THE UNIVERSITY OF CHICAGO

Department of Statistics

DISSERTATION PRESENTATION AND DEFENSE

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Equal Local Levels --- A Global Testing Approach With Application To Trans eQTL Detection

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ABSTRACT

In order to detect trans eQTLs in a given tissue type, it is common to perform an association test between each pair consisting of an expression level for a gene and a genetic variant that is ``trans'' for that gene, for D different genes and M different genetic variants, where D could be on the order of thousands or tens of thousands and M could be on the order of hundreds of thousands or millions. Then, a multiple testing correction, e.g., Bonferroni or FDR, for M * D hypothesis tests would commonly be imposed, in order to try to identify significant (gene, trans eQTL) pairs. Maintaining correct type 1 error without sacrificing power becomes particularly challenging in this context.

For trans eQTLs, we might expect that association signals for individual (gene, trans eQTL) pairs would commonly be of only moderate or weak size, which could make the standard approach hopelessly under-powered. However, if a trans eQTL has moderate or weak association with multiple expression traits, then it might be possible to detect the trans eQTL using a global test, in which, for each SNP, we test the global null hypothesis that the SNP is not associated with the expression levels of any genes for which it is trans, against the alternative hypothesis that is it associated with the expression level for at least one of the genes for which it is trans. In the global testing approach, the number of tests performed is M, so the final multiple testing correction is comparable to that needed for an ordinary genome-wide association study. This work focuses on development of a global test that will be powerful for trans eQTL detection.

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We propose a global testing approach based on equal local levels (ELL), where our approach allows for dependence among the tests. The ELL test statistic is based on Z-scores from tests of association for individual (gene, SNP) pairs. This allows the method to be applied in situations when only summary statistics are available. Another key feature of the method is that it is computationally fast so that it is feasible for genome-wide analysis. We verify the type 1 error of the method and compare its power to other available methods in simulations. We find a huge power improvement over other available approaches for a wide range of values for the number of associated expression traits for a given trans eQTL. We apply ELL to perform trans eQTL mapping in the LG/J x SM/J advanced intercross line of mice, which is a multi-generational outbred population dataset consisting of 523,028 SNPs and expression levels of 15,561 genes recorded for the hippocampus, pre-frontal cortex and striatum.