The Interactions of Selection With Genetic Drift Can Be Complicated Because the Changes in $p$ Induced By Drift are Random and Ever-Changing

Three Important Interactions:
1). Drift on “neutral surfaces” that influence subsequent evolution,
2). Shifting the focus of selection in an epistatic system, and
3). Adaptation through peak shifts (shifting balance).

1. Drift on a neutral surface

Hb-A, S and C

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>AA</th>
<th>AS</th>
<th>SS</th>
<th>AC</th>
<th>CS</th>
<th>CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>No</td>
<td>No</td>
<td>Yes (Severe)</td>
<td>No</td>
<td>Yes (Mild)</td>
<td>NO</td>
</tr>
<tr>
<td>Malarial Resistance</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Viability No Malaria</td>
<td>1</td>
<td>1</td>
<td>0.2</td>
<td>1</td>
<td>0.7</td>
<td>1</td>
</tr>
</tbody>
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The A and C Alleles Define A Set of Neutral Alleles in a Non-malarial Environment: Their Frequencies Are Determined by Genetic Drift and Mutation.
Adaptive Landscape

Once on the ridge, only drift and mutation influence the populations' position on the ridge.

Selection forces the populations to the top of the ridge.

Selection takes those populations that had higher frequencies of C due to drift and/or mutation to the C fixation equilibrium.

Selection takes those populations that had very low frequencies of C due to drift and/or mutation to the A/S polymorphic equilibrium.

Non-malarial environment

Malarial environment

The genotype–phenotype model.

Circles = Genotypes
Colours = Phenotypes
Solid lines = neutral mutations
Dashed lines = non-neutral mutations
Different Neutral Genotypes Define Distinct "Phenotypic Neighborhoods"

Genetic drift can create a diversity of initial conditions for allelic subsets that are neutral under one environmental condition that strongly influence the adaptive outcome when the environment is altered. This adds to the difficulty in predicting the course of adaptive evolution, but it also increases the diversity of adaptive responses shown by populations to altered environments.

2). Shifting the focus of selection in an epistatic system

Epistasis Between ApoE and LDLR

HDL particle containing cholesterol

ApoE

ApoB

LDL particle containing cholesterol

Plasma membrane

LDL receptors

Clathrin
Epistasis Between ApoE and LDLR for LDL Cholesterol

Two Populations

- Frequency ApoE-4 Allele = 0.152
- Frequency ApoE-3 Allele = 0.77
- Frequency LDLR A2 Allele = 0.78
- Frequency ApoE-4 Allele = 0.95
- Frequency ApoE-3 Allele = 0.03
- Frequency LDLR A2 Allele = 0.50
Quantitative Genetic Components As a Function of Allele Frequencies:  
A. \( \varepsilon 4 \) allele at ApoE is Rare, A2 at LDLR Common;  
B. Reversed

Epistatic Shifts in The Focus of Selection Are Important in Some Founder and Bottlenecked Populations: Can Also Convert Epistatic Variance into Additive Variance and Thereby Increase the Additive Variance Even Though Drift Decreases the Genetic Variability at the Molecular Level.
3). Adaptation through peak shifts

Assume a random mating population such that:

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
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<tbody>
<tr>
<td>Fitnesses</td>
<td>1</td>
<td>0.9</td>
<td>0.95</td>
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Eight runs of a computer simulation of an idealized, randomly mating population of size 1000 with an initial \( p = 0.25 \) (<1/3).
Eight runs of a computer simulation of an idealized, randomly mating population of size 100 with an initial $p = 0.25$ (<1/3).

Eight runs of a computer simulation of an idealized, randomly mating population of size 100 with an initial $p = 0.25$, but now $w_{Aa}=0.5$ (stronger selection).
Eight runs of a computer simulation of an idealized, randomly mating population of size 100 with an initial $p = 0.25$.

When populations are isolated and $N$ is small, they rapidly go to fixation and all evolution, both random and adaptive, stops. Hence, peak shifts in isolated demes affect only that deme.

Eight runs of a computer simulation of an idealized, randomly mating population of size 100 with an initial $p = 0.25$, and an island model of gene flow with $m=0.01$ ($Nm=1$).

Note that in contrast to the isolated populations, gene flow among subdivided populations promotes variation in local demes, hence they never completely lose their potential to evolve, and in the long term, peak shifts are more probable.
When selection is stronger in keeping a deme close to the higher peak, the same amount of gene flow or drift is less important relative to selection on the higher peak than on the lower. Thus, for the same amount of gene flow and drift, it is generally more likely to shift from a lower peak to a higher peak than the opposite. Although peak shifts are random at the local deme level, the global probabilities of peak shifts over many demes are biased in favor of higher peaks. Therefore, even though “random” genetic drift is the mechanism for exploring the adaptive surface, the demes preferentially end up on the higher peaks. This in turn causes an increasing shift in gene flow as a force bringing populations to the higher adaptive peaks.

Simulate Role of Gene Flow As a Directional Force With The Source-Sink Model; That is, regard target demes as receiving genetic input from a much larger entity (the species as a whole) with allele frequency $p$. 

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Common Gene Pool From All Local Demes

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<td>$N$</td>
<td>$N$</td>
<td>$N$</td>
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</table>

Local Demes
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Eight runs of a computer simulation of an idealized, randomly mating population of size 100 with an initial $p = 0.25$, and an source-sink model of gene flow with $m=0.01$ and an overall allele frequency of 0.1 (most demes are on or near lower peak).

Although gene flow biases populations to lower peak, still some demes make the transition to upper peak.

Eight runs of a computer simulation of an idealized, randomly mating population of size 100 with an initial $p = 0.25$, and an source-sink model of gene flow with $m=0.01$ and an overall allele frequency of 0.5 (half of the demes are now on or near the upper peak).

As more and more demes shift to the upper peak, the overall $p$ increases and the bias of gene flow accentuates more peak shifts (note deterministic line -- gene flow is now a directional force).
Wright (1931, 1932) called the above model of adaptive evolution the shifting balance theory in which shifting balances between the relative strengths of selection, drift and gene flow allow local demes in a subdivided population to explore the adaptive surface, then preferentially evolve towards the higher peaks in this surface, and ultimately draw other demes towards the higher peaks via asymmetric gene flow.

How Likely is Shifting Balance?

- This mode of adaptive evolution requires:
  A. Population subdivision, with Nm ~ 1
  B. Multiple selective equilibria (adaptive peaks)
- How often do these conditions occur in reality?
Temporal and Spatial Heterogeneity

Collared lizards show different amounts of subdivision and gene flow across their range, from NE Ozarks to TX.

Temporal and Spatial Heterogeneity

- Whole population doesn’t have to be subdivided for shifting balance to occur
- Nor do appropriate conditions have to persist for long to cause an adaptive peak shift
- This shift shapes subsequent evolution of the population
Genetic Architecture

- Shifting balance requires an adaptive landscape with multiple peaks
- Epistatic and/or pleiotropic genetic architecture can lead to this type of landscape
- Solely additive gene effects may lead to a single adaptive peak

Real Biological Systems

- Interactions like epistasis and pleiotropy are the norm
- An allele with the same fitness effect in every genetic background: implausible
- Sickle cell anemia, classic Mendelian single-locus trait--much pleiotropy and epistasis! Several adaptive peaks.
Fisher’s idea of the Adaptive Hypersphere: only one adaptive peak, and a sphere of positions for the population to move that are closer to the peak than it is at present.