Reviewer’s report

Title: Predicting the Difficulty of Pure, Strict, Epistatic Models: Metrics for Simulated Model Selection

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Reviewer: Alison Motsinger-Reif

Reviewer’s report:

The enclosed manuscript presents and compared different metrics to predict the difficulty of detecting simulated epistatic models. The manuscript is very well written, and the demonstration of the limitation of heritability as a simulation metric is an interesting and important point. Additionally, their implementation of these metrics into GAMETES makes the results readily accessible to the community.

While the overall study design is excellent, there a few considerations that should be addressed prior to publication.

Major Concerns:

1) The simulations are done using Hardy-Weinberg proportions, which is reasonable, but the authors should discuss the assumptions that this is making so that users of the software understand these assumptions (such as no selective pressure on the trait being simulated, etc).

2) The authors use a range of machine learning/data mining approaches to compare the difficulty measures, but do not use any traditional statistical approaches. The authors should also demonstrate the results with logistic regression (even if explicitly modeling the simulated model) to see how the different measures of difficulty impact the performance of more traditional approaches. This is important because for example, since SURF and EDM have such similar formulation, this could inflate the importance of EDM in this study as compare to methods such as logistic regression that minimize based on variation.

Minor Concerns:

1) The authors define a "significant" power as power above 0.8. Since they do not really mean statistical significance, using another word would avoid confusion.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable
**Statistical review:** Yes, and I have assessed the statistics in my report.