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Numerical Deconvolution by Least Squares: Use of Prescribed Input Functions

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A new method for numerical deconvolution is described, for use in calculating drug input rates. The method is based on the least-squares criterion and is applicable when the input function can be assumed to take a prescribed form. In particular, an exponential input function and an input function derived from the cube-root dissolution law are considered. The stability of the method to data noise is shown by means of examples, using simulated data.

KEY WORDS: numerical deconvolution; linear systems analysis; calculation of drug input rates; calculation of *in vivo* dissolution rates; exponential and cube-root-law inputs; least-squares fitting.

INTRODUCTION

The use of linear systems analysis as a theoretical basis for the study of the *in vivo* performance of drug delivery systems is becoming widespread (1–4). The advantage of this approach is that a detailed description of the structure of the system (for example, using a compartment model) is unnecessary. A disadvantage, however, has been that the available methods for data analysis are highly sensitive to error in the data (5). This article reports a new approach to the numerical treatment of data, based on the least-squares criterion. By means of analyses of simulated data, the method is shown to be very stable to data noise and is therefore likely to be useful in the routine analysis of pharmacokinetic data.

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INTEGRAL EQUATION FOR LINEAR SYSTEMS

For a linear system, the relationship between an input function $P(t)$ and the resulting response $Q(t)$ can be expressed by (3)

$$Q(t) = \int_0^t F(t-T)P(T)\,dT \tag{1}$$

where $F(t)$ is the response to a unit impulse input. The problem considered here is that of estimating the function $P(t)$ when experimental data are available on $F(t)$ and $Q(t)$. This is usually referred to as "numerical deconvolution."

Equation 1 arises in many fields, and the literature on numerical methods for solving this equation is extensive. Gamel *et al.* (5) have conducted a comparative study of a number of methods, applied to the interpretation of dye-dilution data arising from experiments concerned with blood flow measurement. In brief, they concluded that most of the available methods perform satisfactorily with error-free data but that all the methods they studied were very sensitive to data noise, and frequently failed completely (in the sense that the estimated function bore essentially no resemblance to the true function). Benet and Chiang (3) and Wagner (4) have applied the recurrence method suggested by Rescigno and Segre (6) to pharmacokinetic data. Benet and Chiang (3) mention difficulties which arise because of data error but do not explore this matter in any depth. Wagner (4) treats only exact data. In view of the study by Gamel *et al.* (5), the influence of data noise is considered in some detail in the present article.

In the method outlined in the following section the input function $P(t)$ takes a prescribed form (in the numerical examples, an exponential function and a function derived from the cube-root dissolution law). The functional form of $P(t)$ might be indicated by *in vitro* studies (for example, *in vitro* dissolution studies), by a theoretical model, or from previous experience with similar cases. The method provides estimates of the parameters which apply *in vivo.*

In the following article (9) the use of polynomial functions to represent the unknown input function is described. Since a wide range of functions are amenable to approximation by polynomials, this approach depends to only a minor extent on assumptions concerning the functional form of the input. One use of a polynomial approximation is to indicate a suitable functional form for use with the present method.

USE OF THE LEAST-SQUARES CRITERION

In this section a general outline will be given of the use of the least-squares criterion in numerical deconvolution, and two specific cases of relevance to pharmacokinetic studies will be discussed.

For the sake of simplicity of notation, and since the method can be applied to a general class of problems of which equation 1 is an example, linear operator notation will be used. Equation 1 can be written in the form

$$Q(t) = L\{P(t)\} \tag{2}$$

where L denotes a linear operator. We require that the operator L be "known" in the sense that for any known (admissable) function $X(t)$, the function $Y(t) = L\{X(t)\}$ can be evaluated. When $F(t)$ in equation 1 is known, the linear operator defined by this equation satisfies this condition.

Let $P_e(t)$ denote a particular estimate of the required function $P(t)$. The function

$$Q_e(t) = L\{P_e(t)\} \tag{3}$$

can be evaluated. If $P_e(t)$ is, in some sense, "close to" the true function $P(t)$, we expect $Q_e(t)$ to be similarly "close to" the function $Q(t)$. This expectation and a definite meaning for the phrase "close to" are expressed in the least-squares criterion. We define the residual sum of squares R as follows:[2]

$$R = \sum_{r=1}^{m} [Q(t_r) - Q_e(t_r)]^2 \tag{4}$$

where $t_1, t_2, \ldots, t_m$ are the times at which experimental observations of $Q(t)$ are made. The "best" estimate of $P(t)$ is now defined as that which minimizes R. This is what is meant, in the present context, by the least-squares criterion.

Without further assumptions, little progress can be made. The usual approach in data fitting is to assume that the required function has a specific form, which involves certain parameters. The problem is then to find the values of these parameters to achieve the best fit to the data.

[2]Weights can be introduced by writing equation 4 in the form

$$R = \sum_{r=1}^{m} w_r [Q(t_r) - Q_e(t_r)]^2$$

where w_r is the weight attached to the rth data point. In the following, $w_r = 1$, $r = 1, \ldots, m$.

Following this procedure, we assume that $P(t)$ can be written explicitly as a function of the variable t and parameters $c'_1, c'_2, \ldots, c'_n$.

$$P(t) = W(t, c'_1, c'_2, \ldots, c'_n)$$

The estimate $P_e(t)$ is now written in the form

$$P_e(t) = W(t, c_1, c_2, \ldots, c_n) \tag{5}$$

where $c_1, c_2, \ldots, c_n$ are estimates of the parameters $c'_1, c'_2, \ldots, c'_n$. Using equations 3 and 5, equation 4 becomes

$$R = \sum_{r=1}^{m} [Q(t_r) - L_r\{W(t, c_1, c_2, \ldots, c_n)\}]^2 \tag{6}$$

The notation $L_r\{\ \}$ indicates that this expression is to be evaluated at $t = t_r$; thus if $Y(t) = L\{X(t)\}$, $Y(t_r) = L_r\{X(t)\}$.

The right-hand side of equation 6 is a function of the parameters; writing this function as $U(c_1, c_2, \ldots, c_n)$,

$$R = U(c_1, c_2, \ldots, c_n) \tag{7}$$

The required parameter values are those which minimize R. This can be regarded as a general function minimization problem. The difference between this and more common function minimization problems is in the manner in which the function U is evaluated. In the present case, U will not usually be known analytically, but will be evaluated by a procedure which involves the numerical evaluation of the linear operator expression (for equation 1, a numerical integration). The parameter values which minimize R are inserted into equation 5 to give the estimate $P_e(t)$.

There are many ways of approaching the problem of minimizing R. In the examples considered in the following sections, we are dealing with two-parameter functions which can be written in such a way that R depends linearly on one of the parameters. To take advantage of this feature, the axial iteration technique (7) has been used. By this technique, one parameter is fixed and a minimum is found with respect to the other parameter. On the next iteration, the parameter which is varied on the first iteration is fixed while a minimum is found with respect to the other parameter. The process is repeated and the required minimum is approached by steps parallel to each axis in turn. The process is terminated when the change in parameter values on successive iterations is less than a prescribed amount. The shortcomings of the axial iteration technique are discussed by Dixon (7), the major one being the possibility of slow convergence. This was found to be a problem in some cases, but in no case prohibited the use of the method. The advantage of the axial iteration

technique in the present case is that at each step the minimum with respect to the "linear" parameter is easily found. However, the use of other function minimization procedures might prove to be more satisfactory, at least in some cases.

USE OF PRESCRIBED FUNCTIONS

Exponential Function

In this case, we assume that the function $P(t)$ is an exponential function of time, of the form

$$P(t) = k'D' e^{-k't} \tag{8}$$

where k' and D' are the parameters to be estimated. The symbols k and D will be used to denote particular estimates of these parameters. Equation 8 could represent the dissolution rate of a drug from a dosage form by a first-order process, with rate constant k' and with D' denoting the total amount released. Using equation 8, the residual sum of squares R in equation 6 becomes, on replacing k' and D' by the estimates k and D,

$$R = \sum_{r=1}^{m} [Q(t_r) - kDL_r\{e^{-kt}\}]^2 \tag{9}$$

The linear property of L has been used in placing the term kD outside the operator expression.

The minimum of R with respect to D, for a fixed k, is found by setting the partial derivative $\partial R/\partial D$ at zero. We have

$$\partial R/\partial D = 2Dk^2 \sum_{r=1}^{m} [L_r\{e^{-kt}\}]^2 - 2k \sum_{r=1}^{m} Q(t_r)L_r\{e^{-kt}\} \tag{10}$$

For each k, the value of D which minimizes R is then

$$D = \sum_{r=1}^{m} Q(t_r)L_r\{e^{-kt}\} \Big/ k \sum_{r=1}^{m} [L_r\{e^{-kt}\}]^2 \tag{11}$$

For a given value of k, the expression $L_r\{e^{-kt}\}$ is evaluated numerically, at each time t_r. The required value of D then follows from equation 11.

From equation 10, we have

$$\partial^2 R/\partial D^2 = 2k^2 \sum_{r=1}^{m} [L_r\{e^{-kt}\}]^2$$

This expression is positive for all values of k, indicating that the value of D calculated using equation 11 is indeed a value which minimizes R.

The minimum with respect to k can be found numerically. In the examples which follow, the N.A.G.[3] subroutine E04AAF was used. This subroutine requires a user-supplied subroutine to evaluate the function to be minimized, R, for particular values of the parameter k. Equation 9 provides the basis for this evaluation.

In both cases, the expression $L_r\{\ \}$ is evaluated numerically. This expression has the form

$$L_r\{e^{-kt}\} = \int_0^{t_r} F(t_r - T)e^{-kT}\,dT$$

In the numerical examples which follow, this expression has been evaluated by fitting the data representing $F(t)$ to a polynomial and evaluating the integral using the trapezium rule.

This approach has the advantage of flexibility; only minor changes are required in the program when different inputs are considered. An alternative approach is to represent $F(t)$ by a suitable empirical function (such as a multiexponential function) and evaluate the integral analytically. This approach would be preferable if $F(t)$ and $P(t)$ were known to have the same form for all the data under investigation, provided that the integral can be evaluated.

The method requires an initial estimate of either k or D, since a minimization with respect to either parameter requires a "current" estimate of the other. The obvious choice is to take as an initial estimate of D, the administered dose, which is likely to be at least of the same order of magnitude as the true value. Alternatively, with suitable data, an estimate of D can be found independently by taking the ratio of the total area under the $Q(t)$–time curve to the total area under the $F(t)$–time curve. In fact, if a reliable estimate can be found by this method, the analysis is greatly simplified. A single evaluation is required to find the value of k which minimizes R, using the previously determined value of D.

Cube-Root Law

If the unknown function $P(t)$ in equation 1 represents the *in vivo* release rate of a drug from a tablet, a possible expression to describe the

[3]Nottingham Algorithms Group. The subroutine E04AAF estimates the minimum of the function by fitting a low-order polynomial, finding the minimum of this polynomial, and repeating the process as necessary.

release rate is the following, based on the cube root law:[4]

$$P(t) = (3D'/t'_{dis})(1 - t/t'_{dis})^2 \qquad t \leq t'_{dis}$$
$$= 0 \qquad t > t'_{dis}$$

Using the unit step function, defined as

$$U(t) = 0 \qquad t < 0$$
$$= 1 \qquad t \geq 0$$

a single equation can be written to describe $P(t)$:

$$P(t) = (3D'/t'_{dis})(1 - t/t'_{dis})^2[1 - U(t - t'_{dis})] \tag{12}$$

In this equation D' is the released dose and t'_{dis} is the dissolution time, the time required for the entire dose D' to be released. This equation can be written in various forms. The present form is chosen so that $P(t)$ depends linearly on one of the parameters (D').

The procedure now follows that outlined in the previous section. Introducing equation 12 into equation 6, and replacing D' and t'_{dis} by the estimates D and t_{dis},

$$R = \sum_{r=1}^{m} [Q(t_r) - (3D/t_{dis})L_r\{(1 - t/t_{dis})^2[1 - U(t - t_{dis})]\}]^2 \tag{13}$$

On setting $\partial R/\partial D = 0$, we obtain

$$D = \frac{t_{dis} \sum_{r=1}^{m} Q(t_r)L_r\{(1 - t/t_{dis})^2[1 - U(t - t_{dis})]\}}{3 \sum_{r=1}^{m} [L_r\{(1 - t/t_{dis})^2[1 - U(t - t_{dis})]\}]^2}$$

A second differentiation shows this to be a minimum. Thus, for a given estimate for t_{dis}, this expression yields the value of D which minimizes R. For a given estimate for D, the value of t_{dis} which minimizes R is found numerically, using equation 13, as described in the previous section.

NUMERICAL EXAMPLES USING SIMULATED DATA

The examples which follow are intended to illustrate the results obtained using the proposed method in cases where the exact values of the estimated parameters are known. In view of the study by Gamel *et al.* (5),

[4]Modified from Wagner (8), equation 16.22. The present notation (on the left) is related to the notation in Wagner (8) (on the right) as follows: $P(t) = -dW/dt$, $D' = W_0$, $t'_{dis} = W_0^{1/3}/K_4$.

the influence of data noise has been examined in some detail for selected examples. No attempt at an exhaustive analysis has been made, but the examples chosen are intended to represent situations which might be met in practice.

GENERATION OF DATA

Data were generated by selecting a function $F(t)$, and a function $P(t)$, which were used to calculate values of $Q(t)$, numerically, using equation 1. To selected values of $F(t)$, and to the calculated values of $Q(t)$, noise was added. The resulting values were taken as "raw data" for the calculation of an estimate of $P(t)$ (or of the parameters describing this function). The success of the procedure can be judged by comparing the estimates with the true values.

The function $F(t)$ was taken to be a biexponential function of t:

$$F(t) = A_1 e^{-a_1 t} + A_2 e^{-a_2 t}$$

For simplicity, the values $A_2 = a_2 = 1$ were chosen in all cases, with $a_1 > 1$. This involves no loss of generality and can be achieved with any such function by means of a transformation of the time and concentration scales. The condition $a_1 > 1$ implies that the smaller of the exponential coefficients is chosen as the basis for the transformation of the time scale.

The general character of $F(t)$ can be changed by varying A_1 and a_1. If A_1 is positive, $F(t)$ declines from an initial maximum value, as does the plasma or blood concentration of a drug following intravenous administration. If $A_1 = -1$, $F(t)$ is initially zero, increases to a maximum value, and declines again to zero, which compares with the plasma or blood concentration of a drug following oral administration.

Noise was added to $F(t)$ and $Q(t)$, to obtain the "raw data" used in the analysis, by selecting random numbers from a normal distribution with a prescribed standard deviation (the N.A.G. library subroutine G05AEF[5] was used). The standard deviation was taken to be proportional to the function value, and is expressed as a percentage. Thus a noise level of $x\%$ added to the function value Y is a random number drawn from a normal distribution with mean zero and standard deviation $xY/100$.

In all the examples considered, a single time scale was used, which was the sequence 0.1, 0.2, 0.3, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 2.0. The numbers are the times at which $F(t)$ and $Q(t)$ were evaluated in generating the data.

[5]The subroutine G05AEF is based on a pseudorandom number generator which provides sample values from a uniform distribution over the range (0, 1).

Since the time scales are considered to be normalized, no time units are given. The time scale was selected rather arbitrarily, so that a sufficient variation in $F(t)$ was observed (see Tables III and IV). The number of data points, 11, was chosen as a reasonable number to be expected from a suitably designed experiment.

RESULTS

The influence of data noise on parameter estimates for various cases is shown in Tables I and II and Tables V to VIII.[6]

In Tables I and II the unit impulse response $F(t)$ declines from an initial maximum value and has the character of the plasma or blood concentration of a drug following an intravenous input. For Table I the data were generated (by numerical evaluation of equation 1) using an exponential input function $P(t)$, and the data were analyzed using the asumption that the input function to be calculated has an exponential form.

[6]As in the previous discussion, in all tables a "prime" indicates the exact value of a parameter (D', k', and t'_{dis}) and the corresponding symbol without the superscript indicates an estimate.

Table I. Influence of Data Noise on Parameter Estimates

$F(t) = e^{-5t} + e^{-t}$

$P(t) = kD\,e^{-kt}$ $\quad D' = 0.600 \quad k' = 2.000$

Run No.	Noise levels					
	1%		5%		10%	
	D	k	D	k	D	k
1	0.610	1.955	0.608	1.964	0.601	2.540
2	0.601	2.014	0.600	1.939	0.604	2.300
3	0.600	1.972	0.619	1.800	0.637	2.012
4	0.602	2.009	0.590	1.917	0.630	1.794
5	0.604	1.965	0.583	2.034	0.588	1.979
6	0.602	1.984	0.604	1.966	0.686[b]	1.659[b]
7	0.605	2.027	0.605	1.779	0.597	1.973
8	0.600[a]	1.998[a]	0.641	1.719	0.604	2.264
9	0.599	2.009	0.615	2.010	0.607	1.956
10	0.599	1.981	0.596	1.990	0.593	1.933
Mean[c]	0.602	1.992	0.606	1.912	0.615	2.041
SD[c]	0.003	0.022	0.016	0.102	0.028	0.245

[a,b]Data from which these estimates were derived are given in Table III.

[c]Mean and standard deviation were calculated before rounding estimates to the values reported.

Table II. Influence of Data Noise on Parameter Estimates

$F(t) = e^{-5t} + e^{-t}$

$P(t) = (3D/t_{dis})(1 - t/t_{dis})^{2}$ [a] $\quad D' = 0.600 \quad t'_{dis} = 1.150$

Run No.	Noise levels					
	1%		5%		10%	
	D	t_{dis}	D	t_{dis}	D	t_{dis}
1	0.603	1.139	0.591	1.196	0.600	1.191
2	0.608	1.176	0.608	1.178	0.620	0.911
3	0.602	1.145	0.594	1.156	0.613	0.996
4	0.598	1.163	0.608	1.255	0.634	1.139
5	0.603	1.149	0.585	1.177	0.606	1.212
6	0.602	1.168	0.586	1.143	0.594	1.188
7	0.603	1.161	0.600	1.156	0.664[c]	1.366[c]
8	0.607	1.144	0.590	1.248	0.603	1.203
9	0.601	1.158	0.617	1.278	0.617	1.036
10	0.600[b]	1.151[b]	0.618	1.153	0.609	1.192
Mean[d]	0.603	1.156	0.600	1.194	0.616	1.143
SD[d]	0.003	0.011	0.012	0.046	0.019	0.123

[a] For $t \leq t_{dis}$; $P(t) = 0$ for $t > t_{dis}$.
[b,c] Data from which these estimates were derived are given in Table IV.
[d] See footnote *c* in Table I.

That is, the form of the input function is assumed to be known, the object of the analysis being to determine the values of the parameters involved. Similarly, for Table II, the data were generated and subsequently analyzed using the "cube root" input function. Tables III and IV give examples of the "raw data" used in the analyses reported in Tables I and II, respectively.

The significant feature of the estimates shown in Tables I and II is their stability to data noise. For each noise level, the standard deviation of the estimates as a percentage of the mean (the coefficient of variation) is of the same order of magnitude as the data noise. Also, the mean value, in each case, lies within one standard deviation of the true parameter value.

The estimates of Table II are derived from data which are intended to correspond approximately with those of Table I [compare $Q(t)$ values in Tables III and IV]. It can be seen from a comparison of Tables I and II that the method performs equally well with a "cube root" input as with an exponential input. This was found in all cases. For this reason, the remaining examples report only the results obtained with the exponential input.

Tables V and VI show the estimates obtained with different exponential inputs, using the same unit impulse response $F(t)$ as in Table I. Thus

Table III. Examples of Raw Data Used in the Analyses Reported in Table I

$F(t) = e^{-5t} + e^{-t}$

$P(t) = kD\,e^{-kt}$ $\quad D' = 0.600$ $\quad k' = 2.000$

	Exact values		Values with 1%[a] data noise		Values with 10%[b] data noise	
Time	$F(t)$	$Q(t)$	$F(t)$	$Q(t)$	$F(t)$	$Q(t)$
0.1	1.511	0.180	1.515	0.181	1.425	0.191
0.2	1.187	0.293	1.177	0.291	1.220	0.250
0.3	0.964	0.360	0.972	0.361	1.041	0.320
0.4	0.806	0.394	0.789	0.388	0.702	0.397
0.6	0.599	0.400	0.589	0.399	0.475	0.421
0.8	0.468	0.368	0.473	0.372	0.452	0.402
1.0	0.375	0.327	0.372	0.328	0.400	0.384
1.2	0.304	0.288	0.307	0.286	0.294	0.293
1.4	0.248	0.250	0.249	0.249	0.237	0.291
1.6	0.202	0.211	0.208	0.210	0.185	0.218
2.0	0.135	0.155	0.135	0.153	0.147	0.146

[a,b]The parameter estimates derived using these data are given by items *a* and *b*, respectively, in Table I. These examples were selected as the best (*a*) and worst (*b*) estimates in Table I.

Table IV. Examples of Raw Data Used in the Analyses Reported in Table II

$F(t) = e^{-5t} + e^{-t}$

$P(t) = (3D/t_{dis})(1 - t/t_{dis})^{2}$ [a] $\quad D' = 0.600$ $\quad t'_{dis} = 1.150$

	Exact values		Values with 1%[b] data noise		Values with 10%[c] data noise	
Time	$F(t)$	$Q(t)$	$F(t)$	$Q(t)$	$F(t)$	$Q(t)$
0.1	1.511	0.240	1.515	0.244	1.425	0.255
0.2	1.187	0.390	1.179	0.386	1.220	0.334
0.3	0.964	0.476	0.934	0.474	1.041	0.423
0.4	0.806	0.513	0.796	0.508	0.702	0.516
0.6	0.599	0.495	0.596	0.502	0.475	0.521
0.8	0.468	0.420	0.476	0.416	0.452	0.458
1.0	0.375	0.335	0.375	0.335	0.400	0.393
1.2	0.304	0.263	0.306	0.262	0.294	0.268
1.4	0.248	0.209	0.250	0.207	0.237	0.242
1.6	0.202	0.168	0.202	0.170	0.185	0.174
2.0	0.135	0.118	0.136	0.118	0.147	0.111

[a]For $t \leq t_{dis}$; $P(t) = 0$ for $t > t_{dis}$.

[b,c]The parameter estimates derived using these data are given by items *b* and *c* in Table II. The examples were selected as the best (*b*) and worst (*c*) estimates in Table II.

Table V. Influence of Data Noise on Parameter Estimates

$F(t) = e^{-5t} + e^{-t}$

$P(t) = kD\,e^{-kt}$ $\quad D' = 0.600 \quad k' = 1.000$

Run No.	Noise levels					
	1%		5%		10%	
	D	k	D	k	D	k
1	0.600	1.012	0.608	0.934	0.580	1.042
2	0.612	0.980	0.618	0.963	0.585	1.196
3	0.600	1.006	0.617	0.931	0.588	1.141
4	0.601	0.989	0.638	0.886	0.647	0.989
5	0.599	1.012	0.605	0.923	0.659	0.876
6	0.606	0.986	0.576	1.027	0.582	1.006
7	0.603	0.991	0.611	0.974	0.699	0.878
8	0.598	1.025	0.635	0.858	0.590	1.009
9	0.596	1.009	0.677	0.838	0.598	1.091
10	0.597	1.008	0.616	0.999	0.597	1.016
Mean[a]	0.601	1.002	0.620	0.933	0.613	1.025
SD[a]	0.005	0.014	0.025	0.057	0.039	0.097

[a]See footnote *c* in Table I.

Table VI. Influence of Data Noise on Parameter Estimates

$F(t) = e^{-5t} + e^{-t}$

$P(t) = kD\,e^{-kt}$ $\quad D' = 1.200 \quad k' = 0.500$

Run No.	Noise levels					
	1%		2%		5%	
	D	k	D	k	D	k
1	1.187	0.511	1.263	0.452	1.080	0.569
2	1.225	0.493	1.280	0.465	1.154	0.577
3	1.195	0.506	1.294	0.445	1.104	0.603
4	1.198	0.499	1.346	0.426	1.321	0.486
5	1.178	0.516	1.281	0.436	1.357	0.440
6	1.207	0.498	1.130	0.523	1.174	0.494
7	1.208	0.496	1.230	0.487	1.365	0.474
8	1.168	0.527	1.370	0.405	1.179	0.504
9	1.175	0.514	1.431	0.410	1.235	0.507
10	1.185	0.509	1.263	0.482	1.140	0.537
Mean[a]	1.192	0.507	1.289	0.453	1.211	0.519
SD[a]	0.016	0.010	0.078	0.035	0.098	0.049

[a]See footnote *c* in Table I.

Table VII. Influence of Data Noise on Parameter Estimates

$F(t) = -e^{-5t} + e^{-5}$

$P(t) = kD\,e^{-kt}$ $D' = 1.200$ $k' = 2.000$

Run No.	Noise levels					
	1%		5%		10%	
	D	k	D	k	D	k
1	1.201	2.021	1.208	1.947	1.149	2.131
2	1.220	1.999	1.209	2.060	1.191	2.078
3	1.200	2.020	1.233	1.845	1.214	2.061
4	1.201	1.992	1.271	1.840	1.213	2.123
5	1.203	2.017	1.222	1.835	1.287	1.673
6	1.211	1.983	1.163	2.056	1.155	2.129
7	1.207	2.000	1.210	1.959	1.391	1.885
8	1.202	2.052	1.244	1.773	1.174	2.186
9	1.192	2.045	1.312	1.740	1.155	2.184
10	1.191	2.040	1.226	2.109	1.214	2.050
Mean[a]	1.203	2.017	1.230	1.910	1.214	2.050
SD[a]	0.008	0.022	0.038	0.110	0.071	0.150

[a]See footnote *c* in Table I.

Table VIII. Influence of Data Noise on Parameter Estimates

$F(t) = -e^{-5t} + e^{-t}$

$P(t) = kD\,e^{-kt}$ $D' = 1.200$ $k' = 0.500$

Run No.	Noise levels					
	1%		5%		10%	
	D	k	D	k	D	k
1	1.196	0.505	1.270	0.465	0.978	0.633
2	1.208	0.507	1.275	0.476	1.391	0.416
3	1.201	0.501	1.340	0.435	1.163	0.540
4	1.187	0.508	1.372	0.436	1.220	0.516
5	1.178	0.515	1.372	0.414	1.280	0.471
6	1.200	0.505	1.142	0.517	1.215	0.474
7	1.217	0.494	1.224	0.491	1.204	0.600
8	1.157	0.531	1.371	0.420	1.195	0.502
9	1.158	0.525	1.349	0.459	1.352	0.420
10	1.180	0.511	1.353	0.438	1.105	0.571
Mean[a]	1.188	0.510	1.307	0.455	1.210	0.514
SD[a]	0.019	0.010	0.074	0.031	0.112	0.069

[a]See footnote *c* in Table I.

Tables I, V, and VI illustrate the performance of the method as the constant k takes values greater than, equal to, and less than the smaller exponential coefficient of $F(t)$. The method performs satisfactorily in all cases.

However, with very small values of k failures were encountered. This is to be expected, since, for sufficiently small values of k,

$$P(t) = kD\,e^{-kt}$$
$$\cong kD$$

In this case, $P(t)$ behaves as a one-parameter function (parameter kD) and when an attempt is made to fit a two-parameter function one parameter is indeterminate. Failures of this type were characterized by very rapid convergence (one or two iterations) to estimates which depended markedly on the initial estimate for D.

Failures also occur with very large values of k. In this case, $P(t) \cong D\delta(t)$, where $\delta(t)$ is the unit impulse function. The resulting value of R is independent of k. In practice, the method usually yields an estimate for k which is of the correct order of magnitude. The value of D obtained depends markedly on the initial estimate.

The case in which k is very large is readily identified from inspection of the data. Equation 1 becomes

$$Q(t) \cong DF(t) \tag{14}$$

Thus $Q(t)$ is roughly proportional to $F(t)$. Depending on the value of k, this approximate proportionality might not be observed with the first one or two data points.

Better estimates for D can be found in these cases by making use of approximate expressions which are independent of k. Using equation 14, we obtain in place of equation 11,

$$D = \sum_{r=1}^{m} Q(t_r)F(t_r) \Big/ \sum_{r=1}^{m} F(t_r)^2$$

This equation gives estimates of D which are of the correct order of magnitude, provided that the approximation of equation 14 is a reasonable one.

Tables VII and VIII illustrate the performance of the method with a unit impulse response which has the features of the plasma or blood concentration following an oral solution dose of a drug.

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