The Hong Kong University of Science and Technology

Department of Mathematics

MPhil THESIS EXAMINATION

A Powerful and Adaptive Latent Model for Prioritizing Risk Variants with Functional Annotations

By

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ABSTRACT

The large-scale multiple testing problem is one of the fundamental challenges in genome-wide association studies (GWAS). The traditional approach, Bonferroni correction, is overly conservative. The two-groups model offers a Bayesian perspective in controling false discovery rate, which is a less conservative approach. The major assumption for the two-groups model is exchangeability, essentially an equal prior for all tests. However, in genetic studies, risk variants are not equally important, but are usually enriched in gene regulatory regions or active in cell/tissue types relevant to diseases. This auxiliary information embedded in biologically functional annotation data can be leveraged in risk variants identification. A few FDR-based methods have been developed to integrate GWAS data with functional annotations, but they still have some limitations. First, most of the existing methods assume a linear model for risk variant identification. Second, few of existing methods are scalable to handle a large number of annotations while maintaining good interpretability. To address these issues, we propose a powerful and adaptive latent model (PALM) to integrate cell/tissue-specific functional annotations with summary statistics from GWAS. Extensive simulations as well as real application in 30 GWASs with 127 cell-type/tissue specific functional annotations demonstrate the effectiveness of PALM in risk variant prioritization and its advantages over existing methods.

Date :   **30 May 2022, Monday**

Time :   **10:30 a.m.**

Venue :   **Online via ZOOM**
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