Selection

Lecture 6 ▪ Quantitative Genetics

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asap-bio.github.io/lec-qg-selection.html

Contents

1 The question, and three answers

SELECTION

Selection is **differential reproduction and survival** of individuals due to genetic differences between the individuals.

The question that selection was formulated to answer is why organisms are suited to their circumstances. Three historical answers frame the topic.

1.1 William Paley (1743–1805), *Natural Theology*

- Believed organisms' design implied a designer.
- Known for the *watchmaker analogy* to explain purposeful design in nature.

1.2 Jean-Baptiste Lamarck (1744–1829)

- Proposed the theory of the **inheritance of acquired characteristics**.
- Suggested traits acquired during an organism's lifetime could be passed to offspring.
- Famous example: giraffes stretching their necks to reach higher leaves, leading to longer necks over generations.

1.3 Charles Darwin (1809–1882)

- Organisms best adapted to their environment are more likely to survive and reproduce.
- "Survival of the fittest" as an explanation of how species change over time.

The decisive difference is that Darwin's mechanism requires *heritable variation that already exists* and does not require variation to arise because it is needed. This makes it a quantitative theory rather than a narrative account, and allows the remainder of this lecture to be developed algebraically.

2 Darwin's postulates

1. There is a **surplus of offspring**. Not all offspring can survive and reproduce in the long run.
2. Individuals **differ** in how well they survive and reproduce.
3. At least part of this variation is due to **genetic differences** between the individuals.

All three are necessary. Remove the surplus and there is nothing to select among; remove the variation and there is nothing to choose; remove the genetic basis and the choice has no consequences for the next generation.

3 Types of selection

TWO KINDS

Artificial selection is the *intentional* preferential breeding of some individuals in a population in order to improve the population's genetic characteristics.
Natural selection is differential reproduction and survival due to genetic differences, where the differences are not caused by intentional human interference.

Selection is differential survival and reproduction, and it can act at *any* stage of a life cycle:

1. Survival until reproduction (**viability selection**)
2. **Sexual selection**: who gets to reproduce
3. **Fertility or fecundity selection**: how many offspring
4. **Gametic selection**: competition between gametes

The stages occupy different positions in the life cycle, and the life cycle itself differs between taxa:

Mammals	Flowering plants
Zygote	Zygote
Adult males and females	Sporophyte
Gametes (meiosis)	Spores (meiosis), then gametophyte
Mating	Pollination
Fertilisation, zygote formation	Fertilisation, zygote formation

In plants there is a free-living haploid phase, so selection can act on the *gametophyte* directly, a stage mammals do not have.

4 Viability selection at one locus

Viability selection is due to differences in survival until reproduction. Focus on a single locus with two alleles A and a at frequencies p and q.

4.1 Fitness

Genotypes survive to reproduction with probabilities W_{AA}, W_{Aa}, W_{aa}. Fitness is then just a quantitative trait, and it has a mean like any other:

$$\bar{W} = p^2 W_{AA} + 2pq\, W_{Aa} + q^2 W_{aa}$$

4.2 Fitness of an allele

Exactly as in the one-locus model, define the fitness of an allele as the average effect of that allele, plus the mean:

$$W_A = pW_{AA} + qW_{Aa}$$
$$W_a = pW_{Aa} + qW_{aa}$$

These are consistent with the population mean, as they must be:

$$\begin{aligned} pW_A + qW_a &= p\left(pW_{AA} + qW_{Aa}\right) + q\left(pW_{Aa} + qW_{aa}\right) \\ &= p^2 W_{AA} + 2pq\, W_{Aa} + q^2 W_{aa} = \bar{W} \end{aligned}$$

5 Change in allele frequency

Higher survival for an allele means higher representation in the next generation. Selection therefore induces a change in allele frequencies. The derivation follows.

Deriving Δp

1. A fraction $\bar{W}$ of all individuals survive to reproduce. Among the surviving gene copies, pW_A are A alleles and qW_a are a alleles.
2. The new frequency of A is therefore

$$p' = \frac{pW_A}{pW_A + qW_a} = p\,\frac{W_A}{\bar{W}}$$

3. Subtracting the old frequency,

$$\Delta p = p' - p = p\frac{W_A}{\bar{W}} - p\frac{\bar{W}}{\bar{W}} = p\,\frac{W_A - \bar{W}}{\bar{W}}$$

4. Substituting $\bar{W} = pW_A + qW_a$ and simplifying gives the standard form

$$\boxed{\Delta p = pq\,\frac{W_A - W_a}{\bar{W}}}$$

INTERPRETATION

Δp is zero whenever $W_A = W_a$, that is, whenever the two alleles have the same average fitness. It is also zero when $p = 0$ or $q = 0$. Selection needs both a fitness difference *and* standing variation to produce change, which restates Darwin's postulates algebraically.

IN A BREEDING CONTEXT

In breeding, "survival" means the same thing as "being selected for breeding". In general we assume no differences in reproduction among the selected animals, they are all bred equally. So the whole viability-selection apparatus transfers directly to artificial selection, with W reinterpreted as the probability of being chosen.

6 Fisher's Fundamental Theorem

"The rate of increase in the average fitness of a population is equal to the genetic variance of fitness of that population."
Fisher, R. A., *Annals of Eugenics* (London), 11, 53 (1941)

The theorem follows from the result we just derived in a few lines.

$$\begin{aligned}
\Delta\bar{W} &= 2\,(W_A - W_a)\,\Delta p \\
&= 2\,(W_A - W_a)\;pq\,\frac{W_A - W_a}{\bar{W}} \\
&= \frac{2pq\,(W_A - W_a)^2}{\bar{W}} = \frac{2pq\,\alpha_W^2}{\bar{W}} \\
&= \frac{V_A(W)}{\bar{W}}
\end{aligned}$$

The middle step uses a result established earlier: $2pq\alpha^2$ is the additive genetic variance derived in the one-locus lecture, here applied to fitness.

CONSEQUENCE

$$\Delta \bar{W} = \frac{V_A(W)}{\bar{W}}$$

Since $\bar{W} > 0$ and $V_A(W) \geq 0$, we have $\Delta \bar{W} \geq 0$. Under viability selection, **mean fitness never decreases**. It also tells you when change stops: when the additive genetic variance in fitness is exhausted.

7 Truncation selection and selection intensity

A particularly simple and practically important scheme:

- All individuals with a selection criterion below a **truncation point** t are discarded from breeding.
- All individuals above t are selected for breeding.
- All selected individuals are bred equally.

SELECTION DIFFERENTIAL AND SELECTION INTENSITY

The **selection differential** S is the average phenotypic superiority of the selected individuals, in *phenotypic units*.
The **selection intensity** i is the same superiority expressed in *units of phenotypic standard deviation*:

$$i = \frac{S}{\sigma_P}$$

7.1 Computing S under truncation

If the trait is normally distributed, i depends only on the proportion selected:

Procedure

1. Fix the proportion selected, B.
2. Find the truncation point t in the *standard normal* distribution such that a proportion B lies above it.
3. Find the density $\phi(t)$ at that point.
4. The selection intensity is $i = \dfrac{\phi(t)}{B}$, and the selection differential is $S = i\,\sigma_P$.

Worked example: selecting the top 20%, in R

```
 B <- 0.2
t <- qnorm(0.2, lower.tail = FALSE) # truncation point
phi <- dnorm(t) # density at t
i <- phi / B # selection intensity
Vp <- 2.0
S <- i * sqrt(Vp) # selection differential
```

R gives $i = 1.39981$. Falconer and Mackay (p. 379) tabulate $i = 1.400$, so the computation checks out against the standard reference.

8 From one locus to the breeder's equation

Two treatments have been developed separately: allele-frequency change under fitness differences, and selection on a phenotype. This section shows that they are equivalent.

The effect of selecting on a *quantitative trait* can be modelled at a single locus of small effect. Assume selection is on phenotype alone: we use no information from other traits or from relatives.

8.1 The locus

Two alleles, with genotypes differing by a small additive amount δ:

$$E(y \mid aa) = 0, \qquad E(y \mid Aa) = \delta, \qquad E(y \mid AA) = 2\delta$$

so on this scale the allele substitution effect is $\beta_y = \delta$.

8.2 Translating trait values into fitness

Under truncation selection with proportion B selected, an individual's probability of being selected rises with its phenotype. To first order, a genotype whose mean is higher by δ has its selection probability raised by $\delta\phi$, where ϕ is the standard normal density at the truncation point:

Genotype	aa	Aa	AA
Fitness	B	$B + \delta\phi$	$B + 2\delta\phi$
$\bar{W}$	$B + 2p\delta\phi$		
W_a	$B + p\delta\phi$		
W_A	$B + (1+p)\delta\phi$		
β_W	$\delta\phi$		

One generation of selection at a locus of small effect

1. Substitute into $\Delta p = p\dfrac{W_A - \bar{W}}{\bar{W}}$:

$$\Delta p = p\,\frac{B + (1+p)\delta\phi - (B + 2p\delta\phi)}{\bar{W}} = p\,\frac{q\,\delta\phi}{\bar{W}}$$

2. For a locus of small effect $\bar{W} \approx B$, so $\Delta p \approx p\dfrac{q\delta\phi}{B} = pq\,\delta\,\dfrac{i}{\sigma} = pq\,\beta_y\dfrac{i}{\sigma}$, using $i = \phi/B$.
3. The change in the trait mean is twice the substitution effect times the change in frequency:

$$\Delta G = 2\beta_y \times pq\,\beta_y\frac{i}{\sigma} = 2pq\,\beta_y^2\,\frac{i}{\sigma}$$

4. But $2pq\beta_y^2 = V_A$, so

$$\Delta G = V_A\frac{i}{\sigma} = i\,h^2\frac{\sigma^2}{\sigma} = i\,h^2\sigma$$

RELATION TO THE BREEDER'S EQUATION

Starting from nothing but allele-frequency change at a single locus of small effect, we have arrived at the breeder's equation. The two stories are one story. This also explains *why* the breeder's equation contains h^2 and not H^2: the derivation runs through $2pq\beta_y^2 = V_A$, the additive variance, because only average allele effects are transmitted.

9 The breeder's equation

The derivation above proceeded from the locus. The complementary derivation, from regression, generalises to breeding programmes. We assume non-overlapping generations and that all selected individuals breed equally.

Step 1: covariance between breeding value and phenotype

1. For one individual, V_P is known and $V_A = h^2 V_P$.
2. $\mathrm{Cov}(g_a, y) = \mathrm{Cov}\left(g_a,\ \mu + g_a + g_d + e\right)$
3. $= \mathrm{Cov}(g_a, \mu) + \mathrm{Cov}(g_a, g_a) + \mathrm{Cov}(g_a, g_d) + \mathrm{Cov}(g_a, e) = 0 + V_A + 0 + 0 = V_A$

Step 2: regression, for one individual

1. Knowing the deviation from the mean in y, we predict the deviation in g_a:

$$R = E(g_a \mid y) = E(g_a) + \mathrm{Reg}(g_a \mid y)\,(y - E(y))$$

2. $\mathrm{Reg}(g_a \mid y) = \dfrac{\mathrm{Cov}(g_a, y)}{V_P} = \dfrac{V_A}{V_P} = h^2$, so $R = 0 + h^2 S = h^2 S$.

Step 3: many individuals

1. For a group of n selected individuals, $R = E\left(\dfrac{\sum g_{a,i}}{n}\right) = \dfrac{1}{n}\sum E(g_{a,i})$
2. $= \dfrac{1}{n}\sum E(h^2 S_i) = h^2 \dfrac{\sum S_i}{n} = h^2 S$, so the result carries over unchanged to the group mean.

BREEDER'S EQUATION

Expressing the superiority in standard deviations, $S = i\sigma_P$:

$$R = \Delta G = i\, h^2\, \sigma_P$$

With pure phenotypic selection, this is the predicted gain per generation.

This simplest case generalises in two directions:

- With **more general information** than the animal's own phenotype (relatives, markers), the accuracy term $r_{a,\hat{a}}\sqrt{h^2}$ replaces h^2.
- With **several selection paths** (sires of sires, dams of sires, and so on), the response sums over paths.

10 Correlated response

Genetic correlations describe the relationship between the breeding values for different traits. Consequently, genetic change in one trait induces change in another, whether we want it or not.

The correlated response in trait 2 from selection on trait 1 is

$$\Delta G_2 = \mathrm{Reg}\left(g_{a,2} \mid y_1\right) S_1$$

which requires the joint variance structure of the phenotype of trait 1 and the breeding values of both traits:

$$\mathrm{Var}\begin{pmatrix} y_1 \\ g_{a,1} \\ g_{a,2} \end{pmatrix} = \begin{pmatrix} V_{p1} & \mathrm{Cov}(y_1, g_{a,1}) & \mathrm{Cov}(y_1, g_{a,2}) \\ \mathrm{Cov}(y_1, g_{a,1}) & V_{a1} & \mathrm{Cov}(g_{a,1}, g_{a,2}) \\ \mathrm{Cov}(y_1, g_{a,2}) & \mathrm{Cov}(g_{a,1}, g_{a,2}) & V_{a2} \end{pmatrix}$$

Derivation

1. $\mathrm{Cov}(y_1, g_{a,1}) = \mathrm{Cov}(g_{a,1} + e_1, g_{a,1}) = V_{a1}$.
2. $\mathrm{Cov}(y_1, g_{a,2}) = \mathrm{Cov}(g_{a,1}, g_{a,2}) = r_g\sqrt{V_{a1}V_{a2}}$.
3. Hence $\mathrm{Reg}(g_{a,2} \mid y_1) = \dfrac{r_g\sqrt{V_{a1}V_{a2}}}{V_{p1}} = \dfrac{r_g\sqrt{h_1^2h_2^2}\,\sigma_{p2}}{\sigma_{p1}}$.
4. With $S_1 = i\sigma_{p1}$, the σ_{p1} cancels:

$$\Delta G_2 = i\,\frac{r_g\sqrt{h_1^2h_2^2}\,\sigma_{p2}}{\sigma_{p1}}\,\sigma_{p1} = i\,r_g\sqrt{h_1^2h_2^2}\,\sigma_{p2} = i\,r_g\,h_1h_2\,\sigma_{p2}$$

CORRELATED RESPONSE

$$\Delta G_2 = i\,r_g\,h_1h_2\,\sigma_{p2}$$

Note the symmetry with $\Delta G = ih^2\sigma_P = i\,h\cdot h\,\sigma_P$. The direct response uses h_1 twice; the correlated response replaces one h_1 with h_2 and multiplies by r_g. If r_g is negative, selecting on trait 1 *degrades* trait 2, which is the classic dairy story of yield against fertility.

11 Selection and genetic drift

Genetic drift affects all loci, including those with effects on quantitative traits. Recall its consequences: alleles in a population become more related, genetic variation shrinks, and population means diverge.

11.1 Why selection makes drift worse

1. **Drift.** Selection means breeding only a fraction of a population.
2. **More related individuals.** Related animals are more similar in breeding value and share information, so selecting on estimated breeding value means selecting individuals that are more related than random.

$$\Delta F_{ST} \propto i^2$$

11.2 The variance of a selected group mean

With additive gene action and n individuals with additive genetic values $g_{a,i}$:

$$\begin{aligned}\mathrm{Var}\left(\frac{\sum g_{a,i}}{n}\right) &= \frac{1}{n^2}\sum_{i,j}\mathrm{Cov}\left(g_{a,i}, g_{a,j}\right) \\ &= \frac{1}{n^2}\,n(n-1)\,\mathrm{Cov}\left(g_{a,i}, g_{a,j}\right)_{i\neq j} + \frac{1}{n}\,\mathrm{Cov}\left(g_{a,i}, g_{a,i}\right) \\ &= F_{ST}V_A + \frac{1}{n}\left(1 - F_{ST}\right)V_A\end{aligned}$$

The first term does not shrink with n. However many animals you select, the shared drift component $F_{ST}V_A$ remains, so the outcome of a selection scheme in a small population is **less predictable**, not merely slower.

MAJOR GENES

- Models predict major genes should be rapidly fixed for the desirable allele.
- Genes of small effect may take a very long time.

12 Selection experiments

Natural selection acts in all populations, including domestic animals, so the observed outcome is always a balance between artificial selection, natural selection and drift. Selection experiments are how that balance is studied.

12.1 Why they are conducted

- Demonstrate that a trait is heritable
- Estimate genetic parameters
- Demonstrate that selection is effective
- Detect correlated effects of selection
- Understand the genetic architecture of traits
- Estimate the rate at which new mutations affecting a trait appear

ANATOMY OF A SELECTION EXPERIMENT

- Large enough that the response exceeds the effects of genetic drift.
- **Replicated**, to reduce estimation error and rule out freak results.
- Three sets of lines: **up**, **down** and **control**.
- Control lines are required to rule out environmental trends.

Each requirement answers a specific alternative explanation: drift, chance, and environmental change over the years of the experiment.

12.2 Typical time course

1. Rapid genetic gain, consistent with the breeder's equation.
2. Slowdown in gain due to the **Bulmer effect**.
3. Further slowdown, then cessation of gain, due to exhaustion of genetic variation or counteracting natural selection.
4. End of artificial selection.
5. Regression toward the starting value, driven by natural selection.

12.3 Some observations from real experiments

- The magnitude of regression varies between replicates, because of differences in linkage disequilibrium between QTL and deleterious alleles.

- Occasional **spurts in gain**, when recombination releases a selected allele from its association with a deleterious allele.
- Response to "up" and "down" selection is frequently highly **asymmetric**.

12.4 Long-term experiments

- Long-term selection has *smaller* effects on V_A than expected.
- Candidate interpretations: new mutational variance, or epistatic mechanisms.
- On balance, the accumulation of deleterious alleles *appears* to be a bigger problem than depletion of V_A.

13 Hitchhiking and selective sweeps

Genes on a chromosome are physically linked and inherited together. When selection targets one gene, the surrounding region, including genes that were never selected, may also rise in frequency.

DEFINITIONS

Hitchhiking is the process by which an allele may increase in frequency because it is physically linked to another gene that is the target of selection.
A selective sweep is the sweeping away of variation around a selected site following the fixation of a favourable allele.

13.1 An example: lactase persistence

- Most adult mammals cannot digest milk as adults.
- In humans a mutation enables digestion in adulthood.
- It arose at least twice, once in Africa and once in Europe.
- Selection in favour of lactase persistence was very strong.

The genomic signature is striking. Comparing homozygotes for the persistence allele with non-persistent homozygotes, the homozygous tracts surrounding the locus are much longer in the persistent group, on average by a factor of about **1000**. That is a very long selective sweep: anything linked to the lactase persistence mutation is now frequent, including any recessive deleterious allele that happened to be on the same haplotype, and such recessives are now expressed more often simply because they are more common.

IMPLICATIONS FOR BREEDING

- Selection "drags along" large pieces of genome.
- This may raise the frequency of previously rare recessive deleterious alleles.
- As those alleles become more common, selection against them becomes more effective (the q^2 term grows), which itself slows gain.

A real case: Finnish Ayrshire cattle

- A large QTL for fertility on BTA12.
- It is a **recessive lethal**, a large deletion of about 660 kb.
- Frequency reached $q = 0.17$.

- It has a linked or pleiotropic effect of about +150 kg milk per year.
- Hitchhiking is the natural explanation: the lethal rose to high frequency because it travelled with a strongly favoured milk allele.

In regions subject to hitchhiking the effect can be much greater than simple models predict, and molecular studies confirm that the real effect often exceeds prediction. Note also that in the infinitesimal model V_A does not change due to selection, apart from the Bulmer effect, so hitchhiking is precisely one of the phenomena the infinitesimal model cannot capture.

14 Summary

- Selection acts by changing allele frequencies.
- The outcome is a balance between artificial selection, natural selection and drift.
- Response: $\Delta G = i\, h^2 \sigma_P$.
- Correlated response: $\Delta G_2 = i\, r_g\, h_1 h_2\, \sigma_{p2}$.
- Selection has large effects on genetic drift.
- Hitchhiking matters.

15 Exercises

Exercise 6.1

Change in allele frequency. Selection acts at a locus with two alleles A and a at frequencies $p = 0.99$ and $q = 0.01$. The allele a is a recessive lethal, so the fitnesses are $W_{AA} = 1$, $W_{Aa} = 1$, $W_{aa} = 0$.

1. Compute the mean fitness and the allele substitution effect α.
2. Compute the additive genetic variance V_A in fitness caused by this locus.
3. Compute the expected change in the frequency of A from one generation of selection.

Recall from earlier lectures that $V_A = 2pq\alpha^2$ and that the allele substitution effect is $\alpha = W_A - W_a$.

1. Mean fitness and α.

$$\bar{W} = p^2(1) + 2pq(1) + q^2(0) = 0.9801 + 0.0198 = 0.9999$$

Allele fitnesses: $W_A = pW_{AA} + qW_{Aa} = 0.99(1) + 0.01(1) = 1$, and $W_a = pW_{Aa} + qW_{aa} = 0.99(1) + 0.01(0) = 0.99$.

$$\alpha = W_A - W_a = 1 - 0.99 = 0.01$$

2. Additive genetic variance in fitness.

$$V_A = 2pq\alpha^2 = 2(0.99)(0.01)(0.01)^2 = 1.98 \times 10^{-6}$$

3. Change in allele frequency.

$$\Delta p = pq\frac{W_A - W_a}{\bar{W}} = \frac{(0.99)(0.01)(0.01)}{0.9999} \approx 9.9 \times 10^{-5}$$

Check via Fisher's theorem: $\Delta\bar{W} = V_A/\bar{W} = 1.98 \times 10^{-6}/0.9999 \approx 1.98 \times 10^{-6}$, which is positive, as it must be.
Interpretation. Even against a *lethal*, progress is very slow once the allele is rare: $\Delta p \approx 10^{-4}$ per generation. This corresponds to the result in the Foundations course: selection against a recessive is slow at low frequency because most copies are carried by heterozygotes. It is also why marker-assisted removal of recessive defects is more effective than phenotypic culling.

Exercise 6.2

Intensity of selection.

1. You want to select the top 20% of individuals for a trait with phenotypic variance $V_P = 2.0$. Calculate the selection intensity and the selection differential.
2. For proportions selected B from 1% to 99% in steps of 1%, plot i as a function of B. Describe the shape and explain it.

1. $t =$`qnorm(0.2, lower.tail=FALSE)`$= 0.8416$; $\phi(t) =$`dnorm(0.8416)`$= 0.2800$.

$$i = \frac{\phi(t)}{B} = \frac{0.2800}{0.2} = 1.400, \qquad S = i\,\sigma_P = 1.400 \times \sqrt{2.0} = 1.980$$

So the selected group is on average 1.98 phenotypic units above the population mean.
2. Python for the plot:

```
 import numpy as np, matplotlib.pyplot as plt
from scipy.stats import norm
B = np.arange(0.01, 1.00, 0.01)
t = norm.ppf(1 - B)
i = norm.pdf(t) / B
plt.plot(B, i); plt.xlabel("Proportion selected (B)"); plt.ylabel("Selection
intensity (i)")
plt.show()
```

Shape. i falls monotonically from very high values as $B \to 0$ to zero at $B = 1$, and the curve is steep at small B. Selecting 1% instead of 2% buys a large increase in i; selecting 50% instead of 60% buys very little. Combined with $\Delta F \propto i^2$ from the drift lecture, this is why extremely intense selection is a poor bargain: gain rises ever more slowly while inbreeding rises ever faster.

Exercise 6.3

Correlated response. In Danish Holstein cattle, the heritability of milk protein percentage is $h^2_p = 0.60$ and of milk yield $h^2_m = 0.20$. The genetic correlation between them is $r_g = -0.60$. Set the phenotypic variance of both traits to 1.
Predict the change in milk protein percentage that results from selecting the $B = 0.20$ of cows with the highest milk yield.

Use $\Delta G_2 = i\, r_g\, h_1 h_2\, \sigma_{p2}$, where trait 1 is the trait selected on (milk yield) and trait 2 is the correlated trait (protein percentage).
From Exercise 6.2, $B = 0.20$ gives $i = 1.400$. The heritabilities in standard-deviation form are $h_1 = \sqrt{0.20} = 0.4472$ (yield) and $h_2 = \sqrt{0.60} = 0.7746$ (protein %), and $\sigma_{p2} = 1$.

$$\Delta G_2 = 1.400 \times (-0.60) \times 0.4472 \times 0.7746 \times 1 = -0.291$$

So one generation of selecting the top 20% on milk yield is expected to **reduce** protein percentage by about 0.29 phenotypic standard deviations.

Interpretation. This is the principal practical implication of the section. The unfavourable genetic correlation means that selecting hard on yield degrades composition, and no amount of care in *measuring* yield avoids it. The only remedies are to select on an index that weights both traits, or to accept the loss. Historically, dairy programmes that selected on yield alone did exactly this, which is why balanced indices replaced them.