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Inference for the Location Shift in 3x3 Crossover Studies: the Median-Scaling Method

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ABSTRACT

In the case of non-normal study outcomes, a nonparametric approach may be used for the analysis. Willavize and Morgenthien proposed a nonparametric method to obtain point estimates and confidence intervals for the location shift between treatments in the specific context of a 3-treatment, 3-period, 6-sequence crossover design. This technique allows for the period effect by use of sequence stratification and median-scaling. The aim of this paper is to outline the rationale of the method and to present a SAS® macro to implement this approach based on the HL (Hodges-Lehmann) option of the NPAR1WAY procedure. Depending on the sample size, asymptotic or exact confidence limits can be calculated.

INTRODUCTION

In the case of severe departures from normality in the distribution of the data, the standard approaches based on parametric inference may be inappropriate. In order to deal with non-normal outcomes, several techniques, such as transformations and nonparametric methods, are available. In this paper, the nonparametric median-scaling (MS) method proposed by Willavize and Morgenthien in the context of 3x3 crossover design [1] will be presented. This approach was originally introduced for the analysis of t_{max} (time to maximum plasma concentration of a drug) in pharmacokinetic studies. It should be noted that in the new EMA Guideline on the Investigation of Bioequivalence [2] that went into effect on August 2010 a formal statistical evaluation of t_{max} is no longer requested. However, the applicability of the MS method is clearly not limited to this parameter. This approach requires all the six possible treatment sequences to be used, but allows for unequal allocations of subjects to sequences, tied observations and missing data. Point estimates and confidence intervals (asymptotic or exact) for the location shift between each pair of treatments can be readily obtained using this method.

2-TREATMENT, 2-PERIOD, 2-SEQUENCE CROSSOVER DESIGN

The MS method can be viewed as an extension of the proposal by Cornell [3] and Hauschke et al. [4] for a 2-treatment, 2-period, 2-sequence crossover design. It is therefore useful to examine its underlying rationale. The authors assume that an adequate model for the data is

$$x_{ijk} = \mu + \gamma_i + s_{ij} + \pi_k + \varphi_l + e_{ijk},$$

where μ is the general mean, γ_i is the fixed effect of the i-th sequence, s_{ij} is the random effect of the j-th subject within the i-th sequence, π_k is the fixed effect of the k-th period, φ_l is the fixed effect of the l-th treatment (l = R, T for reference and test treatment, respectively) and e_{ijk} reflects random within-subject error. The model assumes that there is no carry-over. Let x_{ij} denote the difference between periods 1 and 2 for the j-th subject in the i-th sequence, i.e. $x_{ij} = x_{ij1} - x_{ij2}$. From the above model it follows that for a subject in sequence TR (i = 1) and a subject in sequence RT (i = 2), respectively, x_{ij} can be expressed as:

$$x_{1j} = (\pi_1 - \pi_2) + \Delta + (e_{1j1} - e_{1j2})$$
$$x_{2j} = (\pi_1 - \pi_2) - \Delta + (e_{2j1} - e_{2j2}),$$

where $\Delta = \varphi_T - \varphi_R$ is the unknown shift in location due to the test treatment. Thus, when comparing the period differences of two subjects included in different sequence groups (TR vs. RT), we obtain $x_{1j} - x_{2j} = 2\Delta$ + error.
Based on this result, Cornell and Hauschke et al. propose to consider the two sequence groups as independent random samples and to apply parallel-group methods to the within-subject period differences, by calculating the Hodges-Lehmann point estimate and the Moses confidence limits [5,6] of 2Δ and dividing the values obtained by 2. This approach assumes distributions of the response identical in shape and only differing by a shift in location (Δ) under the different treatments. If the shift model is true, the Hodges-Lehmann estimate can be interpreted as the difference between the medians of the two distributions [7].

The inferential procedures used are associated with the Wilcoxon rank sum test, as the confidence interval for Δ is obtained through inversion of this specific hypothesis test. If the effect of period is considered negligible, similar procedures based on the Wilcoxon signed rank test may be preferred.

3-TREATMENT, 3-PERIOD, 6-SEQUENCE CROSSOVER DESIGN

We now consider a 3-treatment, 3-period crossover design where all the six possible treatment sequences are used. The same model above defined for the 2x2 design is assumed to hold. The starting point of the MS method is the sequence stratification, originally proposed by Senn [8]. In order to compare two treatments (say A and B), the six sequences are arranged in pairs, grouping together the sequences where A and B occur in the same periods (for example ABC and BAC). Each pair of sequences constitutes a stratum. The period differences can be expressed as follows.

- Stratum 1 (treatments administered in periods 1 and 2):
  - ABC: $x_{1j} = (\pi_1 - \pi_2) + \Delta + (e_{1j1} - e_{1j2})$;
  - BAC: $x_{2j} = (\pi_1 - \pi_2) - \Delta + (e_{2j1} - e_{2j2})$.
- Stratum 2 (treatments administered in periods 1 and 3):
  - ACB: $x_{3j} = (\pi_1 - \pi_3) + \Delta + (e_{3j1} - e_{3j3})$;
  - BCA: $x_{4j} = (\pi_1 - \pi_3) - \Delta + (e_{4j1} - e_{4j3})$.
- Stratum 3 (treatments administered in periods 2 and 3):
  - CAB: $x_{5j} = (\pi_2 - \pi_3) + \Delta + (e_{5j2} - e_{5j3})$;
  - CBA: $x_{6j} = (\pi_2 - \pi_3) - \Delta + (e_{6j2} - e_{6j3})$.

If the treatment C is ignored, each pair of sequence constitutes a standard AB/BA cross-over. However, the estimates of the treatment difference independently provided by the strata cannot be easily combined since they include different period effects. This problem is solved by introducing the concept of median-scaling, suggested by Lehmann [9] and by Quade [10]. In each stratum the period differences are scaled by subtracting the median difference of the stratum:

$$z_{1j} = x_{1j} - m_1,\ z_{2j} = x_{2j} - m_1,$$
$$z_{3j} = x_{3j} - m_2,\ z_{4j} = x_{4j} - m_2,$$
$$z_{5j} = x_{5j} - m_3,\ z_{6j} = x_{6j} - m_3,$$

where m_p is the median period difference in the p-th stratum (p = 1, 2, 3). The median-scaled period differences are now comparable, allowing us to apply the same approach as in the 2x2 design. The roles of x_{1j} and x_{2j} in the 2x2 design are played by z_{1j}, z_{3j}, z_{5j} and z_{2j}, z_{4j}, z_{6j}, respectively. Therefore, the Hodges-Lehmann point estimate and the Moses confidence interval of 2Δ are obtained by considering z_{1j}, z_{3j}, z_{5j} and z_{2j}, z_{4j}, z_{6j} as two independent samples. The point estimate and the confidence limits should then be divided by 2.

The MS method allows for tied observations, unequal allocation of subjects to sequences and missing data. If for a subject the response is missing for at least one of the treatments involved in the comparison of interest, that subject is not taken into account in the analysis.

If the period effect is ignored, an approach based on the Wilcoxon signed rank test may be applied by considering the data for any two treatments being compared as if they were the only treatments which had been studied.

THE %MSCI MACRO

The %MSCI macro is designed to implement the MS method and allows the calculation of the point estimate and the confidence interval for the location shift between two treatments. In case of relatively small sample size, exact confidence limits can be generated in addition to asymptotic ones. The macro call allows the user to set up quickly the parameters needed for the calculation.

```
%MSCI(ds=,t1=,t2=,alpha=,exact=);
```

Macro %MSCI contains five parameters:

- ds: name of the dataset to be analysed. Each observation must correspond to a subject and the following four variables are required: “sequence”, “p1”, “p2”, “p3”. The treatment sequence has to be coded using the character strings “ABC”, “ACB”, “BAC”, etc. The variables “p1”, “p2” and “p3” correspond to the responses observed in the three treatment periods. For example:

	sequence	p1	p2	p3
1	CAB	3	1	2
2	CAB	1	1	1
3	ACB	1	.	1
4	ACB	1	4	2

- t1 and t2: treatments to be compared, coded using the character strings “A”, “B”, “C”. For example, by specifying t1=B and t2=A the location shift B-A will be evaluated;
- alpha: confidence level of the interval;
- exact: if this parameter is set to 1, the exact confidence limits will be generated in addition to asymptotic ones. Please note that the computation of the exact confidence limits may require a considerable amount of time if many subjects are included in the analysis.

The outline of the macro is very simple:

- the period differences are calculated and the median-scaled differences are derived by subtracting the stratum medians obtained using the MEANS procedure;
- Hodges-Lehmann point estimate and the Moses confidence interval of 2Δ are calculated using the HL option of the NPAR1WAY procedure. If requested, the exact confidence limits are obtained by adding the statement EXACT HL;
- the point estimate and the confidence limits are divided by 2.

The macro is available on request from the author.

EXAMPLE

The analgesic efficacy of 200 mg ibuprofen plus 30 mg codeine (treatment A), 200 mg ibuprofen (treatment B) and placebo (treatment C) was investigated in a clinical trial published in Quiding et al. [11]. The study was a double-blind, randomized crossover trial in 26 coxarthrosis patients with persistent pain. Data from this trial were also analysed by Öhrvik [12] with the aim of illustrating an approach alternative to the MS method. Each of the three treatments was administered in a total of 6 doses and the pain intensity was recorded hourly on a visual analog scale for 8 hours after the 6th dose. The main efficacy variable was the pain intensity index expressed in mm/h defined as

$$\frac{\text{mean pain intensity up to 8 h or until intake of rescue paracetamol}}{\text{8 hours or time interval until intake of rescue paracetamol}}.$$

The data are displayed in the following table with the period differences, the stratum medians and the median-scaled differences for the comparison of ibuprofen plus codeine and placebo (A vs. C).

Stratum	Sequence	Subject	Period 1	Period 2	Period 3	Contrast[1]	Stratum median	Median-scaled difference
1	ACB	6	0.280	1.598	0.486	-1.318	-0.8215	-0.4965
1	ACB	7	1.361	-	3.819	-	-0.8215	-
1	ACB	13	0.886	10.958	3.403	-10.072	-0.8215	-9.2505
1	ACB	23	0.583	3.903	4.389	-3.320	-0.8215	-2.4985
1	CAB	1	0.597	0.056	0.014	0.541	-0.8215	1.3625
1	CAB	10	6.764	0.389	3.625	6.375	-0.8215	7.1965
1	CAB	18	0.620	0.945	0.986	-0.325	-0.8215	0.4965
2	ABC	3	2.764	1.528	3.986	-1.222	0.1850	-1.4070
2	ABC	4	0.472	0.153	0.222	0.250	0.1850	0.0650
2	ABC	14	0.722	0.650	1.986	-1.264	0.1850	-1.4490
2	ABC	24	0.389	3.208	66.000	-65.611	0.1850	-65.7960
2	CBA	11	3.243	2.196	3.058	0.185	0.1850	0.0000
2	CBA	12	1.667	0.224	2.436	-0.769	0.1850	-0.9540
2	CBA	19	2.804	2.278	2.000	0.804	0.1850	0.6190
2	CBA	20	7.167	55.500	19.000	-11.833	0.1850	-12.0180
2	CBA	22	38.042	3.172	1.673	36.369	0.1850	36.1840
2	CBA	25	5.833	3.375	3.361	2.472	0.1850	2.2870

2	CBA	49	6.500	0.820	0.903	5.597	0.1850	5.4120
3	BAC	2	0.820	0.820	1.445	-0.625	0.7295	-1.3545
3	BAC	9	1.991	1.082	2.778	-1.696	0.7295	-2.4255
3	BAC	15	1.181	0.000	0.000	0.000	0.7295	-0.7295
3	BAC	21	3.444	7.403	6.444	0.959	0.7295	0.2295
3	BCA	5	1.542	1.708	1.208	0.500	0.7295	-0.2295
3	BCA	8	7.681	27.833	2.250	25.583	0.7295	24.8535
3	BCA	16	1.431	1.403	0.000	1.403	0.7295	0.6735
3	BCA	50	0.972	2.403	0.319	2.084	0.7295	1.3545

[1] Period 1 – Period 2 for Stratum 1, Period 1 – Period 3 for Stratum 2, Period 2 – Period 3 for Stratum 3.

In this case, the Hodges-Lehmann point estimate and the Moses confidence interval of the location shift are obtained by considering the median-scaled differences from the subjects assigned to sequences ACB, ABC, BAC and the subjects assigned to sequences CAB, CBA and BCA as two independent samples.
In order to compare treatments A and C and to obtain the 95% confidence interval of Δ, the %MSCI macro parameters should be set as follows:

```
%MSCI(ds=dataset,t1=A,t2=C,alpha=0.05,exact=1);
```

By specifying exact=1, we are also requiring the exact confidence limits. After submitting the above code, we obtain the following output.

Parameter	Type	Shift	LowerCL	UpperCL
2*DELTA	Asymptotic	-3.00575	-9.8695	-1.2895
DELTA	Asymptotic	-1.50288	-4.9348	-0.6448
2*DELTA	Exact	-3.00575	-9.8695	-1.2895
DELTA	Exact	-1.50288	-4.9348	-0.6448

In this example, there is no difference between the asymptotic and the exact confidence limits. However, this is not generally the case (try, for example, selecting subjects 1-13 from the above table).

LIMITATIONS

The properties of the MS method in terms of coverage, confidence interval length and bias have been evaluated by Willavize and Morgenthien [1] based on a simulation study. Good performances have been demonstrated by simulating typical data for t_{max}. However, further investigation would be required to confirm the wider applicability of the MS method.

DISCUSSION

The %MSCI macro allows to straightforwardly calculate the point estimate and the confidence interval of location shift between treatments based on the MS method. This approach represents a possible option in the case of non-normal study outcomes when a 3-treatment, 3-period, 6-sequence crossover design is used.

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