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Analyzing Zero-Inflated Continuous Data in Limited Sample Size

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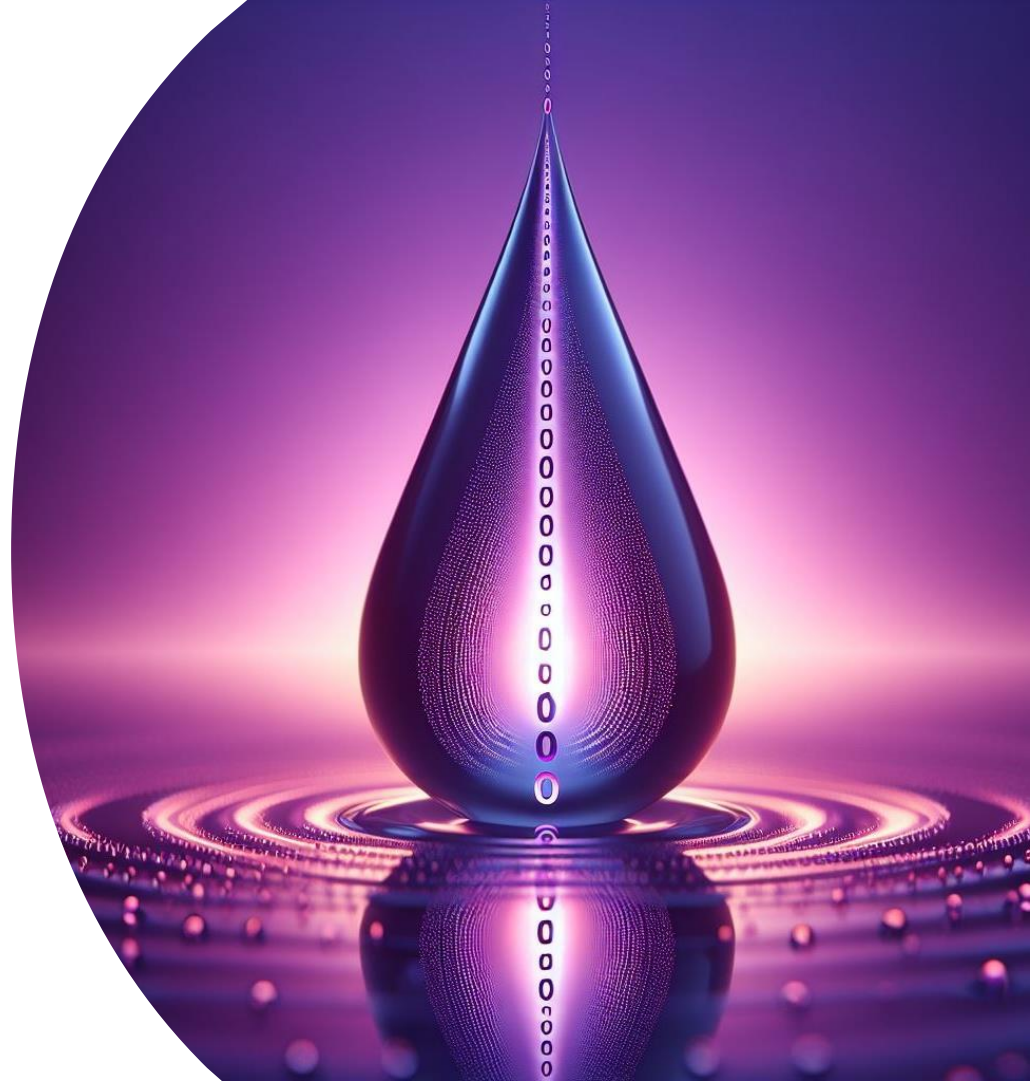
Non Clinical Efficacy and Safety Biostatistics



NCS

Non-Clinical
Statistics
Conference

Wiesbaden, DE / 25-27 September, 2024



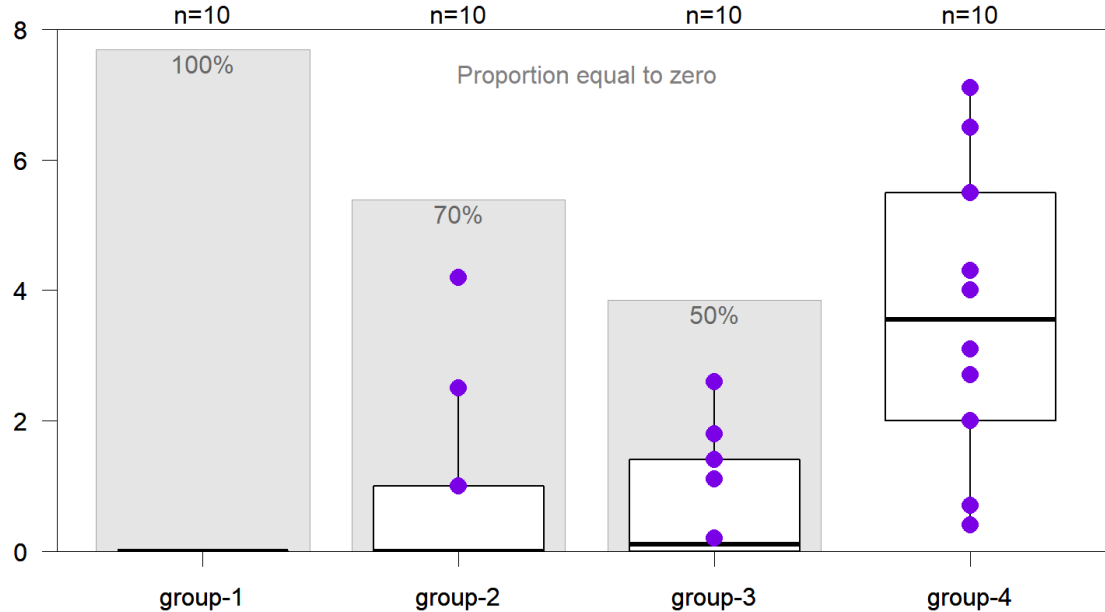
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Introduction

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Motivation example



Summarizing the problem

Challenges:

- Point mass at zero (many ties)
- Skewed distribution (extreme values)
- Small sample size (partly non-informative)

May be also:

- Perfect separation
- Unbalanced sample size
- Variance heterogeneity

Narrowing the problem

To refine the scope of the investigation, certain assumptions were made.

Assumptions:

- Two sample problem
- Independent observations
- The zero values are real, no censoring or LOD
- Sample size ≤ 20 per group (small)

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Methods

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Non-parametric test

Presented are top 4 out of ~20 investigated methods.

BM - Brunner-Munzel test

Also known as the generalized Wilcoxon test.

The Brunner-Munzel test is a non-parametric rank-based, very robust test that can handle ties and heterogeneity of variance.

Neubert, Karin & Brunner, Edgar, 2007. A studentized permutation test for the non-parametric Behrens-Fisher problem. Computational Statistics & Data Analysis, Elsevier, vol. 51(10), pages 5192-5204, June.

Permutation tests

Simple permutation tests are known to be very robust, except in the case of variance heterogeneity, as they assume exchangeability.

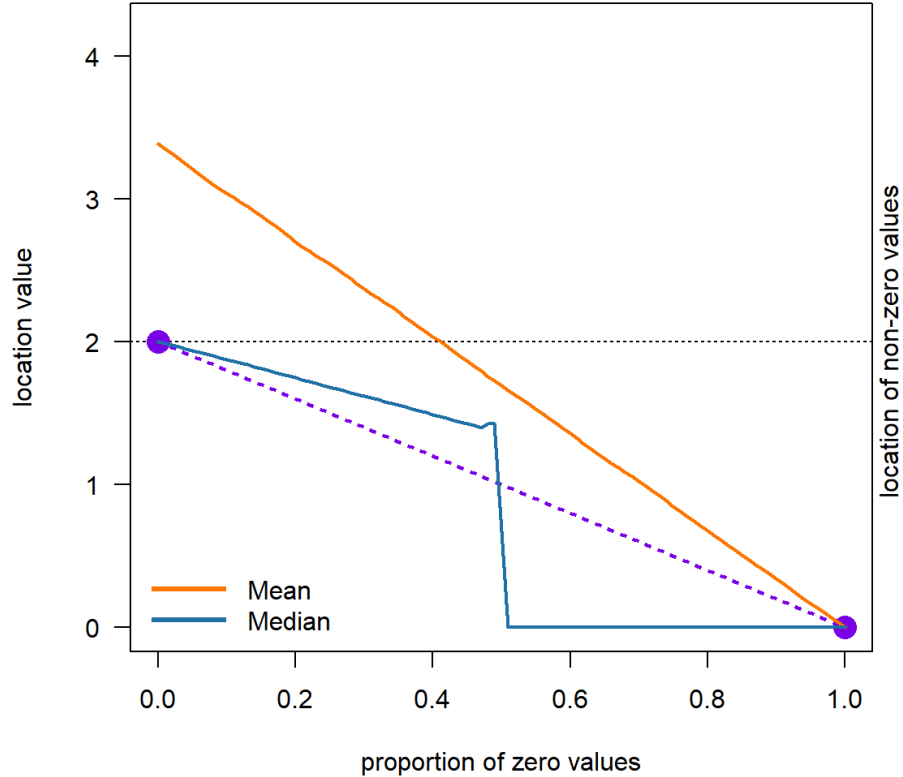
ZWM-p permutation test with zero weighted median

$$ZWM(x) = \frac{\text{median}(x_{pos.}) * N_{pos.}}{N}$$

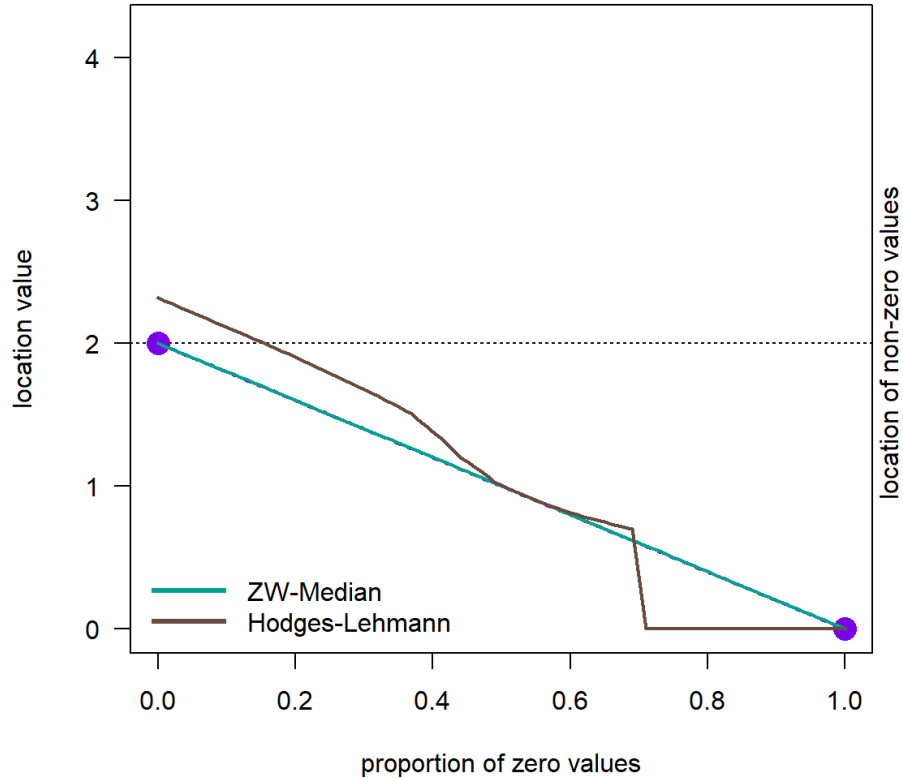
HL-p permutation test with Hodges–Lehmann estimator

Hodges, J.L., and Lehmann, E.L. (1963), Estimates of location based on rank tests. *The Annals of Mathematical Statistics*, **34**, 598–611.

Location parameter



Location parameter

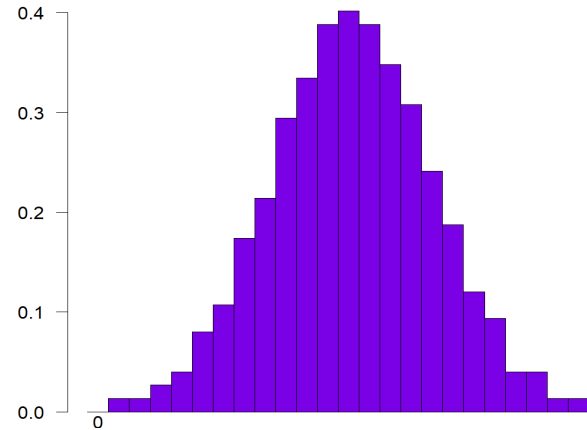
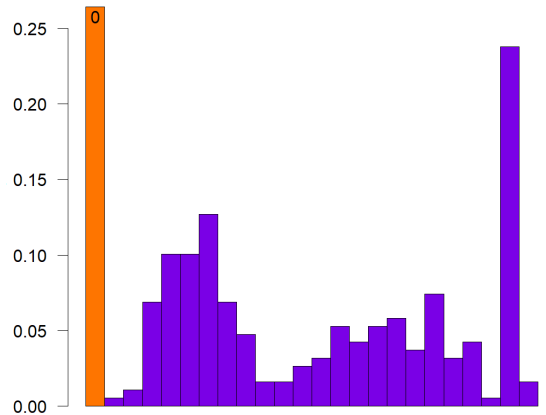


Multiple Transformation

MINT - Multiple Inverse Normal Transformation + Welch's t-test (100 times)

$$INT_r(x) = \Phi^{-1} \left\{ \frac{\text{rank}(x, \text{ties} = \text{random}) - \frac{1}{2}}{n} \right\}$$

p-values of 100 tests are combined with simple median rule.



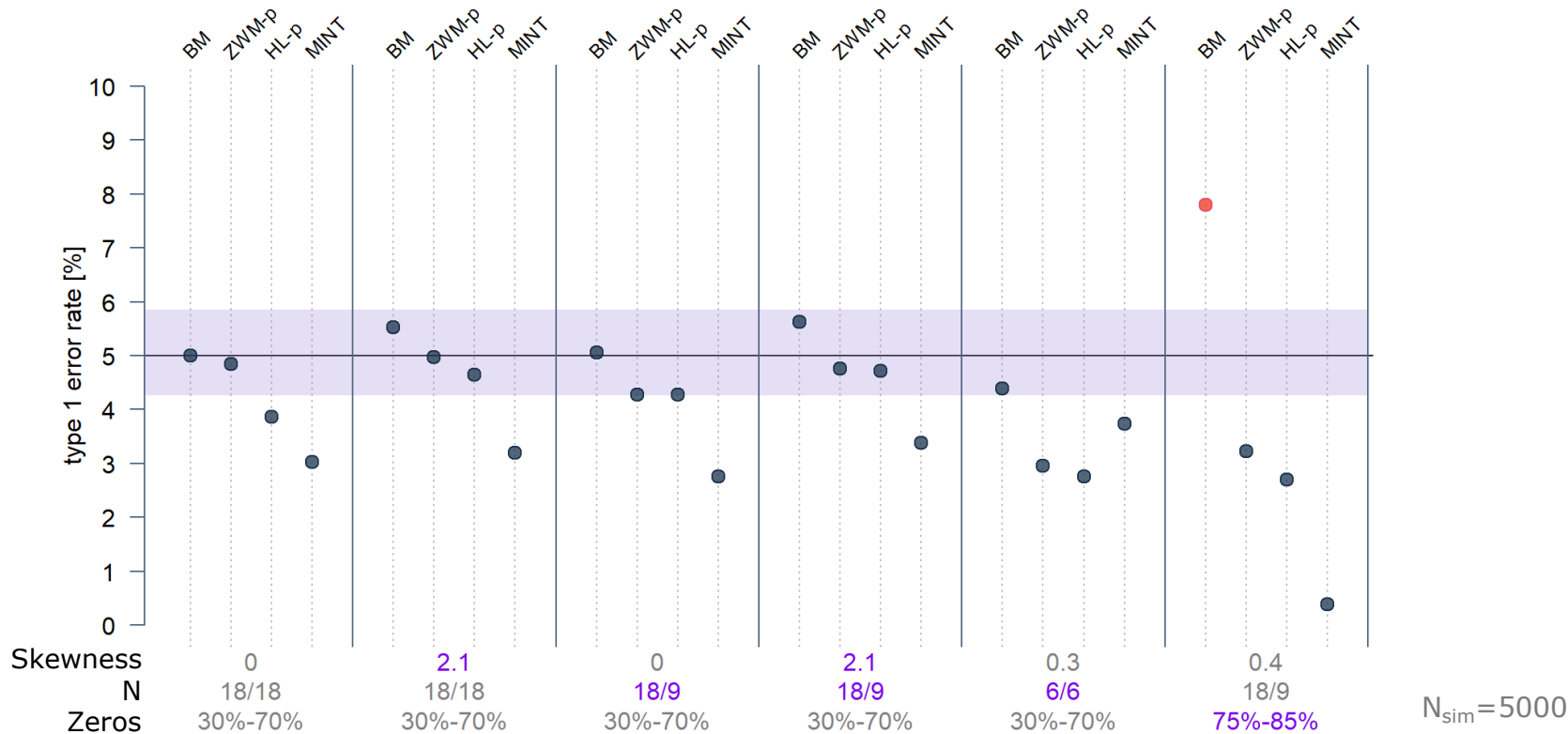
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Simulation Results

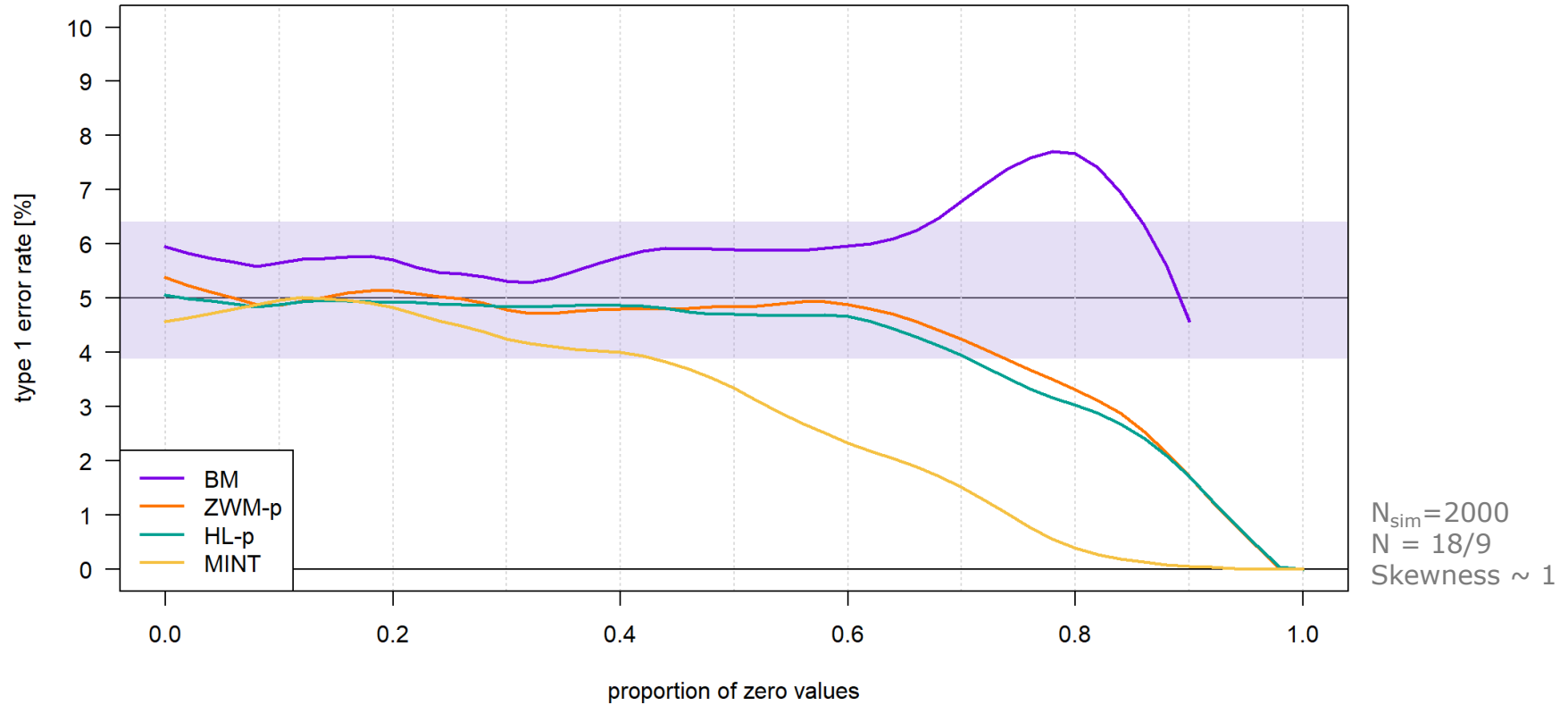
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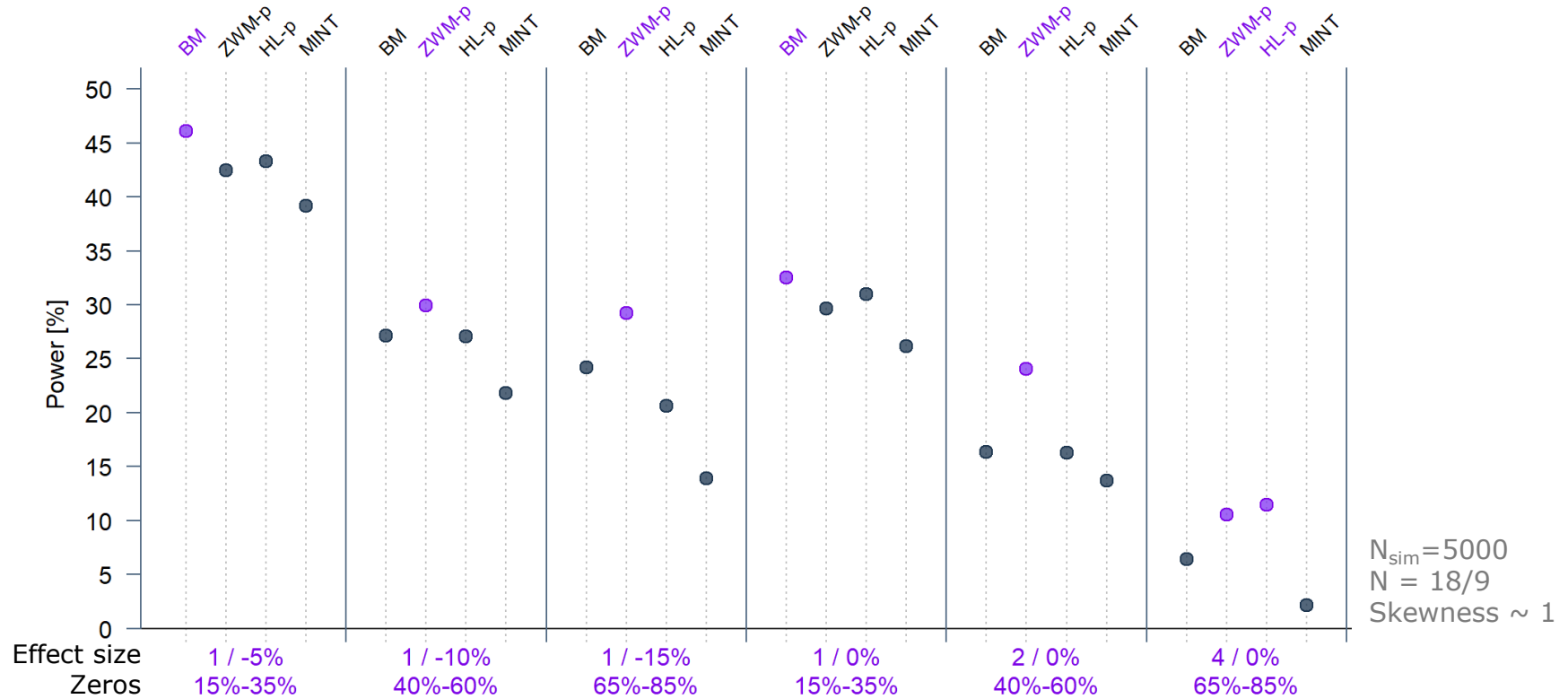
Type 1 error rate



Type 1 error rate



Power



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Conclusion

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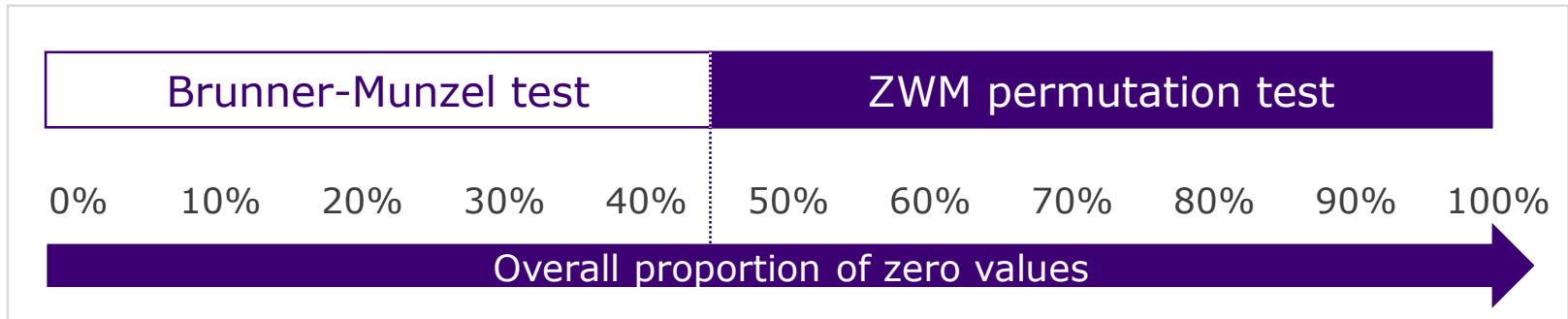
Conclusion

The Brunner-Munzel test is most effective when there is a moderate number of zero values in the data.

In contrast, the ZWM-p test performs better when there are many zeros.

All 4 methods can be generalized to more than 2 groups

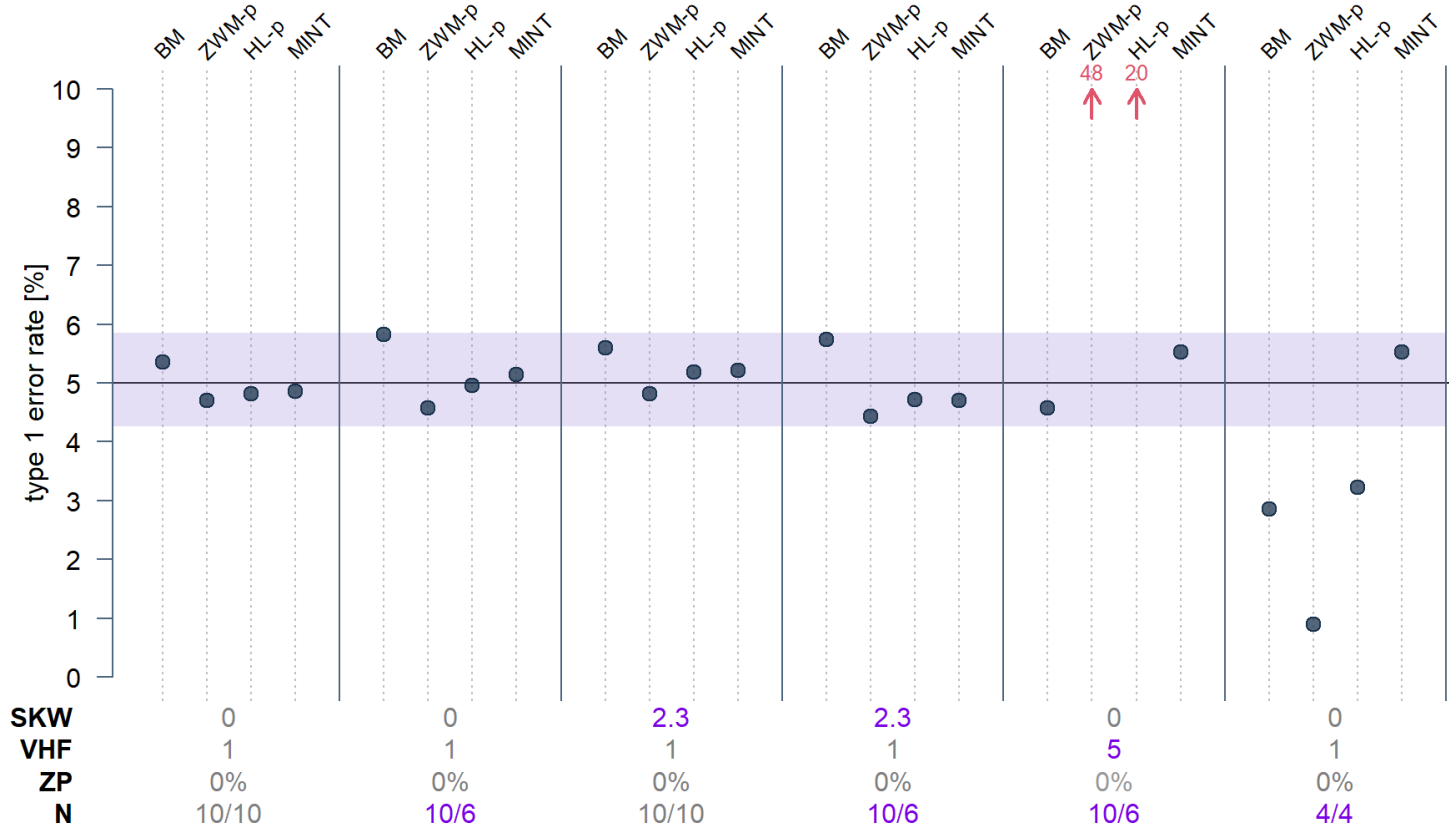
In case of complex design, MINT method may be as well useful, as it is applicable in combination with most parametric methods.



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Thank you
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Type 1 error rate (without zero values)



Artificial data example

Random data generation using g-and-h + binomial distribution.

