Specific Non-parametric Approaches to Analyzing Caries Clinical Trials

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Introduction.

On occasion, a reviewer will point out that the DMF scores used to assess caries activity are not normally distributed. The usual analyses are therefore not valid. The frequently used normal curve test, the *t* test, analysis of variance, and analysis of covariance assume that the study variable follows a normal distribution. Tests of hypotheses and estimation procedures usually pertain to the mean, one of the parameters of the distribution of the response variable. The procedures use the sample mean and variance as estimates of the parameters and are called parametric procedures. Some of these parametric methods require additional assumptions about the data. The *t* test and analysis of variance assume that the standard deviation of the response variable is not affected by treatment. However, if the development of new caries is inhibited by a cariostatic agent, the range of the DMFS and its standard deviation are also reduced. In covariance analysis, we assume that the relationship between a covariate and the response variable is linear. A change of one unit in, say, the initial DMFS is expected to cause the same change in the DMFS increment, whatever the initial score is. The difference in caries increment between two children with zero and two initial DMF surfaces should thus be the same as the difference between two children with initial scores of 14 and 16. This may be an unrealistic premise. The covariance analysis also assumes parallelism. This means that the difference in caries increment between two children with an initial difference of two DMF surfaces will be the same for treated and untreated children. An effective caries prevention protocol may not eliminate new caries completely, but it may retard the process. This can result in a decrease of the regression slope, which predicts the caries increment as a function of the initial DMF surfaces.

The parametric procedures are "robust". They are not substantially affected if the assumptions are not exactly satisfied. Several investigators have studied how much the data may differ from the postulated criteria before the parametric tests become invalid, and also what effect the violations have on the significance level and the discriminating power of the procedures.[1]

Another argument in favor of the continued use of the parametric tests is the central limit theorem. The theorem states that the sum of independent chance variables will tend to a normal distribution if they satisfy some general regularity conditions, such as having a finite variance.[2] A corollary is that the mean of n independent observations, from some reference distribution with mean μ and standard deviation σ, will tend to a normal distribution with mean μ and standard deviation $\sigma/\sqrt{n}$.

The initial DMFS distribution of the 598 children who participated in a study reported by Dr. Albert Kingman will be used to illustrate this tendency.[3] One thousand (1000) samples of sizes five and 20, respectively, have been drawn without replacement from the 598 children. The mean is computed for each sample. Fig. 1 shows the percentage distribution of the baseline DMFS, and of the 1000 means of five and 20 observations drawn from it. The initial DMFS is not normally distributed. The distribution seems to be made up of a number of distinct sub-populations. The 598 children represent only one sample from a conceptually infinite number of samples which can be selected from the target population represented by these children. A mean of 598 values will tend to normality more quickly than a mean based on five or 20 values. This is one of the reasons for using the parametric procedures to evaluate caries clinical trials. Such trials usually have at least 100 children in each study cohort.

The DMFS increment is generally used as the response variable. It is the difference between two DMF scores. The increment is less skewed than the baseline and final DMF surfaces. The percentage distribution of the net DMFS increment of the 598 children is shown in Fig. 2. The histograms of 1000 means of sizes 5 and 20, randomly drawn from this distribution, are also shown.

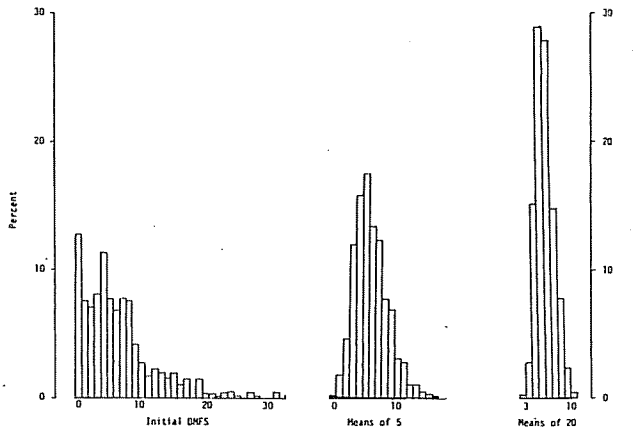

Fig. 1 – Percentage distribution of initial DMFS and of 1000 means of sizes 5 and 20.

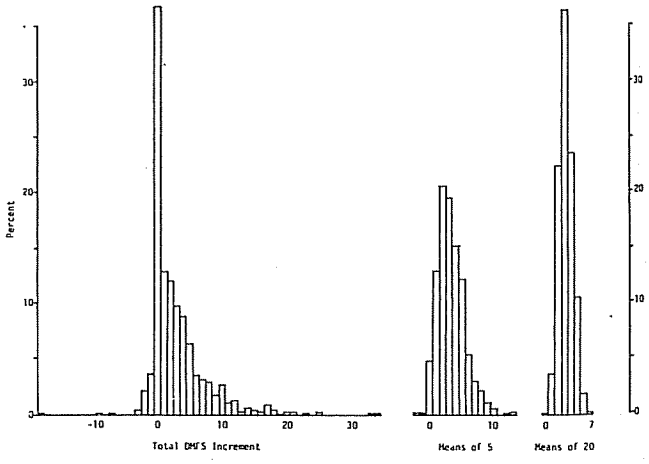

Fig. 2 – Percentage distribution of DMFS increment and of 1000 means of sizes 5 and 20.

When the violations of the various assumptions are deemed to be serious, and especially when the samples are small, a non-parametric or distribution-free method should be employed – two methods which will be demonstrated here, based on a ranking of the responses from low to high. The rank order is used instead of the actual measurement. The advantages of the non-parametric tests are that:

(1) there are fewer and weaker assumptions about the underlying distribution of the response variable,
(2) they are easier to compute, especially for small samples,
(3) the ranks used in many of these procedures are not affected by outliers,
(4) the results are often easier to interpret, and
(5) only slight loss of efficiency occurs when they are used instead of the appropriate parametric test.

One disadvantage is the loss of efficiency if a non-parametric test is used in a situation where a parametric test is valid. The ranking procedures trim the effect of outliers and exaggerate the importance of clusters, by assigning each a different rank. This may be exactly what is desired, but the distortion introduced by the ranking may obscure a mix of distinct subpopulations.

If the response variable is continuous, there should be no tied (equal) observations. Caries data, however, are counts of surfaces or teeth and are thus discrete. Many observations have the same value . These observations must be assigned the average rank of the group of tied values. This requires some extra computation. The ranking of a large number of data becomes a difficult task without the aid of a computer, especially if there are ties. Every wrong rank affects all the higher ranks, and it is easy to miss a value while ranking.

The fluoride rinse trial reported by Dr. Kingman will be used to illustrate some of the distribution-free methods. The total DMFS, which includes caries of teeth erupted during the study period, will be treated as a response variable. There are three study groups: a placebo group, a weekly fluoride rinse group, and a daily fluoride rinse group. The children are subdivided into four risk groups, using the Modified Grainger Severity Index (MGSI).[4] The DMFS increments are listed in Table 1 by treatment group and risk category.

TABLE 1
TOTAL DMFS INCREMENT IN THREE TREATMENT GROUPS BY RISK CATEGORY (MGSI SCORE)

DMFS	Placebo MGSI				Weekly rinse MGSI				Daily Rinse MGSI				
Incr.	1	2	3	4	1	2	3	4	1	2	3	4	Total
−18												1	1
−9							1						1
−7			1										1
−3							1				2		3
−2		4		1		3				1			9
−1		3	2			8	2			4	3		22
0	12	13	4	1	14	22	5	1	15	20	7	2	116
1	5	17	1	1	7	10	8	1	5	14	7	2	78
2	1	11	3		1	20	6	1	4	20	5	1	73
3	2	17	6	1		7	5	3		11	6	1	59
4	1	11	5	2	3	11	2	3		8	5	2	53
5	1	5	3	1		5	5	2	1	9	5	2	39
6	1	6	4	2	1	3	6	1		2	2	1	29
7	1	1	3	1		2	4	3	1	2	3		21
8		4	7	3						3	1	1	19
9		4	1			3		2			1		11
10		2	5	1		3	1			2		3	17
11			1	3			1			1	1		7
12		1	1	2			2				1	1	8
13								1				1	2
14	1			1		1						1	4
15		1				1					1		3
16		1					1	1					3
17			1			1		2		1		1	6
18		1	1			1							3
19											1		1
20			1				1						2
21				2									2
23				1									1
25			1	1									2
33		1											1
35				1									1
Total	25	103	51	25	26	101	51	21	26	98	51	20	598

Wilcoxon Rank Sum Test for Two Independent Samples.

We first consider the comparison of the caries experience in children receiving the placebo (treatment 1) and children who rinsed weekly (treatment 2), and who are in the first MGSI category. These children have no initial DMF. There are 25 such children in treatment group 1 and 26 in treatment group 2. Their 51 DMFS values must be ranked from lowest to highest. The lowest value is 0. Twenty-six children have this value, 12 in group 1 and 14 in group 2. These 26 DMFS values are assigned the average rank, which is (26 X 27) / (2 X 26), or 13.5. There are 12 children with a DMFS increase of one surface. Each is assigned a rank of 26 + (12 X 13) / (2 X 13) or 32.5, etc. The ranking is shown in Table 2. The sum of the ranks, R, for the 25 children in the placebo group is 688. The average rank is (51 X 52) / (2 X 51), or 26. The expected sum of 25 randomly selected integers, from the sequence 1 through 51, is thus 25 X 26, or 650. This is smaller than the observed rank sum of 688.

The sum of squared deviations from the mean for the integers 1,2,3,..n is:

TABLE 2
WILCOXON TWO-SAMPLE COMPARISON OF PLACEBO AND WEEKLY FLUORIDE RINSE GROUPS (LOWEST MGSI LEVEL)

DMFS Increment	Placebo	Weekly Rinse	Total	Cumulative Sum	Rank
0	12	14	26	26	13.5
1	5	7	12	38	32.5
2	1	1	2	40	39.5
3	2	–	2	42	41.5
4	1	3	4	46	44.5
5	1	–	1	47	47.0
6	1	1	2	49	48.5
7	1	–	1	50	50.0
14	1	–	1	51	51.0
Total	25	26	51		
Rank sum:	668	638	1326		
Expected sum:	650				

Sum of squared deviation SS = 11,050, not corrected for ties; SS = 9438, corrected for ties.
$V(r) = 188.76$, $V(R_1) = 2405.76$, and $S(R_1) = 49.05$.

Wilcoxon test: $\frac{688 - 650}{49.05} = 0.77$.

$$SS = n(n^2 - 1) / 12$$

and the variance of a particular ranked value, r, is:

$$V(r) = SS / (n - 1) = n(n + 1) / 12.$$

The variance of the rank sum, R_i, of a random sample of n_i values selected from the n integers (ranked observations without ties) is:

$$V(R_i) = n_i\, V(r)\, fpc,$$

where fpc is the finite population correction term. The fpc is:

$$fpc = \frac{n - n_i}{n}$$

and the variance of the rank sum becomes:

$$V(R_i) = \frac{n_i\, SS\, (n - n_i)}{12\,(n - 1)\, n} = \frac{n_i\,(n - n_i)\,(n + 1)}{12}$$

When observations are equal, their ranks will also be equal. The sum of squares, SS, the variance of a rank V(r), and the variance of the rank sum, V(R), are all smaller than when there are no ties. The sum of squared deviations from the mean, when there are ties, becomes:

$$SS = \Sigma (r - \bar{r})^2 = \frac{n(n^2 - 1) - \Sigma t_j (t_j^2 - 1)}{12},$$

where t_i corresponds to the size of the j-th set of tied ranks. If we let $t_j = 1$ for untied ranks, the computation of SS simplifies to:

$$SS = \frac{n^3 - \Sigma t^3}{12}.$$

The "Total" column of Table 2 provides the values of t_j for the computation of SS. Here SS, uncorrected for ties, is 11,050, and the correction for ties reduces it to 9438. We thus have:

$$V(R_1) = 2405.7647 \text{ and } S(R_1) = \sqrt{V(R_1)} = 49.05.$$

Using the normal curve approximation, we can test whether the observed rank sum of 688 is an unusual finding:

$$Z = \frac{R_1 - E(R_1)}{S(R_1)} \text{ or } \frac{38}{49.05} = 0.77.$$

Often a finite population correction is applied. The absolute difference between the observed and expected rank sum is reduced by 0.5. If we use the finite population correction, Z = 0.76. This test is known as the Wilcoxon rank sum test.[5] Mann and Whitney arrived at the same test, by considering the number of times that responses to treatment 1 precede responses to treatment 2. Their equivalent procedure is known as the Mann-Whitney U-test[6].

Extension of the Wilcoxon Rank Sum Test to more than one stratum.

A rank sum test can be carried out to evaluate the effect of the treatment in each of the four MGSI groups. The results, corrected for continuity, are shown in the next table for each of the k = 1,2,..4 strata.

MGSI category	$d_k = R_k - E(R_k)$	$V(R_k)$	Z	p
1	38.0	2,405.76	0.76	0.447
2	755.0	175,193.28	1.80	0.072
3	263.5	22,192.90	1.76	0.078
4	75.5	2,048.39	1.66	0.097

TABLE 3
COMPARISON OF THREE RINSING PROTOCOLS IN CHILDREN WITHOUT INITIAL DMFS

DMFS Increment	Placebo	Weekly Rinse	Daily Rinse	Total	Cumulative Sum	Rank
0	12	14	15	41	41	21.0
1	5	7	5	17	58	50.0
2	1	1	4	6	64	61.5
3	2	–	–	2	66	65.5
4	1	3	–	4	70	68.5
5	1	–	1	2	72	71.5
6	1	1	–	2	74	73.5
7	1	–	1	2	76	75.5
14	1	–	–	1	77	77.0
Total	25	26	26	77		
Rank sum	1060.5	984.5	958.	3003.0		
Exp. sum	975.0	1014.0	1014.0			

Sum of squared deviations SS = 31,865.5
V(r) = 419.2829.

$$\text{Kruskal-Wallis test statistic } H = \frac{\text{Between groups SS}}{\text{Total MS}}$$

$$= \frac{446.4965}{419.2829} = 1.06$$

The rank sum in each of the four risk groups is larger than expected. However, none of the differences is significant at the 5% level. The evidence can be pooled, keeping the stratification intact, by accumulating the rank differences and their variances:

$$D = \Sigma d_k, \text{ with } V(D) = \Sigma V(d_k).$$

Here, D = 1131.5 and V(D) = 201840.33. The normal deviate is Z = 1131.5 / 449.27, or 2.52 (p = 0.012). This indicates that the weekly rinsing with fluoride has significantly reduced the number of new caries surfaces.

At present, there is no valid test for interaction. The pooling over strata assumes that the treatment effect does not vary from stratum to stratum.

Kruskal-Wallis Test for one stratum.

The observations in the three treatment groups can be pooled and ranked. Table 3 demonstrates the computation of the three rank sums for children in the first risk group. The Kruskal-Wallis test is based on the squared deviations of the observed rank sums from their respective expected values.[7] It is a test of the hypothesis that all the study populations have the same location parameter. The test can be expressed in many forms. If there are no ties, the formula is a simple expression. The formula found in most texts is:

$$H = \Sigma n_i\, (\bar{r}_i - \bar{r})^2 \left[\frac{n(n + 1)}{12}\right]^{-1},$$

where n is the sample size of the i-th treatment group, $\bar{r}_i$ corresponds to the average rank in the i-th treatment group, and $\bar{r}$ equals the average rank: (n + 1) / 2. To correct for ties, H is divided by a correction factor

$$C = \frac{n(n^2 - 1) - \Sigma t_j (t_j^2 - 1)}{n(n^2 - 1)},$$

where t is the size of the j-th set of tied ranks. Another formulation of the Kruskal-Wallis test as the ratio of the

"sum of squares between treatments" and the "total mean square". The numerator of the ratio is the same as the first term in the formula for H above. The total mean square corresponds to V(r), which is SS / (n − 1). The denominator is thus corrected for ties. The test statistic approximately follows a chi-squared distribution with I − 1 degrees of freedom, where I equals the number of treatment groups.

Table 3 illustrates the computation of the test statistic for children who did not have any baseline caries (MGSI group 1). The results for the four MGSI groups are shown in the following table:

MGSI group	K − W Chi-square	p-value
1	1.06	0.589
2	3.80	0.150
3	10.45	0.005
4	4.09	0.127

Combining the Kruskal-Wallis test over strata.

In order to extend the Kruskal-Wallis test to two or more strata, it is convenient to discuss first the Wilcoxon test for one stratum. The two rank sums, R_1 and R_2, corresponding to the two independent treatment groups, are not independent. The rank sums add up to the sum of ranks, namely, n (n + 1) / 2. Therefore, one needs only to evaluate one of the two rank sums. The normal curve approximation expresses the observed difference of the rank sum from the expected value in terms of its standard deviation. In the one-way layout with I > 2 treatments, the I rank sums also add up to the sum of n integers. We need only to consider I − 1 of the sums. Any of the I rank sums can be selected for deletion. The variance of a rank sum, R_i, is:

$$V(R_i) = S^2 n_i \left(1 - \frac{n_i}{n}\right),$$

and the covariance between two rank sums, R_i and R_i', is:

$$\mathrm{Cov}(R_i, R_i') = -\frac{n_i\, n_i'\, S^2}{n},$$

where S^2 = SS / (n − 1).

Let $\underline{V}$ denote the variance-covariance matrix of the I-1 rank sums, and $\underline{V}^{-1}$ its inverse. If we call the vector of I − 1 differences between the observed and expected rank sums $\underline{D}$, the Kruskal-Wallis test can be written as:

$$H = \underline{D}^T (\underline{V}^{-1})\, \underline{D},$$

where $\underline{D}^T$ is the transpose of vector $\underline{D}$.

For the Wilcoxon test, this becomes:

$$(R_1 - E(R_1))\, V(R_1)^{-1}\, (R_1 - E(R_1)).$$

This is the square of the normal curve test shown earlier. It approximately follows a one-degree chi-squared distribution under the null hypothesis. When there are three treatments, we need to examine only two sums. The matrices are two-dimensional, and the computation is relatively simple. If we use the first two of the three rank sums, we have to compute:

$$V(R_1) = S^2 n_1 \left(1 - \frac{n_1}{n}\right) = A$$

$$V(R_2) = S^2 n_2 \left(1 - \frac{n_2}{n}\right) = B$$

$$\mathrm{Cov}(R_1, R_2) = -S^2 \frac{n_1\, n_2}{n} = C.$$

TABLE 4
ALTERNATIVE COMPUTATION OF KRUSKAL-WALLIS TEST

A: One stratum

The variance-covariance matrix of the rank sums for treatments 1 and 2 in the first MGSI category is:

$$\underline{V} = \begin{pmatrix} 7078.8022 & -3539.4011 \\ -3539.4011 & 7220.3783 \end{pmatrix}$$

$$\underline{V}^{-1} = \begin{pmatrix} v^{11} = 0.00018713 & v^{12} = 0.00009173 \\ v^{21} = 0.00009173 & v^{22} = 0.00018346 \end{pmatrix}$$

$$\underline{D} = \begin{pmatrix} d_1 = 85.5 \\ d_2 = -29.5 \end{pmatrix}$$

$H = 85.5^2 \times 0.00018713 + -29.5^2 \times 0.00018346 + 2 \times 85.5 \times -29.5 \times 0.00009173 = 1.06$, with two degrees of freedom.

B: Two or more strata

$$\Sigma\underline{V} = \begin{pmatrix} 588179.7679 & -297996.7018 \\ -297996.7018 & 583008.2868 \end{pmatrix}$$

$$(\Sigma\underline{V})^{-1} = \begin{pmatrix} 0.0000022943 & 0.0000011727 \\ 0.0000011727 & 0.0000023147 \end{pmatrix}$$

$$\Sigma\underline{D} = \begin{pmatrix} 2412.5 \\ -1323.5 \end{pmatrix}$$

H = 9.92, with two degrees of freedom.

The determinant of the matrix, which we need to compute the inverse of the matrix $\underline{V}$, is Q = A X B − C^2. The elements of the inverse matrix are:

$$v^{11} = B/Q$$
$$v^{22} = A/Q$$
$$v^{12} = -C/Q.$$

Let $d_1 = R_1 - E(R_1)$ and $d_2 = R_2 - E(R_2)$, then the Kruskal-Wallis test can be computed as:

$$H = d_1^2 v^{11} + d_2^2 v^{22} + 2\, d_1 d_2 v^{12}.$$

To combine the results of the individual tests for various strata into an overall Kruskal-Wallis-type test, we recommended an overall test, based on the accumulated deviations, $\underline{D}$, and their variance-covariance matrices, $\underline{V}$[8]:

$$H = \Sigma\underline{D}^T\, (\Sigma\underline{V})^{-1}\, \Sigma\underline{D}.$$

The statistic should be referred to a chi-squared distribution with I − 1 degrees of freedom.

Table 4 illustrates the computation of H for the first MGSI group and the stratified Kruskal-Wallis test. The test statistic for the stratified data is 9.92 and leads to rejection of the hypothesis that the three rinses are equally effective in reducing new caries in schoolchildren.

Summary.

The usual parametric procedures are valid for the analysis of most caries clinical trials. If the sample sizes are small, non-parametric procedures should probably be used, such as the Wilcoxon two-sample test or the Kruskal-Wallis test. The Wilcoxon test can be expressed in terms of the difference between one of the rank sums and its expected value. This difference is evaluated in terms of its standard deviation. The Wilcoxon test is extended to produce an overall test, which takes the stratification into account. The procedure accumulates the differences between the rank sum of one of the two treatments and its expected value, and the corresponding variances.

The Kruskal-Wallis test can be expressed in an analysis-of-variance-like form. The test can also be expressed in terms of the differences between the observed and expected rank sums. To extend the test to two or more strata, we need the variance-covariance matrices of I − 1 of the rank sums.

There is presently no test available for interaction. The expected values of the rank sums depend on the sample sizes, and these differ from stratum to stratum. The use of weights, to produce a common expected value for each stratum, may provide a test of interaction. This needs further exploration.

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Specific Non-parametric Approaches to Analyzing Caries Clinical Trials: Discussion of Dr. Varma's Presentation

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Dr. Varma merits thanks for an effective discussion, with an interesting example, of the motivation for and application of non-parametric inference to dental clinical trial data. I will supplement his talk with remarks on three areas:

(i) assumptions underlying "standard" non-parametric analyses;
(ii) general approaches to non-parametric analysis of partial association; and
(iii) the meaning of interaction in non-parametric analysis of variance.

Dr. Varma has indicated that violations of the conventional assumptions of normality, equal variances, and, in the analysis of covariance, linearity suggest use of a non-parametric approach. One must take care to avoid that blurring of distinctions between various assumptions which leads to indiscriminate use of non-parametrics as a presumed cure-all for "ill-conditioned" data. Although much work has been done to develop tractable non-parametric procedures for more complex situations, the most desirable properties of the commonly employed methods, such as the Wilcoxon and Kruskal-Wallis tests, depend upon the assumption that all underlying distributions are simple *translations,* or *location shifts,* of a single parent. Equality of variance under the null hypothesis is implied by this assumption. Further, a symmetric parent distribution may be required if non-parametric inferences are desired about a mean. Examples 1-3 illustrate the need for equality of variance, common functional form, and symmetry of parent distribution if the Wilcoxon test is to give valid inferences about a contrast of means. Each of the situations described invalidates the equiprobable permutation model used to generate the usual null distribution of the Wilcoxon statistic.

Example 1. – Consider comparing two Gaussian (normal) distributions with substantially different variances. A Wilcoxon statistic generated by data from such populations will have a null distribution much more peaked about its mean than the usual tabulated referent, because the observations from the more variable group will almost always surround those from the less variable group. The actual level of the test will be well below the nominal level, and, when the true difference in means is small relative to the larger of the within-group standard deviations, the test may have a much lower power than a parametric test.

Example 2. – Consider comparing distributions of different functional forms – for example, a Gaussian with an exponential distribution. In such a situation, the Wilcoxon test is directed at the hypothesis $P(X > Y) = 1/2$, where X and Y are independent random observations from the respective distributions. This hypothesis is not, in general, equivalent to hypotheses equating location parameters of the two populations, *e.g.,* the hypotheses of equal means or of equal medians. When divided by both sample sizes, the Wilcoxon statistic yields an unbiased estimate of $P(X > Y)$. Thus, if Gaussian and exponential forms with identical first and second moments are compared using the Wilcoxon statistic, it may easily be shown that the test will have asymptotically a Type I error rate of 1.0 against the true hypothesis of equal means. Similarly, when Gaussian and exponential forms with identical medians and variances are compared, the Wilcoxon test will have asymptotically a Type I error rate of 1.0 against the hypothesis of equal medians.

Example 3. – Consider the distributions $A = f_{0,\,1/4}$ and $B = f_{1/2,\,3/4}$ from the two-parameter family