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BONITA JEAN PEURA for the M. S. in STATISTICS
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Title A PROBABILITY MODEL FOR IRRADIATED BACTERIA AND METHODS TO OBTAIN ESTIMATES OF THE PARAMETERS

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A probability model has been developed for the survival of irradiated bacteria with respect to the dose of radiation. This model is applicable to those bacterial taxa to which the target theory applies.

Three estimation procedures are given for the purpose of obtaining estimates of the probability model's parameters. These procedures are: logarithmic estimation, iterative least-squares estimation and weighted iterative least-squares estimation. The possibility of multiple solutions when the latter two procedures are used is explored.

A PROBABILITY MODEL FOR IRRADIATED BACTERIA AND METHODS TO OBTAIN ESTIMATES OF THE PARAMETERS

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BONITA JEAN PEURA

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[redacted]

Chairman of Department of Statistics

[redacted]

Dean of Graduate School

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CHAPTER 1

INTRODUCTION

Within the past three decades intense research has been conducted on the effect of radiation on bacterial cells (6, p. 71). Because the bacterial cell is very minute and its exact structure is unknown, an explanation of radiation damage to the cell is extremely difficult to formulate. The single target theory and multi-target theory (6, p. 68) have been proposed as an explanation.

The single target theory suggests that the biological effect of radiation is due to the production of ionization by the radiation in, or in the immediate vicinity of, some particular molecule or structure (6, p. 69). The multi-target theory suggests that the effect of radiation is due to the production of ionizations by the radiation in, or in the immediate vicinities of, particular molecules or structures (6, p. 69). The effect which will be considered in this thesis is the survival of irradiated bacteria.

A target within the cell is a particular molecule or structure which must be ionized in order to kill the cell. The death of a cell may be caused by ionization in one target (single target theory) or ionizations in several targets (multi-target theory).

The cell's nucleus or even several molecules of the cell could be a target. The ionization of a target is known as a "hit" (6, p. 72).

This thesis will be relevant to all bacterial taxa for which either the single target theory or multi-target theory is applicable.

CHAPTER 2

A PROBABILITY MODEL

When a number of bacteria belonging to a bacterial taxon have been irradiated at various doses, the experimental graphs of the surviving fractions of bacteria plotted against the doses have been observed to be exponential in nature for various taxa (6, p. 73). The curves seem to vary from one exponential term to a linear combination of exponential terms. The exponential curves suggest a probability model for the survival of irradiated cells which is composed of a finite number of exponential terms.

The development of the probability model will be simplified if the terminology and symbols are defined. The following terms and symbols will be used:

(2.1) j will denote a specific kind of target present within a cell. $j = 1, 2, \ldots, k$.

(2.2) Corresponding to each kind of target there is a positive integer n_j denoting the number of targets of the jth kind which are within a cell. $j = 1, 2, \ldots, k$.

(2.3) The total number of targets present within a cell is

$$M = \sum_{i=1}^{k} n_j .$$

(2. 4) Corresponding to every kind of target there is a positive number (non-zero) α_j, for $j = 1, 2, \ldots, k$, such that the mean dose required to "hit" the jth kind of target is $1/\alpha_j$.

(2. 5) The radiation dose is denoted by t, and $0 \leq t < \infty$.

The above notation does not mean that every bacterium has the same kinds of targets. In general, the kinds of targets and the number of targets will vary from one bacterial taxon to another.

The following assumptions are made:

(2. 6) At any dose t, the event that a particular target is hit is independent of the event that any other target within the cell is hit (whether the targets are of the same type or different types).

(2. 7) n_j is known for $j = 1, 2, \ldots, k$.

(2. 8) The distribution of the dose t required to hit a target of the jth kind is exponential with probability density function

$$\alpha_j e^{-\alpha_j t} \quad \text{if } t \geq 0, \quad j = 1, 2, \ldots, k,$$

or $\quad 0 \quad$ if $t < 0$ (3, p. 65).

(2. 9) If there are M targets within a cell, then all of the M targets must be hit in order to kill the cell.

The probability that one target under irradiation of the jth kind is hit before dose t is

(2.10) $$\int_0^t \alpha_j e^{-\alpha_j t'} dt' = 1 - e^{-\alpha_j t} .$$

The probability that n_j targets of the jth kind are hit before dose t is

(2.11) $$[1 - e^{-\alpha_j t}]^{n_j} .$$ This follows from (2.6).

Then the probability that M targets (n_j of type j, j = 1, 2, ..., k) are hit before dose t is

(2.12 $$\prod_{j=1}^{k} [1 - e^{-\alpha_j t}]^{n_j} .$$ Hence, the probability that a cell survives a dose t is

(2.13) $$f(t;A) \equiv 1 - \prod_{j=1}^{k} [1 - e^{-\alpha_j t}]^{n_j},$$ where A is the k-tuple $(\alpha_1, \alpha_2, \ldots, \alpha_k)$.

It should be noted that f(t;A) will vary from one bacterial taxon to another.

Let N denote the number of bacteria irradiated at a dose t, and let x be the number of bacteria which survived the dose t. Then x is distributed binomially with mean Nf(t;A) and variance N[f(t;A)] [1 - f(t;A)] .

Let y = x/N. Then

(2.14) $$E\{y\} = f(t;A),$$ and

(2.15) $$V\{y\} = [f(t;A)][1 - f(t;A)]/N.$$

That is, the mean and variance of an observed proportion of bacteria which survive a dose t are given by equations (2.14) and (2.15).

An important property of the probability model is expressed in the following theorem.

Theorem. Let the following be true:

(i) $0 < \alpha_j$ for $j = 1, 2, \ldots, k$ and $\alpha_j \neq \alpha_i$ for $j \neq i$,

(ii) $\alpha_1 = \min_{j=1}^{k} \alpha_j$, and

(iii) $\psi(t) = \ell n\{f(t;A)\}$ for $0 \leq t < \infty$, where $f(t;A)$ is defined by (2.13), and ℓn denotes the natural logarithim.

Then $\psi(t)$ tends to $-\alpha_1 t + \ell n\, n_1$ as t becomes positively large.

Proof

$\psi(t) = \ell n\{f(t;A)\}$. Hence,

(2.16) $$\psi(t) = -\alpha_1 t + \ell n\, n_1 + \ell n\Big\{1 + \frac{1}{n_1} \sum_{i=2}^{n_1} \binom{n_1}{i} e^{-\alpha_1 t(i-1)} (-1)^{i+1}$$

$$+ \frac{1}{n_1} \sum_{j=2}^{k} \sum_{i=1}^{n_j} \binom{n_j}{i} e^{-t(i\alpha_j - \alpha_1)} (-1)^{i}$$

$$- \frac{1}{n_1} \sum_{\ell<m} \sum_{i=1}^{n_\ell} \sum_{j=1}^{n_m} \binom{n_\ell}{i}\binom{n_m}{j} e^{-t(i\alpha_\ell + j\alpha_m - \alpha_1)} (-1)^{i+j} + \ldots$$

$$+ (-1)^{k+1} \frac{1}{n_1} \sum_{i=1}^{n_1} \sum_{j=1}^{n_2} \cdots \sum_{\ell=1}^{n_k} \binom{n_1}{i}\binom{n_2}{j} \cdots \binom{n_k}{\ell} e^{-t(i\alpha_1 + j\alpha_2 + \ldots + \ell\alpha_k - \alpha_1)} (-1)^{i+j+\ldots+\ell}\Big\}.$$

Since $\alpha_1 = \min_{j=1}^{k} \alpha_j$, it follows that

$$\alpha_1(i - 1) > 0 \quad \text{for} \quad i = 2, 3, \ldots, n_1,$$

$$(i\alpha_j - \alpha_1) > 0 \quad \text{for} \quad j = 2, 3, \ldots, k \text{ and } i = 1, 2, \ldots, n_j,$$

$$(i\alpha_\ell + j\alpha_m - \alpha_1) > 0 \quad \text{for} \quad \ell < m,$$

$$\vdots$$

and
$$(i\,\alpha_1 + j\,\alpha_2 + \ldots + \ell\,\alpha_k - \alpha_1) > 0 .$$

Hence, as t becomes arbitrarily large

$$[e^{-\alpha_1(i-1)t}, e^{-t(i\alpha_j-\alpha_1)}, \ldots, e^{-t(i\alpha_1+j\alpha_2+\ldots+\ell\alpha_k-\alpha_1)}]$$

tends to $[0, 0, \ldots, 0]$. Whence,

$\psi(t) \rightarrow -\alpha_1 t + \ell n\, n_1$ as t becomes arbitrarily large.

This theorem is the basis for the logarithmic estimation procedure which is discussed in the following chapter. The theorem will again be applied in Chapter 4, where the least-squares estimation procedure is given.

Throughout the remainder of the thesis the symbols which were used in this chapter and assumptions (2. 6) through (2. 9) will be used.

CHAPTER 3

THE LOGARITHMIC ESTIMATION PROCEDURE

The logarithmic estimation procedure is a method to obtain an estimate of A in equation (2.13) from experimental data. The principle of the logarithmic procedure is derived from the theorem of Chapter 1.

The model is

(3.1) $$y_i = [f(t_i;A)]\ e^{\epsilon_i} \quad \text{for } i = 1, 2, \ldots, n.$$

y_i is the observed proportion of bacteria which survive a dose t_i. e^{ϵ_i} is a random error variable with mean one and variance $[1-f(t_i;A)]/N_i f(t_i;A)$.

The logarithmic procedure is applicable when k is one. Equation (3.1) then becomes

(3.2) $$y_i = \{1-[1-e^{-\alpha_1 t_i}]^{n_1}\}\ e^{\epsilon_i},\ i = 1, 2, \ldots, n, \text{ and}$$

(3.3) $$\ell n y_i = \ell n\{1-[1-e^{-\alpha_1 t_i}]^{n_1}\} + \epsilon_i,\ i = 1, 2, \ldots, n.$$

From the theorem of Chapter 1,

(3.4) $$\ell n y_i \doteq -\alpha_1 t_\ell + \ell n\, n_1 + \epsilon'_\ell$$ for sufficiently large values of t_ℓ and for $\ell = 1, 2, \ldots, n'$.

The set $\{(t_\ell, y_\ell) \mid \ell = 1, 2, \ldots, n'\}$ is composed of observations which correspond to sufficiently large values of t_ℓ. The elements, (t_ℓ, y_ℓ), may be chosen in the following manner. $\ell n y_i$ is plotted against t_i. The y_ℓ's are chosen so that the curve determined by $\ell n y_\ell$ and t_ℓ is approximately a straight line.

The estimator $\hat{\alpha}_1$ is found by minimizing

(3.5) $\sum(t_\ell;\alpha_1) = \sum_{\ell=1}^{n'} \{\ell n y_\ell + \alpha_1 t_\ell - \ell n\ n_1\}^2$ with respect to the unknown parameter α_1. Then

(3.6) $$\sum_{\alpha_1}(t_\ell;\hat{\alpha}_1) = 0 = \sum_\ell (t_\ell\ \ell n y_\ell + \hat{\alpha}_1 t_\ell^2 - t_\ell\ \ell n\ n_1),$$ and

(3.7) $$\hat{\alpha}_1 = [\ell n\ n_1 \sum_\ell t_\ell - \sum_\ell t_\ell\ \ell n y_\ell] / \sum_\ell t_\ell^2 .$$

In equation (3.4) nothing was stated about the error term ϵ'_ℓ. ϵ'_ℓ has two components, namely ϵ_ℓ and an unknown function, g_ℓ. g_ℓ is the error which is introduced when the approximation of (3.3) is used. The mean and variance of ϵ'_ℓ cannot be evaluated. Hence, the mean and variance of the estimator $\hat{\alpha}_1$ is unknown.

It should be noted that the logarithmic procedure is the same as the method of least squares where no assumptions are made regarding the random error variable ϵ'_ℓ.

Discussion

The logarithmic procedure is a simple method to obtain the estimator $\hat{\alpha}_1$ when k is one. It would be extremely difficult to assume any properties of the random variables ϵ_i and ϵ_ℓ' of equations (3.3) and (3.4), respectively.

As an example, suppose that

(3.8) $y_i = e^{-\alpha t_i + \epsilon_i}$, $i = 1, 2, \ldots, n$, where $E\{e^{\epsilon_i}\} = 1$.

Then

(3.9) $\ell n y_i = -\alpha t_i + \epsilon_i$, $i = 1, 2, \ldots, n$.

Furthermore, let ϵ_i be distributed normally with mean zero and variance V_i. It then follows that y_i of equation (3.8) is distributed lognormally with mean exp $\{-\alpha t_i + V_i|2\}$ and variance $(e^{V_i}-1)$ exp $\{-2\alpha t_i + V_i|2\}$ (1, p. 8). Whence, $E\{e^{\epsilon_i}\} = e^{V_i|2} = 1$. That is, V_i is zero. But this implies that the variance of y_i is always zero, which is untrue. Hence, the assumption that ϵ_i is distributed normally with mean zero and variance V_i is untenable.

The difficulties which would be encountered if ϵ_ℓ' were considered are more severe. Not only would one need the properties of ϵ_i, but the function g_ℓ would have to be known. However, since g_ℓ is unknown the distribution of ϵ_ℓ' is unknown, too.

CHAPTER 4

LEAST-SQUARES ESTIMATION PROCEDURE

The least-squares procedure is an iterative method to obtain the estimator, $\hat{A}$, of the parameter A in the probability model of (2.13). The model

(4.1) $y_i = f(t_i;A) + \epsilon_i$, where $i = 1, 2, \ldots, n$ and $f(t_i;A)$ is defined in equation (2.13), is assumed. ϵ_i is a random error variable with mean zero and variance $[f(t_i;A)][1 - f(t_i;A)]/N_i$. N_i is the number of bacteria irradiated at a dose t_i. y_i is the observed proportion of bacteria which survive a given dose of radiation (t_i). One additional assumption is made, namely, $\alpha_i \neq \alpha_j$ for $i \neq j$.

A simple model will first be used to explain the least-squares method, and then the method will be extended to the general case.

A Simple Model

The model is

(4.2) $y_i = e^{-\alpha t_i} + \epsilon_i$, $i = 1, 2, \ldots, n$, where $E\{\epsilon_i\} = 0$

Let

(4.3) $\sum(t_i;A) = \sum_i (y_i - e^{-\alpha t_i})^2$, where $A = \alpha$.

$\sum(t_i;A)$ is then minimized with respect to the unknown parameter A. Then

$$(4.4)\quad \sum_{\alpha}(t_i;\hat{A}) = 0 = \sum_i (y_i - e^{-\hat{\alpha} t_i})(t_i e^{-\hat{\alpha} t_i}) = \sum_i (y_i t_i e^{-\hat{\alpha} t_i} - t_i e^{-2\hat{\alpha} t_i}),$$

where $\hat{\alpha}$ is the estimator of α.

Equation (4.4) is non-linear with respect to $\hat{\alpha}$. Consequently, (4.4) cannot be solved directly for $\hat{\alpha}$. Let a_{11} be a "guessed" value of $\hat{\alpha}$, and let ϵ be a small positive number (such as .01, .005, etc.). The Taylor series expansions (10, p. 70) of $e^{-\hat{\alpha} t_i}$ and $e^{-2\hat{\alpha} t_i}$ about the point a_{11} are

$$(4.5)\quad \sum_{k=0}^{\infty} \frac{(\hat{\alpha} - a_{11})^k (-t_i)^k e^{-a_{11} t_i}}{k!} \quad \text{and}$$

$$(4.6)\quad \sum_{k=0}^{\infty} \frac{(\hat{\alpha} - a_{11})^k (-2t_i)^k e^{-2a_{11} t_i}}{k!}, \quad \text{respectively.}$$

The first order expansions of $e^{-\hat{\alpha} t_i}$ and $e^{-2\hat{\alpha} t_i}$ about the point a_{11} are

$$(4.7)\quad e^{-a_{11} t_i} - (\hat{\alpha} - a_{11})\, t_i e^{-a_{11} t_i} \quad \text{and}$$

$$(4.8)\quad e^{-2a_{11} t_i} - 2(\hat{\alpha} - a_{11})\, t_i\, e^{-2a_{11} t_i}, \quad \text{respectively.}$$

$e^{-\hat{\alpha} t_i}$ and $e^{-2\hat{\alpha} t_i}$ are replaced by their respective first order expansions in equation (4.4). This newly formed equation is linear with respect to $(\hat{\alpha} - a_{11})$. Then

$$(4.9)\quad (\hat{\alpha} - a_{11}) = \frac{\sum_i y_i t_i e^{-a_{11}t_i} - \sum_i t_i e^{-2a_{11}t_i}}{\sum_i y_i t_i^2 e^{-a_{11}t_i} - 2\sum_i t_i^2 e^{-2a_{11}t_i}} .$$

Let $\delta_{11} = \hat{\alpha} - a_{11}$. If $|\delta_{11}| < \epsilon$, then $\hat{\alpha} = a_{11} + \delta_{11}$ is taken to be the solution of (4.4). Otherwise, $a_{12} = a_{11} + \delta_{11}$ is used as a second "guessed" value for $\hat{\alpha}$. Then a_{11} of (4.9) is replaced by a_{12}. A new δ_{12} is computed and then compared with ϵ. The same process is repeated until a $\delta_{1\ell}$ is obtained such that $|\delta_{1\ell}| < \epsilon$. Then $\hat{\alpha} = a_{1\ell} + \delta_{1\ell}$ is the solution of equation (4.4).

The General Model

The model is the same as the one described by (4.1). Then

$$(4.10)\qquad \sum (t_i;A) = \sum_i [y_i - f(t_i;A)]^2.$$

$\sum(t_i;A)$ is hoped to be minimized with respect to A by setting partial derivatives of $\sum(t_i;A)$ with respect to A equal to zero. This question will arise in a later discussion.

k equations are obtained by taking the partial derivatives of $\sum(t_i;A)$ with respect to A. The equations are:

$$(4.11.1) \sum_{\alpha_1} (t_i;\hat{A}) = 0 = \sum_i [y_i - f(t_i;\hat{A})][f_{\alpha_1}(t_i;\hat{A})],$$

$$(4.11.2) \sum_{\alpha_2} (t_i;\hat{A}) = 0 = \sum_i [y_i - f(t_i;\hat{A})][f_{\alpha_2}(t_i;\hat{A})],$$

$\vdots$

(4.11.k) $\sum_{\alpha_k}(t_i;\hat{A}) = 0 = \sum_i [y_i - f(t_i;\hat{A})][f_{\alpha_k}(t_i;\hat{A})]$,

where $\hat{A} = (\hat{\alpha}_1, \hat{\alpha}_2, \ldots, \hat{\alpha}_k)$ and $\hat{A}$ is a non-zero estimator of A.

If all multiplications within the summation signs of equations (4.11.1) through (4. 11. k) are performed, then in general the equations become

(4. 12) $\sum_{\alpha_j}(t_i;\hat{A}) = 0 = \sum_{i=1}^{n}\sum_{m=1}^{M_j} B_{imj}\, e^{-t_i \hat{B}_{mj}}$, $j = 1, 2, \ldots, k.$

M_j is the total number of terms involved after multiplication. B_{imj} will be either nt_iy_i or nt_i, where n is an integer. The $\hat{B}_{mj}$'s are linear combinations of the $\hat{\alpha}_j$'s.

Let A_1 be a "guessed" value of $\hat{A}$, namely $A_1 = (a_{11}, a_{21}, \ldots, a_{k1})$, let ϵ be a small positive number, let

(4. 13) $D_1 = \hat{A} - A_1$

$= [(\hat{\alpha}_1 - a_{11}), (\hat{\alpha}_2 - a_{21}), \ldots, (\hat{\alpha}_k - a_{k1})] = [\delta_{11}, \delta_{21}, \ldots, \delta_{k1}]$,

and let $\hat{A}$ exist such that (4. 12) is satisfied.

Each exponential term which occurs in equation (4. 12) is expanded in a first order Taylor series expansion about its respective "guessed" value. For example, if $\hat{B}_{11}$ were $\hat{\alpha}_1 + 2\hat{\alpha}_2$, then the first order expansion of $e^{-t_i \hat{B}_{11}}$ about the point $(a_{11} + 2a_{21})$ would be $e^{-t_i(a_{11}+2a_{21})} - [(\hat{\alpha}_1 - a_{11}) + 2(\hat{\alpha}_2 - a_{21})]\, t_i e^{-t_i(a_{11}+2a_{21})}$.

$e^{-t_i \hat{B}_{mj}}$ is replaced by its first order expansion in (4. 12) for $j = 1, 2, \ldots, k$. The resulting k equations will be linear with respect to D_1, namely

(4.14) $\sum_{a_j}(t_i;\hat{A}) = 0$

$$= \sum_{i=1}^{n}\sum_{m=1}^{M_j'} B_{imj}' e^{-t_i g_{mj}} + \sum_{\ell=1}^{k}\sum_{i=1}^{n}\sum_{m=1}^{M_{j\ell}''} \delta_{\ell 1} B_{imj\ell}'' e^{-t_i g_{mj\ell}},$$

for $j=1,2,\ldots,k$. The $g_{mj\ell}$'s are linear combinations of the a_{j1}'s.

The k equations of (4.14) can be expressed in matrix notation as

(4.15) $B_1 \cdot D_1' = Q_1$,

or expanded as

$$(4.16) \left[\sum_{i=1}^{n}\sum_{m=1}^{M_{j\ell}''} B_{imj\ell}'' e^{-t_i g_{mj\ell}}\right] \times \left[\delta_{\ell 1}\right]' = -\left[\sum_{i=1}^{n}\sum_{m=1}^{M_j'} B_{imj}' e^{-t_i g_{mj}}\right],$$

where $j=1,2,\ldots,k$ refers to the jth row and $\ell=1,2,\ldots,k$ refers to the ℓth column. B_1 is a $k \times k$ matrix, D_1' is a $k \times 1$ matrix, and Q_1 is a $k \times 1$ matrix. If B_1^{-1} exists, then $D_1' = B_1^{-1} Q_1$. The δ_{j1}'s are then compared with ϵ. If $|\delta_{j1}| < \epsilon$, then $\hat{\alpha}_j$ is $a_{j1}+\delta_{j1}$. Otherwise, a new "guessed" value, a_{j2}, replaces a_{j1} in (4.16), namely $a_{j2} = a_{j1} + \delta_{j1}$.

Suppose that $|\delta_{11}| < \epsilon$ and $|\delta_{j1}| > \epsilon$ for $j=2,3,\ldots,k$. Then $\hat{\alpha}_1 = a_{11} + \delta_{11}$, $A_2 = (\hat{\alpha}_1, a_{22}, a_{32}, \ldots, a_{k2})$, where $a_{j2} = a_{j1} + \delta_{j1}$ for $j=2,3,\ldots,k$, and $D_2 = [(\hat{\alpha}_1 - \hat{\alpha}_1), (\hat{\alpha}_2 - a_{22}), \ldots, (\hat{\alpha}_k - a_{k2})] = (0, \delta_{22}, \ldots, \delta_{k2})$. In (4.16) $\hat{\alpha}_1$ replaces a_{11}, a_{j2} replaces a_{j1}, for $j=2,3,\ldots,k$, and

δ_{j2} replaces δ_{j1}. This means that column one of the B_1 matrix will be deleted. Then B_1 becomes a kx(k-1) matrix. The row vector $\left[\sum_{i=1}^{n}\sum_{m=1}^{M''_{1\ell}} B''_{iml\ell} e^{-t_i g_{ml\ell}}\right]$, $\ell = 2, 3, \ldots, k$, is subtracted from the k rows of the kx(k-1) B_1 matrix. This new matrix, B_2, is then a (k-1)x(k-1) matrix. Similarly, $\left[\sum_{i=1}^{n}\sum_{m=1}^{M'_1} B'_{iml} e^{-t_i g_{ml}}\right]$ is subtracted from the k rows of the Q_1 matrix, thus forming Q_2, which is a (k-1)x1 matrix. Then

(4.17) $B_2 \cdot D'_2 = Q_2$, and if B_2^{-1} exists, then

(4.18) $D'_2 = B_2^{-1} Q_2$.

The δ_{j2}'s are again compared with ϵ $(j = 2, 3, \ldots, k)$. If $|\delta_{j2}| < \epsilon$, then $\hat{\alpha}_j = a_{j2} + \delta_{j2}$. Otherwise, a third "guessed" value, a_{j3}, replaces a_{j2} in (4.17), namely $a_{j3} = a_{j2} + \delta_{j2}$. However, suppose that $|\delta_{22}| < \epsilon$ and $|\delta_{j2}| > \epsilon$ for $j > 2$. Then the B_2 matrix would be reduced to a (k-2)x(k-2) matrix, B_3, D'_2 becomes a(k-2)x1 matrix, D'_3, and Q_2 reduces to a (k-2)x1 matrix, Q_3, in a manner similar to the preceding discussion. The same procedure is repeated until $|\delta_{j\ell_j}| < \epsilon$ for some ℓ_j and $j = 1, 2, \ldots, k$.

The reduction of the B, D and Q matrices when one or more of the $\delta_{j\ell_j}$'s are less than ϵ would be analogous to the preceding discussion.

Multiple Solutions and Bias

Case 1 Consider the model given by (4.1) with one added restriction. Namely, $n_m \neq n_j$ for $j \neq m$. Let

(4.19) $\hat{A}' = (\hat{\alpha}'_1, \hat{\alpha}'_2, \ldots, \hat{\alpha}'_k)$ such that $\sum(t_i;\hat{A}')$ is an absolute minimum and $\sum(t_i;\hat{A}')$ is the only absolute minimum,

(4.20) $\sum_{\alpha_j}(t_i;A) = 0$ (j 1, 2, ..., k) if and only if $A = \hat{A}'$, and

(4.21) $\hat{A} = (\hat{\alpha}_1, \hat{\alpha}_2, \ldots, \hat{\alpha}_k)$ be the solution to equations (4.11.1) through (4.11.k) obtained by the iterative least-squares procedure for a prechosen ϵ.

Then (1) $\hat{A}'$ is an unbiased estimate of A (4, p. 115),

(2) $|\hat{A}' - \hat{A}| < \epsilon\sqrt{k}$,

(3) $|A - E\{\hat{A}\}| < \epsilon\sqrt{k}$, and

(4) $|\alpha_j - E\{\hat{\alpha}_j\}| < \epsilon$ for $j = 1, 2, \ldots, k$.

That is, the bias of the estimator $\hat{\alpha}_j$ is less than ϵ.

Suppose that there exists an $\hat{A}''$ such that $\sum(t_i;\hat{A}'')$ is not an absolute minimum and $\sum_{\alpha_j}(t_i;\hat{A}'') = 0$ for $j = 1, 2, \ldots, k$. That is, (4.20) is violated.

Let $A_1 = (a_{11}, a_{21}, \ldots, a_{k1})$ be the first guessed value of $\hat{A}$ and let $N(\hat{A}')$ and $N(\hat{A}'')$ be neighborhoods of $\hat{A}'$ and $\hat{A}''$, respectively, such that $N(\hat{A}') \cap N(\hat{A}'') = \emptyset$. If in repeated sampling $A_1 \in N(\hat{A}')$ such that $|\hat{A}' - \hat{A}| < \epsilon\sqrt{k}$ always occurs, then the bias of the estimator $\hat{\alpha}_j (j = 1, 2, \ldots, k)$ is less than ϵ. However, if $A_1 \epsilon N(\hat{A}'')$ such that $|\hat{A}'' - \hat{A}| < \epsilon\sqrt{k}$ occurs, then the bias of $\hat{\alpha}_j$ will be larger than ϵ. Unfortunately, there is no method to determine if $|\hat{A}' - \hat{A}| < \epsilon\sqrt{k}$ or if $|\hat{A}'' - \hat{A}| < \epsilon\sqrt{k}$ occurs. One hopes that the latter would be a rather rare occurrence.

Case 2

The same model as (4.1) is assumed with one added restriction. Namely, $n_1 = n_2 \neq n_j$ for $j > 2$ and $n_m \neq n_j$ for $m \neq j$ and $m, j > 2$.

Let

(4.22) $\hat{A}_1' = (\hat{\alpha}_1', \hat{\alpha}_2', \ldots, \hat{\alpha}_k')$ such that $\sum(t_i; \hat{A}_1')$ is an absolute minimum,

(4.23) $\hat{A}_2' = (\hat{\alpha}_2', \hat{\alpha}_1', \ldots, \hat{\alpha}_k')$,

(4.24) $N(\hat{A}_1')$ and $N(\hat{A}_2')$ be neighborhoods of $\hat{A}_1'$ and $\hat{A}_2'$, respectively,

(4.25) $\hat{A} = (\hat{\alpha}_1, \hat{\alpha}_2, \ldots, \hat{\alpha}_k)$ be the solution to equations (4.11.1) through (4.11.k) obtained by the iterative least-squares procedure for a prechosen ϵ.

Then $\sum(t_i; \hat{A}_2')$ is an absolute minimum (8, p. 7). Let $\hat{A}_1'$ and $\hat{A}_2'$ be the only points for which $\sum(t_i; A)$ is an absolute minimum. Then $\hat{A}_1'$ and $\hat{A}_2'$ are unbiased estimators of A.

Since there are two points for which $\sum(t_i;A)$ is an absolute minimum, this suggests the existence of a stationary point, $\hat{A}''$, such that $\sum_{\alpha_j}(t_i;\hat{A}'') = 0$ for $j=1, 2, \ldots, k$. Suppose that $\hat{A}''$ exists, and let $N(\hat{A}'')$ be a neighborhood about $\hat{A}''$ such that $N(\hat{A}'_1) \cap N(\hat{A}'') = N(\hat{A}'_2) \cap N(\hat{A}'') = \emptyset$.

Let $A_1 = (a_{11}, a_{21}, \ldots, a_{k1})$ be the first guessed value of $\hat{A}$. In repeated sampling suppose that $A_1 \epsilon N(\hat{A}'_1)$ or $A_1 \epsilon N(\hat{A}'_2)$ such that $|\hat{A}'_1 - \hat{A}| < \epsilon\sqrt{k}$ or $|\hat{A}'_2 - \hat{A}| < \epsilon\sqrt{k}$ always occurs. Then the bias of $\hat{\alpha}_j (j=1, 2, \ldots, k)$ would be less than ϵ. However, if $A_1 \epsilon N(\hat{A}'')$ such that $|\hat{A}'' - \hat{A}| < \epsilon\sqrt{k}$, then the bias of $\hat{\alpha}_j (j=1, 2, \ldots, k)$ will be greater than ϵ. As in case one, there is no method to determine which would occur.

General Case

The same model as (4.1) is assumed.

Let $n_1 = n_2 = \cdots = n_a$,

$n_{a+1} = n_{a+2} = \cdots = n_{a+b}$,

$n_{a+b+1} = n_{a+b+2} = \cdots = n_{a+b+c}$,

$\vdots$

and $n_{a+b+c+\ldots+x+1} = n_{a+b+c+\ldots+x+2} = \cdots = n_k$.

Then there are $\underline{a}$ n_j's which equal n_1, $\underline{b}$ n_j's which equal n_{a+1}, $\underline{c}$ n_j's which equal n_{a+b+1}, ..., and $(k-a-b-c-\ldots-x)$ n_j's which equal n_k.

Let

(4.26) $\hat{A}' = (\hat{\alpha}'_1, \hat{\alpha}'_2, \dots, \hat{\alpha}'_k)$ such that $\sum(t_i; \hat{A}')$ is an absolute minimum, and

(4.27) $\hat{A} = (\hat{\alpha}_1, \hat{\alpha}_2, \dots, \hat{\alpha}_k)$ be the solution to equations (4.11.1) through (4.11.k) obtained by the iterative least-squares procedure for a prechosen ϵ.

Then there are $(a!)(b!)(c!)\cdots[(k-a-b-c-\cdots-x)!]$ points such that $\sum(t_i;A)$ is an absolute minimum. Let F denote this number and P denote the set of points, namely

$$P = \{\hat{A}'_m \mid m=1, 2, \dots, F \text{ and } \hat{\alpha}'_1, \hat{\alpha}'_2, \dots, \hat{\alpha}'_k \in \hat{A}'_m\}.$$

Suppose that $\hat{A}'_1, \hat{A}'_2, \dots, \hat{A}'_F$ are the only points for which $\sum(t_i;A)$ is an absolute minimum. Then $\hat{A}'_m$ is an unbiased estimate of A.

Since there are F points for which $\sum(t_i;A)$ is an absolute minimum, this suggests the existence of at least one stationary point, $\hat{A}''$, such that $\sum_{\alpha_j}(t_i;\hat{A}'') = 0$ for $j=1, 2, \dots, k$.

Suppose that $\hat{A}''$ exists. Let $N(\hat{A}'_m)$ and $N(\hat{A}'')$ be neighborhoods of $\hat{A}'_m$ and $\hat{A}''$, respectively, such that $N(\hat{A}'_m) \cap N(\hat{A}'') = \emptyset$ for $m=1, 2, \dots, F$, and let $A_1 = (a_{11}, a_{21}, \dots, a_{k1})$ be the first "guessed" value of $\hat{A}$. If in repeated sampling $A_1 \in N(\hat{A}'_m)$ such that $|\hat{A}'_m - \hat{A}| < \epsilon\sqrt{k}$ always occurs, then the bias of $\hat{\alpha}_j (j=1, 2, \dots, k)$ is less than ϵ. However, if $A_1 \epsilon N(\hat{A}'')$ such that $|\hat{A}'' - \hat{A}| < \epsilon \sqrt{k}$, then the bias of $\hat{\alpha}_j (j = 1, 2, \ldots, k)$ will be greater than ϵ.

The possibility of multiple solutions to equations (4. 11. 1) through (4. 11. k) presents a very delicate situation. If a solution is obtained, one does not know whether it is contained in a neighborhood of the point for which $\sum(t_i;A)$ is an absolute minimum or whether it is in the neighborhood of some stationary point. In the preceding discussion the existence of one stationary point was assumed, but it is possible that more than one stationary point may exist.

The existence of no stationary points is more likely when $n_j \neq n_m$ for $j \neq m$. The existence of only one stationary point is more probable when case 2 occurs. When more than two of the n_j's are equal the existence of more than one stationary point would probably not be a rare occurrence. Whenever one uses the least-squares procedure, one should always be aware of the possibility of multiple solutions.

Weighted Least-Squares Estimation Procedure

The objective of the weighted least-squares procedure is to obtain an estimator of the parameter A in (4. 1) such that the estimator is unbiased and has minimum variance.

Consider the model

(4.28) $y_i = f(t_i;A) + \epsilon_i$, $i = 1, 2, \ldots, n$, $E\{\epsilon_i\} = 0$,

$$V\{\epsilon_i\} = [f(t_i;A)][1-f(t_i;A)]/N_i = P_i(1-P_i)/N_i,$$

$f(t_i;A)$ is defined by equation (2.13), and $\alpha_i \neq \alpha_j$ for $i \neq j$. In order to obtain a minimum variance estimator, weights are given to the y_i's such that

(4.29) $V\{k_i y_i\} = V\{k_j y_j\}$, and

$V\{k_i \epsilon_i\} = V\{k_j \epsilon_j\}$. Then

(4.30) $k_i^2 = N_i/P_i(1-P_i)$, and

(4.31) $V\{k_i y_i\} = V\{k_i \epsilon_i\} = 1$ for $i = 1, 2, \ldots, n$.

The weighted model is

(4.32) $k_i y_i = k_i f(t_i;A) + k_i \epsilon_i$, $i = 1, 2, \ldots, n$, $E\{k_i \epsilon_i\} = 0$,

and $V\{k_i \epsilon_i\} = 1$.

Then

(4.33) $\sum'(t_i;A) = \sum k_i^2 [y_i - f(t_i;A)]^2$.

If $\hat{A}$ were an estimator of A such that $\sum'(t_i;\hat{A})$ is an absolute minimum, then $\hat{A}$ would be an unbiased estimator of A with minimum variance (4, p. 115).

However, k_i cannot be evaluated since the parameter A is unknown. Estimated weights, W_i, will replace the unknown weights k_i. Since $y_i = x_i/N_i$, where x_i is the number of bacteria which survive a dose t_i, and x_i is distributed binomially, it follows that an unbiased estimate of the variance of y_i is

$$(4.33)\qquad v(y_i) = y_i(1-y_i)/N_i = v(\epsilon_i),\ i=1, 2, \ldots, n.$$

Then the estimated weight, W_i, is given by

$$(4.34)\qquad W_i^2 = N_i/y_i(1-y_i),\quad 0 < y_i < 1.$$

The new model is

$$(4.35)\qquad W_i y_i = W_i f(t_i;A) + W_i \epsilon_i,\ i = 1, 2, \ldots, n.$$

Then

$$(4.36)\qquad \sum{}'(t_i;A) = \sum_i W_i^2[y_i - f(t_i;A)]^2, \text{ and}$$

$$(4.37)\qquad \sum{}'_{\alpha_j}(t_i;\hat{A}) = 0 = \sum_i W_i^2[y_i - f(t_i;\hat{A})][f_{\alpha_j}(t_i;\hat{A})],\ j=1,2,\ldots,k.$$

The estimator $\hat{A}$ of (4.37) is obtained by the iterative least-squares procedure.

Discussion

Let $\hat{A}'_1$ exist such that $\sum'(t_i;\hat{A}'_1)$ of (4.36) is an absolute minimum. Furthermore, suppose that $\hat{A}_1$ is the solution to (4.37) obtained by the iterative least-squares procedure for a prechosen ϵ. Consider another estimator $\hat{A}'_2$ such that $\sum(t_i;\hat{A}'_2)$ of (4.10) is an absolute minimum, and let $\hat{A}_2$ be the estimator obtained by the least squares procedure for a prechosen ϵ.

Suppose that in repeated sampling

(4.38) $|\hat{A}'_1 - \hat{A}_1|, \; |\hat{A}'_2 - \hat{A}_2| < \epsilon\sqrt{k}$

always occurs. Then it would be expected that $V\{\hat{A}_1\} < V\{\hat{A}_2\}$. Whether or not this occurs is a difficult question.

In (4.35) the $E\{W_i\epsilon_i\}$ cannot be evaluated.

Since
$$W_i^2 = N_i/y_i(1-y_i)$$
$$= N_i/[f(t_i;A) + \epsilon_i][1 - f(t_i;A) - \epsilon_i],$$
the weight W_i contains the random error variable ϵ_i. It is then possible that the bias of $\hat{A}_1$ is greater than the bias of $\hat{A}_2$ and that $V\{\hat{A}_1\} < V\{\hat{A}_2\}$. However, this cannot be answered theoretically. An empirical study pertaining to this question was done by Monte Carlo methods and appears in Appendix I.

Usually when the method of least-squares is used, the random error variable ϵ_i is assumed to have mean zero and

$V\{\epsilon_i\} = V\{\epsilon_j\} = V$ for $i, j = 1, 2, \ldots, n$. The iterative least-squares procedure does not assume common variance for the ϵ_i's. The weighted iterative least-squares procedure corrects for the lack of uniformity of variance and thereby attempts to procure an estimator with minimum variance.

An Example

$\underline{R_1}$ bacteria were irradiated at six different doses of x-radiation in a buffer solution. The number of surviving bacteria and the proportion of surviving bacteria for each dose appear in Table 1. The dose is expressed as 10^5 Rads.

Table 1

Dose (t_i)	Number Surviving ($x10^6$)	Proportion Surviving (y_i)
0.00	118.5	1.0000
0.62	118.25	0.9979
1.25	111.80	0.9435
2.50	79.75	0.6730
3.75	60.67	0.5120
5.00	47.56	0.4014

The model is assumed to be

(4.39) $y_i = f(t_i;A) + \epsilon_i$

$$= 1 - [1 - e^{-\alpha_1 t_i}][1 - e^{-\alpha_2 t_i}] + \epsilon_i, \; i = 1, 2, \ldots, 6 \text{ and } E\{\epsilon_i\} = 0.$$

Then

(4.40) $\sum(t_i;A) = \sum_i [y_i - f(t_i;A)]^2,$

(4.41) $\sum_{\alpha_1}(t_i;\hat{A}) = 0 = \sum_i [y_i - f(t_i;\hat{A})][t_i e^{-\hat{\alpha}_1 t_i} - t_i e^{-t_i(\hat{\alpha}_1 + \hat{\alpha}_2)}]$, and

(4.42) $\sum_{\alpha_2}(t_i;\hat{A}) = 0 = \sum_i [y_i - f(t_i;\hat{A})][t_i e^{-\hat{\alpha}_2 t_i} - t_i e^{-t_i(\hat{\alpha}_1 + \hat{\alpha}_2)}]$.

ϵ is chosen to be .01.

The "guessed" values a_{11} and a_{21}, which correspond to $\hat{\alpha}_1$ and $\hat{\alpha}_2$, are made in the following manner. A straight line through the origin is fitted to the points of $\ell n y_i$. Then

(4.43) $a'_{11} = [-\sum_i t_i \, \ell n y_i] / \sum_i t_i^2$. Using the data in Table 1, a'_{11} is 0.18. Since the other exponential terms were neglected, 0.19 is used as a_{11}.

a_{21} is found by solving the equation

(4.44) $.4014 = 1 - [1 - e^{-(.19)5}][1 - e^{-a_{21} 5}]$.

The solution is $a_{21} = 0.75$.

All multiplications within the summation signs of equations (4.41) and (4.42) are performed. The exponentials which occur in these equations are:

(4.45) $e^{-\hat{\alpha}_1 t_i}$, $e^{-\hat{\alpha}_2 t_i}$, $e^{-2\hat{\alpha}_1 t_i}$, $e^{-2\hat{\alpha}_2 t_i}$, $e^{-t_i(\hat{\alpha}_1 + \hat{\alpha}_2)}$, $e^{-2t_i(\hat{\alpha}_1 + \hat{\alpha}_2)}$,

$e^{-t_i(2\hat{\alpha}_1 + \hat{\alpha}_2)}$, and $e^{-t_i(\hat{\alpha}_1 + 2\hat{\alpha}_2)}$.

Each exponential of (4.45) is expanded in a first order Taylor series expansion about its corresponding "guessed" value. Then each exponential of (4.41) and (4.42) is replaced by its respective first order expansion. The resulting equations appear in Table 2.

The two equations appearing in Table 2 may be represented by matrix notation as

(4.46) $B_1 \cdot D_1' = Q_1$, or

$$\begin{bmatrix} A_2 & A_3 \\ C_2 & C_3 \end{bmatrix} \times \begin{bmatrix} \delta_{11} \\ \delta_{21} \end{bmatrix} = \begin{bmatrix} -A_1 \\ -C_1 \end{bmatrix}, \text{ where}$$

$\delta_{11} = (\hat{\alpha}_1 - a_{11})$ and $\delta_{21} = (\hat{\alpha}_2 - a_{21})$. From Table 2 it is easily verified that $A_3 = C_2$. B_1 is then a symmetric matrix. Then

(4.48) $D_1' = B_1^{-1} \cdot Q_1$.

The values of $\delta_{j\ell}$ (ℓ refers to the ℓth iteration), $a_{j\ell}$, $\hat{\alpha}_1$, and $\hat{\alpha}_2$ are presented in Table 3.

On the first iteration $\hat{\alpha}_1$ is obtained. Consequently, only one equation is needed to solve for $\hat{\alpha}_2$. Then in Table 2, $A_2 = C_2 = 0$, and equation (1) is subtracted from equation (2). The

Table 2

Equation 1: $0 = A_1 + (\hat{a}_1 - a_{11})\, A_2 + (\hat{a}_2 - a_{22})\, A_3$

Coefficients:	Constants	$(\hat{a}_1 - a_{11})$	$(\hat{a}_2 - a_{22})$
	$\sum y_i t_i e^{-a_{11} t_i}$	$-\sum y_i t_i^2 e^{-a_{11} t_i}$	
	$-\sum y_i t_i e^{-t_i(a_{11}+a_{21})}$	$+\sum y_i t_i^2 e^{-t_i(a_{11}+a_{21})}$	$+\sum y_i t_i^2 e^{-t_i(a_{11}+a_{21})}$
	$-\sum t_i e^{-2a_{11} t_i}$	$+2\sum t_i^2 e^{-2a_{11} t_i}$	
	$-\sum t_i e^{-t_i(a_{11}+a_{21})}$	$+\sum t_i^2 e^{-t_i(a_{11}+a_{21})}$	$+\sum t_i^2 e^{-t_i(a_{11}+a_{21})}$
	$+2\sum t_i e^{-t_i(2a_{11}+a_{21})}$	$-4\sum t_i^2 e^{-t_i(2a_{11}+a_{21})}$	$-2\sum t_i^2 e^{-t_i(2a_{11}+a_{21})}$
	$+\sum t_i e^{-t_i(a_{11}+2a_{21})}$	$-\sum t_i^2 e^{-t_i(a_{11}+2a_{21})}$	$-2\sum t_i^2 e^{-t_i(a_{11}+2a_{21})}$
	$-\sum t_i e^{-2t_i(a_{11}+a_{21})}$	$+2\sum t_i^2 e^{-2t_i(a_{11}+a_{21})}$	$+2\sum t_i^2 e^{-2t_i(a_{11}+a_{21})}$
Totals	A_1	A_2	A_3

Table 2 (Continued)

Equation 2: $0 = C_1 + (\hat{\alpha}_1 - a_{11}) C_2 + (\hat{\alpha}_2 - a_{21}) C_3$

Coefficients:	Constants	$(\hat{\alpha}_1 - a_{11})$	$(\hat{\alpha}_2 - a_{21})$
	$\sum y_i t_i e^{-a_{21} t_i}$		$-\sum y_i t_i^2 e^{-a_{21} t_i}$
	$-\sum y_i t_i e^{-t_i(a_{11}+a_{21})}$	$+\sum y_i t_i^2 e^{-t_i(a_{11}+a_{21})}$	$+\sum y_i t_i^2 e^{-t_i(a_{11}+a_{21})}$
	$-\sum t_i e^{-2a_{21} t_i}$		$+\sum t_i^2 e^{-2a_{21} t_i}$
	$-\sum t_i e^{-t_i(a_{11}+a_{21})}$	$+\sum t_i^2 e^{-t_i(a_{11}+a_{21})}$	$+\sum t_i^2 e^{-t_i(a_{11}+a_{21})}$
	$+\sum t_i e^{-t_i(2a_{11}+a_{21})}$	$-2\sum t_i^2 e^{-t_i(2a_{11}+a_{21})}$	$-\sum t_i^2 e^{-t_i(2a_{11}+a_{21})}$
	$+2\sum t_i e^{-t_i(a_{11}+2a_{21})}$	$-2\sum t_i^2 e^{-t_i(a_{11}+2a_{21})}$	$-4\sum t_i^2 e^{-t_i(a_{11}+2a_{21})}$
	$-\sum t_i e^{-2t_i(a_{11}+a_{21})}$	$+2\sum t_i^2 e^{-2t_i(a_{11}+a_{21})}$	$+2\sum t_i^2 e^{-2t_i(a_{11}+a_{21})}$
Totals	C_1	C_2	C_3

Table 3

ℓ	$a_{1\ell}$	$a_{2\ell}$	$\delta_{1\ell}$	$\delta_{2\ell}$	$\hat{\alpha}_1$	$\hat{\alpha}_2$
1	.19	.75	.0028	-.022	.187	--
2	--	.73	---	+.0721	.187	--
3	--	.80	---	-.0048	.187	.795

resultant is

(4.49) $0 = (C_1 - A_1) + (\hat{\alpha}_2 - a_{21})(C_3 - A_3).$

Then $\hat{\alpha}_1$ replaces a_{11}, and a_{22} replaces a_{21} in (4.41), where $a_{22} = a_{21} + \delta_{21}$. Similarly, on the third iteration a_{23} replaces a_{22}, where $a_{23} = a_{22} + \delta_{22}$.

The estimated model is

(4.50) $\hat{y} = 1 - [1 - e^{-.187t}][1 - e^{-.795t}].$

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APPENDIX 1

AN EMPIRICAL STUDY

Let x_i be distributed binomially, N_i, P_i, with $N_i = 100$, and $P_i = e^{-\alpha t_i}$, where $\alpha = 0.50$. Let $y_i = x_i/100$. Then $E\{y_i\} = P_i$, and $V\{y_i\} = P_i(1 - P_i)/100$.

Consider the models

(1.1) $y_i = e^{-\alpha t_i} + \varepsilon_i$, $i = 1, 2, \ldots, 8$, $E\{\epsilon_i\} = 0$,

(1.2) $y_i = e^{-\alpha t_i + \epsilon_i}$, $i = 1, 2, \ldots, 8, E\{e^{\epsilon_i}\} = 1$, or, equivalently,

(1.3) $\ell n y_i = -\alpha t_i + \epsilon_i$, $i = 1, 2, \ldots, 8$, and

(1.4) $W_i y_i = W_i e^{-\alpha t_i} + W_i \epsilon_i$, $i = 1, 2, \ldots, 8$, where $W_i^2 = 100/y_i(1-y_i)$.

Let $[(1, y_{j1}), (2, y_{j2}), \ldots, (8, y_{j8})]$ be a random sample of size eight which corresponds to a random sample $[(1, x_{j1}), (2, x_{j2}), \ldots, (8, x_{j8})]$, where $j = 1, 2, \ldots, 8$. Eight random samples were obtained by Monte Carlo Methods. The cumulative probability function

(1.5) $$F(x_{ji}) = \sum_{\mu=0}^{x_{ji}} \binom{100}{\mu} P_i^{\mu}(1-P_i)^{100-\mu}$$

was used in the Monte Carlo Method. The values of $F(x_{ji})$ which corresponded to random numbers (7, p. 507-516) were obtained from binomial tables (9, p. 157-172).

The eight binomial populations are given in Table 1.1, and the eight samples obtained by Monte Carlo are given in Table 1.2.

Table 1.1

t	$P_i = e^{-\alpha t_i}$, $\alpha = .50$
1	.61
2	.37
3	.22
4	.14
5	.08
6	.05
7	.03
8	.02

For each of the eight random samples, five different estimates of α were computed. These were:

(1.6) $\hat{\alpha}_1$. The iterative least-squares procedure of Chapter 4 was used. ϵ was chosen to be .01. a_ℓ is a "guessed" value of $\hat{\alpha}_1$. The computing equation is

Table 1.2

Sample	t_i	x_i	y_i
1	1	57	.57
	2	38	.38
	3	19	.19
	4	20	.20
	5	11	.11
	6	3	.03
	7	5	.05
	8	2	.02
2	1	65	.65
	2	31	.31
	3	17	.17
	4	16	.16
	5	6	.06
	6	7	.07
	7	5	.05
	8	0	.00
3	1	59	.59
	2	35	.35
	3	19	.19
	4	12	.12
	5	7	.07
	6	7	.07
	7	1	.01
	8	3	.03
4	1	57	.57
	2	34	.34
	3	24	.24
	4	11	.11
	5	7	.07
	6	2	.02
	7	4	.04
	8	4	.04

Table 1. 2 (continued)

Sample	t_i	x_i	y_i
5	1	61	.61
	2	28	.28
	3	25	.25
	4	13	.13
	5	11	.11
	6	6	.06
	7	2	.02
	8	0	.00
6	1	63	.63
	2	33	.33
	3	15	.15
	4	18	.18
	5	11	.11
	6	5	.05
	7	5	.05
	8	3	.03
7	1	66	.66
	2	26	.26
	3	17	.17
	4	13	.13
	5	12	.12
	6	8	.08
	7	4	.04
	8	3	.03
8	1	57	.57
	2	43	.43
	3	23	.23
	4	11	.11
	5	6	.06
	6	12	.12
	7	3	.03
	8	4	.04

(1.6.1) $\delta_\ell = (\hat{\alpha}_1 - a_\ell)$

$$= \frac{\sum_{i=1}^{8} y_i t_i e^{-a_\ell t_i} - \sum_{i=1}^{8} t_i e^{-2a_\ell t_i}}{\sum_{i=1}^{8} y_i t_i^2 e^{-a_\ell t_i} - 2\sum_{i=1}^{8} t_i^2 e^{-2a_\ell t_i}} .$$

If $|\delta_\ell| < \epsilon$, then $\hat{\alpha}_1 = a_\ell + \delta_\ell$.

(1.7) $\hat{\alpha}_2$. The weighted iterative least-squares procedure of Chapter 4 was used. ϵ was chosen to be .01. a_ℓ is a "guessed" value of $\hat{\alpha}_2$. The computing equation is

(1.7.1) $\delta_\ell = (\hat{\alpha}_2 - a_\ell)$

$$= \frac{\sum_{i=1}^{8} W_i^2 y_i t_i e^{-a_\ell t_i} - \sum_{i=1}^{8} W_i^2 e^{-2a_\ell t_i}}{\sum_{i=1}^{8} W_i^2 y_i t_i^2 e^{-a_\ell t_i} - 2\sum_{i=1}^{8} W_i^2 t_i^2 e^{-2a_\ell t_i}} .$$

If $|\delta_\ell| < \epsilon$, then $\hat{\alpha}_2 = a_\ell + \delta_\ell$.

(1.8) $\hat{\alpha}_3$. The logarithmic estimation procedure of Chapter 3 was used. Then

(1.8.1) $\hat{\alpha}_3 = [-\sum_{i=1}^{8} t_i \ln y_i] / \sum_{i=1}^{8} t_i^2$.

(1.9) $\hat{\alpha}_4$. $\hat{\alpha}_4$ was obtained by Cornell's Method of partial sums, which is presented in Appendix 2. Then

(1.9.1) $S_1 = 1 + \sum_{i=1}^{3} y_i$, $S_2 = \sum_{i=4}^{7} y_i$, and $\hat{\alpha}_4 = -\frac{1}{4}\,\ln(S_2/S_1)$.

(1.10) $\hat{\alpha}_5$. $\hat{\alpha}_5$ is obtained by the Gauss-Newton Method, which is discussed in Appendix 2. a_ℓ is a "guessed" value of $\hat{\alpha}_5$ and ϵ is chosen to be .01. The computing equation is

(1.10.1) $(\hat{\alpha}_5 - a_\ell) = \delta_\ell$

$$= \frac{\sum_{i=1}^{8} t_i e^{-2a_\ell t_i} - \sum_{i=1}^{8} y_i t_i e^{-a_\ell t_i}}{\sum_{i=1}^{8} t_i^2 e^{-2a_\ell t_i}} .$$

These five estimates for each of the eight random samples appear in Table 1.3.

Table 1.3

Sample Number	$\hat{\alpha}_1$	$\hat{\alpha}_2$	$\hat{\alpha}_3$	$\hat{\alpha}_4$	$\hat{\alpha}_5$
1	.4948	.4989	.4817	.4126	.4930
2	.5205	.5147	.4744	.4581	.5256
3	.5295	.5342	.5178	.5159	.5300
4	.5290	.5390	.4945	.5473	.5290
5	.5203	.4926	.5047	.4743	.5206
6	.5114	.5026	.4572	.4219	.5118
7	.5284	.5116	.4552	.4329	.5315
8	.4893	.4885	.4538	.4862	.4850
$\hat{\alpha}_{\cdot j} = \frac{1}{8}\sum_{i=1}^{8} \hat{\alpha}_{ij}$	.5154	.5102	.4799	.4686	.5158
$\lvert \alpha - \hat{\alpha}_{\cdot j} \rvert$	.0154	.0102	.0201	.0314	.0158
$\frac{1}{8}\sum_{i=1}^{8} (\hat{\alpha}_{ij} - \alpha)^2$	4.5271×10^{-4}	4.0413×10^{-4}	9.1383×10^{-4}	2.9172×10^{-3}	5.2828×10^{-4}

APPENDIX 2

OTHER METHODS OF ESTIMATION

Cornell's Method of Partial Sums (2, p. 17-46)

Let $E\{y(t)\} = \lambda^t$, $t = 0, 1, \ldots, 2n-1$, where $\lambda = e^{-\alpha}$ and $\alpha > 0$. Then

(2.1) $$\sum_{t=0}^{n-1} E\{y(t)\} = \sum_{t=0}^{n-1} \lambda^t = (1 - \lambda^n)/(1 - \lambda) = \sum_1, \text{ and}$$

(2.2) $$\sum_{t=n}^{2n-1} E\{y(t)\} = \sum_{t=n}^{2n-1} \lambda^t = \lambda^n(1 - \lambda^n)/(1 - \lambda) = \sum_2$$

Let $S_1 = \sum_{t=0}^{n-1} y(t)$ and let $S_2 = \sum_{t=n}^{2n-1} y(t)$.

Let $\hat{\lambda}$ be an estimator of λ. $\sum_1$ and $\sum_2$ are replaced by S_1 and S_2, respectively in equations (2.1) and (2.2), and $\hat{\lambda}$ replaces λ. Then

(2.3) $S_1 = (1 - \hat{\lambda}^n)/(1 - \hat{\lambda})$, and

(2.4) $S_2 = \hat{\lambda}^n(1 - \hat{\lambda}^n)/(1 - \hat{\lambda})$.

Whence,

(2.5) $\hat{\lambda}^n = S_2/S_1$ or $\hat{\lambda} = (S_2/S_1)^{1/n}$.

Then the estimator of α is

(2.6) $\hat{\alpha} = -(1/n)\ \ln (S_2/S_1)$.

The Gauss-Newton Method (5, p. 1-18)

Let

(2.7) $y_i = e^{-\alpha t_i} + \epsilon_i$, $i = 1, 2, \ldots, n$ and $E\{\epsilon_i\} = 0$.

The first order Taylor series expansion of $e^{-\alpha t_i}$ about the point a_1 is

(2.8) $e^{-a_1 t_i} - (\alpha - a_1) t_i e^{-a_1 t_i}$, where a_1 is a "guessed" value of $\hat{\alpha}$. (2.8) replaces $e^{-\alpha t_i}$ of equation (2.7). Then

(2.9) $y_i = e^{-a_1 t_i} - (\alpha - a_1)\ t_i e^{-a_1 t_i} + \epsilon_i$

$= g(t_i; \alpha, a_1) + \epsilon_i$, and

(2.10) $\sum_i [y_i - g(t_i; \alpha, a_1)]^2 = \sum (t_i; \alpha, a_1)$.

$\sum (t_i; \alpha, a_1)$ is minimized with respect to α. Then

(2.11) $\sum_\alpha (t_i; \hat{\alpha}, a_1) = 0 = \sum_i [y_i - g(t_i; \hat{\alpha}, a_1)]\,[t_i e^{-a_1 t_i}]$

$= \sum_i [y_i t_i e^{-a_1 t_i} - t_i e^{-2a_1 t_i} + (\hat{\alpha} - a_1) t_i^2 e^{-2a_1 t_i}]$,

or

(2.12) $$(\hat{\alpha} - a_1) = \frac{\sum_i t_i e^{-2a_1 t_i} - \sum_i y_i t_i e^{-a_1 t_i}}{\sum_i t_i^2\, e^{-2a_1 t_i}}$$

Let ϵ be a small positive number, and let $\delta_1 = (\hat{\alpha} - a_1)$. Then if $|\delta_1| < \epsilon$, $\hat{\alpha} = a_1 + \delta_1$. Otherwise, a_2 replaces a_1 in (2.12), where $a_2 = a_1 + \delta_1$. δ_2 is computed and compared with . If $|\delta_2| < \epsilon$, then $\hat{\alpha} = a_2 + \delta_2$. Otherwise, a_3 replaces a_2, where $a_3 = a_2 + \delta_2$. The same process is repeated until

$|\delta_\ell| < \epsilon$. Then $\hat{\alpha} = a_\ell + \delta_\ell$.