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Osaka University
Contributions to the Theory of Systematic Statistics, II

—Large Sample Theoretical Treatments of Some Problems Arising from Dosage and Time Mortality Curve.—

By Junjiro OGAWA

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Introduction

In an earlier paper\(^1\) the author has developed some theory of systematic statistics and announced before-hand that he shall deal with problems arising from dosage and time mortality curves as applications. The present paper includes such articles.

Estimation of parameters of dosage mortality curve has been devised by many mathematical statisticians; among others by C.I. Bliss\(^2\) and R.A. Fisher\(^3\), and many contributions have been made by them. On planning experiments for estimating parameters of the dosage mortality curve, Dr. Milton Friedman has written an excellent exposition in Chapter 11 of "Selected Techniques of Statistical Analysis for Scientific and Industrial Research and Production and Management Engineering" by the Statistical Research Group, Columbia University, 1947.

Estimation of parameters and testing statistical hypotheses concerning unknown parameters and design of experiments in both cases of dosage- and time mortality curve are attacked here tracing the formal analogies with the theory of systematic statistics. And it will be seen that some new aspects of the problems will be revealed.
I wish to express here my deep thanks to Dr. Wataru Ohosawa for his kindness of letting his experimental data (§ 7. Illustrative example) at my disposal, and to Dr. Motosaburo Masuyama for his valuable criticism on the author's preliminary report on this subject.

§ 1. Problems.

An important class of statistical problems of frequent occurrence—especially in biological researches—arises from situations in which a characteristic is conceived to be normally distributed among the individuals of a population, but measurement of one individual can show only whether the characteristic is above or below a certain level of some poison. Moreover, as Dr. Milton Friedman showed, problems of the same type frequently occurs also in engineering researches. Our method of approach, which will be developed in the following, apply to all problems of this type, but for the sake of concreteness, we shall give discussions in terms of dosage- and time mortality curves.

1.1. Dosage mortality curve. A typical problem occurs when studying the effect of some drug or poison on a particular kind of animals. It is assumed that there is a population of animals, and associated with each individual animal with a certain lethal dose of the drug or poison, such that the animal would always be killed by a stronger dose and would survive a weaker one. There are independent biological evidences for assuming that the natural logarithms of the lethal doses are normally distributed throughout the population, so that if the proportion of animals expected to survive a given dose is converted into an equivalent normal deviate, then the above assumption is equivalent to stating that the normal deviates are linearly related to the logs of lethal doses.

If the mean log lethal dose, which is often called log $LD\ 50$—or log $50\%$ lethal dose in short—, is $m$ and the standard deviation is $\sigma$, then the linear relation between the normal deviate $u$ converted from the expected survival rate at a given level of log dose $x$ is

$$u = \alpha + \beta x,$$

where

$$\frac{1}{\sqrt{2\pi}\sigma} \int_e^t e^{-\frac{(t-m)^2}{2\sigma^2}} \, dt = \frac{1}{\sqrt{2\pi}} \int_0^t e^{-\frac{t^2}{2}} \, dt,$$

and

$$\alpha = -\frac{m}{\sigma}, \quad \beta = \frac{1}{\sigma}.$$ (1.2)

The experimental animals consist of $k$ groups, drawn at random from the population, of $n_1, \ldots, n_k$ animals, which are given with logs $x_1, \ldots, x_k$. 
from which there are $s_1, \ldots, s_k$ survivors, and therefore $n_k - s_1, \ldots, n_k - s_k$ deaths respectively. Since the proportions of animals expected to survive or to die at log dose levels $x_1, \ldots, x_k$ are respectively

$$P_i = \frac{1}{\sqrt{2\pi}u_i} \int_{-\infty}^{t_i} e^{-\frac{t^2}{2}} dt,$$

$$Q_i = \frac{1}{\sqrt{2\pi}u_i} \int_{t_i}^{\infty} e^{-\frac{t^2}{2}} dt,$$

where

$$u_i = \alpha + \beta x_i,$$

the observed survival rate $s_i/n_i, i = 1, \ldots, k,$ is a respective observation of the population value $P_i, i = 1, \ldots, k.$

The random variables in this case are $s_i, i = 1, \ldots, k,$ and they are mutually independent in the sense of probability. The problems which should be answered here are the estimation of parameters $n$ and $\sigma$ and testing statistical hypotheses concerning $n$ and $\sigma,$ and further the optimum allocation of $n_i, i = 1, \ldots, k$ at each given log dose levels and the optimum spacing of log dose levels $x_i, i = 1, \ldots, k.$

1.2. Time mortality curve. In studying the resistibility of insects of a particular kind to a fixed dose of some poison, measured in time, as Dr. Ohsawa showed, there is a reasonable biological evidence for assuming that the natural logarithm of the lethal time associated with each individual insect is distributed normally throughout the population of insects of that kind. The lethal time of an insect is the life time of the insect given a certain level of dose.

In this case, the experimental material consists of $N$ insects, drawn at random from the population, which are given a fixed dose of some poison, and the survivors $s_i$ and death $d_i = N - s_i$ are observed at $k$ time-points of observation, of which logs are $x_i, i = 1, \ldots, k.$ Since the proportion of insects expected to survive at $t_i = \exp x_i$ observation time point, $i = 1, \ldots, k,$ are respectively

$$P_i = \frac{1}{\sqrt{2\pi}u_i} \int_{-\infty}^{t_i} e^{-\frac{t^2}{2}} dt,$$

where

$$u_i = \alpha + \beta x_i,$$

the observed survival-rates $s_i/N, i = 1, \ldots, k$ are the observations of the population values $P_i, i = 1, \ldots, k,$ respectively.

The problems to be considered in this case are the same as in the case of dosage mortality curve. The essential difference between the two
cases is that the observed survival-rates $s_i/N$, $i = 1, \ldots, k$ are stochastically dependent in the case of time mortality curve.

§ 2. Limiting Distributions of the Observed Survival-rates.

2.1. Dosage mortality curve. Let the frequency function of the distribution of the log lethal dose throughout the population be

$$g(x) = (2\pi \sigma^2)^{-1/2} \exp \left\{ -\left(\frac{x-m}{2\sigma}\right)^2 \right\},$$

then the expected survival-rate at log dose level $x$ is

$$P = \int_{-\infty}^{\infty} g(t) dt = \int_{u}^{\infty} f(t) dt,$$

where

$$f(x) = (2\pi)^{-1/2} \cdot \exp \left\{ -\frac{x^2}{2} \right\},$$

and

$$u = \alpha + \beta x.$$

It is well known that the probability of having $s$ survivors out of $n$ animals is

$$\binom{n}{s} P^s Q^{n-s}.$$

By the famous De Moivre's theorem\(^3\), it follows that the distribution of the standardized variable

$$\frac{s/n - P}{(PQ/n)^{1/2}}$$

approaches the standard standard normal distribution $N(0,1)$, as $n$ tends to infinity. So that, for sufficiently large values of $n$, we may consider the variable $s/n$ (the observed survival-rate) is distributed normally about the mean $P$, the population survival-rate, with the variance $PQ/n$.

If we convert the observed survival-rate $s/n$ into an equivalent normal deviate $z$, i.e.

$$s/n = \int_{z}^{\infty} f(t) dt,$$

then the variable $z$ is distributed asymptotically normal

$$N\left(u, \sqrt{\frac{PQ}{n f^2(u)}}\right).$$

Whence we see that the frequency function of the joint distribution of the variables $z_1, \ldots, z_k$, covverted from the observed survival-rates $s_i/n_i$, \ldots, $s_k/n_k$ is asymptotically

$$(2\pi)^{-k/2} \prod_{i=1}^{k} \frac{1}{P_i Q_i} \cdot \exp \left\{ -\frac{1}{2} \sum_{i=1}^{k} \frac{P_i Q_i}{n_i} (z_i - \alpha - \beta x_i)^2 \right\}.$$
for sufficiently large values of \( n_1, \ldots, n_k \).

2.2. Time mortality curve. In this case, the observed survival-rates \( s_1/N, \ldots, s_k/N \) are converted into equivalent normal deviates \( z_1, \ldots, z_k \) respectively, i.e.

\[
s_i/N = \int_{z_i}^{\infty} f(t) dt, \quad i = 1, \ldots, k.
\]

The probability of obtaining \( s_1, \ldots, s_k \) survivors at log lethal time levels \( x_1, \ldots, x_k \) respectively is

\[
\frac{N!}{(N-s_1)!(s_1-s_2)! \cdots (s_{k-1}-s_k)!(s_k-N)!} s_1^{1-P_1} (P_1-P_2)^{s_2-s_1} \cdots (P_{k-1}-P_k)^{s_k-s_{k-1}} P_k^{s_k},
\]

or putting

\[
d_i = N - s_i, \quad i = 1, \ldots, k.
\]

we have

\[
d_1! (d_2-d_1)! \cdots (d_k-d_{k-1})! (N-d_k)! Q_i d_1 (Q_2-Q_1)^{d_2-d_1} \cdots (Q_k-Q_{k-1})^{d_k-d_{k-1}} (1-Q_k)^{N-d_k}.
\]

Hence, as \( N \) tends to infinity, the variables \( d_1/N, \ldots, d_k/N \), the observed death-rates at successive log lethal time levels, are asymptotically normally distributed in the space of \( k \) dimensions with means \( Q_1, \ldots, Q_k \) and variance-covariance matrix

\[
\begin{pmatrix}
Q_1(1-Q_1) & Q_1(1-Q_2) & \cdots & Q_1(1-Q_k) \\
Q_2(1-Q_1) & Q_2(1-Q_2) & \cdots & Q_2(1-Q_k) \\
\vdots & \vdots & & \vdots \\
Q_k(1-Q_1) & Q_k(1-Q_2) & \cdots & Q_k(1-Q_k)
\end{pmatrix}
\]

Consequently, for sufficiently large values of \( N \), it follows that the frequency function of the joint distribution of \( z_1, \ldots, z_k \) is asymptotically

\[
(N/2\pi)^k f_1 f_2 \cdots f_k \left( \frac{Q_1(Q_2-Q_1) \cdots (Q_k-Q_{k-1})(1-Q_k)}{N} \right)^{-\frac{1}{2}} \times \exp \left\{ -\frac{N}{2} \sum_{i=1}^k \left( \frac{Q_{i+1}-Q_i}{Q_i-Q_{i-1}} \right)^2 \right\} f_0^t (z_i-\alpha-\beta x_i)^2 - 2 \sum_{i=2}^k f_i f_{i-1} (z_i-\alpha-\beta x_i) (z_{i-1}-\alpha-\beta x_{i-1}) \right],
\]

where \( f_i = f(u_i), \ i = 1, \ldots, k \) and \( Q_0 = 0, Q_{k+1} = 1, f_0 = f_{k+1} = 0 \).
§ 3. Estimation of Parameters $\alpha = -m/\sigma$ and $\beta = 1/\sigma$.

3.1 Dosage mortality curve. In this case, the basic distribution is given by (2.6) i.e.

$$h(z_1, \ldots, z_k; \alpha, \beta) = C \cdot \exp\left(-\frac{1}{2}S\right),$$

where

$$S = \sum_{i=1}^{k} \frac{n_i f_i^2}{P_i Q_i} (z_i - \alpha - \beta x_i)^2,$$

and

$$C = (2\pi)^{k/2} \prod_{i=1}^{k} \frac{n_i f_i^2}{P_i Q_i}.$$

which is not interesting to us for the moment. The frequency function given above is formally analogous with that of systematic statistics, but here the coefficients of the quadratic form $S$ are dependent of unknown parameters $\alpha$ and $\beta$.

If the number of dose levels $k$ is sufficiently large, and numbers $n_i$ of test animals at each dose level is sufficiently large, the plotted points $(x_i, z_i), i = 1, \ldots, k$ on the $(x, z)$-plane seem to be almost collinear in all practical situations, so we fit them a straight line by freehand and thus we get a system of rough estimates $\alpha_0, \beta_0$ of $\alpha, \beta$ from the intercept and the slope of the fitted straight line.

Let it be

$$f_i^{(0)} = f(\alpha_0 + \beta_0 x_i), \quad P_i^{(0)} = \int_{0}^{x_0} f(t) dt, \quad i = 1, \ldots, k,$$

and

$$S_0 = \sum_{i=1}^{k} \frac{n_i f_i^{(0)^2}}{P_i^{(0)} Q_i^{(0)}} (z_i - \alpha_0 - \beta_0 x_i)^2,$$

and then, as the first approximation we assume that the frequency function of $z_1, \ldots, z_k$ is asymptotically

$$(2\pi)^{-k/2} \prod_{i=1}^{k} \frac{n_i f_i^{(0)^2}}{P_i^{(0)} Q_i^{(0)}} \cdot \exp\left(-\frac{1}{2}S_0\right),$$

and making use of A. Markoff's theorem on least squares, we obtain the best linear unbiased estimates of $\alpha, \beta$. They should be obtained by solving the system of equations

$$\frac{\partial S_0}{\partial \alpha} |_{x=x_0} = 0, \quad \frac{\partial S_0}{\partial \beta} |_{x=x_0} = 0.$$
Contributions to the Theory of Systematic Statistics, II

Putting

\[ K_1^{(0)} = \sum_{i=1}^{k} n_i f_i^{(0)2} P_i^{(0)Q_i^{(0)}} , \quad K_2^{(0)} = \sum_{i=1}^{k} n_i f_i^{(0)2} x_i , \quad K_3^{(0)} = \sum_{i=1}^{k} n_i f_i^{(0)2} x_i^2 , \]

\[ \Delta_0 = K_2^{(0)} K_3^{(0)} - K_4^{(0)} . \]

and

\[ X_0 = \sum_{i=1}^{k} n_i f_i^{(0)2} z_i , \quad Y_0 = \sum_{i=1}^{k} n_i f_i^{(0)2} x_i z_i , \]

\[ \alpha = \frac{1}{\Delta_0} (K_2^{(0)} X_0 - K_3^{(0)} Y_0) , \quad \beta = \frac{1}{\Delta_0} (-K_3^{(0)} X_0 + K_2^{(0)} Y_0) . \]  

(3.3)

The variances and covariances of \( \hat{\alpha} \) and \( \hat{\beta} \) are

\[ D^2(\alpha) = \frac{K_3^{(0)}}{\Delta_0} , \quad D^2(\hat{\beta}) = \frac{K_2^{(0)}}{\Delta_0} , \quad C(\alpha, \hat{\beta}) = -\frac{K_2^{(0)}}{\Delta_0} . \]  

(3.4)

Taking the estimates \( \alpha, \beta \) thus obtained as rough estimates of \( \alpha, \beta \), and let they be \( \alpha_1, \beta_1 \), respectively, then, as the second approximation, we assume that the frequency function of the joint distribution of \( z_1, \ldots, z_k \) is

\[ (2\pi)^{-k/2} \prod_{i=1}^{k} \sqrt{\frac{n_i f_i^{(1)2}}{P_i^{(1)Q_i^{(1)}}}} \cdot \exp \left\{ -\frac{1}{2} \sum_{i=1}^{k} \frac{n_i f_i^{(1)2}}{P_i^{(1)Q_i^{(1)}}} (z_i - \alpha - \beta x_i)^2 \right\} . \]  

(3.5)

where

\[ f_i^{(1)} = (\alpha_1 + \beta_1 x_i) \quad \text{and} \quad P_i^{(1)} = \int_{z_1 + \beta_1 x_i}^{\infty} f(t) dt , \quad i = 1, \ldots, k . \]

Put

\[ S_1 = \sum_{i=1}^{k} \frac{n_i f_i^{(1)2}}{P_i^{(1)Q_i^{(1)}}} (z_i - \alpha - \beta x_i)^2 . \]

then the best linear unbiased estimates \( \hat{\alpha}, \hat{\beta} \) of \( \alpha, \beta \) should be obtained from the equations

\[ \frac{\partial S_1}{\partial \alpha} \bigg|_{\alpha = \hat{\alpha}} \frac{\partial S_1}{\partial \beta} \bigg|_{\beta = \hat{\beta}} = 0 . \]  

(3.6)

Thus we have

\[ \hat{\alpha} = \frac{1}{\Delta_1} (K_2^{(1)} X_1 - K_3^{(1)} Y_1) , \quad \hat{\beta} = \frac{1}{\Delta_1} (-K_3^{(1)} X_1 + K_2^{(1)} Y_1) , \]

where

\[ K_1^{(1)} = \sum_{i=1}^{k} \frac{n_i f_i^{(1)2}}{P_i^{(1)Q_i^{(1)}}} , \quad K_2^{(1)} = \sum_{i=1}^{k} \frac{n_i f_i^{(1)2} x_i}{P_i^{(1)Q_i^{(1)}}} , \quad K_3^{(1)} = \sum_{i=1}^{k} \frac{n_i f_i^{(1)2} x_i^2}{P_i^{(1)Q_i^{(1)}}} , \]

\[ \Delta_1 = K_2^{(1)} K_3^{(1)} - K_4^{(1)} . \]

and

\[ X_1 = \sum_{i=1}^{k} \frac{n_i f_i^{(1)2} z_i}{P_i^{(1)Q_i^{(1)}}} , \quad Y_1 = \sum_{i=1}^{k} \frac{n_i f_i^{(1)2} x_i z_i}{P_i^{(1)Q_i^{(1)}}} . \]
The variances and covariance of $\hat{\alpha}$ and $\hat{\beta}$ are

$$D^2(\hat{\alpha}) = \frac{K^{(1)}_{1}}{\Delta_1}, \quad D^2(\hat{\beta}) = \frac{K^{(1)}_{1}}{\Delta_1}, \quad C(\hat{\alpha}, \hat{\beta}) = -\frac{K^{(1)}_{2}}{\Delta_1}.$$  \tag{3.7}

We continue the above process until the area of the ellipse of concentration corresponding to the joint distribution of $\hat{\alpha}$ and $\hat{\beta}$ becomes sufficiently small, usually two rounds of computations will be sufficient.

It should be remarked that, when the observed survival-rate is 1 or 0, then the converted normal deviate $u$ is $+\infty$ or $-\infty$, so the experimental data representing 100% or 0% survival-rate are altogether useless for the above calculations. If we consider the quadratic form $S_0$ as rewritten in the form

$$S_0 = \frac{1}{\sum_{i=1}^{k} n_i f^{(0)}_{i}(z_i)} \left\{ (z_i - \alpha_0 - \beta_0 x_i)(\alpha - \alpha_0) - (\beta - \beta_0 x_i)^2 \right\},$$

and replacing $z_i - \alpha_0 - \beta_0 x_i$ by $(P^{(0)}_{i} - s_i)/n_i$, then we have

$$S_0 = \frac{1}{\sum_{i=1}^{k} n_i f^{(0)}_{i}(P^{(0)}_{i})} \left( \alpha_0 + \beta_0 x_i + \frac{P^{(0)}_{i} - s_i}{n_i} - \alpha - \beta x_i \right)^2.$$  \tag{3.8}

If we make use of $S_0$ given above, even 100% or 0% observed survival-rates are available for calculating the best linear unbiased estimates of $\alpha$ and $\beta$. This device is due to R. A. Fisher.\textsuperscript{12}

3.2. Time mortality curve. In this case, the frequency function of the joint distribution of $z_1, \ldots, z_k$ is given by (2.7), i.e.

$$h(z_1, \ldots, z_k; \alpha, \beta) = C \exp \left( -\frac{N}{2} S \right),$$

where

$$S = \frac{1}{\sum_{i=1}^{k} (Q_{i+1} - Q_{i})^{-1}} \left( \sum_{i=1}^{k} \frac{Q_{i+1} - Q_{i}}{Q_{i+1} - Q_{i}} f^{(0)}_{i}(z_i - \alpha - \beta x_i)^2 \right) - 2 \sum_{i=2}^{k} \frac{f^{(0)}_{i-1}}{Q_{i} - Q_{i-1}} (z_i - \alpha - \beta x_i)(z_{i-1} - \alpha - \beta x_{i-1}).$$  \tag{3.9}

First, we estimate parameters $\alpha$ and $\beta$ roughly, for example by free-hand method or as in the following, provided the $k$ is sufficiently large:

$$m_0 = \frac{1}{k} \sum_{i=1}^{k} \left( \frac{d_i}{N} - \frac{d_{i-1}}{N} \right) \cdot \frac{x_{i-1} + x_i}{2},$$

$$\sigma_0^2 = \frac{1}{k} \sum_{i=1}^{k} \left( \frac{d_i}{N} - \frac{d_{i-1}}{N} \right) \cdot \left( \frac{x_{i-1} + x_i}{2} \right)^2 - m_0^2,$$

and then

$$\alpha_0 = -\frac{m_0}{\sigma_0}, \quad \beta_0 = \frac{1}{\sigma_0}.$$
As before, we assume the frequency function of \( z_{1}, \ldots, z_{k} \) to be

\[
h_{0}(z_{1}, \ldots, z_{k}; \alpha, \beta) = \frac{(N/\pi)^{k/2}}{f_{1}^{(0)} f_{2}^{(0)} \cdots f_{k}^{(0)}}\times\left[Q_{1}^{(0)}(Q_{2}^{(0)} - Q_{1}^{(0)}) \cdots (Q_{k}^{(0)} - Q_{k-1}^{(0)})(1 - Q_{k}^{(0)})\right]^{-1/2}\exp\left(-\frac{N}{2}S_{0}\right).
\]

as the first approximation, where

\[
S_{0} = \sum_{i=1}^{k} \frac{Q_{i+1}^{(0)} - Q_{i}^{(0)}}{(Q_{i}^{(0)} - Q_{i-1}^{(0)})} f_{i}^{(0)}(z_{i} - \alpha - \beta x_{i})^{2} - \sum_{i=1}^{k} \frac{f_{i}^{(0)} f_{i-1}^{(0)}}{(Q_{i}^{(0)} - Q_{i-1}^{(0)})}(z_{i} - \alpha - \beta x_{i})(z_{i-1} - \alpha - \beta x_{i-1}).
\]

Hence the best linear unbiased estimates \( \hat{\alpha}, \hat{\beta} \) of \( \alpha, \beta \) should be obtained by solving the system of equations

\[
\frac{\partial S_{0}}{\partial \alpha} \bigg|_{x=x, \beta=\hat{\beta}} = 0, \quad \frac{\partial S_{0}}{\partial \beta} \bigg|_{x=x, \beta=\hat{\beta}} = 0.
\]

Thus we get

\[
\hat{\alpha} = \frac{1}{\Delta_{0}}(K_{2}^{(0)}X_{0} - K_{3}^{(0)}Y_{0}), \quad \hat{\beta} = \frac{1}{\Delta_{0}}(-K_{3}^{(0)}X_{0} + K_{4}^{(0)}Y_{0}),
\]

where

\[
K_{1}^{(0)} = \sum_{i=1}^{k} \frac{(f_{i}^{(0)} - f_{i-1}^{(0)})^{2}}{Q_{i}^{(0)} - Q_{i-1}^{(0)}}, \quad K_{2}^{(0)} = \sum_{i=1}^{k} \frac{(f_{i}^{(0)} x_{i} - f_{i-1}^{(0)} x_{i-1})^{2}}{Q_{i}^{(0)} - Q_{i-1}^{(0)}},
\]

\[
K_{3}^{(0)} = \sum_{i=1}^{k} \frac{(f_{i}^{(0)} - f_{i-1}^{(0)})(f_{i}^{(0)} x_{i} - f_{i-1}^{(0)} x_{i-1})}{Q_{i}^{(0)} - Q_{i-1}^{(0)}},
\]

\[
\Delta_{0} = K_{1}^{(0)} K_{2}^{(0)} - K_{3}^{(0)}^{2},
\]

and

\[
X_{0} = \sum_{i=1}^{k} \frac{(f_{i}^{(0)} - f_{i-1}^{(0)})(f_{i}^{(0)} z_{i} - f_{i-1}^{(0)} z_{i-1})}{Q_{i}^{(0)} - Q_{i-1}^{(0)}}, \quad Y_{0} = \sum_{i=1}^{k} \frac{(f_{i}^{(0)} x_{i} - f_{i-1}^{(0)} x_{i-1})(f_{i}^{(0)} z_{i} - f_{i-1}^{(0)} z_{i-1})}{Q_{i}^{(0)} - Q_{i-1}^{(0)}}.
\]

The variances and covariance of \( \hat{\alpha} \) and \( \hat{\beta} \) are

\[
D^{2}(\hat{\alpha}) = \frac{1}{N} \frac{K_{2}^{(0)}}{\Delta_{0}}, \quad D^{2}(\hat{\beta}) = \frac{1}{N} \frac{K_{1}^{(0)}}{\Delta_{0}}, \quad C(\hat{\alpha}, \hat{\beta}) = -\frac{1}{N} \frac{K_{3}^{(0)}}{\Delta_{0}}.
\]

As in the case of dosage mortality curve, we can raise the precision of approximation by iterative method.

§ 4. Estimation of Unknown Parameters \( m \) and \( \sigma \).

In the preceding section we have dealt with the estimation of \( \alpha \) and \( \beta \), but the parameters which should ultimately be estimated are \( m \) and \( \sigma \), i.e.

\[
m = -\frac{\alpha}{\beta}, \quad \sigma = \frac{1}{\beta}.
\]
If we adopt the estimates
\[
\hat{\alpha} = \frac{-\alpha}{\beta}, \quad \hat{\sigma} = \frac{1}{\beta},
\]
(4.2)
for \( m \) and \( \sigma \) respectively, and if the sample size is large enough, then we have approximately
\[
E(\hat{m}) = m \quad \text{and} \quad E(\hat{\sigma}) = \sigma,
\]
(4.3)
and further
\[
D^2(\hat{m}) = \sigma^2 \cdot D^2(\hat{\alpha}) - 2m\sigma^3 \cdot C(\hat{\alpha}, \hat{\beta}) + m^2\sigma^4 \cdot D^2(\hat{\beta}).
\]
(4.4)
\[
D^2(\hat{\sigma}) = \sigma^4 \cdot D^2(\hat{\beta}).
\]
(4.5)
Hence it follows that
\[
\hat{D}^2(\hat{m}) = \frac{\sigma^2}{N\Delta_0} (K_2^{(0)} - 2m\sigma K_3^{(0)} + m^2\sigma^2 K_1^{(0)})
\]
for dosage mortality curve,
\[
\frac{\sigma^2}{N\Delta_0} \left( \sum_{i=1}^{k+1} \frac{n_i f_i^{(0)}(x_i - m\sigma)^2}{Q_i^{(0)} - Q_i^{(0)}} \right),
\]
(4.5)
for time mortality curve.

If, in some circumstances, we have obtained several estimated values
\[
\hat{\alpha}_i, \hat{\beta}_i, \quad i = 1, \ldots, p, \quad (p \geq 3)
\]
for equal \( n (= n_1 = \cdots = n_p) \) or \( N \) and for the same pair of provisional values \( \alpha_0 \) and \( \beta_0 \), then we can construct a confidence interval for \( m \) as follows.

Let
\[
l_{11} = \frac{1}{p} \sum_{i=1}^{p} (\hat{\alpha}_i - \hat{\alpha})^2, \quad l_{12} = \frac{1}{p} \sum_{i=1}^{p} (\hat{\alpha}_i - \hat{\alpha})(\hat{\beta}_i - \hat{\beta}), \quad l_{22} = \frac{1}{p} \sum_{i=1}^{p} (\hat{\beta}_i - \hat{\beta})^2,
\]
where
\[
\hat{\alpha} = \frac{1}{p} \sum_{i=1}^{p} \hat{\alpha}_i, \quad \hat{\beta} = \frac{1}{p} \sum_{i=1}^{p} \hat{\beta}_i.
\]
and let further
\[
L = l_{11} l_{22} - l_{12}^2,
\]
then the statistic
\[
F = \frac{p-2}{2} \cdot \frac{1}{p-1} \cdot T^2
\]
\[
= \frac{p-2}{2} \left[ \frac{l_{12}^2 (\hat{\alpha} - \alpha)^2 - 2 l_{12} (\hat{\alpha} - \alpha)(\hat{\beta} - \beta) + l_{11} (\hat{\beta} - \beta)^2}{L} \right]
\]
(4.6)
is distributed according to Snedecor’s $F$-distribution of degrees of freedom $(2, p-2)$, where $T^2$ is the square of H. Hotelling’s generalized Student ratio.\textsuperscript{14}

Hence, if we denote by $F^{p-2}_2(100\varepsilon)$ the 100 $\varepsilon$ percent point of the right tail of the $F$-distribution of degrees of freedom $(2, p-2)$, then

$$P(F \leq F^{p-2}_2(100\varepsilon)) = 1 - \varepsilon,$$

whence, we have the confidence region of confidence coefficient $100(1-\varepsilon)$ percent for the true parameter point $(\alpha, \beta)$. The confidence region is the interior of the variable ellipse

$$l_{12}^2(\alpha - \hat{\alpha})^2 - l_{12}(\alpha - \hat{\alpha})(\beta - \hat{\beta}) + l_{11}(\beta - \hat{\beta})^2 = \frac{2}{p-2} F^{p-2}_2(100\varepsilon)$$ \hspace{1cm} (4.7)

on the $(\alpha, \beta)$-plane.

If the level of significance $\varepsilon$ were chosen sufficiently large, so that the ellipse (4.7) does not contain the origin and lies entirely in the first or second quadrant, then we can draw two tangents through the origin

$$\alpha = m_1 \beta \quad \text{and} \quad \alpha = m_2 \beta$$

for which, for example

$$P(-\tilde{m}_1 \leq m \leq -\tilde{m}_2) \geq 1 - \varepsilon.$$ \hspace{1cm} (4.8)

After some elementary calculations, the values $\tilde{m}_1$ and $\tilde{m}_2$ can be seen to be

$$\frac{2}{p-2} F^{p-2}_2(100\varepsilon) l_{12}^2 - \hat{\alpha} \hat{\beta} \pm \frac{2}{p-2} F^{p-2}_2(100\varepsilon) \cdot L_{12}^2 + L_{11}^2 \hat{\beta}^2 - \frac{2}{p-2} F^{p-2}_2(100\varepsilon)$$

as the case may be. Whence we see that the above method is valid so long as the inequality

$$\frac{l_{12}^2 \hat{\alpha}^2 - l_{12}^2 \alpha \hat{\beta} + l_{11}^2 \hat{\beta}^2}{L_{12}^2} \geq \frac{2}{p-1} F^{p-2}_2(100\varepsilon)$$

holds, i.e. the null-hypothesis $\alpha = \beta = 0$ is rejected at the level of significance $\varepsilon$.

§ 5. Testing Statistical Hypotheses Concerning Unknown Parameters.

In the theory of dosage or time mortality curve, as Drs. Ohsawa and Nagasawa\textsuperscript{15} have remarked, the constancy of the standard deviation seems to be the natural consequence which ought to be expected from the theoretical consideration. In fact, if, for two kinds of animals or two
different circumstances, the standard deviations of their dosage or time mortality curves differ substantially, then the straight lines representing linear relations between log lethal dose or time and the converted normal deviate from the expected survival-rate corresponding to that log lethal dose or time level will intersect with each other at a finite point, then the lethal effect of the drug or the resistibility of animals would be reversed at that point, but it seems to be implausible in all situations. Hence, first of all, the statistical hypothesis which requires to be tested is the null-hypothesis that asserts the constancy of standard deviation.

For the sake of brevity, we shall describe the method of testing statistical hypotheses for the case of time mortality curve.

We shall consider the case, for concreteness, when \( p \) different drugs are tested to obtain their lethal effects on the same kind of insects. Let the population density function of log lethal time of the population for the \( \nu \)-th drug be

\[
g_{\nu}(x) = (2\pi\sigma_{\nu}^2)^{-1/2} \exp \left\{ -\frac{(x-m_{\nu})^2}{2\sigma_{\nu}^2} \right\}, \quad \nu = 1, \ldots, p, \tag{5.1}\]

and further let it be

\[\alpha_{\nu} = -m_{\nu}/\sigma_{\nu}, \quad \beta_{\nu} = 1/\sigma_{\nu}, \quad \nu = 1, \ldots, p.\]

The total number of insects tested in respective experiment is constantly equal to \( N \), and the logs of lethal time levels at which observations are made are \( x_1, \ldots, x_k \), and the observed death-rates are

\[d_{1\nu}/N, \quad d_{2\nu}/N, \ldots, d_{k\nu}/N, \quad \nu = 1, \ldots, p.\]

In this case the frequency function of the converted normal deviates

\[z_{1\nu}, z_{2\nu}, \ldots, z_{k\nu}, \quad \nu = 1, \ldots, p\]

is given, for sufficiently large \( N \), approximately by the following;

\[
\left(\frac{N/2\pi}{2}\right)^{\frac{p+k}{2}} \prod_{\nu=1}^{p} f_{1\nu} f_{2\nu} \cdots f_{k\nu} \left[ Q_{1\nu}(Q_{2\nu}-Q_{1\nu}) \cdots (Q_{k\nu}-Q_{k-1\nu})(1-Q_{k\nu}) \right]^{-1/2} \exp \left(-\frac{N}{2} S \right),
\]

where

\[
S = \sum_{\nu=1}^{p} \left\{ \sum_{\nu=1}^{p} \frac{Q_{i+1\nu}-Q_{i-1\nu}}{Q_{i\nu}(Q_{i+1\nu}-Q_{i-1\nu})} f_i(z_{i\nu}-\alpha_{\nu}-\beta_{\nu}x_i) \right. \left. \right. \\
-2 \sum_{i=1}^{k} \frac{f_{i\nu}}{Q_{i\nu}-Q_{i-1\nu}} \left( z_{i\nu}-\alpha_{\nu}-\beta_{\nu}x_i \right) \left( z_{i-1\nu}-\alpha_{\nu}-\beta_{\nu}x_{i-1} \right) \right\}, \tag{5.2}
\]

and

\[
Q_{i\nu} = \int_{-\infty}^{x_{i\nu}} f(t)dt, \quad f_i = f(\alpha_{\nu}+\beta_{\nu}x_i), \quad i = 1, \ldots, k; \quad \nu = 1, \ldots, p.
\]
For the \( v \)-th experimental data, we obtain the provisional values \( \alpha_{ov} \) and \( \beta_{ov} \) by free-hand method graphically, for example, and put
\[
Q_{i}^{(0)} = \int_{-\infty}^{\infty} f(t) dt, \quad f_{i}^{(0)} = f(\alpha_{ov} + \beta_{ov} x_{i}), \quad i = 1, \ldots, k; \quad v = 1, \ldots, p, \tag{5.3}
\]
and then we assume that the frequency function of \( z_{1v}, \ldots, z_{kv}, \nu = 1, \ldots, p \) is approximately equal to
\[
(N/\pi)^{n/2} \prod_{i=1}^{n} f_{i}^{(0)} f_{2i}^{(0)} \cdots f_{ki}^{(0)} \left[ Q_{i}^{(0)}(Q_{2i}^{(0)} - Q_{i}^{(0)}) \cdots (Q_{ki}^{(0)} - Q_{i}^{(0)}) (1 - Q_{i}^{(0)}) \right]^{-1/2} \exp \left( -\frac{N}{2} S_{0} \right),
\]
where
\[
S_{0} = \sum_{v=1}^{n} \left\{ \sum_{i=1}^{k} \left( \frac{Q_{i}^{(0)} - Q_{i-1}^{(0)}}{Q_{i+1}^{(0)} - Q_{i}^{(0)}} \right) f_{i}^{(0)} \cdot (z_{i} - \alpha_{v} - \beta_{v} x_{i})^{2} - 2 \sum_{i=2}^{k} \frac{f_{i}^{(0)} f_{i-1}^{(0)}}{Q_{i}^{(0)} - Q_{i-1}^{(0)}} (z_{i} - \alpha_{v} - \beta_{v} x_{i}) (z_{i-1} - \alpha_{v} - \beta_{v} x_{i-1}) \right\}. \tag{5.4}
\]
To test the homogeneity of the standard deviations \( \sigma_{1} = \sigma_{2} = \cdots = \sigma_{p} \), it will be sufficient to test the null-hypothesis
\[
H_{0} : \beta_{1} = \beta_{2} = \cdots = \beta_{p}. \tag{5.5}
\]
Denote the maximum likelihood estimates of \( \alpha_{v} \) and \( \beta_{v} \) by \( \hat{\alpha}_{v} \) and \( \hat{\beta}_{v} \) respectively, then they should be obtained from the equations
\[
\begin{align*}
K_{1v}^{(0)} \hat{\alpha}_{v} + K_{2v}^{(0)} \hat{\beta}_{v} & = X_{0v}, \\
K_{3v}^{(0)} \hat{\alpha}_{v} + K_{4v}^{(0)} \hat{\beta}_{v} & = Y_{0v},
\end{align*}
\]
where
\[
\begin{align*}
K_{1v}^{(0)} &= \sum_{i=1}^{k-1} \frac{(f_{i}^{(0)} - f_{i-1}^{(0)})^{2}}{Q_{i}^{(0)} - Q_{i-1}^{(0)}}, \quad K_{2v}^{(0)} = \sum_{i=1}^{k-1} \frac{(f_{i}^{(0)} x_{i} - f_{i-1}^{(0)} x_{i-1})^{2}}{Q_{i}^{(0)} - Q_{i-1}^{(0)}}, \\
K_{3v}^{(0)} &= \sum_{i=1}^{k-1} \frac{(f_{i}^{(0)} - f_{i-1}^{(0)}) (f_{i}^{(0)} x_{i} - f_{i-1}^{(0)} x_{i-1})}{Q_{i}^{(0)} - Q_{i-1}^{(0)}}, \\
X_{0v} &= \sum_{i=1}^{k-1} \frac{f_{i}^{(0)} x_{i} - f_{i-1}^{(0)} x_{i-1}}{Q_{i}^{(0)} - Q_{i-1}^{(0)}}, \\
Y_{0v} &= \sum_{i=1}^{k-1} \frac{f_{i}^{(0)} x_{i} - f_{i-1}^{(0)} x_{i-1}}{Q_{i}^{(0)} - Q_{i-1}^{(0)}}, \\
Z_{0v} &= \sum_{i=1}^{k-1} \frac{(f_{i}^{(0)} x_{i} - f_{i-1}^{(0)} x_{i-1})^{2}}{Q_{i}^{(0)} - Q_{i-1}^{(0)}}, \quad \nu = 1, \ldots, p.
\end{align*}
\tag{5.7}
\]
The absolute minimum value \( S_{0a} \) of \( S_0 \) is

\[
S_{0a} = \sum_{v=1}^{n} Z_{0v} - \sum_{v=1}^{n} X_{0v} \hat{\alpha}_v - \sum_{v=1}^{n} Y_{0v} \hat{\beta}_v.
\]  

(5.8)

Similarly, let the maximum likelihood estimates of \( \alpha_v, \beta_v, v = 1, \ldots, p \) under the null-hypotheses \( H_1 \), be \( \hat{\alpha}_v^*, \ldots, \hat{\alpha}_p^* \) and \( \hat{\beta}_v^* \), then they should be obtained from the equations

\[
\begin{align*}
K_{11}^0 \hat{\alpha}_1^* + K_{31}^0 \hat{\beta}_1^* &= X_{01} \\
K_{12}^0 \hat{\alpha}_2^* + K_{32}^0 \hat{\beta}_2^* &= X_{02} \\
&\vdots \\
K_{1p}^0 \hat{\alpha}_p^* + K_{3p}^0 \hat{\beta}_p^* &= X_{0p}
\end{align*}
\]

(5.9)

therefore the relative minimum value \( S_{0r} \) or \( S_0 \) is

\[
S_{0r} = \sum_{v=1}^{n} Z_{0v} - \sum_{v=1}^{n} X_{0v} \hat{\alpha}_v^* - \left( \sum_{v=1}^{n} Y_{0v} \right) \hat{\beta}_v^*.
\]  

(5.10)

By the result of the general theory of linear hypotheses, it follows that the statistic

\[
F = \frac{\sum_{v=1}^{p} \left( X_{0v} (\hat{\alpha}_v - \hat{\alpha}_v^*) + Y_{0v} (\hat{\beta}_v - \hat{\beta}_v^*) \right)}{S_{0a}}
\]

(5.11)

is distributed according to Snedecor’s \( F \)-distribution of degrees of freedom \( (p-1, p(k-2)) \), provided the null-hypothesis \( H_1 \) is true. If we denote the 100\( \varepsilon \) percent point of the right tail of the \( F \)-distribution of degrees of freedom \( (n_1, n_2) \) by \( F_{n_1, n_2}^{100\varepsilon} \), then we reject the null-hypothesis \( H_1 \) when

\[
F \geq F_{(1-\varepsilon, \varepsilon)}^{p(k-2)} \quad \text{or} \quad F \leq 1/F_{1-\varepsilon, \varepsilon}^{p(k-2)},
\]

The probability of committing the error of the first kind is just \( \varepsilon \).

Thus, if the constancy of the standard deviation is already justified, then the problem arises, i.e. the comparison of two means. In this case the basic frequency function is

\[
(N/\pi)^k \prod_{v=1}^{p} f_{v}^{(0)} \cdots \prod_{v}^{p} \left[ Q_{v}^{(0)}(Q_{v}^{(0)} - Q_{1v}^{(0)}) \cdots (Q_{v}^{(0)} - Q_{(1-v)}^{(0)}) (1 - Q_{v}^{(0)}) \right]^{-1/2} \exp \left( -\frac{N}{2} S_0 \right),
\]

where

\[
S_0 = \sum_{i=1}^{k} \left\{ \sum_{v=1}^{p} \frac{Q_i^{(0)} - Q_{i+p}^{(0)}}{(Q_{i+1,v}^{(0)} - Q_{i,v}^{(0)})(Q_{i,v}^{(0)} - Q_{(i-1),v}^{(0)})} f_{i,v}^{(0)} (z_{i,v} - \alpha_v - \beta x_i)^2 \\
- 2 \sum_{i=2}^{k} Q_{i,v}^{(0)} (z_{i,v} - \alpha_v - \beta x_i) (z_{i-1,v} - \alpha_v - \beta x_{i-1}) \right\},
\]  

(5.12)
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and

$$Q_{i(0)} = \int_{-\infty}^{x_0} f(t) dt, f_{i(0)} = f(\alpha_0 + \beta_0 x_i), \quad i = 1, \ldots, k; \quad \nu = 1, 2$$

$$\beta_0 = \frac{1}{2} (\beta_{y1} + \beta_{y2}).$$

If we wish to test the statistical hypothesis that two population means $m_1$ and $m_2$ are equal, it will be sufficient to test the derived null-hypothesis

$$H_2 : \alpha_1 = \alpha_2,$$

because the constancy of the standard deviation has been assumed to be known a priori.

Let the maximum likelihood estimates of $\alpha_1$, $\alpha_2$ and $\beta$ be $\hat{\alpha}_1$, $\hat{\alpha}_2$ and $\hat{\beta}$ respectively, then the absolute minimum value $S_{0\alpha}$ and $S_0$ is

$$S_{0\alpha} = Z_{01} + Z_{02} - X_{01} \hat{\alpha}_1 - X_{02} \hat{\alpha}_2 - (Y_{01} + Y_{02}) \hat{\beta}. \quad (5.13)$$

where $\hat{\alpha}_1$, $\hat{\alpha}_2$ and $\hat{\beta}$ are determined by the following equations.

$$K_{11}^{(0)} \hat{\alpha}_1 + K_{12}^{(0)} \hat{\beta} = X_{01}$$
$$K_{12}^{(0)} \hat{\alpha}_2 + K_{22}^{(0)} \hat{\beta} = X_{02}$$

$$K_{31}^{(0)} \hat{\alpha}_1 + K_{32}^{(0)} \hat{\alpha}_2 + (K_{21}^{(0)} + K_{22}^{(0)}) \hat{\beta} = Y_{01} + Y_{02} \quad (5.14)$$

Similarly, let the maximum likelihood estimates of $\alpha_1 = \alpha_2$ and $\beta$ under the null-hypothesis $H_2$ be $\hat{\alpha}^* \text{ and } \hat{\beta}^*$ respectively, then the relative minium value $S_{0r}$ or $S_0$ is

$$S_{0r} = Z_{01} + Z_{02} - (X_{01} + X_{02}) \hat{\alpha}^* - (Y_{01} + Y_{02}) \hat{\beta}^*, \quad (5.15)$$

where $\hat{\alpha}^*$ and $\hat{\beta}^*$ are determined by the following equations.

$$K_{11}^{(0)} \hat{\alpha}^* + K_{12}^{(0)} \hat{\beta}^* = X_{01} + X_{02}$$
$$K_{31}^{(0)} \hat{\alpha}^* + K_{32}^{(0)} \hat{\alpha}_2 + (K_{21}^{(0)} + K_{22}^{(0)}) \hat{\beta}^* = Y_{01} + Y_{02} \quad (5.16)$$

whence it follows that the statistic

$$F = (2k-3) \frac{S_{0r} - S_{0\alpha}}{S_{0\alpha}} \quad (5.17)$$

is distributed according to Snedcer’s $F$-distribution of degrees of freedom $(1, 2k-3)$, or $t = \sqrt{F}$ is distributed according to Student’s $t$-distribution of degrees of freedom $(2k-3)$. Therefore, if we reject the null-hypothesis $H_2$ when

$$|t| \geq t_{2k-3}(100\varepsilon),$$

then the probability of committing the error of the first kind is just $\varepsilon$, ...
where \( t_{2k-3}(100\%) \) is the 100\% percent point of the \( t \)-distribution of degree of freedom \((2k-3)\).

\[6.\] Design of Experiments

6.1. The optimum allocation of test animals to various dosage levels.

Dr. Milton Friedman\(^{(6)}\) has remarked on the problem of the optimum allocation of experimental materials to various dosage levels. The problem shall be answered in the following manner:

Let

\[ \sum_{i=1}^{k} n_i = N, \quad (6.1) \]

where the total number \( N \) is given, and it is required to determine \( n_1, n_2, \ldots, n_k \) such that the quantity

\[ \Delta_0 = \left( \sum_{i=1}^{k} n_i w_i \right) \left( \sum_{i=1}^{k} n_i w_i x_i^2 \right) - \left( \sum_{i=1}^{k} n_i w_i x_i \right)^2 \quad (6.2) \]

shall be maximized, where

\[ w_i = f_i^{(0)} P_i^{(0)} Q_i^{(0)}, \quad i = 1, \ldots, k. \]

The required values of \( n_1, \ldots, n_k \) will be obtained by solving the following system of linear equations

\[ \begin{align*}
    n_2 \cdot w_2 (x_2 - x_1)^2 + n_3 \cdot w_3 (x_3 - x_1)^2 + \cdots \\
    + n_{k-1} \cdot w_{k-1} (x_{k-1} - x_1)^2 + n_k \cdot w_k (x_k - x_1)^2 = \frac{\lambda}{w_1} \\
    n_1 \cdot w_1 (x_1 - x_2)^2 \\
    + n_3 \cdot w_3 (x_3 - x_2)^2 + \cdots \\
    + n_{k-1} \cdot w_{k-1} (x_{k-1} - x_2)^2 + n_k \cdot w_k (x_k - x_2)^2 = \frac{\lambda}{w_2} \\
    \cdots \\
    n_1 \cdot w_1 (x_1 - x_{k-1})^2 + n_2 \cdot w_2 (x_2 - x_{k-1})^2 + n_3 \cdot w_3 (x_3 - x_{k-1})^2 + \cdots \\
    + n_k \cdot w_k (x_k - x_{k-1})^2 = \frac{\lambda}{w_{k-1}} \\
    n_1 \cdot w_1 (x_1 - x_k)^2 + n_2 \cdot w_2 (x_2 - x_k)^2 + n_3 \cdot w_3 (x_3 - x_k)^2 + \cdots \\
    + n_k \cdot w_k (x_k - x_k)^2 = \frac{\lambda}{w_k}
\end{align*} \quad (6.3) \]

where \( \lambda \) is the Lagrange's multiplier and should be determined by the condition \((6.1)\). For example, if we take the simplest case when \( k = 2 \), \((6.3)\) becomes

\[ n_1 : n_2 = \frac{1}{w_1^2} : \frac{1}{w_2^2}, \quad (6.4) \]

hence the required optimum spacing of \( x_1 \) and \( x_2 \) is such that for which

\[ \Delta_0 = \frac{N^2}{w_1 w_2 \left( \frac{1}{w_1^2} + \frac{1}{w_2^2} \right)} \cdot (x_1 - x_2)^2 \]
is maximum.

In the case of Table 11.1 of Dr. Milton Friedman's data, viewed from the standpoint of the allocation, the determinant of the coefficients corresponding to the system of equations (6.3) contains a factor

\[
\begin{vmatrix}
0 & \binom{5}{6}^2 & \binom{10}{6}^2 & \binom{15}{6}^2 & \binom{20}{6}^2 & \binom{25}{6}^2 & \binom{30}{6}^2 \\
\binom{5}{6} & 0 & \binom{5}{6} & \binom{10}{6} & \binom{15}{6} & \binom{20}{6} & \binom{25}{6} \\
\binom{10}{6} & \binom{5}{6} & 0 & \binom{10}{6} & \binom{15}{6} & \binom{20}{6} & \binom{25}{6} \\
\binom{15}{6} & \binom{10}{6} & \binom{5}{6} & 0 & \binom{10}{6} & \binom{15}{6} & \binom{20}{6} \\
\binom{20}{6} & \binom{15}{6} & \binom{10}{6} & \binom{5}{6} & 0 & \binom{10}{6} & \binom{20}{6} \\
\binom{25}{6} & \binom{20}{6} & \binom{15}{6} & \binom{10}{6} & \binom{5}{6} & 0 & \binom{20}{6} \\
\binom{30}{6} & \binom{25}{6} & \binom{20}{6} & \binom{15}{6} & \binom{10}{6} & \binom{5}{6} & 0
\end{vmatrix} = 0,
\]

so the allocation of \( n_1, \ldots, n_k \) remains undetermined.\(^{20}\)

6.2. Remarks on the optimum spacings for the time mortality curve. When both the mean \( m \) and the standard deviation \( \sigma \) of the time mortality curve are unknown, the most efficient design of experiment for estimating \( m \) and \( \sigma \) jointly must be such that, for any given \( k \), \( \log \) lethal time levels, should be chosen so as to make \( \Delta_0 = K_1^{0}K_2^{0} - K_3^{0} \) maximum. But, as was seen in Part 1\(^{21}\) of my papers, the numerical calculation of such spacings was too cumbersome to be tabulated. Here the following compromises may be helpful in some circumstances. Inspections of Table 6.1 and 6.4\(^{22}\) show that that optimum spacings for estimating the mean only are always more efficient than those for estimating the standard deviation only. So, as the approximate method, we may consult Table 6.1\(^{23}\) for choosing \( \log \) lethal time levels for given \( k = 2, 3, \ldots, 10 \).

§ 7. Illustrative Example\(^{24}\)

Drs. W. Ohsawa and S. Nagasawa obtained the following data, in studying the lethal effect of Kerosene emulsion on Cremastogaster brunea matsumurai Forel. In this experiment the lethal time of each individual insect could be observed because of its peculiar character—the "abdomen erecting reflex". We shall estimate \( m \) and \( \sigma \) by using four lethal time levels,
\[ x_1 = 1.55, \; x_2 = 1.85, \; x_3 = 2.05, \; x_4 = 2.25, \]

and shall test the homogeneity of standard deviations of each dilution level.

| Table 7.1. Percent cumulative frequency tables of log lethal time \( x \) at 20°C with Kerosene emulsion of various dilutions |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| \( D \) | 1.2 | 1.3 | 1.4 | 1.5 | 1.6 | 1.7 | 1.8 | 1.9 | 2.0 | 2.1 | 2.2 | 2.3 | 2.4 | 2.5 |
| 50 | 1 | 1 | 1 | 16 | 30 | 48 | 68 | 84 | 97 | 100 | | | | |
| 75 | 1 | 9 | 18 | 36 | 56 | 77 | 87 | 92 | 97 | 100 | | | | |
| 100 | 1 | 1 | 16 | 42 | 60 | 73 | 93 | 97 | 99 | 100 | | | | |
| 150 | 4 | 8 | 19 | 47 | 71 | 86 | 94 | 99 | 100 | | | | | |
| 200 | 7 | 23 | 37 | 49 | 72 | 89 | 96 | 98 | 99 | 100 | | | | |
| 300 | 3 | 9 | 18 | 39 | 61 | 80 | 93 | 100 | | | | | | |
| 400 | 1 | 5 | 18 | 38 | 56 | 72 | 83 | 92 | 97 | 99 | 100 | | | |
| 600 | 2 | 8 | 20 | 43 | 67 | 80 | 92 | 100 | | | | | | |
| 800 | 2 | 7 | 19 | 37 | 54 | 72 | 86 | 97 | 98 | 100 | | | | |
| 1200 | 1 | 7 | 22 | 39 | 67 | 81 | 94 | 98 | 100 | | | | | |
| 1600 | 2 | 4 | 12 | 38 | 60 | 81 | 90 | 99 | 100 | | | | | |

\[ x_1=1.55, \; x_2=1.85, \; x_3=2.05, \; x_4=2.25 \]

For testing the homogeneity of standard deviations, the statistic \( F \) of \((5.11)\) is calculated as follow:

\[
F = \frac{p(k-2)S_{0a} - S_{a0}}{p-1} \cdot \frac{.090164}{.131390} = 1.51
\]

By rough linear interpolation, we find

\[ F_{10}^{25}(2.5) = 2.66, \; F_{10}^{25}(5) = 2.30, \]

therefore the homogeneity of standard deviations can not be rejected, as was to be expected theoretically.

Examples of computing schemes are shown in Tables 7.2, 7.3, and 7.4. In calculations of \( K_{1}^{(0)}, \; K_{2}^{(0)}, \; K_{3}^{(0)} \) and \( X_0, \; Y_0, \; Z_0 \) the following indentities are utilized as checks.

\[
L_i = \frac{(f^{(0)}_i - f^{(0)}_i)^2}{Q^{(0)}_i - Q^{(0)}_{i-1}} + 2\frac{(f^{(0)}_i - f^{(0)}_i)x_i - f^{(0)}_i x_{i-1})}{Q^{(0)}_i - Q^{(0)}_{i-1}} + \frac{(f^{(0)}_i x_i - f^{(0)}_i x_{i-1})^2}{Q^{(0)}_i - Q^{(0)}_{i-1}}
\]

\[
M_i = \frac{(f^{(0)}_i z_i - f^{(0)}_i z_{i-1})^2}{Q^{(0)}_i - Q^{(0)}_{i-1}} + 2\frac{(f^{(0)}_i z_i - f^{(0)}_i z_{i-1})z_i - f^{(0)}_i z_{i-1}}{Q^{(0)}_i - Q^{(0)}_{i-1}} + \frac{(f^{(0)}_i z_i - f^{(0)}_i z_{i-1})^2}{Q^{(0)}_i - Q^{(0)}_{i-1}}
\]

\[
= \frac{(f^{(0)}_i (z_i + x_i) - f^{(0)}_i (z_{i-1} + x_{i-1}))^2}{Q^{(0)}_i - Q^{(0)}_{i-1}}
\]
and

\[ \sum_{i=1}^{k} L_i = K_1^{0,0} + 2K_1^{0,0} + K_2^{0,0}, \]
\[ \sum_{i=1}^{k} M_i = K_2^{0,0} + 2X_0 + Z_0. \]

Notes and References

9. This is the very reason why we assume the normality of the population
For the sake of simplicity, we shall discuss the point in this case of two samples. When two samples $x_{at}, \ i=1 \ldots \ n_a; \ \omega=a=1, 2$ drawn from the normal populations $N(m_a, \sigma_a) \ \omega=1, 2$ respectively are given, we test the hypothesis of equal variances $\sigma_1^2 = \sigma_2^2$ by means of the statistic

$$F = \frac{n_2-1}{n_1-1} \frac{n_1s_1^2}{n_2s_2^2}$$

where

$$n_a s_a^2 = \sum_{i=1}^{n_a} (x_{ai} - \bar{x}_a)^2, \ \omega=1, 2,$$

and

$$\bar{x}_a = \frac{1}{n_a} \sum_{i=1}^{n_a} x_{ai}, \ \omega=1, 2,$$

If the null-hypothesis of equal variances is accepted, we test the hypothesis of equal means $m_1=m_2$ by means of Fisher’s generalized Student’s ratio

$$t = \sqrt{\frac{n_1n_2(n_1+n_2-2)}{n_1+n_2}} \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{n_1s_1^2 + n_2s_2^2}}$$

We shall mention here the following two points:

1) If in fact the two variances are equal, i.e., $\sigma_1 = \sigma_2$, then under the null-hypothesis of equal means $m_1=m_2$, the two statistics $t$ and $F$ are mutually independent.

2) If the two variances are unequal, i.e., $\sigma_1 \neq \sigma_2$, then under the null-hypothesis of equal means $m_1=m_2$, the two statistics $t$ and $F$ are dependent, and the joint probability element of them is proportional to

$$F^{n_1-3} \left(1 + \frac{n_1-1}{n_2-1} F \right)^{\frac{1}{2}} \left[ \left( \frac{1}{\sigma_1^2} + \frac{n_1n_2s^2}{K^2s_1^2\sigma_1^2} \right)^{n_1-1} + \left( \frac{1}{\sigma_2^2} + \frac{n_1n_2s^2}{K^2s_2^2\sigma_2^2} \right)^{n_2-1} \right]^{-\frac{n_1+n_2-2}{2}} dtdF,$$
where
\[ K^2 = \frac{n_1 n_2 (n_1 + n_2 - 2)}{n_1 + n_2}, \]

In this case, when the hypothesis of equal variances is accepted, the distribution of \( t \) is the conditional distribution of \( t \) under the condition that
\[ 1/F_{n_1 - 1}^{-1}(100\varepsilon/2) \leq F \leq F_{n_2 - 1}^{-1}(100\varepsilon/2), \]

where \( \varepsilon \) denotes the level of significance.
The detailed discussion of such problems as mentioned above will be treated in a separate paper.

18. Milton Friedman, loc. cit.
19. Milton Friedman, loc. cit.
20. From this we can infer that in the case of dosage mortality curve the optimum allocation of \( n_1, \ldots, n_k \) are undeterminate in symmetric spacing. This result seems to me a curious fact, and the statistical implications of this fact are yet unknown to me.
24. The calculations were carried out with the cooperations of Messrs M. Tanaka, Y. Miyamoto, M. Okamoto and S. Yamamoto. The author expresses his hearty thanks to them.
Table 7.2 An example of calculation $K^{(0)}_1, K^{(0)}_2, K^{(0)}_3$ and $X_0, Y_0, Z_0$
(Uncorrected normal deviate)

<table>
<thead>
<tr>
<th>$D=400$</th>
<th>$m_0=1.89$</th>
<th>$a_0=0.207$</th>
<th>$x_0=-9.1304$</th>
<th>$b_0=4.8309$</th>
</tr>
</thead>
<tbody>
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<td>$x_i$</td>
<td>1.55</td>
<td>1.85</td>
<td>2.05</td>
<td>2.25</td>
</tr>
<tr>
<td>$d_d/N$</td>
<td>.01</td>
<td>.38</td>
<td>.72</td>
<td>.92</td>
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<td>$z_i$</td>
<td>-2.32635</td>
<td>-.30548</td>
<td>.58284</td>
<td>1.40507</td>
</tr>
<tr>
<td>$x_0+\beta_0 x_i$</td>
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<td>-.1932</td>
<td>.7729</td>
<td>1.7391</td>
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<tr>
<td>$Q_i^{(0)}$</td>
<td>.050245</td>
<td>.423402</td>
<td>.780207</td>
<td>.958991</td>
</tr>
<tr>
<td>$Q_i^{(0)} - Q_i^{(0)}_{i-1}$</td>
<td>.050245</td>
<td>.373157</td>
<td>.356805</td>
<td>.178784</td>
</tr>
<tr>
<td>$f_i^{(0)}$</td>
<td>.103537</td>
<td>.391562</td>
<td>.295931</td>
<td>.087934</td>
</tr>
<tr>
<td>$f_i^{(0)} x_i$</td>
<td>.160482</td>
<td>.724390</td>
<td>.600659</td>
<td>.197852</td>
</tr>
<tr>
<td>$f_i^{(0)} (1+x_i)$</td>
<td>.264019</td>
<td>.1,115952</td>
<td>.902590</td>
<td>.285786</td>
</tr>
<tr>
<td>$f_i^{(0)} z_i$</td>
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<td>-.119614</td>
<td>.172480</td>
<td>.123553</td>
</tr>
<tr>
<td>$f_i^{(0)} (x_i+z_i)$</td>
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<td>.604776</td>
<td>.779139</td>
<td>.321405</td>
</tr>
<tr>
<td>$f_i^{(0)} - f_i^{(0)}_{i-1}$</td>
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<td>.288025</td>
<td>-.095631</td>
<td>-.207997</td>
</tr>
<tr>
<td>$f_i^{(0)} x_i - f_i^{(0)}<em>{i-1} x</em>{i-1}$</td>
<td>.160482</td>
<td>.563908</td>
<td>-.117731</td>
<td>-.408807</td>
</tr>
<tr>
<td>$f_i^{(0)} (1+x_i) - f_i^{(0)}<em>{i-1} (1+x</em>{i-1})$</td>
<td>.264019</td>
<td>.851933</td>
<td>-.213362</td>
<td>-.616804</td>
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<tr>
<td>$\frac{1}{Q_i^{(0)} - Q_i^{(0)}_{i-1}}$</td>
<td>19.902478</td>
<td>2.679837</td>
<td>2.802651</td>
<td>5.593342</td>
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<tr>
<td>$\left(f_i^{(0)} - f_i^{(0)}_{i-1}\right)^2$</td>
<td>.010720</td>
<td>.082958</td>
<td>.009145</td>
<td>.043263</td>
</tr>
<tr>
<td>$\left(f_i^{(0)} - f_i^{(0)}<em>{i-1}\right) \left(f_i^{(0)} x_i - f_i^{(0)} x</em>{i-1}\right)$</td>
<td>.016616</td>
<td>.162420</td>
<td>.011259</td>
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<td>$\left(f_i^{(0)} x_i - f_i^{(0)} x_{i-1}\right)^2$</td>
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<td>.317992</td>
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<td>.167123</td>
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<tr>
<td>$\left(f_i^{(0)} (1+x_i) - f_i^{(0)}<em>{i-1} (1+x</em>{i-1})\right)^2$</td>
<td>.069706</td>
<td>.725790</td>
<td>.045523</td>
<td>.380447</td>
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<tr>
<td>$\left(f_i^{(0)} (1+x_i) - f_i^{(0)}<em>{i-1} (1+x</em>{i-1})\right)^2$</td>
<td>.081676</td>
<td>.056523</td>
<td>.380447</td>
<td>.081676</td>
</tr>
<tr>
<td>Term</td>
<td>Value</td>
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<td>----------------------------------------------------------------------</td>
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</tr>
<tr>
<td>( \frac{(f_i^{(0)} - f_{i-1}^{(0)})^2}{Q_i^{(0)} - Q_{i-1}^{(0)}} )</td>
<td>0.21335</td>
<td>0.222314</td>
<td>0.025630</td>
<td>0.241985</td>
</tr>
<tr>
<td>( \frac{(f_i^{(0)} - f_{i-1}^{(0)})(f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1})}{Q_i^{(0)} - Q_{i-1}^{(0)}} )</td>
<td>0.330700</td>
<td>0.434259</td>
<td>0.031555</td>
<td>0.475607</td>
</tr>
<tr>
<td>( \frac{(f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1})^2}{Q_i^{(0)} - Q_{i-1}^{(0)}} )</td>
<td>0.512568</td>
<td>0.852167</td>
<td>0.038848</td>
<td>0.934776</td>
</tr>
<tr>
<td>( \frac{(f_i^{(0)} (1 + x_i) - f_{i-1}^{(0)} (1 + x_{i-1})^2}{Q_i^{(0)} - Q_{i-1}^{(0)}} )</td>
<td>1.387322</td>
<td>1.944999</td>
<td>0.127585</td>
<td>2.127970</td>
</tr>
<tr>
<td>( \nu_i )</td>
<td>1.387323</td>
<td>1.944999</td>
<td>0.127588</td>
<td>2.127975</td>
</tr>
<tr>
<td>( f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1} )</td>
<td>-0.240863</td>
<td>0.121249</td>
<td>0.292094</td>
<td>-0.048927</td>
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<tr>
<td>( f_i^{(0)} (x_i + z_i) - f_{i-1}^{(0)} (x_{i-1} + z_{i-1}) )</td>
<td>-0.080381</td>
<td>0.685157</td>
<td>0.174363</td>
<td>-0.457734</td>
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<tr>
<td>( (f_i^{(0)} - f_{i-1}^{(0)} x_i - f_{i-1}^{(0)} z_{i-1}) )</td>
<td>-0.024938</td>
<td>0.039222</td>
<td>-0.027933</td>
<td>0.010177</td>
</tr>
<tr>
<td>( (f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1}) (f_i^{(0)} z_i - f_{i-1}^{(0)} z_{i-1}) )</td>
<td>-0.038654</td>
<td>0.068373</td>
<td>-0.034389</td>
<td>0.020002</td>
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<tr>
<td>( (f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1})^2 )</td>
<td>0.058015</td>
<td>0.014701</td>
<td>0.085319</td>
<td>0.002394</td>
</tr>
<tr>
<td>( (f_i^{(0)} (x_i + z_i) - f_{i-1}^{(0)} (x_{i-1} + z_{i-1}))^2 )</td>
<td>0.006461</td>
<td>0.469440</td>
<td>0.030402</td>
<td>0.209520</td>
</tr>
<tr>
<td>( (f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1}) (f_i^{(0)} z_i - f_{i-1}^{(0)} z_{i-1}) )</td>
<td>-0.496328</td>
<td>0.093585</td>
<td>-0.078286</td>
<td>0.056923</td>
</tr>
<tr>
<td>( (f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1})^2 )</td>
<td>-0.769310</td>
<td>0.183228</td>
<td>-0.096805</td>
<td>0.111878</td>
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<tr>
<td>( (f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1})^2 )</td>
<td>1.154642</td>
<td>0.039396</td>
<td>0.239119</td>
<td>0.013390</td>
</tr>
<tr>
<td>( (f_i^{(0)} x_i + z_i) - f_{i-1}^{(0)} (x_{i-1} + z_{i-1})^2 )</td>
<td>0.281590</td>
<td>1.258023</td>
<td>0.085206</td>
<td>1.171915</td>
</tr>
<tr>
<td>( M_i )</td>
<td>0.128590</td>
<td>1.258019</td>
<td>0.085207</td>
<td>1.171922</td>
</tr>
</tbody>
</table>

\[
L_i = \frac{(f_i^{(0)} - f_{i-1}^{(0)})^2}{Q_i^{(0)} - Q_{i-1}^{(0)}} + 2 \frac{(f_i^{(0)} - f_{i-1}^{(0)})(f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1})}{Q_i^{(0)} - Q_{i-1}^{(0)}} + \frac{(f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1})^2}{Q_i^{(0)} - Q_{i-1}^{(0)}}
\]

\[
M_i = \frac{(f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1})^2}{Q_i^{(0)} - Q_{i-1}^{(0)}} + 2 \frac{(f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1})(f_i^{(0)} z_i - f_{i-1}^{(0)} z_{i-1})}{Q_i^{(0)} - Q_{i-1}^{(0)}} + \frac{(f_i^{(0)} z_i - f_{i-1}^{(0)} z_{i-1})^2}{Q_i^{(0)} - Q_{i-1}^{(0)}}
\]
Table 7.3  An example of calculation of $K_1^{(0)}$, $K_2^{(0)}$, $K_3^{(0)}$ and $X_0, Y_0, Z_0$
(Corrected normal deviate)

<table>
<thead>
<tr>
<th></th>
<th>$x_i$</th>
<th>$d_i/N$</th>
<th>$x_0+\beta_0 x_i$</th>
<th>$Q_i^{(0)}$</th>
<th>$Q_i^{(0)} - Q_{i-1}^{(0)}$</th>
<th>$f_i^{(0)}$</th>
<th>$d_i/N - Q_i^{(0)}$</th>
<th>$d_i/N - Q_i^{(0)}$</th>
<th>$f_i^{(0)} x_i$</th>
<th>$f_i^{(0)}(1+x_i)$</th>
<th>$f_i^{(0)} z_i'$</th>
<th>$f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1}$</th>
<th>$f_i^{(0)}(1+x_i) - f_{i-1}^{(0)}(1+x_{i-1})$</th>
<th>$f_i^{(0)}(x_i+z_i') - f_{i-1}^{(0)}(x_{i-1}+z_{i-1}')$</th>
<th>$(f_i^{(0)} - f_{i-1}^{(0)})^2$</th>
<th>$(f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1})$</th>
<th>$(f_i^{(0)}(1+x_i) - f_{i-1}^{(0)}(1+x_{i-1}))^2$</th>
<th>$(f_i^{(0)}(1+x_i) - f_{i-1}^{(0)}(1+x_{i-1}))^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D=200$,$m_0=1.88$,$\sigma_0=0.203$,$x_0=-9.2611$,$\beta_0=4.9261$</td>
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<tr>
<td>Term</td>
<td>Value 1</td>
<td>Value 2</td>
<td>Value 3</td>
<td>Value 4</td>
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<tr>
<td>$(f_i^{(0)} - f_{i-1}^{(0)}) (f_i^{(0)} z'<em>i - f</em>{i-1}^{(0)} z'_{i-1})$</td>
<td>-0.023953</td>
<td>0.025237</td>
<td>-0.03404</td>
<td>0.004963</td>
<td>0.010021</td>
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<td></td>
</tr>
<tr>
<td>$(f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1})^2$</td>
<td>0.027217</td>
<td>0.319272</td>
<td>0.023735</td>
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<td>0.029056</td>
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<tr>
<td>$(f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1}) (f_i^{(0)} z'<em>i - f</em>{i-1}^{(0)} z'_{i-1})$</td>
<td>-0.037127</td>
<td>0.049485</td>
<td>-0.052382</td>
<td>0.009808</td>
<td>0.022547</td>
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<tr>
<td>$(f_i^{(0)} z'<em>i - f</em>{i-1}^{(0)} z'_{i-1})^2$</td>
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<tr>
<td>$(f_i^{(0)} (x_i + z'<em>i) - f</em>{i-1}^{(0)} (x_{i-1} + z'_{i-1}))^2$</td>
<td>0.003608</td>
<td>0.425913</td>
<td>0.019562</td>
<td>0.184631</td>
<td>0.091645</td>
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</tr>
<tr>
<td>$\frac{1}{Q_i^{(0)} - Q_{i-1}^{(0)}}$</td>
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<tr>
<td>$(f_i^{(0)} - f_{i-1}^{(0)})^2$</td>
<td>0.217782</td>
<td>0.213346</td>
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<td>0.167841</td>
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<tr>
<td>$\frac{Q_i^{(0)} - Q_{i-1}^{(0)}}{Q_i^{(0)} - Q_{i-1}^{(0)}}$</td>
<td>0.168086</td>
<td>0.418330</td>
<td>0.049868</td>
<td>0.498266</td>
<td>0.377680</td>
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<tr>
<td>$(f_i^{(0)} - f_{i-1}^{(0)}) (f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1})$</td>
<td>0.337562</td>
<td>0.418330</td>
<td>0.049868</td>
<td>0.498266</td>
<td>0.377680</td>
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</tr>
<tr>
<td>$\frac{Q_i^{(0)} - Q_{i-1}^{(0)}}{Q_i^{(0)} - Q_{i-1}^{(0)}}$</td>
<td>1.416109</td>
<td>1.870270</td>
<td>0.200437</td>
<td>2.233325</td>
<td>1.772955</td>
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</tr>
<tr>
<td>$(f_i^{(0)} (1 + x_i) - f_{i-1}^{(0)} (1 + x_{i-1}))^2$</td>
<td>1.416109</td>
<td>1.870269</td>
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<td>-0.126641</td>
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<td>0.059404</td>
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<td>-0.713706</td>
<td>0.127135</td>
<td>-0.126641</td>
<td>0.058733</td>
<td>0.059404</td>
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<td>1.105621</td>
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\[ L_t = \frac{(f_i^{(0)} - f_{i-1}^{(0)})^2 + 2 (f_i^{(0)} - f_{i-1}^{(0)}) (f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1}) + (f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1})^2}{Q_i^{(0)} - Q_{i-1}^{(0)}} \]

\[ M_t = \frac{(f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1})^2 + 2 (f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1}) (f_i^{(0)} z'_i - f_{i-1}^{(0)} z'_{i-1}) + (f_i^{(0)} z'_i - f_{i-1}^{(0)} z'_{i-1})^2}{Q_i^{(0)} - Q_{i-1}^{(0)}} \]
### Table 7.4 Calculation of $S_{03}$, $S_{0r}$ and $F$

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<td>$\Delta_0/K_1^{(0)}$</td>
<td>$-K_3^{(0)}X_0 + K_1^{(0)}Y_0/K_1^{(0)}$</td>
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<td>$K_3^{(0)}/K_1^{(0)}\cdot\hat{\beta}^*$</td>
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\[ F = \frac{22 \cdot S_{or} - S_{oa}}{10 \cdot S_{oa}} = 1.51 \]