BGEN 55 - Advanced Genetics II

Deriving $\hat{q} = \sqrt{\mu/s}$

Step-by-Step Mathematical Derivation

📋 Model Assumptions

Before we begin, recall our key assumptions:

- Infinite population size (no genetic drift)
- Random mating
- Recessive deleterious allele (a)
- Mutation rate A → a = μ per generation
- Selection coefficient against aa = s
- Fitness: AA = 1, Aa = 1, aa = 1 - s
- No reverse mutation (a → A negligible)
- No migration

1 Define the Equilibrium Condition

At mutation-selection balance, the input of new a alleles by mutation equals the removal of a alleles by selection:

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Input by mutation = Removal by selection
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Concept: Think of this as a bathtub with water flowing in (mutation) and draining out (selection). At equilibrium, the water level stays constant because inflow equals outflow.

2 Calculate Input by Mutation

Each generation, a fraction μ of A alleles mutate to become a alleles.

Number of A alleles ≈ 2Np (since p ≈ 1 for rare deleterious alleles)
Mutations per generation = 2Np × μ
Since we're working with frequencies, we can use the proportion:

$$\Delta q_{mut} = \mu$$

Why μ and not μp? Because when the deleterious allele is rare, almost all alleles are A (p ≈ 1), so the mutation input is approximately μ.

3 Calculate Removal by Selection

For a recessive deleterious allele, selection only acts against the aa homozygotes.

Frequency of aa genotypes = q^2
Each aa individual has fitness $(1 - s)$
Selection removes a fraction s of aa individuals
Each removed aa individual carries 2 a alleles
But we need the change in allele frequency, not individual count

Using the formula for selection against recessives:

$$\Delta q_{sel} = -sq^2$$

Note: The negative sign indicates that selection decreases the frequency of the deleterious allele.

4 Set Up the Equilibrium Equation

At equilibrium, the net change in q is zero:

$$\Delta q_{mut} + \Delta q_{sel} = 0$$
$$\mu - sq^2 = 0$$

Critical Insight: This simple equation captures the essence of mutation-selection balance. Mutation adds a alleles at rate μ, while selection removes them at rate sq^2.

5 Solve for Equilibrium Frequency

Now we solve the equilibrium equation for q:

$\mu - sq^2 = 0$
$sq^2 = \mu$
$q^2 = \mu/s$

$$\hat{q} = \sqrt{(\mu/s)}$$

Beautiful Result: The equilibrium frequency depends on the square root of the ratio between mutation rate and selection coefficient. This makes intuitive sense - it's a balance between two opposing forces.

6 Interpret the Result

Let's examine what $\hat{q} = \sqrt{\mu/s}$ tells us:

- If μ increases → $\hat{q}$ increases (more mutation input)
- If s increases → $\hat{q}$ decreases (stronger selection)
- The square root means changes are dampened
- If $\mu = s$, then $\hat{q} = 1$ (but this rarely happens)

Biological Significance: This explains why recessive genetic disorders persist in populations. Even with strong selection ($s \approx 1$), they maintain equilibrium frequencies determined by their mutation rates.

7 Numerical Example

Let's apply the formula to a real scenario:

For cystic fibrosis:
$\mu \approx 1 \times 10^{-6}$ (estimated mutation rate)
$s = 1$ (lethal recessive)
$\hat{q} = \sqrt{0.000001 / 1} = \sqrt{0.000001} = 0.001$

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Carrier frequency = 2pq ≈ 2 × 0.001 = 0.002 (1 in 500)
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Note: The actual carrier frequency for cystic fibrosis in European populations is about 1 in 25, suggesting either higher mutation rates or historical heterozygote advantage.

8 Comparison with Other Inheritance Patterns

It's instructive to compare with other cases:

Dominant deleterious: $\hat{q} = \mu/s$
Additive: $\hat{q} = \mu/(hs)$ where h is dominance coefficient
Recessive: $\hat{q} = \sqrt{\mu/s}$ ← We derived this!

Key Difference: Recessive deleterious alleles reach much higher equilibrium frequencies because selection only acts against homozygotes.

9 Limitations and Refinements

Our derivation made several simplifying assumptions:

- Infinite population size
- Constant mutation rate
- No reverse mutation
- No migration
- Random mating
- Selection only on viability

Real-world complexities: In actual populations, genetic drift, fluctuating environments, and other factors modify these predictions. However, the basic $\hat{q} = \sqrt{\mu/s}$ provides an excellent starting point.

10 Practice Derivation

Now try deriving the equilibrium for a dominant deleterious allele:

Given: Selection acts against both Aa and aa genotypes
Find: Show that $\hat{q} = \mu/s$
Hint: For dominants, $\Delta q_{sel} = -sq$

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Your derivation here...
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🎯 Summary of Key Points

- Mutation-selection balance occurs when input equals removal
- For recessives: $\Delta q_{mut} = \mu$, $\Delta q_{sel} = -sq^2$
- Equilibrium: $\mu - sq^2 = 0 \rightarrow \hat{q} = \sqrt{\mu/s}$
- The square root reflects that selection only acts against homozygotes
- This explains persistence of recessive genetic disorders