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: $\underset{p}{\text{zygotes}} \xrightarrow{\text{selection}} \underset{p^*}{\text{adults}} \xrightarrow{\text{mutation}} \underset{p^{**}}{\text{gametes}} \xrightarrow{\text{random union}} \underset{p'}{\text{zygotes}}$

- Fitnesses: $w_A : w_a = 1 : 1 - s$

- p = freq. A, q = freq. a

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

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

$$p' = p^{**} = p^*(1-u) = \frac{(1-u)p}{1-sq} \quad .$$

- 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:

Genotype	AA	Aa	aa
Fitness	1	$1-hs$	$1-s$

- Using approach analogous to that for haploids (substitute $\overline{w}_A$ instead of w_A, etc.):

$$p^* = p\frac{\overline{w}_A}{\overline{w}} \text{ and } p' = (1-u)p^* = (1-u)p\frac{\overline{w}_A}{\overline{w}}$$

- 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 $\hat{q}_{\text{rec}} = \sqrt{u/s}$.
    - 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 $\hat{q}_h \approx u/(hs)$.
    - Approximation fails as h –> 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: $\hat{P}_{aa} = \hat{q}^2_{\text{rec}} = \left(\sqrt{u/s}\right)^2 = u/s$.

  - 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 $\hat{P}_{aa} = \hat{q}^2_{\text{rec}} = \left(\sqrt{u/s}\right)^2 = u/s$.
  - 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 $\hat{q}_h << 1$
  – 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.