

Informative Simultaneous Confidence Intervals for Graphical Multiple Tests

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Graphical multiple tests, as introduced in Bretz et al. (2009), are a powerful tool to design multiple test procedures for clinical trials with multiple endpoints and multiple treatment doses or regimen. With a graphical multiple tests it is easy to account for preferences or hierarchies among the different null hypotheses. These tests control the family wise error rate in the strong sense. They are closed testing procedures and hence come along with major difficulties in extending them to simultaneous confidence intervals (SCIs).

The extension to SCIs is useful because the intervals (usually) provide more information than the multiple tests itself. We may, for instance, wish to exclude parameter values within the alternative hypothesis if the corresponding null hypothesis has been rejected. For instance, this permits to quantify sizes of treatment effects as suggested by regulatory guidelines. Simultaneous confidence intervals are also of particular value in non-inferiority trials in order to improve the pre-specified non-inferiority margin or to claim superiority when the data show compelling evidence for superiority. Unfortunately, the currently known extensions of closed testing procedures provide SCIs that often do not provide additional information on the parameter values from the rejected null hypotheses (see e.g. Strassburger and Bretz, 2008). As it seems impossible to overcome this severe shortcoming, we suggest modifying the given graphical test to receive SCIs that always provides additional information to the cheer hypothesis tests. The modification can be fine-tuned to balance potential power losses due to modification with the information content gained by the SCI. Such SCIs were derived and implemented for the Bonferroni-Holm, Gate-Keeping and Fallback procedures (Brannath and Schmidt, 2014; Schmidt and Brannath, 2014, 2015). In our very recent research we have now extended this approach to the general class of graphical test procedures in Bretz et al. (2009).

In my talk I will provide an introduction to graphical tests and existing SCIs. I will then introduce the construction principle of the informative SCIs with the Gate-Keeping procedure and will finally discuss our recent extension to the general class of graphical tests. The method will be illustrated by examples and simulation results.

References

- Brannath, W. and Schmidt, S. (2014). A new class of powerful and informative simultaneous confidence intervals. *Statistics in Medicine* 33, 3365–86.
- Bretz, F., Maurer, W., Brannath, W., and Posch, M. (2009). A graphical approach to sequentially rejective multiple test procedures. *Statistics in Medicine* 28, 586–604.
- Schmidt, S. and Brannath, W. (2014). Informative simultaneous confidence intervals in hierarchical testing. *Methods of Information in Medicine* 53, 278–283.
- Schmidt, S. and Brannath, W. Informative simultaneous confidence intervals for the fallback Procedure. *Biometrical Journal* 57 (2015) 4, 712–719.
- Strassburger, K. and Bretz, F. (2008). Compatible simultaneous lower confidence bounds for the Holm procedure and other Bonferroni-based closed tests. *Statistics in Medicine* 27, 4914–4927.