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An iterative curve stripping technique for pharmacokinetic parameter estimation

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Non-linear least-squares regression is commonly used for pharmacokinetic parameter estimation. Initial parameter estimates are required as a prelude to non-linear least-squares and the quality of the final parameter estimates may depend on these initial values. Polyexponential curve stripping is frequently used for the provision of initial estimates. It is demonstrated that under certain conditions conventional curve stripping yields biased estimates. A new iterative curve stripping technique is developed and is shown to be free of such bias. The two methods are compared using both simulated and real pharmacokinetic data.

An important element in the analysis and evaluation of the results of a pharmacokinetic study is the fitting of the model (or models) to the data by estimating the model parameters. This should be performed in such a way that the fitted model gives rise to a calculated curve which fits the observations 'best' in some sense. For this purpose the method of non-linear least-squares is generally used and a number of computer programs based on this approach are available (Pfeffer 1973; Metzler et al 1974; Wagner 1975; Pedersen 1977; Gomeni & Gomeni 1979; Peck & Barrett 1979; Messori et al 1983). Non-linear least-squares involves a computerized search procedure which attempts to locate the global minimum on the residual sum of squares (RSS) surface (Bard 1974). The user is required to define a starting point for the search procedure by providing initial estimates of the parameters. These initial parameter estimates are critical if local minima are to be avoided. If the initial parameter estimates are not good the least-squares procedure will not converge on the best values. According to Boxenbaum et al (1974) 'the final parameter estimates will converge to the true estimates *if and only if* the initial estimates were sufficiently close to the true parameter values'. The influence of the initial parameter estimates has been studied by computer simulation techniques (Cobelli & Salvan 1977a,b).

Polyexponential models are frequently used as empirical (Yeh & Kwan 1978) and as mechanistic (Godfrey 1983) models in pharamacokinetics. A number of graphical/numerical techniques have been described (Cornell 1962; Parsons 1968, 1970; Foss 1970; Gomeni & Gomeni 1979; Koup 1981; Smith & Nichols 1983) for the provision of initial parameter estimates for these models. Probably the most popular is the curve stripping technique (Wagner 1975) which is the basis of a number of computer programs (Sedman & Wagner 1976; Brown & Manno 1978; Leferink & Maes 1979; Niazi 1979; le Blanc & Dumas 1983). The curve stripping technique is based on the assumption that the exponential terms may be 'isolated' one at a time and their parameters estimated. This is a reasonable assumption if the relative magnitudes of the exponents are disparate. However, violation of this assumption would be expected to yield biased parameter estimates (Pedersen 1977; Peck & Barrett 1979; Dunne & Wilson 1983). A new iterative approach to curve stripping which makes no such assumption is described in the present paper and compared with the conventional approach as implemented by the computer program CSTRIP (Sedman & Wagner 1976).

THEORY

Assume that the pharmacokinetic behaviour of a particular drug may be described by

$$Y = \sum_{j=1}^{m} C_j \exp(-a_j t) \qquad (1)$$

where Y is the measured response variable (e.g. plasma drug/metabolite concentration) at time t following drug administration, m is the number of exponential terms and C_j and a_j are the coefficients and exponents.

Following administration of the drug, Y is measured on n occasions yielding the data set y_i, t_i i = 1, . . . n and before non-linear least-squares curve fitting, initial estimates of the parameters C_j and a_j must be found. Conventional curve stripping approaches this problem as follows: let the exponents be arranged in order such that

$$a_1 > a_2 > a_3 > \ldots > a_m \quad (2)$$

and assume that for t large enough ($t > T_1$), the first $m - 1$ exponential terms have decayed i.e.

$$\sum_{j=1}^{m-1} C_j \exp(-a_j t) = 0 \qquad t > T_1 \quad (3)$$

then

$$Y = C_m \exp(-a_m t) \qquad t > T_1 \quad (4)$$

hence

$$\ln Y = \ln C_m - a_m t \qquad t > T_1 \quad (5)$$

and a semilogarithmic plot of the terminal observations (y_i, t_i) should be linear with intercept $\ln C_m$ and slope $-a_m$. Consequently linear least-squares regression may be used to produce estimates $\hat{C}_m$ and $\hat{a}_m$. The first set of residuals ($R_{1,i}$) are then calculated by subtracting the estimated values of the last exponential term at the earlier time points from the observed values as follows

$$R_{1,j} = y_i - \hat{C}_m \exp(-\hat{a}_m t_i) \quad t_i < T_1 \quad (6)$$

These residuals correspond to the reduced model consisting of the first $m - 1$ exponential terms i.e.

$$R_1 = \sum_{j=1}^{m-1} C_j \exp(-a_j t) \quad (7)$$

Assuming that for t large enough ($t > T_2$) the first $m - 2$ exponential terms have decayed i.e.

$$\sum_{j=1}^{m-2} C_j \exp(-a_j t) = 0 \qquad t > T_2 \quad (8)$$

then

$$R_1 = C_{m-1} \exp(-a_{m-1} t) \quad t > T_2 \quad (9)$$

hence

$$\ln R_1 = \ln C_{m-1} - a_{m-1} t \quad t > T_2 \quad (10)$$

and a semilogarithmic plot of the terminal residuals may be used to produce estimates $\hat{C}_{m-1}$ and $\hat{a}_{m-1}$.

Continuing in this manner, further sets of residuals are computed until all the parameters have been estimated. The above procedure is based on the assumption that for t large enough ($t > T_k$) the first $m - k$ exponential terms have decayed i.e.

$$\sum_{j=1}^{m-k} C_j \exp(-a_j t) = 0 \quad t > T_k \quad (11)$$

and consequently that the exponential terms may be 'isolated' one at a time and their parameters estimated. This assumption is approximately satisfied if

$$a_1 \gg a_2 \gg a_3 \ldots \gg a_m \quad (12)$$

i.e. if the relative magnitudes of the exponents are disparate.

It would be unnecessary to assume that the fast exponentials had decayed completely (equation (11) above) if they could be evaluated and subtracted from the data to produce 'corrected' data i.e.

$$R^*_{k-1,i} = R_{k-1,i} - \sum_{j=1}^{m-k} C_j \exp(-a_j t_i) \quad (13)$$

or

$$y^*_i = y_i - \sum_{j=1}^{m-1} C_j \exp(-a_j t_i) \quad (14)$$

as appropriate.

Unfortunately, the second term on the right hand sides of equations (13) and (14) cannot be evaluated since the unknown parameters C_j and a_j are involved. If initial estimates of the parameters are used in equations (13) and (14) and the 'corrected' data curve stripped, it may be better than assuming that these terms are zero. Hence the technique may be applied in an iterative fashion as follows:

(a) obtain parameter estimates making assumption (11) above,
(b) 'correct' the data as in equations (13) and (14) using these estimates in place of the parameters,
(c) obtain a new set of parameter estimates by curve stripping the 'corrected' data,
(d) repeat steps (b) and (c) until the parameter estimates fail to improve by a specified amount. Because this procedure makes allowance for the overlap of the exponential terms, no assumption regarding the relative magnitudes of the exponents is necessary.

A computer program called JANA has been developed for the implementation of this iterative curve stripping procedure (Dunne 1985).

METHODS

Simulated experiments were performed by generating data using the appropriate model and adding pseudorandom normal errors. The GGNQF normal random deviate generator (IMSL 1980) was used to produce the errors. In the case of 'noise free' data, the model predicted values (rounded to three places of decimal) were used without any added error.

CSTRIP and the non-linear least-squares program NONLIN (Metzler et al 1974) were run on a DEC-20 mainframe computer. JANA was run on an Apple IIe microcomputer. Curve fitting by NONLIN used the true parameter values as initial estimates.

Since non-linear least-squares can be considered the optimal estimation procedure, the superiority of JANA over CSTRIP was quantified for each data set by calculating

$$S\% = 100.\,(RSS(C) - RSS(J))/(RSS(C) - RSS(N)) \quad (15)$$

where RSS(C), RSS(J) and RSS(N) refer to the residual sums of squares following curve fitting with CSTRIP, JANA and NONLIN, respectively.

RESULTS

Noise free data were generated using a biexponential model corresponding to intravenous drug administration i.e.

$$y = C_1 \exp(-a_1 t) + C_2 \exp(-a_2 t) \qquad (16)$$

with $C_1 = C_2 = 50$, $a_1 = 0{\cdot}10$ and $a_2 = 0{\cdot}02$. There were fifteen data points at t = 0, 1, 2, 3, 4, 5, 7, 10, 15, 20, 30, 50, 75, 100 and 150 units. The data were analysed by CSTRIP and JANA and the results are summarized in Table 1 (Experiment 1). This experiment was repeated three times with the ratio of the exponents (a_1/a_2) decreasing towards unity. These results are also tabulated in Table 1. A biexponential model corresponding to extravascular drug administration without a lag time was used to generate noise free data at the same fifteen sample times as described above. The two coefficients were −50 and +50 and the ratio of the exponents was varied from 5 to 2. The parameters were estimated for each data set using CSTRIP and JANA and the results are summarized in Table 2.

Table 1. Results of curve stripping of computer simulated data. The noise free data were generated from a biexponential (intravenous drug administration) model with the parameter values labelled 'true'. CSTR and JANA are the parameter estimates produced by CSTRIP and JANA, respectively. RSS refers to the residual sum of squares.

Experiment		Parameter C_1	a_1	C_2	a_2	RSS
1	True	50·00	0·10	50·00	0·02	
	CSTR	49·68	0·105	51·00	0·020	0·942
	JANA	50·00	0·100	50·00	0·020	1·12E-6
2	True	50·00	0·06	50·00	0·02	
	CSTR	42·43	0·072	58·40	0·021	2·292
	JANA	50·01	0·060	49·99	0·020	1·30E-6
3	True	50·00	0·04	50·00	0·02	
	CSTR	25·04	0·059	75·48	0·023	1·525
	JANA	49·96	0·040	50·04	0·020	1·30E-6
4	True	50·00	0·03	50·00	0·02	
	CSTR	8·10	0·060	92·22	0·023	0·472
	JANA	49·96	0·030	50·04	0·020	1·59E-6

CSTRIP and JANA were compared using simulated data to which homoscedastic pseudorandom normal errors had been added. The biexponential model described by equation (16) with $C_1 = C_2 = 50$, $a_1 = 0{\cdot}03$ and $a_2 = 0{\cdot}02$ was used to generate data at twenty sample times viz, t = 0, 2, 4, 7, 10, 13, 16, 20, 24, 28, 32, 38, 44, 50, 60, 70, 80, 100, 125 and 150 units. Data sets with increasing error levels were generated and analysed with CSTRIP and JANA.

Table 2. Results of curve stripping of computer simulated data. The noise free data were generated from a biexponential (extravascular drug administration) model with the parameter values labelled 'true'. CSTR and JANA are the parameter estimates produced by CSTRIP and JANA, respectively. RSS refers to the residual sum of squares.

Experiment		Parameter C_1	a_1	C_2	a_2	RSS
1	True	−50·00	0·10	50·00	0·02	
	CSTR	−49·80	0·102	49·80	0·020	0·47
	JANA	−50·00	0·100	50·00	0·020	1·45E-6
2	True	−50·00	0·08	50·00	0·02	
	CSTR	−47·20	0·087	47·20	0·020	1·55
	JANA	−50·00	0·080	50·00	0·020	0·66E-6
3	True	−50·00	0·06	50·00	0·02	
	CSTR	−41·70	0·072	41·67	0·019	1·75
	JANA	−50·01	0·060	50·00	0·020	1·26E-6
4	True	−50·00	0·04	50·00	0·02	
	CSTR	−27·59	0·058	27·57	0·016	2·04
	JANA	−50·01	0·040	50·01	0·020	1·30E-6

There were ten data sets at each noise level and the mean value for S% at each noise level is reported in Table 3. In some cases neither CSTRIP nor JANA were able to strip two exponential terms from the data and the mean S% was consequently based on fewer than ten values as indicated in Table 3. The mean number of iterations performed by JANA is also indicated in Table 3.

Table 3. Mean improvement (S%, see text) using JANA for curve stripping, compared with CSTRIP at 7 levels of homoscedastic error. Also shown are the mean number of iterations (IT) performed by JANA. The number of data sets contributing to each mean is indicated in parentheses.

Standard deviation	Mean S%	Mean IT
0·1 (10)	93·66	296·7
0·2 (10)	87·65	157·3
0·4 (9)	72·53	117·9
0·8 (7)	78·48	147·4
1·5 (7)	75·48	34·9
5·0 (6)	66·49	4·7
10·0 (10)	49·92	7·1

Several pharmacokinetic data sets relating to both intravenous and extravascular drug administration were selected from the literature. The particular data sets were chosen because they had previously been used to validate parameter estimation procedures or to compare two or more such procedures.

Data from four human subjects following bolus intravenous pancuronium administration were used (Pedersen 1977, 1978) to compare the non-linear least-squares programs NONLIN and FUNFIT. The same data were also used by others (Muir & Riegelman 1979; Wijnand & Timmer 1979) for comparison of parameter estimation programs. These data would appear to be best described by the sum of two exponential terms. The data were

analysed by CSTRIP and JANA. For two of the subjects (J.C. & I.A.) JANA was unable to improve on the fit by CSTRIP and gave identical results. The results for the other two subjects (M.C. & B.A.) are shown in Table 4.

Table 4. Parameter estimates for biexponential model of bolus intravenous pancuronium data following analysis with CSTRIP (CSTR) and JANA. RSS refers to the residual sum of squares and IT to the number of iterations performed by JANA.

Subject		Parameter					
		C_1	a_1	C_2	a_2	RSS	IT
M.C.	CSTR	0·849	0·038	0·303	0·003	0·013	—
	JANA	0·936	0·034	0·218	0·002	0·009	3
B.A.	CSTR	0·503	0·032	0·204	0·0024	0·008	—
	JANA	0·588	0·025	0·108	0·0003	0·005	2

Oral tetracycline data were used by Sedman & Wagner (1976) and by Brown & Manno (1978) to test the curve stripping programs CSTRIP and ESTRIP, respectively. These data were analysed by CSTRIP and JANA using both biexponential and triexponential models. The results are shown in Table 5.

level in the data increases. This would not be unexpected since the increasing noise would reduce the effectiveness of making a correction for overlapping exponential terms. This would also explain why the mean number of iterations performed by JANA fell as the error level was increased. It is clear from Table 3 that when there is substantial overlapping of exponential terms the advantage gained by using JANA instead of CSTRIP is significant even with noisy data.

JANA was unable to improve on CSTRIP's parameter estimates for two of the four pancuronium subjects. This may have been due to the fact that the error in the data was greater for these two subjects (Pedersen 1977) and swamped the effect of the overlapping term. Another possible explanation is that little or no 'correction' for an overlapping exponential term was required for these subjects. However, this latter explanation must be discounted since one of these subjects (J.C.) had the lowest exponent ratio of the entire group (Pedersen 1977). In the other two cases JANA improved the fit by 30·8% (M.C.) and 37·5% (B.A.) relative to

Table 5. Parameter estimates for biexponential and triexponential models of oral tetracycline data following analysis with CSTRIP (CSTR) and JANA. L refers to the lag time estimate, RSS to the residual sum of squares and IT to the number of iterations performed by JANA.

Oral tetracycline Model		Parameter								
		C_1	a_1	C_2	a_2	C_3	a_3	L	RSS	IT
Biexp	CSTR	−2·135	1·034	2·134	0·129	—	—	0·61	0·027	—
	JANA	−2·277	0·899	2·275	0·133	—	—	0·54	0·017	21
Triexp	CSTR	−2·820	0·897	0·970	0·463	1·850	0·117	0·59	0·027	—
	JANA	−15·426	0·473	14·418	0·400	1·000	0·079	0·40	0·006	50

DISCUSSION

Tables 1 and 2 show that as the ratio of the exponents (a_1/a_2) decreased, the CSTRIP parameter estimates became more biased as expected. It is clear also that the iterative curve stripping implemented by JANA was not subject to this bias.

There is some evidence in Table 3 that as the level of homoscedastic error was increased successful curve stripping became less likely. However, all ten data sets at the highest error level were successfully stripped. Consequently this effect requires further simulation studies for confirmation. Table 3 shows that on average JANA gave parameter estimates which were a significant improvement in terms of fit (as measured by the RSS) on the estimates produced by CSTRIP. It would appear that the benefit of using JANA rather than CSTRIP diminishes as the noise

CSTRIP. JANA improved the fit of biexponential and triexponential models to the oral tetracycline data relative to CSTRIP by 37·0% and 77·8%, respectively.

In conclusion, it is clear that at worst JANA cannot improve upon CSTRIP's parameter estimates and at best may provide parameter estimates which are as good as those arrived at by non-linear least-squares regression. In general it should provide better initial estimates than CSTRIP and thus increase the likelihood of a successful non-linear least-squares fit, with fewer iterations being required.

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