Reviewer’s report

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

Version: 1 Date: 11 June 2012

Reviewer: William Bush

Reviewer’s report:

Review: predicting Epistatic models

This interesting work evaluates measures of difficulty for multi-locus models, attempting to improve on the use of heritability alone in describing genetic models. The manuscript is well written, and addresses an important issue for readers in this area of statistical development and genetic modeling. I have the following concerns.

Minor Essential Revisions

1. I object to the use of the word “power” which holds a statistical connotation. I prefer the phrase “detection” which properly denotes that the method identifies a model without any evaluation of how likely that identification was to occur by chance alone. Each run of the listed algorithms will produce MANY models, of which you are checking for the presence of the true functional one. You will have an enormous false discovery rate based on how these experiments are designed. This is not relevant to the question you are asking, but the use of the phase “power” implies something which you are not evaluating.

2. Does the difficulty or ease of simulation of these models indicate anything about the likelihood of observing such models for human phenotypes?

3. Can you mathematically relate the EDM measure to heritability to ease its interpretation? Heritability relates to variance, which has known geometric analogs (hypervolume, etc).

4. Please define or comment on the relationship between COR and OR to clarify the differences for readers.

5. Aside from calling it a stochastic search algorithm, UCS is not defined when the acronym is used on page 8.

6. Can you comment a bit more on the decision to select the top 20% of SURF results? This seems like an enormous set of results.

7. Figure 3: the legend from figure 2 should be shown for figure 3 as well, or place them as separate panes of the same figure. The x axis refers to model numbers – this could be confusing to readers.

8. The results of this work might be easier to grasp if we could somehow visualize model complexity increasing as a function of EDM -- perhaps a series of penetrance function plots?
9. Are there guidelines you would recommend when conducting a simulation study? Evaluate models with increasing complexity while holding prevalence and heritability constant? Please comment on the circumstances in which each of the developed metrics would be most useful -- how do I know when to use EDM versus COR?

**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.

**Declaration of competing interests:**

I am a colleague and personal friend of the lead and senior author, but I do not feel that this relationship has impacted my review of this work.