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Estimation of Parameters in a Non-linear Model

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ABSTRAK

Pelbagai proses kimia dan biologi boleh dirangkapkan dalam bentuk fungsi tak linear yang mengandungi beberapa eksponen. Satu kaedah yang cekap tetapi kurang digunakan untuk menentukan parameter-parameter di dalam fungsi tersebut ialah dengan memadankan data kepada suatu model. Kertas kerja ini menghuraikan penggunaan subrutin NAG, EO4HFF dan LSFUN2 bagi analisis data yang disimulasi dan mengandungi dua eksponen. Data itu juga mengandungi selisih bebas bertabur normal. Bagi sisihan dengan selisih piawai kurang daripada 0.3, kaedah ini menyakinkan dan cekap. Pekali-pekali linear dan pemalar masa yang pendek boleh ditentukan dengan kejituan melebihi 98%. Apabila sisihan piawai melebihi 2.0, selisih-selisih di dalam parameter boleh melebihi 12%.

ABSTRACT

A wide variety of chemical and biophysical processes are describable in a non-linear function consisting of a number of exponentials. An efficient but seldom-used method to estimate the parameters is by fitting the data to a model. This paper describes the use of NAG subroutines E04HFF and LSFUN2 for the non-linear analysis of simulated data which conform to a model consisting of two exponentials. The data have been generated with independent and normally distributed errors. For errors with standard deviation less than 0.3, the method proves to be reliable and efficient. The linear coefficient and the shorter time constant have been obtained with an accuracy better than 98%. However, when the standard deviation of the error is greater than 2.0, the error in the estimated parameters can be as large as 12%.

Keywords: NMR non-linear, data fitting

INTRODUCTION

Some experiments in physical and biophysical sciences yield data which can be expressed as a sum of exponentials. Fitting the data to a model enables the identification of the system or the determination of the parameters of the model. In a biological system, one may use a mathematical model to describe the concentrations and amount of a substance as a function of time. In medicine and physiology, compartmental analysis is often used to study

the turnover of radioactive substrates (Goodman and Noble 1969; Phang *et al.* 1969) A typical mathematical model which generally conforms to problems cited above takes the form of

$$S(t) = \Sigma M_j e^{-\lambda_j t}, \ (j = 1, 2 .... P), \qquad (1)$$

where S(t) is the data taken at time t ; M_j and λ_j are the parameters to be determined, and P is the number of terms corresponding to the number of compartments.

If the model consists of two exponentials, then equation (1) takes the form of

$$S(t) = M_1 e^{-\lambda_1 t}, + M_2 e^{-\lambda_2 t} \qquad (2)$$

The common procedure for determining parameters M_1, M_2, λ_1 and λ_2 is to plot $\ln S(t)$ against time t. The values of M_2 and λ_2 are determined (Jacquez 1972), respectively, from the intercept and from the linear slope of the last part of the curve at very long time t. Extrapolating $M_2 e^{-\lambda_2 t}$ and subtracting it from S(t) at all points gives a new function S'(t). If the latter is plotted again as above, a second pair of M_1 and λ_1 is obtained. Thus at the first step, the method assumes that λ_2 is sufficiently smaller than λ_1 for the term $M_2 e^{-\lambda_2 t}$ to dominate the decay curve as $t \rightarrow 0$. The method also assumes that the data is error free. However, the process of linearization may produce inconsistent variance (Bevington 1969; Leipert and Marquart 1976), and thus the most accurately determined coefficients are those obtained in the first step.

This paper illustrates the reliability and the ease of using a computer program to estimate the parameters in functions containing one or two exponentials. Originally the program was prepared to determine the NMR relaxation times from either inversion recovery (IR) or the Carr-Purcell-Meiboom-Gill (CPMG) experiments. The method uses the modified Gauss-Newton algorithm. The advantages over the graphical techniques are (a) that the data need not be error free, (b) that there exists a statistical basis for accepting or rejecting the model and (c) that all parameters are determined simultaneously and are therefore subject to equal error.

The Modified Gauss-Newton Algorithm

If the data contain errors, equation (2) has to be modified as

$$S(t) = \varepsilon + M_1 e^{-\lambda_1 t}, + M_2 e^{-\lambda_2 t} \qquad (3)$$

Provided the errors in the data are small, the most reliable method of fitting the data involves minimization of a sum of squares (Atkins 1969), given by

$$E = \sum_{i=1}^{n} \left[Y_i(t) - S_i(t, P_j) \right]^2 \tag{4}$$

P_j represents λ's and M's, and Y_i (t) is the data at this point. In vector form, equation 4, takes the form of

$$E\ (\bar{P}) = \sum_{i=1}^{n} f_I^2\ (\bar{P}) \tag{5}$$

where $f_I = \left[Y_i - S_i(\bar{P}) \right]$ and $\bar{P}$ denotes the vector values of P_j. At each point i, the modified Gauss-Newton algorithm linearizes the function $S_i(\bar{P})$ about the current value $\bar{P}$ by means of a first-order Taylor series expansion.

$$S\ (\bar{p} + \triangle\ \bar{p}) = S\ (\bar{p}\ ) + \frac{d\bar{s}}{d\bar{p}} (\triangle\ \bar{p}) \tag{6}$$

Here $\frac{d\bar{s}}{d\bar{p}}$ is the Jacobian J of $n \times J$ matrix of partial derivatives S with respect to all parameters . Equation (4) then becomes

$$E\ (\bar{p} + \triangle\ \bar{p}) = \sum_{i=1}^{n} f_I^2\ \ (\bar{p} + \triangle\ \bar{p}) \tag{7}$$

Minimizing E in 7 with respect to all P's will produce the gradient vector,

$$g\ (\bar{p}) = \begin{vmatrix} -2 \sum_{i=1}^{n} f_i\ \ (\bar{p}) \dfrac{\partial f_i}{\partial f_I} (\bar{p}) \\ -2 \sum_{i=1}^{n} f_i\ (\bar{p}) \dfrac{\partial f_i}{\partial f_2} (\bar{p}) \\ -2 \sum_{i=1}^{n} f_i\ \ (\bar{p}) \dfrac{\partial f_i}{\partial f_j} (\bar{p}) \end{vmatrix}$$

$$= -2J^{\mathrm{T}}\ (\bar{p})\ f\ (\bar{p}) \tag{8}$$

The approximation of the gradient at the point

$\bar{P}_{k+1} = \bar{P}_k + \triangle\ \bar{p}$ is given as

$$g(\bar{p} + \triangle \bar{p}) = -2J^T(\bar{p}) f(\bar{p}) + 2J^T(\bar{p}) J(\bar{p}) \triangle \bar{p} \quad (9)$$

(Scale 1985). Here $J^T(\bar{p}) J(\bar{p})$ is the first term of the Hessian matrix E. The solution to (9) is obtained when E is minimum. This requires $g(\bar{p} + \triangle \bar{p})$ to be zero, giving

$$\triangle \bar{p}) = \left[J^T(\bar{p}) J(\bar{p}) \right]^{-1} J^T(\bar{p}) f(\bar{p}) \quad (10)$$

EXPERIMENTAL METHOD

A computer program, FORTRAN 77, was written utilizing the national algorithm group (NAG) subroutines E04HFF and LSFUN2. Computation was carried out on the main frame computer, Honey Well 66 at the University of Aberdeen.

Using equation (3), sets of data were generated with $M_1 = 50.0$, $M_2 = 35.0$,

$T_S = \frac{-1}{\lambda_1} = 85.0$, $T_1 = \frac{-1}{\lambda_2} = 263.0$ and $\varepsilon = 0$

Except the first, all sets contain errors with mean zero and standard deviation 0.2. The errors were the random numbers generated by NAG subroutine G05DDF. Results are shown in Table 1. The number of points n was 27.

In order to determine the effect of increasing errors on the accuracy and on the reliability of the fitting procedure, errors with increasing standard deviation were added to the generated data. Results are shown in Table 2. Experiments similar to those described above are being performed using a personal computer PC 386SX. Early results are encouraging, and will be reported subsequently.

RESULTS

Table 1 illustrates the results of the analysis of 12 sets of data. The constant which was set to zero in the data generation appears to fluctuate between 1.46 to -4.83 about the mean value of -0.39. The short time constant T_S is recovered with small variaton from data to data. The long time constant T_1, however, is found to vary within a larger range of values. Its mean and standard deviation are 276.2, and $\pm$ 74.9 ms respectively. The linear coefficients M_1 and M_2 are recovered with errors less than 2%. If the data contain no errors as indicated in the first row of the table, all parameters are perfectly recovered. This proves conclusively that the computation is correct and that the errors in the parameters are solely due to the errors in the data.

Table 2 shows the results on the effect of increasing the error. For standard deviation below 0.5, the coefficients M_1, M_2 and the short time constant T_s are recovered satisfactorily. The long time constant T tends to decrease from 273.9 $\pm$ 11.8 ms to 249.5 $\pm$ 65.7 ms.

The accuracy and the correctness of fit gets worse as the error increases above 1.0. Above these values, the estimated parameters can be in error by as much as 10%.

TABLE 1
Generated data with $M_1 = 50.0$, $M_2 = 35.0$, $T_s = 85$, $T_l = 263$ and $\varepsilon = 0$ with errors of zero mean and standard deviation 0.2

Data	ε	M_1	M_2	T_s	T_l	E
Error Free	0.00	50.0	35.0	85.0	263.0	0.000
1	-0.37	52.4	32.5	88.4	282.4	0.192
2	-0.43	52.6	32.7	86.4	285.8	0.183
3	-4.83	62.2	27.4	95.8	487.4	0.186
4	0.83	52.8	37.5	86.9	236.2	0.175
5	0.51	49.4	36.4	85.6	228.8	0.166
6	1.46	44.4	41.4	76.9	201.2	0.172
7	0.94	48.4	35.5	85.2	241.1	0.218
8	-1.08	54.7	31.3	88.9	309.2	0.222
9	0.35	46.7	38.8	79.4	244.3	0.175
10	-1.11	54.4	31.4	89.3	310.7	0.150
11	-0.10	49.1	36.3	82.8	263.6	0.225
12	-0.81	42.5	41.2	76.9	223.2	0.177
mean	-0.39	50.8	35.2	85.2	276.2	0.188
$\pm$ std.	$\pm$1.63	$\pm$5.3	$\pm$4.2	$\pm$5.5	$\pm$74.9	

This study demonstrates that the only reliable parameters are the linear coefficients M_1, M_2 and the short time constant, provided the errors in the data are small. Computation is thus sensitive to errors. From this finding, it is concluded that great care must be taken in the design of an experiment and in the collection of data.

The correctness of fit is indicated by the fitting error E. The smaller the value of E, the better will be the fit. This is expected to occur. The tolerance of the analysis with the starting point was also tested by varying the initial values of M_1, M_2, T_s and T_l. It is observed that the analysis was not affected as long as the starting point is between 30% - 70% of the parameter real values.

TABLE 2
Effect of increasing the standard deviation of the error on the estimated parameters

	Std	ε	M_1	M_2	T_s	T_l	E
Data 1	0.3	0.24 ±	50.9 ±	34.2 ±	86.6 ±	273.9 ±	0.323
		0.47	6.5	7.7	8.6	11.8	
Data 2	0.5	0.97 ±	50.9 ±	34.2 ±	85.1 ±	252.9 ±	0.942
		0.66	0.6	0.5	0.8	12.9	
Data 3	1.0	1.14 ±	51.0 ±	34.0 ±	85.9 ±	250.0 ±	1.077
		1.08	1.6	6.5	6.1	70.8	
Data 4	2.0	2.11 ±	54.4 ±	30.8 ±	87.6 ±	249.5 ±	2.156
		1.80	8.7	5.9	7.6	65.7	

CONCLUSIONS

This study examined the reliability and ease of using the modified Gauss-Newton method to analyse simulated data containing independent and normally distributed errors. Satisfactory results, particularly those of the linear coefficients and the short time constant, have been obtained, as long as the errors are small. Such analysis might be categorised as the small residual problem (Jennrich and Ralston 1979). The observation also shows that there is no apparent correlation between the accuracy and the fitting error. This is very clear for T_l. From this observation, it can be concluded that a good fit does not necessarily mean high accuracy in all the estimated parameters.

The ability to resolve the function into its components also depends on the ratio T_l/T_s. According to Atkins (1969), two exponential terms might not be separable if the ratio between the time constants is less than 2. Since the function is non-linear, the accuracy may be affected by the time span of the experiment. Further study is required to examine those factors.

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