Reviewer's report

Title: Global Tests of P-values for Multifactor Dimensionality Reduction Models in Selection of Optimal Number of Target Genes

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Reviewer: Yu Zhang

Reviewer's report:

This manuscript introduces a new method of SNP filtration in order to detect SNP-SNP interaction in disease association studies. The problem itself is very interesting, but I found several technical flaws in the paper, which drastically reduces its readability and value.

Major concerns:

1) A main point of this paper is that it can reduce the number of false positives and make weak interactions more easily detected by filtering out non-interesting SNPs. This is a good idea, but it is insufficiently demonstrated in the paper.

The authors seem to assume that, once the non-interesting SNPs are removed, the remaining SNPs will have smaller number of tests and thus increase power and reduce FDR. This, however, will happen only if the filtration procedure is completely independent of the interaction testing procedure. That is, the signal used for filtration should be independent of the signal used for testing interaction, otherwise, there's a selection bias. The authors need to demonstrate that the selection bias did not occur, either by theory, or by simulation. But none are presented in the paper. In fact, I believe there is a selection bias based on method description, and thus the authors need to use simulated and realistic GWAS datasets to demonstrate its value. Or, to what scale of the data the method would work well.

2) On the other hand, if the authors do not claim that their method reduce FDR or increase power, then the only merit I can see from filtration is computational cost, which unfortunately is not illustrated as well. Also, from the algorithm description, it seems to me that the method could be computationally expensive for large datasets.

3) It is confusing to me why the authors mentioned scenarios A and B? Is scenario B ever considered in the test procedure? In fact, a correct hypothesis would be H0: p~unif(0,1) marginally, but are correlated overall, and Ha: P(P<p)>p.

Assuming independence is wrong, even if SNPs are independent. This is because k-way combinations of SNPs share SNPs, which introduce correlation.

4) All tests 2-6 are based on the assumption of independent p-values, which is inappropriate due to the reason I mentioned in (3). As a result, the type I error of
your tests will be inflated. These are not reflected in your simulation study, because all p-values are not generated from k-way testing, but directly simulated from unif(0,1). Therefore the current simulation does not justify the validity of the procedure. Also, test 1 is not sufficiently described: exactly how the p-values are determined from a supreme of Brownian bridge? and whether or not it accounts for dependence?

5) P9: All variables in ReliefF’s code are not defined, and no comments are shown about what each step is doing. So it is completely unreadable for anyone who does not known ReliefF ahead of time.

Minor points:
1) P10: Test 3, m is used as the number of p-value, which is inconsistent with the notations in other tests.
2) P11: Test 5, it should be S_N, not S_n. Correspondingly, formula for W needs to be modified, because W does not include the n^2 uniform random values.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

No competing interests