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ON A CLASS OF DISTRIBUTION-FREE TESTS FOR GROWTH CURVES ANALYSES

It is noted that a class of distribution-free tests, based upon a family of multivariate rank statistics studied by Puri and Sen [30], may be used to compare the effects of experimental treatments on growth. An illustration of the proposed testing procedures is given.

1. Introduction. The analysis of growth and response curves is of continuing interest in the sciences, and has engendered an extensive assortment of appropriate statistical methodology. For example, Wishart [42] recommended that a general regression model be fitted to each curve and that the effects of the experimental treatments be evaluated by analyzing the coefficient sof the model. Box [4], recognizing that successive observations on each experimental unit may be correlated, proposed that simple univariate analysis of variance be instead applied to successive differences in growth values. Greenhouse and Geisser [17] noted that the tests for treatment effects from the univariate analysis of variance are appropriate only if the data conform to particular covariance structures, and suggested correction factors otherwise; their work has been extended by Huyhn and Feldt [20]. Parametric techniques of analysis based upon the univariate analysis of variance are summarized by Bliss [3] and Winer [41]. Elston and Grizzle [10] (see also [9]) described a method of obtaining confidence bands for estimated time-response curves, based on the mixed model of the analysis of variance. Church [8] presented a method whereby a principal component analysis is used to transform the growth curves into orthogonal components which thereupon may further be analyzed. Snee [38] synthesized the univariate analysis of variance and the principal component analysis approaches; he recommended that the model suggested by Mandel [27] for the analysis of two-way tables be adopted for the analysis of response curves. In an extension of this work, Snee et al. [39] recently proposed a group of parsimonious models for the analysis of animal growth curves.

Potthoff and Roy [29] generalized the usual multivariate analysis of variance (MANOVA) model by the introduction of a post-matrix in the expectation equation, and showed that, by means of this generalization, growth curves analyses could be performed with MANOVA techniques. This elegant approach was extended and improved in a series of papers by C. R. Rao [33]-[35] (see also [21]). The testing procedure advocated by Rao, based on notions of the multivariate analysis of covariance, was further developed by Grizzle and Allen [18]; in particular, their approach leads to methods of estimating parameters and performing tests that can easily be implemented with standard multivariate linear model programs. The generalized growth model introduced by Potthoff and Roy has also been studied from a Bayesian viewpoint by Geisser [14], [15] and by Fearn [11].

In certain experimental situations, however, it may be inadvisable or improper to model the growth data parametrically. For example, in a recent animal immunotherapy experiment (to be described in greater detail later), it was observed that tumor growth curves in a homogeneous population of mice subject to identical experimental conditions were vastly heterogeneous: tumor growth was roughly exponential in certain mice, whereas other mice exhibited tumor regressions which cannot be modeled exponentially. To deduce an "average" representation or parametric growth curve that would typify such heterogeneous responses would be highly misleading. Perforce one must therefore rely upon nonparametric or distribution-free procedures to analyze such data. A number of such techniques have recently been proposed for these analyses. For example, Zerbe [43], [44] has developed randomization tests for the comparison of growth curves with an assumed known parametric structure. Lehmacher and Wall [25] and Lehmacher [24] have introduced generalizations of the Friedman rank test for the comparison of samples of response curves. In this paper, it is noted that a class of distribution-free tests, based upon suitably defined multivariate rank statistics, may be used to compare the effects of experimental treatments on growth. This class of distribution-free tests devolves from the basic rank permutation principle introduced by Chatterjee and Sen [5], [6] and further developed by Puri and Sen [30]-[32] (see also Ghosh et al. [16] and Bhapkar and Patterson [2]). The multivariate rank statistics, and attendant distribution theory, are described in Section 2, and testing procedures are discussed in Section 3. The procedures are then illustrated in Section 4 with data from the animal immunotherapy experiment mentioned previously. Certain concluding remarks are given in Section 5.

2. Distribution theory. Let

$$X_j^{(k)} = (X_{1j}^{(k)}, X_{2j}^{(k)}, \ldots, X_{pj}^{(k)})', \quad 1 \leqslant j \leqslant n_k,$$

be independent random p-vectors from population Π_k with continuous cumulative distribution function F_k for $k = 1, 2, \ldots, c$. It is desired to test the null hypothesis

$$H_0: F_1 = F_2 = \ldots = F_c \equiv F, \tag{1}$$

where F is an arbitrary element in $\mathcal{F}$, the set of all continuous p-variate distributions, against the alternative that at least one inequality among the F_k obtains.

A distribution-free method of testing this hypothesis, the test based on a suitably defined multivariate rank statistic, may be devised upon using the basic rank permutation principle introduced by Chatterjee and Sen [5], [6], and discussed in detail by them (see also [30]). Under this principle, all permutations of the $N = \sum_{k=1}^{c} n_k$ vectors of observations are equally likely under the null hypothesis. Let P_N denote the permutation probability measure generated by the $N!/\Pi n_k!$ possible distinct permutations of the observed data vectors among the c groups. In this section, distribution theory for a particular multivariate rank statistic will be described; this theory devolves from the completely specified permutational probability law P_N. Appropriate test functions for (1) are discussed in the subsequent section.

Corresponding to $X_j^{(k)}$, let $R_j^{(k)} = (R_{1j}^{(k)}, R_{2j}^{(k)}, \ldots, R_{pj}^{(k)})'$, $1 \leqslant j \leqslant n_k$, $1 \leqslant k \leqslant c$, denote the vector of ranks: $R_{ij}^{(k)}$ is the rank of $X_{ij}^{(k)}$ among all N observed values for the i-th coordinate. Let

$$S_i^{(k)} = n_k^{-1} \sum_{j=1}^{n_k} a_i(R_{ij}^{(k)}),$$

where the a_i $(i = 1, 2, \ldots, p)$ are univariate score functions related to generating functions φ_i on $[0, 1]$ by either

$$a_i(j) = \varphi_i\big(j/(N+1)\big)$$

or

$$a_i(j) = \mathrm{E}\varphi_i(U_j^{(i)}), \quad j = 1, 2, \ldots, N. \tag{2}$$

In (2), for each i, $U_1^{(i)} < \ldots < U_N^{(i)}$ denote the order statistics in a sample of size N from the uniform distribution on $[0, 1]$. Without loss of generality, it is assumed that the score functions a_i are chosen to satisfy

$$\bar{a}_i = N^{-1} \sum_{j=1}^{N} a_i(j) = 0,$$

so that

$$\bar{\varphi}_i = \int_0^1 \varphi_i(x)\,dx = 0;$$

it is furthermore assumed that each φ_i can be expressed as the difference of two nondecreasing, absolutely continuous, square integrable functions on $[0,1]$.

From the rank permutational principle, the conditional moments of the $S_i^{(k)}$ may be readily found. Puri and Sen [30], for example, show that

$$\mathrm{E}[S_i^{(k)}|P_N] = 0$$

and

$$\mathrm{cov}[S_i^{(k)}, S_j^{(m)}|P_N] = (\delta_{km}N - n_k)v_{ij,N}/n_k(N-1),$$

where δ_{km} is the Kronecker delta, and $v_{ij,N}$, the (i,j)-th element of the $p \times p$ covariance matrix V_N, is given by

$$v_{ij,N} = N^{-1}\sum_{k=1}^{c}\sum_{m=1}^{n_k} a_i(R_{im}^{(k)})a_j(R_{jm}^{(k)}). \tag{3}$$

As will be noted in the next section, a suitable test of the null hypothesis (1) may be based on the permutation distribution of the $S_i^{(k)}$. Nevertheless, it is of interest to determine the asymptotic distribution of the $S_i^{(k)}$ because the permutation test may become unwieldy with increasing sample size. However, in order to derive this joint conditional asymptotic distribution, some additional structure must be imposed on F. If H_0 obtains for some $F \in \mathscr{F}$, then, marginally,

$$v_{ii,N} = N^{-1}\sum_{k=1}^{c}\sum_{m=1}^{n_k} a_i(R_{im}^{(k)})^2 \to \int_0^1 \varphi_i^2(t)\,dt, \quad i = 1,2,\ldots,p, \tag{4}$$

and, jointly,

$$v_{ii',N} = N^{-1}\sum_{k=1}^{c}\sum_{m=1}^{n_k} a_i(R_{im}^{(k)})a_{i'}(R_{jm}^{(k)}) \tag{5}$$

$$\to \int\int \varphi_i[F_{[i]}(u)]\varphi_{i'}[F_{[i']}(v)]\,dF_{[i,i']}(u,v), \quad 1 \leqslant i < i' \leqslant p,$$

where $F_{[i]}$ denotes the i-th marginal distribution of F, and $F_{[i,i']}$ denotes the joint distribution of the i-th and i'-th coordinates. The convergence in probability of (4) is a well-known univariate result (cf. [19], p. 161), and that of (5) follows as in Theorem 4.2 of [30] (see also Theorem 3.1 of [31]). It should be noted that the joint distribution of the $S_i^{(k)}$ is degenerate because for fixed i we have

$$\sum_{k=1}^{c} n_k S_i^{(k)} \equiv 0.$$

This leads in general to consideration solely of $\{S_i^{(k)}: i = 1,2,\ldots,p,\ k = 1,2,\ldots,c-1\}$. So as to preclude degeneracy with this restricted set of random variables, assume under H_0 that $F \in \mathscr{F}_0 \subset \mathscr{F}$, where $\mathscr{F}_0$ is the

set of continuous p-variate distributions such that the $p \times p$ covariance matrix $V = (v_{ij})$, where v_{ij} is obtained by substituting the limiting values (4) and (5) for $v_{ij,N}$, is nonsingular. Then we have the following theorem, proved by Chatterjee and Sen.

THEOREM 1. *Under the assumptions stipulated previously, the joint permutation distribution of the* $p(c-1)$ *random variables* $\{S_i^{(k)}, i = 1, 2, \ldots, p, k = 1, 2, \ldots, c-1\}$ *is asymptotically, as* $N \to \infty$, $n_k/N \to \lambda_k$, $0 < \lambda_k < 1$, *a* $p(c-1)$*-variate normal distribution.*

It follows as an immediate corollary that *the asymptotic unconditional null distribution of the* $\{S_i^{(k)}\}$ *is also* $p(c-1)$*-variate normal.*

Suppose now that $\{F_{1N}, F_{2N}, \ldots, F_{cN}\}$ is a sequence of distributions contiguous to some $F \in \mathcal{F}_0$ in the sense of Hájek and Šidák ([19], p. 202). Here, F_{kN} denotes the underlying distribution of the n_k observations drawn from the population Π_k $(k = 1, 2, \ldots, c)$. Let

$$H_N(x) = N^{-1} \sum_{k=1}^{c} n_k F_{kN}(x).$$

The following theorem is useful for the power considerations of Section 3:

THEOREM 2. *With the assumptions of Theorem* 1, *under the sequence of alternatives* $H_{1N}: \{F_{1N}, F_{2N}, \ldots, F_{cN}\}$, *the joint asymptotic distribution of the* $\{S_i^{(k)}, i = 1, 2, \ldots, p, k = 1, 2, \ldots, c-1\}$ *is* $p(c-1)$*-variate normal, with the same covariance structure as under* H_0, *but with limiting means*

$$\mathrm{E}[S_i^{(k)}] = \mu_i^{(k)} = \lim_{N \to \infty} \int \varphi_i\big(H_{[i]}(x)\big) dF_{[i]}(x),$$

where $H_{[i]}$ *and* $F_{[i]}$ *are the* i*-th marginal distributions of* H_N *and* F_{kN}, *respectively.*

Theorem 2 may be proved as in [30]. Alternatively, a more direct proof may be provided upon exploiting the properties of contiguity, as in [28].

The limiting distribution of the $\{S_i^{(k)}\}$ under general alternatives may also be found, e.g., by using results of Puri and Sen [31] or Koziol [22], [23]. Indeed, the corollary to Theorem 1 establishing the unconditional limiting null distribution of the $\{S_i^{(k)}\}$, as well as Theorem 2, could instead be established as special cases of the limiting distribution under general alternatives. In this regard, the interested reader is referred to the aforementioned papers for further details.

3. Test statistics based on $\{S_i^{(k)}\}$. Under the null hypothesis, each of the $S_i^{(k)}$ should be close to zero, their null expected value. Chatterjee and Sen [5], [6] argue that, for general alternatives, a test statistic that reflects the numerical largeness of any of the $S_i^{(k)}$ would therefore be desirable. Accordingly, they propose that a positive definite quadratic form

in these values be formulated. Puri and Sen [30]-[32] note that, after some algebraic simplification, the overall quadratic form in the $p(c-1)$ linearly independent $S_i^{(k)}$ may be written as

$$L_N = \sum_{k=1}^{c} n_k [S^{(k)}]' V_N^{-1} [S^{(k)}], \tag{6}$$

where $S^{(k)} = (S_1^{(k)}, S_2^{(k)}, \ldots, S_p^{(k)})'$, and the elements of V_N are given in (3). Under P_N, the permutation distribution of L_N is strictly distribution-free whenever H_0 obtains; hence an exact size α test can be constructed upon reference to all $N!/\Pi n_k!$ possible permuted values of L_N. Chatterjee and Sen [5], [6] give specific details concerning median and rank-sum tests based on this premise. By Theorem 1, the permutation test procedure based on L_N is simplified in large samples: one either rejects or fails to reject H_0 as $L_N \geqslant$ or $< X^2_{\alpha,p(c-1)}$, the $100(1-\alpha)\%$ point of the χ^2-distribution with $p(c-1)$ degrees of freedom.

A second class of test statistics is suggested from the theory of rank tests for randomized blocks (cf. [19] and [26]). Let

$$S_k = \sum_{i=1}^{p} S_i^{(k)}, \qquad k = 1, 2, \ldots, c.$$

Then the vector $S = (S_1, S_2, \ldots, S_{c-1})'$ has mean 0 and permutation covariance matrix

$$W_N = (N-1)^{-1} e' V_N e [(N/n_k)\, \delta_{kq} - 1]$$

under H_0, where $e' = (1, 1, \ldots, 1)$. A permutation test procedure may be based upon the quadratic form

$$M_N = S' W_N^{-1} S = (N-1)(e' V_N e)^{-1} S' \left[\frac{n_k}{N} \delta_{kq} + \frac{n_k n_q}{N n_c} \right] S \tag{7}$$

$$= \left(\frac{N-1}{N} \right) (e' V_N e)^{-1} \sum_{k=1}^{c} n_k S_k^2,$$

since

$$\sum_{k=1}^{c} n_k S_k = 0.$$

Under the permutation principle, suitably large values of M_N would lead to rejection of H_0. Moreover, by Theorem 1, M_N is asymptotically distributed as a χ^2 random variate with $c-1$ degrees of freedom under H_0, which affords an approximate α-level testing procedure with finite samples.

It is of interest to compare the testing procedures based on L_N and M_N. Suppose for concreteness that under $\{H_{1N}\}$, the sequence of local alternatives delineated in Theorem 2, we have

$$F_{kN}(x) = F(x+\theta^{(k)}N^{-1/2}),$$

where $F \in \mathscr{F}_0$ and $\theta^{(k)} = (\theta_1^{(k)}, \theta_2^{(k)}, \ldots, \theta_p^{(k)})'$. It follows from Theorem 2 that, under $\{H_{1N}\}$, L_N asymptotically has a noncentral χ^2-distribution with $p(c-1)$ degrees of freedom. Furthermore, Puri and Sen [30] prove that the noncentrality parameter Δ_L is given by

$$\Delta_L = \sum_{k=1}^{c} \lambda_k (\mu^{(k)})' V^{-1} (\mu^{(k)}),$$

where

$$\mu^{(k)} = (\mu_1^{(k)}, \mu_2^{(k)}, \ldots, \mu_p^{(k)})$$

with

$$\mu_i^{(k)} = \theta_i^{(k)} \int \frac{d}{dx} \varphi_i\big(F_{[i]}(x)\big)\, dF_{[i]}(x), \qquad i = 1, 2, \ldots, p.$$

Similarly, under $\{H_{1N}\}$, M_N is asymptotically noncentral χ^2 with $c-1$ degrees of freedom and noncentrality parameter

$$\Delta_M = (e'Ve)^{-1} \sum_{k=1}^{c} \lambda_k [e'\mu^{(k)}]^2.$$

Since L_N and M_N, indexed by unequal degrees of freedom, have different asymptotic distributions, specific comparisons in terms of Pitman efficiency are difficult. In terms of Bahadur efficiency, the statistic with the larger noncentrality parameter is to be preferred. In this regard, it is by no means certain that Δ_L dominates Δ_M. For example, suppose that F factors into the product of its identically distributed marginals, and that $\mu_i^{(k)} = \gamma_k$, say, for $k = 1, 2, \ldots, c$. Then

$$\Delta_L = \sum_{k=1}^{c} \lambda_k (p\gamma_k^2 / v_{11})$$

and

$$\Delta_M = (pv_{11})^{-1} \sum_{k=1}^{c} \lambda_k (p\gamma_k)^2 = \Delta_L.$$

In this situation, both statistics have the same noncentrality parameter, and hence are indistinguishable in terms of Bahadur efficiency. In actuality, nevertheless, M_N would be a more powerful test than L_N, because it has fewer degrees of freedom.

If information is available concerning the functional form of F, then the score functions φ_i may be chosen so as to optimize the power performances of L_N and M_N. Further details may be found in [30].

4. An example. A recent experiment by Schlager et al. [36] demonstrated that a combination of normal spleen cells, immune RNA, and tumor antigen, injected together five days subsequent to the inoculation of guinea pig hepatoma cells, induced total regression of the tumors. Investigators at the Cancer Center of the University of California at San Diego have conducted a series of experiments to ascertain whether a similar regimen of immunotherapy would prove efficacious with colon carcinomas. (Results and inferences from these experiments are reported in greater detail by Fukushima et al. [12], [13].) In these experiments, each of a homogeneous population of BALB/c mice was injected with a fixed number of CT-26 (mouse colon carcinoma) tumor cells. Five days later, the population was randomly divided into subgroups, and each group was then subjected to a different regimen of immunotherapy. The mice were then observed for some period, and the sizes of the tumors were systematically recorded. Upon analyses of the tumor growth curves from these experiments, it was concluded that the sequential administration of syngeneic spleen cells, anti-CT-26 immune RNA, and CT-26 tumor antigen significantly inhibited the growth of colon carcinoma in BALB/c mice.

A later experiment was designed to evaluate the specificity of the tumor growth inhibitory response observed in earlier experiments. In this study, tumor antigen extracted from BP/B5 tumor cells and immune RNA extracted from the lymphoid tissues of sheep immunized with BP/B5 were substituted for CT-26 tumor antigen and CT-26 immune RNA in various experimental groups. (BP/B5 is antigenically unrelated to CT-26.) In Fig. 1, median tumor sizes of the experimental groups, each consisting of 12 animals, versus time are plotted. There is some indication in Fig. 1 that the normal spleen cells + CT-26 I-RNA + CT-26 TA treatment group differs from the other experimental groups in terms of tumor growth. A distribution-free test of the null hypothesis of no difference in tumor growth rates among the five groups would be appropriate, because growth rates within any particular group may not be homogeneous if tumor regressions were to occur. Hence the statistics L_N and M_N in (6) and (7), respectively, may be calculated to test this null hypothesis.

With regard to computational aspects of the calculations, randomization was used to assign ranks to tied observations. As Hájek and Šidák ([19], Section III.8.1) note, this technique does not affect the significance levels of the resulting tests. For simplicity, the score functions $a_i(\cdot)$ were chosen as $a_i(j) = j - 61/2$ $(j = 1, 2, \ldots, 61,\ i = 1, 2, \ldots, 21)$ since data were collected on 21 different days. This choice of $a_i(\cdot)$ yields Wilcoxon

scores, and thereby a test statistic, that is the analogue of the Kruskal-Wallis and Friedman nonparametric statistics for one-way and two-way layouts, respectively. With these a_i, it was found that $L_N = 140.9$ ($p = .0001$) and $M_N = 38.2$ ($p < .0001$). By comparison, if normal scores are used for the $a_i(\cdot)$, then $L_N = 135.1$ ($p = .0004$) and $M_N = 38.2$ ($p < .0001$). When this analysis was repeated, excluding the normal

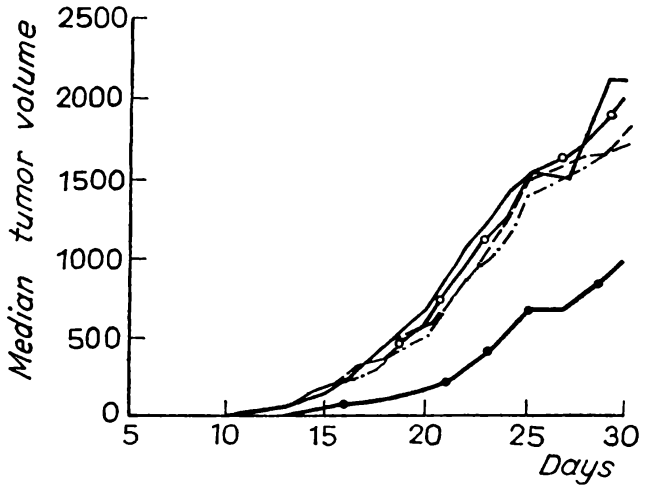

Fig. 1. Growth of CT-26 induced tumors in response to various therapeutic regimens
Tumor volumes (mm^3) represent medians of 12 animals

——— no treatment, – ● – spleen cells + αCT-26 I-RNA + CT-26 TA, –·– spleen cells + αBP/B5 I-RNA+BP/B5 TA, –○– spleen cells + αCT-26 I-RNA+BP/B5 TA, – – – spleen cells + αBP/B5 I-RNA+CT-26 TA

spleen cell + CT-26 I-RNA + CT-26 TA group from the calculations, both L_N and M_N failed to be significant. One might thereby conclude that the anti-tumor effect is specific in that both anti-CT-26 I-RNA and CT-26 TA are required in order to retard the growth rate of CT-26 tumor transplants; if I-RNA from the lymphoid organs of sheep immunized with the antigenically unrelated tumor BP/B5 was substituted for anti-CT-26 I-RNA or if TA extracted from BP/B5 cells was substituted for CT-26 TA, the anti-tumor effect against CT-26 transplants was abrogated.

5. Summary and concluding remarks. The basic multivariate rank invariance principle introduced by Chatterjee and Sen [5], [6] leads to a class of distribution-free tests that may be used to compare the effects of experimental treatments on growth. These tests were described in Section 3, and an illustration of their use was given in Section 4.

One might regard the test statistic L_N from (6) as an omnibus testing procedure in that L_N should be sensitive to any departures from the null hypothesis (1). If no prior information is available concerning the alternative of interest, L_N should be the appropriate statistic upon which inference is to be based. However, since there is no best test of (1), the very

omnibus nature of L_N also means that there exist other procedures for assessing (1) that will be more powerful than L_N against particular alternatives. For example, it was shown in Section 3 that the statistic M_N from (7) will be more powerful than L_N if there is a stochastic ordering of distributions under the alternative. This type of alternative seems quite reasonable in animal experiments in which treatment effects can essentially be summarized by growth curves. Indeed, in the example in Section 4, M_N was a more sensitive statistic than L_N to the departures from the null hypothesis evidenced in the data. The discussion by Terpstra [40] is of relevance here: if precise knowledge of the anticipated alternative is available, one could possibly define generalized versions of the statistic M_N from (7) by incorporating arbitrary weightings

$$\tilde{S}_k = \sum_{i=1}^{p} b_i^{(k)} S_i^{(k)},$$

where the weights $b_i^{(k)}$ might be chosen to optimize the power properties of the resultant test. Such weighted versions of M_N might also be appropriate for particular directional alternatives and for alternatives of location shift at some time point during the experiment. Barlow et al. [1] elegantly summarized multivariate approaches to the former problem, and Chernoff and Zacks [7] introduced a Bayesian approach to the latter problem which has since stimulated widespread interest (see, e.g., [37] for a multivariate generalization of the Chernoff-Zacks results). A second means of increasing the power of the generalized class of test statistics devolving from M_N is by appropriate choice of a score function. Inasmuch as the example in Section 4 indicates that the choice of a score function alters the resulting test statistics only very slightly, one might be content with Wilcoxon or normal scores, which are readily available and reflective of sensitivity to light to moderate tail behavior of the underlying distributions.

Finally, it should perhaps be noted that the nonparametric approaches for the comparison of growth curves proposed by Lehmacher and Wall [25] and Lehmacher [24], although superficially similar to the procedures described herein, differ fundamentally from them: Lehmacher and Wall consider the k-th sample of n_k growth curves as a design of n_k independent randomized blocks "treated" by p different points in time, whereas in this paper each set of observations at a fixed time point constitutes a "randomized block" with treatment classifications, but the blocks are not assumed to be independent. Accordingly, Lehmacher and Wall rank the coordinate values of each individual observation $X_j^{(k)}$ across the p time periods, this ranking proceeding independently for each of the observed vectors $X_j^{(k)}$. In contrast, herein the ranking encompasses all the individual (marginal)

observations at every time period, and the rankings at different time periods proceed independently of one another. As Lehmacher [24] points out, the test procedures advocated by himself and Wall are insensitive to alternatives in which there are either level or monotone increasing differences in growth patterns among the c treatment groups. In particular, their procedures would be rather insensitive to those alternatives for which the statistic M_N would perform well.

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References

[1] R. E. Barlow, D. J. Bartholomew, J. M. Bremner and H. D. Brunk, *Statistical inference under order restrictions*, J. Wiley, New York 1972.

[2] V. P. Bhapkar and K. W. Patterson, *On some nonparametric tests for profile analysis of several multivariate samples*, J. Multivariate Anal. 7 (1977), p. 265-277.

[3] C. L. Bliss, *Statistics in biology*, Vol. 2, McGraw-Hill, New York 1970.

[4] G. E. P. Box, *Problems in the analysis of growth and wear curves*, Biometrics 6 (1950), p. 362-389.

[5] S. K. Chatterjee and P. K. Sen, *Non-parametric tests for the bivariate two-sample location problem*, Calcutta Statist. Assoc. Bull. 13 (1964), p. 18-58.

[6] — *Nonparametric tests for the multisample multivariate location problem*, p. 197-228 in: R. C. Bose et al. (eds.), *Essays in probability and statistics in memory of S. N. Roy*, Univ. of North Carolina Press, Chapel Hill 1966.

[7] H. Chernoff and S. Zacks, *Estimating the current mean of a normal distribution which is subjected to changes in time*, Ann. Math. Statist. 35 (1964), p. 999-1018.

[8] A. Church, Jr., *Analysis of data when the response is a curve*, Technometrics 8 (1966), p. 229-246.

[9] R. C. Elston, *On estimating time-response curves*, Biometrics 20 (1964), p. 643-647.

[10] — and J. E. Grizzle, *Estimation of time-response curves and their confidence bands*, ibidem 18 (1962), p. 148-159.

[11] T. Fearn, *A Bayesian approach to growth curves*, Biometrika 62 (1975), p. 89-100.

[12] M. Fukushima, M. E. M. Colmerauer, S. K. Nayak, J. A. Koziol and Y. H. Pilch, *Immunotherapy of a murine colon cancer with syngeneic spleen cells, immune RNA and tumor antigen*, International Journal of Cancer 29 (1982), p. 107-112.

[13] — *Antitumor effect of syngeneic spleen cells treated with immune RNA and tumor antigen*, ibidem 29 (1982), p. 113-117.

[14] S. Geisser, *Bayesian analysis of growth curves*, Sankhyā, Ser. A, 32 (1970), p. 53-64.

[15] — *Growth curve analysis*, p. 89-115 in: P. R. Krishnaiah (ed.), *Handbook of statistics*, Vol. 1, North-Holland, Amsterdam 1980.

[16] M. Ghosh, J. E. Grizzle and P. K. Sen, *Nonparametric methods in longitudinal studies*, J. Amer. Statist. Assoc. 68 (1973), p. 29-36.

[17] S. W. Greenhouse and S. Geisser, *On methods in the analysis of profile data*, Psychometrika 24 (1959), p. 95-112.

[18] J. E. Grizzle and D. M. Allen, *Analysis of growth and dose response curves*, Biometrics 25 (1969), p. 357-381.

[19] J. Hájek and Z. Šidák, *Theory of rank tests*, Academic Press, New York 1967.

[20] H. Huyhn and L. S. Feldt, *Conditions under which m. s. ratios in repeated measurement designs have exact F distributions*, J. Amer. Statist. Assoc. 65 (1970), p. 1582-1589.

[21] C. G. Khatri, *A note on a MANOVA model applied to problems in growth curve*, Ann. Inst. Statist. Math. 18 (1966), p. 75-86.

[22] J. A. Koziol, *Multivariate rank statistics for shift alternatives*, Ph. D. dissertation, Dept. of Statistics, The University of Chicago, 1974.

[23] — *Asymptotic normality of multivariate linear rank statistics under general alternatives*, Appl. Math. 24 (1979), p. 326-347.

[24] W. Lehmacher, *A new nonparametric approach to the comparison of k independent samples of response curves, II. A k sample generalization of the Friedman test*, Biom. J. 21 (1979), p. 123-130.

[25] — and K. D. Wall, *A new nonparametric approach to the comparison of k independent samples of response curves*, ibidem 20 (1978), p. 261-273.

[26] E. L. Lehmann, *Nonparametrics: statistical methods based on ranks*, Holden-Day, San Francisco 1975.

[27] J. Mandel, *A new analysis of variance model for nonadditive data*, Technometrics 13 (1971), p. 1-18.

[28] K. M. Patel, *Hájek-Šidák approach to the asymptotic distribution of multivariate rank order statistics*, J. Multivariate Anal. 3 (1973), p. 57-70.

[29] R. F. Potthoff and S. N. Roy, *A generalized multivariate analysis of variance model useful especially for growth curve problems*, Biometrika 51 (1964), p. 313-326.

[30] M. L. Puri and P. K. Sen, *On a class of multivariate multisample rank-order tests*, Sankhyā, Ser. A, 28 (1966), p. 353-376.

[31] — *A class of rank order tests for a general linear hypothesis*, Ann. Math. Statist. 40 (1969), p. 1325-1343.

[32] — *Nonparametric methods in multivariate analysis*, J. Wiley, New York 1971.

[33] C. R. Rao, *The theory of least squares when the parameters are stochastic and its application to the analysis of growth curves*, Biometrika 52 (1965), p. 447-458.

[34] — *Covariance adjustment and related problems in multivariate analysis*, in: P. R. Krishnaiah (ed.), *Multivariate analysis*, Vol. 1, Academic Press, New York 1966.

[35] — *Least square theory using an estimated dispersion matrix and its application to measurement of signals*, p. 353-372 in: Proc. Fifth Berkeley Symp. Math. Statist. Prob., Vol. 1, Univ. of California Press, Berkeley 1967.

[36] S. I. Schlager, R. E. Paque and S. Dray, *Complete and apparently specific local tumor regression using syngeneic or xenogeneic "tumor-immune" RNA extracts*, Cancer Research 35 (1975), p. 1907-1914.

[37] A. K. Sen and M. S. Srivastava, *On multivariate tests for detecting changes in mean*, Sankhyā, Ser. A, 35 (1973), p. 173-186.

[38] R. D. Snee, *On the analysis of response curve data*, Technometrics 14 (1972), p. 47-62.

[39] — R. D. Acuff and J. R. Gibson, *A useful method for the analysis of growth studies*, Biometrics 35 (1979), p. 835-848.

[40] T. J. Terpstra, *Asymptotic power and efficiency of a class of k-sample rank tests against trend and the determination of optimal tests*, Memorandum 135, Dept. of Applied Mathematics, Twente Univ. of Technology, Enschede, The Netherlands, 1976.

[41] B. J. Winer, *Statistical principles in experimental design*, 2nd ed., McGraw-Hill, New York 1971.

[42] J. Wishart, *Growth-rate determinations in nutrition studies with the bacon pig and their analysis*, Biometrika 30 (1938), p. 16-28.

[43] G. O. Zerbe, *Randomization analysis of randomized blocks extended to growth and response curves*, Comm. Statist. Theory Methods, Ser. A, 8 (1979), p. 191-205.

[44] — *Randomization analysis of the completely randomized design extended to growth and response curves*, J. Amer. Statist. Assoc. 74 (1979), p. 215-221.

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