**Selection and Mutation**

– Consider cases with no “back mutation” (i.e., no mutation to advantageous types)

  • This is often a good approximation to the real world since:

    (1) backward mutation is usually 2 or more orders of magnitude smaller than forward mutation.

    (2) many more deleterious alleles will be eliminated by selection than are created by mutation so deleterious alleles are rare anyway.

  • Note: our focus is on deleterious mutations here since in these cases, selection opposes mutation as an evolutionary force.

1) Haploid mutation-selection balance:

  • Life Cycle: 
    
    \[ \text{zygotes} \xrightarrow{\text{selection}} \text{adults} \xrightarrow{\text{mutation}} \text{gametes} \xrightarrow{\text{random union}} \text{zygotes} \]

    \[ p \xrightarrow{\text{selection}} p^* \xrightarrow{\text{mutation}} p^{**} \xrightarrow{\text{random union}} p' \]

  • Fitnesses: 
    
    \[ w_A : w_a = 1:1 - s \]

    \[ p = \text{freq. } A, \quad q = \text{freq. } a \]

  • After selection: 
    
    \[ p^* = p \cdot \frac{w_A}{w} = p \left( \frac{1}{1 - sq} \right) \]

  • Let \( u = A \rightarrow a \) mutation rate (ignore back mutation \( a \rightarrow A \): i.e., \( v = 0 \)), then
    
    \[ p' = p^{**} = p^*(1 - u) = \frac{(1 - u)p}{1 - sq} \]

  • At equilibrium, \( p' = p \) and \( \hat{q}_{\text{hap}} = 1 - \hat{p}_{\text{hap}} = u/s \).
    
    – I.e., \( \hat{q}_{\text{hap}} \) = ratio of mutation rate to rate of selective elimination.

  • Note:
    
    – \( u = 10^{-6} \), \( s = 0.01 \) implies \( \hat{q} = 10^{-4} \)

    – Recall: not all mutations are deleterious.
      
      • polymorphisms of selectively neutral alleles are maintained by a balance between mutation and random genetic drift.

2) Diploid mutation-selection balance:

<table>
<thead>
<tr>
<th>Genotype</th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitness</td>
<td>1</td>
<td>(1 - hs)</td>
<td>(1 - s)</td>
</tr>
</tbody>
</table>

• Using approach analogous to that for haploids (substitute \( \overline{w}_A \) instead of \( w_A \), etc.):
\[ p^* = p \frac{W_A}{W} \text{ and } p' = (1 - u)p^* = (1 - u)p \frac{W_A}{W} \]

- Setting \( p' = p \), can solve for equilibrium frequency of deleterious \( a \) allele (\( \hat{q} = 1 - \hat{p} \)):
  - Two cases of interest:
    
    (a) **Recessive Mutant:** \( h = 0 \)
    
    - Solving for equilibrium shows \( \hat{q}_{\text{rec}} = \sqrt{us} \).
    - Note: \( u < s \) so \( \hat{q}_{\text{rec}} > \hat{q}_{\text{hap}} \) for the same \( u, s \).

    (b) **Partial Dominance:** \( h > 0 \)
    
    - By ignoring \( \hat{q}_{\text{rec}}^2 \) in the equilibrium equations, find that \( \hat{q}_h \approx us(hs) \).
    - Approximation fails as \( h \to 0 \) (recessive case).
    - Since most affected individuals are heterozygous, \( \hat{q}_h \) is approximately the ratio of the mutation rate to average selective disadvantage.

- **General Comments**
  
  - Fraction of affected individuals is the same in haploids as in diploids
    
    - e.g., haploid affecteds: \( \hat{q}_{\text{hap}} = us \); recessive affecteds: \( \hat{P}_{aa} = \hat{q}_{\text{rec}}^2 = us(hs) \).
  
  - Can often use observed frequencies and known fitnesses of affected individuals to estimate the mutation rate.

**Mutation Load**

- How does mutation impair average population fitness?
  - J.B.S. Haldane asked (& answered) this question in 1937.
    - Interest was rekindled (by H. J. Muller) after Hiroshima and Nagasaki bombed using atomic weapons.

  - For a single recessive locus, can define this effect as follows:
    
    - Frequency of the affected individuals is \( \hat{P}_{aa} = \hat{q}_{\text{rec}}^2 = (\sqrt{us})^2 = u/s \).
    - Fitness lowered by a relative amount \( s \) per affected individual
    - Total reduction in fitness: \((u/s) \times s = u\)
    - This is the “mutation load” for a recessive deleterious.
      - notice that the mutation load is independent of \( s \).

  - Similarly, for partially dominant mutations
    
    - Assume \( \hat{q}_h \ll 1 \)
    
    - Frequency of affecteds = frequency of heterozygotes = \( 2\hat{q}_h(1-\hat{q}_h) \approx 2\hat{q}_h \approx (2u)/hs \).
    - Mutation load (total reduction in fitness): \((2u/hs) \times hs = 2u\).
      - Again, mutation load is independent of \( s \).
Punch Line: Mutation load depends only on mutation rate and not on a mutant's fitness effects (i.e., $s$).

Why is this?
- Highly deleterious mutations equilibrate at low frequencies;
- Mildly deleterious mutations equilibrate at high frequencies;
- Net effect in either case is the same.

Muller: “One mutation equals one death”

- At equilibrium, each new mutation in a population is offset by the loss of another one due to selection.

- Small selection coefficient means only that the risk of death for an affected individual is smaller, not that the total number of deaths is smaller.

  - Either
    - many individuals have smaller probabilities of death,
    - or few individuals have a high probability of death.

- Ethical dilemma: do medical advances relieve suffering?
  - Individual suffering is generally reduced.
  - Result is that more individuals suffer mild effects.