Osaka Mathematical Journal
Vol. 4, No. 1, May, 1952

Contributions to the Theory of Systematic Statistics, II

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

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Contents

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 deviced 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[4] 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[5] 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[6] 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 meam log lethal dose, which is often called log LD 50— or log 50% lethal dose in short —, is m and the standard deviation is σ, then the linear relation between the normal deviate u converted from the expected survival rate at a given level of log dose x is

$$u=\alpha+\beta x, \tag{1.1}$$

where

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

and

$$\alpha=-\frac{m}{\sigma}, \quad \beta=\frac{1}{\sigma} \tag{1.2}$$

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

$$P_i = \frac{1}{\sqrt{2\pi}} \int_{u_i}^{\infty} e^{-\frac{t^2}{2}} dt, \tag{1.3}$$

$$i = 1, \dots, k,$$

$$Q_i = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{u_i} e^{-\frac{t_2}{2}} dt, \tag{1.4}$$

where

$$u_i = \alpha + \beta x_i, \qquad i = 1, \dots, k, \tag{1.5}$$

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

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

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, $i = 1, \dots, k$. Since the proportion of insects expected to survive at $t_i = exp\, x_i$ observation time point, $i = 1, \dots, k$ are respectively

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

where $\qquad i = 1, \dots, k,$

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

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

$$g(x)=(2\pi\sigma^2)^{-1/2}\exp\{-(x-m)^2/2\sigma^2\}, \tag{2.1}$$

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

$$P=\int_x^\infty g(t)dt=\int_u^\infty f(t)dt,$$

where

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

and

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

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

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

By the famous De Moivre's theorem[3], it follows that the distribution of the standardized variable

$$(s/n-P)/(PQ/n)^{\frac{1}{2}} \tag{2.2}$$

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.

$$s/n=\int_z^\infty f(t)dt, \tag{2.3}$$

then the variable z is distributed asymptotically normal

$$N\left(u,\sqrt{\frac{PQ}{nf^2(u)}}\right). \tag{2.4}$$

Whence we see that the frequency function of the joint distribution of the variables $z_1, \ldots, z_k$, coverted from the observed survival-rates s_1/n_1, $\ldots$, s_k/n_k is asymptotically

$$(2\pi)^{-k/2}\prod_{i=1}^k\sqrt{\frac{n_i\cdot f^2(u_i)}{P_iQ_i}}\cdot\exp\left\{-\frac{1}{2}\sum_{i=1}^k\frac{n_i\cdot f^2(u_i)}{P_iQ_i}(z_i-\alpha-\beta x_i)^2\right\}, \tag{2.5}$$

for sufficiently large values of $n_1, \ldots, n_k$.

2.2. Time motality 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.

$$s_i/N = \int_{z_i}^{\infty} f(t)td, \qquad i = 1, \ldots, k.$$

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

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

or putting

$$\begin{aligned} d_i &= N - s_i \\ Q_i &= 1 - P_i \end{aligned} \qquad i = 1, \ldots, k.$$

we have

$$\frac{N!}{d_1!(d_2-d_1)!\ldots(d_k-d_{k-1})!(N-d_k)!}Q_1^{d_1}(Q_2-Q_1)^{d_2-d_1}\cdots$$
$$(Q_k-Q_{k-1})^{d_k-d_{k-1}}(1-Q_k)^{N-d_k}.$$

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 dememsions with means $Q_1, \ldots, Q_k$ and variance-covariance matrix

$$\begin{pmatrix} \frac{Q_1(1-Q_1)}{N} & \frac{Q_1(1-Q_2)}{N} & \cdots\cdots & \frac{Q_1(1-Q_k)}{N} \\ \frac{Q_1(1-Q_2)}{N} & \frac{Q_2(1-Q_2)}{N} & \cdots\cdots & \frac{Q_2(1-Q_k)}{N} \\ \cdots & \cdots & \cdots & \cdots \\ \frac{Q_1(1-Q_k)}{N} & \frac{Q_2(1-Q_k)}{N} & \cdots\cdots & \frac{Q_k(1-Q_k)}{N} \end{pmatrix}. \tag{2.6}$$

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

$$\begin{aligned} &(N/2\pi)^{\frac{k}{2}} f_1 f_2 \cdots f_k [Q_1(Q_2-Q_1)\ldots(Q_k-Q_{k-1})(1-Q_k)]^{-\frac{1}{2}} \\ &\times \exp\left\{-\frac{N}{2}\left[\sum_{i=1}^{k}\frac{Q_{i+1}-Q_{i-1}}{(Q_{i+1}-Q_i)(Q_i-Q_{i-1})}f_i^2\cdot(z_i-\alpha-\beta x_i)^2\right.\right. \\ &\left.\left.-2\sum_{i=2}^{k}\frac{f_i f_{i-1}}{Q_i-Q_{i-1}}(z_i-\alpha-\beta x_i)(z_{i-1}-\alpha-\beta x_{i-1})\right]\right\}, \end{aligned} \tag{2.7}$$

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.

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

where

$$S=\sum_{i=1}^{k}\frac{n_i f_i^2}{P_iQ_i}(z_i-\alpha-\beta x_i)^2, \tag{3.1}$$

and

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

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 α and β.

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), $i=1,\dots,k$ on the (x,z)-plane seem to be almost collinear in all practical situations,[9] so we fit them a straight line by freehand and thus we get a system of rough estimates α_0, β_0 of α, β from the intercept and the slope of the fitted straight line[10].

Let it be

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

and

$$S_0=\sum_{i=1}^{k}\frac{n_i f_i^{(0)2}}{P_i^{(0)}Q_i^{(0)}}(z_i-\alpha-\beta x_i)^2, \tag{3.2}$$

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

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

and making use of A. Markoff's theorem on least squares, we obtain the best linear unbiased estimates[11] $\hat{\alpha}$, $\hat{\beta}$ of α, β. They should be obtained by solving the system of equations

$$\left.\frac{\partial S_0}{\partial\alpha}\right|_{\substack{\alpha=\hat{\alpha}\\ \beta=\hat{\beta}}}=0,\quad \left.\frac{\partial S_0}{\partial\beta}\right|_{\substack{\alpha=\hat{\alpha}\\ \beta=\hat{\beta}}}=0.$$

Putting

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

$$\Delta_0=K_2^{(0)}K_2^{(0)}-K_3^{(0)2},$$

and

$$X_0=\sum_{i=1}^{k}\frac{n_i f_i^{(0)2}z_i}{P_i^{(0)}Q_i^{(0)}},\quad Y_0=\sum_{i=1}^{k}\frac{n_i f^{(0)2}x_i z_i}{P_i^{(0)}Q_i^{(0)}},$$

$$\alpha=\frac{1}{\Delta_0}(K_2^{(0)}X_0-K_3^{(0)}Y_0)\quad \hat{\beta}=\frac{1}{\Delta_0}(-K_3^{(0)}X_0+K_1^{(0)}Y_0). \tag{3.3}$$

The variances and covariences of $\hat{\alpha}$ and $\hat{\beta}$ are

$$D^2(\alpha)=\frac{K_2^{(0)}}{\Delta_0},\ D^2(\hat{\beta})=\frac{K_1^{(0)}}{\Delta_0},\ C(\hat{\alpha},\hat{\beta})=-\frac{K_3^{(0)}}{\Delta_0}. \tag{3.4}$$

Taking the estimates α, β thus obtained as rough estimates of α, β, and let they be α_1, β_1, respectively, then, as the second approximation, we assume that the frequency function of the joint distribution of $z_1, \dots, z_k$ is

$$(2\pi)^{-k/2}\prod_{i=1}^{k}\sqrt{\frac{n_i f_i^{(1)2}}{P_i^{(1)}Q_i^{(1)}}}\cdot\exp\left\{-\frac{1}{2}\sum_{i=1}^{k}\frac{n_i f_i^{(1)2}}{P_i^{(1)}Q_i^{(1)}}(z_i-\alpha-\beta x_i)^2\right\}, \tag{3.5}$$

where

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

Put

$$S_1=\sum_{i=1}^{k}\frac{n_i f_i^{(1)2}}{P_i^{(1)}Q_i^{(1)}}\cdot(z_i-\alpha-\beta x_i)^2,$$

then the best linear unbiased estimates $\hat{\alpha}$, $\hat{\beta}$ of α, β should be obtained from the equations

$$\left.\frac{\partial S_1}{\partial\alpha}\right|_{\substack{\alpha=\hat{\alpha}\\ \beta=\hat{\beta}}}=0,\quad \left.\frac{\partial S_1}{\partial\beta}\right|_{\substack{\alpha=\hat{\alpha}\\ \beta=\hat{\beta}}}=0. \tag{3.6}$$

Thus we have

$$\hat{\alpha}=\frac{1}{\Delta_1}(K_2^{(1)}X_1-K_3^{(1)}Y_1),\quad \hat{\beta}=\frac{1}{\Delta_1}(-K_3^{(1)}X_1+K_1^{(1)}Y_1),$$

where

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

$$\Delta_1=K_1^{(1)}K_2^{(1)}-K_3^{(1)2},$$

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

$$D^2(\hat{\alpha}) = \frac{K_2^{(1)}}{\Delta_1}, \quad D^2(\hat{\beta}) = \frac{K_1^{(1)}}{\Delta_1}, \quad C(\hat{\alpha}, \hat{\beta}) = -\frac{K_3^{(1)}}{\Delta_1}. \tag{3.7}$$

We continue the above process untill 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

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

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

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

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 α and β. This device is due to R. A. Fisher.[12]

3. 2. Time mortality curve. In this case, the frequency function of the joint distribution of $z_1, \dots, z_k$ is given by (2. 7), i. e.

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

where

$$S = \sum_{i=1}^{k} \frac{Q_{i+1} - Q_{i-1}}{(Q_{i+1} - Q_i)(Q_i - Q_{i-1})} f_i^2 \cdot (z_i - \alpha - \beta x_i)^2$$

$$- 2 \sum_{i=2}^{k} \frac{f_i f_{i-1}}{Q_i - Q_{i-1}} (z_i - \alpha - \beta x_i)(z_{i-1} - \alpha - \beta x_{i-1}). \tag{3.9}$$

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

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

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

and then

$$\alpha_0 = -\frac{m_0}{\sigma_0}, \quad \beta_0 = \frac{1}{\sigma_0}.$$

As before, we assume the frequency function of $z_1, \dots, z_k$ to be

$$h_0(z_1, \dots, z_k ; \alpha, \beta) = (N/\pi)^{k/2} f_1^{(0)} f_2^{(0)} \dots f_k^{(0)}$$
$$\times \left[Q_1^{(0)} (Q_2^{(0)} - Q_1^{(0)}) \dots (Q_k^{(0)} - Q_{k-1}^{(0)})(1 - Q_k^{(0)}) \right]^{-1/2} \cdot \exp\left(-\frac{N}{2} S_0\right).$$

as the first approximation, where

$$S_0 = \sum_{i=1}^{k} \frac{Q_{i+1}^{(0)} - Q_{i-1}^{(0)}}{(Q_{i+1}^{(0)} - Q_i^{(0)})(Q_i^{(0)} - Q_{i-1}^{(0)})} f_i^{(0)} \cdot (z_i - \alpha - \beta x_i)^2$$
$$- \sum_{i=2}^{k} \frac{f_i^{(0)} f_{i-1}^{(0)}}{Q_i^{(0)} - Q_{i-1}^{(0)}} (z_i - \alpha - \beta x_i)(z_{i-1} - \alpha - \beta x_{i-1}) . \tag{3.10}$$

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

$$\left.\frac{\partial S_0}{\partial \alpha}\right|_{\substack{\alpha=\hat{\alpha} \\ \beta=\hat{\beta}}} = 0, \quad \left.\frac{\partial S_0}{\partial \beta}\right|_{\substack{\alpha=\hat{\alpha} \\ \beta=\hat{\beta}}} = 0 .$$

Thus we get

$$\hat{\alpha} = \frac{1}{\Delta_0}(K_2^{(0)} X_0 - K_3^{(0)} Y_0), \quad \hat{\beta} = \frac{1}{\Delta_0}(-K_3^{(0)} X_0 + K_1^{(0)} Y_0), \tag{3.11}$$

where

$$K_1^{(0)} = \sum_{i=1}^{k+1} \frac{(f_i^{(0)} - f_{i-1}^{(0)})^2}{Q_i^{(0)} - Q_{i-1}^{(0)}}, \quad K_2^{(0)} = \sum_{i=1}^{k+1} \frac{(f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1})^2}{Q_i^{(0)} - Q_{i-1}^{(0)}},$$
$$K_3^{(0)} = \sum_{i=1}^{k+1} \frac{(f_i^{(0)} - f_{i-1}^{(0)})(f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1})}{Q_i^{(0)} - Q_{i-1}^{(0)}},$$
$$\Delta_0 = K_1^{(0)} K_2^{(0)} - K_3^{(0)2},$$

and

$$X_0 = \sum_{i=1}^{k+1} \frac{(f_i^{(0)} - f_{i-1}^{(0)})(f_i^{(0)} z_i - f_{i-1}^{(0)} z_{i-1})}{Q_i^{(0)} - Q_{i-1}^{(0)}}, \quad Y_0 = \sum_{i=1}^{k+1} \frac{(f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1})(f_i^{(0)} z_i - f_{i-1}^{(0)} z_{i-1})}{Q_i^{(0)} - Q_{i-1}^{(0)}}.$$

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

$$D^2(\hat{\alpha}) = \frac{1}{N} \frac{K_2^{(0)}}{\Delta_0}, \quad D^2(\hat{\beta}) = \frac{1}{N} \frac{K_1^{(0)}}{\Delta_0}, \quad C(\hat{\alpha}, \hat{\beta}) = -\frac{1}{N} \frac{K_3^{(0)}}{\Delta_0}. \tag{3.12}$$

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 σ.

In the preceding section we have dealt with the estimation of α and β, but the parameters which should ultimately be estimated are m and σ, i.e.

$$m = -\frac{\alpha}{\beta}, \quad \sigma = \frac{1}{\beta}. \tag{4.1}$$

If we adopt the estimates

$$\hat{m} = -\frac{\hat{\alpha}}{\hat{\beta}}, \quad \hat{\sigma} = \frac{1}{\hat{\beta}}, \tag{4.2}$$

for m and σ respectively, and if the sample size is large enough, then we have approximately

$$E(\hat{m}) = m \quad \text{and} \quad E(\hat{\sigma}) = \sigma, \tag{4.3}$$

and further

$$D^2(\hat{m}) = \sigma^2 \cdot D^2(\hat{\alpha}) - 2m\sigma^3 \cdot C(\hat{\alpha}, \hat{\beta}) + m^2\sigma^4 \cdot D^2(\hat{\beta}).$$
$$D^2(\hat{\sigma}) = \sigma^4 \cdot D^2(\hat{\beta}). \tag{4.4}$$

Hence it follows that

$$D^2(m) = \begin{cases} \dfrac{\sigma^2}{\Delta_0}(K_2^{(0)} - 2m\sigma K_3^{(0)} + m^2\sigma^2 K_1^{(0)}) = \dfrac{\sigma^2}{\Delta_0}\sum_{i=1}^{k} \dfrac{n_i f_i^{(0)2}}{P_i^{(0)} Q_i^{(0)}}(x_i - m\sigma)^2, \\ \qquad\qquad \text{for dosage mortality curve,} \\ \dfrac{\sigma^2}{N\Delta_0}(K_2^{(0)} - 2m\sigma K_3^{(0)} + m^2\sigma^2 K_1^{(0)}) \\ \quad = \dfrac{\sigma^2}{N\Delta_0}\sum_{i=1}^{k+1} \dfrac{\{f_i^{(0)}(x_i - m\sigma) - f_{i-1}^{(0)}(x_{i-1} - m\sigma)\}^2}{Q_i^{(0)} - Q_{i-1}^{(0)}}, \\ \qquad\qquad \text{for time mortality curve.} \end{cases} \tag{4.5}$$

If, in some circumstances, we have obtained several estimated values

$$\hat{\alpha}_i, \hat{\beta}_i, \quad i = 1, \dots, p, \ (p \geqq 3)$$

for equal $n(= n_1 = \cdots = n_k)$ or N and for the same pair of provisional values α_0 and β_0, then we can construct a confidence interval for m as follows:[13]

Let

$$l_{11} = \frac{1}{p}\sum_{i=1}^{p}(\hat{\alpha}_i - \hat{\alpha})^2, \quad l_{12} = l_{21} = \frac{1}{p}\sum_{i=1}^{p}(\hat{\alpha}_i - \hat{\alpha})(\hat{\beta}_i - \hat{\beta}), \quad l_{22} = \frac{1}{p}\sum_{i=1}^{p}(\hat{\beta}_i - \hat{\beta})^2,$$

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

$$F = \frac{p-2}{2} \cdot \frac{1}{p-1} \cdot T^2$$
$$= \frac{p-2}{2}\left[\frac{l_{22}}{L}(\hat{\alpha} - \alpha)^2 - 2\frac{l_{12}}{L}(\hat{\alpha} - \alpha)(\hat{\beta} - \beta) + \frac{l_{11}}{L}(\hat{\beta} - \beta)^2\right] \tag{4.6}$$

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.[14]

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

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

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

$$\frac{l_{22}}{L}(\alpha-\hat{\alpha})^2-\frac{l_{12}}{L}(\alpha-\hat{\alpha})(\beta-\hat{\beta})+\frac{l_{11}}{L}(\beta-\hat{\beta})^2 = \frac{2}{p-2}F^2_{p-2}(100\varepsilon) \qquad (4.7)$$

on the (α, β)-plane.

If the level of significance ε 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

$$\alpha = \tilde{m}_1\beta \quad \text{and} \quad \alpha = \tilde{m}_2\beta$$

for which, for example.

$$P(-\tilde{m}_1 \leqq m \leqq -\tilde{m}_2) \geqq 1-\varepsilon\,. \qquad (4.8)$$

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

$$\frac{\frac{2}{p-2}F^2_{p-2}(100\varepsilon)l_{12}-\hat{\alpha}\cdot\hat{\beta}\pm\sqrt{\frac{2}{p-2}F^2_{p-2}(100\varepsilon)\cdot L\left(\frac{l_{22}}{L}\hat{\alpha}^2-2\frac{l_{12}}{L}\hat{\alpha}\cdot\hat{\beta}+\frac{l_{11}}{L}\hat{\beta}^2-\frac{2}{p-2}F^2_{p-2}(100\varepsilon)\right)}}{\frac{2}{p-2}F^2_{p-2}(100\varepsilon)\cdot l_{11}-\hat{\alpha}^2} \qquad (4.9)$$

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

$$\frac{l_{22}}{L}\hat{\alpha}^2-2\frac{l_{12}}{L}\hat{\alpha}\,\hat{\beta}+\frac{l_{11}}{L}\hat{\beta}^2 \geqq \frac{2}{p-1}F^2_{p-2}(100\varepsilon)$$

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

§ 5. Testing Statistical Hypotheses Concerning Unknown Parameters.

In the theory of dosage or time mortality curve, as Drs. Ohsawa and Nagasawa[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 resitibility 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 ν-th drug be

$$g_\nu(x) = (2\pi\sigma_\nu^2)^{-1/2} \exp\left\{-(x-m_\nu)^2/2\sigma_\nu^2\right\}, \quad \nu = 1, \dots, p, \qquad (5.1)$$

and further let it be

$$\alpha_\nu = -m_\nu/\sigma_\nu, \quad \beta_\nu = 1/\sigma_\nu, \quad \nu = 1, \dots, p.$$

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 $x_1, \dots x_k$, and the observed death-rates are

$$d_{1\nu}/N, \; d_{2\nu}/N, \dots, d_{k\nu}/N, \quad \nu = 1, \dots, p.$$

In this case the frequency function of the converted normal deviates

$$z_{1\nu}, z_{2\nu}, \dots, z_{k\nu}, \quad \nu = 1, \dots, p$$

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

$$(N/2\pi)^{\frac{pk}{2}} \prod_{\nu=1}^{p} f_{1\nu} f_{2\nu} \dots f_{k\nu} \Big[Q_{1\nu}(Q_{2\nu}-Q_{1\nu}) \dots (Q_{k\nu}-Q_{k-1,\nu})(1-Q_{k\nu})\Big]^{-1/2} \exp\left(-\frac{N}{2}S\right).$$

where

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

and

$$Q_{i\nu} = \int_{-\infty}^{\alpha_\nu+\beta_\nu x_i} f(t)dt, \; f_{i\nu} = f(\alpha_\nu+\beta_\nu x_i), \quad i = 1, \dots, k; \; \nu = 1, \dots, p.$$

For the ν-th experimental data, we obtain the provisional values $\alpha_{0\nu}$ and $\beta_{0\nu}$ by free-hand method graphically, for example, and put

$$Q_{i\nu}^{(0)} = \int_{-\infty}^{\alpha_{0\nu}+\beta_{0\nu}x_i} f(t)dt\,, \quad f_{i\nu}^{(0)} = f(\alpha_{0\nu}+\beta_{0\nu}x_i)\,, \quad i=1,\dots,k\,;\ \nu=1,\dots,p\,, \tag{5.3}$$

and then we assume that the frequency function of $z_{1\nu},\dots,z_{k\nu}$, $\nu=1,\dots,p$ is approximately equal to

$$(N/\pi)^{pk/2}\prod_{\nu=1}^{p} f_{1\nu}^{(0)} f_{2\nu}^{(0)}\dots f_{k\nu}^{(0)}\Big[Q_{1\nu}^{(0)}(Q_{2\nu}^{(0)}-Q_{1\nu}^{(0)})\dots(Q_{k\nu}^{(0)}-Q_{k-1,\nu}^{(0)})(1-Q_{k\nu}^{(0)})\Big]^{-1/2} \exp\left(-\frac{N}{2}S_0\right),$$

where

$$S_0 = \sum_{\nu=1}^{n}\left\{\sum_{i=1}^{k}\frac{Q_{i+1,\nu}^{(0)}-Q_{i-1,\nu}^{(0)}}{(Q_{i+1,\nu}^{(0)}-Q_{i\nu}^{(0)})(Q_{i\nu}^{(0)}-Q_{i-1,\nu}^{(0)})} f_{i\nu}^{(0)2}\cdot(z_{i\nu}-\alpha_\nu-\beta_\nu x_i)^2 \right.$$
$$\left. -2\sum_{i=2}^{k}\frac{f_{i\nu}^{(0)}f_{i-1,\nu}^{(0)}}{Q_{i\nu}^{(0)}-Q_{i-1,\nu}^{(0)}}(z_{i\nu}-\alpha_\nu-\beta_\nu x_i)(z_{i-1,\nu}-\alpha_\nu-\beta_\nu x_{i-1})\right\}. \tag{5.4}$$

To test the homogeneity of the standard deviations

$$\sigma_1 = \sigma_2 = \cdots = \sigma_p\,,$$

it will be sufficient to test the null-hypothesis

$$H_1:\ \beta_1 = \beta_2 = \cdots = \beta_p\,. \tag{5.5}$$

Denote the maximum likelihood estimates of α_ν and β_ν by $\hat{\alpha}_\nu$ and $\hat{\beta}_\nu$ respectively, then they should be obtained from the equations

$$\left.\begin{aligned} K_{1\nu}^{(0)}\hat{\alpha}_\nu + K_{3\nu}^{(0)}\hat{\beta}_\nu &= X_{0\nu} \\ K_{3\nu}^{(0)}\hat{\alpha}_\nu + K_{2\nu}^{(0)}\hat{\beta}_\nu &= Y_{0\nu} \end{aligned}\right\},\quad \nu=1,\dots,p\,. \tag{5.6}$$

where

$$K_{1\nu}^{(0)} = \sum_{i=1}^{k+1}\frac{(f_{i\nu}^{(0)}-f_{i-1,\nu}^{(0)})^2}{Q_{i\nu}^{(0)}-Q_{i-1,\nu}^{(0)}}\,,\quad K_{2\nu}^{(0)} = \sum_{i=1}^{k+1}\frac{(f_{i\nu}^{(0)}x_i-f_{i-1,\nu}^{(0)}x_{i-1})^2}{Q_{i\nu}^{(0)}-Q_{i-1,\nu}^{(0)}}\,,$$

$$K_{3\nu}^{(0)} = \sum_{i=1}^{k+1}\frac{(f_{i\nu}^{(0)}-f_{i-1,\nu}^{(0)})(f_{i\nu}^{(0)}x_i-f_{i-1,\nu}^{(0)}x_{i-1})}{Q_{i\nu}^{(0)}-Q_{i-1,\nu}^{(0)}}\,,$$

$$X_{0\nu} = \sum_{i=1}^{k+1}\frac{(f_{i\nu}^{(0)}-f_{i-1,\nu}^{(0)})(f_{i\nu}^{(0)}z_{i\nu}-f_{i-1,\nu}^{(0)}z_{i-1,\nu})}{Q_{i\nu}^{(0)}-Q_{i-1,\nu}^{(0)}}\,, \tag{5.7}$$

$$Y_{0\nu} = \sum_{i=1}^{k+1}\frac{(f_{i\nu}^{(0)}x_i-f_{i-1,\nu}^{(0)}x_{i-1})(f_{i\nu}^{(0)}z_{i\nu}-f_{i-1,\nu}^{(0)}z_{i-1,\nu})}{Q_{i\nu}^{(0)}-Q_{i-1,\nu}^{(0)}}\,,$$

$$Z_{0\nu} = \sum_{i=1}^{k+1}\frac{(f_{i\nu}^{(0)}z_{i\nu}-f_{i-1,\nu}^{(0)}z_{i-1,\nu})^2}{Q_{i\nu}^{(0)}-Q_{i-1,\nu}^{(0)}}\,,\qquad \nu=1,\dots p\,.$$

The absolute minimum value S_{0a} of S_0 is

$$S_{0a}=\sum_{\nu=1}^{p} Z_{0\nu}-\sum_{\nu=1}^{p} X_{0\nu}\cdot\hat{\alpha}_{\nu}-\sum_{\nu=1}^{p} Y_{0\nu}\hat{\beta}_{\nu}. \tag{5.8}$$

Similarly, let the maximum likelihood estimates of $\alpha_\nu, \beta_\nu, \nu=1,\dots,p$ under the null-hypotheses H_1, be $\hat{\alpha}_1^*,\dots,\hat{\alpha}_p^*$ and $\hat{\beta}^*$, then they should be obtained from the equations

$$\left.\begin{aligned}
&K_{11}^{(0)}\hat{\alpha}_1^* && +K_{31}^{(0)}\hat{\beta}^*=X_{01}\\
&\quad K_{12}^{(0)}\hat{\alpha}_2^* && +K_{32}^{(0)}\hat{\beta}^*=X_{02}\\
&\qquad\ddots && \quad\vdots\qquad\quad\vdots\\
&\qquad\quad K_{1p}^{(0)}\hat{\alpha}_p^* && +K_{3p}^{(0)}\hat{\beta}^*=X_{0p}\\
&K_{31}^{(0)}\hat{\alpha}_1^*+K_{32}^{(0)}\hat{\alpha}_2^*+\cdots+K_{3p}^{(0)}\hat{\alpha}_p^* && +(K_{21}^{(0)}+\cdots+K_{2p}^{(0)})\hat{\beta}^*=Y_{01}+\cdots+Y_{0p}
\end{aligned}\right\} \tag{5.9}$$

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

$$S_{0r}=\sum_{\nu=1}^{p} Z_{0\nu}-\sum_{\nu=1}^{p} X_{0\nu}\hat{\alpha}_{\nu}^*-\left(\sum_{\nu=1}^{p} Y_{0\nu}\right)\hat{\beta}^*, \tag{5.10}$$

By the result of the general theory of linear hypotheses[16], it follows that the statistic

$$F=\frac{p(k-2)}{p-1}\frac{\sum_{\nu=1}^{p}\left\{X_{0\nu}(\hat{\alpha}_\nu-\hat{\alpha}_\nu^*)+Y_{0\nu}(\hat{\beta}_\nu-\hat{\beta}^*)\right\}}{S_{0a}} \tag{5.11}$$

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 100ε percent point of the right tail of the F-distribution of degrees of freedom (n_1, n_2) by $F_{n_2}^{n_1}(100\varepsilon)$, then we reject the null-hypothesis H_1 when

$$F \geqq F_{p(k-2)}^{p-1}(100\,\varepsilon/2) \quad\text{or}\quad F\leqq 1/F_{p-1}^{p(k-2)}(100\,\varepsilon/2).$$

The probability of committing the error of the first kind is just ε.

Thus, if the constancy of the standard deviation is already justified, then the problem arises, i.e. the comparison of two means.[17] In this case the basic frequency function is

$$(N/\pi)^k\prod_{\nu=1}^{2} f_{1\nu}^{(0)}f_{2\nu}^{(0)}\dots f_{k\nu}^{(0)}\left[Q_{1\nu}^{(0)}(Q_{2\nu}^{(0)}-Q_{1\nu}^{(0)})\dots(Q_{k\nu}^{(0)}-Q_{k-1,\nu}^{(0)})(1-Q_{k\nu}^{(0)})\right]^{-1/2}\cdot \exp\left(-\frac{N}{2}S_0\right),$$

where

$$S_0=\sum_{\nu=1}^{2}\left\{\sum_{i=1}^{k}\frac{Q_{i+1,\nu}^{(0)}-Q_{i-1,\nu}^{(0)}}{(Q_{i+1,\nu}^{(0)}-Q_{i\nu}^{(0)})(Q_{i\nu}^{(0)}-Q_{i-1,\nu}^{(0)})}f_{i\nu}^{(0)2}(z_{i\nu}-\alpha_\nu-\beta x_i)^2\right.$$
$$\left.-2\sum_{i=2}^{k}\frac{f_{i\nu}^{(0)}f_{i-1,\nu}^{(0)}}{Q_{i\nu}^{(0)}-Q_{i-1,\nu}^{(0)}}(z_{i\nu}-\alpha_\nu-\beta x_i)(z_{i-1,\nu}-\alpha_\nu-\beta x_{i-1})\right\}, \tag{5.12}$$

and

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

$$\beta_0=\frac{1}{2}(\beta_{\nu 1}+\beta_{\nu 2})\,.$$

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

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

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

Let the maximum likelihood estimates of α_1, α_2 and β be $\hat{\alpha}_1, \hat{\alpha}_2$ and $\hat{\beta}$ respectively, then the absolute minimum value S_{0a} and S_0 is

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

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

$$\left.\begin{aligned} K_{11}^{(0)}\hat{\alpha}_1 \qquad\qquad\quad +K_{31}^{(0)}\hat{\beta}&=X_{01}\\ K_{12}^{(0)}\hat{\alpha}_2+K_{32}^{(0)}\hat{\beta}&=X_{02}\\ K_{31}^{(0)}\hat{\alpha}_1+K_{32}^{(0)}\hat{\alpha}_2+(K_{21}^{(0)}+K_{22}^{(0)})\hat{\beta}&=Y_{01}+Y_{02}\end{aligned}\right\} \tag{5.14}$$

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

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

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

$$\left.\begin{aligned}(K_{11}^{(0)}+K_{12}^{(0)})\hat{\alpha}^*+(K_{31}^{(0)}+K_{32}^{(0)})\hat{\beta}^*&=X_{01}+X_{02}\\ (K_{31}^{(0)}+K_{32}^{(0)})\hat{\alpha}^*+(K_{21}^{(0)}+K_{22}^{(0)})\hat{\beta}^*&=Y_{01}+Y_{02}\end{aligned}\right\}, \tag{5.16}$$

whence it follows that the satistic

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

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

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

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

§ 6. Design of Experiments

6. 1. The optinum allocation of test animals to various dosage levels. Dr. Milton Friedman[18] 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

$$\sum_{i=1}^{k} n_i = N, \tag{6.1}$$

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

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

shall be maximized, where

$$w_i = f_i^{(0)2} / P_i^{(0)} Q_i^{(0)}, \quad i = 1, \dots, k.$$

The required values of $n_1, \dots, n_k$ will be obtained by solving the following system of linear equations

$$\left.\begin{array}{ll}
n_2 \cdot w_2(w_2 - x_1)^2 + n_3 \cdot w_3(x_3 - x_1)^2 + \cdots & \\
\quad + n_{k-1} \cdot w_{k-1}(x_{k-1} - x_1)^2 + n_k \cdot w_k(x_k - x_1)^2 = & \dfrac{\lambda}{w_1} \\
n_1 \cdot w_1(x_1 - x_2)^2 + n_3 \cdot w_3(x_3 - x_2)^2 + \cdots & \\
\quad + n_{k-1} \cdot w_{k-1}(x_{k-1} - x_2)^2 + n_k \cdot w_k(x_k - x_2)^2 = & \dfrac{\lambda}{w_2} \\
\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots & \\
n_1 \cdot w_1(x_1 - x_{k-1})^2 + n_2 \cdot w_2(x_2 - x_{k-1})^2 + n_3 \cdot w_3(x_3 - x_{k-1})^2 + \cdots & \\
\quad + n_k \cdot w_k(x_k - x_{k-1})^2 = & \dfrac{\lambda}{w_{k-1}} \\
n_1 \cdot w_1(x_1 - x_k)^2 + n_2 \cdot w_2(x_2 - x_k)^2 + n_3 \cdot w_3(x_3 - x_k)^2 + \cdots & \\
\quad + n_{k-1} \cdot w_{k-1}(x_{k-1} - x_k)^2 = & \dfrac{\lambda}{w_k}
\end{array}\right\} \tag{6.3}$$

where λ 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

$$n_1 : n_2 = \frac{1}{w_1^2} : \frac{1}{w_2^2}, \tag{6.4}$$

hence the required optinum spacing of x_1 and x_2 is such that for which

$$\Delta_0 = \frac{N^2}{w_1 w_2}\left(\frac{1}{w_1^2} + \frac{1}{w_2^2}\right)^{-2} \cdot (x_1 - x_2)^2$$

is maximum.

In the case of Table 11. 1[19] of Dr. Milton Friedman's data, viwed from the stand point of the allocation, the determinant of the coefficients corresponding to the system of equations (6. 3) contains a factor

$$\begin{vmatrix} 0 & \left(\frac{5}{6}\right)^2 & \left(\frac{10}{6}\right)^2 & \left(\frac{15}{6}\right)^2 & \left(\frac{20}{6}\right)^2 & \left(\frac{25}{6}\right)^2 & \left(\frac{30}{6}\right)^2 \\ \left(\frac{5}{6}\right)^2 & 0 & \left(\frac{5}{6}\right) & \left(\frac{10}{6}\right)^2 & \left(\frac{15}{6}\right)^2 & \left(\frac{20}{6}\right)^2 & \left(\frac{25}{6}\right)^2 \\ \left(\frac{10}{6}\right)^2 & \left(\frac{5}{6}\right) & 0 & \left(\frac{5}{6}\right)^2 & \left(\frac{10}{6}\right)^2 & \left(\frac{15}{6}\right)^2 & \left(\frac{20}{6}\right)^2 \\ \left(\frac{15}{6}\right)^2 & \left(\frac{10}{6}\right)^2 & \left(\frac{5}{6}\right)^2 & 0 & \left(\frac{5}{6}\right)^2 & \left(\frac{10}{6}\right)^2 & \left(\frac{15}{6}\right)^2 \\ \left(\frac{20}{6}\right)^2 & \left(\frac{15}{6}\right)^2 & \left(\frac{10}{6}\right)^2 & \left(\frac{5}{6}\right)^2 & 0 & \left(\frac{5}{6}\right)^2 & \left(\frac{10}{6}\right)^2 \\ \left(\frac{25}{6}\right)^2 & \left(\frac{20}{6}\right)^2 & \left(\frac{15}{6}\right)^2 & \left(\frac{10}{6}\right)^2 & \left(\frac{5}{6}\right)^2 & 0 & \left(\frac{5}{6}\right)^2 \\ \left(\frac{30}{6}\right)^2 & \left(\frac{25}{6}\right)^2 & \left(\frac{20}{6}\right)^2 & \left(\frac{15}{6}\right)^2 & \left(\frac{10}{6}\right)^2 & \left(\frac{5}{6}\right)^2 & 0 \end{vmatrix} = 0,$$

so the allocation of $n_1, \dots, n_k$ remains undetermined.[20]

6. 2. Remarks on the optimum spacings for the time mortality curve. When both the mean m and the standard deviation σ of the time mortality curve are unknown, the most efficient design of experiment for estimating m and σ jointly must be such that, for any given k, log lethal time levels, should be chosen so as to make $\Delta_0 = K_1^{(0)} K_2^{(0)} - K_3^{(0)2}$ 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 optinum 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 $k = 2, 3, \dots, 10$.

§ 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 σ by using four lethal time levels,

$$x_1 = 1.55, \quad x_2 = 1.85, \quad x_3 = 2.05, \quad x_4 = 2.25,$$

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	98	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		

$x_1 = 1.55$ $\quad x_2 = 1.85$ $\quad x_3 = 2.05$ $\quad x_4 = 2.25$

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

$$F = \frac{p(k-2)}{p-1} \frac{S_{0r} - S_{0a}}{S_{0a}} = \frac{22}{10} \cdot \frac{.090164}{.131390} = 1.51$$

By rough linear interpolation, we find

$$F_{22}^{10}(2.5) = 2.66, \quad F_{22}^{10}(5) = 2.30,$$

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.

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

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

$$M_i \equiv \frac{(f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1})^2}{Q_i^{(0)} - Q_{i-1}^{(0)}} + 2\frac{(f_i^{(0)} x_i - f_{i-1}^{(0)} x_{i-1})(f_i^{(0)} z_i - f_{i-1}^{(0)} z_{i-1})}{Q_i^{(0)} - Q_{i-1}^{(0)}} + \frac{(f_i^{(0)} z_i - f_{i-1}^{(0)} z_{i-1})^2}{Q_i^{(0)} - Q_{i-1}^{(0)}}$$

$$= \frac{(f_i^{(0)}(x_i + z_i) - f_{i-1}^{(0)}(x_{i-1} + z_{i-1}))^2}{Q_i^{(0)} - Q_{i-1}^{(0)}},$$

and

$$\sum_{i=1}^{k} L_i = K_1^{(0)} + 2K_3^{(0)} + K_2^{(0)},$$

$$\sum_{i=1}^{k} M_i = K_2^{(0)} + 2X_0 + Z_0 .$$

Notes and References

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8. See for example, H. Cramér, "Math. Meth. of Statist." 16. 4, pp. 198–200.
9. This is the very reason why we assume the normality of the population
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17. For the sake of simplicity, we shall discuss the point in this case of two samples. When two samples $x_{\alpha i}$, $i=1\ldots\ldots, n_\alpha : \alpha=1, 2$ drawn from the normal populations $N(m_\alpha, \sigma_\alpha)$ $\alpha=1, 2$ 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

$$n_\alpha s_\alpha^2 = \sum_{i=1}^{n_\alpha}(x_{\alpha i}-\bar{x}_\alpha)^2, \quad \alpha=1.\ 2,$$

and

$$\bar{x}_\alpha = \frac{1}{n_\alpha}\sum_{i=1}^{n_\alpha} x_{\alpha i}, \quad \alpha=1.\ 2,$$

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 depenendent, and the joint probability element of them is proportional to

$$F^{\frac{n_1-3}{2}}\left(1+\frac{n_1-1}{n_2-1}F\right)^{\frac{1}{2}}\left[\left(\frac{1}{\sigma_1^2}+\frac{n_1n_2t^2}{K^2\sigma_1^2\sigma_2^2\left(\frac{n_1}{\sigma_1^2}+\frac{n_2}{\sigma_2^2}\right)}\right)\frac{n_1-1}{n_2-1}F+\left(\frac{1}{\sigma_2^2}+\frac{n_1n_2t^2}{K^2\sigma_1^2\sigma_2^2\left(\frac{n_1}{\sigma_1^2}+\frac{n_2}{\sigma_2^2}\right)}\right)\right]^{-\frac{n_1+n_2-1}{2}} dtdF,$$

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

$$1/F^{n_2-1}_{n_1-1}(100\varepsilon/2) \leqq F \leqq F^{n_1-1}_{n_2-1}(100\varepsilon/2),$$

where ε 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 $n_1, \cdots n_k$ 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.
21. J. Ogawa. loc. cit. pp. 176–213.
22. J. Ogawa, loc. cit. p. 199.
23. J. Ogawa, loc. cit. p. 196.
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 $K_1^{(0)}$, $K_2^{(0)}$, $K_3^{(0)}$ and X_0, Y_0, Z_0
(Uncorrected normal deviate)

$D=400$ $m_0=1.89$ $\sigma_0=0.207$ $\alpha_0=-9.1304$ $\beta_0=4.8309$										
x_i		1.55		1.85		2.05		2.25		
d_i/N		.01		.38		.72		.92		
z_i		-2.32635		-.30548		.58284		1.40507		
$\alpha_0+\beta_0 x_i$		-1.6425		-.1932		.7729		1.7391		
$Q_i^{(0)}$		.050245		.423402		.780207		.958991		
$Q_i^{(0)}-Q_{i-1}^{(0)}$	.050245		.373157		.356805		.178784		.041009	1.000000
$f_i^{(0)}$		.103537		.391562		.295931		.087934		
$f_i^{(0)}x_i$		.160482		.724390		.606659		.197852		
$f_i^{(0)}(1+x_i)$		.264019		1.115952		.902590		.285786		
$f_i^{(0)}z_i$		-.240863		-.119614		.172480		.123553		
$f_i^{(0)}(x_i+z_i)$		-.080381		.604776		.779139		.321405		
$f_i^{(0)}-f_{i-1}^{(0)}$	.103537		.288025		-.095631		-.207997		-.087934	.000000
$f_i^{(0)}x_i-f_{i-1}^{(0)}x_{i-1}$	.160482		.563908		-.117731		-.408807		-.197852	.000000
$f_i^{(0)}(1+x_i)-f_{i-1}^{(0)}(1+x_{i-1})$	.264019		.851933		-.213362		-.616804		-.285786	.000000
$\frac{1}{Q_i^{(0)}-Q_{i-1}^{(0)}}$	19.902478		2.679837		2.802651		5.593342		24.384891	
$(f_i^{(0)}-f_{i-1}^{(0)})^2$	.010720		.082958		.009145		.043263		.007732	
$(f_i^{(0)}-f_{i-1}^{(0)})(f_i^{(0)}x_i-f_i^{(0)}x_{i-1})$	.016616		.162420		.011259		.085031		.017398	
$(f_i^{(0)}x_i-f_{i-1}^{(0)}x_{i-1})^2$	.025754		.317992		.013861		.167123		.039145	
$(f_i^{(0)}(1+x_i)-f_{i-1}^{(0)}(1+x_{i-1}))^2$	.069706		.725790		.045523		.380447		.081676	

$\frac{(f_i^{(0)}-f_{i-1}^{(0)})^2}{Q_i^{(0)}-Q_{i-1}^{(0)}}$	.213355	.222314	.025630	.241985	.188544	.891828
$\frac{(f_i^{(0)}-f_{i-1}^{(0)})(f_i^{(0)}x_i-f_{i-1}^{(0)}x_{i-1})}{Q_i^{(0)}-Q_{i-1}^{(0)}}$	.330700	.434259	.031555	.475607	.424248	1.697369
$\frac{(f_i^{(0)}x_i-f_{i-1}^{(0)}x_{i-1})^2}{Q_i^{(0)}-Q_{i-1}^{(0)}}$	.512568	.852167	.038848	.934776	.954746	3.292906
$\frac{(f_i^{(0)}(1+x_i)-f_{i-1}^{(0)}(1+x_{i-1}))^2}{Q_i^{(0)}-Q_{i-1}^{(0)}}$	1.387322	1.944999	.127585	2.127970	1.991514	
L_i	1.387323	1.944999	.127588	2.127975	1.991587	9.579472
$f_i^{(0)}z_i-f_{i-1}^{(0)}z_{i-1}$	−.240863	.121249	.292094	−.048927	−.123553	
$f_i^{(0)}(x_i+z_i)-f_{i-1}^{(0)}(x_i+z_{i-1})$	−.080381	.685157	.174363	−.457734	−.321405	
$(f_i^{(0)}-f_{i-1}^{(0)})(f_i^{(0)}z_i-f_{i-1}^{(0)}z_{i-1})$	−.024938	.034922	−.027933	.010177	.010865	
$(f_i^{(0)}x_i-f_{i-1}^{(0)}x_{i-1})(f_i^{(0)}z_i-f_{i-1}^{(0)}z_{i-1})$	−.038654	.068373	−.034389	.020002	.024445	
$(f_i^{(0)}z_i-f_{i-1}^{(0)}z_{i-1})^2$	.058015	.014701	.085319	.002394	.015265	
$(f_i^{(0)}(x_i+z_i)-f_{i-1}^{(0)}(x_{i-1}+z_{i-1}))^2$	.006461	.469440	.030402	.209520	.103301	
$\frac{(f_i^{(0)}-f_{i-1}^{(0)})(f_i^{(0)}z_i-f_{i-1}^{(0)}z_{i-1})}{Q_i^{(0)}-Q_{i-1}^{(0)}}$	−.496328	.093585	−.078286	.056923	.264942	−.159164
$\frac{(f_i^{(0)}x_i-f_{i-1}^{(0)}x_{i-1})(f_i^{(0)}z_i-f_{i-1}^{(0)}z_{i-1})}{Q_i^{(0)}-Q_{i-1}^{(0)}}$	−.769310	.183228	−.096380	.111878	.596089	.025505
$\frac{(f_i^{(0)}z_i-f_{i-1}^{(0)}z_{i-1})^2}{Q_i^{(0)}-Q_{i-1}^{(0)}}$	1.154642	.039396	.239119	.013390	.372260	1.818807
$\frac{(f_i^{(0)}(x_i+z_i)-f_{i-1}^{(0)}(x_{i-1}+z_{i-1}))^2}{Q_i^{(0)}-Q_{i-1}^{(0)}}$	.281590	1.258023	.085206	1.171915	2.518984	
M_i	.128590	1.258019	.085207	1.171922	2.518985	6.162723

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

$$M_i=\frac{(f_i^{(0)}x_i-f_{i-1}^{(0)}x_{i-1})^2}{Q_i^{(0)}-Q_{i-1}^{(0)}}+2\frac{(f_i^{(0)}x_i-f_{i-1}^{(0)}x_{i-1})(f_i^{(0)}z_i-f_{i-1}^{(0)}z_{i-1})}{Q_i^{(0)}-Q_{i-1}^{(0)}}+\frac{(f_i^{(0)}z_i-f_{i-1}^{(0)}z_{i-1})^2}{Q_i^{(0)}-Q_{i-1}^{(0)}}$$

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)

$D=200$ $m_0=1.88$ $\sigma_0=0.203$ $\alpha_0=-9.2611$ $\beta_0=4.9261$

x_i		1.55		1.85		2.05		2.25		
d_i/N		.00		.37		.72		.96		
$\alpha_0+\beta_0 x_i$		−1.6256		−.1478		.8374		1.8226		
$Q_i^{(0)}$		.052020		.441251		.798814		.965807		
$Q_i^{(0)}-Q_{i-1}^{(0)}$	.052020		.389231		.357563		.166993		.034193	1.000000
$f_i^{(0)}$		.106347		.394605		.280955		.075759		
$d_i/N-Q_i^{(0)}$		−.052020		−.071251		−.078814		−.005807		
$\frac{d_i/N-Q_i^{(0)}}{f_i^{(0)}}$		−.488740		−.180563		−.280522		−.076651		
$z_i'=\alpha_0+\beta_0 x_i+\frac{d_i/N-Q_i^{(0)}}{f_i^{(0)}}$		−2.114340		−.348363		.556878		1.745949		
$f_i^{(0)}x_i$		.164977		.730019		.575958		.170458		
$f_i^{(0)}(1+x_i)$		.271414		1.124624		.856913		.246217		
$f_i^{(0)}z_i'$		−.225044		−.137466		.156458		.132271		
$f_i^{(0)}-f_{i-1}^{(0)}$	.106437		.288168		−.113650		−.205196		−.075759	.000000
$f_i^{(0)}x_i-f_{i-1}^{(0)}x_{i-1}$	.164977		.565042		−.154061		−.405500		−.170458	.000000
$f_i^{(0)}(1+x_i)-f_{i-1}^{(0)}(1+x_{i-1})$	.271414		.853210		−.267711		−.610696		−.246217	.000000
$f_i^{(0)}(x_i+z_1')$		−.060067		.592553		.732416		.302729		
$f_i^{(0)}z_i'-f_{i-1}^{(0)}z_{i-1}'$	−.225044		.087578		.293924		−.024187		−.132271	.000000
$f_i^{(0)}(x_i+z_i')-f_{i-1}^{(0)}(x_{i-1}+z_{i-1}')$	−.060067		.652620		.139863		−.429687		−.302729	.000000
$(f_i^{(0)}-f_{i-1}^{(0)})^2$	.011329		.083041		.012916		.042105		.005739	
$(f_i^{(0)}-f_{i-1}^{(0)})(f_i^{(0)}x_i-f_{i-1}^{(0)}x_{i-1})$	.017560		.162827		.017509		.083207		.012914	
$(f_i^{(0)}(1+x_i)-f_{i-1}^{(0)}(1+x_{i-1}))^2$	.073666		.727967		.071669		.372950		.060362	

$(f_i^{(0)}-f_{i-1}^{(0)})(f_i^{(0)}z_i'-f_{i-1}^{(0)}z_{i-1}')$	−.023953	.025237	−.033404	.004963	.010021	
$(f_i^{(0)}x_i-f_i^{(0)}x_{i-1})^2$	.027217	.319272	.023735	.164430	.029056	
$(f_i^{(0)}x_i-f_{i-1}^{(0)}x_{i-1})(f_i^{(0)}z_i'-f_{i-1}^{(0)}z_{i-1}')$	−.037127	.049485	−.045282	.009808	.022547	
$(f_i^{(0)}z_i'-f_{i-1}^{(0)}z_{i-1}')^2$	.050645	.007670	.086391	.000585	.017496	
$(f_i^{(0)}(x_i+z_i')-f_{i-1}^{(0)}(x_{i-1}+z_{i-1}'))^2$	.003608	.425913	.019562	.184631	.091645	
$\dfrac{1}{Q_i^{(0)}-Q_{i-1}^{(0)}}$	19.223375	2.569168	2.796710	5.988275	29.245752	
$\dfrac{(f_i^{(0)}-f_{i-1}^{(0)})^2}{Q_i^{(0)}-Q_{i-1}^{(0)}}$	.217782	.213346	.036122	.252136	.167841	.887227
$\dfrac{(f_i^{(0)}-f_{i-1}^{(0)})(f_i^{(0)}x_i-f_{i-1}^{(0)}x_{i-1})}{Q_i^{(0)}-Q_{i-1}^{(0)}}$	.337562	.418330	.048968	.498266	.377680	1.680806
$\dfrac{(f_i^{(0)}x_i-f_{i-1}^{(0)}x_{i-1})^2}{Q_i^{(0)}-Q_{i-1}^{(0)}}$	.523203	.820263	.066380	.984652	.849765	3.244263
$\dfrac{(f_i^{(0)}(1+x_i)-f_{i-1}^{(0)}(1+x_{i-1}))^2}{Q_i^{(0)}-Q_{i-1}^{(0)}}$	1.416109	1.870270	.200437	2.233325	1.772965	
L_i	1.416109	1.870269	.200438	2.233320	1.772966	7.493102
$\dfrac{(f_i^{(0)}-f_{i-1}^{(0)})(f_i^{(0)}z_i'-f_{i-1}^{(0)}z_{i-1}')}{Q_i^{(0)}-Q_{i-1}^{(0)}}$	−.460458	.064838	−.093421	.029720	.293072	−.166249
$\dfrac{(f_i^{(0)}x_i-f_{i-1}^{(0)}x_{i-1})(f_i^{(0)}z_i'-f_{i-1}^{(0)}z_{i-1}')}{Q_i^{(0)}-Q_{i-1}^{(0)}}$	−.713706	.127135	−.126641	.058733	.659404	.004925
$\dfrac{(f_i^{(0)}z_i'-f_{i-1}^{(0)}z_{i-1}')^2}{Q_i^{(0)}-Q_{i-1}^{(0)}}$	.273568	.019706	.241611	.003503	.511684	1.750072
$\dfrac{(f_i^{0}(x_i+z_i')-f_{i-1}^{(0)}(x_{i-1}+z_{i-1}'))^2}{Q_i^{(0)}-Q_{i-1}^{(0)}}$	.069358	1.094242	.054709	1.105621	2.680227	
M_i	.069358	1.094239	.054709	1.105621	2.680257	5.004185

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

$$M_i=\frac{(f_i^{(0)}x_i-f_{i-1}^{(0)}x_{i-1})^2}{Q_i^{(0)}Q_{i-1}^{(0)}}+2\frac{(f_i^{(0)}x_i-f_{i-1}^{(0)})(f_i^{(0)}z_i'-f_{i-1}^{(0)}z_{i-1}')}{Q_i^{(0)}-Q_{i-1}^{(0)}}+\frac{(f_i^{(0)}z_i'-f_{i-1}^{(0)}z_{i-1}')^2}{Q_i^{(0)}-Q_{i-1}^{(0)}}$$

Table 7.4 Calculation of S_{oa}, S_{or} and F

D	50	75	100	150	200	300	400	600	800	1200	1600	Row Total
$K_1^{(0)}$	.813952	.871578	.820217	.839886	.887227	.855783	.891828	.848957	.880954	.838883	.838477	
$K_2^{(0)}$	2.456681	2.896531	2.666772	2.930010	3.244263	3.031965	3.292906	2.976464	3.218807	2.939795	2.996759	
$K_3^{(0)}$	1.402007	1.571614	1.467473	1.558446	1.680806	1.598780	1.697369	1.577911	1.669309	1.559821	1.575599	
X_0	−.107406	−.082122	−.288582	−.027539	−.166249	−.122173	−.159164	−.159409	−.130714	−.230128	−.102055	
Y_0	.034626	.153789	−.197510	.169015	.004925	.031262	.025505	−.060801	.049619	−.179113	.026109	.057429
Z_0	1.204362	1.472705	2.612710	1.253442	1.750072	1.549207	1.818807	1.311787	1.623457	1.637236	1.326056	17.559841
$K_1^{(0)}K_2^{(0)}$	1.999620	2.524553	2.187332	2.460874	2.878398	2.594704	2.936706	2.526896	2.835589	2.466144	2.512911	
$K_3^{(0)2}$	1.965624	2.469971	2.153477	2.428754	2.825109	2.556097	2.881062	2.489803	2.786584	2.433042	2.482512	
$\Delta_0 = K_1^{(0)}K_2^{(0)} - K_3^{(0)2}$	.033996	.054582	.033855	.042120	.053289	.038607	.055644	.037093	.049005	.033102	.030399	
$K_2^{(0)}X_0$	−.263862	−.237869	−.769871	−.080690	−.539355	−.370424	−.524112	−.474475	−.420743	−.676529	−.305855	
$K_3^{(0)}Y_0$	.048546	.241697	−.289841	.263401	.008278	.049981	.043291	−.095939	.082829	−.279384	.041137	
$K_2^{(0)}X_0 - K_3^{(0)}Y_0$	−.312408	−.479563	−.480030	−.344091	−.547633	−.420409	−.567403	−.378536	−.503572	−.397145	−.346992	
$K_1^{(0)}Y_0$	.028184	.134039	−.162001	.141953	.004192	.026753	.022746	−.051618	.043712	−.150255	.021892	
$K_3^{(0)}Y_0$	−.150584	−.129064	−.423486	−.042918	−.279432	−.195328	−.270160	−.251533	−.218201	−.358958	−.160798	
$-K_3^{(0)}X_0 + K_1^{(0)}Y_0$	.178768	.263103	.261485	.284871	.283624	.222081	.292906	.199915	.261913	.208703	.182690	
$\hat{\alpha}_\nu = \dfrac{K_2^{(0)}X_0 - K_3^{(0)}Y_0}{\Delta_0}$	−9.189552	−8.786102	−14.178199	−8.169302	−10.276661	−10.889449	−10.197020	−10.205052	−10.275931	−11.997613	−11.414586	
$\hat{\beta}_\nu = \dfrac{-K_3^{(0)}X_0 + K_1^{(0)}Y_2}{\Delta_0}$	5.258501	4.820325	7.723674	6.763319	5.322374	5.752350	5.263928	5.389561	5.344618	6.304846	6.009737	

$X_0\hat{\alpha}$,	.987013	.721532	4.091804	.224976	1.708485	1.330397	1.622998	1.626777	1.343208	2.760987	1.164917	17.583092
$Y_0\hat{\beta}$,	.182081	.741313	-1.525503	1.143102	.025148	.179830	.134256	−.327691	.265195	-1.129280	.156908	−.154641
$1/K_1^{(0)}$	1.228574	1.147349	1.219190	1.190638	1.127073	1.168521	1.121292	1.177913	1.135146	1.192061	1.192639	
$\Delta_0/K_1^{(0)}$	.041767	.062624	.041276	.050150	.060062	.045113	.062393	.043692	.055628	.039460	.036255	.538420
$\dfrac{-K_3^{(0)}X_0+K_1^{(0)}Y_0}{K_1^{(0)}}$	.219630	.301870	.318800	.339178	.319665	.259506	.328433	.235483	.297309	.248787	.217883	3.086544
$\hat{\beta}^*$	5.732595											
$K_3^{(0)}/K_1^{(0)}$	1.722467	1.803182	1.789128	1.855544	1.894391	1.867507	1.903247	1.858642	1.894909	1.859402	1.879120	
$K_3^{(0)}/K_1^{(0)}\cdot\hat{\beta}^*$	9.874206	10.336912	10.256346	10.637082	10.859776	10.705661	10.910544	10.654842	10.862746	10.659199	10.772234	
$X_0/K_1^{(0)}$	−.131956	−.094222	−.351836	−.032789	−.187375	−.142762	−.178469	−.187770	−.148379	−.274327	−.121715	
$\hat{\alpha}^*=X_0/K_1^{(0)}-K_3^{(0)}/K_1^{(0)}\cdot\hat{\beta}^*$	−10.006162	−10.431134	−10.608182	−10.669871	−11.047151	−10.848423	−11.089013	−10.842612	−11.011125	−10.933526	−10.893949	
$X_0\cdot\alpha^*$	1.074722	.856626	3.061330	.293838	1.836578	1.325384	1.764972	1.728410	1.439308	2.516110	1.111782	17.009070
$(\sum Y_0)\hat{\beta}^*$	.329217											
S_{or}	.221554											
S_{oa}	.131390											
$S_{or}-S_{oa}$	.090164											
$S_{or}-S_{oa}/S_{oa}$	.686232											

$$F=\frac{22}{10}\,\frac{S_{or}-S_{oa}}{S_{oa}}=1.51$$