**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**:  
    
    \[ \text{zygotes} \xrightarrow{\text{selection}} \text{adults} \xrightarrow{\text{mutation}} \text{gametes} \xrightarrow{\text{random union}} \text{zygotes} \]

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

  • **p** = freq. A, **q** = freq. a

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

  • Let \( u = A \rightarrow a \) mutation rate (ignore back mutation \( A \rightarrow a \): i.e., \( v = 0 \)), then

    \[ p' = p_\ast (1 - u) = \frac{(1 - u)p}{1 - sq} \]

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

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

    1. **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 $\bar{w}_A$ instead of $w_A$, etc.):

\[ p^* = p \frac{\bar{w}_A}{\bar{w}} \text{ and } p' = (1-u)p^* = (1-u)p \frac{\bar{w}_A}{\bar{w}} \]

- Setting $p' = p$, can solve for equilibrium frequency of deleterious $a$ allele ($\hat{q} = 1 - \hat{p}$):
  - Two cases of interest:
    
    \[ \hat{q}_{\text{rec}}^2 = u/s \]
    
    \[ \hat{q}_{\text{rec}} > \hat{q}_{\text{hap}} \text{ for the same } u, s. \]

    (a) Recessive Mutant: $h = 0$
    - Solving for equilibrium shows $\hat{q}_{\text{rec}} = \sqrt{u/s}$.
    - Note: $u < s$ so $\hat{q}_{\text{rec}} > \hat{q}_{\text{hap}}$ for the same $u, s$.

    (b) Partial Dominance: $h > 0$
    - By ignoring $\hat{q}^2$ in the equilibrium equations, find that $\hat{q}_h = u(\sqrt{hs})$.
    - 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: $\hat{q}_{\text{hap}} = u/s$;
    
    recessive affecteds: $\hat{P}_{\text{aa}} = \hat{q}_{\text{rec}}^2 = (\sqrt{u/s})^2 = u/s$.

  - 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 $\hat{P}_{\text{aa}} = \hat{q}_{\text{rec}}^2 = (\sqrt{u/s})^2 = u/s$.
  
  - 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 $\approx$ frequency of heterozygotes = $2\hat{q}_h (1 - \hat{q}_h) = 2\hat{q}_h = (2u)f(hs)$.
  – 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.