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SOME PROBLEMS ON THE USE OF NEGATIVE EXPONENTIAL CURVES IN BIOLOGY

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March 1965
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SOME PROBLEMS ON THE USE OF NEGATIVE EXPONENTIAL CURVES IN BIOLOGY

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FOREWORD

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ABSTRACT

Many biologic processes give responses that decrease rapidly over time to some asymptote \( C \approx 0 \). The mathematical expressions that describe the various phenomena vary in complexity and form. To fit a curve to data in any such situation, one must consider both the formula for the trend and the nature of the deviations or error terms. A discussion of these problems is given to indicate to the data analyst the possible choices that are his, relative to assumptions about error terms and relative to technics or methods of estimation. No new analytic procedures are given.

It is noted that several methods of estimation are being studied for certain assumed model equations. The results of these random sampling experiments will be reported in subsequent papers.
SOME PROBLEMS ON THE USE OF NEGATIVE EXPONENTIAL CURVES IN BIOMEDICAL APPLICATIONS

1. INTRODUCTION

Many biologic processes give responses that decrease rapidly over time to some asymptote $C \geq 0$. The mathematical expressions that describe the various phenomena vary in complexity and form. To fit a curve to data in any such situation, one must consider both the formula for the trend and the nature of the deviations or error terms. The intent of the discussion that follows will be to help indicate to the data analyst the possible choices that are his, relative to assumptions about error terms and relative to technics or methods of estimation. No new analytic procedures are proposed. First, there will be a consideration of equation motivation. This will be followed by a discussion of the error terms in the model equations. Possible extensions of certain models will be noted, followed by a discussion of various estimation methods. Hypothesis testing is briefly discussed, with a final section devoted to concluding remarks.

2. MOTIVATION OF THE MODEL EQUATIONS

For a continuous process such as an organism's blood-sugar level, a scientist might simply observe that following the ingestion of a meal, there is an increase and a subsequent decrease of the level of the sugar in the blood. It might be further observed that the shape of the declining curve from the highest point attained appears to be of a negative exponential form, $y = \alpha \exp(-\gamma t)$. By trying various transformations, a straight line might be obtained when the logarithm of the response is plotted against time, or the ratio of the observation at time $t$ to that at time $t - 1$ might give a constant for all values of $t$. This is empirical curve fitting or modeling. No rationale is presented for the choice of the equation. Such empirical curve fitting may in turn suggest mechanisms and thus lead to better understanding, of course.

In opposition to empirical curve fitting is the mechanistic approach. From first principles, the scientist tries to predict the equation or the form of the response as a function of time. For a simplified example, consider the rate of the nitrogen washout of the lung for an animal breathing room air and placed on pure oxygen. The room air concentration of nitrogen is about 79%. Respiration depth is kept at a constant level; rate is allowed to vary. The nitrogen concentration of each expired volume of air is determined. If the total resting lung volume is denoted by $v$ and the volume of inspired air at each breath by $\Delta v$, then initially, or at time zero,

\[
\begin{align*}
FN_2(0) &= \text{concentration of nitrogen} = .79 \\
Fo_2(0) &= \text{concentration of oxygen} = .21 \\
VN_2(0) &= \text{volume of nitrogen} = .79v \\
Vo_2(0) &= \text{volume of oxygen} = .21v
\end{align*}
\]

and after the first breath of pure oxygen,

\[
\begin{align*}
FN_2(1) &= \frac{VN_2(0)}{VN_2(0) + Vo_2(0) + \Delta v} \\
&= \frac{.79v}{.79v + (.21v + \Delta v)} \\
&= \frac{.79}{v + \Delta v} \\
&= .79u_v, \\
\end{align*}
\]

\[
\begin{align*}
Fo_2(1) &= \frac{.21v + \Delta v}{.79v + .21v + \Delta v} \\
VN_2(1) &= FN_2(1)v = .79u_v \\
Vo_2(1) &= Fo_2(1)v = \frac{.21 + \Delta v}{v + \Delta v} (v) \\
&= v - .79u_v, \\
\end{align*}
\]

where

\[
\begin{align*}
\gamma &= \frac{v}{v + \Delta v}.
\end{align*}
\]
The concentration after the second breath will be

\[ FN_2(2) = \frac{\sqrt{v_2(1)}}{\sqrt{v_2(1) + v_2(1) + \Delta v}} = \frac{.79\omega\sqrt{v}}{v + \Delta v} = .79\omega\left(\frac{v}{v + \Delta v}\right) = .79\omega^2. \]

Continuing in the same manner, it can be shown that

\[ FN_2(t) = .79\omega^t; \]

\( \omega \) is called the dilution ratio. Thus, the concentration at breath \( t \) is found by multiplying the concentration at breath \( t - 1 \) by the dilution ratio \( \omega \), or \( FN_2(t) = \omega FN_2(t - 1) \). The equation is generated from mechanical principles that are peculiar to this biologic process.

Parenthetically, it should be observed that for many applications, the implication is that observations are made at discrete and usually equidistant time points. For some situations, the response cannot be measured and may possibly not even be defined at nonintegral values of \( t \). For others, the process may be truly continuous but with sampling performed at fixed time intervals. In still other situations, the independent variable may not be chronologic time, but only time related. Thus, in respiration studies, the concentration of a gas in each volume of expired air may be determined. If respiration rate is not fixed, the actual time between breaths is not fixed. In this case, it may be desirable to view breath number as the time meter.

More complicated equations, such as the sum of two or more negative exponential terms, may be found in similar ways: by trial and error and past experience, a curve may be fitted empirically; or from a knowledge of the mechanisms involved, an equation may be derived to describe the response. In both approaches, there is probably a tendency toward parsimony—i.e., one attempts to explain or fit the data with the simplest expression. And in most curve-fitting situations the distinction between arbitrary curve fitting and mechanistic modeling is not as clear cut as indicated above. There is very likely a bit of empiricism as well as theory generation in nearly every curve-fitting situation.

Not only might the equation to be fitted be arrived at in many different ways, but different-appearing equations are used to describe the same process. That is, the same process may be represented by different equations. For example, in the nitrogen washout example above, the equation \( FN_2(t) = \omega FN_2(t - 1) \) led to \( FN_2(t) = .79\omega^t \). In general, an \( m \)th order difference equation may be thought of as the model equation. Yet, its solution will be the sum of \( m \) exponential terms. Which equation one uses to fit to the data will depend largely on the assumptions about the error terms, a consideration of which will be the subject of the next section.

That a given process can be described in different ways is rather obvious; the point is that since biologists present equations in many forms, the data analyst should be able to recognize the "best" equation to use in curve fitting, regardless of how the process is described.

3. THE NATURE OF THE ERROR TERM

When a random error term is added to the mathematical equations, they are then referred to as stochastic or model equations. It is at this point that the curve fitter needs to take note, for there are many assumptions which can be made about the error terms. Consider the model equation

\[ y_t = \eta_t + \epsilon_t = \alpha e^{-\beta t} + \epsilon_t, \]

where \( y_t \) is the observation at time \( t \); \( \alpha \) is the true time-zero or initial value; \( \beta \), the rate constant; \( \epsilon_t = \exp(-\beta) \); and \( \epsilon_t \), the error term.

Consideration will first be given to the possible components of \( \epsilon_t \). It may consist of a combination of several sources or kinds of "error"; e.g., model error, measurement error, and a kind of replication-by-time interaction error. For brevity, and for reasons which will be given later, the last kind of error will be referred to as process-control error.
A model error may derive from an improper choice of a mathematical expression, even though the fit to the data using the incorrect equation may be considered adequate. The model error will most likely constitute a bias, an overfitting or underfitting in various regions of the curve. Its major effect will be to increase the mean square deviation about the fitted line. It is assumed in what follows that there is no model error in $e_t$.

The measurement error, referred to herein as $\delta$, may be viewed in the usual way: it is the technic error introduced into the observation when the measurement is being obtained. It may involve only sensing error, the observation being automatically recorded, or it may consist of a combination of errors, a human reading error, the error in sensing, plus an error in one or more analytic procedures. It is usually assumed to have zero mean for each time $t$.

For certain problems, the most important source of error is that due to nonregular or random behavior of the response from time to time. This deviation or error is considered to be random over experiments. It arises when the organism invokes some complicated control to correct for overproduction or underproduction of the measured quantity. For example, the metabolic rate of the quantity studied may be considered a constant, on the average. The true amount present at time $t$, however, may be $\omega t + \nu$, where $\nu$ is the process control error. For the same animal, in a replicated experiment, $\nu$ may vary so that the average of $\nu$, $t$ fixed, over all these re-runs may reasonably be assumed to be zero. The sign and size of $\nu$ is determined by a host of factors in the organism, so that it is truly a random element at any point $t$. Thus, the term $\epsilon$ will be written as the sum of two elements, $\nu$ and $\delta$; i.e.,

$$e_t = \nu + \delta_t. \quad (2)$$

The next question to be considered is whether the error terms are time dependent. The nature of the biologic process being studied and frequency of sampling are relevant factors. If the process is continuous with measurements being continuously made, then both $\nu$ and $\delta$ will be continuous curves. In this case, one can imagine that the error deviations form an undulating curve, weaving around the average response curve. Thus, the deviation at time $t + \Delta t$ will be functionally dependent on the deviation at time $t$. The commonest departure from a continuous process, continuously observed, is obtained in situations where sampling is at equally spaced time intervals. In what follows, $\Delta t$ is taken to be greater than zero and constant. A measure of the time dependency between two observations in time is the covariance of the two observations. First, the covariance of the $\nu$ will be discussed. If the sampling interval, $\Delta t$, is small, then as observed above, $\nu$ and $\nu + \Delta t$ are functionally dependent and would behave as positively correlated quantities. If $\Delta t$ is sufficiently large, one might observe a zero correlation between $\nu$ and $\nu + \Delta t$; an overyield at time $t$ in no way affects the response at time $t + \Delta t$. If the overyield at time $t$ gave rise to an undercorrection at time $t + \Delta t$, a negative correlation would obtain.

Correlations among the $\delta$ may be quite different from those among the $\nu$. For example, $\delta$ and $\delta + \Delta t$ may be positively correlated for all $\Delta t$. This could obtain if an observer is recording the response of a system which has been showing a steady but definite decrease in time and if the response tends to level out or asymptote, the observer is likely to remember the response at a previous reading and unconsciously round to effect a nonincreasing response. This kind of behavior essentially creates a moving average of the $\delta$. Thus, for a particular system the covariance of $\nu$ and $\nu + \Delta t$ may be negative and the covariance of $\delta$ and $\delta + \Delta t$, positive. For most systems, it seems reasonable to assume that all $\nu$ are independent of all $\delta$.

As mentioned earlier, the assumptions about the error terms are made with some particular equation in mind. If the comments regarding the $\epsilon$ are made for equation 1, the next problem is to study the resulting effect on the error terms when one uses another representation of the process. For example, $\nu = \alpha \exp (-\beta t)$.
satisfies the equation \( y_t = \omega y_{t-1} + \xi_t \), where \( \omega \) is equal to \( \exp(-\beta) \) and where \( y_t = \alpha \exp(-\beta t) = E(y_t) \). Then the equation
\[
y_t = \omega y_{t-1} + \xi_t
\]is another way of writing equation 1. For this situation, it is apparent that the assumptions made about \( \epsilon_t \) are the same as those for \( \xi_t \) since \( \epsilon_t \) and \( \xi_t \) are identical.

Next, consider a variation of equation 3, the first order stochastic difference equation
\[
y_t = \omega y_{t-1} + \xi_t \tag{4}
\]
The solution of 4 is also equation 1, but now the error term \( \epsilon_t \) of equation 1 is a function of \( \xi_0, \xi_1, \ldots, \xi_t \). It is instructive to study the process, starting at time zero. The time-zero reading, \( y_0 \), consists of a constant, \( \alpha \), say, plus a random error \( \xi_0 \), or \( y_0 = \alpha + \xi_0 \) where \( \alpha \) is the true time-zero value. For the nitrogen washout study mentioned earlier, \( \alpha = .79 \), the nitrogen concentration of air near sea level. Building up equation 1 from 4,
\[
y_1 = \omega y_0 + \xi_1 = \omega(\alpha + \xi_0) + \xi_1 = \omega \alpha + \omega \xi_0 + \xi_1
\]
\[
y_2 = \omega y_1 + \xi_2 = \omega(\omega \alpha + \omega \xi_0 + \xi_1) + \xi_2 = \omega^2 \alpha + \omega^2 \xi_0 + \omega \xi_1 + \xi_2
\]
\[
y_t = \omega^t \alpha + \sum_{i=0}^{t-1} \omega^i \xi_i \tag{5}
\]
Equating 5 with 1, indicates that
\[
y_t = \sum_{i=0}^{t-1} \omega^i \xi_i = \omega y_{t-1} + \xi_t \tag{6}
\]
With an ID(0, \( \sigma^2 \)) assumption (independently distributed with zero mean, variance \( \sigma^2 \)) for the \( \xi_i \), then
\[
\text{Cov}(\epsilon_t, \xi_t) = \omega^k \sigma^2 \left( \frac{1 - \omega^2(1-k+1)}{1-\omega^2} \right), \quad k = 0, 1, 2, \ldots, t. \tag{7}
\]
Model equation 4 is commonly referred to as a simple autoregression model (see Anderson (1)). Note that as \( t \) becomes large, the variance approaches \( \sigma^2(1 - \omega^2)^{-1} \) and for \( k \) small relative to \( t \), the \( k \)th lag correlation coefficient approaches \( \omega^k \).

Instead of writing the autocorrelation model as 4 or 5, it is frequently written as a pair of equations,
\[
y_t = \omega y_{t-1} + \epsilon_t
\]
\[
\epsilon_t = \rho \epsilon_{t-1} + \xi_t \tag{8}
\]
If \( \rho = \omega \), equation 8 is equivalent to equation 5; if \( \rho = 0 \), equation 8 is equivalent to equation 3. In this more general formulation, one can see that if \( \rho \) is negative, adjacent observations are negatively correlated. This becomes somewhat clearer if one writes \(-\rho \) for \( \rho \) in 8. Then the single equation analogous to equation 5 is
\[
y_t = \omega y_{t-1} + \sum_{i=0}^{t-1} (-\rho)^i \xi_i \tag{9}
\]
If the \( \xi_t \) are ID(0, \( \sigma^2 \)), then
\[
\text{Cov}(y_t, y_{t-k}) = (-\rho)^k \sigma^2 \left( \frac{1 - \rho^2(1-k+1)}{1-\rho^2} \right), \quad k = 0, 1, 2, \ldots, t. \tag{10}
\]
As \( t \) increases and \( k \) is relatively small, the \( k \)thlag correlation coefficient very nearly becomes \((-\rho)^k \). Thus, all odd lag correlations are negative and all even are positive. This model may be appropriate when the system corrects itself for overproductions and underproductions as the time course proceeds. Again, it should be noted that the observed lag correlations will be as indicated only if the sampling period coincides with the "correcting" period. The importance of the frequency of this time sampling in relation to the system's assumed behavior cannot be over emphasized.

A model equation that is similar to equations 4 and 8 is the moving average model,
\[
y_t = \omega y_{t-1} + \epsilon_t \tag{11}
\]
\[
\epsilon_t = \sum_{i=0}^{t-1} m_i \xi_{t-1} \tag{12}
\]
For example, if
\[
m_i = \begin{cases} 1 & \text{for } i = 0 \\ -\rho & \text{for } i = 1 \\ 0 & \text{otherwise} \end{cases}
\]
then
\[
\epsilon_t = -\rho \xi_{t-1} + \xi_t \tag{13}
\]
Assuming the \( \xi_t \) are ID(0, \( \sigma^2 \)), then using the values of \( m_i \) from equation 12,
\[
\text{Cov}(y_t, y_{t-k}) = \begin{cases} (1 + \rho^2) \sigma^2 & \text{for } k = 0 \\ -\rho^2 & \text{for } k = 1 \\ 0 & \text{for } k = 2, \ldots, t. \end{cases} \tag{13}
\]
From equation 13, note that the first lag correlation coefficient is \( \rho^2(1 + \rho^2) \) and all
higher lag correlation coefficients are zero. This will provide for a simpler kind of corrective action by the system than does equation 9.

Model equation 3 may be described as a mechanical system. It is appropriate when the response at time t is made up of two parts: a constant times the true response at time t - 1 plus a random error term. The error term at time t is independent of all other error terms. Thus, this model may be used when there is only an independent measurement error. Equations 4, 8, and 11, on the other hand, are more properly called feedback or historical models for the errors on previous occasions affect the observation at time t. Most biologic systems are probably of this latter type. A historical model that allows for situations where the process control and measurement errors are correlated in different patterns, and, thus, is perhaps more realistic than equation 8, is

\[ y_t = \alpha^{wa} + \epsilon_t = \alpha^{wa} + \epsilon_t + \delta_t, \]

where

\[ \epsilon_t = -\rho \epsilon_{t-1} + \gamma_t = \sum_{i=1}^{\infty} (-\rho)^{i-1} \eta_i. \]  

(14)

and

\[ \delta_t = \sum_{j=1}^{k} m_j x_{t-j}. \]

If the measurement errors are independent, then \( m_0 = 1 \) and all other \( m_j \) are zero. As stated earlier, if there is no replication, then \( \eta_t \) and \( \delta_t \) are inseparable. Even though there is no hope of separation of the two, it may be helpful to imagine the errors as behaving in this fashion. Depending on the relative size of the variances of \( \eta_t \) and \( \delta_t \), one may be able to predict what the net effect will be.

Another whole class of models are those where the error is proportional to the level of the measured response. These models have utility, especially when the range of \( y_t \) is several fold. Furthermore, they are more manageable under logarithmic transformation, allowing for simple estimators for the parameters of the equation. The model equation is

\[ y_t = \alpha e^{-\beta t} + \epsilon_t. \]  

(15)

One can take the logarithm of both sides of the equation and if the \( \epsilon_t \) are \( ID(0, \sigma^2) \), proceed to estimate the parameters in the usual manner since the variance of \( \ln(y_t) \) is \( \sigma^2 \) and the covariances are zero. To see how different autocorrelation patterns among the \( \epsilon_t \) may affect the model, however, equation 15 is written in another form. For \( \epsilon_t \) small, \( \epsilon_t = 1 + \epsilon_t \); and writing, as before, \( y_t = \alpha e^{-\beta t} \), then \( y_t \) can be expressed approximately as

\[ y_t = \alpha e^{-\beta t} + \eta_t. \]  

(16)

This equation may be written as

\[ y_t = \omega \eta_{t-1} + \eta_t. \]  

(17)

If the \( \epsilon_t \) in 15 are \( ID(0, \sigma^2) \), then the error terms in 16 are \( ID(0, \sigma^2) \). Equation 17 corresponds to the mechanical system as given in equation 3, with error proportional to the true response at time t. The difference equation analogous to equation 17, corresponding to the autocorrelation model equation 4, is

\[ y_t = \omega y_{t-1} + \eta_t. \]  

(18)

By assuming that the process starts at time zero so that \( y_0 = \alpha + \rho_0 \delta_0 \), then the solution of equation 18 is

\[ y_t = \frac{\alpha^{wa}}{1 - \rho \epsilon_t}. \]  

(19)

To a first degree of approximation, \( \frac{1}{1 - \epsilon_t} = 1 + \epsilon_t \), so that

\[ \frac{1}{1 - \epsilon_t} = 1 + \epsilon_t + \frac{1}{2} \epsilon_t \epsilon_t, \]

\[ + \frac{1}{3} \epsilon_t \epsilon_t + \frac{1}{4} \epsilon_t \epsilon_t. \]

Thus, equation 19 can be written as

\[ y_t = \frac{\alpha^{wa}}{1 - \epsilon_t} = \omega y_{t-1} + \eta_t (\frac{\epsilon_t}{1 - \epsilon_t}). \]

(20)

Another way of arriving at this same form is to assume that the error term in 18 is proportional to the true response at time t rather than to the observed response, i.e.,

\[ y_t = \omega y_{t-1} + \eta_t \delta_t. \]  

(20)

Then the solution is

\[ y_t = \frac{\alpha^{wa}}{1 - \epsilon_t} \Sigma \epsilon_t^{wa-1} \eta_t \delta_t \]

\[ - \omega^{wa} + \eta_t (\frac{\epsilon_t}{1 - \epsilon_t}). \]  

(21)
If the $\hat{\xi}$ in equation 21 are assumed to be $ID(0,\sigma^2)$, then $E(y_t) = \omega^t$ and
\[
\text{Cov}(y_t, y_{t-k}) = (t - k + 1) \sigma^2 \frac{1}{\rho^t}.
\]
The $k^{th}$ lag correlation coefficient is $(1 - \frac{k}{t+1})^\sigma$; for $k$ small relative to $t$ it approaches unity as $t$ becomes large. This result states that once the response is far enough along in time and veers to a particular side of the average response curve, then the observational curve would tend to stay on the same side for the remainder of the experiment. There appears to be no way one can distinguish this kind of anomaly from organism (animal-to-animal) variability, especially if the experiment cannot be repeated on the same organism. To allow for continued recrossing of the average response curve, negative correlation between adjacent error deviations may be postulated. Thus, model equations may be written for the proportional error models that allow for the control of the system similar to that allowed in equations 4 and 11.

For model equation 21, the variance of $\ln(y_t)$ is $(t + 1)\sigma^2$ for an $ID(0,\sigma^2)$ assumption on the $\hat{\xi}$. If the variance of $\ln(y_t)$ is not an increasing function of $t$, one may either postulate
\[
\hat{\xi} = \rho \hat{\xi}_{t-1} + \xi,
\]
where $\rho$ may be negative, or specify a moving average relationship for the $\hat{\xi}$, such as
\[
\hat{\xi} = \sum_{i=1}^{k} m_i \hat{\xi}_{t-i}.
\]
For these two cases, the model equations corresponding to 21 may be written as
\[
y_t = \eta_1 (1 + \xi) = \eta_1 (1 + \sum_{i=1}^{k} \rho^{i-1} \xi) \quad (25)
\]
and
\[
y_t = \eta_1 (1 + \xi) = \eta_1 (1 + \sum_{i=1}^{k} m_i \xi_{t-i}) \quad (26)
\]
respectively. Note that with restrictions 23 and 24 on the error terms, and with the $ID(0,\sigma^2)$ assumption of the $\hat{\xi}$, the variances and covariances of $\ln(y_t)$ will have the same pattern as for the nonproportional error models. Thus, for equation 25, variance $\ln(y_t)$ is approximately $\frac{\omega^2}{1 - \rho^2}$ for $t$ large, and for equation 26, the variance is $\omega^2 \sum m_i^2$.

If the range of $\eta$ is small, the fitted equations for the proportional error models differ little from their nonproportional counterparts; for these situations one might prefer to use the proportional error models for estimation purposes, since the logarithmic transformation linearizes the mathematical expressions. A discussion of estimation problems is given in a later section.

4. INCREASED COMPLEXITY OF THE MODEL

Greater flexibility in the model is obtained by extending equation 1 to the sum of two or more exponentials,
\[
y_t = \sum_{i=1}^{m} \alpha_i \eta^i + \epsilon_t.
\]
For the mechanical model, the $\epsilon_t$ are independent; for the autocorrelation models, they are functions of previous random error terms. For both types of models, $m^{th}$ order difference equations may be written similar to those equations involving one exponential term. Furthermore, the $\epsilon_t$ may be assumed to be proportional to the level of the response and with different autocorrelation patterns as discussed in the previous section.

When the number of exponential terms is three or more, there arises the question of the determination of the number of true terms in the model equation. For three exponential terms, there are 6 constants to be fitted to the data, usually assuring one a reasonable fit. This will be discussed more fully in the next section, but it does lead one to consider whether it is reasonable to postulate that $\omega$ is continuously distributed. For some biologic applications $\omega$ can assume only a finite number of values, for others (see reference 2, for example), a continuous distribution is quite attractive. An example of this is the nitrogen washout problem discussed above; one may consider the smallest volumes $v_i$, as those for the individual alveoli. Recall that the resting and expanded volume of the alveoli are used to determine the $v_i$. From the thousands of $v_i$, one can visualize the resulting distribution formed by grouping all those that fall in the interval $\omega_c + \Delta \omega$. If one denotes this frequency distribution by
If \( f(\omega) d\omega \) is the expression for \( y \), corresponding to equation 27 is
\[
y(t) = \int f(\omega) d\omega + i_t,
\]
where the \( i_t \) in this equation may be assumed to be independent or autocorrelated. Furthermore, either of these two assumptions on the error terms may be used when the \( i_t \) are proportional to the response at time \( t \). The model equation is not specified, of course, until the expression for \( f(\omega) d\omega \) is named. In this laboratory, the normal probability density has been used for \( f(\omega) d\omega \) in studying equation 28.

To either equation 27 or 28, a term for the asymptote may be added. For some applications considered in this laboratory, it has seemed desirable to modify equation 28 by multiplying the integral by a positive constant \( \gamma \). For \( \gamma = 1 \), this procedure would have limited usefulness unless one were quite sure that \( m = 1 \) and he also had a very good estimate of \( \alpha \).

For \( m \geq 2 \) exponential terms, Cornell (4) has proposed a scheme whereby one groups the data into \( 2m \) equal sample-size categories, which are nonoverlapping in time, and for each category calculates the sum of the responses. By using the fact that each partial sum is a geometric series with an equal number of terms, he is able, through algebraic manipulation, to estimate the \( 2m \) parameters. The scheme appears to work for well-conditioned data. If further refinement is desired in the estimates of the parameters obtained, they may be used as initial or starting values for the more tedious Gauss-Newton iterative scheme.

For the proportional error model, various biologic research workers (see, for example, reference 5) have proposed a "peel-off" method, using a plot of the logarithm of the response versus the meter as a working graph. This procedure implicitly assumes equation 15 or an extension thereof as the basic model. For \( m = 1 \), the resulting scatter of points lies approximately on a straight line. For \( m \geq 2 \), the procedure is started by observing that the points at the right-hand end of the scatter diagram lie approximately on a straight line. To this portion of the data, a straight line is fitted and extrapolated back to the response axis. Deviations are then calculated between the observed and predicted \( y \). If the logarithm of the deviations appear to be linear, a line is fitted to these data and the procedure is completed, with \( m = 2 \). If the logarithm of the second set of deviations has a definite curvature, the second line is fitted only to the straight-line portion of the deviations, and this line is extrapolated back to the response axis.
The process is continued until all data points are fitted.

The rationale for the procedure is clear enough: as t becomes large, the effect of the smallest \( a_i \), \( i = 1, 2, \ldots, m - 1 \), are washed out, leaving only the effect of \( a_m \), the largest \( a \) in the far right-hand end of the curve. From this portion of the data \( a_m \) and the associated \( \alpha_m \) are estimated. One then calculates \( y_i(d_i) = y_i - \alpha_m a_m \) and plots \( \ln[y_i(d_i)] \) versus \( t \). The next step allows one to estimate \( a_{m-1} \) and \( \alpha_{m-1} \). This scheme is followed until the parameters of all exponential terms are estimated. If the \( a_i \) are few (\( m \) no greater than 3, say) and well separated; and further, if each \( \alpha \) is a reasonable proportion of \( \Sigma a_i \), this procedure gives a quite satisfactory estimate. This technique has been programmed for a digital computer; some random sampling experiments performed in this laboratory will be reported in a later paper. As for other similarly obtained estimates, the values found in this manner may be used as initial or starting values for the Gauss-Newton iterative procedure. As for all methods, the assumptions about the error terms must be considered. If the proportional errors are independent, this method gives good estimates of the parameters.

Another estimation scheme for the parameters in equation 27 was given a number of years ago by Prony and discussed by Whitaker et al. (6). Prony formally treated the difference equation

\[
y_1 + \gamma_1 y_{t-1} + \gamma_2 y_{t-2} + \ldots + \gamma_m y_{t-m} = e_t \tag{29}
\]

as a multiple regression problem, considering \( y_t \) as the dependent variable and \( y_{t-1}, y_{t-2}, \ldots, y_{t-m} \) as m independent variables. The \( \gamma_s \) may be estimated by ordinary least squares and are, apart from sign, the elementary symmetric functions of the \( a_i \) i.e., \( \gamma_1 = -\Sigma a_i, \gamma_2 = \Sigma a_i a_{i+1}, \) etc. Then by using the estimates of the \( \gamma_s \) in a polynomial of degree \( m \), the \( a_i \) can be obtained as the \( m \) roots. They can then be substituted in equation 27 and the \( \alpha \) obtained by ordinary least squares. Householder (7) has observed that the procedure has two serious drawbacks: "... it provides no means for weighting the observations in accordance with their supposed precision. Second, it provides no criterion for determining the number of exponentials required for the fitting..." Assuming known weights for the \( y_t \), he gives an iterative technique for getting individual least squares estimates and provides, also, a criterion for deciding on the number of exponential terms needed for an adequate fit. For \( m = 1 \), Prony's method provides an estimator of \( y_1 = -a_1 \), which is equivalent to one of the unsophisticated estimates of the lag 1 autocorrelation coefficient—namely, \( \sum y_i y_{i-1} \).

The estimation of the parameters of equation 28 is somewhat more difficult than for those of 27. By using the normal probability density function as the law to describe the distribution of the random variable \( u_t \) the problem is to estimate the mean and variance of this distribution from the data. Since the right-hand side of equation 28 gives the \( t^\text{th} \) moment of \( u_t \) about the origin, one can get preliminary estimates of \( \mu \) and \( \sigma^2 \) by using the method of moments thus,

\[
y_1 = \mu, \quad y_2 = \sigma^2 + \mu^2,
\]

where \( \mu \) stands for "is an estimate of."

These initial estimates can be used in the Gauss-Newton procedure to obtain more refined estimates. A requirement of knowledge of the weights for the \( y_t \) exists here as in all estimation problems, of course. The results of empirical sampling studies using a modified version of model equation 28, with errors proportional to the true response, will be reported in a subsequent paper.

For most of the Gauss-Newton estimation approaches, it has been the experience of this laboratory that considerable improvement in convergence as well as speed of convergence is obtained if one adds to the Gauss-Newton scheme the method of the path of steepest ascent. The reader is referred to D. W. Marquardt's discussion (8) of this modification. Yet, even this approach sometimes fails owing to the high correlation of the estimates of the parameters. In some data the correlation is in
excess of ± 0.98. Thus, convergence is not always possible even for the most sophisticated iterative procedures.

6. THE NUMBER OF EXPONENTIAL TERMS

Determining the number of exponential terms is a serious problem when \( m \geq 3 \) — i.e., distinguishing between \( m = 3 \) and \( m = 4 \) is not easy when the covariances of the \( y_j \) must be estimated from the data. Carried one step further, deciding whether one has a finite but large number of terms as opposed to an infinite number is indeed difficult. The problem is especially complicated by the fact that the estimates of the parameters are highly correlated. The situation is roughly analogous to two other statistical procedures: determining the degree of a polynomial when there is no replication error and determining the number of common factors in factor analysis studies. In the latter situation, the “tests” are usually administered only once and the factoring is performed on a correlation matrix; thus, there is no external estimate of error available for assessing statistical significance.

As indicated earlier, Householder’s scheme (7) for determining the number of exponential terms requires knowledge of the proper weights for the \( y_j \); i.e., it requires the known variance-covariance matrix of the \( e_i \), aside from the constant multiplier \( \sigma^2 \). Thus, this technique is of little use in most practical situations. Watson (9) has discussed the problems of estimating regression coefficients when an incorrect transformation is used on the \( e_i \); that is, when assumed weights for the \( y_j \) are in error. He is not too hopeful of the approach of transforming the \( e_i \) to remove effect of the autocorrelation in least squares analysis when the covariance of the \( y_j \) must be estimated from the data. Thus, until better approaches are found, the data processor must proceed with the curve fitting even though the proper weights are not known. About all one can do is either assume that the \( y_j \) are independent and have equal variances, or use some transformation that will at least give equal variances for the \( y_j \), and look at the mean square deviation about the fitted line. Corresponding to polynomial curve fitting where the statistical significance of the coefficient of the last fitted term is assessed after each step, one can add exponential terms until the mean square of the residuals is satisfactorily small. However, there is no test of statistical significance available for determining the number of exponential terms when the weights of the \( y_j \) are unknown. The reader is referred to a discussion by Siddiqi (10) of the problems of significance testing of regression coefficients in linear models, when the errors are correlated. Even if the weights of the \( y_j \) are known, however, this step-by-step fitting scheme may not distinguish between the \( m \) term model 27 and the continuous model 28. By using the normal law for the density of the \( f(\omega) \) in model 28, only two constants are fitted to the data; for model 27, \( 2m \) constants are fitted. If \( m \) is large, then in general one would expect a better fit for model 27 than for the two-parameter continuous models. Therefore, other information must be brought to bear on model choice; the choice at any point in time will be based on intuition coupled with one’s understanding of the biologic process under study.

Results of random sampling studies are planned in this laboratory for models with relatively small \( m \). Attempts will be made to fit \( m + n, m + n - 1, \ldots, m, m - 1, \ldots, m - n \) exponential terms to the artificially generated data for various error patterns. It is hoped that from these studies, some notion can be obtained about the number of terms necessary for an “adequate” fit as well as some feeling about the effect of unequal weights for the \( y_j \) on the estimates of the parameters when the weights are not assumed known.

7. CONCLUDING REMARKS

For exponential-decay data, the major problem facing a curve fitter is in proper model choice. This includes consideration of not only the proper mathematical expression to be fitted but also rather intimate knowledge of the nature of the error terms. These problems have been discussed and comments have been
made about a variety of models and error assumptions that one may consider.

It has also been emphasized that no really good procedures are available for curve fitting if the variance-covariance matrix of the error terms is not known or assumed to be known.

For certain assumed model equations, various methods of estimation of the parameters are being studied in this laboratory. Under investigation is the model equation 27, \( m = 2 \) and 3, with the \( e \) independent and proportional to the true response at time \( t \). The performance of the peel-off procedure is under study. The estimates from this procedure are used as starting values for a modified Gauss-Newton iterative scheme. Also planned are studies where \( m \) is fixed and an attempt is made to fit \( m + n, m + n - 1, \ldots, m, m - 1, m - 2, \ldots, m - n \) terms. The effect of sample size on estimating procedures is also to be looked into. Finally, a modified version of model 28 is under study and will be fitted to some empirical data once good estimating procedures are developed for the parameters of that model equation. The results of these investigations will be presented in subsequent reports.

The computer for which programs have been and are being written is a Philco 2000, 8K memory.

REFERENCES


Some Problems on the Use of Negative Exponential Curves in Biology


Danford, M. Bryan

March 1965

SAM-TR-65-4

Task No. 631901

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Many biologic processes give responses that decrease rapidly over time to some asymptote C > 0. The mathematical expressions that describe the various phenomena vary in complexity and form. In order to fit a curve to data in any such situation, one must consider both the formula for the trend and the nature of the deviations or error terms. A discussion of these problems is given so as to indicate to the data analyst the possible choices that are his, relative to assumptions about error terms and relative to technics or methods of estimation. No new analytical procedures are given.

It is noted that several methods of estimation are being studied for certain assumed model equations. The results of these random sampling experiments will be reported in subsequent papers.
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