Reviewer's report

Title: ATHENA: A Knowledge-Based Hybrid Backpropagation-Grammatical Evolution Neural Network Algorithm for Discovering Epistasis among Quantitative Trait Loci

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Reviewer: Mehmet Koyuturk

Reviewer's report:

The authors propose and test several methods on enhancing the performance of grammatical evolution algorithms in detecting epistatic interactions in GWAS. The paper is very well-written, proposed approaches are sound, and the effectiveness of these approaches are demonstrated by comprehensive experimental studies. An important point of improvement, though, would be to provide more details on the methods, which will help the relatively unfamiliar reader to appreciate the main methodological contributions of this paper.

In particular, I believe that the authors can address the following points to make the methods more accessible to the reader:

- The definition for semi-partial correlation coefficient requires explanation. What does R mean? What does Y mean? What is the difference between k and k’?

- The mapping of the biological problem to the computational abstraction needs to be explained. How is an epistatic interaction represented by a neural network? How is an individual solution coded? How is TBXO implemented and how is it different in the context of this problem as compared to other crossover techniques? Small graphic examples that give illustrative answers to these questions can be very helpful.

- How is the cross-validation done to select the best NN model? What does CV interval mean?

Minor points and typos:

- The use of the term "individual" could be confusing in the context of this problem, since it might refer to an individual in the population from which the GWAS data was collected or it can refer to an individual solution in the context of the GE algorithm. The authors should take care while using this term throughout (e.g., I was confused with the use of the term on Page 13 at first sight).

- Page 10: very minimal -&gt; very low

- Page 10: A recently developed a tool -&gt; A recently developed tool

- Page 14: only when used TBXO is used -&gt; only when TBXO is used

- Page 16: upper panel of Fig. 2, dashed line -&gt; upper panel of Fig. 3, dashed line
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.