Long-Term Response and Selection limits

Bruce Walsh lecture notes
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Detailed reading: online chapters 23, 24
Idealized Long-term Response in a Large Population

Additive variance (and hence response) should be roughly constant over the first few generations, giving a nearly linear response.

As generations proceed, sufficient allele frequency change should accrue to significantly alter genetic variances.

They can potentially increase or decrease, depending on starting frequencies.

Eventually, all initial standing additive variation is exhausted and a selection limit (or plateau) reached.
When the alleles favored by selection are dominant, response slows down considerably as these become common. Response can be so slow as to suggest a limit.
This apparent limit caused by inefficient selection against heterozygotes. Inbreeding can increase efficiency.

Example: Falconer (1971) increased mouse litter size

An apparent limit was seen. Four sublines created and subjected to both inbreeding and selection

A line created by then crossing these inbred-selected sublines was itself selected. Result was an improvement of 1.5 mice/litter over apparent limit

Falconer’s interpretation: Many recessive alleles decreasing litter size were segregating in the line, some of which were lost in the sublines.
Deterministic Single-Locus Theory of Response

Suppose the genotypic values of $aa:aA:AA$ are $0: a(1+k): 2a$, and let $p = \text{freq}(A)$

The contribution to the mean trait value from this locus is

$$m(p) = 2ap[1 + (1-p)k]$$

Thus, the contribution is $A$ is fixed, given it starts at value $p_0$ is

$$m(1) - m(p_0) = 2a(1- p_0)(1- p_0k)$$
Total contribution to response for additive ($k=0$), A dominant ($k=1$), A recessive ($k=-1$)
Allele frequency at which half the final response occurs
Total contribution to selection limit and the frequency at which half this contribution occurs

<table>
<thead>
<tr>
<th></th>
<th>Total Contribution</th>
<th>$p_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A$ additive ($k = 0$)</td>
<td>$2a(1 - p_0)$</td>
<td>$(1 + p_0)/2$</td>
</tr>
<tr>
<td>$A$ dominant ($k = 1$)</td>
<td>$2a(1 - p_0)^2$</td>
<td>$1 - [(1 - p_0(2 - p_0)/2]^{1/2}$</td>
</tr>
<tr>
<td>$A$ recessive ($k = -1$)</td>
<td>$2a(1 - p_0^2)$</td>
<td>$[(1 - p_0^2)/2]^{1/2}$</td>
</tr>
</tbody>
</table>
Allele frequency Dynamics over time

If the selection intensity on the trait is $i$, the expected (deterministic) change in allele frequency is

$$\Delta p \approx \frac{a \cdot i}{\sigma_z} p(1-p) \left[1 + k(1-2p)\right]$$

The curves for response under different $n$ number of loci were generated assuming $V_E = 100$, and

$$\Delta p_t = \frac{a \cdot i \cdot p_t(1-p_t)}{\sigma_z(t)} = \frac{a \cdot i \cdot p_t(1-p_t)}{\sqrt{\sigma_A^2(t) + \sigma_E^2}} \approx \frac{a \cdot i \cdot p_t(1-p_t)}{\sqrt{2na^2p_t(1-p_t) + 100}}$$
Deterministic time for response

How long does it take to reach p given start at $p_0$

$$t_{p_0,p} \approx s^{-1} \ln \left( \frac{p (1 - p_0)}{p_0 (1 - p)} \right)$$  \hspace{1cm} \text{A additive}$$

$$t_{p_0,p} \approx s^{-1} \frac{1}{2} \left[ \ln \left( \frac{p (1 - p_0)}{p_0 (1 - p)} \right) - \frac{1}{p} + \frac{1}{p_0} \right]$$  \hspace{1cm} \text{A recessive}$$

$$t_{p_0,p} \approx s^{-1} \frac{1}{2} \left[ \ln \left( \frac{p (1 - p_0)}{p_0 (1 - p)} \right) + \frac{1}{1 - p} - \frac{1}{1 - p_0} \right]$$  \hspace{1cm} \text{A dominant}$$

$$s = (a/\sigma_z)^*i \quad \text{Note time scales as 1/s}$$
Effect of the number of loci on limit. N equal loci, Each with $p_0 = 0.5$. $V_A = 100$, $V_E = 100$,

<table>
<thead>
<tr>
<th>n</th>
<th>$a$</th>
<th>$R(\infty)$</th>
<th>$R(\infty)/\sigma_z(0)$</th>
<th>$t_{0.5} \times i$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>6.32</td>
<td>31.6</td>
<td>2.2</td>
<td>1.7</td>
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<tr>
<td>10</td>
<td>4.47</td>
<td>44.7</td>
<td>3.2</td>
<td>2.5</td>
</tr>
<tr>
<td>25</td>
<td>2.82</td>
<td>70.7</td>
<td>5.0</td>
<td>3.9</td>
</tr>
<tr>
<td>50</td>
<td>2.00</td>
<td>100.0</td>
<td>7.1</td>
<td>5.5</td>
</tr>
<tr>
<td>100</td>
<td>2.41</td>
<td>141.4</td>
<td>10.0</td>
<td>7.8</td>
</tr>
<tr>
<td>250</td>
<td>0.89</td>
<td>223.6</td>
<td>15.8</td>
<td>12.3</td>
</tr>
<tr>
<td>500</td>
<td>0.63</td>
<td>316.2</td>
<td>22.4</td>
<td>17.4</td>
</tr>
</tbody>
</table>

allele effect  Limit  Limit in Phenotypic SDs  Time to reach 1/2 limit
Estimating Selection Limits and Half-lives

Since a limit is approached asymptotically, a typical measure is the half-life of response.

The limit and half-life are usually estimated from the data by curve fitting.

James (1965) suggested fitting an exponential curve,

\[ R(t) = a + bS_c^t + e \]

Alternatively, a quadratic regression can be used

General problem with any method: limit is extrapolated from the data.
Eisen (1972) looked at 22 generations of selection for 12-day litter weight in mice.

Both the exponential and quadratic models had $r^2 = 0.81$, so cannot distinguish between models based on differential fit.

<table>
<thead>
<tr>
<th>Estimate</th>
<th>Model</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection limit</td>
<td>Quadratic</td>
<td>5.79 ± 0.84</td>
</tr>
<tr>
<td></td>
<td>Exponential</td>
<td>8.18 ± 0.29</td>
</tr>
<tr>
<td>Half-life</td>
<td>Quadratic</td>
<td>8.58</td>
</tr>
<tr>
<td></td>
<td>Exponential</td>
<td>12.48</td>
</tr>
</tbody>
</table>
General Features of Long-term Selection Experiments

• Selection routinely results in mean phenotypes far outside of the base-population range.
• Response can be very uneven. Bursts of accelerated response can be seen. Variances (genetic and phenotypic) can increase throughout experiment.
• Reproductive fitness usually declines as selection proceeds.
• Most populations appear to approach a selection limit. (Although this may simply be an artifact of short time scales/small $N_e$.)
• Considerable additive variation may be present at an apparent selection limit.
Cautionary Notes on Limits

• Scale effects can be important

• It is extremely important to recognize that most long-term experiments are a biased sample

• Most “long-term” experiments are less than 40 generations

• Controlled experiments over 20 generations typically restricted to a few model organisms.
Increases in Variances and Accelerated Responses

Contrary to the expectations of idealized response, phenotypic and additive variance often increase during the course of response, resulting in bursts of response.

One obvious source are rare favorable alleles whose frequency increases under selection, increasing the variance.

For example, consider the response when we have 100 loci with $a = 0.5$ and $p = 0.5$ plus one major gene ($a = 10$) at low frequency ($p = 0.05$). Assume this locus is either additive ($k = 0$) or recessive ($k = -1$).
Note the burst of response as this allele increases in frequency
$h^2$ increases as this allele becomes more common
Once the allele becomes sufficiently common, its frequency rapidly increases. As it goes to fixation, $h^2$ decreases.

Note the delay for the recessive
Two other potential sources for these bursts in response are:

1) Major alleles generated by mutation during the experiment.

Yoo (1980) selected for increased abdominal bristle number in Drosophila. 5 of 6 replicate lines showed accelerated response after 20 generations of selection. Yoo was able to correlate many of these bursts with the appearance of new major alleles that were also lethal as homozygotes.
2) Accelerated response can also occur when recombination joins favorable linked alleles.

Thoday selected for increased sternopleural bristle number in Drosophila, observing a burst of response around 20 generations. He was able to show using polygenic mapping that the population initially consisted mainly of -- gametes plus a few + - and - + gametes. Selection increased these to the point where + - / - + heterozygotes occurred and recombined to give ++
Conflicts Between Natural and Artificial Selection

- Selection increases the amount of inbreeding.
- Loci favored by artificial selection can be in linkage disequilibrium with alleles having deleterious effects on fitness.
- Alleles favored by selection can have deleterious effects on fitness.
  - **Direct effects**: The trait value favored by artificial selection is deleterious to natural selection
  - **Pleiotropic effects**: Alleles effect both the trait and also(via other pathways) fitness. The trait value itself has no fitness effects.
Frankham et al.’s Drosophila experiment

Frankham et al. Selected for increased ethanol tolerance in Drosophila. They attempted to reduce the expected decline in mean fitness by culling those pairs showing reduced reproductive fitness.

Their logic is that if deleterious fitness effects during selection were largely caused by rare recessives (which increase by inbreeding during selection), then culling a small fraction of the lowest fitness individuals would cull those homozygotes for these recessives, reducing their effect.

Following artificial selection, adults were placed in vials. Those yielding the lowest number of pupae were culled, creating an HS line.

The HS line showed the same response as a line without reproductive culling (ethanol selection only). Further, the HS line showed the same fitness as the base-population (unselected) line.
A similar study on 30 years of selection on chickens, where the lowest reproducing adults were also culled, showed similar results.

The inbreeding effect of selection results from finite population size being further exaggerated by selection. These effects should not be as pronounced in lines using larger $N_e$.

However, if fitness declines arise because of linkage disequilibrium between naturally and artificially selected loci, or if loci have pleiotropic effects on both fitness and the trait, or if the trait itself is under natural selection, the response is expected to decay upon relaxation of selection.

Such a decay upon relaxation is also possible if maternal effects and/or epistasis has been important to the response. However, we expect an increase in fitness upon relaxation if this reduction in the mean upon stopping selection is due to natural selection.
Example: Cruz & Wiley (1980) observations on egg rejection Rates in Weaver Birds on the island of Hispaniola

Village Weaver Bird introduced from Africa 200 years ago.

Studies in Africa show female Weavers recognize their own eggs, and eject foreign eggs

This rejection postulated to occur in response to selective pressure from the brood parasite, the Didric Cuckoo.

Average African rates of rejection 40-55%. Rejection rates on Hispaniola around 12%

Since Hispaniola (until the 1970’s) free of brood parasites, potential relaxation of response in absence of selective pressure
What is the nature of selection limits?

Changing selection schemes and inbreeding offer two approaches for characterizing any remaining variance.

If additive variance is present, lines should show a reversed response, when line subjected in opposite direction.

Presence of non-additive variance indicated if the lines show inbreeding depression (change in mean upon inbreeding).
### Summary of some apparent selection limits

<table>
<thead>
<tr>
<th>Trait</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced thorax length in Drosophila</td>
<td>Exhaustion of $V_A$. No change under inbreeding, no reversed response.</td>
</tr>
<tr>
<td>Increased body weight in mice</td>
<td>Exhaustion of $V_A$. No reversed response.</td>
</tr>
<tr>
<td>Egg production in Drosophila</td>
<td>Exhaustion of $V_A$. Significant non-additive variance.</td>
</tr>
<tr>
<td>Wing length in Drosophila</td>
<td>Significant $V_A$ at limit. Segregating lethals and an overdominant locus for wing length</td>
</tr>
<tr>
<td>Reduced body size in mice</td>
<td>Opposing natural selection. Reversed response, relaxation of mean. Reduction in viability</td>
</tr>
<tr>
<td>Abdominal bristles in Drosophila</td>
<td>Segregating homozygote lethal increases bristles as a heterozygote</td>
</tr>
<tr>
<td>Pupal weight in Tribolium</td>
<td>Opposing natural selection. Significant $V_A$ at limit. Decay in response under relaxed selection</td>
</tr>
<tr>
<td>Shank length in Chickens</td>
<td>Opposing natural selection. Trait negatively correlated with hatchability</td>
</tr>
<tr>
<td>Litter size in mice</td>
<td>Negative genetic correlations btw direct &amp; material effects</td>
</tr>
<tr>
<td>Increased mouse body size</td>
<td>Negative correlation btw weight &amp; litter size</td>
</tr>
<tr>
<td>Increase mouse litter size</td>
<td>Apparent limit due to slow response from dominant alleles</td>
</tr>
</tbody>
</table>
Long-Term Response in Finite Populations

Fixation probabilities for favorable QTL alleles

\[ U(q_0) \sim q_0 + 2N_e s \, q_0(1 - q_0) \quad \text{for} \quad 2N_e |s| < 1 \]

Selection dominates fixation dynamics when

\[ 4N_e \, s = 4N_e \, i \, a / \sigma_z \gg 1 \quad \text{or} \]

\[ 4N_e i \gg \sigma_z / a = 1/d^* \]

Hence, by increasing \( 4N_e i \), favorable alleles of smaller effect (and/or at lower frequencies) become increasingly likely to be fixed.
Selection Limits Under Drift and Selection

The expected contribution under drift from an allele at frequency $q_0$ is

$$\Delta = m(q_\infty) - m(q_0)$$

$q_\infty = 1$ w.p. $U(q_0)$, else $= 0$ w.p. $1 - U(q_0)$

Hence, for an additive locus,

$$E[\Delta] = 2a[U(q_0) - q_0]$$

Recalling for weak selection $U(q_0) \sim q_0 + 2N_es q_0(1 - q_0)$, $s = i a / \sigma_z$

$$E[\Delta] = 4N_e(i a / \sigma_z ) a q_0(1 - q_0),$$

$$= 2N_e i \left[ 2a^2 q_0(1 - q_0) \right] / \sigma_z$$

$$= 2N_e i \sigma_A^2(0) / \sigma_z = 2N_e R(1)$$
Robertson’s Theory of Selection Limits

The expected selection limit is $R(\infty) = 2N_e R(1)$

Or $2N_e$ times the initial response. This result is due to Robertson (1960)

More generally, under weak selection,

$$R(t) \approx 2N_e \left(1 - e^{-t/2N_e}\right) R(1)$$

The expected time until 50% of the response is

$$t_{0.5} = 1.4 N_e$$
Optimal Long-term Response

A key result of Robertson’s theory can be seen by writing the limiting response $2N_e R(1)$ as

$$\sigma_A^2(0) / \sigma_z$$

Hence, there are tradeoffs between a larger short-term response (larger $i$, small $N_e$) and the optimal long-term response (smaller $i$, larger $N_e$).

Robertson showed optimal response is choosing half of the individuals, as this maximizes $2N_e i$. 
Tests of Robertson’s Theory

Robertson’s theory applies to the expected response from the existing variance in the base population.

It assumes weak selection on the underlying loci. Stronger selection on the underlying loci decreases both $R(\infty)$ and $t_{0.5}$. Hence, it provides upper limits.

Robertson’s theory ignores new mutation input. Hence, tests of its fit typically occur in very small populations where the base-population variances is exhausted before new mutational input becomes important.
Robertson's Theory predicts that the selection limit should increase as we increase $N_e i$. This is generally seen.

For example, Jones et al (1968) looked at increased abdominal bristle number in *Drosophila* under different $N_e$ and $i$ values,

<table>
<thead>
<tr>
<th>$N_e$</th>
<th>$i$</th>
<th>$R(50)$</th>
<th>$N_e$</th>
<th>$i$</th>
<th>$R(50)$</th>
<th>$N_e$</th>
<th>$i$</th>
<th>$R(50)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1.6</td>
<td>16.3</td>
<td>20</td>
<td>1.7</td>
<td>20.3</td>
<td>40</td>
<td>1.7</td>
<td>31.7</td>
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<td>1.0</td>
<td>16.4</td>
</tr>
</tbody>
</table>

For fixed $N_e$, limit decreases as we decrease $i$

For fixed $i$, limit increases as we increase $N_e$
Cumulative Response at 50 generations as a function of $N_{ei}$
Weber’s Selection Experiment on Drosophila Flight Speed

Perhaps the largest long-term selection experiment is Weber’s (1996) for improved flight speed in Drosophila. Over 9,000,000 flies were scored for flight speed in two replicate populations subjected to over 250 generations of response.

The resulting \( N_e \) was 500 - 1000 with an average \( i = 2.11 \) (\( p = 0.045 \) saved)

Flight speed at start = 2cm/second. At gen 100, 170 cm/sec. At generation 250, 200-225 cm/sec

Response continued through the first 100+ generations, while an apparent plateau was reached around 220 - 250 generations

Little slippage in the mean upon relaxation of selection. Fitness of selected lines decreased only 6-7% (by generations 50 and 85)
**Illinois Long-Term Selection Experiment**

Started in 1896 by Hopkins, and continues today.

Selection for increased and decreased oil and protein content

After 90 generations, a fairly constant response was seen for increased oil, with a 22 $\sigma_A$ increase.

Selection for low oil was stopped at 87 generations, due to difficulty in selecting individuals with reduced oil.

The line selected for increased protein showed no limit after 90 generations, with a 27$\sigma_A$ increase.

The down-selected lines for protein showed an apparent limit, likely due to scale effects.
Variance in Response

What is the variance about the expected limit?

The expected response $\Delta$ takes on values

$$\Delta = \begin{cases} 2a - m(q_0) & \text{with probability } u(q_0) \\ 0 - m(q_0) & \text{with probability } 1 - u(q_0) \end{cases}$$

This gives the variance in response as

$$\sigma^2 [\Delta] = 4a^2 u(q_0) [1 - u(q_0)]$$

With weak selection, $u(q_0) \sim q_0$, giving

$$\sigma^2 \left[ R^{(\infty)} \right] \approx 4 \sum a^2 q_0 (1 - q_0) = 2\sigma_A^2(0)$$
Response from Mutational Input

There is strong evidence that new mutations (not present at the start of selection) significantly contribute to response even over the short time scale of most “long-term” experiments.

Recall (Lecture 7) that the equilibrium additive variance under drift and mutation is just $2N_e \sigma_m^2$, while the additive variance contributed by mutation in generation $t$ is

$$\sigma_{A,m}^2(t) \approx 2N_e \sigma_m^2 \left[ 1 - \exp\left(-t/2N_e\right) \right]$$

Hence, the response in generation $t$ from mutational input is

$$r_m(t) = i \frac{\sigma_{A,m}^2(t)}{\sigma_z} \approx 2N_e i \frac{\sigma_m^2}{\sigma_z} \left[ 1 - \exp\left(-t/2N_e\right) \right]$$
For $t \gg 2N_e$, the per-generation response from mutation approaches an asymptotic limit of

$$\tilde{r}_m = 2N_e \frac{i \sigma_m^2}{\sigma_z} = i \frac{\tilde{\sigma}_A^2}{\sigma_z}$$

The cumulative response at generation $t$, including decay of the original variance plus new mutation input is

$$R^{(t)} = 2N_e \frac{i}{\sigma_z} \left( t \sigma_m^2 + [1 - \exp(-t/2N_e)] \left[ \sigma_A^2(0) - 2N_e \sigma_m^2 \right] \right)$$

Asymptotic response from new mutations

Decay of initial variation
When does the response from new mutations equal the response from existing variation?

We can show (see notes) that the solution is $t^* = 2Ne \log(1+\phi)$, where

$$\phi = \frac{h^2}{(1 - h^2) 2Ne (\sigma_m^2 / \sigma_E^2)}$$
Example: Yoo’s (1980a) selection experiment on bristle number in Drosophila

80 generations of selection, observing an increase of 0.3 bristle per generation over generations 50 to 80.

Base population had $\sigma^2_E \sim 4$, $\sigma^2_z \sim 5$, $h^2 \sim 0.2$. Selection used $i \sim 1.4$, with an approximate $Ne = 60$

Taking the average bristle number value of $\sigma^2_m / \sigma^2_E \sim 0.001$ gives $\sigma^2_m \sim 0.004$

Equilibrium additive variance is $2Ne \sigma^2_m \sim 0.48$

Asymptotic rate of response $\sim i * 0.48 / (0.48+4)^{1/2} \sim 0.40$

At $t = 60$, we only see 40% of this, or 0.13

At $t = 60$, response from initial variation is 0.38

Hence, at $t = 60$, 75% from initial variation, 25% from new mutations