ROBUST STATISTICAL PROCEDURES IN PROBLEMS OF LINEAR REGRESSION WITH SPECIAL REFERENCE TO QUANTITATIVE BIO-ASSAYS, II

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The present paper is a continuation of an earlier one by the same title (part I), where some robust statistical procedures in indirect (quantitative) parallel line assays were considered. We consider here similar procedures for slope-ratio assays, where the basic problems are the following: (i) estimation of (linearized) dosage-response regressions, (ii) testing validity of the fundamental assumption of identity of the intercepts of two dosage-response regression lines, and (iii) estimation of the relative potency of a test preparation with respect to a standard one. The first problem is the same as in parallel line assays, treated in detail in Sen [1971], while the others are studied here. The theory is illustrated by numerical data.

1. INTRODUCTION

Consider an indirect quantitative slope-ratio assay involving a standard and a test preparation, each administered at several specified doses to several subjects whose responses are observed. The dosage (dose-metameter) z is taken as $(\text{dose})^{\lambda}$, where $\lambda(>0)$ is specified. The response (metameters) for the two preparations are then expressed as

$$Y_S = \alpha_S+\beta_S z+e_S \quad \text{and} \quad Y_T = \alpha_T+\beta_T z+e_T, \tag{1.1}$$

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where α_S, α_T are the intercepts, β_S, β_T are the slopes of the two disage-response regression lines, and it is assumed that the errors e_S, e_T have a common (unknown) distribution

$$G(e) = P\{e_S \leq e\} = P\{e_T \leq e\}, \quad -\infty < e < \infty. \tag{1.2}$$

If the test preparation behaves as it is a dilution or concentration of the standard one, we have

$$\alpha_S = \alpha_T = \alpha \text{ (unknown)}, \quad \text{and} \quad \beta_T = \rho^{\lambda}\beta_S, \quad \rho > 0, \tag{1.3}$$

where ρ is the relative potency of the test preparation with respect to the standard one. The equality of the intercepts α_S and α_T constitutes the fundamental assumption of the slope-ratio assay, and the ratio of the slopes provides the relative potency.

In standard textbooks, such as in Finney [1952, ch. 7 and 8], or elsewhere in the literature, $G(e)$ is usually assumed to be normal or logistic, and the test for H_o: $\alpha_S = \alpha_T$ and the estimate of $\rho = (\beta_T/\beta_S)^{1/\lambda}$ are then based on the maximum likelihood estimates of α_S, α_T, β_S and β_T. As has been discussed in Section 1 of Sen [1971], these (so called parametric) procedures, like their counterparts in parallel line assays, are sensitive to gross-errors or outliers, and may be quite inefficient when the actual $G(e)$ is different from the assumed one; also for $G(e)$ belonging to the class of distributions with "heavy tails" (such as the Cauchy or the double exponential distribution), they are usually inefficient. In the same spirit as in Sen [1971], some alternative more robust procedures are developed here.

In Section 2, we start with robust tests for the validity of the fundamental assumption of the assay. Section 3 is devoted to point estimates of ρ, while

Section 4 deals with the interval estimates of ρ. Throughout the paper, we take $\lambda=1$ [see (1.3)]; for $\lambda\neq 1$, we need only to change ρ by ρ^{λ} and the consequent changes are not very elaborate. Also, for the convenience of reading, most of the mathematical derivations are given in the mathematical appendix. Finally, in notations and motivations, the paper has a close proximity with its first part (Sen [1971]), which should be read first.

2. TEST FOR THE VALIDITY OF THE FUNDAMENTAL ASSUMPTION

We have usually either a 2k-point or a (2k+1)-point design, where k is a positive integer. In the 2k-point design, n subjects are used for each of $k(\geq 2)$ equally spaced dosages of each preparation. In (2k+1)-point design, in addition to the two sets of $k(\geq 1)$ doses, n subjects are also assigned to zero dose (controls or blanks). For the standard and the test preparations, we denote the k doses by $x_{1j} = aj/k$ and $x_{2j} = bj/k$, $j=1,\dots,k$, where a and b are known scale factors. Thus, the corresponding dosages are

$$z_{1j} = j/k = (x_{1j}/a), \quad z_{2j} = j/k = (x_{2j}/b), \quad 1\leq j\leq k, \tag{2.1}$$

so that, on writing,

$$\beta_S^* = a\beta_S \quad \text{and} \quad \beta_T^* = b\beta_T = (b\rho/a)\beta_S^*, \tag{2.2}$$

we have from (1.1), (1.3), (2.1) and (2.2)

$$Y_S = \alpha_S+\beta_S^* z+e_S, \quad Y_T = \alpha_T+\beta_T^* z+e_T, \tag{2.3}$$

where the errors e_S and e_T have the distribution $G(e)$, defined in (1.2). For the control or blanks, we have

$$Y^o = \alpha + e^o, \tag{2.4}$$

where e^o has also the distribution G(e). This leads to the following table of responses.

	Preparation						
	Control	Standard			Test		
Dosage	0	1/k	...	k/k	1/k	...	k/k
	Y_1^o	$Y_{11}^{(1)}$	...	$Y_{k1}^{(1)}$	$Y_{11}^{(2)}$	...	$Y_{k1}^{(2)}$
Responses	⋮	⋮	⋱	⋮	⋮	⋱	⋮
	Y_n^o	$Y_{1n}^{(1)}$	...	$Y_{kn}^{(1)}$	$Y_{1n}^{(2)}$	...	$Y_{kn}^{(2)}$

[In a 2k-point design, there is no control, and hence, the corresponding column has to be deleted.]

We start with 2k-point designs and review very briefly the standard parametric test and its limitations. For the two lines in (2.3), treated separately, the least squares estimates of β_S^* and β_T^* are, respectively,

$$\tilde{\tilde{\beta}}_S^* = [12/nk(k^2-1)][\textstyle\sum_{j=1}^k \sum_{r=1}^n Y_{jr}^{(1)}(j - \frac{k+1}{2})] = \tilde{\tilde{\beta}}_1 \text{ (say)}, \tag{2.6}$$

$$\tilde{\tilde{\beta}}_T^* = [12/nk(k^2-1)][\textstyle\sum_{j=1}^k \sum_{r=1}^n Y_{jr}^{(2)}(j - \frac{k+1}{2})] = \tilde{\tilde{\beta}}_2 \text{ (say)}. \tag{2.7}$$

Thus, for normal G(e), the test for H_o: $\alpha_S = \alpha_T$ is based on the Student t-statistic

$$t = (\bar{Y}^{(1)} - \bar{Y}^{(2)} - [(k+1)/2k][\tilde{\tilde{\beta}}_1 - \tilde{\tilde{\beta}}_2])/(q_{n,k} S_e), \tag{2.8}$$

where $\bar{Y}^{(i)} = (nk)^{-1} \sum_{j=1}^{k} \sum_{\ell=1}^{n} Y_{j\ell}^{(i)}$, i=1,2, N=nk, and

$$S_e^2 = (2N-4)^{-1} \sum_{i=1}^{2} \sum_{j=1}^{k} \sum_{r=1}^{n} (Y_{jr}^{(i)} - \bar{Y}^{(i)} - \tilde{\tilde{\beta}}_i [j/k-(k+1)2k])^2, \qquad (2.9)$$

$$q_{n,k}^2 = \frac{2}{N}(1+3(k+1)/(k-1)) = 4(2k+1)/[nk(k-1)]. \qquad (2.10)$$

Now, S_e^2 carrys 2N-4 degrees of freedom and unbiasedly estimates $\sigma^2(G)$, the variance of the distribution G(e). When G is normal and $\alpha_S = \alpha_T$, t has the Student t-distribution with 2N-4 degrees of freedom. Therefore, the power of the test depends on $|\alpha_S - \alpha_T|/(\sigma(G) q_{n,k})$, and hence, $q_{n,k}$ measures the efficacy of the test. The smaller is the value of $q_{n,k}$, the greater is the power of the test. We consider the following table first.

TABLE 2.1. Values of $q_{n,k}$ for Small n and k

n	k = 2	3	4	5	6
2	2.236	1.524	1.226	1.049	.931
3	1.825	1.246	1.000	.857	.760
4	1.582	1.080	.866	.742	.658
5	1.414	.966	.775	.664	.587
6	1.291	.882	.707	.606	.537
7	1.195	.819	.655	.561	.498
8	1.116	.764	.613	.524	.465
9	1.054	.720	.577	.494	.439
10	1.000	.683	.548	.470	.416

It is quite clear from the above table that unless nk is large, the test is of little power. For example, if $|\alpha_S - \alpha_T|/\sigma(G) = 1$, the power of the test corresponding to 5% level of significance for various (n,k) are as follows: (i) 0.15 for n=10, k=2, (ii) 0.21 for n=7, k=3, (iii) 0.22 for n=5, k=4, (iv) 0.23 for n=4, k=5, (v) 0.22 for n=3, k=6, and (vii) 0.68 for n=10, k=6. Hence, in order to have a test for H_o: $\alpha_S=\alpha_T$ having a specified level of significance (viz., 0.05, 0.01 etc.) and a reasonable power for alternatives not too apart, we require nk to be large.

We develop first a robust rank test for H_o: $\alpha_S=\alpha_T$ when N=nk is assumed to be large. For this, we consider the robust estimators of β_S^* and β_T^*, derived in the same manner as in Sen [1968, 1961]. Let

$$W_{\ell j,sr}^{(i)} = k(Y_{\ell s}^{(i)}-Y_{jr}^{(i)})/(\ell-j),\quad 1\leq j<\ell\leq k,\ 1\leq r,\ s\leq n, \tag{2.11}$$

for i=1,2. Thus, for each i(=1,2), we have a set of $N^* = \binom{k}{2}n^2$ $W^{(i)}$'s, which when arranged in ascending order of magnitudes yield the order statistics

$$W_{(1)}^{(i)} \leq \dots \leq W_{(N^*)}^{(i)} \quad \text{for} \quad i=1,2. \tag{2.12}$$

Then, our proposed estimators of β_S^* and β_T^* are

$$\hat{\hat{\beta}}_S^* = \begin{cases} W_{(M^*+1)}^{(1)}, & \text{if} \quad N^*=2M^*+1, \\ \tfrac{1}{2}[W_{(M^*)}^{(1)} + W_{(M^*+1)}^{(1)}], & \text{if} \quad N=2M^*; \end{cases} \tag{2.13}$$

$$\hat{\hat{\beta}}_T^* = \begin{cases} W_{(M^*+1)}^{(2)}, & \text{if} \quad N=2M^*+1, \\ \tfrac{1}{2}[W_{(M^*)}^{(2)} + W_{(M^*+1)}^{(2)}], & \text{if} \quad N=2M^*, \end{cases} \tag{2.14}$$

where M* is a positive integer. Consider then the following aligned observations

$$\hat{Y}_{jr}^{(1)} = Y_{jr}^{(1)} - \hat{\hat{\beta}}_S^*(j/k), \quad \hat{Y}_{jr}^{(2)} = Y_{jr}^{(2)} - \hat{\hat{\beta}}_T^*(j/k),\ 1\leq r\leq n,\ 1\leq j\leq k. \tag{2.15}$$

For each $i(=1,2)$, consider the set of $\binom{N+1}{2} = N^{**}$ midranges

$$\hat{V}_{\ell j,sr}^{(i)} = \tfrac{1}{2}(\hat{Y}_{jr}^{(i)} + \hat{Y}_{\ell s}^{(i)}),\ 1\leq j<\ell\leq k,\ 1\leq r,\ s\leq n;\quad 1\leq j=\ell\leq k,\ 1\leq r\leq s\leq n, \tag{2.16}$$

and we combine the two sets of midranges into a pooled set of $2N^{**}$ observations, whose order values are denoted by

$$\hat{V}_{(1)} \leq \cdots \leq \hat{V}_{(2N^{**})}. \tag{2.17}$$

Then, as in Sen [1971], as a pooled sample estimator of the hypothetical common value of $\alpha_S=\alpha_T=\alpha$, is the following

$$\hat{\hat{\alpha}} = \tfrac{1}{2}[\hat{V}_{(N^{**})} + \hat{V}_{(N^{**}+1)}]. \tag{2.18}$$

Using (2.15) and (2.18), we obtain the <u>ultimate aligned observations</u>

$$\hat{\hat{Y}}_{jr}^{(1)} = Y_{jr}^{(1)} - \hat{\hat{\alpha}} - (j/k)\hat{\hat{\beta}}_S^*, \quad \hat{\hat{Y}}_{jr}^{(2)} = Y_{jr}^{(2)} - \hat{\hat{\alpha}} - (j/k)\hat{\hat{\beta}}_T^*, \tag{2.19}$$

for $1\leq r\leq n$, $1\leq j\leq k$. Consider then the two one-sample Wilcoxon signed rank statistics, based on (2.19), defined by

$$\hat{T}_i = \sum_{j=1}^{k} \sum_{r=1}^{n} \tilde{R}_{jr}^{(i)}\ \mathrm{Sign}(\hat{\hat{Y}}_{jr}^{(i)}), \quad i=1,2, \tag{2.20}$$

where sign u=1,0 or -1 according as u is >, = or <0, and

$$\tilde{R}_{jr}^{(i)} = \text{Rank of } |\hat{\hat{Y}}_{jr}^{(i)}| \text{ among } |\hat{\hat{Y}}_{11}^{(i)}|,\ldots,|\hat{\hat{Y}}_{kn}^{(i)}|, \tag{2.21}$$

for $1\leq j\leq k$, $1\leq r\leq n$, $i=1,2$. Our proposed test statistic is

$$Q_N = [3(k-1)/(2k+1)N(N+1)(2N+1)](\hat{T}_1^2 + \hat{T}_2^2). \tag{2.22}$$

It follows from Theorem 5.1 (in the appendix) that under H_o: $\alpha_S=\alpha_T$, Q_N has asymptotically a chi-square distribution with 1 degree of freedom (D.F.). On the other hand, if $\alpha_S\neq\alpha_T$, one of the two $\hat{T}_i$ will be stochastically highly negative and the other one stochastically highly positive, and hence, Q_N will be numerically large, in probability. This leads us to consider the following test procedure:

> reject (accept) H_o: $\alpha_S=\alpha_T$ if $Q_N\geq(<)\chi^2_{1,\varepsilon}$, the upper 100ε% point of the chi-square distribution with 1 D.F., where ε (0<ε<1) is the level of significance of the test. (2.23)

Note that the aligned observations in (2.19) are based on robust estimates of the intercepts and the slopes, and also, Q_N is based on the Wilcoxon signed rank statistics which are known to be robust. This leads us to conclude that the above test in (2.23) is robust for gross-errors, outliers and for distributions with 'heavy tails'.

A comparison of the two tests in (2.8) and (2.23) [made in Theorem 5.2 in the appendix] reveals that the asymptotic relative efficiency (A.R.E.) of Q_N with respect to t is given by

$$e_{Q,t} = 12\sigma^2(G)[\int_{-\infty}^{\infty} g^2(e)de]^2. \tag{2.24}$$

Since this agrees with the A.R.E. result studied in detail in Sen [1971], we omit the details here.

It needs to be mentioned at this point that the approximation of the upper $100\varepsilon\%$ point of the null distribution of Q_N by $\chi^2_{1,\varepsilon}$ holds only for large nk. For example, when $\varepsilon \geq 0.05$, for k=2, n needs to be ≥ 16, for k=3, $n \geq 9$ and for k=4, $n \geq 7$. For larger k, we need smaller values of n. However, in view of Table 2.1 (citing limitations of the parametric test for small nk) and (2.24) (having reasonable properties, discussed in Sen [1971]), Q_N poses itself as a strong competitor of t in (2.8).

It is also possible to construct an exact rank test for H_o: $\alpha_S = \alpha_T$ on the following principle. Consider the set of observations $Y^{(1)}_{1r},\ldots,Y^{(1)}_{kr}$ $(Y^{(2)}_{1r},\ldots,Y^{(2)}_{kr})$, derive the least squares estimator of α_S (α_T), and denote it by $\hat{\alpha}_{Sr}(\hat{\alpha}_{Tr})$, for r=1,...,n. When k=2, $\hat{\alpha}_{Sr} = 2Y^{(1)}_{1r} - Y^{(1)}_{2r}$, $\hat{\alpha}_{Tr} = 2Y^{(2)}_{1r} - Y^{(2)}_{2r}$, r=1,...,n. Then, we have two sets of variables

$$\hat{\alpha}_{S1},\ldots,\hat{\alpha}_{Sn} \quad \text{and} \quad \hat{\alpha}_{T1},\ldots,\hat{\alpha}_{Tn}, \tag{2.25}$$

where the distributions of $\hat{\alpha}_{Sr}$ and $\hat{\alpha}_{Tr}$ are identical under H_o: $\alpha_S = \alpha_T$; otherwise they differ only by $\alpha_S - \alpha_T$. Hence, we are in a position to use the Wilcoxon two-sample rank sum test based on

$$W = \sum_{r=1}^{n} R_{1r} - \sum_{r=1}^{n} R_{2r}, \tag{2.26}$$

where R_{1r} = Rank of $\hat{\alpha}_{Sr}$ among $\hat{\alpha}_{S1},\ldots,\hat{\alpha}_{Sn}$, $\hat{\alpha}_{T1},\ldots,\hat{\alpha}_{Tn}$, and R_{2r} = rank of $\hat{\alpha}_{Tr}$

among $\hat{\alpha}_{S1},\ldots,\hat{\alpha}_{Tn}$, r=1,...,n. The critical values of W are tabulated in Owen [1962, pp. 331-339], where ε_n, the level of significance is a multiple of $\binom{2n}{n}^{-1}$. We may, however, note that the test is based on a mating of the responses within various rows, which needs to be done on a random basis so as to insure the validity of the procedure.

To illustrate the above procedures, we consider the following data from Wood [1946].

TABLE 2.2. An Assay of Riboflavin in Malt
(in units of 0.05 ml. N/10 NaOH)

Standard Preparation: unit = 0.2 μg riboflavin (=a)

Test Preparation: unit = 0.05 g malt (=b)

Blanks	Standard		Test	
z=0	$z_S=\frac{1}{2}$	$z_S=1$	$z_T=\frac{1}{2}$	$z_T=1$
38	97	167	80	121
45	100	164	88	124
40	105	159	90	122
44	98	156	82	122

[We shall first disregard the blanks and formulate our procedures on the 4-point design. Later on, while considering the (2k+1)-point designs, we make use of the whole table.]

Since here k=2 and n=4, we have N*=16, N**=36. The 16 divided differences of the standard preparation are

140, 134, 124, 118, 134, 128, 118, 112, 124, 118, 108, 102, 138, 132, 122, 116,

and for the test preparation these are

82, 88, 84, 84, 66, 72, 68, 68, 62, 68, 64, 64, 78, 84, 80, 80.

Thus, $\hat{\hat{\beta}}_S^* = \frac{1}{2}(124+124)=124$ and $\hat{\hat{\beta}}_T^* = \frac{1}{2}(72+78)=75$.

Hence, the aligned observations, defined by (2.15), are, respectively,

35,38,43,36,43,40,35,32, and 42.5,50.5,52.5,44.5,46,49,47,47.

The two corresponding sets of mid-ranges [defined by (2.16)] are

35,36.5,39,35.5,39,27.5,35,33.5,38,40.5,37,
40.5,29,36.5,35,43,39.5,43,41.5,39,37.5,36,39.5,38,
35.5,34,43,41.5,39,37.5,40,37.5,36,35,33.5,32;
42.5,46.5,47.5,43.5,44.25,45.75,44.75,44.75,50.5,51.5,47.5,48.25,
49.75,48.75,48.75,52.5,47.5,49.25,50.75,49.75,49.75,44.5,45.25,46.75,
45.75,45.75,46,47.5,46.5,46.5,49,48,48,47,47,47.

Hence, $\hat{\hat{\alpha}}$, defined by (2.18), is equal to $\frac{1}{2}(42.5+43)=42.75$. Consequently, the ultimate aligned observations, defined by (2.19), are, respectively,

-7.75, -4.75, 0.25, -6.75, 0.25, -2.75, -7.75, -10.75;
-0.25, 7.75, 9.75, 1.75, 3.25, 6.25, 4.25, 4.25.

Hence, by (2.20)-(2.22), we obtain that

$$Q_N = \{(-30)^2 + (34)^2\}/\{8 \times 255\} = 1.008.$$

As explained earlier, for n=4, k=2, we are not in a position to use $\chi^2_{1,\varepsilon}$ as the critical value of Q_N. In fact, we do not prescribe the use of Q_N for such (k,n). We compute t and W in (2.8) and (2.26), and compare these.

By (2.6)-(2.8), we have $t = -9.25/6.28 = -1.47$, whereas the 5% critical value of $|t|$ at 12 D.F. is 2.179. Hence, we accept H_o: $\alpha_S=\alpha_T$. The estimates of α_S and α_T derived from the different rows are

27, 36, 51, 40 and 39, 52, 58, 40.

Thus, W, defined by (2.26), is equal to -9, whereas the 5.6% critical value of $|W|$ is 14. Hence, we also accept H_o: $\alpha_S=\alpha_T$ by this procedure. Note that $P\{|t|>1.47|12 \text{ D.F.}, H_o\} \approx .166$, $P\{|W|>9|H_o\} \approx .196$ are also quite close to each other.

Let us consider now the case of (2k+1)-point designs. This is actually a 3-sample problem, with regressions specified by (2.3) and (2.4). [For control, no regression.] Thus, we have to test here H_o: $\alpha_S=\alpha_T=\alpha$. On the other hand, even if $\alpha_S=\alpha_T\neq\alpha$, the fundamental assumption is satisfied and the estimation of ρ is validated. Thus, insofar as the fundamental assumption is concerned, for testing H_o: $\alpha_S=\alpha_T$, we can use a Student t-statistic which has the same numerator as in (2.8), while in the denominator, S_e is replaced by S'_e, where

$$S_e'^2 = \{(2kn-4)s_e^2 + \textstyle\sum_{r=1}^{n}(Y_r^o-\bar{Y}^o)^2\}/((2k+1)n-5); \quad \bar{Y}^o = \frac{1}{n}\textstyle\sum_{r=1}^{n} Y_r^o, \qquad (2.26)$$

and the degrees of freedom is now $(2k+1)n-5$ instead of $2kn-4$. Thus, the controls, add to D.F. and thereby increase the sensitivity of the test. However, $q_{n,k}$, defined by (2.8), (2.10), remains unchanged, and hence, by Table 2.1, we gather the same conclusions about the poor performance of the test for small nk. The rank tests based on Q_N and W remain the same, as here the data on control group is not made use of.

3. POINT ESTIMATION OF RELATIVE POTENCY

Let us define $\bar{Y}^o$ as in (2.27), and let

$$\bar{Y}_j^{(i)} = n^{-1} \sum_{r=1}^{n} Y_{jr}^{(i)} \quad \text{for} \quad 1 \leq j \leq k \quad \text{and} \quad i=1,2. \tag{3.1}$$

In the classical parametric method, we minimize

$$Q(\alpha, \beta_S^*, \beta_T^*) = \sum_{j=1}^{k} \{(\bar{Y}_j^{(1)} - \alpha - \beta_S^* j/k)^2 + (\bar{Y}_j^{(2)} - \alpha - \beta_T^* j/k)^2\} + (\bar{Y}^o - \alpha)^2, \tag{3.2}$$

(where for a 2k-point design, $(\bar{Y}^o - \alpha)^2$ has to be dropped), and get the least squares estimators of α, β_S^* and β_T^*, denoted by $\tilde{\alpha}$, $\tilde{\beta}_S^*$ and $\tilde{\beta}_T^*$, respectively. Then, by (2.2), we have

$$\tilde{\rho} = (a/b)(\tilde{\beta}_T^* / \tilde{\beta}_S^*). \tag{3.3}$$

In the procedure, to be proposed, we replace the $\bar{Y}_j^{(i)}$ and $\bar{Y}^o$ by their robust competitors. Define

$$\tilde{Y}_j^{(i)} = \underset{1 \leq r \leq r' \leq n}{\text{median}} \{\tfrac{1}{2}[Y_{jr}^{(i)} + Y_{jr'}^{(i)}]\}, \quad 1 \leq j \leq k, \ i=1,2; \tag{3.4}$$

$$\tilde{Y}^o = \underset{1 \leq r \leq r' \leq n}{\text{median}} \{\tfrac{1}{2}[Y_r^o + Y_{r'}^o]\}. \tag{3.5}$$

For a 2k-point design, we then minimize

$$\sum_{j=1}^{k} \{(\tilde{Y}_j^{(1)} - \alpha - \beta_S^* j/k)^2 + (\tilde{Y}_j^{(2)} - \alpha - \beta_T^* j/k)^2\} \tag{3.6}$$

with respect to α, β^*_S and β^*_T and, parallel to (3.3), obtain the estimator

$$\rho^*=(a/b)[f_1Q^*_2-f_2Q^*_1]/[f_1Q^*_1-f_2Q^*_2], \tag{3.7}$$

where

$$Q^*_1 = k^{-1}\sum_{j=1}^{k} j\tilde{Y}_j^{(1)} - \frac{k+1}{2}\tilde{Y}, \quad Q^*_2 = k^{-1}\sum_{j=1}^{k} j\tilde{Y}_j^{(2)} - \frac{k+1}{2}\tilde{Y}, \tag{3.8}$$

$$\tilde{Y} = \frac{1}{2k}\sum_{i=1}^{2}\sum_{j=1}^{k}\tilde{Y}_j^{(i)}, \quad f_1 = \frac{(k+1)(5k+1)}{24k} \text{ and } f_2 = -\frac{(k+1)^2}{8k}. \tag{3.9}$$

For a (2k+1)-point design, we obtain by minimizing

$$(\tilde{Y}^o-\alpha)^2 + \sum_{j=1}^{k}\{(\tilde{Y}_j^{(1)}-\alpha-\beta^*_S j/k)^2 + (\tilde{Y}_j^{(2)}-\alpha-\beta^*_T j/k)^2\} \tag{3.10}$$

with respect to α, β^*_S and β^*_T and then using (2.2) that

$$\rho^{**} = (a/b)[f_1^oQ^{**}_2-f_2^oQ^{**}_1]/[f_1^oQ^{**}_1-f_2^oQ^{**}_2], \tag{3.11}$$

where

$$Q^{**}_i = k^{-1}\sum_{j=1}^{k} j\tilde{Y}_j^{(i)} - \frac{k+1}{2}\tilde{\tilde{Y}},\ i=1,2; \quad \tilde{\tilde{Y}} = \frac{1}{2k+1}[\tilde{Y}^o + \sum_{j=1}^{k}(\tilde{Y}_j^{(1)}+\tilde{Y}_j^{(2)})], \tag{3.12}$$

$$f_1^o = (k+1)(5k^2+5k+2)/[12k(2k+1)], \quad f_2^o = -(k+1)^2/4(2k+1). \tag{3.13}$$

The properties of the estimates ρ^* and ρ^{**} depend on the situations where n is large or n is small but k is large. In the first case, it follows from Sen [1971] and Puri and Sen [1971, chapter 6] that $n^{\frac{1}{2}}[\tilde{Y}^o-\alpha]$, $n^{\frac{1}{2}}[\tilde{Y}_j^{(1)}-\alpha-\beta^*_S j/k]$ and

$n^{\frac{1}{2}}[\tilde{Y}_j^{(2)}-\alpha-\beta_T^* j/k]$, j=1,...,k, are all independently and approximately normally distributed with zero means and a common variance

$$\gamma^2(G) = [12(\int_{-\infty}^{\infty} g^2(e)de)^2]^{-1}. \tag{3.14}$$

Consequently, by (3.8)-(3.13), along with a theorem in Rao [1965, p. 321], it follows that (i) $n^{\frac{1}{2}}(\rho^*-\rho)$ has approximately a normal distribution with zero mean and variance

$$\gamma^2(G)[f_1(a^2+b^2\rho^2)+2ab\ \rho\ f_2]/[b^2(\beta_S^*)^2(f_1^2-f_2^2)], \tag{3.15}$$

and (ii) $n^{\frac{1}{2}}(\rho^{**}-\rho)$ has approximately a normal distribution with zero mean and variance

$$\gamma^2(G)[f_1^o(a^2+b^2\rho^2) + 2ab\ \rho\ f_2^o]/[b^2(\beta_S^*)^2(f_1^{o2}-f_2^{o2})]. \tag{3.16}$$

A comparison with the parametric estimator $\tilde{\rho}$, in (3.3), again leads to the A.R.E. of ρ^* (or ρ^{**}) with respect to $\tilde{\rho}$ as equal to $e_{Q,t}$, defined by (2.24).

In the second case, when n is small and regarded as fixed, if we denote by $\lambda_n(G) = n\ \mathrm{Var}\{\tilde{Y}^o\}$, then the A.R.E. of ρ^* or ρ^{**} with respect to $\tilde{\rho}$ is equal to

$$\sigma^2(G)/\lambda_n(G) = e_n(G), \quad \text{say}. \tag{3.17}$$

In general, $e_n(G)$ depends on G and n in a rather involved manner. However, as noted in Sen [1971], for $n \geq 4$, this is usually quite close to $e_{Q,t}$.

Looking at the Table 2.2, we note that

$$\tilde{Y}^{o} = 41.75,\ \tilde{Y}_1^{(1)} = 99.5,\ \tilde{Y}_2^{(1)} = 161.5,\ \tilde{Y}_1^{(2)} = 85,\ \tilde{Y}_2^{(2)} = 122. \tag{3.18}$$

Thus, by (3.7)-(3.9),

$$\rho^* = 4(200.75/294.25) = 2.73,$$

and by (3.11)-(3.13),

$$\rho^{**} = 4(35.50625/51.86875) = 2.74.$$

4. ROBUST CONFIDENCE INTERVALS FOR ρ

In the same spirit as in Sen [1971], we consider here the following two procedures.

(i) Procedure I. As in Sen [1968, 1971], we provide first robust and distribution-free confidence intervals for β_S^* and β_T^*, which in turn provide a confidence interval for ρ.

For a 2k-point design, we define the divided differences as in (2.11). For a (2k+1)-point design, in addition to these, we have

$$W_{jo,rs}^{(i)} = k(Y_{js}^{(i)} - Y_r^{o})/j,\ 1 \leq j \leq k,\ 1 \leq r,\ s \leq n;\ i=1,2. \tag{4.1}$$

Thus, for a (2k+1)-point design, we have $\binom{k+1}{2}n^2$ divided differences for each preparation, whereas there are $\binom{k}{2}n^2$ for the 2k-point design. Then, as in (2.21) through (2.23) of Sen [1971], for every n and k, we can find an $\varepsilon_n (0<\varepsilon_n<1)$, such that for any G,

$$P\{W_{(m_1)}^{(1)} < \beta_S^* < W_{(m_2+1)}^{(1)} \mid \beta_S^*\} = 1-\varepsilon_n, \tag{4.2}$$

$$P\{W^{(2)}_{(m_1)} < \beta^*_T < W^{(2)}_{(m_2+1)} | \beta^*_T\} = 1-\varepsilon_n, \tag{4.3}$$

where the $W^{(i)}_{(\ell)}$, $\ell=1,\ldots,\binom{k}{2}n^2$ [or $\binom{k+1}{2}n^2$] are the ordered values of the divided differences (for the given i),

$$m_1 = \tfrac{1}{2}(N^*-U^*_n),\ m_2 = \tfrac{1}{2}(N^*+U^*_n),\ N^* = \binom{k}{2}n^2 \text{ [or } \binom{k+1}{2}n^2\text{]}, \tag{4.4}$$

and U^*_n is the upper $50\varepsilon_n$% point of the numerator of Kendall's tau statistic, under the null situation, when there are k (or k+1) distinct regression constants. Values of U^*_n in various simple cases (e.g., k=2 etc.) are available in Owen [1962, pp. 331-345]. Thus, writing $\gamma_n = 2\varepsilon_n$, we have from (4.2), (4.3) and some simple deductions that for any G,

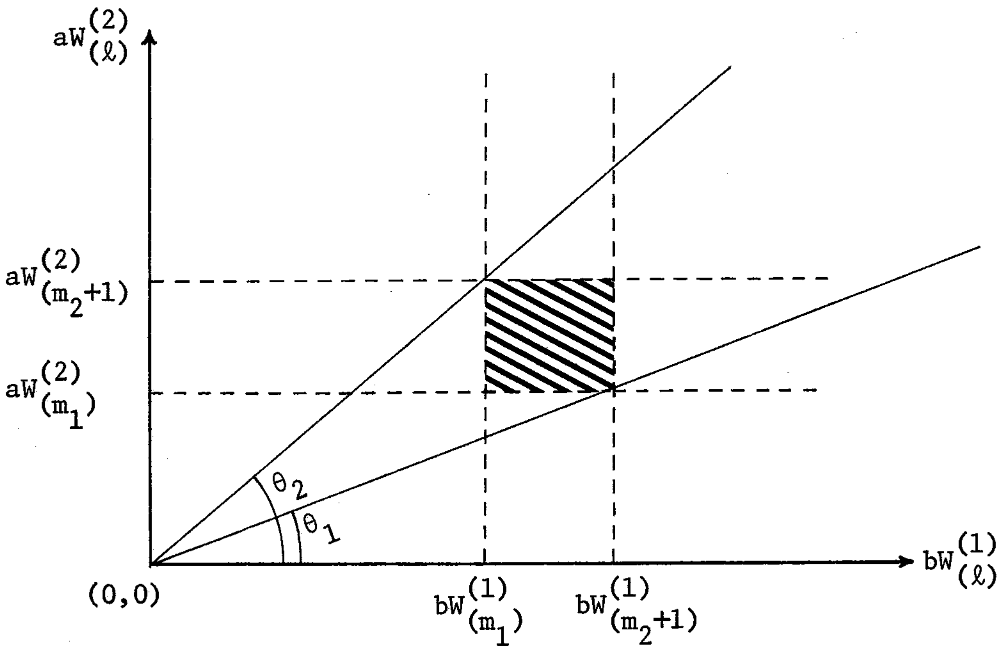
$$P\{W^{(1)}_{(m_1)}<\beta^*_S<W^{(1)}_{(m_2+1)}, W^{(2)}_{(m_1)}<\beta^*_T<W^{(2)}_{(m_2+1)} | \beta^*_S,\beta^*_T\} \geq 1-\gamma_n, \tag{4.5}$$

which implies that for any G,

$$P\{(aW^{(2)}_{(m_1)})/(bW^{(1)}_{(m_2+1)}) < \rho < (aW^{(2)}_{(m_2+1)})/(bW^{(1)}_{(m_1)}) | \rho\} \geq 1-\gamma_n. \tag{4.6}$$

The above confidence interval can be obtained graphically as follows:

FIGURE 4.1. Confidence interval for ρ



Then, $\hat{\rho}_L = (aW^{(2)}_{(m_1)})/(bW^{(1)}_{(m_2+1)}) = \tan\theta_1$ and $\hat{P}_U = (aW^{(2)}_{(m_2+1)})/(bW^{(1)}_{(m_1)}) = \tan\theta_2$. For large nk (or n(k+1)), one can again approximate m_1, m_2 and U^*_n as in (2.22)-(2.23) of Sen [1971].

A characteristic property of the above confidence interval is its distribution-freeness, that is, it is a confidence interval for ρ (with confidence coefficient bounded below by $1-\gamma_n$) valid for all G. On the other hand, if G is assumed to be normal, the conventional confidence interval for ρ is based on the Fieller theorem (viz., Finney [1952, pp. 27-29]), whose validity is open to question when G is not normal. This broader scope for (4.6) is usually achieved at the cost of a band which is usually wider than the one provided by the Fieller theorem. One reason for this is that whereas in (4.5), we consider a rectangular confidence band for (β_S^*, β_T^*), in Fieller's theorem, we consider an ellipse for the same, and the two tangents, which provide the confidence interval for the ratio, are closer to each other in the later case. This drawback can be avoided in the second procedure considered below, provided nk (or (k+1)n) is large. For a numerical illustration of the procedure in (4.5), we refer to section 4 of Sen [1971], where essentially a similar procedure is considered for the parallel line assay.

(ii) Procedure II. This is essentially a large sample procedure where we use the asymptotic normality of ρ^* (or ρ^{**}), defined in (3.7) [or (3.11)] and a consistent estimator of $\gamma^2(G)$, appearing in its variance.

Let $\tau_{\frac{1}{2}\varepsilon_n}$ be the upper $50\varepsilon_n\%$ point of the standard normal distribution, where ε_n $(0<\varepsilon_n<1)$ is such that (4.2) and (4.3) hold. Then, from Sen [1968, 1971], it follows that on defining m_1 and m_2 as in (4.4), for a 2k-point design,

$$\frac{\{n(k^2-1)k\}^{\frac{1}{2}}\{\frac{1}{2}[W^{(1)}_{(m_2+1)}-W^{(1)}_{(m_1)}+W^{(2)}_{(m_2+1)}-W^{(2)}_{(m_1)}]\}}{2\,\tau_{\frac{1}{2}\varepsilon_n}} \overset{P}{\to} \Big(\int_{-\infty}^{\infty} g^2(e)de\Big)^{-1}, \tag{4.7}$$

while for a (2k+1)-point design,

$$\frac{\{n(k+1)k(k+2)\}^{\frac{1}{2}}\{\frac{1}{2}[W^{(1)}_{(m_2+1)}-W^{(1)}_{(m_1)}+W^{(2)}_{(m_2+1)}-W^{(2)}_{(m_1)}]\}}{2\,\tau_{\frac{1}{2}\varepsilon_n}} \overset{P}{\to} \Big(\int_{-\infty}^{\infty} g^2(e)de\Big)^{-1}. \tag{4.8}$$

Thus, from (3.15) and (4.7), we obtain that a consistent estimator of the variance of $n^{\frac{1}{2}}(\rho^*-\rho)$ is

$$\hat{\delta}^2_{nk} = \frac{n(k^2-1)k[W^{(1)}_{(n_2+1)}-W^{(1)}_{(m_1)}+W^{(2)}_{(m_2+1)}-W^{(2)}_{(m_1)}]^2}{12[4\tau_{\frac{1}{2}\varepsilon_n} b\hat{\beta}^*_S]^2} [f_1(a^2+(b\rho^*)^2)+2ab\rho^* f_2], \quad (4.9)$$

where ρ^* is defined by (3.7) and $\hat{\beta}^*_S = (f_1Q^*_1-f_2Q^*_2)/(f^2_1-f^2_2)$. Consequently, we have the following (asymptotic) $100(1-\varepsilon_n)\%$ confidence interval for ρ:

$$\rho^* - \tau_{\frac{1}{2}\varepsilon_n} \hat{\delta}_{n,k} \leq \rho \leq \rho^* + \tau_{\frac{1}{2}\varepsilon_n} \hat{\delta}_{n,k},$$

which simplifies to

$$\rho^*-([W^{(1)}_{(m_2+1)}-W^{(1)}_{(m_1)}+W^{(2)}_{(m_2+1)}-W^{(2)}_{(m_1)}]/4b\hat{\beta}^*_S) \times$$
$$(nk(k^2-1)[f_1(a^2+(b\rho^*)^2)+2ab\rho^* f_2]/12)^{\frac{1}{2}}$$
$$\leq \rho \leq \rho^* + ([W^{(1)}_{(m_2+1)}-W^{(1)}_{(m_1)}+W^{(2)}_{(m_2+1)}-W^{(2)}_{(m_1)}]/4b\hat{\beta}^*_S) \times$$
$$(nk(k^2-1)[f_1(a^2+(b\rho^*)^2)+2ab\rho^* f_2]/12)^{\frac{1}{2}}. \quad (4.10)$$

Similarly, for the (2k+1)-point design, upon letting $\bar{\beta}^*_S = (f^o_1Q^{**}_1-f^o_2Q^{**}_2)/(f^{o2}_1-f^{o2}_2)$, we have the (asymptotic) $100(1-\varepsilon_n)\%$ confidence interval for ρ, given below.

$$\rho^{**}-([W^{(1)}_{(m_2+1)}-W^{(1)}_{(m_1)}+W^{(2)}_{(m_2+1)}-W^{(2)}_{(m_1)}]/4b\bar{\beta}^*_S) \times$$
$$(\frac{nk(k+1)(k+2)}{12}[f^o_1(a^2+(b\rho^{**})^2)+2ab\rho^{**}f^o_2])^{\frac{1}{2}}$$
$$\leq \rho \leq \rho^{**} + ([W^{(1)}_{(m_2+1)}+W^{(1)}_{(m_1)}+W^{(2)}_{(m_2+1)}-W^{(2)}_{(m_1)}]) \times$$
$$(\frac{nk(k+1)(k+2)}{12}[f^o_1(a^2+(b\rho^{**})^2)+2ab\rho^{**}f^o_2])^{\frac{1}{2}}. \quad (4.11)$$

The A.R.E. of (4.10) or (4.11) with respect to their parametric counterpart derived by the Fieller theorem agrees with (2.24).

We complete this section by a numerical illustration of (4.10) for the data in Table 2.2. For the 4-point design (controls deleted), we have from the tables of the Wilcoxon two sample statistics (viz., Owen [1962, pp. 331-339]), for $\varepsilon_n = .057$, $U_n^* = 12$. Thus, $m_1=2$, $m_2=14$. Hence,

$$W_{(2)}^{(1)}=108, \quad W_{(15)}^{(1)}=134, \quad W_{(2)}^{(2)}=64, \quad W_{(15)}^{(2)}=84, \quad a/b=4,\ k=2,\ n=4.$$

So that (4.10) reduces to

$$2.73-.44 = 2.39 \leq \rho \leq 2.73+.44 = 3.07,$$

and the confidence coefficient is 0.943.

By the use of the Fieller theorem on the least squares estimators, we obtain on using the 5.7% point of the standard normal distribution, that for the same 4-point design, a 94.3% confidence interval for ρ is

$$2.38 \leq \rho \leq 3.06,$$

while the use of the 5.7% point of the Student's t-distribution with 12 D.F. results in a slightly wider band. It seems that the above two confidence intervals are practically the same. In general, for nearly normal G(e), when there are no outliers, we expect a close agreement of the two, while for G(e) widely differing from a normal distribution, we expect a better performance with (4.10).

A similar computation is involved in (4.11) dealing with a (2k+1)-point design.

5. MATHEMATICAL APPENDIX

We present here the mathematical derivations of the distribution theory of Q_N, defined by (2.22). We consider the following sequence $\{H_N\}$ of alternative hypotheses

$$H_N: \quad \alpha_S-\alpha_T = N^{-\frac{1}{2}}\theta, \ N=nk, \ \theta \text{ real and finite}, \tag{5.1}$$

so that the null case follows readily by letting $\theta=0$.

THEOREM 5.1. Under $\{H_N\}$ in (5.1), Q_N, defined by (2.22), has asymptotically a chi-square distribution with 1 degree of freedom and non-centrality parameter

$$\Delta_Q = 3(k-1)\theta^2\left(\int_{-\infty}^{\infty} g^2(e)de\right)^2/(2k+1). \tag{5.2}$$

Proof. Let c(u) be equal to 1, 0 or -1 according as u is >, = or <0, and let

$$U_n^{(i)}(b) = \sum_{1\le j<\ell\le k} \sum_{r=1}^{n} \sum_{s=1}^{n} c([Y_{\ell s}^{(i)}-b\ell/k]-[Y_{jr}^{(i)}-bj/k]), \tag{5.3}$$

i=1,2, and

$$W_{n(a,b)}^{(i)} = \binom{N+1}{2}^{-1} \Sigma_S \; e(Y_{jr}^{(i)}+Y_{\ell s}^{(i)}-2a-b(j+\ell)/k), \tag{5.4}$$

i=1,2, where a and b are running variables, and the summation S extends over all possible $1\leq j<\ell\leq k$, $1\leq r$, $s\leq n$ and $1\leq j=\ell\leq k$, $1\leq r\leq s\leq n$. Note that, by definition,

$$\hat{T}_1 = [N(N+1)]W_n^{(1)}(\hat{\alpha},\hat{\hat{\beta}}_S^*),\ \hat{T}_2 = [N(N+1)]W_n^{(2)}(\hat{\alpha},\hat{\hat{\beta}}_T^*); \tag{5.5}$$

$$W_n^{(1)}(\hat{\alpha},\hat{\hat{\beta}}_S^*) + W_n^{(2)}(\hat{\alpha},\hat{\hat{\beta}}_T^*) \simeq 0; \tag{5.6}$$

Also, from Sen [1968], we have

$$|N^{\frac{1}{2}}(\hat{\hat{\beta}}_S^*-\beta_S^*)| = O_p(1),\ |N^{\frac{1}{2}}(\hat{\hat{\beta}}_T^*-\beta_T^*)| = O_p(1), \tag{5.7}$$

where $\hat{\hat{\beta}}_S^*$ and $\hat{\hat{\beta}}_T^*$ are defined by (2.13) and (2.14). Consequently, on using Theorem 3.3 of Ghosh and Sen (1971), it follows that

$$|U_n^{(1)}(\beta_S^*) + (\hat{\hat{\beta}}_S^*-\beta_S^*)[nk(k^2-1)]^{\frac{1}{2}}(\int_{-\infty}^{\infty} g^2(e)de)| \xrightarrow{P} 0, \tag{5.8}$$

$$|U_n^{(2)}(\beta_T^*) + (\hat{\hat{\beta}}_T^*-\beta_T^*)[nk(k^2-1)]^{\frac{1}{2}}(\int_{-\infty}^{\infty} g^2(e)de)| \xrightarrow{P} 0. \tag{5.9}$$

Also, by the same method of proof as in Theorem 3.3 of Ghosh and Sen (1971), it follows that for every fixed $I = \{x: |x|<k<\infty\}$,

$$\sup_{a,b\in I}|N^{\frac{1}{2}}\{W_n^{(1)}(\alpha_S+N^{-\frac{1}{2}}a,\beta_S^*+N^{-\frac{1}{2}}b) - W_n^{(1)}(\alpha_S,\beta_S^*)\} + [a+b(k+1)/2k](\int_{-\infty}^{\infty} g^2(e)de)| \xrightarrow{P} 0, \tag{5.10}$$

$$\sup_{a,b\ I}\left|N^{\frac{1}{2}}\{W_n^{(2)}(\alpha_T+N^{-\frac{1}{2}}a,\beta_T^*+N^{-\frac{1}{2}}b)-W_n^{(2)}(\alpha_T,\beta_T^*)\}\right.$$

$$\left.+\ [a+b(k+1)/2k]\left(\int_{-\infty}^{\infty} g^2(e)de\right)\right| \overset{P}{\to} 0. \tag{5.11}$$

Defining the $\hat{V}^{(i)}_{\ell j,sr}$ as in (2.16), we let for each $i(=1,2)$,

$$\hat{\alpha}^{(i)} = \text{median}\{V^{(i)}_{\ell j,sr};\ 1\le j<\ell\le k,\ 1\le r,\ s\le n,\ 1\le j=\ell\le k,\ 1\le r\le s\le n\}, \tag{5.12}$$

So that, by definition,

$$W_n^{(1)}(\hat{\alpha}^{(1)},\hat{\hat{\beta}}_S^*) = o_p(N^{-\frac{1}{2}}) = W_n^{(2)}(\hat{\alpha}^{(2)},\hat{\hat{\beta}}_T). \tag{5.13}$$

Hence, by (5.5), (5.6), (5.10), (5.11), (5.12) and (5.13), it follows that

$$[N(N+1)]^{-1}\ \hat{T}_i = (\hat{\alpha}^{(i)}-\hat{\alpha})\left(\int_{-\infty}^{\infty} g^2(e)de\right) + o_p(N^{-\frac{1}{2}}),\ i=1,2; \tag{5.14}$$

$$N^{\frac{1}{2}}|\hat{\alpha} - \tfrac{1}{2}(\hat{\alpha}^{(1)} + \hat{\alpha}^{(2)})| \overset{P}{\to} 0. \tag{5.15}$$

Also, by (5.10), (5.11) and the same method of proof as in Theorem 6.1 of Sen [1968], it follows that

$$\mathcal{L}\left(\left(\int_{-\infty}^{\infty} g^2(e)de\right)\sqrt{6N(k-1)/(2k+1)}\ (\hat{\alpha}^{(1)}-\alpha_S)\right) \to \mathcal{N}(0,1), \tag{5.16}$$

$$\mathcal{L}\left(\left(\int_{-\infty}^{\infty} g^2(e)de\right)\sqrt{6N(k-1)/(2k+1)}\ (\hat{\alpha}^{(2)}-\alpha_T)\right) \to \mathcal{N}(0,1). \tag{5.17}$$

Hence, from (2.22), (5.14), (5.15), (5.16) and (5.17), we get that

$$Q_N \overset{P}{\sim} 6\left(\int_{-\infty}^{\infty} g^2(e)de\right)^2\{(\hat{\alpha}^{(1)}-\hat{\alpha})^2 + (\hat{\alpha}^{(2)}-\hat{\alpha})^2\}(k-1)/(2k+1)$$

$$\overset{P}{\sim} 3\left(\int_{-\infty}^{\infty} g^2(e)de\right)^2(\hat{\alpha}^{(1)}-\hat{\alpha}^{(2)})^2(k-1)/2k+1) \qquad (5.18)$$

which has a non-central chi square with one degree of freedom and non-centrality parameter Δ_Q, defined by (5.2). Q.E.D.

THEOREM 5.2. Under $\{H_N\}$ in (5.1), the A.R.E. of Q_N with respect to t, in (2.8), is equal to $e_{Q,t}$, defined by (2.24).

Proof. Along the same line as in Sen and Puri (1970), it follows that S_e^2, defined by (2.9), converges in probability to $\sigma^2(G)$ as $nk\to\infty$. Also, $\bar{Y}^{(i)}$, $\tilde{\tilde{\beta}}_i$, i=1,2, being all linear in the $Y_{jr}^{(i)}$, are jointly asymptotically normally distributed whenever $\sigma^2(G)<\infty$. Hence, some routine computations yield that under $\{H_N\}$ in (5.1), t, defined by (2.8), is asymptotically normal with mean $\theta/[q_{n,k}\sqrt{N}\,\sigma(G)]$ and unit variance i.e., t^2 is asymptotically a non-central chi-square variable with one degree of freedom, and non-centrality parameter

$$\Delta_t = \lim_{N\to\infty} \theta^2/(Nq_{n,k}^2\sigma^2(G)) = \theta^2(k-1)/[4(2k+1)\sigma^2(G)]. \qquad (5.19)$$

Therefore the theorem follows from (5.2) and (5.19). Q.E.D.

Résumé

Dans un essai indirect de type pente-rapport les trois problèmes fondamentaux sont les suivants: (a) la détermination de la régression (rendue linéaire) dose-réponse. (b) le test de la validité de la supposition fondamentale que deux droites de régression dose-réponse aient la même

intercepte. (c) l'estimation de la puissance relative d'une préparation-épreuve quant à une préparation étendarde.

Le premier problème est le même que dans un essai desdroites parallèles, examiné en détail par Sen (1971). Pour (b) et (c) on considère ici quelques procédés robustes, simples et efficaces utilisant des statistiques de rang bein connues (e.g., la statistique de Wilcoxon en cas d'un ou deux échantillons, le coefficient tau de Kendall, etc.) Les propriétés diverses de ces méthodes sont étudiées et comparées avec celles des procédés paramétriques étendardes. La théorie est illustrée par des exemples nombreux.

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