7. Species BL in 4-way competition

Summary

Two new procedures for parameter estimation have been demonstrated, and have been shown to work well on a range of test systems. The first technique involves smoothing the curve of the state variables in order to calculate the derivatives from the curve, and is suitable for finding initial parameter estimates. The second technique, based on the global optimization technique of Bremermann, has been used to improve parameter values found by the first method.

In addition, calculation of the expected accuracy of the parameter estimates have been made. This has been done with a technique by Rosenbrock and Storey. These have been compared with the accuracy actually attained by our methods, and in many cases the accuracy of our parameter estimates compare favorably to the predicted accuracy. This calculation has been used to demonstrate the difficulty of identifying the parameters in systems whose solutions are sums of exponentials.

References

[1] Rosenbrock, H., Storey, C.: Computational Techniques for Chemical Engineers. Oxford: Pergamon Press 1966.
[2] Davis, R., Ottaway, J.: Applications of optimization procedures to tracer kinetic data. Math. Bios. I. *13*, 265 (1972).
[3] Swann, W. H.: A survey of non-linear optimization techniques. F. E. B. S. Letters *2*, 539 (1969).
[4] Himmelblau, D. M., et al.: Determination of Rate constants for complex kinetic models. Ind. Eng. Chem. Fundam. *6*, 539 (1967).

[5] Swartz, J.: Parameter estimation in biological systems. Ph. D. Thesis, University of California, Berkeley, 1973.
[6] Chandler, J., et al.: A program for efficient integration of rate equations and least-squares fitting of chemical reaction data. Comput. Biomed. Res. *5*, 515 (1972).
[7] Squire, W.: A simple integral method for system identification. Math. Biosi. *10*, 145 (1971).
[8] Ralston, A.: A First Course in Numerical Analysis. New York: McGraw-Hill 1965.
[9] Bremermann, H.: A method of unconstrained global optimization. Math. Biosi. *9*, 1 (1970).
[10] Bellman, R., et al.: Inverse problems in ecology. J. Theoret. Biol. *11*, 164 (1966).
[11] Garfinkel, D.: A simulation study of the effect on simple ecological systems of making rate of increase of population density-dependent. J. Theoret. Biol. *14*, 46 (1967).
[12] Roth, R., Roth, M.: Data unscrambling and the analysis of inducible enzyme synthesis. Math. Biosi. *5*, 57 (1969).
[13] Lanczos, C.: Applied Analysis. Englewood Cliffs, N.J.: Prentice-Hall 1956.
[14] Vandermeer, J.: The competitive structure of communities: an experimental approach with protozoa. Ecology *50*, 362 (1970).
[15] Gause, G.: The Struggle for Existence. New York: Hafner 1934, reprinted 1964.

Dr. J. Swartz
School of Public Health
Environmental Health Sciences
University of California
Berkeley, CA 94720, U.S.A.

Prof. H. Bremermann
Department of Mathematics
University of California
Berkeley, CA 94720, U.S.A.