Reviewer’s report

Title: Unified Cox model based multifactor dimensionality reduction method for gene-gene interaction analysis of the survival phenotype

Version: 0 Date: 24 Sep 2018

Reviewer: Ruowang Li

Reviewer's report:

The paper proposed an extension to the MDR method to detect gene-gene interactions. In particular, the authors extended the Cox-MDR and UM-MDR to create a new method, Cox UM-MDR. The new method was designed to be more efficient because it eliminates the need for cross-validations and permutation testing. If successful, the method would be a valuable tool for detecting interactions in censored data.

While the goal of the method was clear, the paper itself needs some major revisions.

Major:

1. Because Cox UM-MDR is an extension of an existing method. A more thorough description of the original UM-MDR method is needed. The statement "As described in Yu et al. [16], the UM-MDR method includes a classification step and a modelling step." is not enough to understand how UM-MDR works.

2. "In order to estimate , we can permute the trait a few times, say 5 or 10, and take the sample mean for statistic ". Is 5 or 10 times permutation enough to accurately estimate the mean? How to check this quantitatively?

3. In simulation. We generate simulation datasets from different penetrance functions … yielding 70 epistasis models with various penetrance functions, as described in [10]. The various penetrance functions need to be shown in the paper.

4. Fixing = , = . seems like a really strong assumption. It limits the indicator variable to have the same effect as the covariate.

5. In table 1, the adjusted type 1 errors are also not close to 5%. In fact, they are all much lower than 5%. If the null distribution is specified correctly, they should be very close to 5%
6. Also in table 1. was the p-value, PBonf, being corrected by the Bonferroni correction or by adjusting for the non-centrality. Both adjustments were mentioned in the text and they all point to the same table.

7. The result section was a little confusing. It is a mixture of methods, results and results interpretation. The design of the simulation studies should be in the method section.

8. A major issue with all the power plots. Since the x-axis only have 7 data points (different heritabilities) and they are not equally spaced. The power at each X shouldn't be connected. Also, even if they are connected, they should be connected via a line because there are no data points between different heritabilities. But the plots have lots of non-linear changes in power when there shouldn't be any data points.

9. If the real data is not publicly available nor previously described, then more description of the data is needed. What are the demographic variables? What are the 139 SNPs?

10. "The Venn diagram in Figure 4 shows the number of SNP pairs that have a p-value less than 0.05 for testing \( 0: = 0 \) without adjusting multiple testing by the four models above". Why not adjusting for multiple testing?

11. These two statements are contradictory. 1. "perhaps because the algorithm of Cox UM-MDR for detecting SNP interaction is quite different from that of the Cox model and yields inconsistent results." 2. It is reasonable to compare the power of both Cox UM-MDR and Cox-MDR by significance testing for the interaction effects in a Cox model.

Minor

1. Most complex diseases are associated with multiple genes and their interactions. Needs a citation

2. Spacing is inconsistent in the abstract

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