Ranking the Fittest and the Flattest: Applications of the Rank Epistasis Model

Extension of: "Mapping the Peaks: Fitness Landscapes of the Fittest and the Flattest" (Franklin et al., 2019)

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Goal

The goal of this project is to apply a rank-based epistasis metric to fit and flat populations of digital organisms to test and develop more biologically relevant measures of levels of epistasis in genotypes.

Motivation

The "Survival of the Flattest" phenomenon, wherein selection in a population with high mutation rate favors robustness over pure replication speed, was first described nearly 20 years ago [1]. Since then, work has continued on uncovering the various mechanisms behind this process, including application of quasi-species models [2, 3] and investigation into the role of metabolic trade-off [4].

Most recently, Franklin et al. (2019) described a variety of metrics that distinguish "fit" populations (those under selection for rapid reproduction) from "flat" populations (those under selection for mutational robustness). Among others, they note fitness of single-mutant variants among flat populations was lower than in fit populations, while rates of positive epistatic interactions were higher in flat populations than in fit.

They further propose that the increased rate of positive epistasis in flat populations is in reality a result of a decrease in negative epistasis, as negative epistatic interactions are more likely to be lethal. However, this hypothesis is difficult to test using their measure of epistasis.

Additionally, Franklin et al.'s measurement of epistasis relies upon knowing precisely the fitness of each genotype in the population, a metric that is impossible to apply to biological systems. In biological systems, if fitness can be measured at all, it can often be measured only relative to other organisms in the population. Therefore, a metric to compare fitness ranks rather than fitness values may prove more useful for extensions of these recently-developed fittest and flattest metrics.

Therefore, I propose application of an in-development model of "rank epistasis" to fit and flat populations of digital organisms. This model calculates the impact of mutation of a single site on the fitness rankings of the overall population (the "epistatic load") by comparing how fitness rankings change across single-mutant variants.

Hypothesis

I predict that this rank epistasis metric will support Franklin et al. (2019)'s suspicion that flat populations experience more positive epistasis only because negative epistasis is so frequently lethal. If negative epistasis is indeed present in equal measure in fit and flat populations, the rank epistasis model should show similar levels of epistasis in each population. since the fitness of organisms *relative to each other* will not change if only the fitness of the population *overall* drops.

Methods

First, we will simulate populations on a fitness landscape that contains a high but narrow peak and a lower but flatter peak at varying mutation rates. This will give us fit and flat populations from which to draw. The populations' genomes will be binary, to make single-mutant variant creation more feasible.

Next, by capturing those adapted populations from MABE, we will first rank each individual. Then, we will create single-mutant variants for each site in the genome for each organism in the population.

For all mutants with a mutation at the same site, we will re-load that population into MABE using the population loader function and run them on the same landscape as the original wild-type organisms, and rank their fitness in the same way.

Using edit-distance metrics for the two lists of fitnesses for each organism, we will then compare the rankings in order to create our metric of rank epistasis between the populations.

Timeline

2/21	Have the World to run the experiments
2/28	Running fit and flat replicates
3/7	Create single-mutant variants
3/12	Running single-mutant variants
3/27	Begin analyzing rankings
4/15	Begin writing report
5/2	Final Reports Due

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3. Codoner, F.M., J.A. Daros, R.V. Sole, & S.F. Elena (2006). The fittest versus the flattest: Experimental confirmation of the quasispecies effect with subvial pathogens. *PLoS Pathogens* 2(12): e136.
4. Beardmore, R.E., I. Gudelj, D.A. Lipson, & L.D. Hurst (2011). Metabolic trade-offs and the maintenance of the fittest and the flattest. *Nature* 472: 342-346.
5. Franklin, J. T. LaBar, & C. Adami. (2019) Mapping the peaks: Fitness landscapes of the fittest and the flattest. *Artificial Life* 25: 250-262.