Modeling the Emergence of Epistatic Gene Combinations as a Phenotypic Function of Evolution

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What is epistasis?

Epistasis can produce wholes greater than the sum of their parts.

...a phenomenon where an expression of an organism is the result of a combination of interacting genes.
Example of Epistasis

Epistasis drives variation of dog coat color
Does nature have a preference for epistasis?

In other words, on the whole, will natural selection promote genetic configurations having a higher degree of genetic interaction over configurations that are less interdependent?
Variables and Methods

**Variables**

- $N = \text{number of loci within a species genome}$
- $K = \text{epistatic value of the organism } \{K \mid 0 < K \leq N - 1\}$
- $v_i = \text{locus fitness value } \{v_i \mid -1, 0, 1\}$
- $\psi_{i,j} = \text{epistatic fitness coefficient}$

**Fitness Calculations**

**Case 1: No Epistasis ($K=0$):**

Total Organism Fitness = $\sum_{i=0}^{n} v_i$

**Case 2: Epistasis ($0 < K \leq N-1$):**

Total Organism Fitness = $\sum_{i=0}^{n} v_i + \sum_{i=0}^{n} \sum_{j=0}^{k+1} \psi_{i,j} v_{i,j}$

**Key Methods**

- Each organism is haploid and has 8 genes.
- Each offspring is given a 6.67% chance for stepwise mutation of its $K$ value.
- Replication may only occur when an organism has a total fitness value $> 80$.
- Organisms with total fitness values between 0 and 79 have a chance of being eliminated at each pass.
- Organisms having a total fitness value $< 0$ are instantly eliminated.
Indexed Lookup Tables

Each $K$ has its own lookup table consisting of $2^{k+1}$ rows representing every possible combination of Boolean values.

A single uniform probability distribution is used to generate random fitness coefficients ($\psi_n$) for each row in every table.

The range of fitness values is identical for every table, regardless of the number of rows.
Software Framework

Simulation Engine (SE)

C PROGRAM

*.csv output

Analysis Engine (AE)

MYSQL

R / SPREADSHEET

Forward Time Simulation

PASS 1
PASS 2
PASS 3
PASS 4
PASS 5
PASS 6
PASS 7
Samples containing ~20 identically configured simulations for three distinct durations (time spans) were compared.

<table>
<thead>
<tr>
<th></th>
<th>SAMPLE 1</th>
<th>SAMPLE 2</th>
<th>SAMPLE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DURATION</strong></td>
<td>20 passes</td>
<td>25 passes</td>
<td>30 passes</td>
</tr>
<tr>
<td><strong># SIMULATIONS</strong></td>
<td>19 simulations*</td>
<td>20 simulations</td>
<td>19 simulations*</td>
</tr>
<tr>
<td><strong>AVG FITNESS, START</strong></td>
<td>18.262</td>
<td>-19.416</td>
<td>-20.676</td>
</tr>
<tr>
<td><strong>AVG FITNESS, END</strong></td>
<td>364.674</td>
<td>354.490</td>
<td>351.545</td>
</tr>
<tr>
<td><strong>AVG FITNESS, CHANGE</strong></td>
<td>346.412</td>
<td>373.907</td>
<td>372.220</td>
</tr>
<tr>
<td><strong>AVG INITIAL COUNT</strong></td>
<td>10 organisms</td>
<td>10 organisms</td>
<td>10 organisms</td>
</tr>
<tr>
<td><strong>AVG FINAL COUNT</strong></td>
<td>330 organisms</td>
<td>332 organisms</td>
<td>503 organisms</td>
</tr>
</tbody>
</table>
Results: Zooming In on Each Sample

Over the duration of each simulation:

- 20 pass sample had a 15.9% increase in K
- 25 pass sample had a 21.0% increase in K
- 30 pass sample had a 22.9% increase in K
Summary

The results suggest that:

• The mechanics of natural selection provide an arithmetic incentive for epistasis.

• Epistatic networks may leverage mutations for outsized fitness gains (aka "radical differentiation").

• Outsized fitness gains may fragment a population and drive speciation.
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