The infinitesimal model and its extensions

Bruce Walsh lecture notes
Bonus lecture (not given)
Uppsala EQG 2012 course
version 7 Feb 2012

Selection (and drift) compromise predictions of selection response by changing allele frequencies and generating disequilibrium.

Predicting changes in allele frequencies are especially problematic as to do so requires very intimate knowledge of the underlying genetical details, such as the effects and frequencies of all alleles. As these are essentially unobservable for all but the most trivial cases, these are often referred to as the microscopic (unobservable) parameters of the system.

Ideally, we would like to have macroscopic-based (observable) predictors of response, based on easily-measured quantities, such as genetic variances.

Under the infinitesimal model, allele frequencies are unchanged by selection, and thus σ^2_a is assumed constant.

Large changes in the mean occur by summing infinitesimal Allele frequency changes over a large number of loci

Suppose n loci, allele freq p, effect a. Mean = 2npa

$\sigma^2_A = \sigma^2_a = 2na^2p(1-p)$, so a must scale as $n^{-1/2}$ for variance to remain bounded for large n.

$$\Delta\mu = 2na\Delta p, \quad \text{thus} \quad \Delta p = \Delta\mu/(2na)$$

$$\text{Since } a \text{ is of order } n^{-1/2}, \ \Delta p \text{ is of order } 1/(n \cdot n^{-1/2}) = n^{-1/2}$$

$$\begin{aligned}\Delta\sigma_a^2 &= 2na^2p'(1-p') - 2na^2p(1-p)\\ &= 2na^2\Delta p(1-2p-\Delta p)\\ &\approx a\,(1-2p)\,\Delta\mu\end{aligned}$$

Since a is order $n^{-1/2}$, changes in variance of order of $\Delta\mu/n^{1/2}$

Bottom line: When the number of loci is small, and each have roughly equal effect, can get very larges changes in the mean with no appreciable change in the allele frequencies or (more importantly) the variance

Gaussian continuum-of-alleles (COA) models

Kimura found that if new mutations have small effects relative to the existing variation at the locus, then the distribution of effects (in an infinite population) converges to a normal.

COA models make the assumption that the distribution of breeding values *at each locus* is gaussian (and jointly multivariate normal over a vector of loci), which can only be strictly correct for an infinite number of alleles / locus

This assumption of Gaussian distribution of effects at each locus is much more restrictive than the assumption that the distribution of the *total* genotypic value is normal.

While the distribution of total genotypic values is gaussian under continuum-of-alleles model, the central limit theorem allows the sum of non-normal distributions across loci to converge to a gaussian.

Thus, COA models are a very restrictive subset of all possible models that can lead to the infinitesimal.

The advantage of COA models is that we can assume a finite number of loci, and hence partly accommodate allele frequency change.

Gaussian COA models attempt to bridge the infinitesimal on one hand with models allowing allele frequency change on the other.

Under COA assumptions, consider drift.
hence, selection does not change allele freq,
but drift can

$$\Delta\,\sigma_a^2(t) = -\frac{\sigma_a^2(t)}{2N_e}$$

$$\Delta\,d(t) = -\frac{1}{2}\left[\left(1+\frac{1}{N_e}\right)d(t) + \left(1-\frac{1}{N_e}\right)\kappa\,h^2(t)\,\sigma_A^2(t)\right]$$

More generally, suppose there are n loci of equal effect as well as drift (finite N_e)

$$\Delta \sigma_a^2(t) = -\left[\frac{\sigma_a^2(t)}{2N_e} + \left(1 - \frac{1}{N_e}\right) \frac{\kappa\, h^2(t)\, \sigma_A^2(t)}{2n} \right]$$

$$\Delta d(t) = -\frac{1}{2}\left[\left(1 + \frac{1}{N_e}\right) d(t) + \left(1 - \frac{1}{n}\right)\left(1 - \frac{1}{N_e}\right) \kappa\, h^2(t)\, \sigma_A^2(t) \right]$$

The effect of drift on d is fairly small and can usually be ignored

What does response look like under these Models?

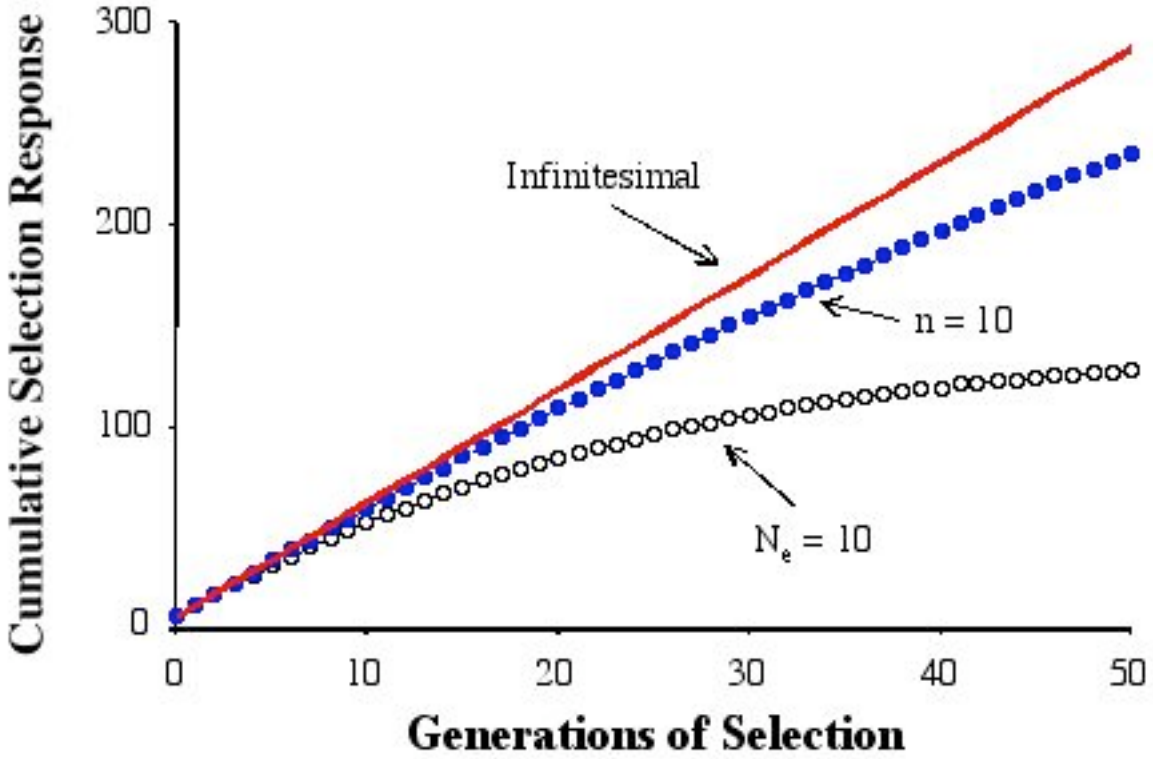
Again, the additive variation in generation t is

$$\sigma^2_A(t) = \sigma^2_a(t) + d(t)$$

$$\sigma^2_z(t) = \sigma^2_A(t) + \sigma^2_E$$

$$h^2(t) = \sigma^2_A(t) / \sigma^2_z(t)$$

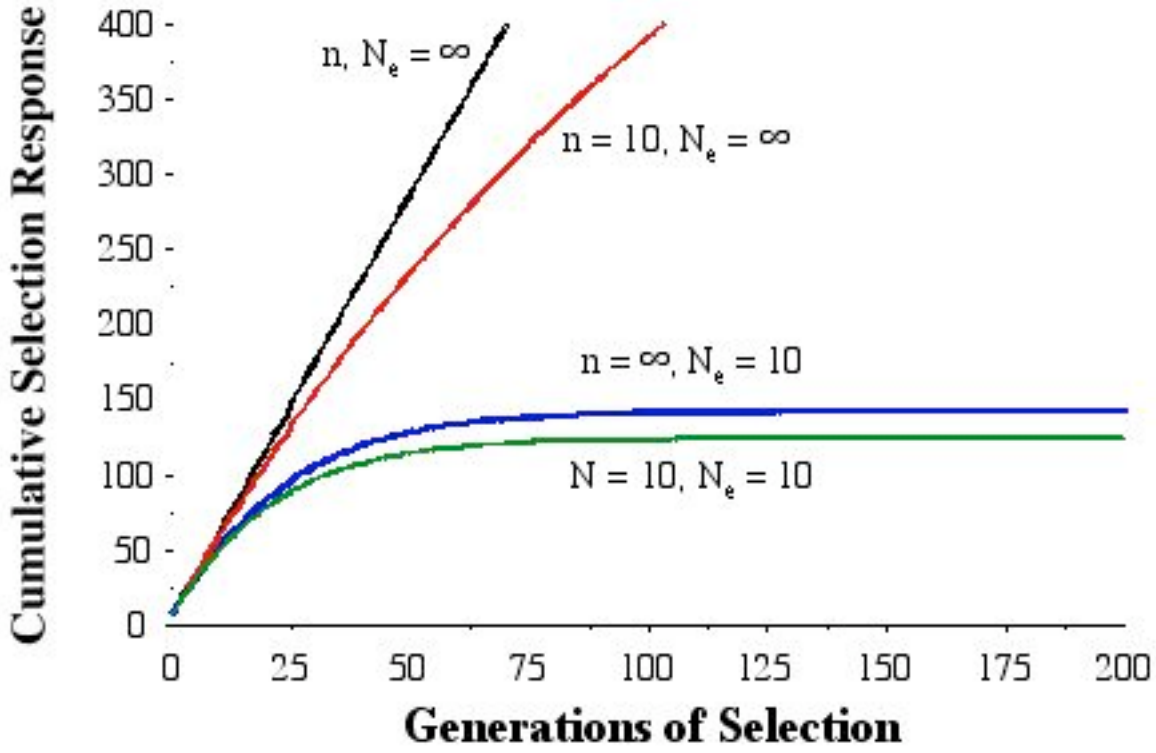
$$R(t) = h^2(t)S(t)$$



(i) Infinitesimal Ne = n = ∞

(ii) Ne = 10, n = ∞

(iii) Ne = ∞, n = 10


Cumulative Selection Response
400
350
300
250
200
150
100
50
0
0
25
50
75
100
125
150
175
200
Generations of Selection
n, $N_e = \infty$
n = 10, $N_e = \infty$
n = ∞, N_e = 10
N = 10, N_e = 10

When loci vary in effects, an important concept is the effective number of loci

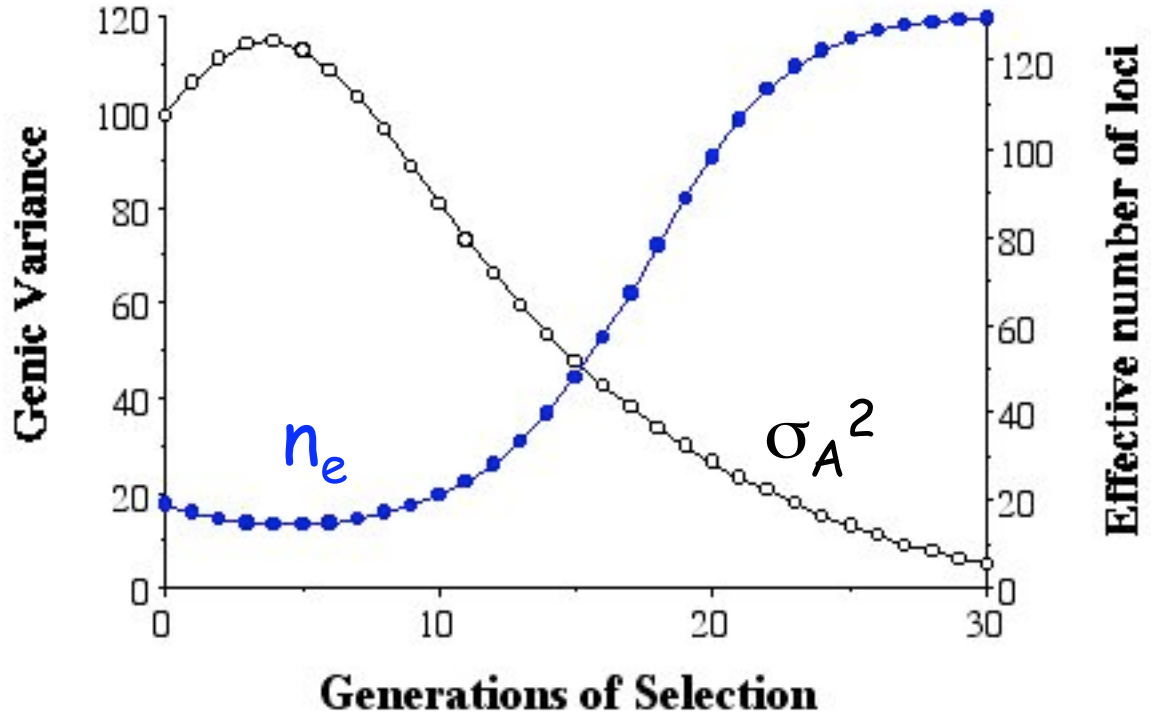
Replace n by n_e, $$n_e = \frac{n}{1 + cv^2}$$

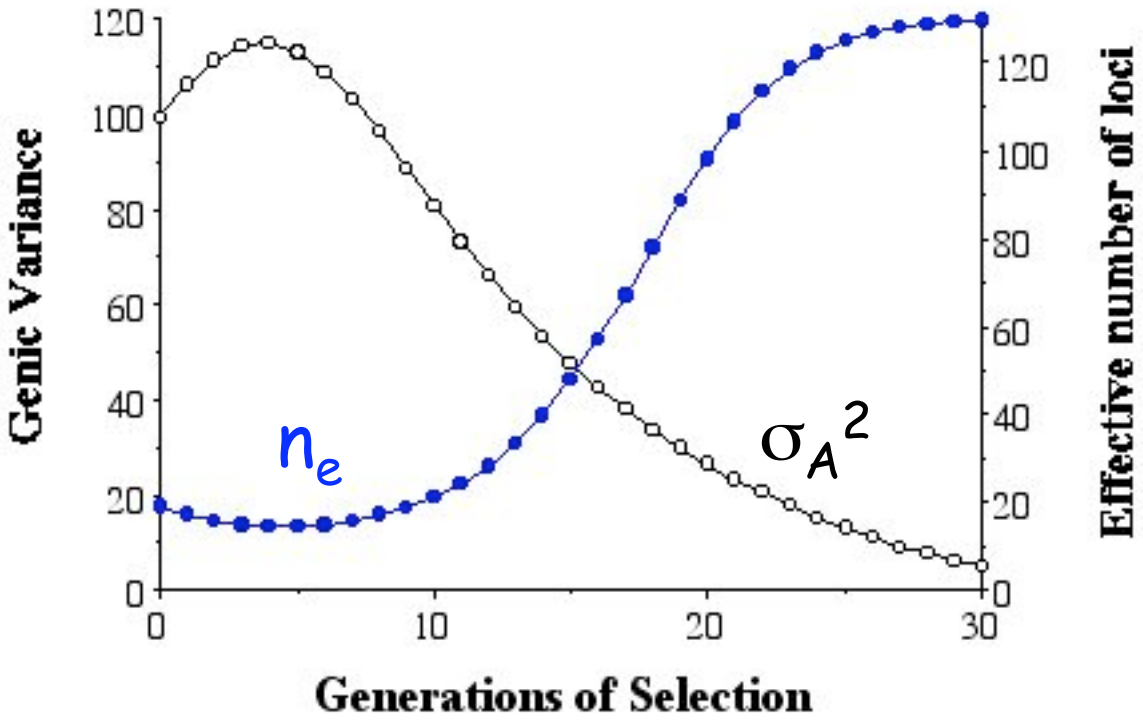
cv is the coefficient of variation in the genic variance contributed by each locus

$$cv = \sigma\left(\sigma^2_{ai}\right) / E[\,\sigma^2_{ai}\,]$$

where σ^2_{ai} is the genic variance contributed by locus i.

Example 24.3. Consider an additive model with both major and minor loci. There are five major loci, each with frequency $p = 0.25$ and effect $a = 5.16$, and 125 minor loci, each with $p = 0.5$ and $a = 0.89$. The resulting initial genic variance is $\sigma_a^2 = 100$ and we assume a initial heritability of $h^2 = 0.5$. Finally, we assume truncation selection with the uppermost 20% saved (further details for this model are given in Example 26.2). We ignore any effects of disequilibrium, focusing on how the genic variance (open circles) and the effective number of loci n_e (filled circles) change over time due simply to allele frequency changes.





While there are 130 loci in this system, initially the effective number is around 20, due to the large coefficient of variance in the locus-specific genic variances. As we start selection, the additive variance initially increases, as the major alleles increase their frequencies toward 0.5 (where they have maximal additive variance). Such an increase in variance is not predicted by COA models. Notice that the effective number of loci further decreases during this increase in variance, as the coefficient in variation for the locus-specific variance increases as the genic variances at each major locus increases. As these major loci become fixed, the total genic variance decreases, while the effective number of loci increases, reflecting a decrease in the coefficient of variation.

In class project

Assume an initial $h^2 = 0.3$, d(0) = 0, phenotypic variance of 100, and the upper 2% selection

Compute the cumulative response over 10 generations for

- Ne = 1000, n = 5
- Ne = 100, n = 100
- Ne = n = ∞

$$\Delta \sigma_a^2(t) = -\left[\frac{\sigma_a^2(t)}{2N_e} + \left(1 - \frac{1}{N_e}\right) \frac{\kappa\, h^2(t)\, \sigma_A^2(t)}{2n} \right]$$

$$\Delta d(t) = -\frac{1}{2}\left[\left(1 + \frac{1}{N_e}\right) d(t) + \left(1 - \frac{1}{n}\right)\left(1 - \frac{1}{N_e}\right) \kappa\, h^2(t)\, \sigma_A^2(t) \right]$$

Barton and Turelli: Nongaussian distributions of genotypic effects

Turelli and Barton examined selection response under general models

Take home message: Models do not close

- Genotypic variance & skew needed to predict response in mean
- Skew & Kurotsis needed to predict response in Variance, and so on

$$\boldsymbol{\Delta}_{\mu_G} \simeq \mathbf{M} \nabla \ln \overline{w}$$

$$\boldsymbol{\Delta}_{\mu_G} = \begin{bmatrix} \Delta\mu_{1,G} \\ \Delta\mu_{2,G} \\ \Delta\mu_{3,G} \\ \vdots \end{bmatrix}, \qquad \nabla \ln \overline{w} = \begin{bmatrix} \dfrac{\partial \ln \overline{w}}{\partial \mu_{1,z}} \\ \dfrac{\partial \ln \overline{w}}{\partial \mu_{2,z}} \\ \dfrac{\partial \ln \overline{w}}{\partial \mu_{3,z}} \\ \vdots \end{bmatrix}$$

$$\mathbf{M} = 2 \sum_i \begin{bmatrix} \mu_{2,i} & \mu_{3,i} & (\mu_{4,i} - 3\mu_{2,i}^2) & \cdots \\ \mu_{3,i} & (\mu_{4,i} - \mu_{2,i}^2) & (\mu_{5,i} - 4\mu_{3,i}\,\mu_{2,i}) & \cdots \\ (\mu_{4,i} - 3\mu_{2,i}^2) & (\mu_{5,i} - 4\mu_{3,i}\,\mu_{2,i}) & (\mu_{6,i} - \mu_{3,i}^2 - 6\mu_{2,i}\,\mu_{4,i} + 9\mu_{2,i}^2) & \cdots \\ \vdots & \vdots & \vdots & \ddots \end{bmatrix}$$

$$\Delta\mu_G \simeq h^2 S + \left(\frac{\delta(\sigma_z^2) + S^2}{2\sigma_z^4}\right) M_3$$

$$\Delta\sigma_A^2 \simeq \frac{S}{\sigma_z^2} M_3 + \left(\frac{\delta(\sigma_z^2) + S^2}{\sigma_z^4}\right) \sum_i^n \left(\mu_{4,i} - \mu_{2,i}^2\right)$$

$$\Delta\mu_{3,G} \simeq \frac{S}{\sigma_z^2} M_4 + \left(\frac{\delta(\sigma_z^2) + S^2}{\sigma_z^4}\right) \sum_i^n \left(\mu_{5,i} - 4\,\mu_{3,i}\,\mu_{2,i}\right)$$

Even assuming phenotypic selection described by change in mean and variance alone, models do still not close.

Changes assume no allele frequency change (all LD)

Barton & Turelli also examined models where only LD contributes to changes, still complex

$$\Delta\mu = \sigma_A^2 L_1 + K_{g,3} L_2 + K_{g,4} L_3 + K_{g,5} L_4$$

$$\Delta\sigma_A^2 = \frac{\sigma_a^2 - \sigma_A^2}{2} - \frac{\Delta\mu^2}{2} + \frac{K_{g,3}}{2} L_1 + \left(\sigma_A^4 + \frac{K_{g,4}}{2}\right) L_2 + \left(3\sigma_A^2 K_{g,3} + \frac{K_{g,5}}{2}\right) L_3 + \left(3K_{g,3}^2 + 4\sigma_A^2 K_{g,4} + \frac{K_{g,6}}{2}\right) L_4$$