NOTE FOR SUBGROUP CONFIRMATION

Xiaowei Yin

As for as I know, there are 2 directions to conduct subgroup confirmation or validation. The first one is to do the confirmation based on the data that has just been used to identify the subgroup. Here the bias introduced from post-selection inference should be considered. The second is to design another clinical trial to enroll more sample to validate the identified subgroup. This needs proper design to get enough evidence for the heterogenous treatment effect.

1 post-selection inference

The subgroup confirmatory analysis can be classified into the prespecified analysis and the post hoc analysis. A prespecified subgroup analysis is one that is planned and documented before any examination of the data, preferably in the study protocol. Post hoc analyses refer to those in which the hypotheses being tested are not specified before any examination of the data. Wang et al. (2007) Here we focus on post hoc analysis.

Subgroup identification can be seen as a problem of model selection, and there is a well acknowledged problem of post-selection bias in this area. Kuchibhotla et al. (2022) The subgroup (or submodel) that is selected from a data-driven model selection process will lead to bias in simultaneous inference based on the same data and on the selected subgroup. This is partly because the inference using the same data for model selection potentially changes the distribution of model parameters under null hypothesis, thus making the hypothesis test fail to control the type one error, leading to an overoptimistic result.

Therefore, in subgroup confirmation, it's important for us to keep this in mind and consider how to adjust the bias introduced from the post-selection inference.

1.1 Adjusted bootstrap

Guo and He (2021) proposed a resampling based method to address subgroup selection bias. To be specific, they developed a bias-reduced estimator and a valid one-sided confidence bound on the selected subgroup effect size. The bias-reduced estimator is constructed based on an adjusted bootstrap aiming to learn about the bias when the number of best subgroup is greater than one.

$$\beta^*_{\text{max,modified}} = \max_{i\in[k]} (\beta^*_i + d_i)$$

$$\hat{\beta}_{\text{max,reduced}} = \hat{\beta}_{\text{max}} - E^* \left[\beta^*_{\text{max,modified}} - \hat{\beta}_{\text{max}} \right]$$

Theorem 1. Under Assumptions 1.1 and 1.2, and for any 0< r<0.5 , we have,

$$\sup_{x \in R} \mid P^* \left(\sqrt{n} \left(\beta^*_{\text{max,modified}} - \hat{\beta}_{\text{max}} \right) \leq x \right) - P \left(\sqrt{n} \left(\hat{\beta}_{\text{max}} - \beta_{\text{max}} \right) \leq x \right) \mid \to 0$$

as $n \to \infty$, in probability w.r.t. P.

The modified estimator is designed to estimate the bias distribution of the estimated best subgroup treatment effect between the bootstrap estimator and the full sample estimator. Then, under the theorem 1 proposed in this paper that the bias of bootstrap estimator to the full sample estimator and the bias of the estimated best subgroup treatment effect and the true best subgroup treatment effect is asymptoticly of the same distribution.

The reduced estimator is adjusted by the bias learned from the bootstrap, and the paper used it to construct a lower bound estimator, which is a more reliable.

Furthermore, they presented on another work that the adjusted estimator can not only reduce the bias on the inference of post-hoc identified subgroups, but also be adopted in the subgroup validation trial to obtain a more powerful estimator that make use of the data from both the discovery and the validation stage.

2 Experiment design for confirmation trial

There are different ways to perform the subgroup confirmation trialTanniou et al. (2016). For example, Fallback designs are used when prior evidence on the biomarker is less convincing. In this 2 stage design, the first stage tests the overall sample at a reduced alpha level. If the overall test is significant at that reduced level, then the trail stops and the treatment would be recommended for all patients. Otherwise the subgroup test is performed in the second stage. Note that there are methods Spiessens and Debois (2010) use the correlation between both stage's test statistics and take into account the correlation between test statistics to calculate adjusted significance levels.

However, in the fallback designs, the complementary subgroup is not tested, which is unwanted because we may depend on the significance of treatment effect in complementary subgroup to decide whether there is a global treatment effect or the treatment effect is restricted to the targeted subgroup only.Alosh and Huque (2013)

Interim analyses might identify a potential subpopulation of interest, if not identified previously. Here, Chen and Beckman (2009) provided a method that controls the type I error rate by optimally splitting the overall significance level.

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