BGEN 55 - Advanced Genetics II

Worked Examples: Mutation-Selection Balance

Step-by-Step Problem Solutions

Key Formulas:

Recessive: $\hat{q} = \sqrt{(\mu/s)}$ | Dominant: $\hat{q} = \mu/s$ | Additive: $\hat{q} = \mu/(hs)$

Example 1: Cystic Fibrosis Calculation

Problem: Cystic fibrosis is caused by recessive mutations in the CFTR gene. The estimated mutation rate is $\mu = 6.7 \times 10^{-7}$ per generation. Assuming it's a lethal disorder (s = 1), calculate:

a) The expected equilibrium frequency of the CF allele

b) The expected carrier frequency in the population

c) The number of carriers in a population of 1 million people

Solution:

Step 1: Identify known values
$\mu = 6.7 \times 10^{-7}$
s = 1 (lethal recessive)
Use recessive formula: $\hat{q} = \sqrt{(\mu/s)}$

Step 2: Calculate equilibrium allele frequency
$\hat{q} = \sqrt{(6.7 \times 10^{-7} / 1)} = \sqrt{(6.7 \times 10^{-7})}$
$\hat{q} = \sqrt{6.7} \times \sqrt{10^{-7}} = 2.588 \times 10^{-3.5}$
Better approach: $\hat{q} = \sqrt{(0.00000067)} = 0.000818$

Step 3: Calculate carrier frequency
Carrier frequency = $2pq \approx 2\hat{q}$ (since $p \approx 1$)
Carriers = 2 × 0.000818 = 0.001636 (0.1636%)

Step 4: Calculate number of carriers
In 1 million people: 1,000,000 × 0.001636 = 1,636 carriers

Final Answers:

a) $\hat{q} = 0.000818$ (0.0818%)

b) Carrier frequency = 0.001636 (0.1636%)

c) 1,636 carriers in 1 million people

💡 **Reality Check:** Actual CF carrier frequency in European populations is about 1 in 25 (4%), suggesting either higher mutation rates or historical heterozygote advantage.

Example 2: Dominant Disorder

Problem: Achondroplasia (a form of dwarfism) is caused by dominant mutations with $s = 0.8$ (reduced fitness). The mutation rate is estimated at $\mu = 1.4 \times 10^{-5}$. Calculate the expected equilibrium frequency.

Solution:

Step 1: Identify inheritance pattern
Achondroplasia is dominant, so we use: $\hat{q} = \mu/s$

Step 2: Apply the formula
$\hat{q} = (1.4 \times 10^{-5}) / 0.8 = 1.75 \times 10^{-5}$

Step 3: Interpret the result
$\hat{q} = 0.0000175$ (0.00175%)
Since it's dominant, this is both the allele frequency and the disease frequency

Final Answer: $\hat{q} = 1.75 \times 10^{-5}$

💡 **Comparison:** Notice how much lower the equilibrium frequency is for dominant disorders compared to recessive ones, even with similar mutation rates.

Example 3: Partial Dominance

Problem: A genetic disorder has additive inheritance with dominance coefficient $h = 0.25$. The mutation rate is $\mu = 2 \times 10^{-6}$ and the selection coefficient is $s = 0.5$. Calculate the equilibrium frequency.

Solution:

Step 1: Use the additive formula

For additive inheritance: $\hat{q} = \mu/(hs)$

Step 2: Substitute values
$\hat{q} = (2 \times 10^{-6}) / (0.25 \times 0.5) = 0.000002 / 0.125 = 1.6 \times 10^{-5}$

Step 3: Interpret the result
$\hat{q} = 0.000016$ (0.0016%)

Final Answer: $\hat{q} = 1.6 \times 10^{-5}$

💡 **Understanding h:** The dominance coefficient h ranges from 0 (recessive) to 1 (dominant). Here $h = 0.25$ means the heterozygote has 25% of the fitness reduction of the homozygote.

Example 4: Finding Mutation Rate from Observed Frequency

Problem: Tay-Sachs disease is a recessive lethal disorder ($s = 1$) that occurs at a frequency of 1 in 3,600 births in Ashkenazi Jewish populations. Estimate the mutation rate assuming mutation-selection balance.

Solution:

Step 1: Convert disease frequency to allele frequency
Disease frequency $= q^2 = 1/3600 = 0.000278$
Therefore $q = \sqrt{0.000278} = 0.01667$

Step 2: Use the equilibrium formula
$\hat{q} = \sqrt{\mu/s} \rightarrow \mu = \hat{q}^2 \times s$

Step 3: Calculate mutation rate
$\mu = (0.01667)^2 \times 1 = 0.000278 \times 1 = 2.78 \times 10^{-4}$

Final Answer: $\mu = 2.78 \times 10^{-4}$ per generation

💡 **Interpretation:** This mutation rate seems quite high. The actual explanation for Tay-Sachs frequency in Ashkenazi Jews likely involves founder effects and possible historical heterozygote advantage rather than just mutation-selection balance.

Example 5: Multiple Calculations

Problem: Compare three different genetic disorders:

- Disorder A: Recessive, $\mu = 10^{-6}$, $s = 1$
- Disorder B: Dominant, $\mu = 10^{-6}$, $s = 0.5$
- Disorder C: Recessive, $\mu = 10^{-5}$, $s = 0.1$

Calculate and compare their equilibrium frequencies.

Solution:

Disorder A (Recessive, $\mu = 10^{-6}$, $s = 1$)
$\hat{q} = \sqrt{(10^{-6}/1)} = \sqrt{10^{-6}} = 10^{-3} = 0.001$

Disorder B (Dominant, $\mu = 10^{-6}$, $s = 0.5$)
$\hat{q} = 10^{-6}/0.5 = 2 \times 10^{-6} = 0.000002$

Disorder C (Recessive, $\mu = 10^{-5}$, $s = 0.1$)
$\hat{q} = \sqrt{(10^{-5}/0.1)} = \sqrt{(10^{-4})} = 10^{-2} = 0.01$

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Comparison:
Disorder A: q^= 0.001
Disorder B: q^= 0.000002
Disorder C: q^= 0.01
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💡 **Patterns:** Disorder C has the highest frequency due to high mutation rate and weak selection. Disorder B has the lowest frequency because dominant selection is more efficient.

Practice Problems

Problem 1: Phenylketonuria (PKU) is a recessive disorder with $s = 0.7$ (reduced fitness due to dietary restrictions). If the mutation rate is 4×10^{-6}, what is the expected equilibrium frequency?

Problem 2: Huntington's disease is a dominant lethal disorder ($s = 1$) that appears in mid-life. If the mutation rate is 1×10^{-6}, what is the expected disease frequency?

Problem 3: Sickle cell anemia is a recessive disorder, but heterozygotes have advantage against malaria. This creates a balanced polymorphism rather than mutation-selection balance. Explain why the standard $\hat{q} = \sqrt{(\mu/s)}$ formula doesn't apply.

Problem 4: If a recessive disorder has an equilibrium frequency of 0.0025 and $s = 0.8$, what is the mutation rate?

🎯 Problem-Solving Strategy

1. Identify the inheritance pattern (recessive, dominant, additive)
2. Choose the correct formula
3. Substitute the given values
4. Calculate carefully, watching units and exponents
5. Interpret the result in biological context
6. Compare with real-world data when possible
