ROBUST STATISTICAL PROCEDURES IN QUANTITATIVE BIO-ASSAYS, I

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For the estimation of the dose-response regression and of the relative potency in an indirect quantitative assay, robust procedures based on simple rank statistics are developed. Tests for the validity of the fundamental assumption in a parallel line assay based on simple rank statistics are also studied. Various properties of these procedures are considered and compared with those of the standard parametric procedures. The theory is illustrated by numerous examples.

1. INTRODUCTION

In an indirect (quantitative) assay, specified doses are given, each to several subjects, and their responses are recorded. For a dose z, we designate the probability distribution of the response U_z (random variable) by $P_z(u) = P\{U_z \leq u\}$. The expected response μ_z (may be the mean or the median of the distribution P_z) expressed as a function $\mu(z)$ of the dose z is known as the dose-response regression. In practice, often, linearizing transformations on z and U_z are used to achieve linear dose-response regression. A very commonly used dosage is $x = \log^z$, and with a suitable response-metameter $Y = Y_z(=\mu^{-1}(z))$, we have then

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

where e represents the chance variation component, whose distribution is denoted

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by G(e) (unknown). Standard parametric procedures for the estimation of α and β are either based on the method of maximum likelihood or the method of least squares; for details, we refer to Finney [1952, Chapters 3-5]. It may be noted that, in practice, the form of G(e) is seldom known, and also the assumption that G(e) is normal is rarely met in reality. This casts some doubts on the optimality and scope of applicability of the first method. In fact, the performance of the maximum likelihood estimates may be quite poor when the true and the assumed form of G(e) are widely different, for example, if G(e) is Cauchy but we assume it to be normal, the resulting estimates are inconsistent. The method of least squares provides the minimum variance unbiased estimates among the class of linear estimates of (α,β). However, these estimates are not necessarily optimum, unless normality or some other conditions are imposed on G(e). For example, for logistic or double exponential G(e), the most efficient estimates of (α,β) are different from the least squares estimate. In fact, not only the least squares estimates are based on the assumption that G(e) has a finite variance [required for their consistency], but also these estimates are quite inefficient for distributions with "heavy tails". Besides, both the above procedures are vulnerable to "gross-errors" and sensitive to outliers. Our first problem is to provide suitable robust estimates for α and β which remain valid for a broad class of G(e), and which are less sensitive to gross errors and outliers. In Section 2 of the paper, we study this problem with theory adapted from Sen [1968] and Sen and Puri [1969].

Suppose now we have a standard and a test preparations with the respective (linearized) dosage-response regressions

$$Y_S = \alpha_S+\beta_S x+e_S,\ Y_T = \alpha_T+\beta_T x+e_T, \tag{1.2}$$

where the errors e_S and e_T both have the common (unknown) distribution G(e). If the test preparation behaves as it is a dilution (or concentration) of the standard one, we have

$$\beta_S = \beta_T = \beta \text{ (unknown) and } \alpha_T - \alpha_S = \beta \log \rho, \tag{1.3}$$

where $\rho(>0)$ stands for the relative potency of the test preparation with respect to the standard. (1.3) constitutes the fundamental assumption of the parallel line assay in (1.2). Tests for the validity of this assumption, based on the assumption that G(e) is normal, are considered in detail in Finney [1952, Chapters 3-5], and these are subject to the criticisms as mentioned in the preceeding paragraph. In Section 3 of the paper, we have developed a robust test procedure for this problem. Finally, when (1.3) holds, we are interested in a robust estimate of the relative potency ρ. The parametric estimate, being based on the standard estimates of β and $\alpha_T - \alpha_S$, is subject to the criticisms of the preceeding paragraph. In Section 4 of the paper, the details of this problem are worked out.

In this paper, we specifically consider the case of parallel line assays in symmetrical designs (for definitions, see Finney [1952, Chapters 3-5]). The case of asymmetrical designs and of the slope-ratio assays will be considered in a subsequent paper. For direct assays, procedures, similar to those in the current paper, are developed earlier by the author (Sen [1963, 1964, 1965]) and by Shorack [1966], among others. The major bulk of the theory in the current paper is mainly adapted from Sen [1968, 1969] and Sen and Puri [1969]. For the convenience of the reading of the paper, the proofs of some of the results are supplied in the appendix; the reader if not familiar with the large sample theory of nonparametric inference may skip this section.

2. ROBUST ESTIMATION OF THE DOSAGE-RESPONSE REGRESSION

We denote the dosages corresponding to the $k(\geq 2)$ doses $z_1,\ldots,z_k$ by $x_1 = \log z_1,\ldots,x_k = \log z_k$, and the responses (metameters) for the dose z_i by $Y_{i1},\ldots,Y_{in_i}$, $1\leq i\leq k$. Let $n = \sum_{i=1}^{k} n_i$ be the total number of subjects.

(a) Procedure I. We use the results in Sen [1968] for the estimation of β in (1.1). For the estimation of α, we use then the results of Adichie [1967] and Sen and Puri [1969]. It has been shown by these authors that these estimates are robust in linear regression models. We denote by

$$W_{ij,rs} = (Y_{js}-Y_{ir})/(x_j-x_i),\ 1\leq r\leq n_i,\ 1\leq s\leq n_j, \tag{2.1}$$

for $1\leq i<j\leq k$. Also, let $N = \Sigma_{1\leq i<j\leq k}(n_i n_j)$ be the total number of $W_{ij,rs}$. We arrange the N values in (2.1) in ascending order of magnitude, and denote these ordered values by

$$W_{(1)} \leq W_{(2)} \leq \cdots \leq W_{(N)}. \tag{2.2}$$

Then, our desired estimate of β in (1.1) is

$$\beta^* = \begin{cases} W_{(m+1)} & \text{if } N=2m+1, \\ \tfrac{1}{2}[W_{(m)}+W_{(m+1)}], & \text{if } N=2m, \end{cases} \tag{2.3}$$

where $m(\geq 0)$ is an integer. Let us now write

$$Y^*_{ir} = Y_{ir}-\beta^* x_i,\ 1\leq r\leq n_i,\ 1\leq i\leq k. \tag{2.4}$$

For the n Y^*_{ir} in (2.5), we define the $N^* = \binom{n+1}{2}$ mid-ranges by

$$V_{ij,rs} = \tfrac{1}{2}[Y^*_{ir}+Y^*_{js}], \text{ for } 1\leq r\leq s\leq n_i,\ 1\leq i=j\leq k \text{ and } 1\leq r\leq n_i,\ 1\leq s\leq n_j,\ 1\leq i<j\leq k. \tag{2.5}$$

The ordered values of the $V_{ij,rs}$ are denoted by

$$V_{(1)} \leq V_{(2)} \leq \cdots \leq V_{(N^*)}. \tag{2.6}$$

Then, our desired estimate of α in (1.1) is

$$\alpha^* = \begin{cases} V_{(m^*+1)}, & \text{if } N^*=2m^*+1, \\ \frac{1}{2}[V_{(m^*)}+V_{(m^*+1)}], & \text{if } N^*=2m^*, \end{cases} \tag{2.7}$$

where $m^*(\geq 0)$ is an integer.

We illustrate the estimates by means of the following data, adapted (in part only) from Finney [1952, p. 100].

TABLE 2.1. Responses in an assay of cod-liver oil for vitamin D_3

Response Y	Dose z[B.S.I. units/100g. of food]		
	5.76	9.60	16.00
Y = 10(u-30)	35	62	116
u = bone ash %	30	67	105
	24	95	91
	37	62	94

Here the dosage is $x = \log_a^z - \log_a^{9.6}$, where $a = (5/3)^{\frac{1}{2}}$. Thus, the dosages corresponding to the three doses are -2, 0 and 2. Also, $n_1=n_2=n_3=4$, so that $n=12$, $N=48$ and $N^*=78$. The 48 values of the $W_{ij,rs}$ in (2.1) are the following:

13.5, 16, 30, 13.5, 16, 18.5, 32.5, 16, 19, 21.5, 35.5, 19, 12.5, 15, 29, 12.5, 20.25, 17.5, 14, 14.75, 21.5, 18.75, 15.75, 16, 23, 20.25, 16.75, 17.5, 19.75, 17, 13.5, 14.25, 27, 21.5, 14.5, 16, 24.5, 19, 12, 13.5, 10.5, 5, -2, -.5, 27, 21.5, 14.5, 16.

Thus, $W_{(24)}=16$ and $W_{(25)}=16.75$. Hence,

$$\beta^* = \tfrac{1}{2}(16+16.75) = 16.375. \tag{2.8}$$

The 12 values of Y^*_{ir}, defined by (2.4), are

67.75, 62.75, 56.75, 69.75, 62, 67, 95, 62, 83.25, 72.25, 58.25, 61.25.

Thus, the 78 mid-ranges, defined by (2.5), are as follows:

67.75, 65.25, 62.25, 68.75, 64.875, 67.375, 81.375, 64.875, 75.5, 70, 63,
64.5, 62.75, 59.75, 66.25, 62.375, 64.875, 78.875, 62.375, 73, 67.5, 60.5,
62, 56.75, 63.25, 59.375, 61.875, 70.875, 59.375, 70, 64.5, 57.5, 59, 69.75,
65.875, 68.375, 82.375, 65.875, 76.5, 71, 64, 65.5, 62, 64.5, 78.5, 62,
72.625, 67.125, 60.125, 61.625, 67, 81, 64.5, 75.125, 69.625, 62.625, 64.125,
95, 78.5, 89.125, 83.625, 76.625, 78.125, 62, 72.625, 67.125, 60.125, 61.625,
83.25, 77.75, 70.75, 72.25, 72.25, 65.25, 66.75, 58.25, 59.75, 61.25.

Thus, $V_{(39)} = V_{(40)} = 65.875$. Hence,

$$\alpha^* = 65.875. \tag{2.9}$$

The dosage-response equation is then estimated as

$$Y = 65.875 + 16.375x. \tag{2.10}$$

It may be noted that the least squares estimates are

$$\hat{\alpha} = (126+286+406)/12 = 68.167, \ \hat{\beta} = [406-126]/12 = 17.5; \tag{2.11}$$

$$Y = 68.167 + 17.5x. \tag{2.12}$$

(b) Procedure II. Here we employ the method of least squares not on the original observations (Y_{ir}) but on suitable statistics computed for the

different doses. To be precise, we let

$$\tilde{Y}_i = \underset{1\le r\le s\le n_i}{\text{median}} \{\tfrac{1}{2}[Y_{ir}+Y_{is}]\},\ 1\le i\le k, \tag{2.13}$$

and then minimising $\Sigma_{i=1}^{k} n_i[\tilde{Y}_i-\alpha-\beta x_i]^2$ with respect to the choice of (α,β), obtain the estimates

$$\tilde{\beta} = \textstyle\sum_{i=1}^{k} n_i\tilde{Y}_i(x_i-\bar{x})/\sum_{i=1}^{k} n_i(x_i-\bar{x})^2,\ \tilde{\alpha} = \sum_{i=1}^{k} n_i\tilde{Y}_i/n-\tilde{\beta}\bar{x}, \tag{2.14}$$

where $\bar{x} = n^{-1}\sum_{i=1}^{k} n_i x_i$. It may be noted that if in (2.14), we replace the $\tilde{Y}_i$ by $\bar{Y}_i(=n_i^{-1}\sum_{r=1}^{n_i} Y_{ir})$, we obtain the classical least squares estimates. The reason that in (2.14), $\bar{Y}_i$ is replaced by $\tilde{Y}_i$ is that the latter is known to be a more robust estimator of μ_{Z_i}.

To illustrate the computation of $(\tilde{\alpha},\tilde{\beta})$, we again consider the data in Table 2.1. Then, for the three dosages, the mid-ranges are

(i) 35, 32.5, 29.5, 36, 30, 27, 33.5, 24, 30.5, 37;

(ii) 62, 64.5, 78.5, 62, 67, 81, 64.5, 95, 78.5, 62;

(iii) 116, 110.5, 103.5, 105, 105, 98, 99.5, 91, 92.5, 94.

Thus, $\tilde{Y}_1 = (30.5+32.5)/2 = 31.5$, $\tilde{Y}_2 = (64.5+67)/2 = 65.75$ and $\tilde{Y}_3 = (99.5+103.5)/2 = 101.5$. Since $n_1=n_2=n_3=4$, we obtain from (2.14) that $(\bar{x}=0)$

$$\tilde{\alpha} = 66.25 \quad \text{and} \quad \tilde{\beta} = 17.5. \tag{2.15}$$

The estimated dosage-response line is thus

$$Y = 66.25 + 17.5x. \tag{2.16}$$

If we look at the data in Table 2.1, we might suspect that for the second dose, the response 95 may be an outlier. It is seen that its influence on the

least square procedure is to make the intercept $(\hat{\alpha})$ higher than its normal value; the effect is diminished in both the procedures considered above. Computationally, $(\tilde{\alpha},\tilde{\beta})$ is simpler than that of (α^*,β^*). But, unless $n_i \geq 3$, $\tilde{Y}_i = \bar{Y}_i$, and hence, $(\tilde{\alpha},\tilde{\beta})$ may not possess the robustness property to a great extent. Thus, we will prescribe the use of $(\tilde{\alpha},\tilde{\beta})$ only when each n_i is ≥ 3. Secondly, if we have a large number of subjects for a small number of doses, as we shall see later on, $(\tilde{\alpha},\tilde{\beta})$ and (α^*,β^*) have almost the same properties. But, if the number of doses is large but not the number of subjects per dose, usually, $(\tilde{\alpha},\tilde{\beta})$ may be less efficient than (α^*,β^*). This is due to the fact that the $\tilde{Y}_i$ may not utilize fully the information extractable from the comparisons of the individual Y_{ir} and Y_{js} when $i \neq j$. In the example considered, both the procedures yield quite satisfactory results.

(c) Properties of the estimates. For simplicity of presentation, we consider now the case of symmetric designs where $n_1 = \ldots = n_k = n_o (\geq 1)$, $n = kn_o$, and where by proper choice of scale, $x_{i+1} - x_i = 1$, $i = 1,2,\ldots,k-1$, and $\bar{x} = (\sum_{i=1}^{k} x_i)/k = 0$. Note that even when this assumption is not met, the properties of the estimates are retained, but the expressions for their variances and their efficiencies will be more complicated. We let $C^2 = \frac{1}{k}\sum_{i=1}^{k} x_i^2 (>0)$, and assume that the distribution $G(e)$ admits of a continuous density function $g(e)$ for which

$$\gamma(G) = \int_{-\infty}^{\infty} g^2(e)de < \infty. \tag{2.17}$$

This assumption is, of course, true when G is normal, logistic, Cauchy, double exponential or any other distribution with a bounded density function. Whenever the variance of the distribution $G(e)$ exists, we denote it by $\sigma^2(G)$. Also, let $\sigma_o^2(G) = [12\gamma^2(G)]^{-1}$.

It then follows from Sen [1968] (after some simplifications) that (i) the

distribution of β^*, defined by (2.4), is symmetric about β (inplying the unbiasedness of the estimate), (ii) β^* is a robust and translation-invariant estimate of β, and (iii) for large (nk), $n^{\frac{1}{2}}C[\beta^*-\beta]$ has approximately the normal distribution with zero mean and variance $\sigma_0^2(G)$. In particular, β^* is less sensitive to outliers or gross errors than that of the least squares estimate $\hat{\beta}$. Upon noting that whenever $\sigma^2(G)$ is finite, for large (nk), $n^{\frac{1}{2}}C[\hat{\beta}-\beta]$ has approximately the normal distribution with zero mean and variance $\sigma^2(G)$, we obtain that the asymptotic relative efficiency (ARE) of β^* with respect to $\hat{\beta}$ is

$$e_1(G) = \sigma^2(G)/\sigma_0^2(G) = 12\sigma^2(G)\gamma^2(G). \tag{2.18}$$

Now, (2.18) is a well-known expression in nonparametric theory. It is equal to $3/\pi = 0.955$ when G is normal, is bounded below by 0.864 for any G, while can be quite high. In fact, for the double exponential or logistic distribution, it is greater than unity. Thus, whereas β^* can not be too inefficient as compared to $\hat{\beta}$, it can be more efficient, particularly for distributions with "heavy tails".

For α^*, we impose the restriction of symmetry on G(e). In most of the cases, the linearizing transformations usually induce symmetry on the tolerance distribution, and, in any case, it is much less restrictive than the assumption that G(e) is normal, logistic, double exponential or Cauchy, each of which is symmetric. It follows from the results of Adichie [1967], Sen [1968] and Sen and Puri [1969] that α^* is a translation-invariant, robust and consistent estimate of α. Also, for large n, $n^{\frac{1}{2}}[\alpha^*-\alpha]$ has approximately the normal distribution with zero mean and variance $\sigma_0^2(G)$. Comparison with the variance of the least squares estimator $\hat{\alpha}$ again leads to the ARE $e_1(G)$, defined in (2.18). Hence, the details are omitted. The large sample theory for (α^*,β^*) demands the sole condition that

n is large, without any distinction whether n_o is large and k fixed, or n_o is fixed and k large, or both large.

The properties of the estimates $(\tilde{\alpha},\tilde{\beta})$ (cf. procedure II) depend on the situations (a) n_o large, k fixed or large and (b) n_o small, k large. If n_o is large, $n_o^{\frac{1}{2}}(\tilde{Y}_i-\alpha-\beta x_i)$ has approximately the normal distribution with zero mean and variance $\sigma_o^2(G)$, for i=1,...,k, and hence, by the definition of $(\tilde{\alpha},\tilde{\beta})$, it follows that (i) $n^{\frac{1}{2}}(\tilde{\alpha}-\alpha)$ has approximately the normal distribution with zero mean and variance $\sigma_o^2(G)$ and (ii) $n^{\frac{1}{2}}C[\tilde{\beta}-\beta]$ has also the same distribution. Thus, the estimates $(\tilde{\alpha},\tilde{\beta})$ have the same ARE as those of (α^*,β^*). On the other hand, if n_o is small, we denote by $\nu^2_{n_o}(G) = n_o \mathrm{Var}[\tilde{Y}_i]$. Then, it can be shown that for large k, both $n^{\frac{1}{2}}(\tilde{\alpha}-\alpha)$ and $n^{\frac{1}{2}}C[\tilde{\beta}-\beta]$ have approximately the normal distribution with zero mean and variance $\nu^2_{n_o}(G)$. Thus, the ARE of $\tilde{\alpha}(\tilde{\beta})$ with respect to $\alpha^*(\beta^*)$ is equal to

$$e_2^{(n_o)}(G) = \sigma_o^2(B)/\nu_{n_o}(G) = \{12\gamma^2(G)\nu_{n_o}(G)\}^{-1}, \tag{2.19}$$

which depends on n_o as well as G(e). For n_o=1 or 2, $\tilde{Y}_i \equiv \bar{Y}_i$, and hence, $\nu_{n_o}(G) = \sigma^2(G)$. Thus, (2.19) equals to the reciprocal of (2.18). Also, as n_o increases, $\nu_{n_o}(G) \to 1/\sigma_o^2(G)$, so that (2.19) approaches unity. But, for finite n_o, the exact expression for $\nu_{n_o}(G)$ is too complicated, even for the standard distributions like normal, logistic or the double exponential. For the normal distribution, some Monte Carlo studies reveal that for $n_o \geq 4$, (2.19) is fairly close to one.

(d) Robust confidence intervals for (α,β). We define c(u)=1, 0 or -1 according as u>, = or <0. Let then

$$U_n(b) = \sum_{1\leq j<\ell\leq k} \sum_{r=1}^{n_j} \sum_{s=1}^{n_\ell} c([Y_{\ell s}-bx_\ell]-[Y_{jr}-bx_j]), \tag{2.20}$$

which is the difference of the number of positive and the number of negative differences of the type $(Y_{\ell s}-bx_{\ell})-(Y_{jr}-bx_j)$, $1\leq r\leq n_j$, $1\leq s\leq n_\ell$, $1\leq j<\ell\leq k$, and is the numerator of Kendall's [1955] tau. Note that under H_o: $\beta=0$, the distribution of $U_n(0)$ is symmetric about zero and is independent of G(e) (cf. Kendall [1955]). Thus, we can always select a U_n^*, such that

$$P\{|U_n(0)| \leq U_n^* | H_o: \beta=0\} = 1-\varepsilon_n, \tag{2.21}$$

where ε_n [depends on $(k,n_1,\ldots,n_k)$] is close to a given ε(viz., .05 etc.). The distribution of $U_n(0)$ is discrete, and hence, ε_n, for small n, may not be exactly equal to ε. When k=2, U_n^* can be easily obtained from the table for the Wilcoxon-Mann-Whitney statistic given in Owen [1962, pp. 340-348], while for k>2 and $n\geq 12$, we use the following approximation for U_n^*. Let

$$V_n = \{n(n-1)(2n+5) - \textstyle\sum_{j=1}^{k} n_j(n_j-1)(2n_j+5)\}/18 \tag{2.22}$$

and let $\tau_{\varepsilon/2}$ be the upper 50ε% point of the standard normal distribution. Then, according as N is even or odd, we take U_n^* as the largest even or odd integer contained in $\tau_{\varepsilon/2}\sqrt{V_n}$. Note that for odd (even) N, U_n^* is always odd (even). Let then $m_1 = \frac{1}{2}(N-U_n^*)$ and $m_2 = \frac{1}{2}(N+U_n^*)$. Proceeding then as in Sen [1968] and equating $U_n(b)$ to $\pm U_n^*$, we obtain that

$$P\{W_{(m_1)} < \beta < W_{(m_2+1)} | \beta\} = 1-\varepsilon_n, \tag{2.23}$$

where the $W_{(i)}$ are defined by (2.2).

Thus, for the data in Table 2.1, we have n=12, N=48, V_n=186.67, and hence, for $\varepsilon\simeq 0.05$, U_n^*=26. Then, $m_1 = \frac{1}{2}[48-26] = 11$ and $m_2 = \frac{1}{2}[48+26] = 37$. Thus, we have a 95% confidence interval for β based on $U_n(b)$ [and hence on $W_{(1)}\leq\ldots\leq W_{(N)}$] is

$$13.5 < \beta < 20.25. \tag{2.24}$$

Let now T_n be the sum of the positive ranks in the Wilcoxon one-sample signed-rank situation; the null distribution of T_n (for $n \leq 20$) is tabulated in Owen [1962, pp. 325-330]. For large n, $(T_n - \frac{1}{4}n(n+1))/\{n(n+1)(2n+1)/24\}^{\frac{1}{2}}$ is distributed normally with zero mean and unit variance. Thus, we can always find a T_n^* such that under the hypothesis (H_o) of symmetry,

$$P\{|T_n - \frac{n(n+1)}{4}| \leq T_n^* | H_o\} = 1-\varepsilon_n. \tag{2.25}$$

For $n \leq 20$, the values of $T_n^* + (n+1)n/4 = T_n^{*\prime}$ (say) are tabulated in Owen [1962, pp. 325-330], while for $n>20$, we may take

$$T_n^* = \text{nearest integer to } \tau_{\varepsilon/2}(n(n+1)(2n+1)/24)^{\frac{1}{2}}. \tag{2.26}$$

Let then $m_1^* = n(n+1)/4 - T_n^*$ and $m_2^* = n(n+1)/4 + T_n^*$. We define the $V_{(i)}$ as in (2.5) and (2.6). Proceeding then as in Sen and Puri [1969], we have

$$P\{V_{(m_1^*)} \leq \alpha \leq V_{(m_2^*+1)} | \alpha\} \simeq 1-\varepsilon_n. \tag{2.27}$$

Thus, for the data in Table 2.1, n=12, and hence from Owen [1962, p. 328], for $\varepsilon_n \simeq .052$, $T_n^{*\prime}=63$. Thus, $m_1^*=15$, $m_2^*=63$. Hence, an (approximately) 94.8% confidence interval for α [based on the $V_{(i)}$] is

$$61.875 < \alpha < 75.125. \tag{2.28}$$

It may be noted that (2.23), (2.24), (2.27) and (2.28) are valid for a wide class of G(e), whereas the parametric confidence intervals for (α,β), based on the assumed normality of G(e), may lose its validity for non-normal G(e). The ARE of these intervals again agree with (2.18) (cf. Sen and Puri [1969]) and the robustness properties are also retained by (2.23) and (2.27).

3. TEST FOR THE VALIDITY OF THE FUNDAMENTAL ASSUMPTION

Consider now a symmetrical 2k-point ($k\geq 2$) design with k doses of each preparation (standard and the test) such that successive doses bear a constant ratio $D(>1)$ to one-another, and $n_o(\geq 1)$ subjects are used for each dose. Thus, for each preparation $n=kn_o$ subjects are used. For the standard and the test preparations, we denote the k doses by $Z_{1j}=aD^{j-1}$, $a>0$ and $Z_{2j}=abD^{j-1}$, $b>0$, $1\leq j\leq k$, respectively. Thus, the corresponding dosages are

$$x_{1j} = \log_D Z_{1j} = (j-1) + \log_D a,\ x_{2j} = \log_D Z_{2j} = (j-1) + \log_D(ab), \tag{3.1}$$

for $j=1,2,\ldots,k$. If we write $x_j = (j-(k+1)/2)$, $1\leq j\leq k$, we can then rewrite the equations in (1.2) as

$$Y_S = \alpha_S^*+\beta_S x_j+e_S,\ Y_T = \alpha_T^*+\beta_T x_j+e_T, \tag{3.2}$$

where

$$\alpha_S^* = \alpha_S+\beta_S[\log_D a+(k-1)/2],\ \alpha_T^* = \alpha_T+\beta_T[\log_D ab+(k-1)/2]. \tag{3.3}$$

Hence, with this change in the scale and origin of the dosage, we have the two sets of responses:

	Standard Preparation			Test Preparation		
dosage	x_1	x_2	x_k	x_1	x_2	x_k
	$Y_{11}^{(1)}$	$Y_{21}^{(1)}$	$Y_{k1}^{(1)}$	$Y_{11}^{(2)}$	$Y_{21}^{(2)}$	$Y_{k1}^{(2)}$
	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
	$Y_{1n_o}^{(1)}$	$Y_{2n_o}^{(1)}$	$Y_{kn_o}^{(1)}$	$Y_{2n_o}^{(2)}$	$Y_{2n_o}^{(2)}$	$Y_{kn_o}^{(2)}$

(3.4)

It follows from (3.2) and (3.4) that

$$Y_{jr}^{(1)} = \alpha_S^* + \beta_S x_j + e_{jr}^{(1)}, \quad Y_{\ell s}^{(2)} = \alpha_T^* + \beta_T x_\ell + e_{\ell s}^{(2)}, \tag{3.5}$$

where the $e_{jr}^{(1)}$ and $e_{\ell s}^{(2)}$ have the common distribution $G(e)$. Our problem is to test the null hypothesis

$$H_o: \quad \beta_S = \beta_T = \beta \text{ (unknown)}, \tag{3.6}$$

against $\beta_S \neq \beta_T$.

As in (2.1), we let (after noting that $x_\ell - x_j = \ell - j$),

$$W_{\ell j,rs}^{(i)} = (Y_{\ell s}^{(i)} - Y_{jr}^{(i)})/(\ell - j), \; 1 \leq r, \; s \leq n_o, \; 1 \leq j < \ell \leq k, \; i = 1,2. \tag{3.7}$$

Thus, we have two sets of $N(=\binom{k}{2} n_o^2)$ values, which we pool together into a combined set of 2N observations. The corresponding ordered variables are denoted by

$$W_{(1)}^* \leq W_{(2)}^* \leq \cdots \leq W_{(2N)}^* \tag{3.8}$$

Our pooled sample estimate of β [assuming (3.7) to hold], defined in the same fashion as in Sen [1969], is then

$$\beta^* = \tfrac{1}{2}[W_{(N)}^* + W_{(N+1)}^*]. \tag{3.9}$$

Let us now define $U_n^{(i)}(\beta^*)$, $i=1,2$, as in (2.20), that is,

$$U_n^{(i)}(\beta^*) = \sum_{1 \leq j < \ell \leq k} \sum_{r=1}^{n_o} \sum_{s=1}^{n_o} c(Y_{\ell s}^{(i)} - Y_{jr}^{(i)} - \beta^*(x_\ell - x_j)), \; i = 1,2. \tag{3.10}$$

Also, V_n, defined by (2.22), reduces here to

$$V_n = \{k n_o [(k n_o + 1)(2k n_o + 5) - (n_o + 1)(2n_o + 5)]/18\}. \tag{3.11}$$

Our proposed test statistic is

$$S_n = \{[U_n^{(1)}(\beta^*)]^2 + [U_n^{(2)}(\beta^*)]^2\}/V_n. \tag{3.12}$$

If (3.6) holds, β^* estimates the common β, and hence, both the $U_n^{(i)}(\beta^*)$ are close to zero. This implies that S_n will be stochastically small. On the other hand, if (3.6) does not hold, β^* will estimate something in between β_S and β_T, and as a result, both $U_n^{(i)}(\beta^*)$, i=1,2, will be different from zero. Thus, S_n will be stochastically large. This suggests that one may frame the test procedure as follows:

$$\text{If } S_n \begin{cases} \geq S_{n,\varepsilon}, \text{ reject } H_o \text{ in (3.6)}, \\ < S_{n,\varepsilon}, \text{ accept } H_o, \end{cases} \tag{3.13}$$

where $S_{n,\varepsilon}$ is such that $P\{S_n \geq S_{n,\varepsilon} | H_o\} = \varepsilon$, the level of significance.

The distribution theory of S_n is studied in the Mathematical Appendix. It follows that if n is not small, $S_{n,\varepsilon}$ can be approximated by $\chi^2_{1,\varepsilon}$, the upper $100\varepsilon\%$ point of the chi-square distribution with 1 degree of freedom.

To illustrate the test, we consider the following data, adapted from Finney [1952, p. 150]:

TABLE 3.1. Diameters of Zones of inhibition in an assay of Pennicillin (in units of 0.25 mm)

Plate No	Standard Prep. (units per ml)		Test Prep. (dilution)	
	50	200	0.25	1
I	92	108	68	90
II	95	111	74	91
III	93	108	72	91
IV	90	107	75	88
dosage x	$-\frac{1}{2}$	$\frac{1}{2}$	$-\frac{1}{2}$	$\frac{1}{2}$

For the two preparations, the values of the $W^{(i)}_{j\ell,rs}$ are

16, 19, 16, 15, 13, 16, 13, 12, 15, 18, 15, 14, 18, 21, 18, 17;

22, 23, 23, 20, 16, 17, 17, 14, 18, 19, 19, 16, 15, 16, 16, 13.

Thus, in the combined set of 32, $W_{(16)}=W_{(17)}=16$. Hence, $\beta^*=16$. Thus, the values of the $Y^{(i)}_{jr}-\beta^* x_j$, for the two sets, are

$$\begin{array}{lll} \text{(i)} & 100, 103, 101, 98; & 100, 103, 100, 99, \\ \text{(ii)} & 76, 82, 80, 83; & 82, 83, 83, 80. \end{array} \tag{3.14}$$

Hence, by (3.10), $U^{(1)}_n(\beta^*)=-1$ and $U^{(2)}_n(\beta^*)=5$. Also, by (3.11), $V_n = \{8(7\cdot 21-3\cdot 13)/18\} = 48$. Consequently, by (3.12),

$$S_n = \{1^2+5^2\}/48 = 0.542.$$

Since, $2n=16$, we may approximate $S_{n,\varepsilon}$ by $\chi^2_{1,\varepsilon}$, and hence, the critical value of S_n at 5% level of significance is approximately equal to 3.856. Clearly, with great confidence, we may accept the null hypothesis H_o in (3.6).

Properties of the test. The test based on S_n has approximately the level of significance ε. Since for the estimation of β [under (3.6)], we have used a robust estimate β^* [which is substituted in the $U^{(i)}_n$], and since the $U^{(i)}_n(\beta^*)$, $i=1,2$, are less sensitive to outliers or gross errors, it follows that the test based on S_n is also robust for outliers and gross errors. The ARE of S_n with respect to the classical variance-ratio statistic (used under the assumption that G(e) is normal) is shown, in the appendix, to be equal to $e_1(G)$, defined by (2.18). Hence, the robust-efficiency of S_n follows from the discussions following (2.18).

4. ROBUST ESTIMATION OF THE RELATIVE POTENCY

It follows from (1.3) and (3.3) that when $\beta_S=\beta_T=\beta$,

$$\log_D(b\rho) = [\alpha_T^*-\alpha_S^*]/\beta = \delta/\beta, \text{ say.} \tag{4.1}$$

The dilution b and ratio D are known.

In the parametric theory, we derive the standard least squares estimates $(\hat{\delta},\hat{\beta})$ of δ and β, and then obtain the derived estimate $\hat{\rho}$ of ρ by

$$\log_D(b\hat{\rho}) = \hat{\delta}/\hat{\beta} \ . \tag{4.2}$$

Since $\hat{\delta}$ and $\hat{\beta}$ are subject to the criticisms of section 1, the estimate $\hat{\rho}$ is also so. To derive a robust estimate of ρ, we therefore derive first robust estimates of δ and β.

Under (3.6), we use as a robust estimate of β, the estimator β^* in (3.9). Note that β^*, being the median of the 2N divided differences, is less sensitive to outliers or gross errors than $\hat{\beta}$, which is a weighted linear function of these differences (cf. Sen [1968], for details).

To estimate δ, we define as in (2.4)

$$Y_{jr}^{*(i)} = Y_{jr}^{(i)} - \beta^* x_j, \ 1\leq r\leq n_o, \ 1\leq j\leq k; \ i=1,2. \tag{4.3}$$

Consider then the n^2 differences of the type $Y_{\ell s}^{*(2)}-Y_{jr}^{*(1)}$, and define

$$\delta^* = \underset{\substack{1\leq r\leq n_o,\ 1\leq j\leq k \\ 1\leq s\leq n_o,\ 1\leq \ell\leq k}}{\text{median}} [Y_{\ell s}^{*(2)}-Y_{jr}^{*(1)}], \tag{4.4}$$

where for an even $n^2(=2m)$, δ^* is defined as the average of the mth and (m+1)th ordered values. Our proposed estimate of δ is δ^*.

To illustrate its computation, we consider again the data in Table 3.1.

The estimate β^* is 16 and the values of the $Y^{*(i)}$ are given in (3.14). Thus, the 64 differences are

$$-[24, 18, 20, 17, 18, 17, 17, 20, 27, 21, 23, 20, 21, 20, 20, 23, 25,$$
$$19, 21, 18, 19, 18, 18, 21, 22, 16, 18, 15, 16, 15, 15, 18, 24, 18,$$
$$20, 17, 18, 17, 17, 20, 27, 21, 23, 20, 21, 20, 20, 23, 24, 18, 20,$$
$$17, 18, 17, 17, 20, 23, 17, 19, 16, 17, 16, 16, 19].$$

Hence, δ^*, the average of the 32nd and the 33rd ordered values, is equal to -19.

Once δ^* and β^* are obtained, our derived estimate of ρ is ρ^*, where

$$\log_D(b\rho^*) = \delta^*/\beta^*. \tag{4.5}$$

Thus, for the data in Table 3.1, where b=1/200 and D=4, we have

$$\log_4(\rho^*/200) = -19/16 = -1.1875 \text{ or } \rho^* = 38.75.$$

Properties of the estimate. Since δ^* and β^* are both translation-invariant, consistent and robust estimates, it follows that ρ^* is also consistent, robust and dilution-invariant. In the mathematical appendix, it is shown that for large n, $(n/2)^{\frac{1}{2}}(\delta^*-\delta)$ and $(2nC^2)^{\frac{1}{2}}(\beta^*-\beta)$ (where $C^2=k^{-1}\sum_{j=1}^{k}x_j^2$) are asymptotically independent and each distributed according to normal distribution with mean 0 and variance $\sigma_o^2(G)$, where $\sigma_o^2(G)$ is defined immediately after (2.17). This means that for large n, $n^{\frac{1}{2}}(\delta^*/\beta^*-\delta/\beta)$ is distributed normally with zero mean and variance

$$\zeta_o^2 = [\sigma_o^2(G)/\beta^2][2(1+(\delta/2\,C)^2)], \text{ where } \beta\neq 0. \tag{4.6}$$

Hence, by some standard results on transformations of statistics, we have for large n, $n^{\frac{1}{2}}(\rho^*-\rho)$ distributed (approximately) according to a normal distribution with zero mean and variance

$$[\sigma^*_\rho(G)]^2 = [\rho(\log_e D)]^2 \zeta_o^2, \text{ when } \beta \neq 0. \tag{4.7}$$

It can also be shown that for $\hat{\rho}$, defined by (4.2), if $\sigma^2(G)$ is finite, then for large n, $n^{\frac{1}{2}}(\hat{\rho}-\rho)$ has (approximately) the normal distribution with zero mean and variance

$$[\sigma_\rho(G)]^2 = (\rho \log_e D)^2 [\sigma^2(G)/\beta^2][2(1+(\delta/2\beta C)^2)], \tag{4.8}$$

provided $\beta \neq 0$. Thus, the ARE of ρ^* with respect to $\hat{\rho}$ is

$$e(G) = [\sigma_\rho(G)/\sigma_{\rho^*}(G)]^2 = \sigma^2(G)/\sigma_o^2(G) = e_1(G), \tag{4.9}$$

where $e_1(G)$ is defined by (2.18). Hence, ρ^* possesses all the robust-efficiency properties as of β^* in section 2. For brevity, these are not reproduced again.

Robust confidence limits for ρ. Let us first consider some robust confidence intervals for β and δ. We define the $U_n^{(i)}(\beta)$, i=1,2, as in (3.10) (with β^* replaced by β). Then, by hypothesis that $\beta_S=\beta_T=\beta$, $U_n^{(i)}(\beta)$ has the same distribution as $U_n^{(i)}(0)$ under H_o: $\beta=0$ is symmetric about 0 and is known, and as $U_n^{(1)}(0)$ and $U_n^{(2)}(0)$ are independent, it follows that $U_n = U_n^{(1)}(0) + U_n^{(2)}(0)$ has also a distribution (under H_o: $\beta=0$) symmetric about zero and it does not depend on the unknown G(e). If we have a 4-point design (i.e., k=2), the distribution of U_n can readily be obtained by convolution from the distributions of the $U_n^{(1)}(0)$ and $U_n^{(2)}(0)$, each of which agrees with the distribution of the Wilcoxon-Mann-Whitney statistic, tabulated in Owen [1962, pp. 331-339]. In this special design, we have provided in Table 4.1, values of U_n^* and ε_n (near about zero) for which

$$P\{|U_n| \leq U_n^* | H_o: \beta=o\} = 1-\varepsilon_n. \tag{4.10}$$

TABLE 4.1. Table for the values of (U_n^*, ε_n) in (4.10) for $2 \leq n_o \leq b$, k=2

n_o	ε_n	U_n^*	n_o	ε_n	U_n^*	n_o	ε_n	U_n^*	n_o	ε_n	U_n^*	n_o	ε_n	U_n^*
2	.055	6	3	.170	8	4	.128	14	5	.089	22	6	.034	36
2	.165	4	4	.007	24	5	.012	32	5	.122	20	6	.046	34
3	.005	16	4	.016	22	5	.019	30	6	.009	44	6	.061	32
3	.015	14	4	.028	20	5	.030	28	6	.013	42	6	.079	30
3	.040	12	4	.050	18	5	.044	26	6	.018	40	6	.101	28
3	.090	10	4	.082	16	5	.064	24	6	.025	38	6	.128	26

For $n_o \geq 7$, k=2 or for $k \geq 3$, $n_o \geq 4$, we may approximate U_n^* by the largest even integer contained in $\tau_{\frac{1}{2}\varepsilon}(2V_n)^{\frac{1}{2}}$, where V_n is defined by (3.11). We also define $M_1 = N - \frac{1}{2}U_n^*$, $M_2 = N + \frac{1}{2}U_n^*$, and let the $W^*_{(i)}$ be defined as in (3.8). Then, by the same technique as in Sen [1968, 1969], it follows that

$$P\{W^*_{(M_1)} < \beta < W^*_{(M_2+1)} | \beta\} = 1 - \varepsilon_n. \tag{4.11}$$

For the data in Table 3.1, k=2, n_o=4, and hence, from Table 4.1, for ε_n=.028, U_n^*=20. This leads to M_1=6 and M_2=26. Thus, a 97.2% confidence interval for β, based on the $W^{(i)}_{j\ell,rs}$, is

$$14 < \beta < 19. \tag{4.12}$$

Let now U_n be the number of positive differences $X_i - X_j$, $1 \leq i \leq n$, $1 \leq j \leq n$, in two samples of equal size n. The distribution of U (under the hypothesis (H_o) of the identity of their distributions) is tabulated in Owen [1962, pp. 331-339]. Let then U_n^* be such that

$$P\{U_n \leq U_n^* | H_o\} = 1 - \tfrac{1}{2}\varepsilon_n, \tag{4.13}$$

where ε_n (depends only on n) is close to a given ε. For $n \leq 10$, we refer to Owen [1962], while for n>10,

$$U_n^* = [\frac{n^2}{2} + \tau_{\frac{1}{2}\varepsilon}\{n^2(2n+1)/12\}^{\frac{1}{2}}], \tag{4.14}$$

where [s] denotes the largest integer contained in s. Let then $M_2^* = U_n^*$, $M_1^* = n^2 - U_n^*$, and define $Y_{jr}^{*(i)}$, $1 \le r \le n_o$, $1 \le j \le k$, i=1,2 as in (4.3). Also, let $V_{j\ell,rs}^* = Y_{\ell s}^{*(2)} - Y_{jr}^{*(1)}$, $1 \le r, s \le n_o$, $1 \le j, \ell \le k$ be the n^2 differences whose ordered values are denoted by $V_{(1)}^* \le V_{(2)}^* \le \ldots \le V_{(n^2)}^*$. Then, our proposed confidence interval for δ is given by

$$P\{V_{(M_1^*)}^* < \delta < V_{(M_2^*+1)}^* | \delta\} \simeq 1-\varepsilon_n. \tag{4.15}$$

The derivation of (4.15) is briefly sketched in the appendix.

For the data in Table 3.1, n=8, so that for $\varepsilon_n = .028$, $U_n^* = 52$ (cf. Owen [1962, p. 345]). Hence, $M_1^* = 12$ and $M_2^* = 52$. Thus, from the set of 64 values given after (4.4), we obtain that a 97.2% confidence interval for δ is

$$-22 < \delta < -17. \tag{4.16}$$

To obtain robust confidence intervals for ρ, we consider here two procedures. The first procedure yields comparatively wider confidence bands, but is relatively more simple to work with. The second procedure should be used only for large n.

(a) Procedure I. Corresponding to a given confidence coefficient $1-\varepsilon$, we select ε_1 and ε_2 such that $\varepsilon_1+\varepsilon_2=\varepsilon$ and they are nearly (if possible exactly) equal. Let us then obtain, as in (4.11) and (4.15), confidence intervals for β and δ, with respective confidence coefficient $1-\varepsilon_1$ and $1-\varepsilon_2$. Then, by the Bonferroni inequality, we obtain that

$$P\{W_{(M_1)}^* < \beta < W_{(M_2+1)}^*,\ V_{(M_1^*)}^* < \delta < V_{(M_2^*+1)}^* | \beta,\delta\} \ge 1-\varepsilon. \tag{4.17}$$

[For large n, the right hand side of (4.17) can be taken to be equal to $(1-\varepsilon_1)(1-\varepsilon_2)(\geq 1-\varepsilon)$, as the two U_n in (4.10) and (4.13) are asymptotically independent.] Depending upon the signs of $V^*_{(M_1^*)}$ and $V^*_{(M_2^*+1)}$, we may have (a), (b), or (c) of Figure 4.1. [Note that we assume that $\beta>0$. If $\beta<0$, we can simply rotate the axis of x and derive similar conclusion. If $\beta=0$, both the preparations have no effect (with respect to the variation of x), and hence, there is no question about their relative potency. In fact, if $W^*_{(M_1)} < 0 < W^*_{(M_2+1)}$, the procedure to be considered breaks down.]

We then draw two straight lines passing through the origin (0) and touching the rectangular confidence region at the two extremities. Let the equations of these two lines be $\delta=m_1\beta$ and $\delta=m_2\beta$, respectively. Note that

$$m_1 = V^*_{(M_1^*)}/W^*_{(M_2+1)} \quad \text{if} \quad V^*_{(M_1)}>0; \qquad m_2 = V^*_{(M_2^*+1)}/W^*_{(M_1)} \quad \text{if} \quad V^*_{(M_2^*+1)}>0$$
$$= V^*_{(M_1^*)}/W^*_{(M_1)} \quad \text{if} \quad V^*_{(M_1)}<0, \qquad = V^*_{(M_2^*+1)}/W^*_{(M_2+1)} \quad \text{if} \quad V^*_{(M_2^*+1)}<0.$$

Let us define

$$\log_D(b\rho_i^*) = m_i, \quad i=1,2. \tag{4.18}$$

Then, we have

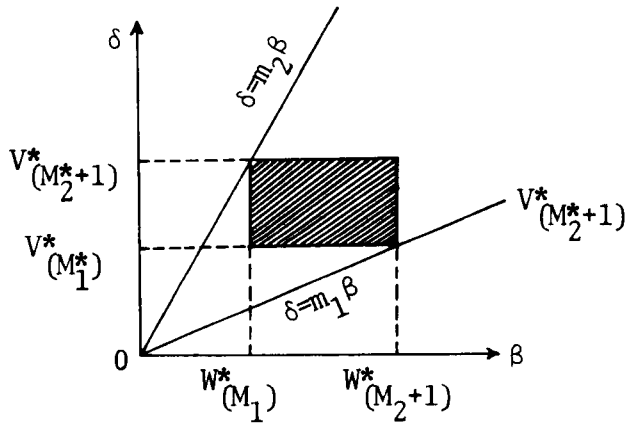
$$P\{\rho_1^* \leq \rho \leq \rho_2^* | \rho\} \geq 1-\varepsilon. \tag{4.19}$$

Thus, from (4.12) and (4.16), we have $m_1 = -22/14$ and $m_2 = -17/19$. Hence, a confidence interval for ρ with confidence coefficient ≥ 0.944 is given by

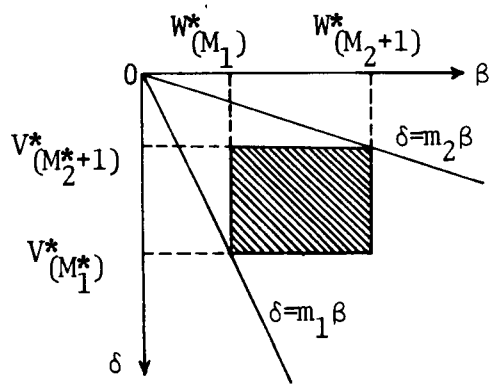
$$22.7 \leq \rho \leq 57.9. \tag{4.20}$$

Figure 4.1. Simultaneous confidence band for (α,β)

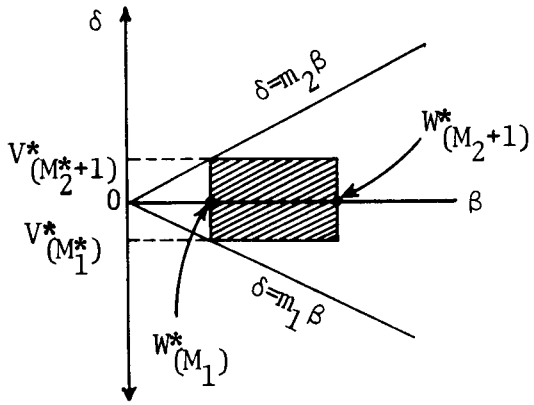
(a)



(b)



(c)



This appears to be somewhat wider than the corresponding parametric confidence band ($31.2 \leq \rho \leq 53.2$) given in Finney [1952, p. 153]. One of the main reasons for this discrepancy is the fact that whereas in the parametric case, the simultaneous confidence band for (β,δ) can be obtained as an ellipse with axes parallel to the two axes (β,δ), the same is not done in (4.17). With an ellipse, the two tangents $\delta=(m_1\beta, m_2\beta)$ come more close to each other, and hence, ρ_1^* and ρ_2^* are more close to each other. This drawback can be avoided in the second procedure considered below.

(b) Procedure II. Following Sen [1966, 1968], we first provide a consistent estimator of $\sigma_o^2(G) = \{12 \int_{-\infty}^{\infty} g^2(x)dx\}^{-1}$. We define M_1^*, M_2^*, $V^*_{(M_1^*)}$ and $V^*_{(M_2^*+1)}$ as in (4.15). Then, along the lines of theorem 6.2 of Sen [1968], it can be shown that

$$\frac{n^3(2n+1)}{24}\left[\frac{V^*_{(M_2^*+1)}-V^*_{(M_1^*)}}{M_2^*-M_1^*+1}\right]^2 = \hat{\sigma}_o^2(G) \xrightarrow{p} \sigma_o^2(G). \tag{4.21}$$

We then estimate $\sigma_{\rho^*}(G)$ by $\hat{\sigma}_{\rho^*}$, where

$$\hat{\sigma}^2_{\rho^*} = [\rho^*(\log_e D)]^2[2\hat{\sigma}_o^2(G)/\beta^{*2}][1+(\delta^*/3\beta^* C)^2], \tag{4.22}$$

where ρ^*, δ^*, and β^* are defined by (4.5), (4.4) and (3.9), respectively. It follows that $\hat{\sigma}_{\rho}^*$ is a consistent estimator of σ_{ρ}^*. Hence, for large n, we have by virtue of the asymptotic normality of $n^{\frac{1}{2}}(\rho^*-\rho)$ that

$$P\{\rho^*-n^{-\frac{1}{2}}\tau_{\varepsilon/2}\hat{\sigma}_{\rho^*} \leq \rho \leq \rho^*+n^{-\frac{1}{2}}\tau_{\varepsilon/2}\hat{\sigma}_{\rho^*}|\rho\} \simeq 1-\varepsilon. \tag{4.23}$$

In the given example, we have from (4.16) that

$$\hat{\sigma}_o^2(G) = \frac{512(17)}{24}\,\frac{25}{41\times 41} = \frac{217600}{40344} = 5.3936,$$

and hence,

$$(\hat{\sigma}_{\rho^*})^2 = [38.75\times1.3863]^2[5.3936/256][2\times2.410] = 310.38.$$

Noting that for $\varepsilon=0.05$, $\tau_{\frac{1}{2}\varepsilon}=1.96$ and $n=8$, we obtain from (4.21) that an approximately 95% confidence interval for ρ is

$$26.70 = 38.75-12.05 \leq \rho \leq 38.75+12.05 = 50.80 \tag{4.24}$$

Apart from a shift (of about 2.5) to the left, (4.24) agrees fairly well with the parametric confidence interval for ρ given in Finney [1952, p. 153].

5. MATHEMATICAL APPENDIX

(i) Distributional properties of S_n, defined in (3.12). For the set of N differences $W^{(1)}_{j\ell,rs}$ and $W^{(2)}_{j\ell,rs}$ for the standard and the test preparations, we denote the respective medians by β^*_S and β^*_T. Thus, as in (2.3), β^*_S and β^*_T are robust and consistent estimates of β_S and β_T, and by definition $U^{(1)}_n(\beta^*_S) = U^{(2)}_n(\beta^*_T) = 0$. Using now the results of Ghosh and Sen [1970] and proceeding as in theorems 6.1 and 6.2 of Sen [1968] and lemma 3.3 of Sen [1969], it follows that if $|n^{\frac{1}{2}}(\beta_S-\beta_T)|$ is bounded (and hence, under (3.6)), as $n\to\infty$,

$$[U^{(1)}_n(\beta^*)/V_n^{\frac{1}{2}} - \sqrt{n}\, c(\beta^*_S-\beta^*)/\sigma_o(G)] \xrightarrow{p} 0, \tag{5.1}$$

$$[U^{(2)}_n(\beta^*)/V_n^{\frac{1}{2}} - \sqrt{n}\, C(\beta^*_T-\beta^*)/\sigma_o(G)] \xrightarrow{p} 0, \tag{5.2}$$

where $\sigma^2_o(G)$ is defined after (2.17) and $kC^2 = x_1^2+\ldots+x_k^2$. Since, by definition, $U^{(1)}_n(\beta^*) + U^{(2)}_n(\beta^*) = 0$, by some simple steps [using (5.1) and (5.2)], it follows immediately that

$$n^{\frac{1}{2}}C[\beta^*-\tfrac{1}{2}(\beta^*_S+\beta^*_T)] \xrightarrow{p} 0, \text{ as } n\to\infty. \tag{5.3}$$

Thus, from (3.12), (5.1), (5.2) and (5.3), it follows that whenever $|n^{\frac{1}{2}}(\beta_S-\beta_T)|$ is bounded,

$$[S_n - (n/2)C^2[\beta_S^* - \beta_T^*]^2/\sigma_o^2(G)] \xrightarrow{p} 0 \text{ as } n \to \infty. \tag{5.4}$$

Writing now $(n/2)C^2[\beta_S^* - \beta_T^*]^2/\sigma_o^2(G) = (n/2)C^2\{[\beta_S^* - \beta_S] - [\beta_T^* - \beta_T] + [\beta_S - \beta_T]\}^2/\sigma_o^2(G)$, and noting that by virtue of theorem 6.1 of Sen [1968], $\sqrt{n}\, C[\beta_S^* - \beta_S]$ and $\sqrt{n}\, C[\beta_T^* - \beta_T]$ are independent and asymptotically normally distributed with zero mean and variance $\sigma_o^2(G)$, it readily follows from (5.4) that under (3.6) (i.e., when $\beta_S = \beta_T$), S_n has asymptotically a chi-square distribution with 1 d.f. (degree of freedom).

Consider now the sequence of alternative hypotheses $\{H_n\}$, where

$$H_n: \quad \beta_S - \beta_T = n^{-\frac{1}{2}}\theta, \ \theta \text{ real and finite.} \tag{5.5}$$

Then again from (5.4) and the discussion following it, it follows that under $\{H_n\}$, S_n has asymptotically a non-central chi-square distribution with 1 d.f. and the non-centrality parameter

$$\Delta_S = C^2\theta^2/2\sigma_o^2(G). \tag{5.6}$$

The variance-ratio ($\mathcal{F}$-) criterion for testing H_o in (3.6) is also asymptotically (under $\{H_n\}$) distributed according to a non-central chi-square distribution with 1 d.f. and non-centrality parameter

$$\Delta_{\mathcal{F}} = C^2\theta^2/2\sigma^2(G); \tag{5.7}$$

the result follows directly from (2.11) and (2.12) of Sen [1969]. Hence, the ARE of the S_n-test with respece to the $\mathcal{F}$-test is

$$e(G) = \Delta_S/\Delta_{\mathcal{F}} = \sigma^2(G)/\sigma_o^2(G) = e_1(G), \tag{5.8}$$

where $e_1(G)$ is defined by (2.18).

(ii) Properties of (β^*,δ^*) of section 4. By virtue of (5.3) and theorem 6.1 of Sen [1968], it immediately follows that when $\beta_S=\beta_T=\beta$, $\sqrt{2n}\, C[\beta^*-\beta]$ is asymptotically normally distributed with zero mean and variance $\sigma_o^2(G)$.

We denote by $\hat{U}_{n,n}$ the two-sample Wilcoxon-Mann-Whitney statistic based on the two sets $\{Y_{jr}^{*(1)},\ 1\le r\le n_o,\ 1\le j\le k\}$ and $\{Y_{jr}^{*(2)},\ 1\le r\le n_o,\ 1\le j\le k\}$, defined by (4.3). Also, we denote by $U_{n,n}$ the same statistic when based on the two sets of errors $\{e_{jr}^{(1)},\ 1\le r\le n_o,\ 1\le j\le k\}$ and $\{e_{jr}^{(2)},\ 1\le r\le n_o,\ 1\le j\le k\}$, defined by (3.5). Since, under (3.6), $n^{\frac{1}{2}}[\beta^*-\beta]$ is bounded in probability, and within each set $\sum_1^k x_j=0$, it follows readily from theorem 3.1 of Jurečková [1969] that (when $\alpha_S^*=\alpha_T^*$) as $n\to\infty$,

$$|\hat{U}_{n,n}-U_{n,n}|/[\mathrm{Var}(U_{n,n})]^{\frac{1}{2}} \xrightarrow{p} 0. \tag{5.9}$$

Consequently, noting that $U_{n,n}$ (or $\hat{U}_{n,n}$) is a particular case of Kendall's tau (with only two possible values of the independent variables), we proceed as in theorem 7.1 and in (7.1) of Sen [1968], and conclude that if δ_o^* be the median of the n^2 differences $[Y_{\ell s}^{(2)}-\beta x_\ell]-[Y_{jr}^{(1)}-\beta x_j]$, $1\le r,\ s\le n_o$, $1\le j,\ \ell\le k$, then as $n\to\infty$,

$$|n^{\frac{1}{2}}(\delta^*-\delta_o^*)| \xrightarrow{p} 0. \tag{5.10}$$

Again from theorem 6.1 of Sen [1968], it follows that $(n/2)^{\frac{1}{2}}(\delta_o^*-\delta)$ is asymptotically normally distributed with zero mean and variance $\sigma_o^2(G)$. Hence, by (5.10), $(n/2)^{\frac{1}{2}}(\delta^*-\delta)$ is also asymptotically normally distributed with zero mean and variance $\sigma_o^2(G)$. Then (4.15) is a direct consequence of (5.9), (5.10) and theorem 2 of Sen [1966].

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