### Temporal Heterogeneity

![Temporal Heterogeneity](image1)

### Environmental Heterogeneity/Grain

<table>
<thead>
<tr>
<th>Physical Grain</th>
<th>Spatial</th>
<th>Temporal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coarse</td>
<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
</tr>
<tr>
<td>Fine</td>
<td><img src="image4" alt="Image" /></td>
<td><img src="image5" alt="Image" /></td>
</tr>
</tbody>
</table>
COARSE-GRAINED TEMPORAL HETEROGENEITY

- Populations can move through time by reproduction.
- Although the environment may be constant for the individuals of any one generation, heterogeneity can occur across generations.
- Gene pools do not change instantly in response to a changed environment, but usually there is a time lag before the gamete frequencies can fully adjust. These time lags in turn are strongly influenced by the genetic architecture and other factors that influence the average excess.
- E.g., with the introduction of the Malaysian agricultural complex into sub-Saharan Africa, there was a rapid response by the $S$ allele to the new environment, but a slow response by the $C$ allele.

E.g., *Adalia bipunctata*

German populations have a genetically based color polymorphism and two generations per year (Timofeeff-Ressovsky 1940). One generation hibernates over winter as adults and comes out in the spring. The second generation lives over the summer and into the autumn.
The black forms survive better in the summer, but the red forms survive hibernation much better. This results in an annual cycle with the red forms being 63.4% of the population in April and the black forms 58.7% of the population in October.

Note that the red form is most common in the spring, just as the environmental conditions favoring the black forms are beginning. By autumn, the black forms predominate, yet the red form is better adapted to hibernation. Thus, the time lags inherent in the evolutionary response yield seemingly maladaptive consequences.
A one locus, two allele model of coarse-grained seasonal selection (Hoekstra 1975)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zygotic Frequency at Beginning of Cycle</td>
<td>$p^2$</td>
<td>$2pq$</td>
<td>$q^2$</td>
</tr>
<tr>
<td>Fitness in Environment 1</td>
<td>$w_1$</td>
<td>1</td>
<td>$r_1$</td>
</tr>
<tr>
<td>Genotype Frequency After Selection</td>
<td>$p^2w_1$</td>
<td>$2pq$</td>
<td>$q^2r_1$</td>
</tr>
<tr>
<td>Zygotic Frequency at Second Generation</td>
<td>$p^2(w_1+q)^2$</td>
<td>$2pq(w_1+q(r_1+p))$</td>
<td>$q^2r_1^2$</td>
</tr>
<tr>
<td>Fitness in Environment 2</td>
<td>$w_2$</td>
<td>1</td>
<td>$r_2$</td>
</tr>
<tr>
<td>Genotype Frequency After One Cycle</td>
<td>$p^2w_2$</td>
<td>$2pqw_2$</td>
<td>$q^2w_2$</td>
</tr>
</tbody>
</table>

Where:

$w_i = p^2w_{i1} + 2pqw_{i1} + q^2w_{i1}$

$w_{aa} = w_i(w_1+p) + q^2r_1$

$w_{Aa} = p^2w_1 + 2pqw_1 + q^2w_1$

$w_{AA} = p^2w_1 + 2pqw_1 + q^2w_1$

$w_1 = p^2w_{i1} + 2pqw_{i1} + q^2w_{i1}$

$w_2 = p^2w_{i1} + 2pqw_{i1} + q^2w_{i1}$

$w_{i1} = p^2w_{i1} + 2pqw_{i1} + q^2w_{i1}$

$w_i = p^2w_{i1} + 2pqw_{i1} + q^2w_{i1}$

$w_{i0} = p^2w_{i1} + 2pqw_{i1} + q^2w_{i1}$

$w_{i0} = p^2w_{i1} + 2pqw_{i1} + q^2w_{i1}$

A one locus, two allele model of coarse-grained seasonal selection (Hoekstra 1975)

- Note that the cycle fitnesses are all of the form $w_i = p^2w_{i1} + 2pqw_{i1} + q^2w_{i1}$ where we let $i=2$ correspond to AA, $i=1$ to Aa, and $i=0$ to aa.
- This mathematical form is identical to that of the model of competitive selection given earlier.
- This means that all the results inferred from the frequency-dependent model of competition can be applied to this model of cyclical selection.
  - the polymorphism is protected when the geometric mean of the homozygote fitnesses over the environment cycle is less than that of the heterozygote.
  - there is the potential for multiple equilibrium
  - the initial state of the gene pool can influence the evolutionary outcome
  - Fisher’s fundamental theorem can be violated
  - The system can display chaotic dynamic behavior.
Time Lags And Maladaptive Traits

• Haldane and Jayakar (1963) showed how a trait that is normally mildly selected against but that is strongly selected for about once in every 20 generations can persist in high frequencies in a population.
• A possible example of this is the trait type 2 diabetes mellitus.
• Type 2 diabetes is one of the more common diseases affecting humanity, with at least 250 million cases worldwide and increasing at an alarming rate.
• Adult onset diabetes alone accounted for 15% of the total health care costs in the US in 2003.

Type 2 Diabetes

[Diagram showing the relationship between genes, environment, and Type 2 diabetes factors]
Type 2 Diabetes


Type 2 Diabetes

• Neel (1962) suggested a possible answer to why T2DM is so common: the thrifty genotype hypothesis.
• The same genetic states that predispose one to diabetes also result in a quick insulin trigger even when the phenotype of diabetes is not expressed.
• Such a quick trigger is advantageous when individuals suffer periodically from famines since it would minimize renal loss of precious glucose and result in more efficient food utilization.
• When food is more plentiful, selection against these genotypes would be mild because the age of onset of the diabetic phenotype is typically after most reproduction and because the high sugar, high calorie diets found in modern societies that help trigger the diabetic phenotype are very recent in human evolutionary history.

Type 2 Diabetes

• Basic prediction of the thrifty genotype hypothesis:

• Populations with a history of periodic famine should be more prone to diabetes than populations without such a history when exposed to modern high calorie, high carb diets.
Type 2 Diabetes

The Pima Indians have a history of severe famine and now have a high rate of diabetes.

<table>
<thead>
<tr>
<th>Population grouping</th>
<th>Region</th>
<th>Percentage prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europeans</td>
<td>Britain</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Germany</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Australia (1981)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Australia (2002)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>United States</td>
<td>8</td>
</tr>
</tbody>
</table>

Populations Without A History of Frequent Famines
Type 2 Diabetes

- Several studies indicated that SNP44 in the Calpain-10 gene is associated with increased risk for type II diabetes.
- Vander Molen et al. (2004) studied variation around this SNP in various populations.
- The results showed a strong signature of selection rapidly increasing the frequency of this SNP in Mexican Americans, a population at extremely high risk to diabetes and a history of famines.

Most of the Common Systemic Diseases in Humans Have Been Related to a variant of the Thrifty Genotype Hypothesis

- Humans have been selected for large brain size.
- This large size is accomplished by extra growth after birth.
Most of the Common Systemic Diseases in Humans Have Been Related to a variant of the Thrifty Genotype Hypothesis

• Much of this post-natal brain growth is due to the unique way in which humans have evolved to use fat.

• Humans have the fattest infants of all other mammals except sea mammals.

• The same genes selected to meet this demand also predispose adult humans in the modern environment to cardiovascular and Alzheimer’s disease.

Most of the Common Systemic Diseases in Humans Have Been Related to a variant of the Thrifty Genotype Hypothesis

The fact that diseases such as type II diabetes have shown dramatic increases, often over just a few years, shows that phenotypes can change rapidly in response to changing environments with little or no underlying genetic evolution. Hence, just as with counter-gradient selection, changes with phenotype over time must be interpreted cautiously with regard to evolution.

One interesting interaction between phenotypic plasticity and evolution is GENETIC ASSIMILATION.
Genetic assimilation occurs when selection acts upon heritable variation in phenotypic plasticity to turn a phenotype directly stimulated by an altered environment (plasticity) into a fixed phenotypic response no longer sensitive to the ancestral environmental triggers (assimilation).

E.g., Paedomorphy in *Ambystoma*

Poor nutrition, darkness, and low temperature all tend to reduce the production of TH in ambystomid salamanders, resulting in phenotypic plasticity for the timing of metamorphosis. Indeed, metamorphosis can be completely prevented under appropriate environmental conditions, resulting in aquatic larval forms that became sexually mature and thereby bypass the terrestrial adult phase completely. Such sexually mature aquatic salamanders are called paedomorphs.
E.g., Paedomorphy in *Ambystoma*

During the glacial period, fossils from the western area consist of giant paedomorphs. Clade 4-1 was confined to the Ozarks during the Pleistocene, where there are few permanent ponds. It then expanded westwards, but lost the capacity for paedomorphy.

As the climate changed, clade 4-2 expanded eastward, retaining the ability to produce paedomorphs, particularly in colder, permanent ponds.
E.g., Paedomorphy in *Ambystoma*

Within historic times, clades 4-1 and 4-2 have begun to overlap in range. Both now live in permanent ponds together, but only clade 4-2 salamanders can yield paedomorphs.

*Ambystoma mexicanum* lives in permanent lakes in the mountainous region of Mexico. This environment favors paedomorphy, but when placed in environments that favor metamorphosis in other tiger salamanders, *A. mexicanum* fails to undergo metamorphosis.
E.g., Paedomorphy in *Ambystoma*

We seem to have a strange, almost Lamarckian phenomenon: paedomorphy and metamorphosis were plastic, but when a salamander population is placed in an environment that favors metamorphosis, it becomes genetically incapable of paedomorphy; whereas a second population found in an environment that favors paedomorphy becomes genetically incapable of metamorphosis. Somehow, prolonged exposure to the environment favoring a particular phenotypic response has become “genetically assimilated” and is now expressed (or not expressed) regardless of the environment.

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E.g., Paedomorphy in *Ambystoma*

One explanation is threshold selection.
Another explanation is neutral mutations. E.g., Paedomorphy in *Ambystoma*

Prolonged environmental suppression of metamorphosis could make the genes in this pathway effectively neutral. Hence they could now accumulate loss of function mutations, and hence are now genetically incapable of metamorphosis.

**Epigenetic assimilation**

Epigenetics is the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence.
Stöger (2008. The thrifty epigenotype: An acquired and heritable predisposition for obesity and diabetes? BioEssays 30:156-166) argues that virtually all animals have been selected to be metabolically plastic in dealing with feast/famine conditions.

Epigenetic assimilation

Epigenetic assimilation
Intrauterine growth retardation (IUGR) has been linked to later development of type 2 diabetes in adulthood by permanently modifying gene expression of susceptible cells. Studies in the IUGR rat also demonstrate that an abnormal intrauterine environment induces epigenetic modifications of key genes regulating beta-cell development (Simmons. 2007. Pediatr Res 61:64R-67R).
Epigenetic assimilation

Note: The Thrifty Genotype and the Thrifty Epigenetic Phenotype Hypotheses Are Not Mutually Exclusive.
Fine-Grained Spatial and Temporal Heterogeneity

Recall Fisher’s Model:

\[ P_{ij} = \mu + g_i + e_j \]

The phenotypes associated with genotype \( i \) are always modeled as having an environmental variance, and the genotypic values and deviations are simply averages over all individuals sharing this genotype.

Hence, fine-grained heterogeneity can be incorporated into the “constant-fitness” (i.e., average \( g_i \)) model.
Fine-Grained Heterogeneity

There are three circumstances in which this approach is inadequate:

1. Survival of a new mutant – when a mutation first appears, it is found in only one or a few individuals the first several generations, and the variance in fitness can have a major impact on its probability of survival.

2. Selection in local populations with small variance effective size – sampling error of allele frequencies can’t be ignored, and neither can the sampling error of fitness.

3. Models of how organisms adapt to fine-grained heterogeneity.

Survival of a new mutant (A) in a large random mating population

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Fitness</td>
<td>1+s</td>
<td>1</td>
</tr>
<tr>
<td>Variance in Fitness</td>
<td>1+s+σ²</td>
<td>1</td>
</tr>
</tbody>
</table>

\[
\Pr(A \text{ survives}) = \frac{2s}{1 + s + \sigma_s^2}
\]
Survival of a new mutant (A) in a large random mating population

<table>
<thead>
<tr>
<th>Genotype</th>
<th>A’a</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Fitness</td>
<td>1+s</td>
<td>1+s</td>
<td>1</td>
</tr>
<tr>
<td>Variance in Fitness</td>
<td>1+s+σ²</td>
<td>1+s+σ²</td>
<td>1</td>
</tr>
</tbody>
</table>

Note, A and A’ are “neutral” alleles with respect to each other in terms of average fitness; yet, natural selection will favor the fixation of the mutant with the smaller variance in fitness. I.e, favor homeostasis to fine-grained heterogeneity.

Fixation of a favorable allele (A) in a finite random mating population

<table>
<thead>
<tr>
<th>Genotype</th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Fitness</td>
<td>1+2s</td>
<td>1+s</td>
<td>1</td>
</tr>
</tbody>
</table>

Let the selection coefficient be a random variable with mean s and variance v in response to fine grained heterogeneity. If v =0, then the probability of fixation of A in an ideal deme of size N is:

\[ u = \frac{1 - e^{-2s}}{1 - e^{-4Ns}} \]

But with v>0, then:

\[ u = \frac{1 - e^{-2(1-\gamma_{2N})}}{1 - e^{-4N(1-\gamma_{2N})}} \]
Modeling The Evolution of Homeostasis and Threshold Effects

It is often observed that organisms have effective short term homeostatic mechanisms to buffer against fine-grained heterogeneity, but these mechanisms break down if extreme environments persist, and then are replaced by longer-term homeostatic mechanisms (which often are more costly).

e.g., plants subject to flooding:

• Short-term; switch to anaerobic metabolism in their roots

• Long-term: anaerobic metabolism is less efficient than aerobic metabolism and produces toxins, therefore switch to other mechanisms such as forming adventitious roots, absorbing oxygen through the stomata in the leaves and transporting it to the roots, and forming lenticels for gaseous exchange.
Modeling The Evolution of Homeostasis and Threshold Effects

Models show that short-term solutions are favored when the environment does not persist in any one state for very long.

When environmental states can persist for long periods, favor a mixture of short-term and long-term homeostatic mechanisms.