

JUMP: replicability analysis of high-throughput experiments with applications to spatial transcriptomic studies

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Abstract

Motivation: Replicability is the cornerstone of scientific research. The current statistical method for high-dimensional replicability analysis either cannot control the false discovery rate (FDR) or is too conservative.

Results: We propose a statistical method, JUMP, for the high-dimensional replicability analysis of two studies. The input is a high-dimensional paired sequence of p -values from two studies and the test statistic is the maximum of p -values of the pair. JUMP uses four states of the p -value pairs to indicate whether they are null or non-null. Conditional on the hidden states, JUMP computes the cumulative distribution function of the maximum of p -values for each state to conservatively approximate the probability of rejection under the composite null of replicability. JUMP estimates unknown parameters and uses a step-up procedure to control FDR. By incorporating different states of composite null, JUMP achieves a substantial power gain over existing methods while controlling the FDR. Analyzing two pairs of spatially resolved transcriptomic datasets, JUMP makes biological discoveries that otherwise cannot be obtained by using existing methods.

Availability: An R package JUMP implementing the JUMP method is available on CRAN (<https://CRAN.R-project.org/package=JUMP>).

Contact: hongyuancao@gmail.com

Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

Replicability is the cornerstone of modern scientific research. We study conceptual replicability, where consistent results are obtained from studies using different procedures and populations that target the same scientific questions. Replicability is related to but different from meta-analysis. Both approaches look at cross-experiment summaries. In a meta-analysis, the null hypothesis is that there is no effect in all studies. On the other hand, in replicability analysis, the alternative hypothesis is that the effects exist in all studies and the null hypothesis is a composite null, i.e., at least one study does not have an effect. Methods designed for meta-analysis, such as Fisher's method (Fisher, 1925), the Šidák's method (Šidák, 1967), the Lancaster's method (Lancaster, 1961) and the minimum of p -values are not applicable for replicability analysis.

We focus on the replicability analysis of genomic data produced by high-throughput experiments (Li et al., 2011; Phyltron et al., 2018; Heng and Fithian, 2020; Bogomolov and Heller, 2022). In a high-throughput experiment, many candidates are evaluated for their association with a biological feature of interest, and those with significant associations are identified for further analysis. We aim to simultaneously identify replicable features from high-throughput experiments in multiple studies. To analyze a single high-throughput experiment, an acute problem is the multiple comparison. A classic method for multiple comparisons is the false discovery rate (FDR) control approach proposed in Benjamini and Hochberg (1995) (BH). The false discovery rate is defined as the expected value of the ratio of false rejections over total rejections. Suppose we have m hypotheses. The BH procedure works as follows. First, order p -values $p_{(1)} \leq \dots \leq p_{(m)}$. Second, find the largest i_0 such that $p_{(i_0)} \leq \alpha i_0 / m$. Third, reject hypotheses corresponding to $p_{(1)}, \dots, p_{(i_0)}$. Under the assumption that p -values from the null are independent and follow standard

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Table of Contents Pdf Analysis Throughput Experiments Mathematical Computational

1. Understanding the eBook Pdf Analysis Throughput Experiments Mathematical Computational
 - The Rise of Digital Reading Pdf Analysis Throughput Experiments Mathematical Computational
 - Advantages of eBooks Over Traditional Books
2. Identifying Pdf Analysis Throughput Experiments Mathematical Computational
 - Exploring Different Genres
 - Considering Fiction vs. Non-Fiction
 - Determining Your Reading Goals
3. Choosing the Right eBook Platform
 - Popular eBook Platforms
 - Features to Look for in an Pdf Analysis Throughput Experiments Mathematical Computational
 - User-Friendly Interface
4. Exploring eBook Recommendations from Pdf Analysis Throughput Experiments Mathematical Computational
 - Personalized Recommendations
 - Pdf Analysis Throughput Experiments Mathematical Computational User Reviews and Ratings
 - Pdf Analysis Throughput Experiments Mathematical Computational and Bestseller Lists
5. Accessing Pdf Analysis Throughput Experiments Mathematical Computational Free and Paid eBooks

- Pdf Analysis Throughput Experiments Mathematical Computational Public Domain eBooks
- Pdf Analysis Throughput Experiments Mathematical Computational eBook Subscription Services
- Pdf Analysis Throughput Experiments Mathematical Computational Budget-Friendly Options
- 6. Navigating Pdf Analysis Throughput Experiments Mathematical Computational eBook Formats
 - ePub, PDF, MOBI, and More
 - Pdf Analysis Throughput Experiments Mathematical Computational Compatibility with Devices
 - Pdf Analysis Throughput Experiments Mathematical Computational Enhanced eBook Features
- 7. Enhancing Your Reading Experience
 - Adjustable Fonts and Text Sizes of Pdf Analysis Throughput Experiments Mathematical Computational
 - Highlighting and Note-Taking Pdf Analysis Throughput Experiments Mathematical Computational
 - Interactive Elements Pdf Analysis Throughput Experiments Mathematical Computational
- 8. Staying Engaged with Pdf Analysis Throughput Experiments Mathematical Computational
 - Joining Online Reading Communities
 - Participating in Virtual Book Clubs
 - Following Authors and Publishers Pdf Analysis Throughput Experiments Mathematical Computational
- 9. Balancing eBooks and Physical Books Pdf Analysis Throughput Experiments Mathematical Computational
 - Benefits of a Digital Library
 - Creating a Diverse Reading Collection Pdf Analysis Throughput Experiments Mathematical Computational
- 10. Overcoming Reading Challenges
 - Dealing with Digital Eye Strain
 - Minimizing Distractions
 - Managing Screen Time
- 11. Cultivating a Reading Routine Pdf Analysis Throughput Experiments Mathematical Computational
 - Setting Reading Goals Pdf Analysis Throughput Experiments Mathematical Computational
 - Carving Out Dedicated Reading Time
- 12. Sourcing Reliable Information of Pdf Analysis Throughput Experiments Mathematical Computational
 - Fact-Checking eBook Content of Pdf Analysis Throughput Experiments Mathematical Computational
 - Distinguishing Credible Sources
- 13. Promoting Lifelong Learning
 - Utilizing eBooks for Skill Development

- Exploring Educational eBooks

14. Embracing eBook Trends

- Integration of Multimedia Elements
- Interactive and Gamified eBooks

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