The conditional saddlepoint approximation for fast and accurate large-scale hypothesis testing

Ziang Niu, Jyotishka Ray Choudhury, Eugene Katsevich

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[Note: To fit into JRSSB's limit of 30 pages double-spaced, we need our exposition to be as tight as possible. We must reserve the main text for only the most important things, and use the appendix for everything else.]

1 Introduction

- Sparse data + large number of tests creates statistical and computational challenges. Statistically, we need accurate tail probabilities due to multiplicity correction. Computationally, doing resampling for many hypothesis tests is expensive.
- Examples: Single-cell CRISPR screens and GWAS for rare variants and rare diseases. [Not too much detail about the applications; will provide more later.]
- Some literature review.
- Our contributions: We propose to reconcile statistical accuracy with computational speed by leveraging SPA for resampling-based procedures. However, SPA has not been properly justified for any resampling-based procedures, and has not been applied in the context of CI testing. To overcome these challenges, we make two central contributions:

    1. Establish theoretical justification for SPA in the context of resampling-based hypothesis testing, where conditioning must be accounted for. This justifies the SPA for classical resampling-based procedures, like the sign-flipping test, 70 years after these approximations were first proposed. It also loosens the assumptions of SPA, not requiring continuity or lattice assumptions, establishing a new result even for the classical (unconditional) SPA.
    2. To extend this useful approximation to CI testing, we apply the SPA to the dCRT to arrive at the spaCRT, the first SPA for a CI testing procedure. We provide theoretical justification for the spaCRT in general, and in a variety of specific modern settings. We provide the R package `spacrt` to implement the spaCRT, which is available on GitHub.

We demonstrate in simulation studies inspired by the single-cell CRISPR screen and GWAS applications that spaCRT delivers fast and accurate inference. We apply the spaCRT to accelerate the analysis of a real single-cell CRISPR screen dataset by a factor of about 250.

2 The conditional saddlepoint approximation

- Conditional SPA theorem
- Application to sign-flipping test
- Unconditional version

3 The spaCRT methodology

- Brief background on dCRT and GCM
- The spaCRT methodology
- Example: Bernoulli sampling

4 Theoretical guarantees for spaCRT

- General results on approximation accuracy and Type-I error
- Specific results for different regression techniques

5 Numerical simulations

[Especially if we want to include both examples in the main text, details of simulation setup and methods compared will need to be deferred to supplement.]

6 Real data analysis

7 Discussion

8 Acknowledgments

[The union of the acknowledgment sections of the two papers.]