

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

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Agenda

- Purpose of the **median-scaling (MS)** method
- 2-treatment, 2-period, 2-sequence crossover design
- 3-treatment, 3-period, 6-sequence crossover design
- The **%MSCI** macro
- Limitations of the MS method
- Questions

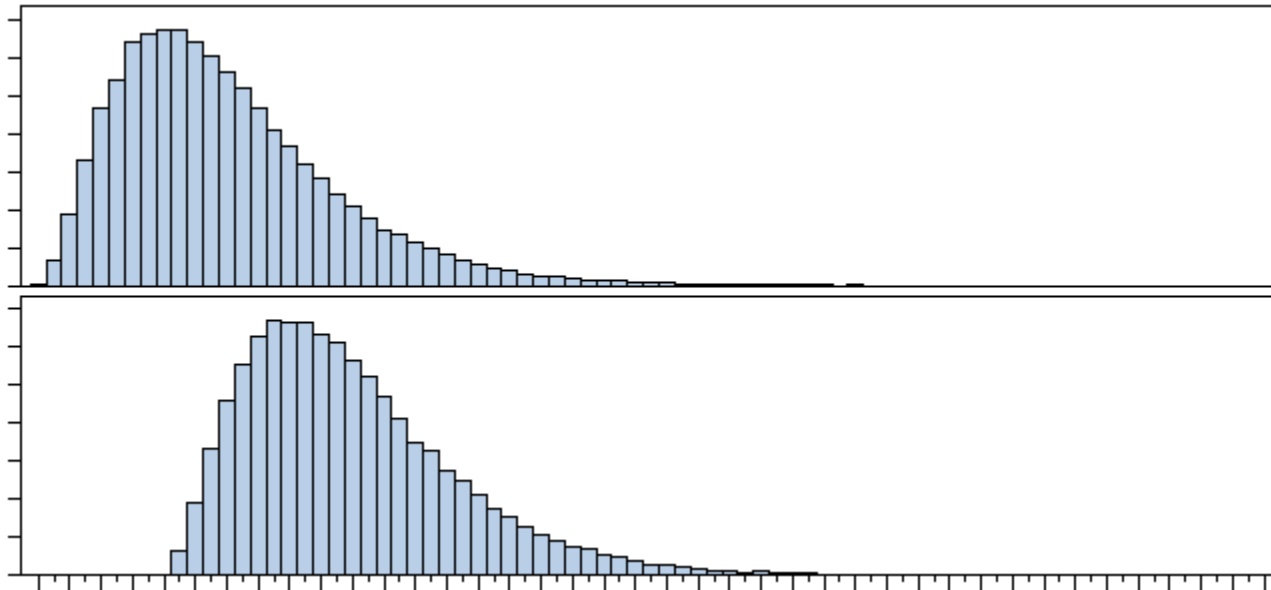
Purpose of the MS method

- To obtain the point estimate and the confidence interval (exact or asymptotic) for the **location shift** between treatments (no p-values)
- Applicable with **3x3 crossover designs** where all **six possible treatment sequences** are used
- The effect of **period** is taken into account
- **Nonparametric** method useful when the assumptions of the standard approaches based on parametric inference are not valid (e.g., severe departures from normality)
- Originally introduced for the analysis of **t_{max}** by Willavize and Morgenthien (Pharmaceut Statist 2008)

Location shift

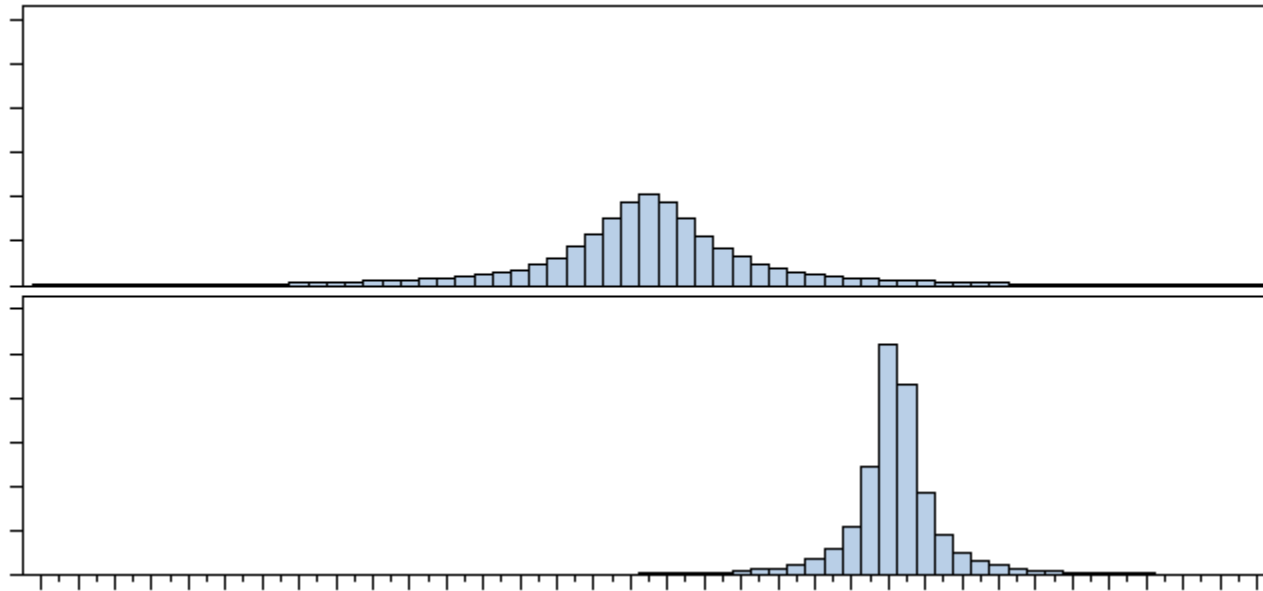
- The location shift estimated using the MS method can be interpreted as the difference between treatment medians (or means) if the shift model holds:

$$G(x) = F(x+\Delta)$$



Location shift

- Or if the underlying distributions are symmetric with heterogenous variances



- In this case the exact confidence interval should be used instead of the asymptotic one (Rosenkranz, Pharmaceut Statist 2009)

Location shift

- Rosenkranz also observes that

“when the variables to be compared arise from differences like changes from baseline, there is a good chance for an (almost) symmetrical distribution”.

2x2, 2-sequence crossover design

- The MS method can be viewed as an **extension** of an approach for a 2x2, 2-sequence crossover design
- Let assume that an adequate model for the data is

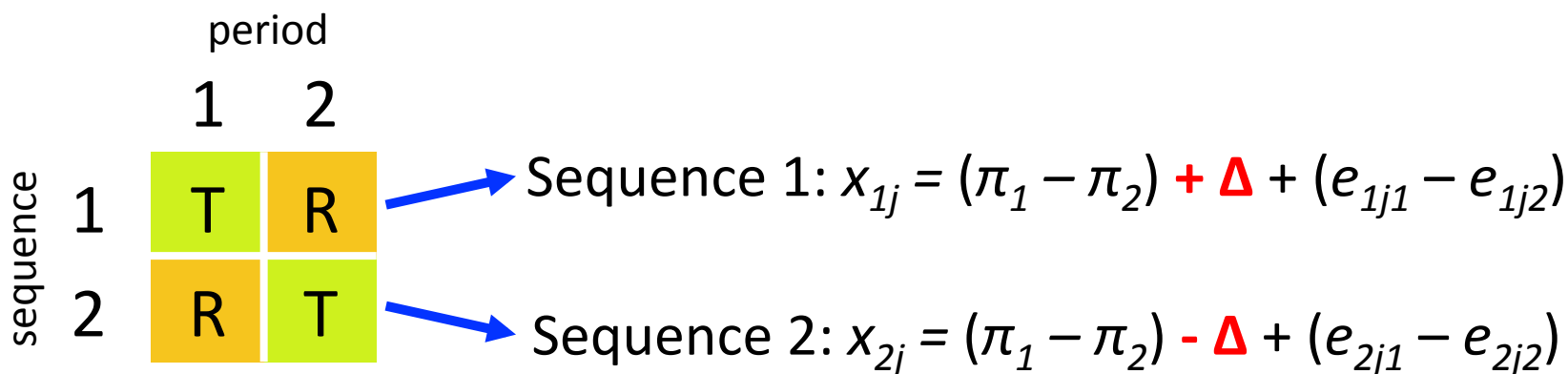
$$x_{ijk} = \mu + \gamma_i + s_{ij} + \pi_k + \varphi_l + e_{ijk}$$

- μ : general mean
- γ_i : fixed effect of the i -th sequence
- s_{ij} : random effect of the j -th subject within the i -th sequence
- π_k : fixed effect of the k -th period
- φ_l : fixed effect of the l -th treatment ($l = R, T$)
- e_{ijk} : random within-subject error
- **no** carry-over

2x2, 2-sequence crossover design

- Let x_{ij} denote the **difference between periods 1 and 2** for the j -th subject in the i -th sequence:

$$x_{ij} = x_{ij1} - x_{ij2}$$



$$\Delta = \varphi_T - \varphi_R:$$

unknown shift in location due to the test treatment

2x2, 2-sequence crossover design

- Thus, when comparing the period differences of two subjects included in different sequence groups (TR vs. RT), we obtain

$$\begin{aligned} X_{1j} - X_{2j} &= \\ &= (\cancel{\pi_1} - \pi_2) + \Delta + (e_{1j1} - e_{1j2}) - [(\cancel{\pi_2} - \pi_1) - \Delta + (e_{2j1} - e_{2j2})] = \\ &= 2\Delta + \text{error} \end{aligned}$$

2x2, 2-sequence crossover design

- Based on this result, the following approach is adopted
 - the two sequence groups are considered as **independent random samples**
 - **parallel-group** methods are applied to the **within-subject period differences**
 - the **Hodges-Lehmann** point estimate and confidence limits are calculated for **2Δ**
 - the values obtained are divided by 2

2x2, 2-sequence crossover design

- 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 test
- If the period effect is considered negligible, similar procedures based on the **Wilcoxon signed rank test** may be preferred.

3x3, 6-sequence crossover design

- The same model defined for the 2x2 design is assumed to hold
- The starting point is the **sequence stratification**: in order to compare two treatments (say A and B), the sequences are arranged in pairs, grouping together the sequences where A and B occur in the same periods

		period			
		1	2	3	
sequence	1	A	B	C	→ Stratum 1: treatments administered in periods 1 and 2
	2	B	A	C	
	3	A	C	B	→ Stratum 2: treatments administered in periods 1 and 3
	4	B	C	A	
	5	C	A	B	→ Stratum 3: treatments administered in periods 2 and 3
	6	C	B	A	

3x3, 6-sequence crossover design

		period				
		1	2	3		
sequence	1	A	B	C	Stratum 1	$\underline{ABC}: x_{1j} = (\pi_1 - \pi_2) + \Delta + (e_{1j1} - e_{1j2})$
	2	B	A	C		$\underline{BAC}: x_{2j} = (\pi_1 - \pi_2) - \Delta + (e_{2j1} - e_{2j2})$
	3	A	C	B	Stratum 2	$\underline{ACB}: x_{3j} = (\pi_1 - \pi_3) + \Delta + (e_{3j1} - e_{3j3})$
	4	B	C	A		$\underline{BCA}: x_{4j} = (\pi_1 - \pi_3) - \Delta + (e_{4j1} - e_{4j3})$
	5	C	A	B	Stratum 3	$\underline{CAB}: x_{5j} = (\pi_2 - \pi_3) + \Delta + (e_{5j2} - e_{5j3})$
	6	C	B	A		$\underline{CBA}: x_{6j} = (\pi_2 - \pi_3) - \Delta + (e_{6j2} - e_{6j3})$

- The estimates of the treatment difference independently provided by the strata cannot be easily combined since they include **different period effects**

3x3, 6-sequence crossover design

- This problem is solved by introducing the concept of **median-scaling**
 - Data from different experiments could be made **comparable** by subtracting some estimate of the location of each experiment from all observations of the experiment
 - In our case :
 - experiment = **stratum**
 - the **stratum median** is subtracted from all observations within the stratum
- Then, the **median-scaled period differences** from all the strata can be ranked together

3x3, 6-sequence crossover design

- An estimate of the location of each experiment...
 - m_p = **median period difference** in stratum p ($p= 1, 2, 3$)
- ...is subtracted from all observations of the experiment:

median-scaled period differences

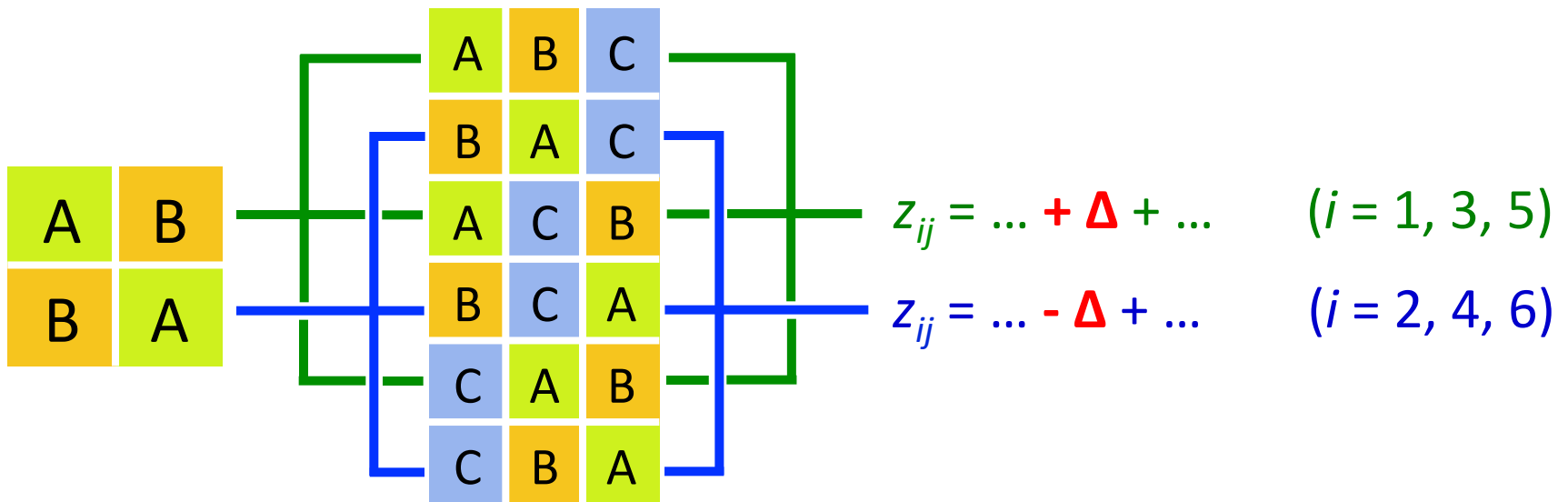
		period			
		1	2	3	
sequence	1	A	B	C	Stratum 1
	2	B	A	C	
	3	A	C	B	Stratum 2
	4	B	C	A	
	5	C	A	B	Stratum 3
	6	C	B	A	

<u>ABC</u> : $z_{1j} = x_{1j} - m_1$
<u>BAC</u> : $z_{2j} = x_{2j} - m_1$
<u>ACB</u> : $z_{3j} = x_{3j} - m_2$
<u>BCA</u> : $z_{4j} = x_{4j} - m_2$
<u>CAB</u> : $z_{5j} = x_{5j} - m_3$
<u>CBA</u> : $z_{6j} = x_{6j} - m_3$



3x3, 6-sequence crossover design

- Now we are allowed to apply the same approach as in the **2x2 design**



- The roles of x_{1j} (A before B in the sequence) and x_{2j} (B before A in the sequence) in the 2x2 design are now played by z_{1j}, z_{3j}, z_{5j} and z_{2j}, z_{4j}, z_{6j} , respectively.

3x3, 6-sequence crossover design

- What has changed from the method used with 2x2 design?
 - z_{1j} , z_{3j} , z_{5j} and z_{2j} , z_{4j} , z_{6j} are considered as independent random samples
 - parallel-group methods are applied to the **median-scaled** within-subject period differences
 - the Hodges-Lehmann point estimate and confidence limits are calculated for 2Δ
 - the values obtained are divided by 2

3x3, 6-sequence crossover design

- The MS method allows for
 - **tied observations**
 - **unequal allocation** of subjects to sequences
 - **missing data** (if for a subject the response is missing for at least one treatment 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 have been studied

3x3, 6-sequence crossover design

- **Example**
 - We are interested in the comparison A vs. C
 - Note that the comparison between A and C requires a different grouping of sequences the the one used to compare A and B

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

↑
Stratum 1: treatments
administered in periods 1 and 2

↑
Period 1 – Period 2

The %MSCI macro

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

- **ds**: dataset to be analysed
 - each observation must correspond to a subject
 - 4 variables required: sequence (“ABC”, ACB”, etc.) and p1, p2, p3 (responses observed in the three treatment periods)

	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 (t1=A, t2=B: A-B will be evaluated)
- **alpha**: confidence level of the interval
- **exact**: if =1, also the exact confidence limits will be generated

The %MSCI macro

```
%MSCI(ds=dataset,t1=A,t2=C,alpha=.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 (Moses)	-2.15325	-26.2080	-0.3875
DELTA	Asymptotic (Moses)	-1.07663	-13.1040	-0.1938
2*DELTA	Exact	-2.15325	-25.1035	-0.4525
DELTA	Exact	-1.07663	-12.5518	-0.2263

Limitations

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



Any questions?



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