Units and targets of selection

Units of selection (units that predict response)

Targets of selection (what does selection see?)

Units of adaptation (what does selection adapt?)

We think like a gamete (for transmission) but selection doesn’t see gametes so we use fitness of individuals (for selection)

The Unit of Selection:

the level of genetic organization that allows the prediction of the genetic response to selection
Predicting response

change in allele frequency \[ \Delta p = \frac{p}{W} a_x \] always true

Change in phenotype (target) \[ R = h^2 s \]

response

heritability

selection differential

genes to phenotype
phenotype to fitness

When do you need to incorporate more information?

\[ R = h^2 s \]

1. additional predictor interacts in phenotype

2. this effect is heritable

Not accurate
WHEN BOTH ARE TRUE
Dominance and inbreeding

\[ R = h^2 s \]

1. Partner allele interacts to give phenotype

2. This effect is heritable

Inbreeding

Inbreeding

Not accurate when both are true

Because there is a unit (two alleles at a locus) that has effects not completely predicted by lower lever (one allele), and that unit has continuity across generations

Epistasis and linkage disequilibrium

\[ R = h^2 s \]

1. Second locus interacts to give phenotype

2. This effect is heritable

Linkage disequilibrium

Epistasis

Linkage disequilibrium

Not accurate when both are true

Because there is a unit (two loci) that has effects not completely predicted by lower level (one locus), and that unit has continuity across generations
Fitnesses in population genetics are assigned to genotypic classes of individuals rather than individuals themselves; the genotypic classes can be single locus genotypes, or two locus genotypes, etc.

The unit of selection is the level of genetic organization to which a fitness phenotype can be assigned that allows the response to selection to be accurately predicted.

This means that the unit of selection must have genetic continuity across the generations.

Asexuals

The unit of selection (inheritance) is arguably the whole genome. A new mutation occurs in one background, and stays there.
Meiosis and sexual reproduction break up multilocus complexes in outbreeding species (as a function of both physical recombination and assortment, and system of mating), which reduces the size of the unit of selection.

Selection upon epistatic complexes builds up higher level units.

The Unit of Selection is a dynamic compromise between selection building up complexes and effective recombination breaking them down. The unit of selection can change as the population evolves or experiences altered demographic conditions.
Recombination is not uniformly distributed in the human genome, but rather is concentrated into "hotspots" that separate regions of low to no recombination.

Region of overlap of the inferred intervals of all 26 recombination and gene conversion events not likely to be artifacts.

LD in the human LPL gene

Haplotype tree topology and natural selection

(a) Neutral  (b) Positive  (c) Balancing  (d) Background
### Haplotype Network in 5’ Region of LPL

```
<table>
<thead>
<tr>
<th>84R</th>
<th>49N</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>23J</td>
</tr>
<tr>
<td>5'–4</td>
<td>5'–8</td>
</tr>
<tr>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

Positive (Directional) or Extreme Background Selection
```

### Haplotype Network in 3’ Region of LPL

```
<table>
<thead>
<tr>
<th>3'-9</th>
<th>3'-11</th>
<th>3'-7SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>38</td>
<td>64J</td>
</tr>
<tr>
<td>51</td>
<td>38</td>
<td>64J</td>
</tr>
<tr>
<td>55</td>
<td>55</td>
<td>64J</td>
</tr>
</tbody>
</table>

Positive (Diversifying or Balancing) Selection
```
Recombinants and Post-Recombinational Evolution in LPL

12 Recombination Events Occurred Between T-1 Haplotypes With T-2,3, or 4 Haplotypes

Successful recombinants were T2,T3,T4 receiving 5’ end from T1
Reverse recombinants were not successful

In All 12 Cases, the 5’ End Was Of The T-1 Type. Under Neutrality, This Has A Probability of $(1/2)^{12} = 0.002$.

Therefore, the 5’ End Experienced A Selective Sweep Enhanced By Recombination
For *LPL*, the unit of selection is *smaller* than the gene because of the recombination hotspot in the middle of this locus.

The Unit of Selection:
Quantitative Genetic Components As a Function of Allele Frequencies:  
A. ε4 allele at ApoE is Rare, A2 at LDLR Common;  
B. Reversed

Epistasis Is Present, But Recombination Is High: The Unit of Selection Is A Single Locus.

Epistasis Strong, Recombination Weak; The Unit of Selection Is A Multilocus Complex
Epistasis Strong, Recombination Intermediate; The Unit of Selection Is A Multilocus Complex, But Only Selected Haplotype Shows Extensive LD: Must Be Constantly Built Up By Selection

Supergenes

Long non-recombining segments that act as single units of selection

Often caused by chromosomal inversions that suppress recombination

May lead to build-up of epistatically interacting complexes

Batesian mimic, *Heliconius numata*

How do they keep from getting intermediate patterns?

Due to two chromosomal inversions that suppress recombination

Target of Selection: the level of biological organization that displays the phenotype under selection.
Targets below the individual or units of adaptation below the individual

Selection within the individual

Genes that violate Mendel’s rules

Organismal fitness isn’t always maximized:

1. genetic constraints on trait building (dominance, epistasis, linkage, pleiotropy)
2. other forces (gene flow, mutation, drift).
3. Selection targets at lower levels

   Within organism selection

   Reduction of organismal fitness

   Conflict between different genes

   Suppression of effects of one gene by another
Between-individual selection versus within-individual processes

Mutation and selection:

\[ \Delta q = \frac{q}{W} \Delta a + \Delta q_{\text{mutation}} \]

between within

But the within individual process is not faithful replication, but failure of faithful replication.

Gene conversion

Gene conversion creates new haplotypes. Acts much like mutation in evolution, and indeed is often indistinguishable from it, although it always results in homoplasy. But here alleles are replicating themselves.
Walsh (Genetics 105: 461-468, 1983)

1 Locus, 2 Allele Model (A and a) Such That:

χ = the probability of an unequal gene conversion event

¿ = the conditional probability that a converts to A given an unequal conversion occurs

1-χ = the probability of getting a 1:1 ratio of Mendelian Segregation

¿¿ = probability of segregation yielding only A alleles

¿(1-¿) = probability of segregation yielding only a alleles

Then the segregation ratio A:a in Aa heterozygotes is:

\[ \frac{1}{2} (1 - \chi) + \chi \beta : \frac{1}{2} (1 - \chi) + \chi (1 - \beta) \text{ or } k:1-k \text{ where } k = \frac{1}{2} (1 - \chi) + \chi \beta \]

A is fixed if k > 1/2, and a is fixed if k < 1/2, at a rate dependent upon the frequency of heterozygotes in the population

---

Gene conversion
(let t be a converting allele)

<table>
<thead>
<tr>
<th>Adult Population</th>
<th>Tt</th>
<th>Tt</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTT</td>
<td>Gtt</td>
<td>Gtt</td>
</tr>
</tbody>
</table>

Mechanisms of Producing Gametes (Violation of Mendel’s First Law)

<table>
<thead>
<tr>
<th>Gene Pool (Population of Gametes)</th>
<th>T</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t</td>
<td>T</td>
</tr>
<tr>
<td>( p' = G_{tt} + kG_{Tt} )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( q' = G_{TT} + (1-k)G_{Tt} )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[ p' = G_{tt} + kG_{Tt} = G_{tt} + \frac{1}{2}G_{TT} - \frac{1}{2}G_{Tt} + kG_{Tt} = p + G_{Tt}(k-1/2) \]

\[ \Delta p = p' - p = G_{Tt}(k-1/2) \]
Gene conversion

The total change in allele frequency is:

\[ \Delta p = p^* - p = p^* - p' + p - p \]

where \( a_i \) is the average excess at the individual level

\[ \Delta p = p' \frac{a_i}{W} + pq(k - \frac{1}{2}) \]

where \( k = \frac{1}{2}(1 - \gamma) + \gamma \beta \)

Change due to selection at the level of the individual.

Change due to selection at the level of the gamete.

These may be in opposite directions - conflict

Weak form of within-individual selection because:
(1) \( k \) is usually small
(2) sites don’t have a lot of control over whether they are replicated

The t-complex in mice

20 cM region of chromosome 17 of the mouse genome that constitutes about 1% of the mouse genome. Inversions suppress most recombination in this region that contains genes for sperm motility, capacitation, binding to the zona pellucida of the oocyte, binding to the oocyte membrane, and penetration of the oocyte – and also notochord development. Because of strong epistasis and low recombination, it behaves as a unit of selection that can be modeled as a single locus (A SUPERGENE).
The t-complex in mice

A single Unit of Selection can have more than one Target of Selection

At the individual level, the t-alleles affect viability:

\[
p' = G_{tt} + kG_{tT} + \frac{1}{2}G_{TT} = G_{tt} + \frac{1}{2}G_{TT} + kG_{tT} = p + G_{T}(k-\frac{1}{2})
\]

\[
\Delta p = p' - p = G_{T}(k-\frac{1}{2})^{1/2}
\]

Need this 1/2 for t-alleles because the meiotic drive is expressed only in males.
The *t*-complex in mice

A single Unit of Selection can have more than one Target of Selection

\[
\begin{array}{ccc}
TT & Tt & tt \\
1 & 1-s & 0 \\
\end{array}
\]

Assume random mating; then meiotic drive changes
The gamete frequencies to \( p' = p + pq(k^{-1/2}) \):

After fertilization, selection at the individual level is governed by:

\[
a_t = q'(1 - s - \bar{w}) + p'(-\bar{w})
\]

Where \( \bar{w} = q'^2 + 2p'q'(1 - s) \)

---

The *t*-complex in mice

The total change in allele frequency is:

\[
\Delta p = p'' - p = p'' - p' + p' - p \\
= p' \frac{a_t}{\bar{w}} + pq(k - \bar{w})
\]

Change due to selection individual 
level; always negative. 

Change due to selection at the level of 
the gamete; always positive.

Can also write this as:

\[
pq(\bar{w})(k - \bar{w})/(\bar{w}) = pq(p_{AA}(k - \bar{W}_{AA})/\bar{W}_{AA})
\]

because the frequency of A in Aa’s \((p_{Aa})\) is \( \frac{1}{2} \) and 
the mean fitness within Aa’s is \( \bar{w} \).
The t-complex in mice

Male sterility in hermaphrodites

Lobelia spicata

Thymus vulgaris

Many species have male sterility inherited “cytoplasmically” -
though the mother only, sometimes due to genes in mitochondria.

Nuclear genes often restore male fertility
Mitochondrial selection

M male fertile
m male-sterile (no pollen but compensate by raising c times as many eggs)

\[ p, q \] frequencies

\[ \begin{array}{c}
M \quad m \\
1 \quad c \\
M \quad m
\end{array} \]

\[ \begin{array}{c}
M \quad m \\
1 \quad 0 \\
M \quad m
\end{array} \]

\[ p_e' = ..., \quad q_e' = .... \]

m favored if \( c > 1 \)

Autosomal selection

AA, Aa male fertile
aa male-sterile (no pollen but compensate by raising c times more eggs)

\[ p^2, 2pq, q^2 \]

\[ \begin{array}{c}
AA \quad Aa \\
1 \quad 1/2 \\
A \quad a
\end{array} \]

\[ \begin{array}{c}
A \quad a \\
0 \\
A \quad a
\end{array} \]

\[ p_e' = \frac{p^2}{W_e} + \frac{pq}{W_e} \quad q_e' = \frac{pq}{W_e} + \frac{q^2c}{W_e} \]

\[ p_p' = \frac{p^2}{W_p} + \frac{pq}{W_p} \quad q_p' = \frac{pq}{W_p} + \frac{0}{W_p} \]

\[ q' = \frac{1}{2}(q_e' + q_p') \]

\[ \Delta q > 0 \text{ when } c > \frac{2-q}{1-q} \]

\[ \text{when } q \text{ is rare } c > 2 \]

\[ \text{when } q \text{ is common } c > \infty \]
Selective conflict

Mitochondria: \( c > 1 \) give up pollen for any gain in eggs
Autosomal: \( c > 2 \) to \( \infty \) depending on frequency must at least double eggs

So anytime \( 1 < c < \frac{(2-q)}{(1-q)} \),
mitochondria are selected to cause male sterility,
but autosomes are selected to restore it

Conflict almost as if they were different species

Origin of eukaryotes

Came from a protobacterium in the Rickettsiales

Target of selection can be within (or below) the organism
Co-replicons

A set of genes who replicate through the same pathways with the same probabilities

A set of genes that where selection would act the same (given the same fitnesses)

A set of genes that “agree”: i.e. where selection would create similar outcomes

Mitochondrial – give up pollen for any gain in eggs: \( c > 1 \)
Autosomal – give up pollen only if it doubles eggs: \( c > 2 \)
3 sex-chromosome co-replicons

Male parent

sex chrom. autos. gene 1 autos. gene 2

XY A₁ A₂
A₁ a₁ A₂ a₂

sperm that will make daughters

all X genes go to daughters only
all Y genes go to sons only
autosomes go to both equally

X chromosome selection

X normal sex ratio
× no sons (but compensate by raising c times more daughters)

XY p q frequencies

fathers

½ c

transmission

X daughters

X X

p_d’ = ....

q_d’ = ....

X favored if c > 1
Y chromosome selection

Y normal sex ratio
y no sons (but compensate by raising c times more daughters)

\[
\begin{array}{c|c|c}
Y & X & X_y \\
\hline
XY & \frac{1}{2}c & \frac{1}{2}c \\
X_y & 0 & 0 \\
\end{array}
\]

\[
p = \frac{1}{2}, \quad q = \frac{1}{2}
\]

\[
y \text{ favored when } 0 > \frac{1}{2} \text{ NEVER}
\]

Autosomal selection in fathers

AA, Aa normal sex ratio
aa no sons (but compensate by raising c times more eggs)

\[
\begin{array}{c|c|c|c}
AA & Aa & aa & f = 1 \\
\hline
p^2 & 2pq & q^2 & \text{fathers}
\end{array}
\]

\[
\begin{align*}
\frac{p_d'}{W_d} & = \frac{p^2}{W_d} + \frac{pq}{W_d} \\
\frac{q_d'}{W_d} & = \frac{pq}{W_d} + \frac{q^2c}{W_d}
\end{align*}
\]

\[
\frac{p_s'}{W_s} = \frac{p^2}{W_s} + \frac{pq}{W_s} \\
\frac{q_s'}{W_s} = \frac{pq}{W_s} + \frac{0}{W_s}
\]

\[
q' = \frac{1}{2} (q_d' + q_s')
\]

through fathers only - multiply by \( \frac{1}{2} \) to include mothers with no selection

\[
\Delta q > 0 \text{ when } c > 2\quad \text{ when } q \text{ is rare}
\]

\[
c > \frac{2 - q}{1 - q} \quad \text{ when } q \text{ is common}
\]
Three coreplicons
(for loss of sons to gain daughters)

X chromosome genes: \( \text{if } c > 1 \)

Y chromosome genes: \( \text{NEVER} \)

Autosomes: \( \text{if } c > (2-q)/(1-q) \)

X-chromosome drive in stalk-eyed flies,
\textit{Cyrtodiopsis}

<table>
<thead>
<tr>
<th>Species</th>
<th>No. of female mates</th>
<th>Total progeny</th>
<th>Sex ratio (percent males)</th>
<th>( x^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{C. dalmanii}</td>
<td>6</td>
<td>207</td>
<td>0.004 ± 0.004</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>1207</td>
<td>0.109 ± 0.010</td>
<td>18.1</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>216</td>
<td>0.136 ± 0.017</td>
<td>25</td>
</tr>
<tr>
<td>\textit{C. whitii}</td>
<td>9</td>
<td>208</td>
<td>0.000 ± 0.000</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>792</td>
<td>0.000 ± 0.000</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>580</td>
<td>0.004 ± 0.005</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>421</td>
<td>0.012 ± 0.008</td>
<td>21.2</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>153</td>
<td>0.256 ± 0.058</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Values are ± SE.
* Homogeneity in sex ratio among females. In no case is \( P < 0.05 \).
Some sperm don’t develop

Why doesn’t it spread to fixation?
1. fertility effect in males?

males mated to 8 females each

2 males mated to each female

But this just means $1 < c < 2$, X driver will still spread
Why doesn’t it spread to fixation?

2. Effects in females favor intermediate values

3. Conflict: suppressor genes on the Y chromosome

X chromosome genes: if $c > 1$

Y chromosome genes: NEVER

Autosomes: if $c > (2-q)/(1-q)$
Molecular Drive (Dover)

"The nuclear genomes of eukaryotes are subject to a continual turnover through unequal exchange, gene conversion, and DNA transposition. ... Both stochastic and directional processes of turnover occur within nuclear genomes."
Gene conversion can be a major source of genetic variation in multigene families. Gene conversion increases the number of haplotypes in multigene systems, particularly when the tract length is short. If there is diversifying selection (e.g., MHC, S alleles), selection often favors these new haplotypes, even if the source of the converted segment is a pseudogene.
Transposition: Mutator

A flower of Petunia hybrida transposon genotype derived from the inbred line W138 showing a large number of white-pink sectors (see Ramulu et al., ANL:10: 19-21, 1998).

Transposition: Many ways to change or disrupt genome

Transposition: Direct Phenotypic Effects

Transposition: Horizontal & Vertical Transfer

Numbers (Percentages) of Tested Strains Collected in Four Major Geographical Regions during Five Time Periods according to Their Ability to Suppress P Activity

<table>
<thead>
<tr>
<th>PERIOD</th>
<th>Americas</th>
<th>Europe and Asia</th>
<th>Africa</th>
<th>Orient and Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1920-49</td>
<td>11 (100)</td>
<td>0 (0)</td>
<td>10 (100)</td>
<td>0</td>
</tr>
<tr>
<td>1950-59</td>
<td>11 (84.6)</td>
<td>2 (15.4)</td>
<td>11 (100)</td>
<td>0</td>
</tr>
<tr>
<td>1960-69</td>
<td>6 (31.6)</td>
<td>13 (68.4)</td>
<td>24 (85.7)</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>1970-79</td>
<td>4 (7.5)</td>
<td>49 (92.5)</td>
<td>35 (51.5)</td>
<td>33 (48.5)</td>
</tr>
<tr>
<td>1980-86</td>
<td>1 (3.6)</td>
<td>27 (96.4)</td>
<td>50 (55.5)</td>
<td>40 (44.5)</td>
</tr>
</tbody>
</table>

* Strains that have high susceptibility to P factor activity.


Transposition: Horizontal Transfer

Transposition: Evolutionary Co-option (or exaptation)

TE’s (brown segments) have been co-opted for both transcriptional and post-transcriptional regulation. Can build up regulatory networks in evolution.


---

Transposition: Mutator

(A) Transposable elements (TEs) implicated in the generation of primate-specific traits.

(B) Types of events mediated by TEs underlying primate-specific traits. Passive events entail TE-mediated duplications, inversions or deletions. Domestication refers to the TE becoming a new gene.

(C) Aspects of primate phenotype affected by TEs.

Unequal Exchange

(a) By breakage and joining

(b) By crossing-over between repetitive DNA

Key:
- break
- repetitive DNA segments
- rejoining
- crossover

Globin gene family

Ancestral globin gene

α- and β-Globin gene family on chromosome 16 and 11
Unequal Exchange Can Also Create New Types of Genes

Unequal Exchange:
Concerted Evolution

Gene Duplication Without Concerted Evolution

Gene Duplication With Concerted Evolution
Unequal Exchange: Concerted Evolution


- \( n \) = number of repeats in a multigene family
- \( N \) = ideal population size
- \( \mu \) = neutral mutation rate per repeat per generation

\[ 1/(2N) \] = probability of fixation of new mutant at homologous sites

\[ \alpha \] = probability of a repeat converting a paralogous repeat to its state
(Molecular drive exists such that a neutral mutant will eventually go to fixation at all paralogous sites as well)

\[ 1/(2Nn) \] = probability of fixation of a new mutant at all homologous and paralogous sites

\[ 2Nn\mu \] = expected number of new mutants per generation

Rate of neutral evolution in multigene family evolving in concert =

\[ (2Nn\mu) \times 1/(2Nn) = \mu \] = Same neutral rate as if it were a single locus!
Unequal Exchange: Concerted Evolution

Recall that the time to neutral coalescence of all homologous copies of a gene to a common ancestral form = $4N$

The time to neutral coalescence of all homologous and paralogous copies in a multi-gene family to a common ancestral form = $2/(1-\tau)$ where $\tau$ is the Maximum of one of two forms:

1. $1-1/(2N)$
2. $1-\alpha$

In the first case ($\alpha>1/(2N)$; that is molecular drive is more powerful than drift), then $t = 2/[1-1/(2N)] = 2/[1/(2N)] = 4N = \text{the same rate of coalescence as a single locus and no effect of } \alpha!$

In the second case ($\alpha<1/(2N)$; that is molecular drive is weak compared to drift), $\alpha$ dominates the coalescence process!

Therefore, molecular drive has its biggest evolutionary impact when it is Weak compared to drift. Under these conditions, the multigene family will have much diversity among paralogous copies within a chromosome.

Concerted Evolution With Selection

Simple co-dominant model:
start with fixation of $a$ allele, fitness $aa$ is 1
mutation creates $A$ allele, with fitness of
$Aa$ being $1+s$, and $AA$ $1+2s$
Under Neutrality, Probability of Fixation of $A$ is:

$$\frac{1}{2N}$$

Kimura showed that fixation probability here is:

$$Prob(\text{fixation}) = \frac{1 - e^{-2s}}{1 - e^{-4Ns}}$$

Where $\overline{p}$ is the initial frequency; that is, $1/(2N)$
Concerted Evolution With Selection

Considered a similar model, but now assume that we have a multigene family with \( n \) copies and that the mutant \( A \) allele can spread due to molecular mechanisms leading to concerted evolution. Then, the probability of fixation of \( A \) is given by:

\[
\text{Prob}(\text{fixation}) = \frac{1 - e^{-2s}}{1 - e^{-4nNa}}
\]

Concerted evolution has the effect to increase the "effective" population size, so that weak selection works more efficiently in a multigene family – the opposite of Dover!

Molecular Drive Does NOT Negate The Importance of Other Evolutionary Forces.
Molecular Drive INTERACTS With Other Evolutionary Forces In Determining the Path of Evolution.